Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2953132 A1 2016/01/07

(21) 2 953 132

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) **Date de dépôt PCT/PCT Filing Date:** 2015/06/30
(87) **Date publication PCT/PCT Publication Date:** 2016/01/07
(85) **Entrée phase nationale/National Entry:** 2016/12/20
(86) **N° demande PCT/PCT Application No.:** US 2015/038712
(87) **N° publication PCT/PCT Publication No.:** 2016/004136
(30) **Priorités/Priorities:** 2014/07/01 (US62/019,756); 2015/06/28 (US62/185,678)

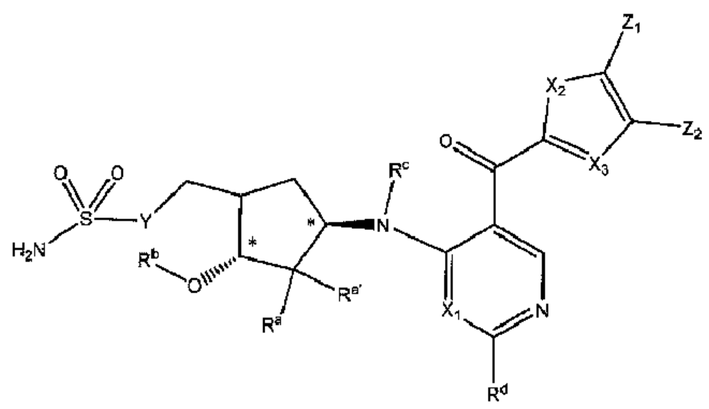
(51) **Cl.Int./Int.Cl.** ***A61K 31/44*** (2006.01), ***A61K 31/506*** (2006.01), ***C07D 239/24*** (2006.01)

(71) **Demandeur/Applicant:**
MILLENIUM PHARMACEUTICALS, INC., US

(72) **Inventeurs/Inventors:**
ENGLAND, DYLAN, US;
FREEZE, SCOTT, US;
HU, ZHIGEN, US;
LANGSTON, STEVEN P., US;
MCINTYRE, CHARLES, US;
MIZUTANI, HIROTAKE, US;
...

(74) **Agent:** BORDEN LADNER GERVAIS LLP

(54) **Titre : COMPOSES HETEROARYLE UTILES EN TANT QU'INHIBITEURS DE L'ENZYME D'ACTIVATION SUMO**
(54) **Title: HETEROARYL COMPOUNDS USEFUL AS INHIBITORS OF SUMO ACTIVATING ENZYME**



(I);

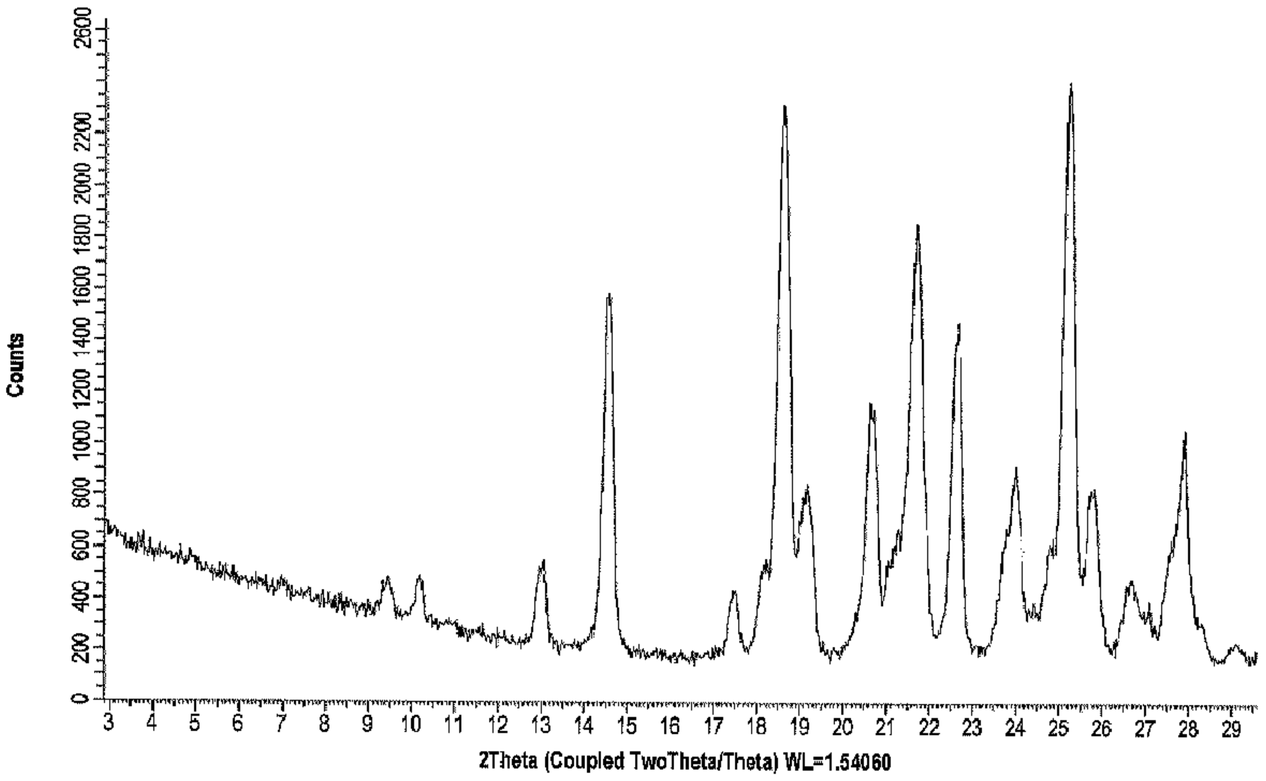


FIG. 1

(57) **Abrégé/Abstract:**
Disclosed are chemical entities which are compounds of formula (I); or pharmaceutically acceptable salts thereof; wherein Y, R^a, $R^{a'}$, R^b, R^c, X_1, X_2, X_3, R^d, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked

(21) **2 953 132**

(13) **A1**

(72) **Inventeurs(suite)/Inventors(continued):** ONO, KOJI, JP; XU, HE, US; DUFFEY, MATTHEW O., US

(57) **Abrégé(suite)/Abstract(continued):**
positions indicate absolute stereochemistry. Chemical entities according to the disclosure can be useful as inhibitors of Sumo Activating Enzyme (SAE). Further provided are pharmaceutical compositions comprising a compound of the disclosure and methods of using the compositions in the treatment of proliferative, inflammatory, cardiovascular, and neurodegenerative diseases or disorders.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 January 2016 (07.01.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/004136 A1

(51) **International Patent Classification**:
A61K 31/44 (2006.01) *C07D 239/24* (2006.01)
A61K 31/506 (2006.01)

(21) **International Application Number**:
PCT/US2015/038712

(22) **International Filing Date**:
30 June 2015 (30.06.2015)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
62/019,756 1 July 2014 (01.07.2014) US
62/185,678 28 June 2015 (28.06.2015) US

(72) **Inventors; and**
(71) **Applicants** : **DUFFEY, Matthew O.** [US/US]; 5050 S. Lake Shore Dr. #2717, Chicago, IL 60615 (US). **ENGLAND, Dylan** [CA/US]; 9 Wayne Road, Milford, MA 01757 (US). **FREEZE, Scott** [US/US]; 67 Gates St, Unit 1, Boston, MA 02127 (US). **HU, Zhigen** [CN/US]; 64B Marshall Street, Somerville, MA 02145 (US). **LANGSTON, Steven, P.** [US/US]; 164 Mill Road, Andover, MA 01845 (US). **MCINTYRE, Charles** [US/US]; 230 Brookline Street, Apt. 1, Cambridge, MA 02139 (US). **MIZUTANI, Hirotake** [US/US]; 264 Massachusetts Ave., #209, Arlington, MA 02474 (US). **ONO, Koji** [JP/JP]; c/o TAKEDA PHARMACEUTICAL COMPANY LIMITED, 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-0012 (JP). **XU, He** [CN/US]; 43 Glover Road, Needham, MA 02494 (US).

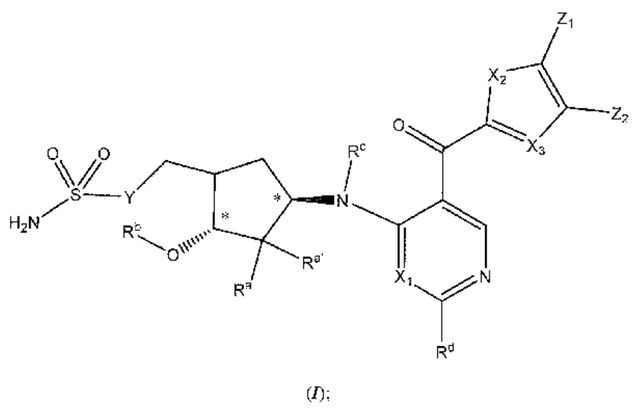
(74) **Agent**: **BREIER, Adam, M.**; Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, 901 New York Avenue NW, Washington, DC 20001-4413 (US).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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,

[Continued on next page]

(54) **Title**: HETEROARYL COMPOUNDS USEFUL AS INHIBITORS OF SUMO ACTIVATING ENZYME

(57) **Abstract**: Disclosed are chemical entities which are compounds of formula (I); or pharmaceutically acceptable salts thereof; wherein Y, R^a, $R^{a'}$, R^b, R^c, X_1, X_2, X_3, R^d, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. Chemical entities according to the disclosure can be useful as inhibitors of Sumo Activating Enzyme (SAE). Further provided are pharmaceutical compositions comprising a compound of the disclosure and methods of using the compositions in the treatment of proliferative, inflammatory, cardiovascular, and neurodegenerative diseases or disorders.



(I);

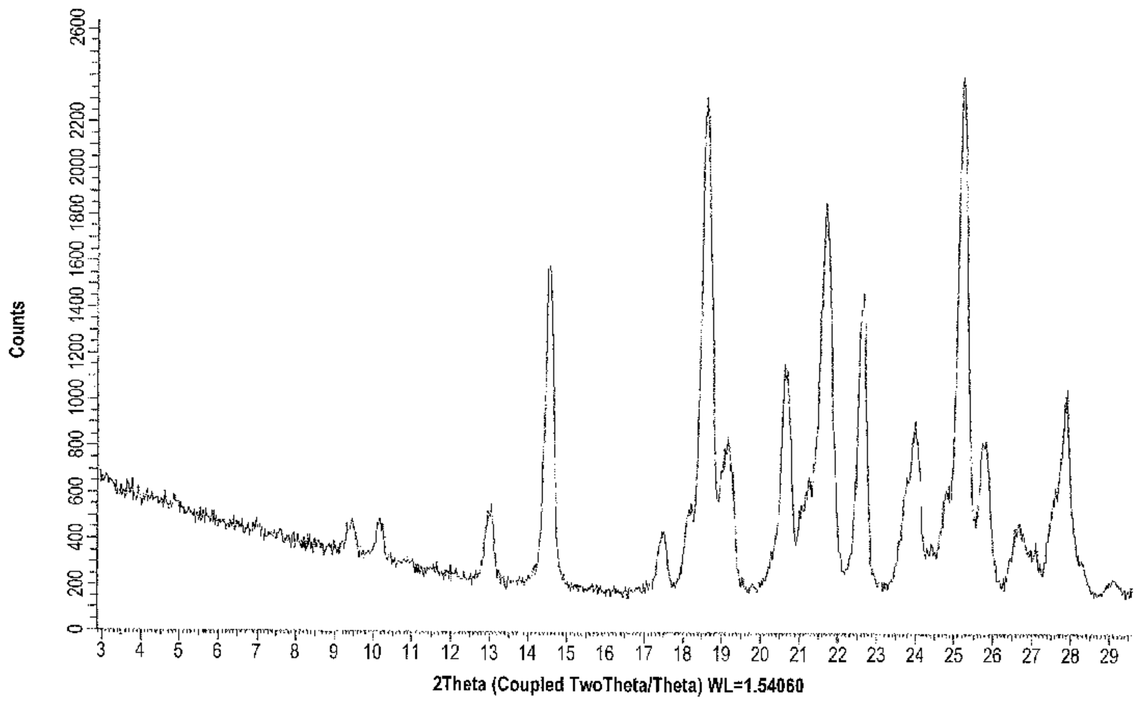


FIG. 1

WO 2016/004136 A1

WO 2016/004136 A1

SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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))*

DEMANDE OU BREVET VOLUMINEUX

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

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 317

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 317

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

HETEROARYL COMPOUNDS USEFUL AS INHIBITORS OF SUMO ACTIVATING ENZYME

INTRODUCTION

[0001] This application claims the benefit of United States Provisional Patent Application No. 62/019,756, filed July 1, 2014, and United States Provisional Patent Application No. 62/185,678, filed June 28, 2015, all of which are incorporated by reference in their entirety.

[0002] Small ubiquitin-like modifier (SUMO) is a member of the ubiquitin-like protein (Ubl) family that is covalently conjugated to cellular proteins in a manner similar to Ub-conjugation (Kerscher, O., Felberbaum, R., and Hochstrasser, M. 2006. Modification of proteins by ubiquitin and ubiquitin-like proteins. *Annu Rev Cell Dev Biol.* 22:159-80). Mammalian cells express three major isoforms: SUMO1, SUMO2 and SUMO3. SUMO2 and SUMO3 share ~95% amino acid sequence homology but have ~45% sequence homology with SUMO1 (Kamitani, T., Kito, K., Nguyen, H. P., Fukuda-Kamitani, T., and Yeh, E. T. 1998. Characterization of a second member of the sentrin family of ubiquitin-like proteins. *J Biol Chem.* 273(18):11349-53). SUMO proteins can be conjugated to a single lysine residue of a protein (monosumoylation) or to a second SUMO protein that is already conjugated to a protein forming a SUMO chain (*polysumoylation*). Only SUMO2/3 can form such chains because they possess internal consensus SUMO modification sites (Tatham, M. H., Jaffray, E., Vaughan, O. A., Desterro, J. M., Botting, C. H., Naismith, J. H., Hay, R. T. 2001. Polymeric chains of SUMO-2 and SUMO-3 are conjugated to protein substrates by SAE1/SAE2 and Ubc9. *J Biol Chem.* 276(38):35368-74). An additional isoform, SUMO4, is found in kidney, lymph node and spleen cells, but it is not known whether SUMO4 can be conjugated to cellular proteins.

[0003] SUMO1, SUMO2 and SUMO3 are activated in an ATP-dependent manner by the SUMO-activating enzyme (SAE). SAE is a heterodimer that consists of SAE1 (SUMO-activating enzyme subunit 1) and SAE2 (UBA2). SAE, like other E1 activating enzymes, uses ATP to adenylate the C-terminal glycine residue of SUMO. In a second step, a thioester intermediate is then formed between the C-terminal glycine of SUMO and a cysteine residue in SAE2. Next, SUMO is transferred from the E1 to the cysteine residue of the SUMO conjugating enzyme (E2), UBC9. Unlike the Ub pathway that contains many E2 enzymes, Ubc9 is currently the only known conjugating enzyme for SUMO and functions with SUMO1, SUMO2 and SUMO3 proteins. SUMO proteins are then conjugated to the target protein, either directly or in conjunction with an E3 ligase, through isopeptide bond formation with the epsilon amino group of a lysine side chain on a target protein. Several SUMO E3 ligases, including PIAS (protein inhibitor of activated signal transducer and activator of transcription protein) proteins and Ran-binding protein 2 (RanBP2), and polycomb 2 (Pc2), have been identified (Johnson, E. S., and Gupta, A. A. 2001. An E3-like factor that promotes SUMO conjugation to the yeast septins. *Cell.* 106(6):735-44; Pichler, A., Gast, A., Seeler, J. S., Dejean, A.; Melchior, F. 2002. The nucleoporin RanBP2 has SUMO1 E3 ligase activity. *Cell.* 108(1):109-20; Kagey, M. H.,

Melhuish, T. A., and Wotton, D. 2003. The polycomb protein Pc2 is a SUMO E3. *Cell.* 113(1):127-37). Once attached to cellular targets, SUMO modulates the function, subcellular localization, complex formation and/or stability of substrate proteins (Müller, S., Hoege, C., Pyrowolakis, G., and Jentsch, S. 2001. SUMO, ubiquitin's mysterious cousin. *Nat Rev Mol Cell Biol.* 2(3):202-10). SUMO-conjugation is reversible through the action of de-sumoylating enzymes called SENPs (Hay, R. T. 2007. SUMO-specific proteases: a twist in the tail. *Trends Cell Biol.* 17(8):370-6) and the SUMO proteins can then participate in additional conjugation cycles.

[0004] SAE-initiated SUMO-conjugation plays a major role in regulating diverse cellular processes, including cell cycle regulation, transcriptional regulation, cellular protein targeting, maintenance of genome integrity, chromosome segregation, and protein stability (Hay, R. T. 2005. SUMO: a history of modification. *Mol Cell.* 18(1):1-12; Gill, G. 2004. SUMO and ubiquitin in the nucleus: different functions, similar mechanisms? *Genes Dev.* 18(17):2046-59). For example, SUMO-conjugation causes changes in the subcellular localization of RanGAP1 by targeting it to the nuclear pore complex (Mahajan, R., Delphin, C., Guan, T., Gerace, L., and Melchior, F. 1997. A small ubiquitin-related polypeptide involved in targeting RanGAP1 to nuclear pore complex protein RanBP2. *Cell.* 88(1):97-1070). Sumoylation counteracts ubiquitination and subsequently blocks the degradation of IκB, thereby negatively regulating NF-κB activation (Desterro, J. M., Rodriguez, M. S., Hay, R. T. 1998. SUMO-1 modification of IkappaBalpha inhibits NF-kappaB activation. *Mol Cell.* 2(2):233-9). Sumoylation has been reported to play an important role in transcription exhibiting both repressive and stimulatory effects. Many of the transcriptional nodes that are modulated play important roles in cancer. For example, sumoylation stimulates the transcriptional activities of transcription factors such as p53 and HSF2 (Rodriguez, M. S., Desterro, J. M., Lain, S., Midgley, C. A., Lane, D. P., and Hay, R. T. 1999. SUMO-1 modification activates the transcriptional response of p53. *EMBO J.* 18(22):6455-61; Goodson, M. L., Hong, Y., Rogers, R., Matunis, M. J., Park-Sarge, O. K., Sarge, K. D. 2001. Sumo-1 modification regulates the DNA binding activity of heat shock transcription factor 2, a promyelocytic leukemia nuclear body associated transcription factor. *J Biol Chem.* 276(21):18513-8). In contrast, SUMO-conjugation represses the transcriptional activities of transcription factors such as LEF (Sachdev, S., Bruhn, L., Sieber, H., Pichler, A., Melchior, F., Grosschedl, R. 2001. PIASy, a nuclear matrix-associated SUMO E3 ligase, represses LEF1 activity by sequestration into nuclear bodies. *Genes Dev.* 15(23):3088-103) and c-Myb (Bies, J., Markus, J., and Wolff, L. 2002. Covalent attachment of the SUMO-1 protein to the negative regulatory domain of the c-Myb transcription factor modifies its stability and transactivation capacity. *J Biol Chem.* 277(11):8999-9009). Thus, SUMO-conjugation controls gene expression and growth control pathways that are important for cancer cell survival.

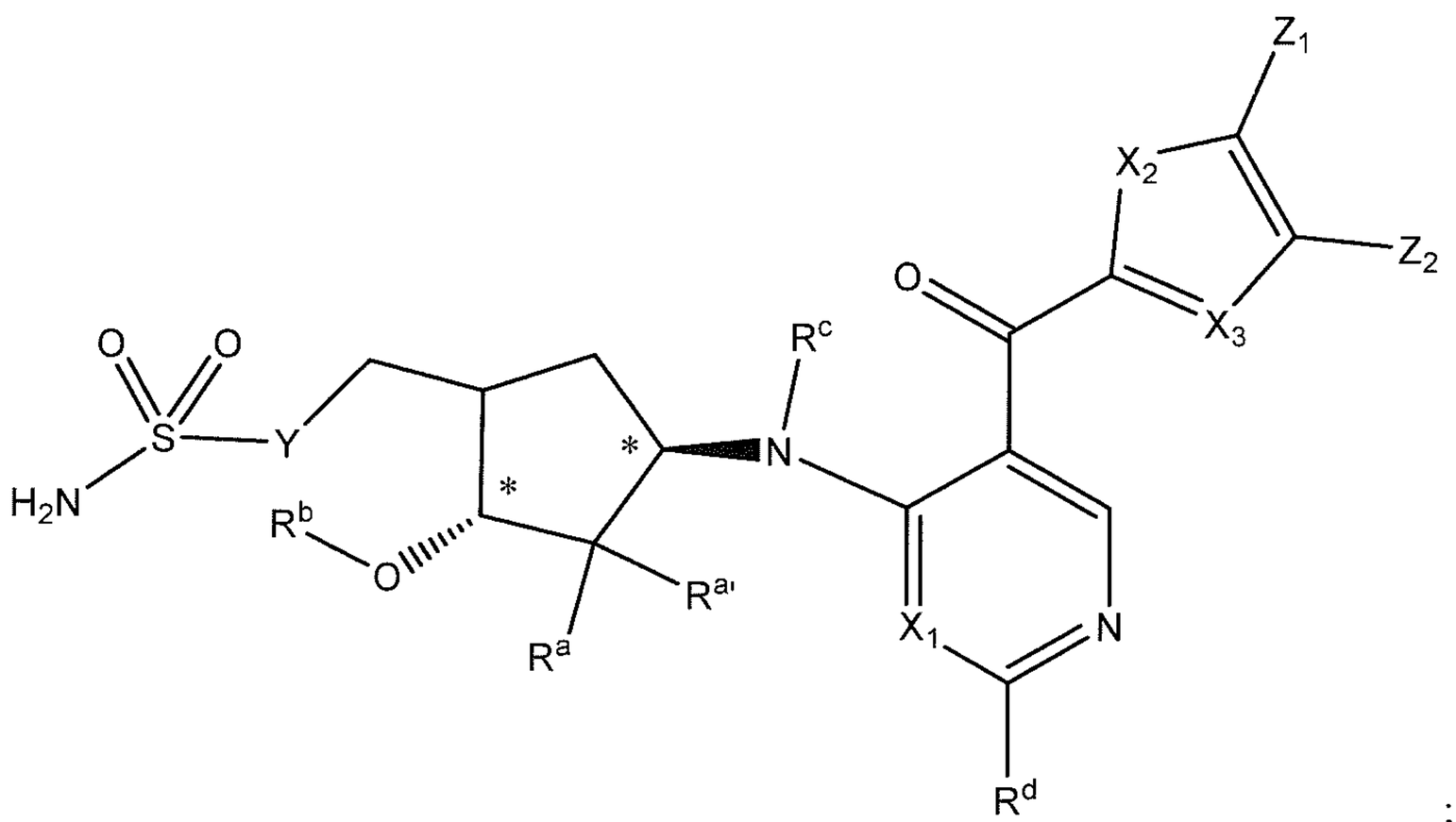
[0005] Altered expression of SAE pathway components have been noted in a variety of cancer types: (Moschos, S. J., Jukic, D. M., Athanassiou, C., Bhargava, R., Dacic, S., Wang, X., Kuan, S. F., Fayewicz, S. L., Galambos, C., Acquafondata, M., Dhir, R., and Becker, D. 2010. Expression analysis

of Ubc9, the single small ubiquitin-like modifier (SUMO) E2 conjugating enzyme, in normal and malignant tissues. Hum Pathol. 41(9):1286-980); including multiple myeloma (Driscoll, J. J., Pelluru, D., Lefkimmiatis, K., Fulciniti, M., Prabhala, R. H., Greipp, P. R., Barlogie, B., Tai, Y. T., Anderson, K. C., Shaughnessy, J. D. Jr., Annunziata, C. M., and Munshi, N. C. 2010. The sumoylation pathway is dysregulated in multiple myeloma and is associated with adverse patient outcome. *Blood.* 115(14):2827-34); and breast cancer (Chen, S. F., Gong, C., Luo, M., Yao, H. R., Zeng, Y. J., and Su, F. X. 2011. Ubc9 expression predicts chemoresistance in breast cancer. *Chin J Cancer.* 30(9):638-44), In addition, preclinical studies indicate that Myc-driven cancers may be especially sensitive to SAE inhibition (Kessler, J. D., Kahle, K. T., Sun, T., Meerbrey, K. L., Schlabach, M. R., Schmitt, E. M., Skinner, S. O., Xu, Q., Li, M. Z., Hartman, Z. C., Rao, M., Yu, P., Dominguez-Vidana, R., Liang, A. C., Solimini, N. L., Bernardi, R. J., Yu, B., Hsu, T., Golding, I., Luo, J., Osborne, C. K., Creighton, C. J., Hilsenbeck, S. G., Schiff, R., Shaw, C. A., Elledge, S. J., and Westbrook, T. F. 2012. A SUMOylation-dependent transcriptional subprogram is required for Myc-driven tumorigenesis. *Science.* 335(6066):348-53; Hoellein, A., Fallahi, M., Schoeffmann, S., Steidle, S., Schaub, F. X., Rudelius, M., Laitinen, I., Nilsson, L., Goga, A., Peschel, C., Nilsson, J. A., Cleveland, J. L., and Keller, U. 2014. Myc-induced SUMOylation is a therapeutic vulnerability for B-cell lymphoma. *Blood.* 124(13):2081-90). Since SUMO-conjugation regulates essential cellular functions that contribute to the growth and survival of tumor cells, targeting SAE could represent an approach to treat proliferative disorders such as cancer.

[0006] SAE inhibitors may also be applicable for the treatment of other diseases and conditions outside of oncology. For example, SUMO modifies proteins that play important roles in neurodegenerative diseases (Steffan, J. S., Agrawal, N., Pallos, J., Rockabrand, E., Trotman, L. C., Slepko, N., Illes, K., Lukacsovich, T., Zhu, Y. Z., Cattaneo, E., Pandolfi, P. P., Thompson, L. M., Marsh, J. L. 2004. SUMO modification of Huntington and Huntington's disease pathology. *Science.* 304(5667):100-4); Dorval, V., and Fraser, P. E. 2006. Small ubiquitin-like modifier (SUMO) modification of natively unfolded proteins tau and alpha-synuclein. *J Biol Chem.* 281(15):9919-24; Ballatore, C., Lee, V. M., and Trojanowski, J. Q. 2007. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci.* 8(9):663-72). Sumoylation also has been reported to play important role in pathogenic viral infection, inflammation and cardiac function (Lee, H. R., Kim, D. J., Lee, J. M., Choi, C. Y., Ahn, B. Y., Hayward, G. S., and Ahn, J. H. 2004. Ability of the human cytomegalovirus IE1 protein to modulate sumoylation of PML correlates with its functional activities in transcriptional regulation and infectivity in cultured fibroblast cells. *J Virol.* 78(12):6527-42; Liu, B., and Shuai, K. 2009. Summon SUMO to wrestle with inflammation. *Mol Cell.* 35(6):731-2; Wang, J., and Schwartz, R. J. 2010. Sumoylation and regulation of cardiac gene expression. *Circ Res.*107(1):19-29).

[0007] It would be beneficial therefore to provide new SAE inhibitors that possess good therapeutic properties, especially for the treatment of proliferative, inflammatory, cardiovascular and neurodegenerative disorders.

[0008] This application provides chemical entities which are inhibitors of SAE and accordingly are useful for the treatment of proliferative, inflammatory, cardiovascular and neurodegenerative disorders. The chemical entities of the present disclosure are represented by Formula (***I***):



;

(***I***)

or a pharmaceutically acceptable salt thereof;

wherein:

stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry;

Y is -O-, -CH_2-, or -N(H)-;

R^a is hydrogen, fluoro, -NH_2, or hydroxyl;

$R^{a'}$ is hydrogen or fluoro, provided that when R^a is -NH_2 or hydroxyl, $R^{a'}$ is hydrogen;

R^b is hydrogen or, together with the oxygen to which it is attached, forms a prodrug;

R^c is hydrogen or C_{1-4} alkyl;

R^d is hydrogen, halogen, -CF_3, or C_{1-4} alkyl;

X_1 is C(H), C(F), or N;

X_2 is S or O;

X_3 is C(R^{x3}) or N;

R^{x3} is hydrogen, methyl, or halogen;

Z_1 is hydrogen, halogen, cyano, R^{z3}, -S-R^{z3}, -S(O)-R^{z3}, or -$S(O)_2$-R^{z3};

R^{z3} is an optionally substituted phenyl, an optionally substituted 5- to 7-membered cycloaliphatic, an optionally substituted 5- to 7-membered heterocyclyl, or an optionally substituted C_{1-4} aliphatic;

wherein Z_1 is not hydrogen, halogen, methyl, or cyano if Z_2 is hydrogen or methyl; and

(a) Z_2 is a ring system having an optionally substituted 5- to 7-membered heterocyclyl with 1-2 heteroatoms or an optionally substituted 5- to 7-membered cycloaliphatic fused to

(i) an optionally substituted 5-membered heteroaryl or an optionally substituted 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) an optionally substituted 9-membered heteroaryl or an optionally substituted 10-membered aryl or heteroaryl to form a tricyclic group;

OR

(b) Z_2 is L-R^e wherein L is –L_1-, -V_1-L_2-, or –L_1-V_1-L_2-;

L_1 is a C_{1-3} alkylene chain wherein 1 or 2 saturated carbon atoms are optionally substituted by (R^f)($R^{f'}$) and in which there are optionally one or two degrees of unsaturation;

each R^f is independently hydrogen; hydroxyl; -N(R^h)($R^{h'}$); C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; -O-C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; or, together with $R^{f'}$ and the carbon atom to which they are attached, form =CH_2, or a 3- to 6-membered carbocycle or 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle;

each $R^{f'}$ is independently hydrogen; C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; -O-C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; or, together with R^f and the carbon atom to which they are attached, form =CH_2, or a 3- to 6-membered carbocycle or 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle; wherein if R^f is hydroxyl, $R^{f'}$ is not -O-C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl;

R^h and $R^{h'}$ are each independently hydrogen or C_{1-4} alkyl;

V_1 is -S-, -O-, -S(O)-, -$S(O)_2$-, -C(O)- or -N(R^g)-;

L_2 is a C_{0-2} alkylene chain wherein one saturated carbon atom is optionally substituted by $(R^f)(R^{f'})$;

R^g is hydrogen or C_{1-4} alkyl; and

either (i) R^e is hydrogen, hydroxyl, halogen, $-CF_3$, or an optionally substituted C_{1-4} aliphatic,

with the proviso that R^e is not hydrogen if R^f and $R^{f'}$ are present and form a ring;

OR (ii) R^e is a ring chosen from optionally substituted 6-membered aryl, optionally substituted 5-to 6-membered heteroaryl, optionally substituted 3- to 7-membered cycloaliphatic, or optionally substituted 4- to 7-membered heterocyclyl, which is optionally fused to a second optionally substituted 6-membered aryl, optionally substituted 5-to 6-membered heteroaryl, optionally substituted 3- to 7-membered cycloaliphatic, or optionally substituted 4- to 7-membered heterocyclyl;

OR

Z_2 is hydrogen.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 is an XRPD pattern of compound I-257b Form 1.

[0010] FIG. 2 is an XRPD pattern of compound I-263a Form 1.

[0011] FIG. 3 is an XRPD pattern of compound I-256b Form 1.

[0012] FIG. 4 shows a differential scanning calorimetry (DSC) thermogram for I-263a Form 1.

[0013] FIG. 5 shows a thermogravimetric analysis (TGA) thermogram for I-263a Form 1.

[0014] FIG. 6 shows a raman pattern for I-263a Form 1 including data in the region of 500 cm^{-1} to 3000 cm^{-1}.

[0015] FIG. 7 shows a raman pattern for I-263a Form 1 including data in the region of 200 cm^{-1} to 1600 cm^{-1}.

[0016] FIG. 8 shows a differential scanning calorimetry (DSC) thermogram for I-257b Form 1.

[0017] FIG. 9 shows a thermogravimetric analysis (TGA) thermogram for I-257b Form 1.

[0018] FIG. 10 shows a raman pattern for I-257b Form 1 including data in the region of 500 cm^{-1} to 3000 cm^{-1}.

[0019] FIG. 11 shows a raman pattern for I-257b Form 1 including data in the region of 200 cm^{-1} to 1600 cm^{-1}.

[0020] FIG. 12 shows a differential scanning calorimetry (DSC) thermogram for I-256b Form 1.

[0021] FIG. 13 shows a thermogravimetric analysis (TGA) thermogram for I-256b Form 1.

[0022] FIG. 14 is an XRPD pattern of compound I-263a Form 2.

[0023] FIG. 15 is an XRPD pattern of compound I-263a Form 3.

[0024] FIG. 16 shows a thermogravimetric analysis (TGA) thermogram for I-263a Form 3.

[0025] FIG. 17 shows a differential scanning calorimetry (DSC) thermogram for I-263a Form 3.

DETAILED DESCRIPTION

[0026] Chemical entities of the present disclosure include those described generally for formula (*I*), above, and are further illustrated by the classes, subclasses, and species disclosed herein. It will be appreciated that preferred subsets described for each variable herein can be used for any of the structural subsets as well. As used herein, the following definitions shall apply unless otherwise indicated.

[0027] As described herein, chemical entities of the present disclosure may be optionally substituted with one or more substituents, such as are disclosed generally above, or as exemplified by particular classes, subclasses, and species disclosed herein. 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, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible chemical entity. The term "substitutable," when used in reference to a designated atom, means that attached to the atom is a hydrogen radical, which hydrogen atom can be replaced with the radical of a suitable 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. Combinations of substituents envisioned by this disclosure are, for instance, those that result in the formation of stable or chemically feasible chemical entities.

[0028] A stable chemical entity or chemically feasible chemical entity is one in which the chemical structure is not substantially altered when kept at a temperature from about –80°C to about +40°C, in the absence of moisture or other chemically reactive conditions, for at least a week, or a chemical entity which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a patient.

[0029] The phrase "one or more substituents," as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[0030] As used herein, the term "independently selected" means that the same or different values may be selected for multiple instances of a given variable in a single chemical entity.

[0031] As used herein, "a 3-7-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10-membered partially unsaturated, or aromatic bicyclic ring system having 0-5 heteroatoms

independently selected from nitrogen, oxygen, or sulfur" includes cycloaliphatic, heterocyclic, aryl and heteroaryl rings.

[0032] As used herein, the term "aromatic" includes aryl and heteroaryl groups as described generally below and herein.

[0033] The term "aliphatic" or "aliphatic group," as used herein, means an optionally substituted straight-chain or branched C_{1-12} hydrocarbon, or a cyclic C_{1-12} hydrocarbon which is completely saturated or which contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic," "cycloalkyl," or "cycloalkenyl"). For example, suitable aliphatic groups include optionally substituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, or (cycloalkyl)alkenyl. Unless otherwise specified, in various embodiments, aliphatic groups have 1–12, 1–10, 1–8, 1–6, 1–5, 1–4, 1–3, or 1-2 carbon atoms.

[0034] The term "alkyl," used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain saturated hydrocarbon group having 1–12, 1–10, 1–8, 1–6, 1–5, 1–4, 1–3, or 1-2 carbon atoms.

[0035] The term "alkenyl," used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one double bond and having 2-12, 2-10, 2-8, 2-6, 2-5, 2-4, or 2-3 carbon atoms.

[0036] The term "alkynyl," used alone or as part of a larger moiety, refers to an optionally substituted straight or branched chain hydrocarbon group having at least one triple bond and having 2-12, 2-10, 2-8, 2-6, 2-5, 2-4, or 2-3 carbon atoms.

[0037] The terms "cycloaliphatic," "carbocycle," "carbocyclyl," "carbocyclo," or "carbocyclic," used alone or as part of a larger moiety, refer to an optionally substituted saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 ring carbon atoms. In some embodiments, the cycloaliphatic group is an optionally substituted monocyclic hydrocarbon having 3-8 or 3-6 ring carbon atoms. Cycloaliphatic groups include, without limitation, optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, or cyclooctadienyl. The terms "cycloaliphatic," "carbocycle," "carbocyclyl," "carbocyclo," or "carbocyclic" also include optionally substituted bridged or fused bicyclic rings having 6-12, 6-10, or 6-8 ring carbon atoms, wherein any individual ring in the bicyclic system has 3-8 ring carbon atoms.

[0038] The term "cycloalkyl" refers to an optionally substituted saturated ring system of about 3 to about 10 ring carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0039] The term "cycloalkenyl" refers to an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to

about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0040] The terms "haloaliphatic," "haloalkyl," "haloalkenyl" and "haloalkoxy" refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, which is substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. The term "fluoroaliphatic" refers to a haloaliphatic wherein the halogen is fluoro, including perfluorinated aliphatic groups. Examples of fluoroaliphatic groups include, without limitation, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 1,1,2-trifluoroethyl, 1,2,2-trifluoroethyl, and pentafluoroethyl.

[0041] The term "heteroatom" refers to one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0042] The terms "aryl" and "ar-," used alone or as part of a larger moiety, e.g., "aralkyl," "aralkoxy," or "aryloxyalkyl," refer to an optionally substituted C_{6-14} aromatic hydrocarbon moiety comprising one to three aromatic rings. In at least one embodiment, the aryl group is a C_{6-10} aryl group. Aryl groups include, without limitation, optionally substituted phenyl, naphthyl, or anthracenyl. The terms "aryl" and "ar-," as used herein, also include groups in which an aryl ring is fused to one or more cycloaliphatic rings to form an optionally substituted cyclic structure such as a tetrahydronaphthyl, indenyl, or indanyl ring. The term "aryl" may be used interchangeably with the terms "aryl group," "aryl ring," and "aromatic ring."

[0043] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. In at least one embodiment, the aralkyl group is C_{6-10} aryl C_{1-6} alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0044] The terms "heteroaryl" and "heteroar-," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 14 ring atoms, such as 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 pi electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, for instance mono-, bi-, or tricyclic, such as mono- or bicyclic. In the context of "heteroar" entities, the term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. For example, a nitrogen atom of a heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. When a heteroaryl is substituted by a hydroxy group, it also includes its corresponding tautomer. The terms "heteroaryl" and "heteroar-," as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocycloaliphatic rings. Nonlimiting examples of heteroaryl groups include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl,

pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0045] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 8-membered monocyclic or 7–10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, for instance one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or NR^+ (as in N-substituted pyrrolidinyl).

[0046] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and thiamorpholinyl. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, for instanct mono-, bi-, or tricyclic, and such as mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted. Additionally, a heterocyclic ring also includes groups in which the heterocyclic ring is fused to one or more aryl rings.

[0047] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic (e.g., aryl or heteroaryl) moieties, as herein defined.

[0048] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, such as from 1 to 6, from 1 to 5, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. An optionally substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is optionally replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group and also include those described in the specification herein. It will be appreciated that two substituents of the alkylene group may be taken together to form a ring system. In certain embodiments, two

substituents can be taken together to form a 3-7-membered ring. The substituents can be on the same or different atoms.

[0049] An alkylene chain also can be optionally interrupted by a functional group. An alkylene chain is "interrupted" by a functional group when an internal methylene unit is interrupted by the functional group. Examples of suitable "interrupting functional groups" are described in the specification and claims herein, and include double and/or triple bonds between carbons in the alkylene chain.

[0050] For purposes of clarity, all bivalent groups described herein, including, e.g., the alkylene chain linkers described above, are intended to be read from left to right, with a corresponding left-to-right reading of the formula or structure in which the variable appears.

[0051] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted." In addition to the substituents defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group also include and are generally selected from -halo, $-NO_2$, -CN, $-R^+$, $-C(R^+)=C(R^+)_2$, $-C\equiv C-R^+$, $-OR^+$, $-SR^\circ$, $-S(O)R^\circ$, $-SO_2R^\circ$, $-SO_3R^+$, $-SO_2N(R^+)_2$, $-N(R^+)_2$, $-NR^+C(O)R^+$, $-NR^+C(S)R^+$, $-NR^+C(O)N(R^+)_2$, $-NR^+C(S)N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-R^\circ$, $-NR^+CO_2R^+$, $-NR^+SO_2R^\circ$, $-NR^+SO_2N(R^+)_2$, $-O-C(O)R^+$, $-O-CO_2R^+$, $-OC(O)N(R^+)_2$, $-C(O)R^+$, $-C(S)R^\circ$, $-CO_2R^+$, $-C(O)-C(O)R^+$, $-C(O)N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(O)N(R^+)-OR^+$, $-C(O)N(R^+)C(=NR^+)-N(R^+)_2$, $-N(R^+)C(=NR^+)-N(R^+)-C(O)R^+$, $-C(=NR^+)-N(R^+)_2$, $-C(=NR^+)-OR^+$, $-N(R^+)-N(R^+)_2$, $-C(=NR^+)-N(R^+)-OR^+$, $-C(R^\circ)=N-OR^+$, $-P(O)(R^+)_2$, $-P(O)(OR^+)_2$, $-O-P(O)-OR^+$, and $-P(O)(NR^+)-N(R^+)_2$, wherein R^+, independently, is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group, or two independent occurrences of R^+ are taken together with their intervening atom(s) to form an optionally substituted 5-7-membered aryl, heteroaryl, cycloaliphatic, or heterocyclyl. Each R° is, independently, an optionally substituted aliphatic, aryl, heteroaryl, cycloaliphatic, or heterocyclyl group.

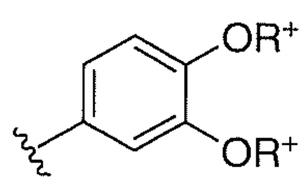
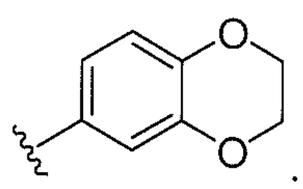
[0052] An aliphatic or heteroaliphatic group, or a non-aromatic carbocyclic or heterocyclic ring may contain one or more substituents and thus may be "optionally substituted." Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic carbocyclic or heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, $=C(R^*)_2$, $=N-N(R^*)_2$, =N-OR*, =N-NHC(O)R*, $=N-NHCO_2R^\circ$ $=N-NHSO_2R^\circ$ or =N-R* where R° is defined above, and each R* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group.

[0053] In addition to the substituents defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring also include and are generally selected from $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-C(O)OR^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-S(O)_2R^+$,

$-S(O)_2N(R^+)_2$, $-C(S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-N(R^+)S(O)_2R^+$; wherein each R^+ is defined above. A ring nitrogen atom of a heteroaryl or non-aromatic heterocyclic ring also may be oxidized to form the corresponding N-hydroxy or N-oxide chemical entity. A nonlimiting example of such a heteroaryl having an oxidized ring nitrogen atom is N-oxidopyridyl.

[0054] As detailed above, in some embodiments, two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) to form a monocyclic or bicyclic ring selected from 3–13-membered cycloaliphatic,

3–12-membered heterocyclyl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, 6–10-membered aryl, or 5–10-membered heteroaryl having 1–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0055] Exemplary rings that are formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) include, but are not limited to the following: a) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^+)_2$, where both occurrences of R^+ are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^+ (or any other variable similarly defined in the specification or claims herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR^+ , these two occurrences of R^+ are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring: . It will be appreciated that a variety of other rings (e.g., spiro and bridged rings) can be formed when two independent occurrences of R^+ (or any other variable similarly defined in the specification and claims herein) are taken together with their intervening atom(s) and that the examples detailed above are not intended to be limiting.

[0056] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present chemical entities are within the scope of the present disclosure. Unless otherwise stated, all tautomeric forms of the chemical entities disclosed herein are within the scope of the present disclosure. Additionally,

unless otherwise stated, structures depicted herein are also meant to include chemical entities that differ only in the presence of one or more isotopically enriched atoms. For example, chemical entities having the present structures where there is a replacement of hydrogen by deuterium or tritium, or a replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure. Such chemical entities are useful, as a nonlimiting example, as analytical tools or probes in biological assays.

[0057] It is to be understood that, when a disclosed chemical entity has at least one chiral center, the present disclosure encompasses one enantiomer of inhibitor free from the corresponding optical isomer, a racemic mixture of the inhibitor, and mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a mixture is enriched in one enantiomer relative to its optical isomers, the mixture contains, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95%, 99%, or 99.5%.

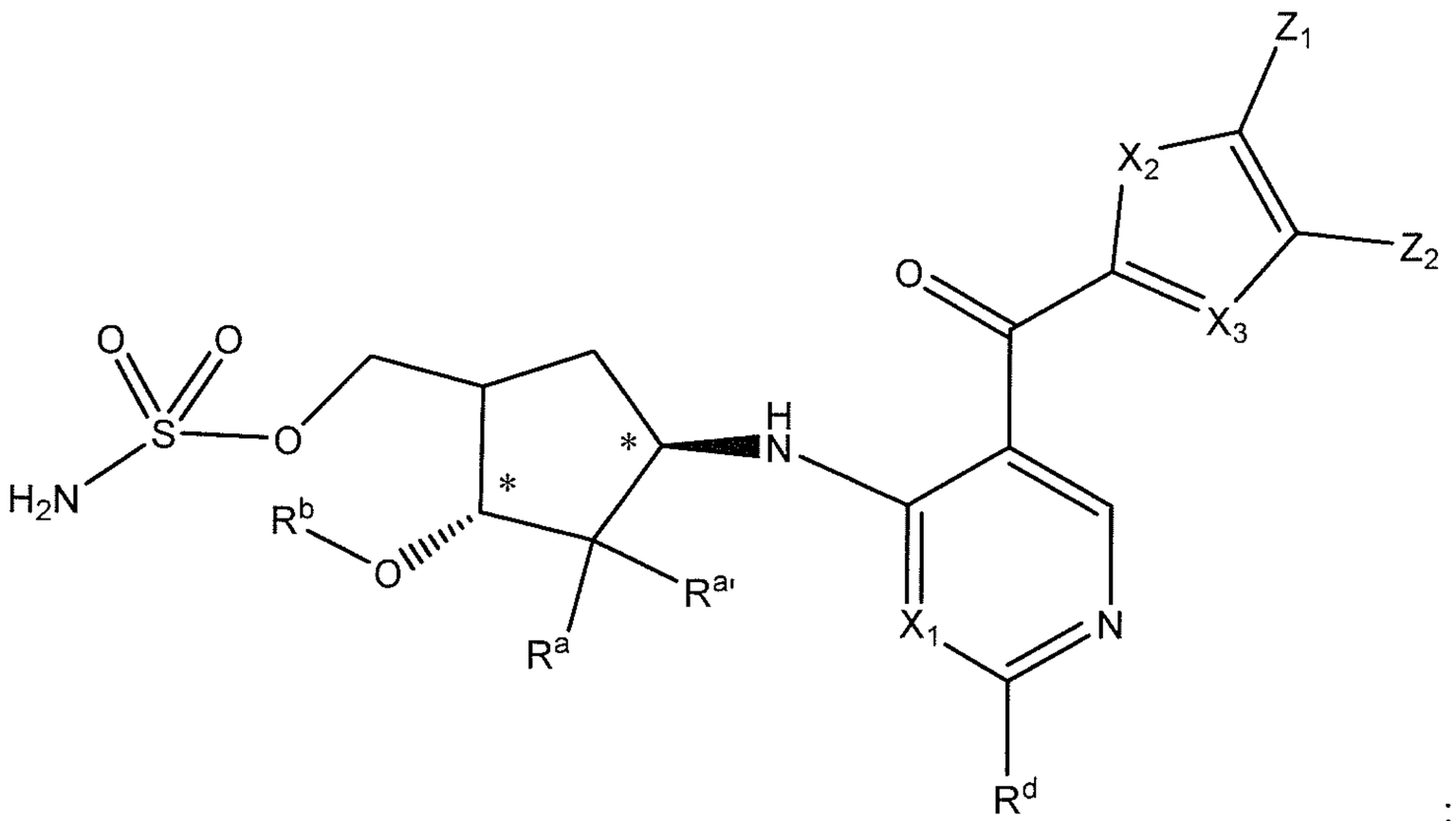
[0058] The enantiomers of the present disclosure may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[0059] When a disclosed chemical entity has at least two chiral centers, the present disclosure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diasteromeric pairs, mixtures of diasteromers, mixtures of diasteromeric pairs, mixtures of diasteromers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diasteromeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s). When a mixture is enriched in one diastereomer or diastereomeric pair(s) relative to the other diastereomers or diastereomeric pair(s), the mixture is enriched with the depicted or referenced diastereomer or diastereomeric pair(s) relative to other diastereomers or diastereomeric pair(s) for the chemical entity, for example, by a molar excess of at least 50%, 75%, 90%, 95%, 99% or 99.5%.

[0060] The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Specific procedures for chromatographically separating diastereomeric pairs of precursors used in the preparation of chemical entities disclosed herein are provided the examples herein.

[0061] For the avoidance of doubt, for chemical entities described herein, where the chemical entity is a single diastereomer and the absolute configuration of the chiral centers is known the name of the chemical entity reflects the assigned configuration at each stereochemical center; for example chemical entity **I-43**: {(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate. Where the chemical entity is a single diastereomer and the absolute configuration is known at some of the chiral centers but is unknown at one chiral center, the name reflects the two possibilities separated by an "or"; for example chemical entity **I-1a**: [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate. Where the chemical entity is a mixture of two or more diastereomers the name reflects the two or more possibilities by using "and" between the names of the individual diastereomers that make up the mixture; for example chemical entity **I-1**: [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate.

[0062] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***I-a***):

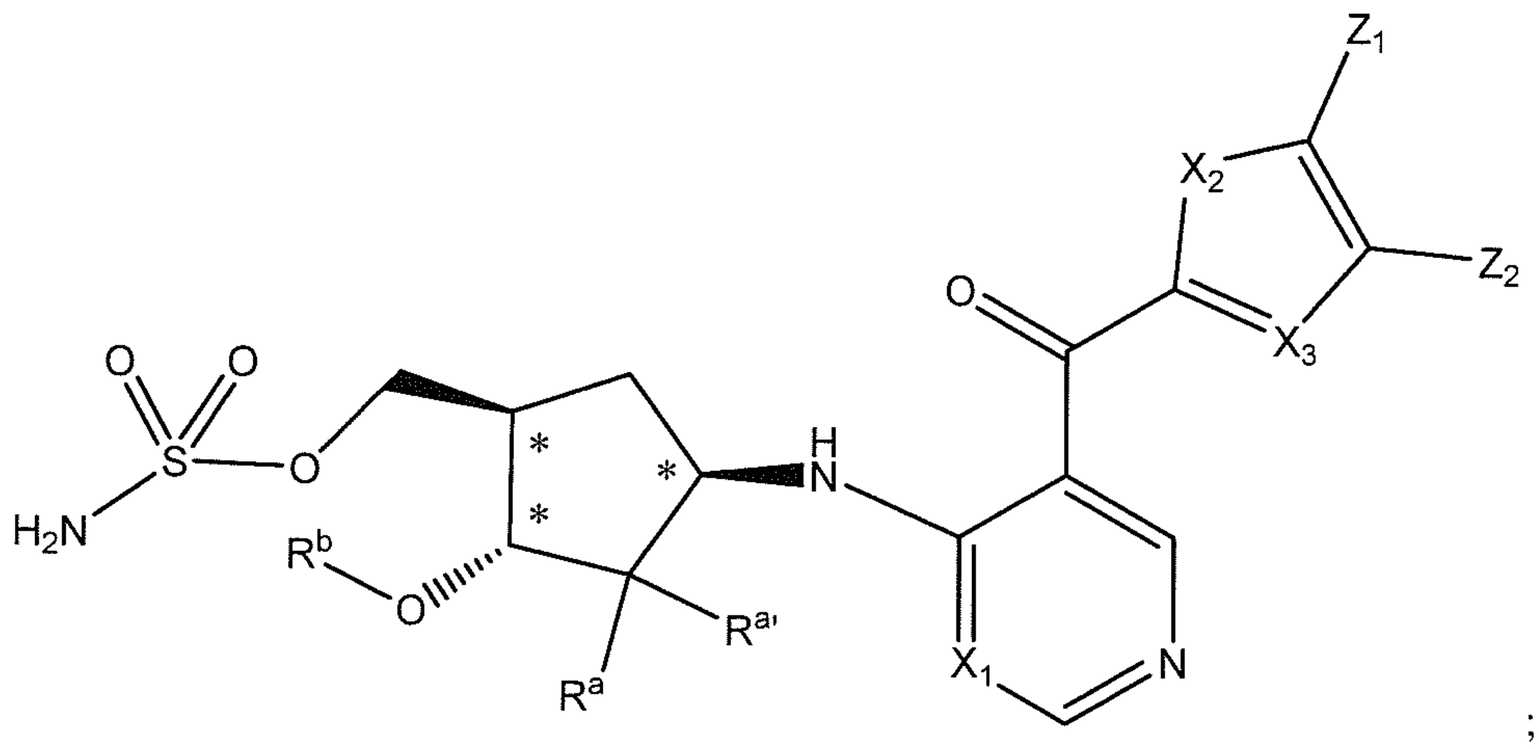


(***I-a***)

or a pharmaceutically acceptable salt thereof;

wherein R^a, $R^{a'}$, R^b, X_1, X_2, X_3, R^d, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

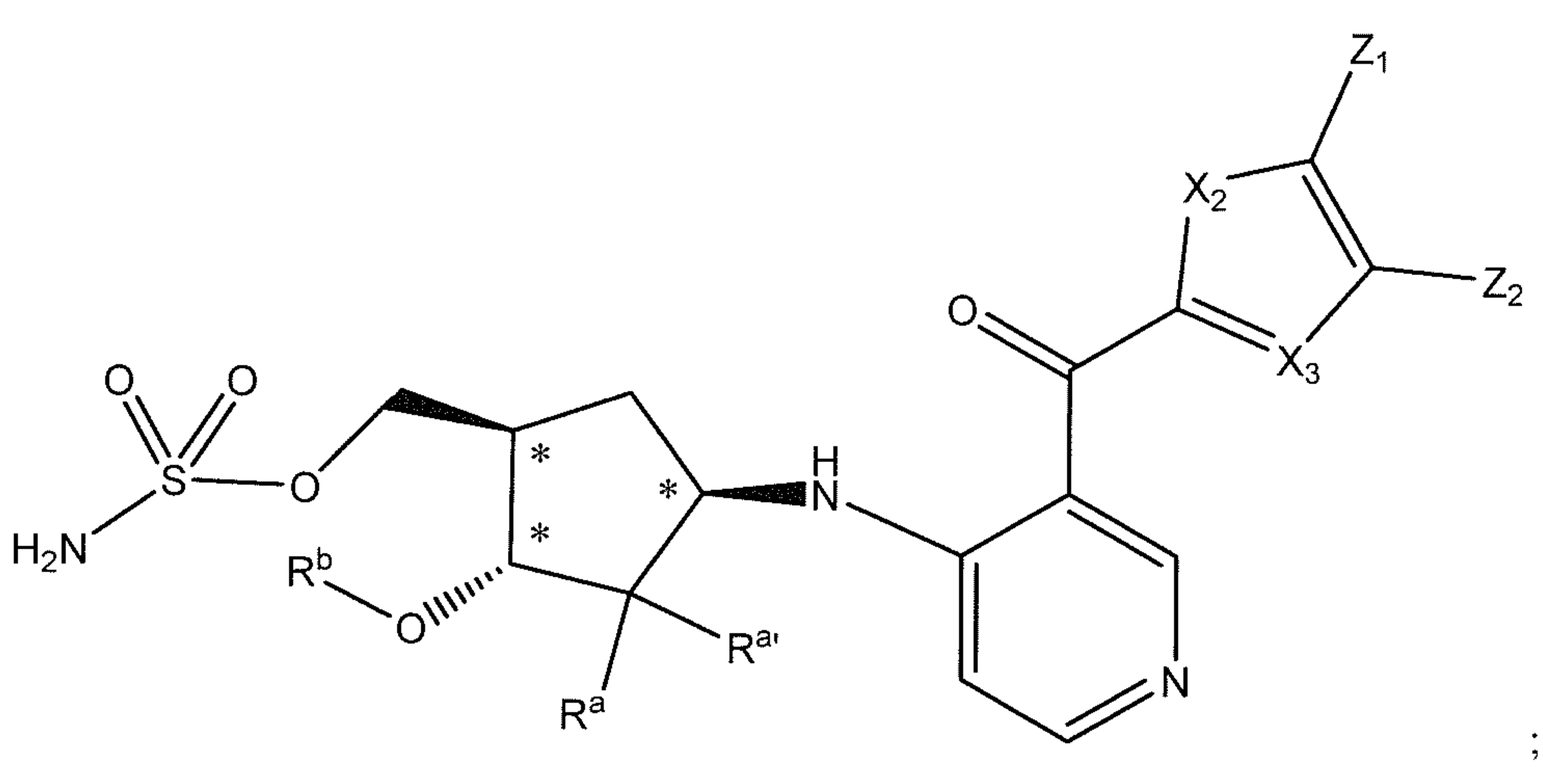
[0063] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***II***):



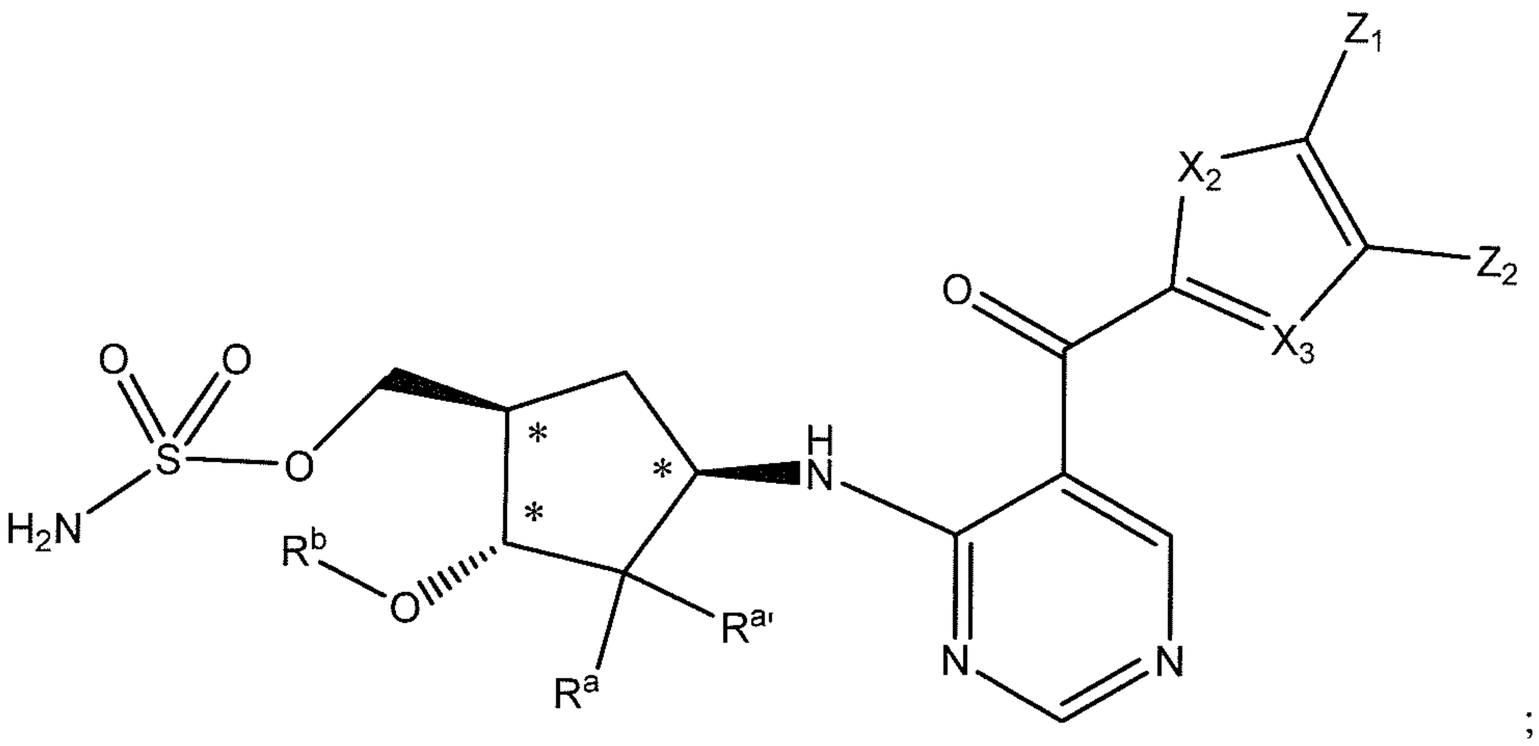
(*II*)

wherein R^a, $R^{a'}$, R^b, X_1, X_2, X_3, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0064] In some embodiments, the chemical entity of formula (*I*) is represented by formula (*II-a*) or (*II-b*):



(*II-a*)

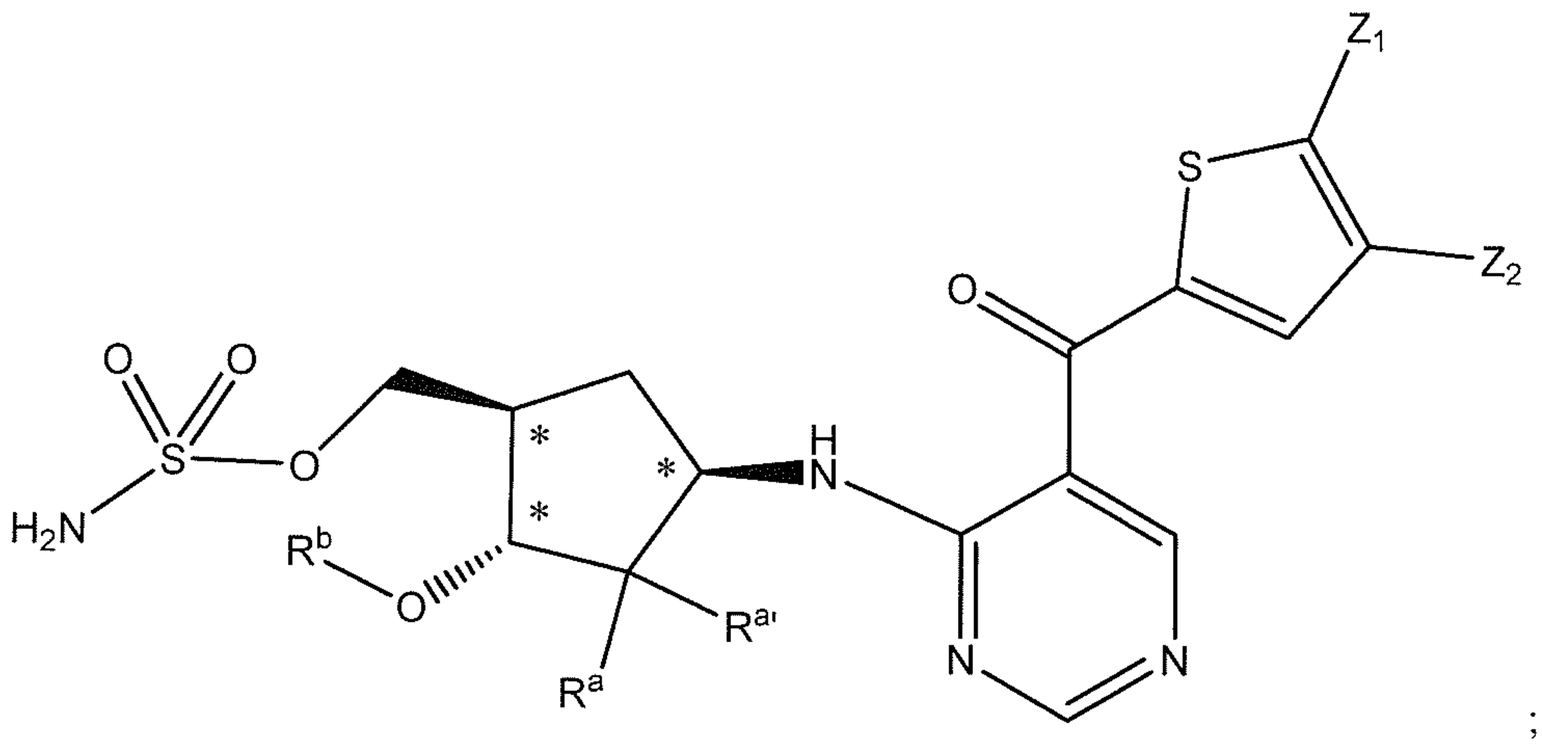


(*II-b*)

or a pharmaceutically acceptable salt thereof;

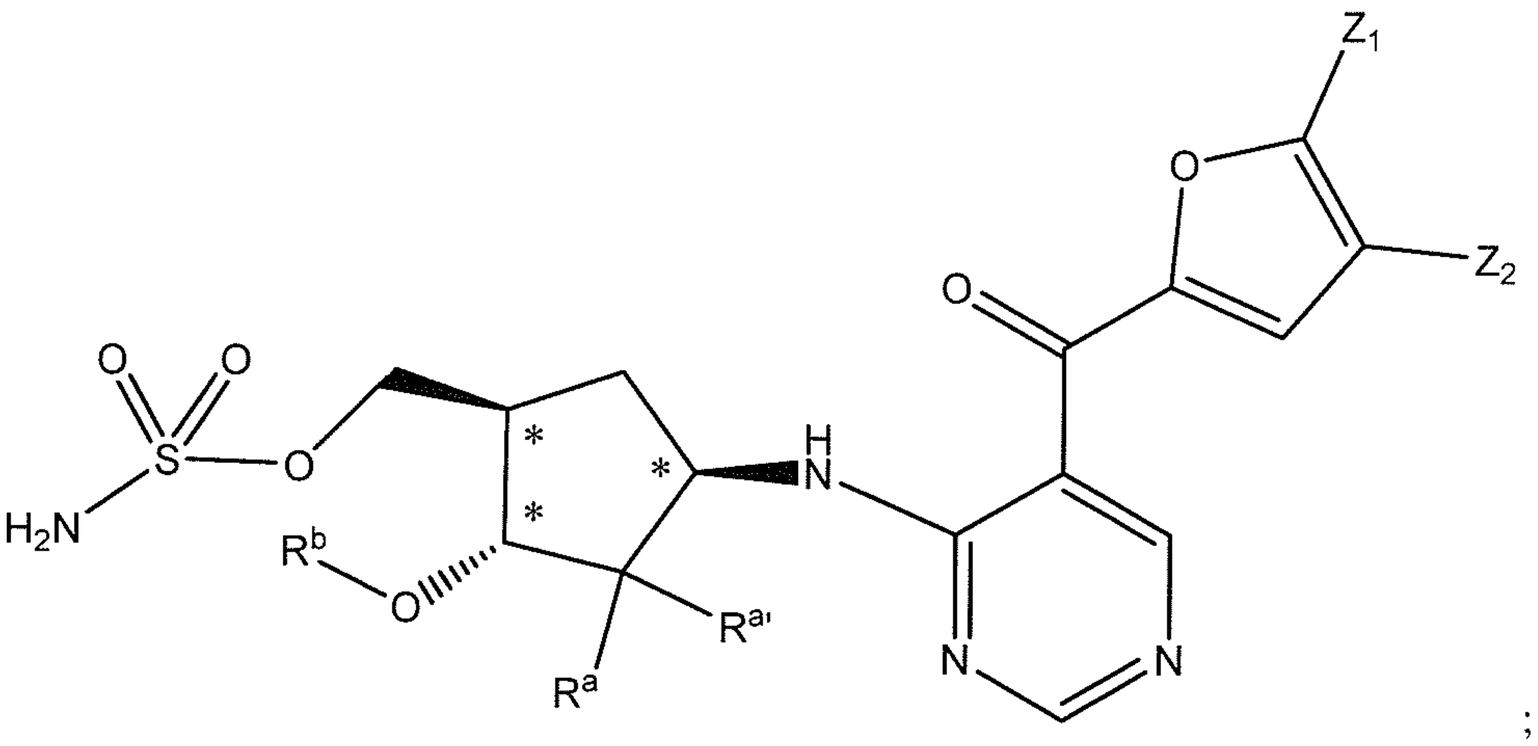
wherein R^a, $R^{a'}$, R^b, X_2, X_3, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***II-a***) wherein R^a, $R^{a'}$, R^b, X_2, X_3, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***II-b***) wherein R^a, $R^{a'}$, R^b, X_2, X_3, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0065] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***III-a***) or (***III-b***):



;

(***III-a***)



;

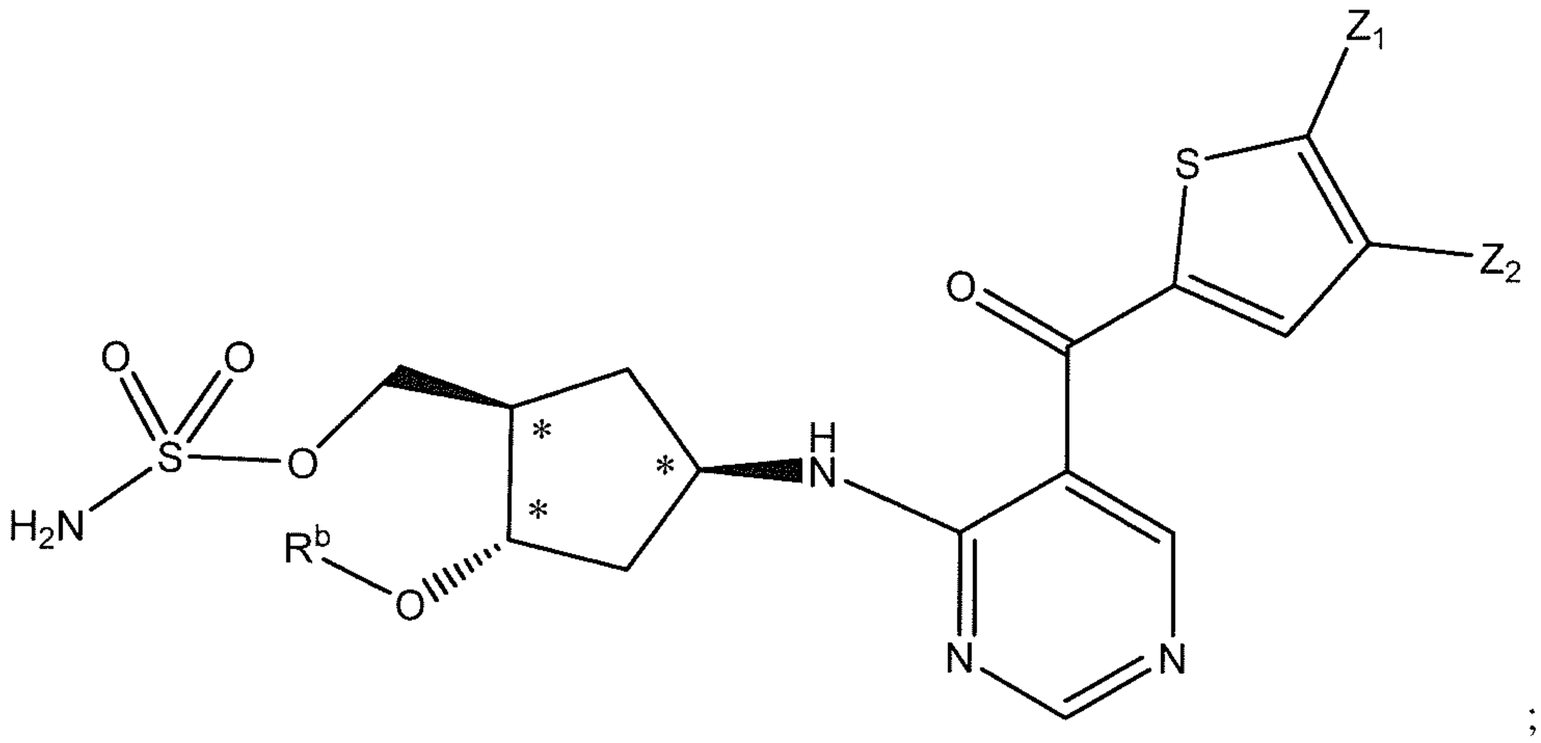
(***III-b***)

or a pharmaceutically acceptable salt thereof;

wherein R^a, $R^{a'}$, R^b, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical

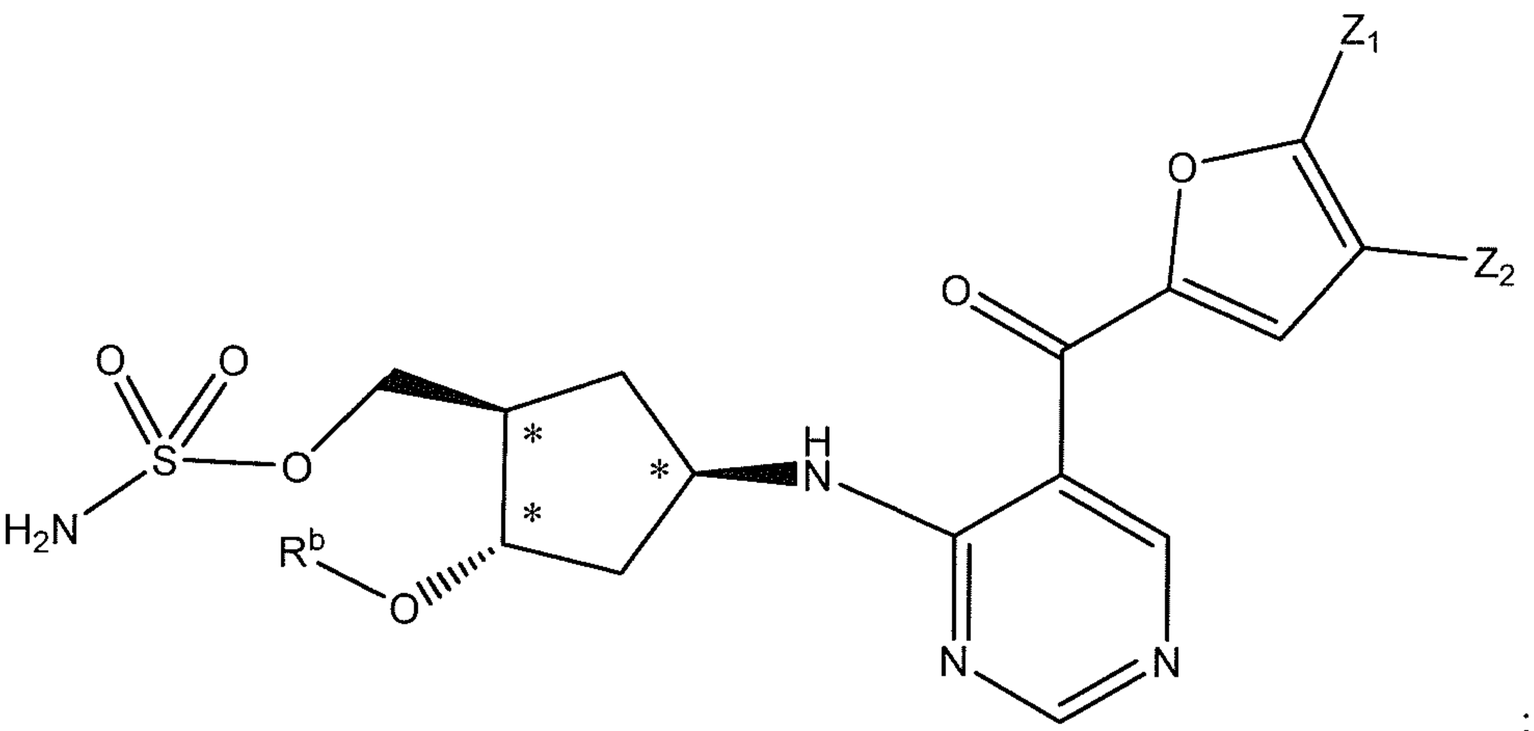
entity of formula (***I***) is represented by formula (***III-a***) wherein R^a, $R^{a'}$, R^b, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***III-b***) wherein R^a, $R^{a'}$, R^b, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0066] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***IV-a***) or (***IV-b***):



;

(***IV-a***)



.

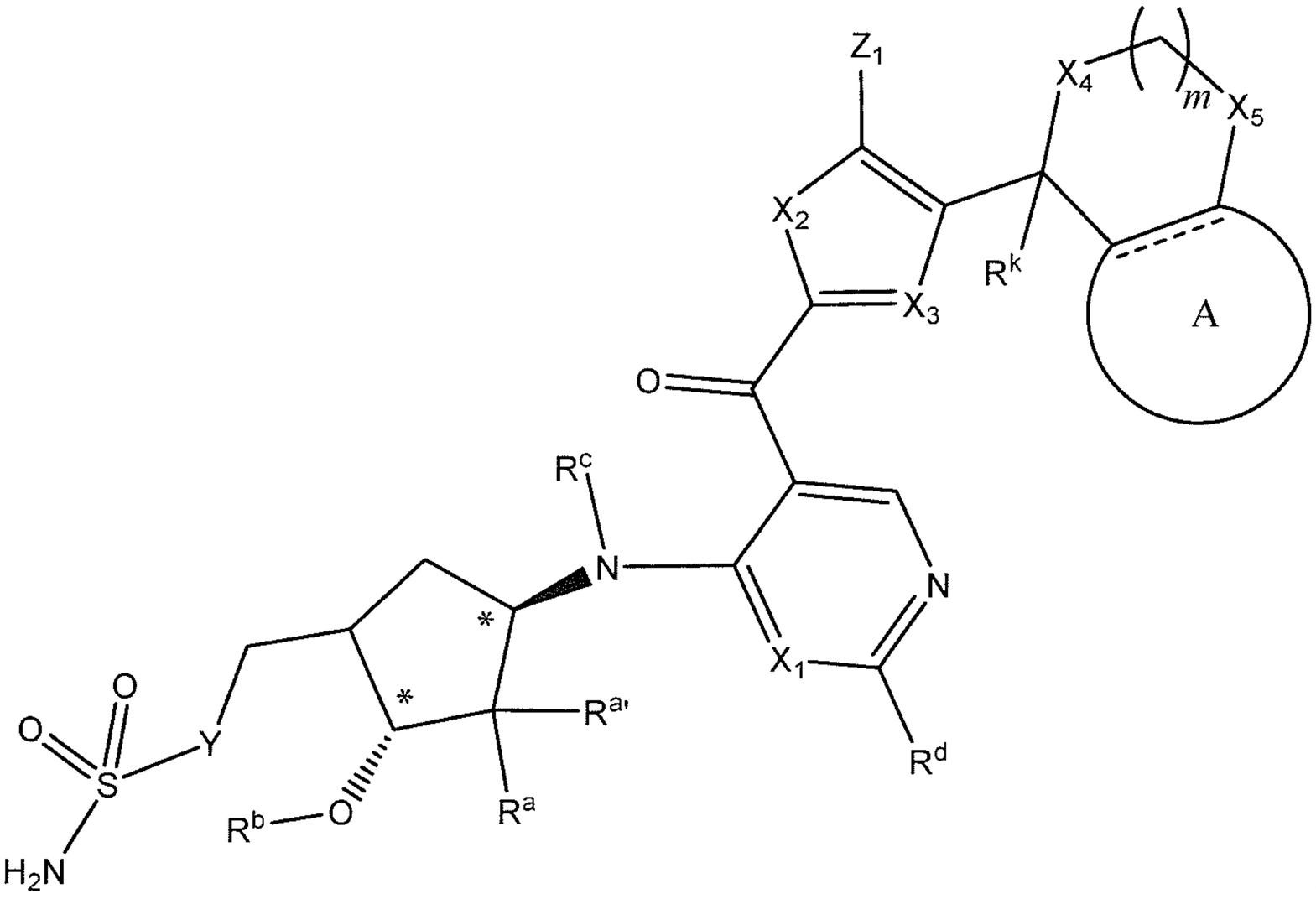
(***IV-b***)

or a pharmaceutically acceptable salt thereof;

wherein R^b, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***IV-a***) wherein R^b, Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***IV-b***) wherein R^b,

Z_1, and Z_2 have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0067] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***V***):



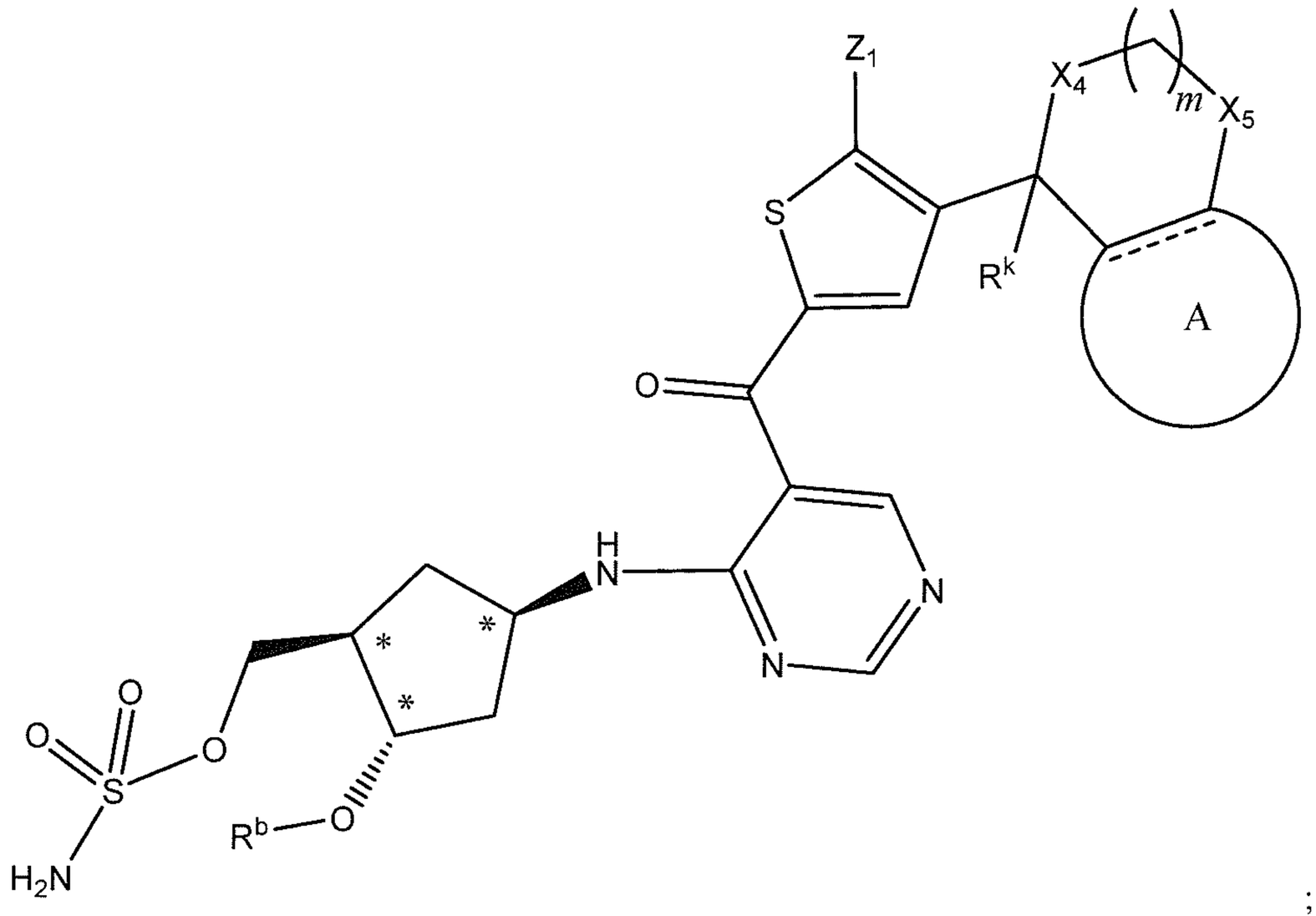
;

(***V***)

or a pharmaceutically acceptable salt thereof;

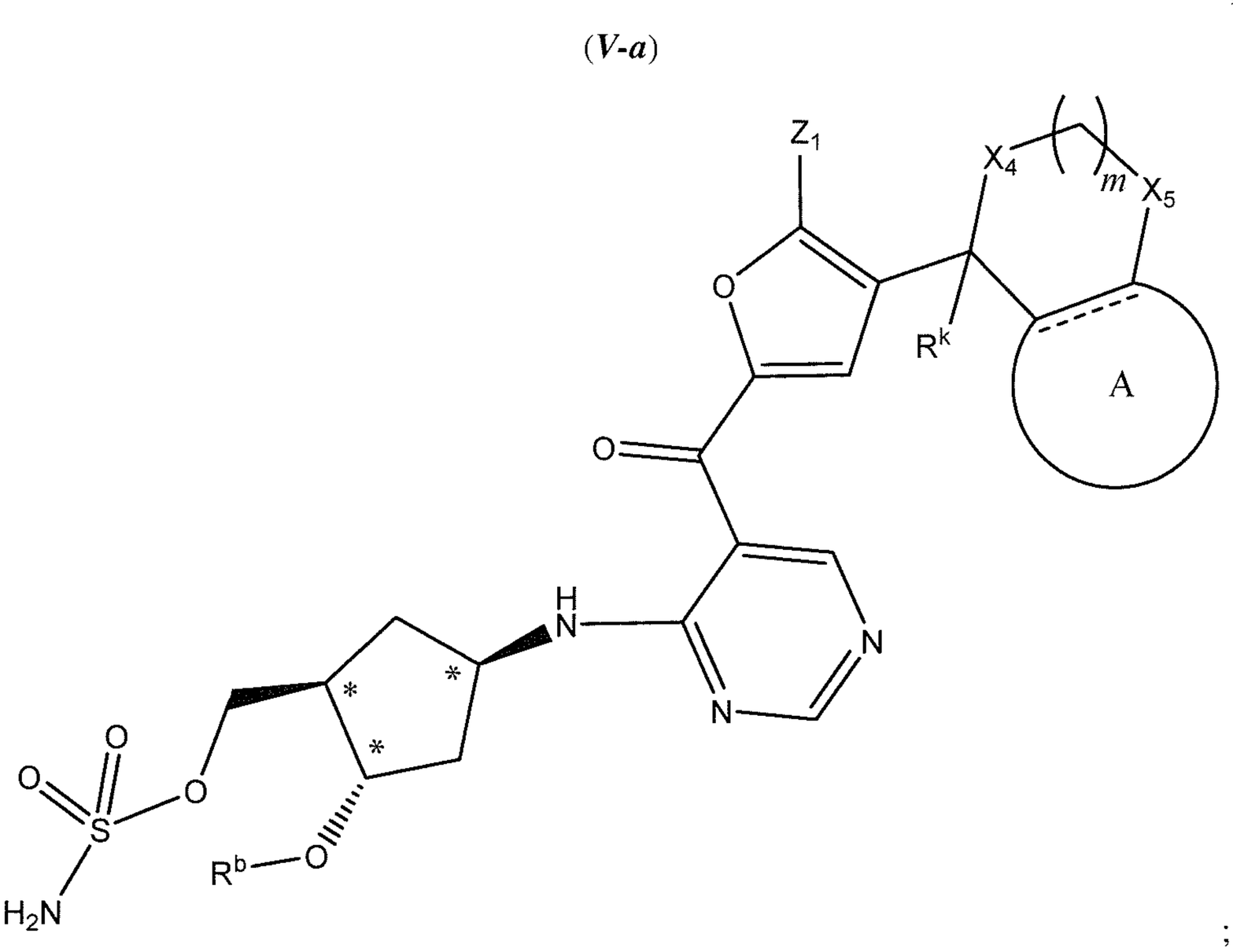
wherein dashed lines indicate single or double bonds and Y, R^a, $R^{a'}$, R^b, R^c, X_1, X_2, X_3, R^d, Z_1, R^k, X_4, X_5, *m*, and Ring A have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0068] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***V-a***) or (***V-b***):



;

(*V-a*)



;

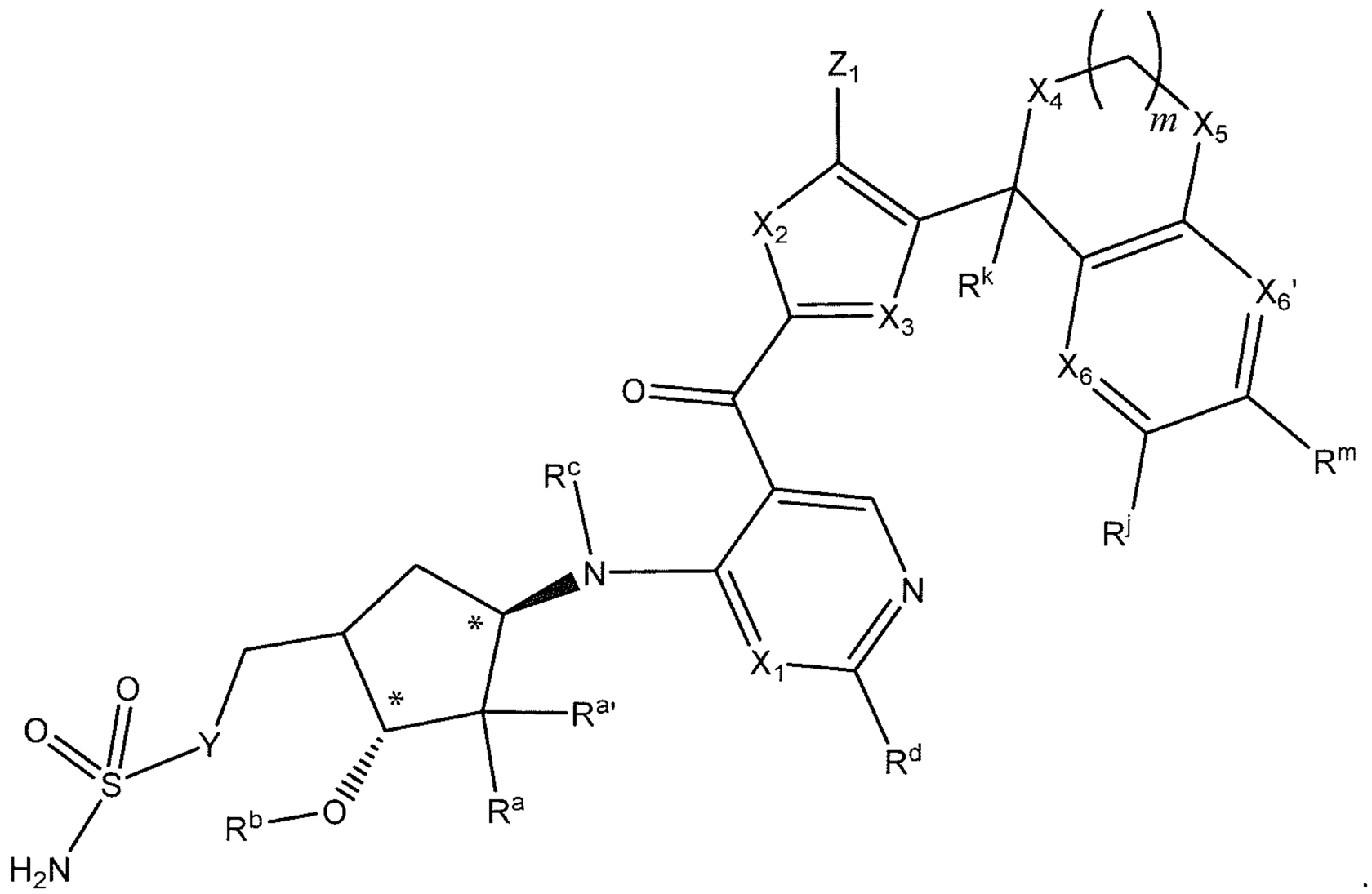
(*V-b*)

or a pharmaceutically acceptable salt thereof;

wherein dashed lines indicate single or double bonds and R^b, Z_1, R^k, X_4, X_5, *m*, and Ring A have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*V-a*) wherein R^b, Z_1, R^k, X_4, X_5, *m*, and Ring A have the values described herein and

stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*V-b*) wherein R^b, Z_1, R^k, X_4, X_5, *m*, and Ring A have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0069] In some embodiments, the chemical entity of formula (*I*) is represented by formula (*VI*):



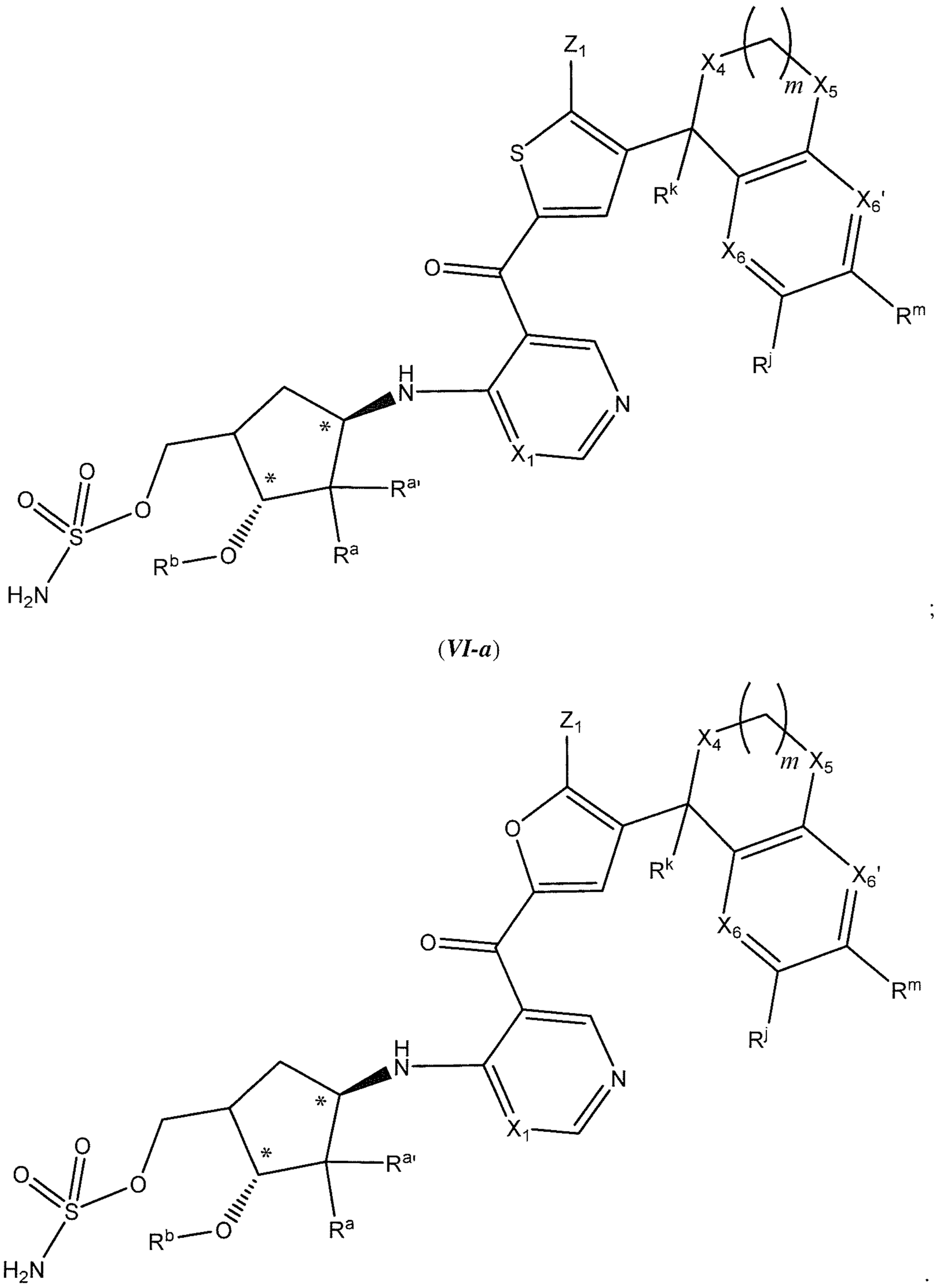
;

(*VI*)

or a pharmaceutically acceptable salt thereof;

wherein Y, R^a, $R^{a'}$, R^b, R^c, X_1, X_2, X_3, R^d, Z_1, R^k, X_4, X_5, *m*, X_6, X_6', R^j, and R^m have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0070] In some embodiments, the chemical entity of formula (*I*) is represented by formula (*VI-a*) or (*VI-b*):



;

(*VI-a*)

;

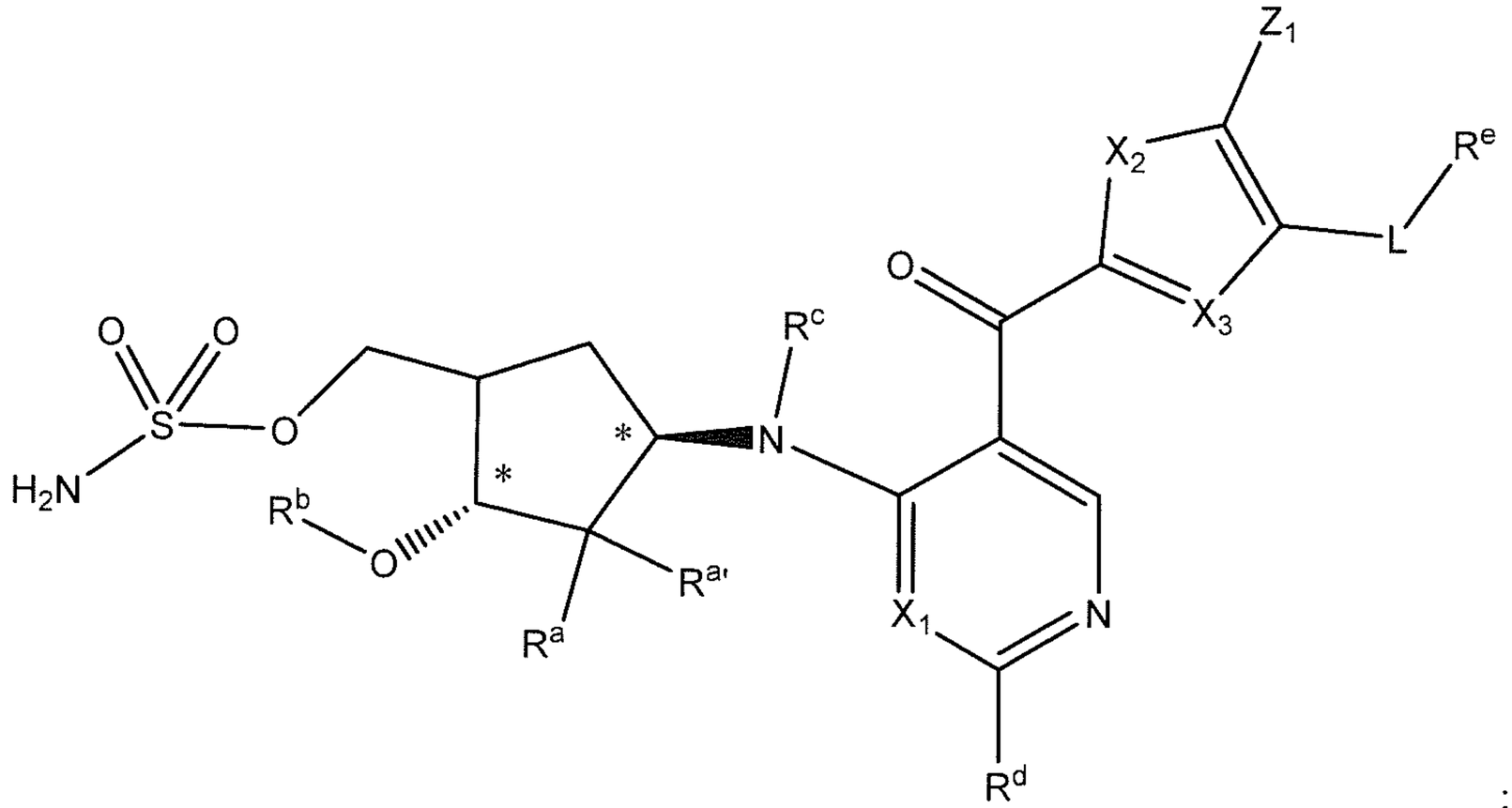
(*VI-b*)

or a pharmaceutically acceptable salt thereof;

wherein R^a, $R^{a'}$, R^b, X_1, Z_1, R^k, X_4, X_5, *m*, X_6, X_6', R^j, and R^m have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*VI-a*) wherein R^a, $R^{a'}$, R^b, X_1, Z_1, R^k, X_4, X_5, *m*, X_6, X_6', R^j, and R^m have the values described herein and stereochemical

configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***VI-b***) wherein R^a, $R^{a'}$, R^b, X_1, Z_1, R^k, X_4, X_5, m, X_6, X_6', R^j, and R^m have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

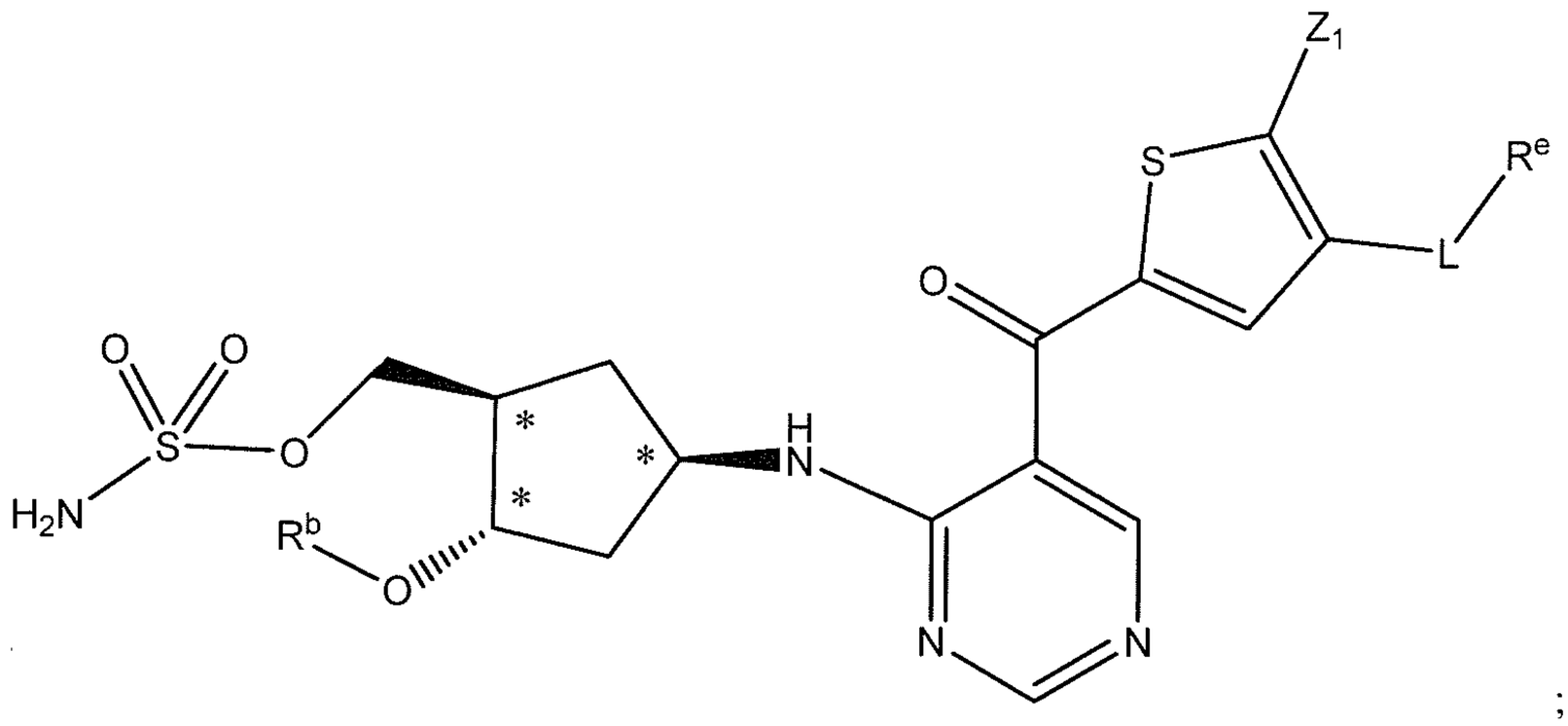
[0071] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***VII***):



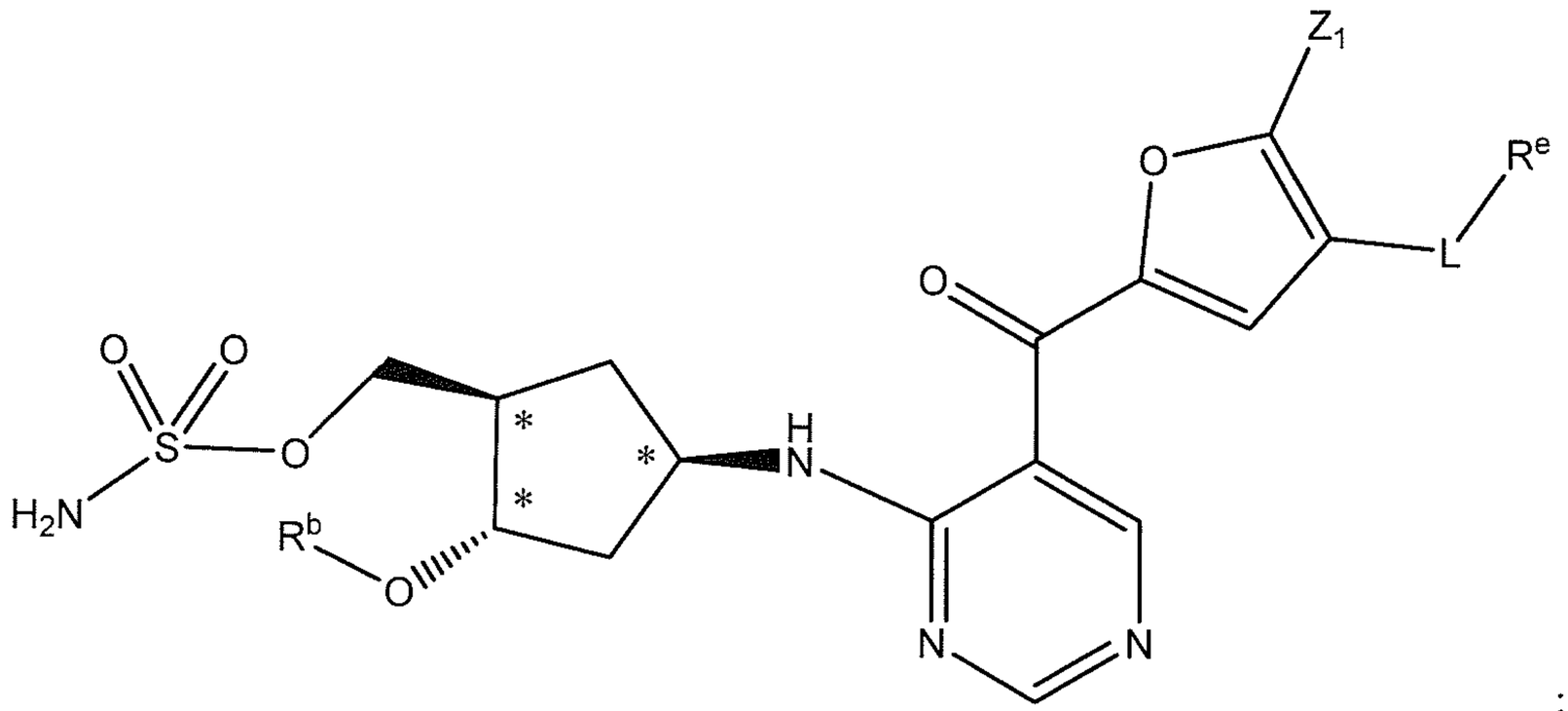
(***VII***)

wherein R^a, $R^{a'}$, R^b, R^c, X_1, R^d, Z_1, X_2, X_3, L, and R^e have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0072] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***VII-a***) or (***VII-b***):



(***VII-a***)



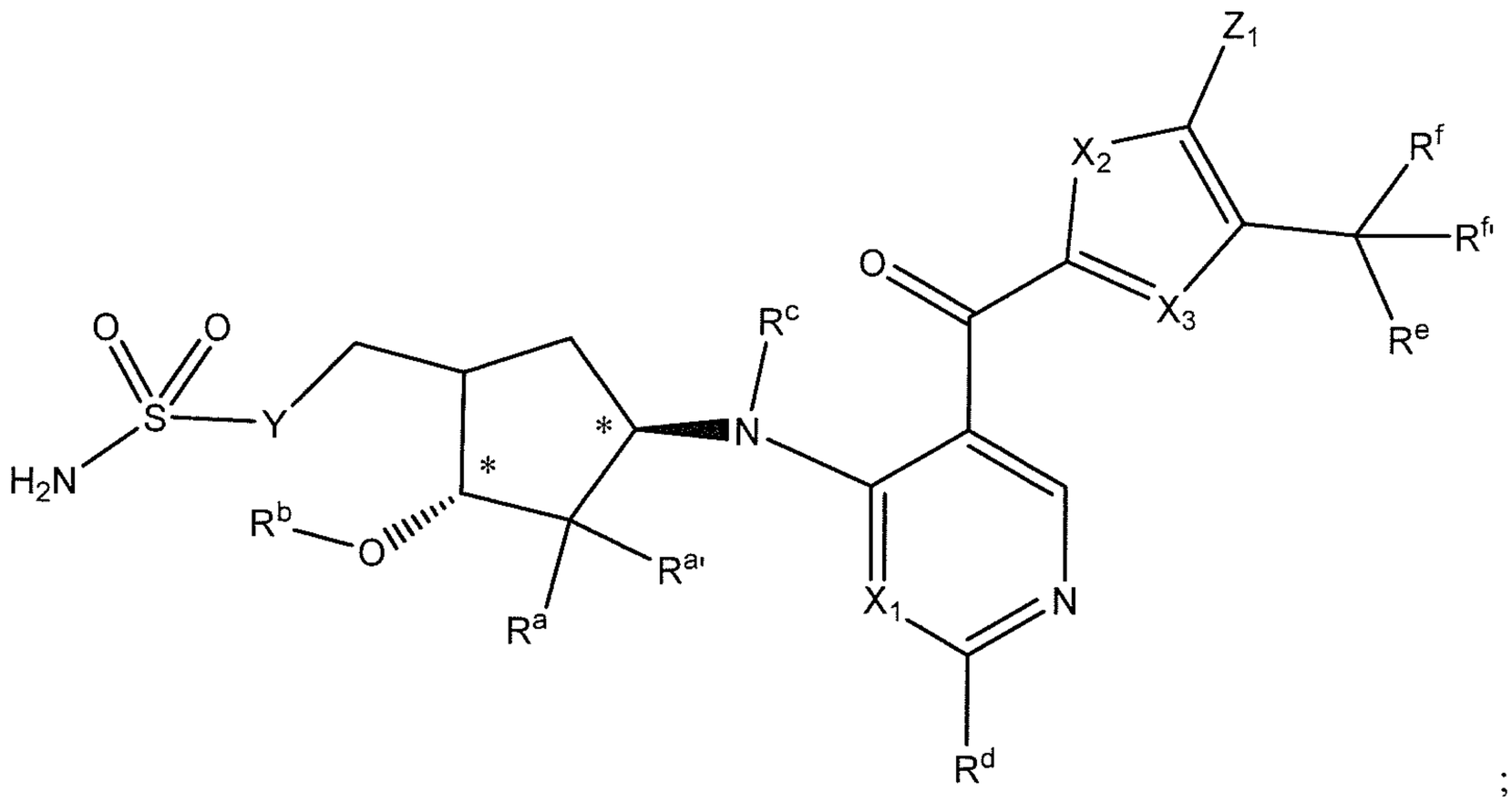
;

(*VII-b*)

or a pharmaceutically acceptable salt thereof;

wherein R^b, Z_1, L, and R^e have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*VII-a*) wherein R^b, Z_1, L, and R^e have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*VII-b*) wherein R^b, Z_1, L, and R^e have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0073] In some embodiments, the chemical entity of formula (*I*) is represented by formula (*VIII*):



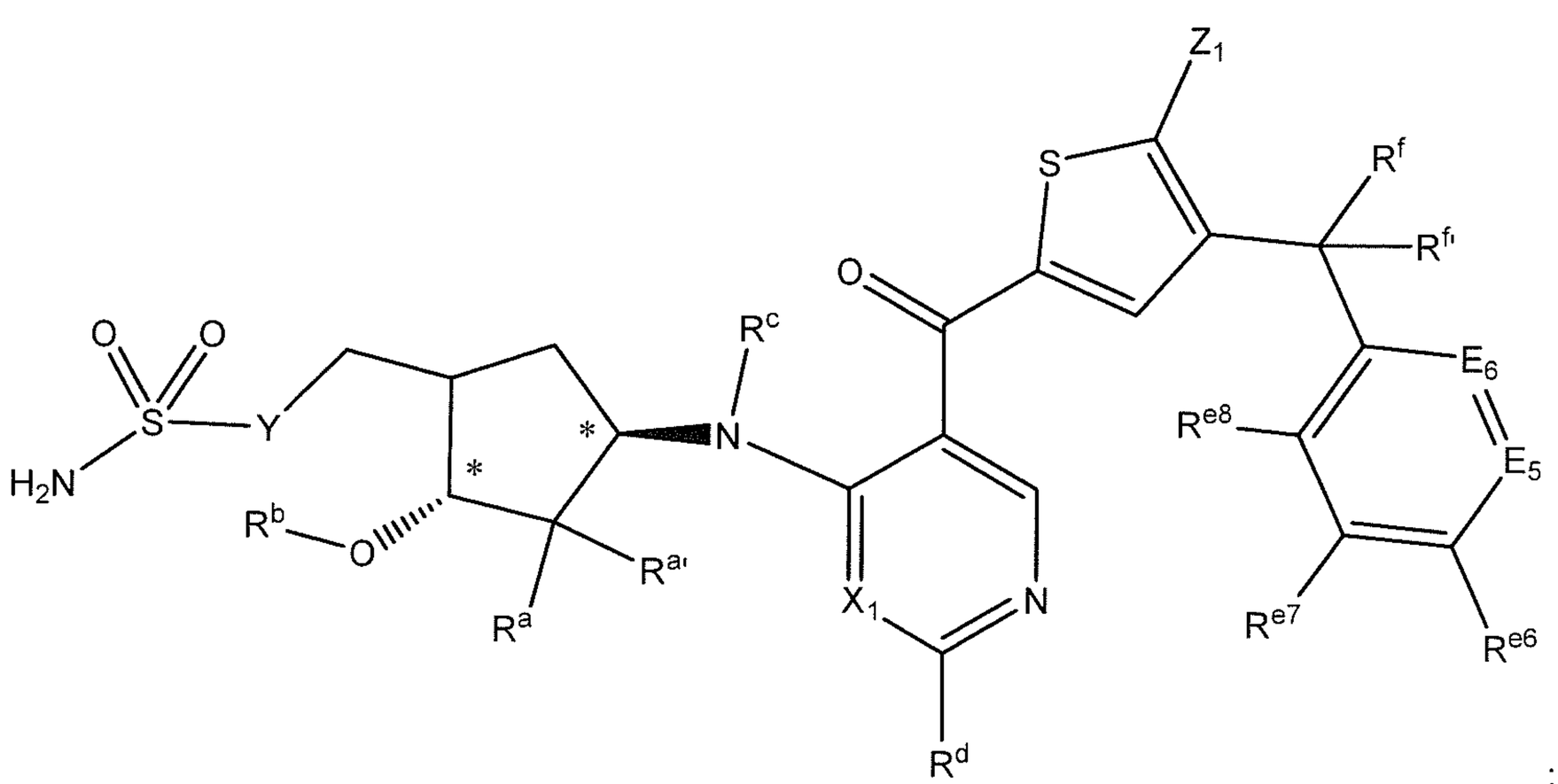
;

(*VIII*)

or a pharmaceutically acceptable salt thereof;

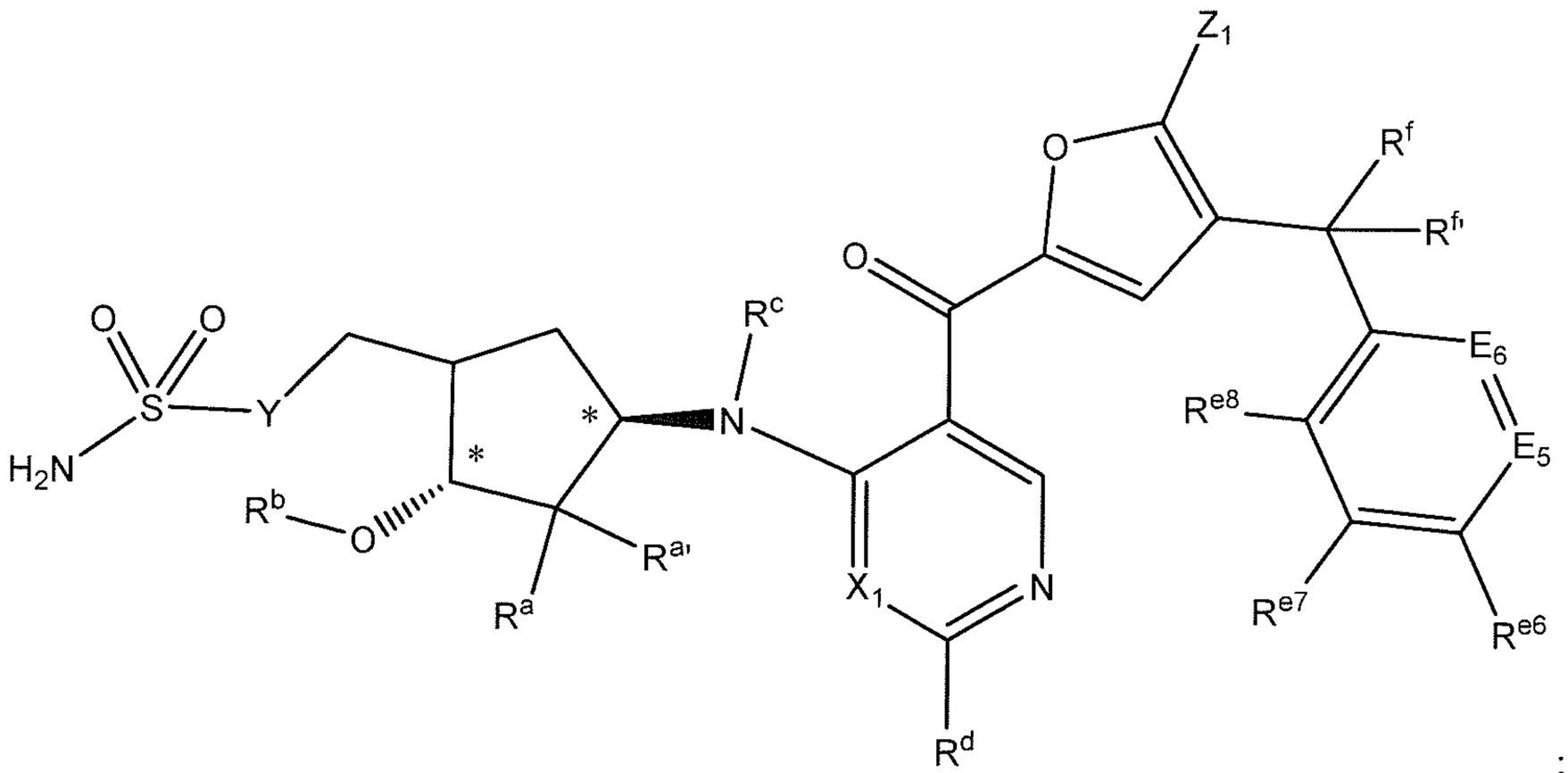
wherein Y, R^a, $R^{a'}$, R^b, R^c, X_1, X_2, X_3, R^d, Z_1, R^f, $R^{f'}$, and R^e have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0074] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***VIII-a***) or (***VIII-b***):



;

(***VIII-a***)



.

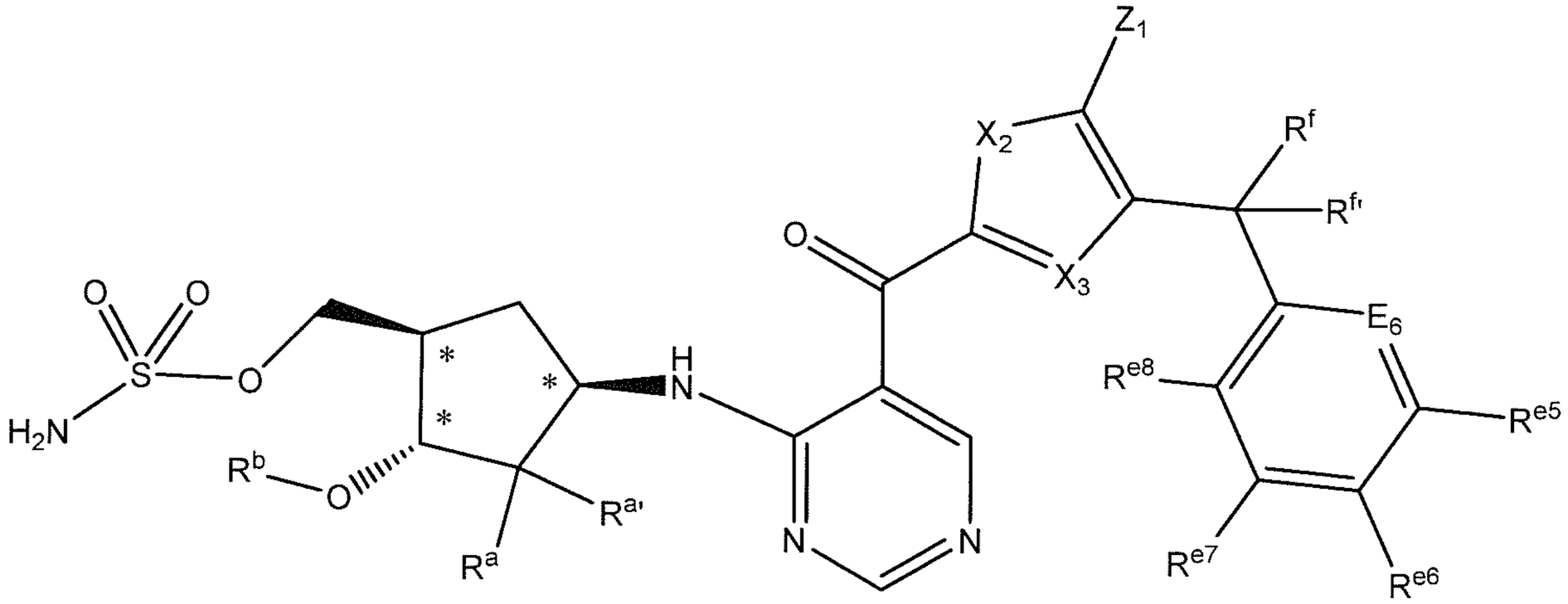
(***VIII-b***)

or a pharmaceutically acceptable salt thereof;

wherein Y, R^a, $R^{a'}$, R^b, X_1, R^c, R^d, Z_1, R^f, $R^{f'}$, E_5, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (***I***) is represented by formula (***VIII-a***) wherein Y, R^a, $R^{a'}$, R^b, X_1, R^c, R^d, Z_1, R^f, $R^{f'}$, E_5, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In

some embodiments, the chemical entity of formula (*I*) is represented by formula (*VIII-b*) wherein Y, R^a, $R^{a'}$, R^b, X_1, R^c, R^d, Z_1, R^f, $R^{f'}$, E_5, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0075] In some embodiments, the chemical entity of formula (*I*) is represented by formula (*IX*):



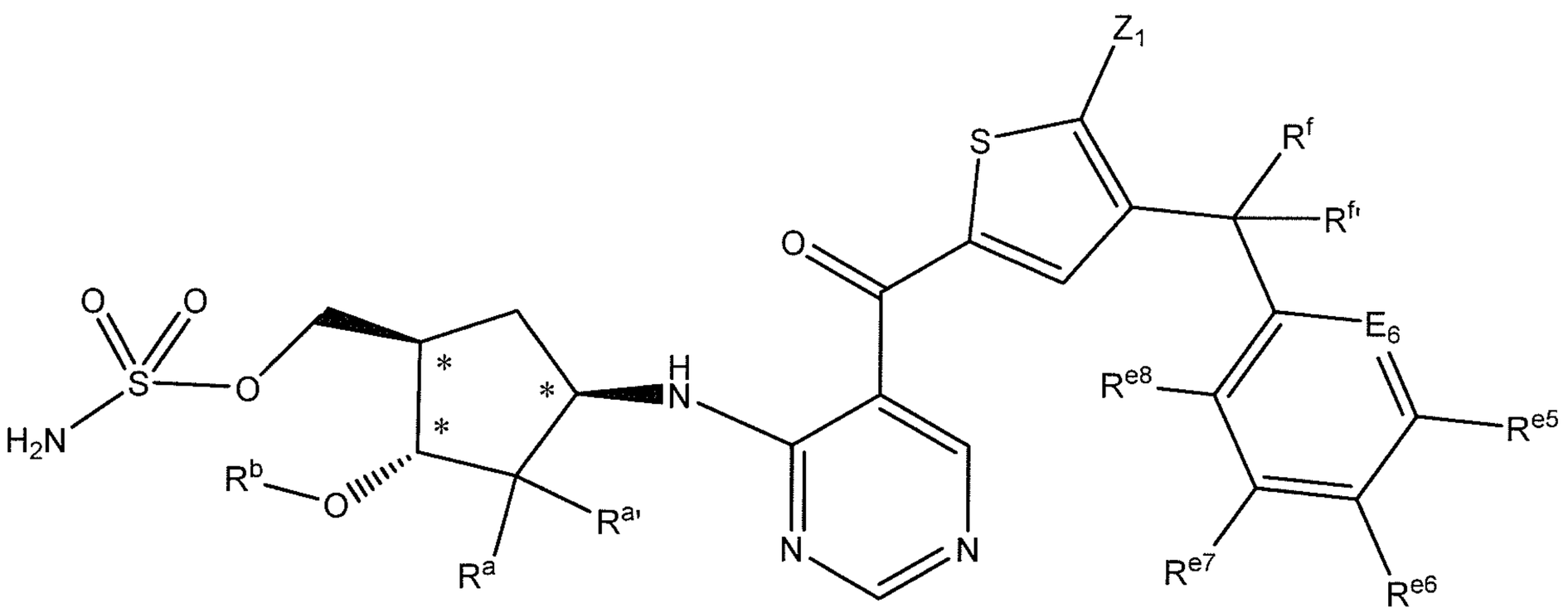
;

(*IX*)

or a pharmaceutically acceptable salt thereof;

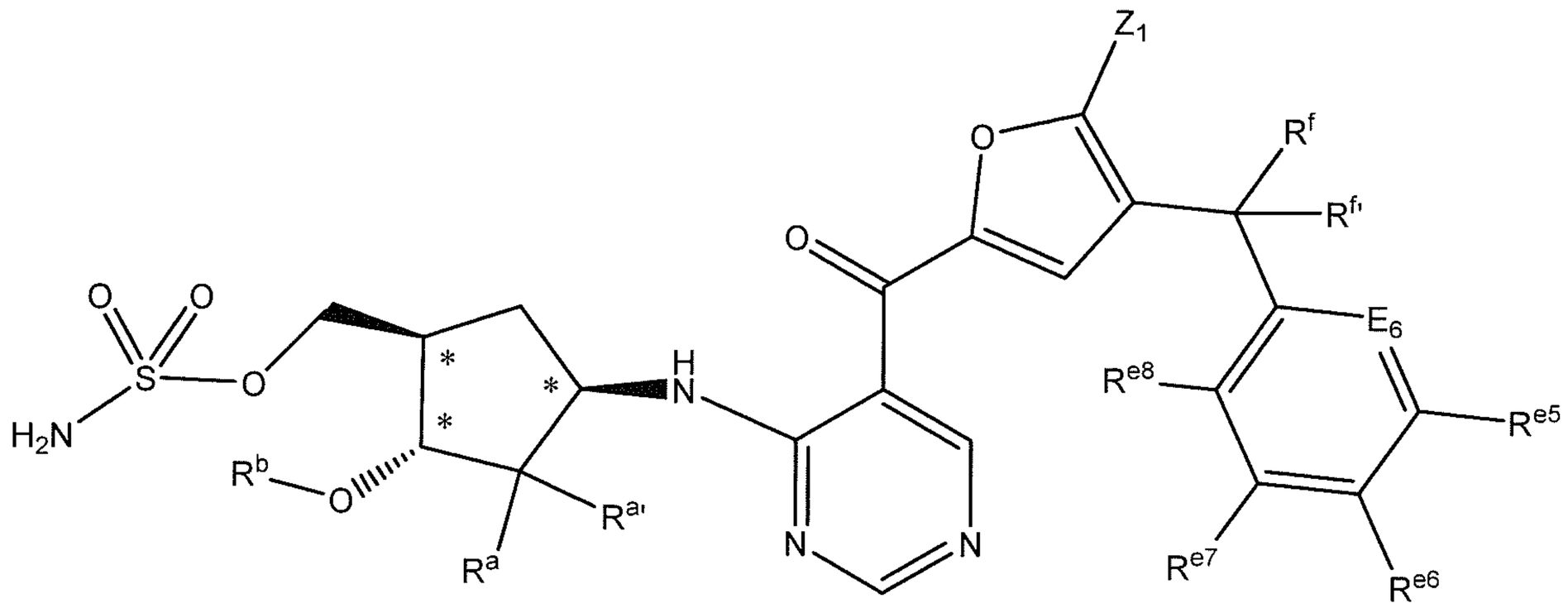
wherein R^a, $R^{a'}$, R^b, X_2, X_3, Z_1, R^f, $R^{f'}$, R^{e5}, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0076] In some embodiments, the chemical entity of formula (*I*) is represented by formula (*IX-a*) or (*IX-b*):



;

(*IX-a*)



;

(*IX-b*)

or a pharmaceutically acceptable salt thereof;

wherein R^a, $R^{a'}$, R^b, Z_1, R^f, $R^{f'}$, R^{e5}, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*IX-a*) wherein R^a, $R^{a'}$, R^b, Z_1, R^f, $R^{f'}$, R^{e5}, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry. In some embodiments, the chemical entity of formula (*I*) is represented by formula (*IX-b*) wherein R^a, $R^{a'}$, R^b, Z_1, R^f, $R^{f'}$, R^{e5}, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein and stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry.

[0077] The following values are described for any of formulas (*I*), (*I-a*), (*II*), (*II-a*), (*II-b*), (*III-a*), (*III-b*), (*IV-a*), (*IV-b*), (*V*), (*V-a*), (*V-b*), (*VI*), (*VI-a*), (*VI-b*), (*VII*), (*VII-a*), (*VII-b*), (*VIII*), (*VIII-a*), (*VIII-b*), (*IX*), (*IX-a*), or (*IX-b*).

[0078] In some embodiments, Y is –O-, $-CH_2-$, or -N(H)-. In some embodiments, Y is –O-. In some embodiments, Y is $-CH_2-$. In some embodiments, Y is –N(H)-.

[0079] In some embodiments, R^a is hydrogen, fluoro, $-NH_2$, or -OH. In some embodiments, R^a is hydrogen, fluoro or -OH. In some embodiments, R^a is hydrogen or -OH. In some embodiments, R^a is hydrogen. In some embodiments, R^a is -OH.

[0080] In some embodiments, $R^{a'}$ is hydrogen or fluoro; provided that when R^a is $-NH_2$ or -OH, $R^{a'}$ is hydrogen. In some embodiments, $R^{a'}$ is hydrogen.

[0081] In some embodiments, R^a is hydrogen and $R^{a'}$ is hydrogen. In some embodiments, R^a is fluoro and $R^{a'}$ is fluoro. In some embodiments, R^a is $-NH_2$ and $R^{a'}$ is hydrogen. In some embodiments, R^a is hydrogen and $R^{a'}$ is fluoro. In some embodiments, R^a is -OH and $R^{a'}$ is hydrogen. In some embodiments, R^a is fluoro or hydrogen and $R^{a'}$ is fluoro.

[0082] In some embodiments, R^c is hydrogen or C_{1-4} alkyl. In some embodiments, R^c is hydrogen or methyl. In some embodiments, R^c is hydrogen.

[0083] In some embodiments, R^d is hydrogen, halogen, $-CF_3$, or C_{1-4} alkyl. In some embodiments, R^d is hydrogen, fluoro, chloro, or methyl. In some embodiments, R^d is hydrogen.

[0084] In some embodiments, X_1 is C(H), C(F) or N. In some embodiments, X_1 is C(H) or N. In some embodiments, X_1 is C(H). In some embodiments, X_1 is N.

[0085] In some embodiments, X_2 is S or O. In some embodiments, X_2 is S. In some embodiments, X_2 is O.

[0086] In some embodiments, X_3 is $C(R^{x3})$ or N, wherein R^{x3} has the values described herein. In some embodiments, X_3 is $C(R^{x3})$, wherein R^{x3} has the values described herein. In some embodiments, X_3 is N. In some embodiments, X_3 is C(H).

[0087] In some embodiments, R^{x3} is hydrogen, methyl, or halogen. In some embodiments, R^{x3} is hydrogen, methyl, fluoro, or chloro. In some embodiments, R^{x3} is hydrogen or methyl. In some embodiments, R^{x3} is hydrogen.

[0088] In some embodiments, Z_1 is hydrogen, halogen, cyano, R^{z3}, $-S-R^{z3}$, $-S(O)-R^{z3}$, or $-S(O)_2-R^{z3}$, wherein R^{z3} has the values described herein, and wherein Z_1 is not hydrogen, halogen, methyl, or cyano if Z_2 is hydrogen or methyl.

[0089] In some embodiments, Z_1 is hydrogen; halogen; cyano; phenyl optionally substituted with one or more independently selected halogens; 5- to 7-membered cycloaliphatic or heterocyclyl optionally fused to a 6-membered aryl, wherein the 5- to 7-membered cycloaliphatic or heterocyclyl optionally fused to a 6-membered aryl is optionally substituted with one or more independently selected halogens; C_{1-4} fluoroaliphatic; or a C_{1-4} aliphatic group optionally substituted with one or more hydroxyl, C_{1-4} alkoxy, phenyl optionally substituted with one more independently selected halogens, 5- or 6-membered cycloaliphatic, 5- or 6-membered heterocyclyl, or $-N(R^{z5})_2$; wherein each R^{z5} independently has the values described herein; and wherein Z_1 is not hydrogen, halogen, methyl, or cyano if Z_2 is hydrogen or methyl. In some embodiments, Z_1 is phenyl, halophenyl, or 5- to 7-membered cycloaliphatic or heterocyclyl optionally fused to a 6-membered aryl, wherein the 5- to 7-membered cycloaliphatic or heterocyclyl optionally fused to a 6-membered aryl is optionally substituted with one or more halogen. In some embodiments, Z_1 is a C_{1-4} aliphatic group (i) substituted with one or more phenyl, halophenyl, 5- or 6-membered cycloaliphatic or heterocyclyl, and (ii) optionally substituted with one or more hydroxyl, $-OC_{1-4}$ aliphatic, halogen, C_{1-4} aliphatic, acetyl, $-OCH_3$, $-CH_2OCH_3$, cyano, $-N(R^{z5})_2$, $-CH_2NH_2$, $-CO_2H$, or $-CF_3$, wherein each R^{z5} independently has the values described herein.

[0090] In some embodiments, Z_1 is hydrogen; halogen; cyano; or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, C_{1-4} alkoxy, $-N(R^{z5})_2$, or phenyl optionally substituted with one more independently selected halogens wherein each R^{z5} independently has the values described herein; wherein Z_1 is not hydrogen, halogen, methyl, or cyano if Z_2 is hydrogen or methyl. In some embodiments, Z_1 is hydrogen, chloro, or methyl, and Z_2 is not hydrogen or methyl. In some embodiments, Z_1 is hydrogen, and Z_2 is not hydrogen or methyl. In some embodiments, Z_1 is chloro,

and Z_2 is not hydrogen or methyl. In some embodiments, Z_1 is methyl, and Z_2 is not hydrogen or methyl.

[0091] In some embodiments, R^{z3} is an optionally substituted phenyl, an optionally substituted 5- to 7-membered cycloaliphatic, an optionally substituted 5- to 7-membered heterocyclyl, or an optionally substituted C_{1-4} aliphatic. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which are optionally substituted with n occurrences of R^2, wherein n and R^2 have the values described herein. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which may be substituted with one or more independently selected R^{z4}, wherein each R^{z4} independently has the values described herein. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which are optionally substituted with one to three independently selected R^{z4}, wherein each R^{z4} independently has the values described herein. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which may be substituted with one to two independently selected R^{z4}, wherein each R^{z4} independently has the values described herein. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which may be substituted with one R^{z4}, wherein R^{z4} has the values described herein. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, or C_{1-4} aliphatic, any of which may be substituted with one to three R^{z4}, wherein each R^{z4} independently has the values described herein. In some embodiments, R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, or C_{1-4} aliphatic, any of which may be substituted with one R^{z4}, wherein R^{z4} has the values described herein.

[0092] In some embodiments, each occurrence of R^{z4} is independently hydroxyl, halogen, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z5})_2$, $-C(O)R^{z6}$, $-C(O)_2R^{z5}$, 5- or 6-membered cycloaliphatic or heterocyclyl, or a phenyl optionally substituted with one or more independently selected halogens, wherein each R^{z5} independently has the values described herein and R^{z6} has the values described herein. In some embodiments, each occurrence of R^{z4} is independently halogen, cyano, C_{1-4} aliphatic, or C_{1-4} fluoroaliphatic. In some embodiments, each occurence of R^{z4} is independently chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, ethyne, cyclopropyl, or phenyl. In some embodiments, each occurrence of R^{z4} is independently chloro, bromo, fluoro, iodo, methyl, ethyl, difluoromethoxy, trifluoromethoxy, ethyne, cyclopropyl, or phenyl. In some embodiments, each occurence of R^{z4} is independently chloro, bromo, fluoro, methyl, ethyl, or trifluoromethyl. In some embodiments, each occurrence of R^{z4} is independently chloro, bromo, iodo, or methyl.

[0093] In some embodiments, each R^{z5} is independently hydrogen or C_{1-4} alkyl. In some embodiments, each R^{z5} is independently hydrogen or methyl. In some embodiments, R^{z5} is hydrogen.

In some embodiments, R^{z5} is methyl. In some embodiments, each R^{z5} is independently methyl or ethyl.

[0094] In some embodiments, R^{z6} is C_{1-4} alkyl. In some embodiments, R^{z6} is methyl. In some embodiments, R^{z6} is methyl or ethyl.

[0095] In some embodiments, (a) Z_2 is a ring system having an optionally substituted 5- to 7-membered heterocyclyl with 1-2 heteroatoms or an optionally substituted 5- to 7-membered cycloaliphatic fused to

(i) an optionally substituted 5-membered heteroaryl or an optionally substituted 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) an optionally substituted 9-membered heteroaryl or an optionally substituted 10-membered aryl or heteroaryl to form a tricyclic group;

OR (b) Z_2 is L-R^e wherein L and R^e have the values described herein;

OR (c) Z_2 is hydrogen.

[0096] In some embodiments, (a) Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to

(i) a 5-membered heteroaryl or a 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) a 9-membered heteroaryl or a 10-membered aryl or heteroaryl to form a tricyclic group;

wherein the ring system is optionally substituted by n occurrences of R^2, wherein n and R^2 have the values described herein;

OR

(b) Z_2 is L-R^e wherein L is $–L_1$-, $-V_1-L_2$-, or $–L_1-V_1-L_2$-;

R^e is either:

(i) hydrogen, hydroxyl, halogen, $-CF_3$, or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, halogen, or C_{1-4} aliphatic,

with the proviso that R^e is not hydrogen if R^f and $R^{f'}$ are present and form a ring;

OR (ii) a ring chosen from 3- to 7-membered cycloaliphatic or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5- to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, wherein the R^e ring or rings are optionally substituted by n occurrences of R^2, wherein n and R^2 have the values described herein;

L_1 is a C_{1-3} alkylene chain wherein 1 or 2 saturated carbon atoms are optionally substituted by $(R^f)(R^{f'})$ and in which there are optionally one or two degrees of unsaturation;

V_1 is -S-, -O-, -S(O)-, $-S(O)_2$-, -C(O)- or $-N(R^g)$-, wherein R^g has the values described herein;

L_2 is a C_{0-2} alkylene chain wherein one saturated carbon atom is optionally substituted by $(R^f)(R^{f'})$;

wherein R^f and R^{f_1} have the values described herein.

[0097] In some embodiments, (a) Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to

(i) a 5-membered heteroaryl or a 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) a 9-membered heteroaryl or a 10-membered aryl or heteroaryl to form a tricyclic group;

wherein the ring system is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and the ring system is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or 4- to 6-membered heterocycle;

each occurrence of R^{z7} is independently hydrogen or C_{1-4} alkyl;

each occurrence of R^{z8} is independently C_{1-4} alkyl;

T_2 is a C_1-C_2 alkylene chain; and

R^{z9} is cyano, $-NO_2$, $-N(R^{z7})_2$, $-OR^{z7}$, $-C(O)R^{z8}$, $-C(O)_2R^{z7}$, or $-C(O)N(R^{z7})_2$;

OR

(b) Z_2 is L-R^e wherein either:

(i) R^e is hydrogen, hydroxyl, halogen, $-CF_3$, or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, halogen, or C_{1-4} aliphatic,

with the proviso that R^e is not hydrogen if R^f and R^{f_1} are present and form a ring;

OR (ii) R^e is a ring chosen from 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, R^e being optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy,

S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and which is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a spirocyclic 4- to 6-membered heterocycle;

each occurrence of R^{z7} is independently hydrogen or C_{1-4} alkyl;

each occurrence of R^{z8} is independently C_{1-4} alkyl;

T_2 is a C_1-C_2 alkylene chain; and

R^{z9} is cyano, $-NO_2$, $-N(R^{z7})_2$, $-OR^{z7}$, $-C(O)R^{z8}$, $-C(O)_2R^{z7}$, or $-C(O)N(R^{z7})_2$.

[0098] In some embodiments, (a) Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to

(i) a 5-membered heteroaryl or a 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) a 9-membered heteroaryl or a 10-membered aryl or heteroaryl to form a tricyclic group;

wherein the ring system is optionally substituted by n occurrences of R^2, wherein n and R^2 have the values described herein.

[0099] In some embodiments, Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to

(i) a 5-membered heteroaryl or a 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) a 9-membered heteroaryl or a 10-membered aryl or heteroaryl to form a tricyclic group;

wherein the ring system is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and the ring system is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or 4- to 6-membered heterocycle;
wherein each R^{z7} independently has the values described herein and R^{z8}, T_2, and R^{z9} have the values described herein.

[00100] In some embodiments, Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to a 5-membered heteroaryl or a 6-membered aryl or heteroaryl to form a bicyclic group; wherein the ring system is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and the ring system is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a spirocyclic 4- to 6-membered heterocycle;

wherein each R^{z7} independently has the values described herein and R^{z8}, T_2, R^{z9} have the values described herein.

[00101] In some embodiments, Z_2 is a 6-membered heterocyclyl, the heterocyclyl containing 1 N or O atom, fused to a 6-membered aryl or heteroaryl ring to form a bicyclic group, wherein the ring system is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and the ring system is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or 4- to 6-membered heterocycle; wherein each R^{z7} independently has the values described herein and R^{z8}, T_2, and R^{z9} have the values described herein.

[00102] In some embodiments, R^{z7} is hydrogen or C_{1-4} alkyl. In some embodiments, R^{z7} is hydrogen or methyl. In some embodiments, R^{z7} is hydrogen. In some embodiments, R^{z7} is methyl. In some embodiments, R^{z7} is methyl or ethyl.

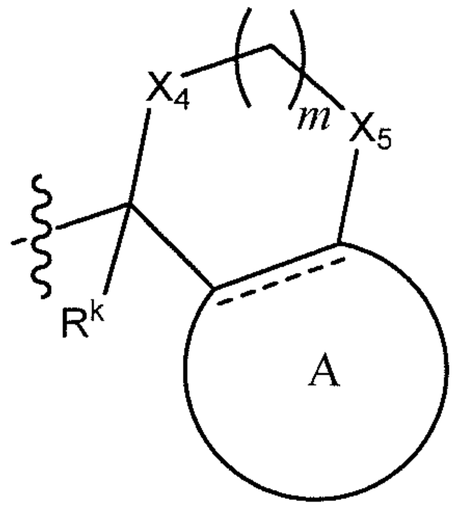
[00103] In some embodiments, R^{z8} is C_{1-4} alkyl. In some embodiments, R^{z8} is methyl. In some embodiments, R^{z8} is methyl or ethyl.

[00104] In some embodiments, T_2 is an optionally substituted C_{1-2} alkylene chain. In some embodiments, T_2 is a C_1.C_2 alkylene chain optionally substituted with 0-3 independent occurrences of R^{t2}, wherein R^{t2} has the values described herein. In some embodiments, T_2 is a C_{1-2} alkylene chain. In some embodiments, T_2 is $–CH_2$-CH_2-. In some embodiments, T_2 is $–C(CH_3)_2$-. In some embodiments, T_2 is $–CH_2$-.

[00105] In some embodiments, each occurrence of R^{t2} is independently C_{1-4} alkyl. In some embodiments, each occurrence of R^{t2} is independently methyl or ethyl. In some embodiments, R^{t2} is methyl.

[00106] In some embodiments, R^{z9} is cyano, $-N(R^{z7})_2$, $-OR^{z7}$, $-C(O)R^{z8}$, $-C(O)_2R^{z7}$, or $-C(O)N(R^{z7})_2$, wherein R^{z7} and R^{z8} have the values described herein.

[00107] In some embodiments, Z_2 is



(*a-i*)

wherein X_4, X_5, R^k, *m*, and Ring A have the values described herein.

[00108] In some embodiments, R^k is hydrogen or methyl. In some embodiments, R^k is deuterium. In some embodiments, R^k is hydrogen.

[00109] In some embodiments, X_4 is S, O, or $N(R^{n4})$, wherein R^{n4} has the values described herein. In some embodiments, X_4 is O or $N(R^{n4})$, wherein R^{n4} has the values described herein. In some embodiments, X_4 is $N(R^{n4})$, wherein R^{n4} has the values described herein. In some embodiments, X_4 is O or N(H). In some embodiments, X_4 is O. In some embodiments, X_4 is N(H).

[00110] In some embodiments, R^{n4} is hydrogen or C_{1-4} alkyl. In some embodiments, R^{n4} is hydrogen or methyl. In some embodiments, R^{n4} is hydrogen.

[00111] In some embodiments, X_5 is O, C(O), or $C(R^{x5})(R^{x5'})$, wherein R^{x5} and $R^{x5'}$ have the values described herein. In some embodiments, X_5 is O. In some embodiments, X_5 is $C(R^{x5})(R^{x5'})$. In some embodiments, X_5 is CD_2. In some embodiments, X_5 is O, C(O), or $C(R^{x5})(R^{x5'})$, wherein X_5 is not O if X_4 is $N(R^{n4})$ or S. In some embodiments, X_5 is CH_2.

[00112] In some embodiments, R^{x5} is hydrogen, halogen, hydroxyl, or C_{1-4} alkyl, or R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a spirocyclic 3-6 membered carbocycle or a spirocyclic 4-6 membered heterocycle comprising one heteroatom chosen from O, N, or S. In some embodiments, R^{x5} is hydrogen, fluoro, hydroxyl, or C_{1-4} alkyl, or R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a spirocyclic 3-6 membered carbocycle or a spirocyclic 4-6 membered heterocycle comprising one heteroatom chosen from O, N, or S. In some embodiments, R^{x5} is hydrogen, fluoro, hydroxyl, or C_{1-4} alkyl. In some embodiments, R^{x5} is hydrogen, fluoro, chloro, hydroxyl, or methyl. In some embodiments, R^{x5} is hydrogen or methyl. In some embodiments, R^{x5} is hydrogen.

[00113] In some embodiments, $R^{x5'}$ is hydrogen, halogen or C_{1-4} alkyl, or R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a spirocyclic 3-6 membered carbocycle or a spirocyclic 4-6 membered heterocycle comprising one heteroatom chosen from O, N, or S, wherein $R^{x5'}$ is not halogen if R^{x5} is hydroxyl. In some embodiments, $R^{x5'}$ is hydrogen, fluoro, or C_{1-4} alkyl, or R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a spirocyclic 3-6 membered carbocycle or a spirocyclic 4-6 membered heterocycle comprising one

heteroatom chosen from O, N, or S, wherein $R^{x5'}$ is not halogen if R^{x5} is hydroxyl. In some embodiments, $R^{x5'}$ is hydrogen, fluoro, or C_{1-4} alkyl, wherein $R^{x5'}$ is not fluoro if R^{x5} is hydroxyl. In some embodiments, $R^{x5'}$ is hydrogen, fluoro, chloro, or methyl, wherein $R^{x5'}$ is not fluoro if R^{x5} is hydroxyl. In some embodiments, $R^{x5'}$ is hydrogen.

[00114] In some embodiments, R^{x5} is hydrogen, halogen, hydroxyl, or C_{1-4} alkyl and $R^{x5'}$ is hydrogen. In some embodiments, R^{x5} is hydrogen, fluoro, chloro, hydroxyl, or methyl and $R^{x5'}$ is hydrogen. In some embodiments, R^{x5} is hydrogen or methyl and $R^{x5'}$ is hydrogen. In some embodiments, R^{x5} is hydrogen and $R^{x5'}$ is hydrogen. In some embodiments, R^{x5} is fluoro and $R^{x5'}$ is fluoro. In some embodiments, R^{x5} is methyl and $R^{x5'}$ is methyl. In some embodiments, R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, a spirocyclic 3-6 membered carbocycle or a spirocyclic 4-6 membered heterocycle comprising one heteroatom chosen from O, N, or S. In some embodiments, R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a spirocyclic 3-6 membered carbocycle. In some embodiments, R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a cyclopropyl ring. In some embodiments, R^{x5} and $R^{x5'}$ are independently hydrogen or fluoro; or, together with the carbon to which they are attached, form a cyclopropyl ring.

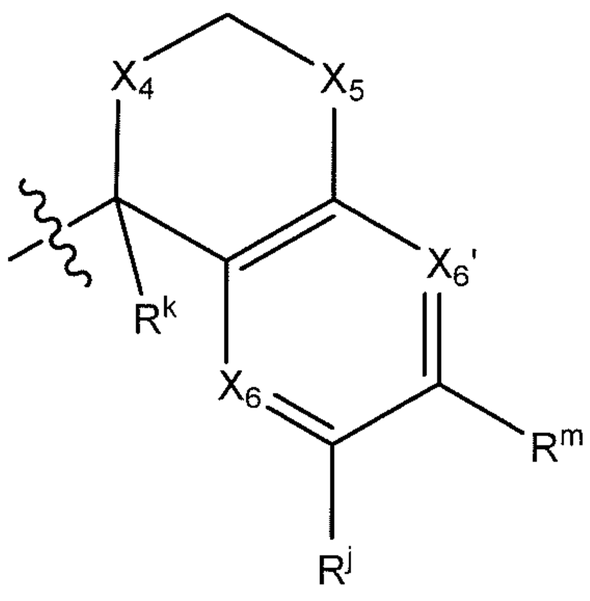
[00115] In some embodiments, Ring A is a fused 5-membered heteroaryl or 6-membered aryl or heteroaryl, and is optionally substituted with 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein R^{z7}, R^{z8}, T_2, and R^{z9} have the values described herein. In some embodiments, Ring A is a fused 6-membered aryl or heteroaryl having one heteroatom and is optionally substituted with 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein R^{z7}, R^{z8}, T_2, and R^{z9} have the values described herein.

[00116] In some embodiments, Ring A is a fused 5-membered heteroaryl or 6-membered aryl or heteroaryl, and is optionally substituted with 1-3 independent occurrences of chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, isopropyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, cyano, ethyne, cyclopropyl, or phenyl. In some embodiments, Ring A is a fused 6-membered aryl or heteroaryl, and is optionally substituted with 1-3 independent occurrences of chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, isopropyl, tert-butyl, methoxy,

ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, cyano,ethyne, cyclopropyl, or phenyl.

[00117] In some embodiments, Ring A is a fused phenyl or pyridyl, and is optionally substituted with 1-3 independent occurrences of chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, isopropyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, cyano, ethyne, cyclopropyl, or phenyl. In some embodiments, Ring A is a fused 6-membered aryl or heteroaryl, and is optionally substituted with 1-3 independent occurrences of chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, isopropyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, cyano, diethylamino, ethyne, cyclopropyl, or phenyl.

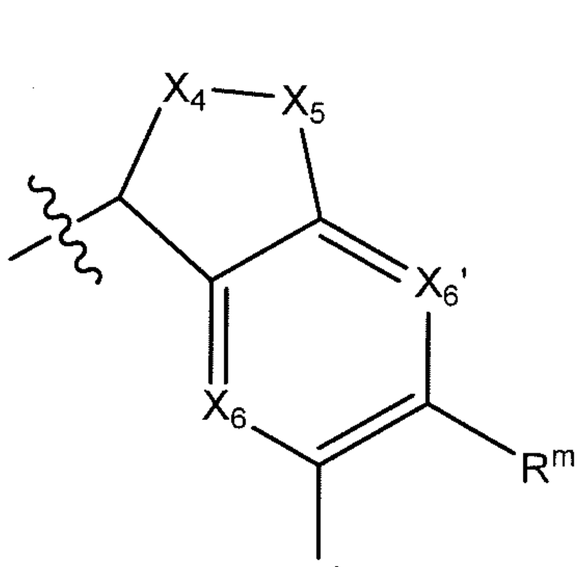
[00118] In some embodiments, Z_2 is



(*a-ii*)

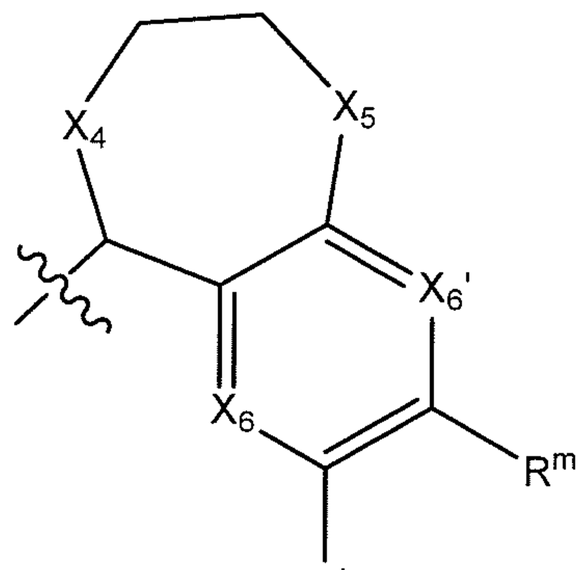
wherein X_4, X_5, X_6, X_6', R^m, and R^j have the values described herein.

[00119] In some embodiments, Z_2 is



(*a-iii*)

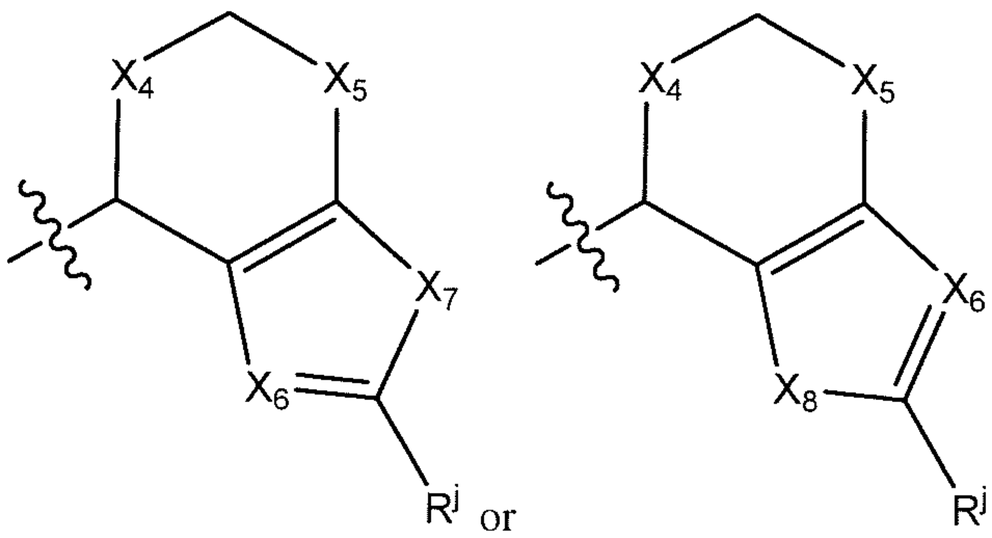
, or



(*a-iv*)

wherein X_4, X_5, X_6, X_6', R^m, and R^j have the values described herein. In some embodiments, Z_2 is (*a-iii*), wherein X_4, X_5, X_6, X_6', R^m, and R^j have the values described herein. In some embodiments, Z_2 is (*a-iv*), wherein X_4, X_5, X_6, X_6', R^m, and R^j have the values described herein.

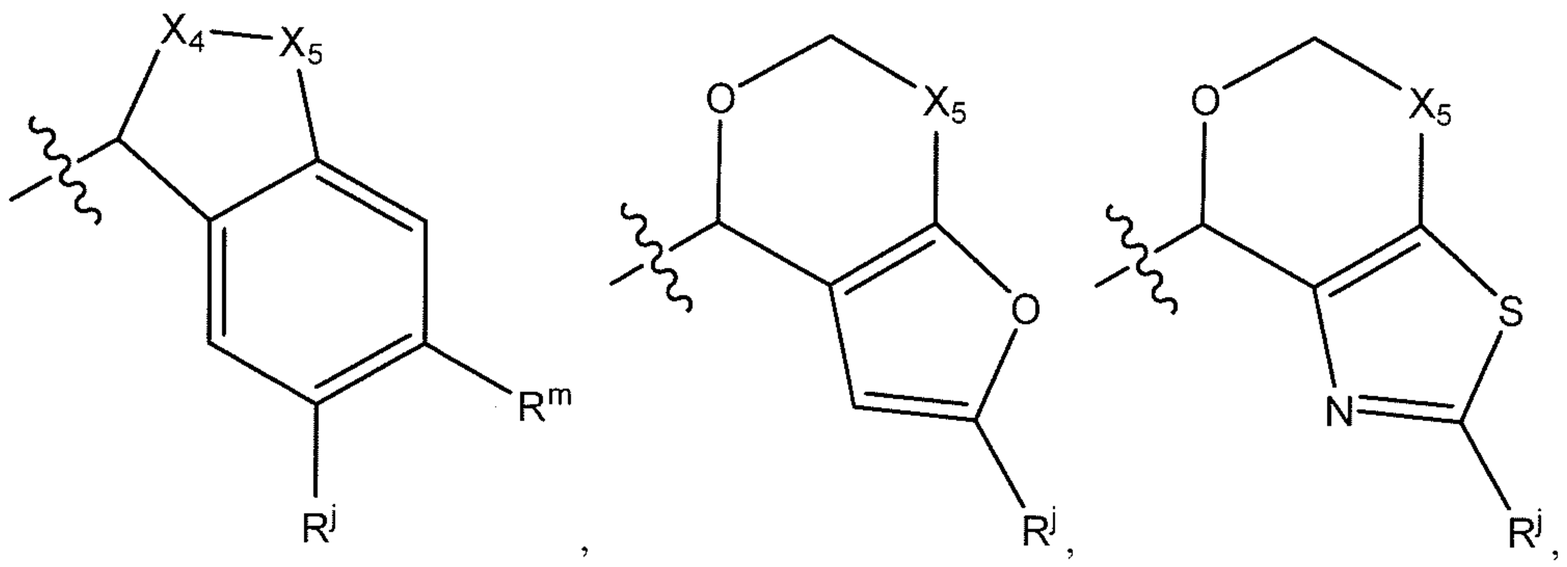
[00120] In some embodiments, Z_2 is



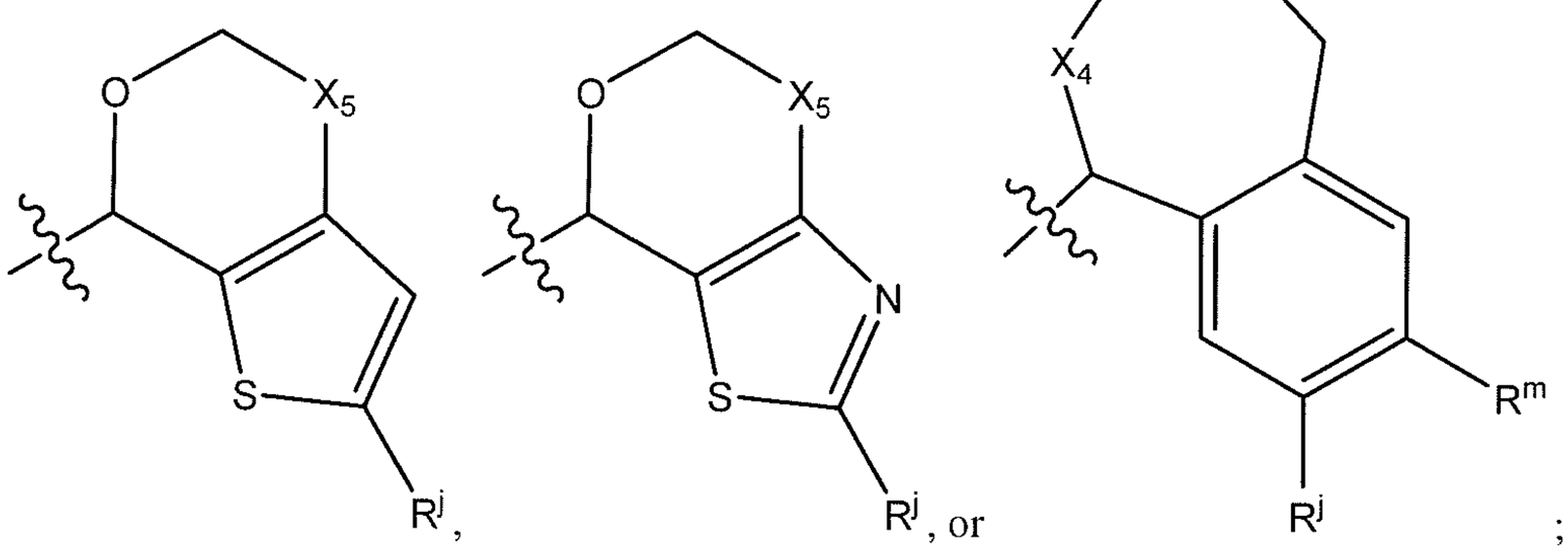
(*a-v*) (*a-vi*)

wherein X_4, X_5, X_6, X_7, X_8, and R^j have the values described herein. In some embodiments, Z_2 is (*a-v*), wherein X_4, X_5, X_6, X_7, X_8, and R^j have the values described herein. In some embodiments, Z_2 is (*a-vi*), wherein X_4, X_5, X_6, X_7, X_8, and R^j have the values described herein. In some embodiments, X_7 is O or S. In some embodiments, X_8 is S or N(H).

[00121] In some embodiments, Z_2 is



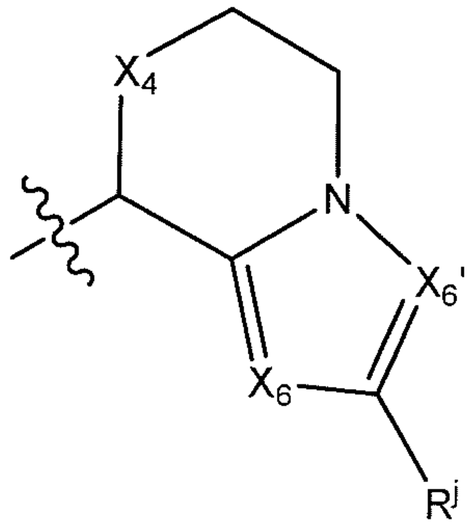
(*a-vii*) (*a-viii*) (*a-ix*)



(*a-x*) (*a-xi*) (*a-xii*)

wherein X_4, X_5, R^m, and R^j have the values described herein. In some embodiments, Z_2 is (*a-vii*), wherein X_4, X_5, R^m, and R^j have the values described herein. In some embodiments, Z_2 is (*a-viii*), wherein X_5 and R^j have the values described herein. In some embodiments, Z_2 is (*a-ix*), wherein X_5 and R^j have the values described herein. In some embodiments, Z_2 is (*a-x*), wherein X_5 and R^j have

the values described herein. In some embodiments, Z_2 is (***a-xi***), wherein X_5 and R^j have the values described herein. In some embodiments, Z_2 is (***a-xii***), wherein X_4, R^m, and R^j have the values described herein. In some embodiments, Z_2 is



(***a-xiii***)

wherein X_4, X_6, X_6', and R^j have the values described herein.

[00122] In some embodiments, X_6 is N or $C(R^{x6})$, wherein R^{x6} has the values described herein. In some embodiments, X_6 is N or C(H). In some embodiments, X_6 is N. In some embodiments, X_6 is $C(R^{x6})$, wherein R^{x6} has the values described herein. In some embodiments, X_6 is C(H).

[00123] In some embodiments, R^{x6} is hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein. In some embodiments, R^{x6} is hydrogen, chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, ethyne, or cyclopropyl. In some embodiments, R^{x6} is hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$. In some embodiments, R^{x6} is hydrogen, fluoro, chloro, bromo, iodo, or methyl. In some embodiments, R^{x6} is hydrogen, fluoro, chloro, or methyl. In some embodiments, R^{x6} is hydrogen, fluoro, or chloro. In some embodiments, R^{x6} is hydrogen.

[00124] In some embodiments, X_6' is N or $C(R^{x6'})$, wherein $R^{x6'}$ has the values described herein. In some embodiments, X_6' is N or $C(R^{x6})$, wherein R^{x6} has the values described herein. In some embodiments, X_6' is N or C(H). In some embodiments, X_6' is N. In some embodiments, X_6' is $C(R^{x6'})$, wherein $R^{x6'}$ has the values described herein. In some embodiments, X_6' is C(H).

[00125] In some embodiments, $R^{x6'}$ is hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein. In some embodiments, $R^{x6'}$ is hydrogen, chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio,

dimethylamino, diethylamino, ethyne, or cyclopropyl. In some embodiments, $R^{x6'}$ is hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$. In some embodiments, $R^{x6'}$ is hydrogen, fluoro, chloro, bromo, iodo, or methyl. In some embodiments, $R^{x6'}$ is hydrogen, fluoro, chloro, bromo, iodo, or methyl. In some embodiments, $R^{x6'}$ is hydrogen, fluoro, chloro, or methyl. In some embodiments, $R^{x6'}$ is hydrogen, fluoro, or chloro. In some embodiments, $R^{x6'}$ is hydrogen.

[00126] In some embodiments, R^j is hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein. In some embodiments, R^j is hydrogen, chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, ethyne, or cyclopropyl. In some embodiments, R^j is hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$. In some embodiments, R^j is methyl, ethyl, isopropyl, hydrogen, fluoro, chloro, bromo, cyclopropyl, $-C\equiv CH$ or $-CF_3$. In some embodiments, R^j is hydrogen, fluoro, chloro, bromo, iodo, or methyl. In some embodiments, R^j is hydrogen, fluoro, chloro, or methyl. In some embodiments, R^j is hydrogen, fluoro, or chloro. In some embodiments, R^j is hydrogen. In some embodiments, R^j is fluoro or chloro. In some embodiments, R^j is methyl. In some embodiments, R^j is fluoro. In some embodiments, R^j is chloro.

[00127] In some embodiments, R^m is hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein. In some embodiments, R^m is hydrogen, chloro, bromo, fluoro, iodo, methyl, ethyl, propyl, tert-butyl, methoxy, ethoxy, isopropoxy, tert-butoxy, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, trifluoromethylthio, dimethylamino, diethylamino, ethyne, or cyclopropyl. In some embodiments, R^m is hydrogen, fluoro, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$. In some embodiments, R^m is hydrogen, fluoro, chloro, bromo, iodo, or methyl. In some embodiments, R^m is hydrogen, fluoro, chloro, or methyl. In some embodiments, R^m is hydrogen, fluoro, or chloro. In some embodiments, R^m is hydrogen.

[00128] In some embodiments, each R^{x6}, $R^{x6'}$, R^j and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein and at least one of R^{x6}, $R^{x6'}$, R^j and R^m is hydrogen. In some embodiments, each of R^{x6}, $R^{x6'}$, R^j, and R^m is independently hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl,

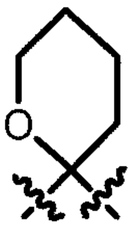
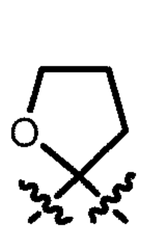
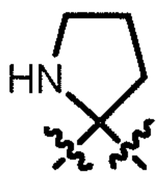
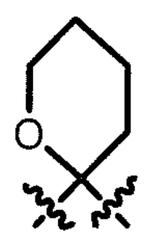
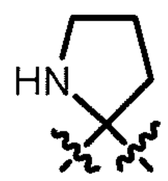
CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$; wherein at least one of R^{x6}, R^{x7}, R^j and R^m is hydrogen. In some embodiments, each R^{x6}, $R^{x6'}$, R^j and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein and at least one of R^{x6}, $R^{x6'}$, R^j and R^m is hydrogen. In some embodiments, each of R^{x6}, $R^{x6'}$, R^j, and R^m is independently hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$; wherein at least two of R^{x6}, R^{x7}, R^j and R^m are hydrogen. In some embodiments, each R^{x6}, $R^{x6'}$, R^j and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein and at least one of R^{x6}, $R^{x6'}$, R^j and R^m is hydrogen. In some embodiments, each of R^{x6}, $R^{x6'}$, R^j, and R^m is independently hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$; wherein at least two of R^{x6}, R^{x7}, R^j and R^m are hydrogen.

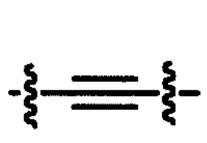
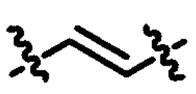
[00129] In some embodiments, R^{x6} is hydrogen; $R^{x6'}$ is hydrogen; and R^j and R^m are independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein. In some embodiments, R^{x6} is hydrogen; $R^{x6'}$ is hydrogen; and R^j and R^m are independently hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$. In some embodiments, R^{x6} is hydrogen; $R^{x6'}$ is hydrogen; R^m is hydrogen; and R^j is methyl, ethyl, isopropyl, hydrogen, fluoro, chloro, bromo, cyclopropyl, $-C\equiv CH$ or $-CF_3$. In some embodiments, R^{x6} is hydrogen; $R^{x6'}$ is hydrogen; R^m is hydrogen; and R^j is hydrogen, fluoro, chloro, or methyl.

[00130] In some embodiments, m is 0-2. In some embodiments, m is 1-2. In some embodiments, m is 0-1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

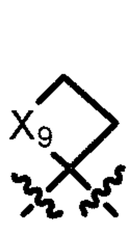
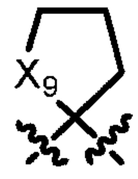
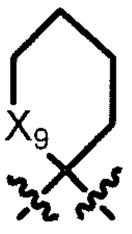
[00131] In some embodiments, Z_2 is L-R^e.

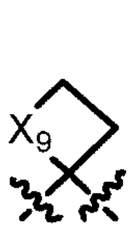
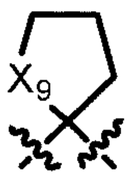
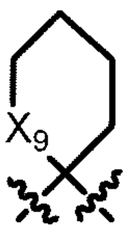
[00132] In some embodiments, L is $-L_1-$, $-V_1-L_2-$, or $-L_1-V_1-L_2-$, wherein L_1, V_1, and L_2 have the values described herein. In some embodiments, L is $-C(R^f)(R^{f'})-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(=CH_2)-$, $-C(R^f)(R^{f'})-C(=CH_2)-$, $-C(R^f)(R^{f'})-C\equiv C-$, $-C(R^f)(R^{f'})-O-$, $-C(R^f)(R^{f'})-S-$, $-C(R^f)(R^{f'})-N(R^g)-$, $-C(R^f)(R^{f'})-N(R^g)-CH_2-$, $-C(R^f)(R^{f'})-CH_2-$, $-C(R^f)(R^{f'})-CH_2-CH_2-$, or $-C(O)-C(R^f)(R^{f'})-$, wherein R^f, $R^{f'}$, and R^g have the values described herein. In some embodiments, L is $-C(R^f)(R^{f'})-$, $-S-$, $-C(=O)-$, $-C(R^f)(R^{f'})-O-$, $-C(R^f)(R^{f'})-S-$, $-C(R^f)(R^{f'})-N(R^g)-$, $-C(R^f)(R^{f'})-CH_2-$ or $-C(R^f)(R^{f'})-C\equiv C-$, wherein R^f, $R^{f'}$, and R^g have the values described herein.

[00133] In some embodiments, L is -CH_2-, -CH(OH)-, -C(OH)(CH_3)-, -CH(NH_2)-, -C(CH_3)(NH_2)-, -CH_2-CH_2-, -S(O)-, , , or . In some embodiments, L is -CH(OH)- or -C(OH)(CH_3)-. In some embodiments, L is -CH(NH_2)- or -C(CH_3)(NH_2)-. In some embodiments, L is -CH(OH)- or -CH(NH_2)-. In some embodiments, L is -C(CH_3)(OH)- or -C(CH_3)(NH_2)-. In some embodiments, L is , , or . In some embodiments, L is -CH(OH)-. In some embodiments, L is -C(OH)(CH_3)-. In some embodiments, L is -CH(NH_2)-. In some embodiments, L is -C(CH_3)(NH_2)-. In some embodiments, L is -CH_2-CH_2-. In some embodiments, L is -S(O)-. In some embodiments, L is . In some embodiments, L is . In some embodiments, L is .

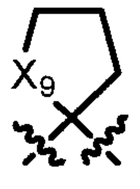
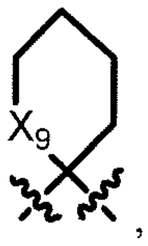
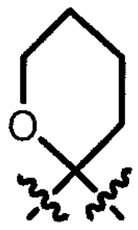
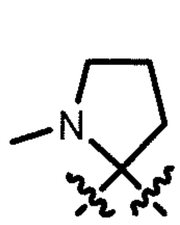
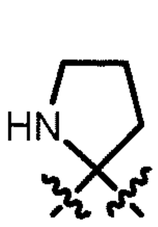
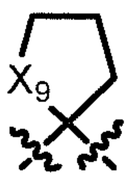
[00134] In some embodiments, L_1 is a C_{1-3} alkylene chain wherein 1 or 2 saturated carbon atoms are optionally substituted by (R^f)($R^{f'}$) and in which there are optionally one or two degrees of unsaturation, wherein R^f and $R^{f'}$ have the values described herein. In some embodiments, L_1 is -C(R^f)($R^{f'}$)-, wherein R^f and $R^{f'}$ have the values described herein. In some embodiments, L_1 is -CH_2-. In some embodiments, L_1 is , , , or .

[00135] In some embodiments, each R^f is independently hydrogen; hydroxyl; -N(R^h)($R^{h'}$); C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; -O-C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; or, together with $R^{f'}$ and the carbon atom to which they are attached, form C=CH_2, a 3- to 6-membered carbocycle, or a 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle. In some embodiments, each R^f is independently hydrogen, hydroxyl, N(R^h)($R^{h'}$), -OCH_3, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3, wherein R^h and $R^{h'}$ have the values described herein, or, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form a 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle. In some embodiments, each R^f is independently hydrogen, hydroxyl, N(R^h)($R^{h'}$), -

OCH_3, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3, or, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form , , or , wherein X_9 has the values described herein. In some embodiments, each R^f is independently hydrogen, hydroxyl, $N(R^h)(R^{h'})$, C_{1-4} alkoxy, cyclopropyl, or C_{1-4} alkyl optionally substituted with hydroxyl or -OCH_3. In some embodiments, each R^f is independently hydrogen, C_{1-4} alkyl, or cyclopropyl. In some embodiments, each R^f is independently hydrogen, methyl, ethyl, or isopropyl. In some embodiments, each R^f is independently hydrogen or methyl. In some embodiments, each R^f is hydrogen.

[00136] In some embodiments, each $R^{f'}$ is independently hydrogen; C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; -O-C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl; or, together with R^f and the carbon atom to which they are attached, form $C{=}CH_2$, a 3- to 6-membered carbocycle, or a 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle; wherein if R^f is hydroxyl, $R^{f'}$ is not -O-C_{1-4} aliphatic optionally substituted with hydroxyl, -OCH_3, or cyclopropyl. In some embodiments, each $R^{f'}$ is independently hydrogen, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3, or, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form a 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle; or, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form , , or , wherein X_9 has the values described herein. In some embodiments, each $R^{f'}$ is independently hydrogen, cyclopropyl, or C_{1-4} alkyl optionally substituted with hydroxyl or -OCH_3. In some embodiments, each $R^{f'}$ is independently hydrogen, C_{1-4} alkyl, or cyclopropyl. In some embodiments, each $R^{f'}$ is independently hydrogen, methyl, ethyl, or isopropyl. In some embodiments, each $R^{f'}$ is independently hydrogen or methyl. In some embodiments, each $R^{f'}$ is hydrogen.

[00137] In some embodiments, each R^f is independently hydrogen, hydroxyl, $N(R^h)(R^{h'})$, -OCH_3, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3; and each $R^{f'}$ is independently hydrogen, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3, wherein at least one of R^f and $R^{f'}$ comprises at least one heteroatom; or, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form a 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle. In some emdodiments, together

with the carbon atom to which they are attached, R^f and $R^{f'}$ form , ,or , wherein X_9 has the values described herein. In some emdodiments, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form , , , , , or . In some emdodiments, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form , wherein X_9 has the values described herein. In some emdodiments, each R^f is independently hydrogen, hydroxyl, $N(R^h)(R^{h'})$, C_{1-4} alkoxy, cyclopropyl, or C_{1-4} alkyl optionally substituted with hydroxyl or $-OCH_3$; and each $R^{f'}$ is independently hydrogen, cyclopropyl, or C_{1-4} alkyl optionally substituted with hydroxyl or $-OCH_3$. In some embodiments, each R^f and $R^{f'}$ is independently hydrogen, C_{1-4} alkyl, or cyclopropyl; or are taken together to form $=CH_2$. In some embodiments, each R^f and $R^{f'}$ is independently hydrogen, methyl, ethyl, or isopropyl. In some embodiments, each R^f and $R^{f'}$ is independently hydrogen or methyl.

[00138] In some embodiments, R^h and $R^{h'}$ are each independently hydrogen or C_{1-4} alkyl. In some embodiments, R^h and $R^{h'}$ are each independently hydrogen or methyl. In some embodiments, R^h and $R^{h'}$ are each hydrogen. In some embodiments, R^h is hydrogen or C_{1-4} alkyl. In some embodiments, R^h is hydrogen or methyl. In some embodiments, R^h is hydrogen. In some embodiments, R^h is hydrogen or C_{1-4} alkyl and $R^{h'}$ is hydrogen. In some embodiments, R^h is hydrogen or methyl and $R^{h'}$ is hydrogen. In some embodiments, R^h is methyl and $R^{h'}$ is methyl.

[00139] In some embodiments, X_9 is O, $N(R^h)$, or S, wherein R^h has the values described herein. In some embodiments, X_9 is O, N(H), $N(CH_3)$, or S. In some embodiments, X_9 is O. In some embodiments, X_9 is N(H). In some embodiments, X_9 is $N(CH_3)$. In some embodiments, X_9 is S.

[00140] In some embodiments, V_1 is -S-, -O-, -S(O)-, $-S(O)_2-$, -C(O)- or $-N(R^g)-$, wherein R^g has the values described herein. In some embodiments, V_1 is -C(O)- or $-N(R^g)-$, wherein R^g has the values described herein. In some embodiments, V_1 is -S-, -S(O)-, or $-S(O)_2-$. In some embodiments, V_1 is -O-.

[00141] In some embodiments, R^g is hydrogen or C_{1-4} alkyl. In some embodiments, R^g is hydrogen, methyl, ethyl, or isopropyl. In some embodiments, R^g is hydrogen or methyl. In some embodiments, R^g is hydrogen. In some embodiments, R^g is methyl.

[00142] In some embodiments, L_2 is a C_{0-2} alkylene chain wherein one saturated carbon atom is optionally substituted by $(R^f)(R^{f'})$, wherein R^f and $R^{f'}$ have the values described herein. In some

embodiments, L_2 is -C(R^f)($R^{f'}$)-. In some embodiments, L_2 is -CH_2-. In some embodiments, L_2 is -CH_2-CH_2-. In some embodiments, L_2 is absent.

[00143] In some embodiments, R^e is either (i) hydrogen, hydroxyl, halogen, -CF_3, or an optionally substituted C_{1-4} aliphatic, with the proviso that R^e is not hydrogen if R^f and $R^{f'}$ are present and form a ring; OR (ii) R^e is a ring chosen from optionally substituted 6-membered aryl, optionally substituted 5-to 6-membered heteroaryl, optionally substituted 3- to 7-membered cycloaliphatic, or optionally substituted 4- to 7-membered heterocyclyl, which is optionally fused to a second optionally substituted 6-membered aryl, optionally substituted 5-to 6-membered heteroaryl, optionally substituted 3- to 7-membered cycloaliphatic, or optionally substituted 4- to 7-membered heterocyclyl. In some embodiments, R^e is hydrogen, hydroxyl, halogen, -CF_3, or C_{1-4} alkyl optionally substituted with one or more hydroxyl, halogen, or C_{1-4} alkyl, with the proviso that R^e is not hydrogen if R^f and $R^{f'}$ are present and form a ring. In some embodiments, R^e is hydroxyl, halogen, -CF_3, or C_{1-4} alkyl optionally substituted with one or more hydroxyl, halogen, or C_{1-4} alkyl.

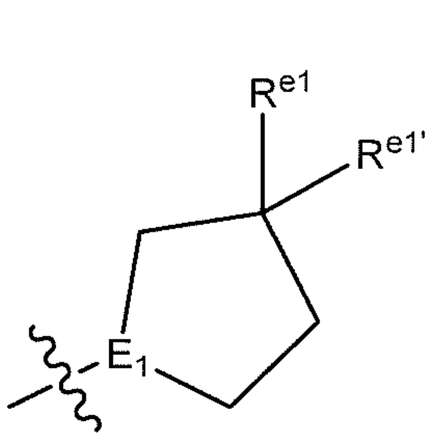
[00144] In some embodiments, R^e is an optionally substituted ring chosen from 3- to 7-membered cycloaliphatic or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5- to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, which is optionally substituted. In some embodiments, R^e is a ring chosen from 3- to 7-membered cycloaliphatic or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5- to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, wherein the R^e ring or rings are optionally substituted by n occurrences of R^2, wherein n and R^2 have the values described herein.

[00145] In some embodiments, R^e is a ring chosen from 3- to 7-membered cycloaliphatic or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5- to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, wherein the R^e ring or rings are optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, -$N(R^{z7})_2$, -$C(O)R^{z8}$, -$S(O)R^{z8}$, -$S(O)_2R^{z8}$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -$OC(O)N(R^{z7})_2$, -$N(R^{z7})C(O)R^{z8}$, -$N(R^{z7})SO_2R^{z8}$, -$N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and which is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a 4- to 6-membered heterocycle, wherein each R^{z7} independently has the values described herein and R^{z8}, T_2, and R^{z9} have the values described herein. In some embodiments, R^e is R^R which is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, -$N(R^{z7})_2$, -$C(O)R^{z8}$, -$S(O)R^{z8}$, -$S(O)_2R^{z8}$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -$OC(O)N(R^{z7})_2$, -$N(R^{z7})C(O)R^{z8}$, -$N(R^{z7})SO_2R^{z8}$, -$N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and which is

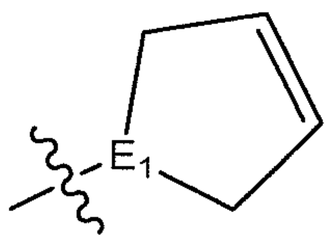
optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a 4- to 6-membered heterocycle, wherein each R^{z7} independently has the values described herein and R^R, R^{z8}, T_2, and R^{z9} have the values described herein.

[00146] In some embodiments, R^e is a 5- to 7-membered cycloaliphatic ring or a 5- to 7-membered heterocyclyl having only one heteroatom, wherein the ring is optionally substituted. In some embodiments, R^e is a 5- to 7-membered cycloaliphatic ring or a 5- to 7-membered heterocyclyl having only one heteroatom, wherein the ring is optionally substituted by n occurrences of R^2, wherein n and R^2 have the values described herein. In some embodiments, R^e is a 5- to 7-membered cycloaliphatic ring or a 5- to 7-membered heterocyclyl having only one heteroatom, wherein the ring is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, -$N(R^{z7})_2$, -$C(O)R^{z8}$, -$S(O)R^{z8}$, -$S(O)_2R^{z8}$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -$OC(O)N(R^{z7})_2$, -$N(R^{z7})C(O)R^{z8}$, -$N(R^{z7})SO_2R^{z8}$, -$N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and which is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a 4- to 6-membered heterocycle, wherein each R^{z7} independently has the values described herein and R^{z8}, T_2, and R^{z9} have the values described herein.

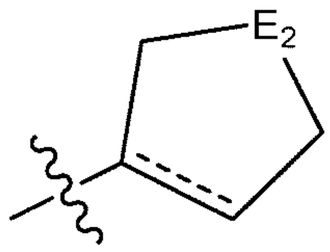
[00147] In some embodiments, R^e is



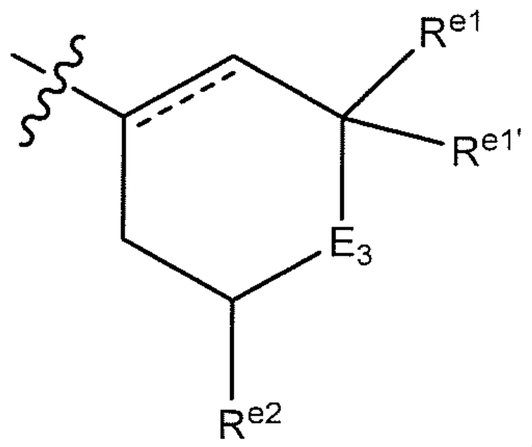
(b-i)



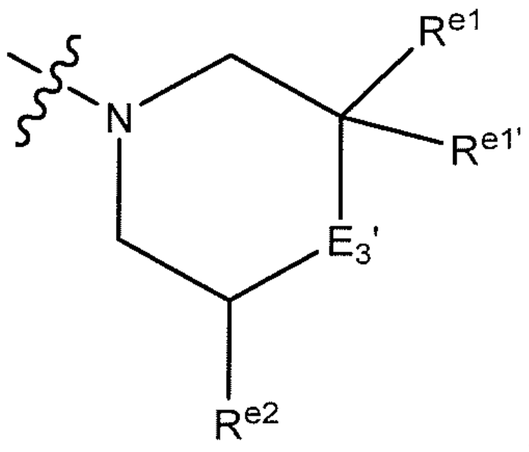
(b-ii)



(b-iii)

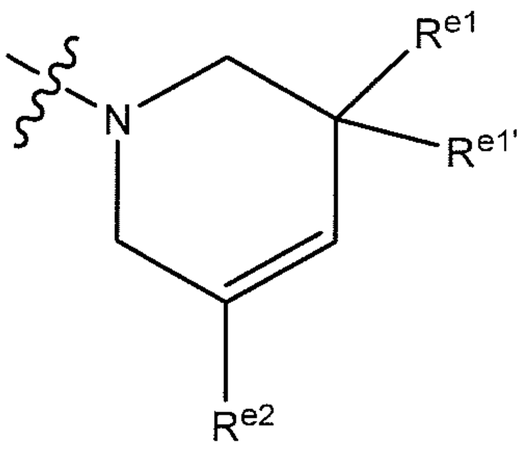


(b-iv)



(b-v)

, or



(b-vi)

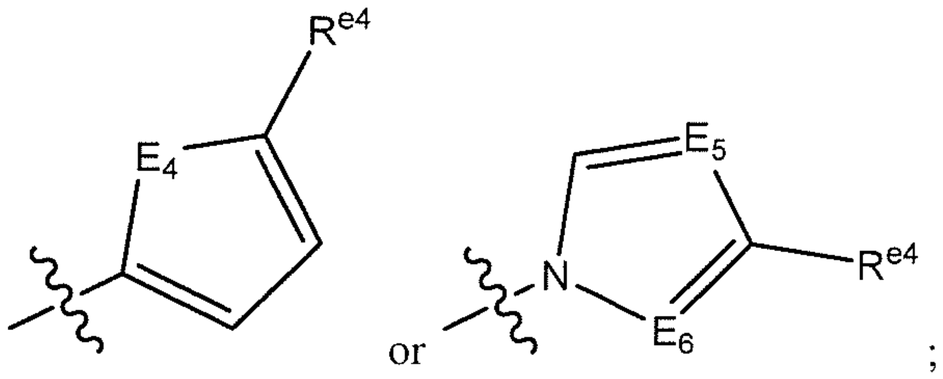
;

wherein E_1, E_2, E_3, E_3', R^{e1}, $R^{e1'}$, and R^{e2} have the values described herein and dashes indicate single or double bonds. In some embodiments, R^e is (***b-i***) wherein E_1, R^{e1}, and $R^{e1'}$ have the values described herein. In some embodiments, R^e is (***b-ii***) wherein E_1 has the values described herein. In some embodiments, R^e is (***b-iii***) wherein E_2 has the values described herein and dashes indicate single or

double bonds. In some embodiments, R^e is (***b-iv***) wherein E_3, R^{e1}, $R^{e1'}$, and R^{e2} have the values described herein and dashes indicate single or double bonds. In some embodiments, R^e is (***b-v***) wherein E_3', R^{e1}, $R^{e1'}$, and R^{e2} have the values described herein. In some embodiments, R^e is (***b-vi***) wherein R^{e1}, $R^{e1'}$, and R^{e2} have the values described herein. In some embodiments, E_1 is N or C(H). In some embodiments, E_2 is O, S, or CH_2. In some embodiments, E_3 is O, S, $N(R^{e3})$, or $C(H)(R^{e3})$, wherein R^{e3} has the values described herein. In some embodiments, E_3' is O, $N(R^{e3})$ or $C(H)(R^{e3})$, wherein R^{e3} has the values described herein. In some embodiments, R^{e1} and $R^{e1'}$ are each independently hydrogen or fluoro. In some embodiments, R^{e2} is hydrogen or methyl. In some embodiments, R^{e3} is hydrogen or methyl.

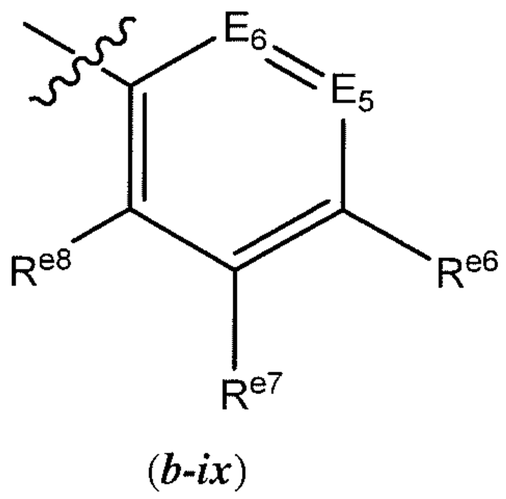
[00148] In some embodiments, R^e is a 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, wherein the R^e ring or rings are optionally substituted. In some embodiments, R^e is a 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, wherein the R^e ring or rings are optionally substituted with n occurrences of R^2, wherein n and R^2 have the values described herein. In some embodiments, R^e is a 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, wherein the R^e ring or rings are optionally substituted with 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$ or a 3- to 6-membered cycloaliphatic or 4- to 6-membered heterocyclyl, wherein each R^{z7} independently has the values described herein. In some embodiments, R^e is a 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally substituted with 1-3 independent occurrences of chloro, fluoro, bromo, iodo, methyl, ethyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C{\equiv}CH$.

[00149] In some embodiments, R^e is



(b-vii) ***(b-viii)***

wherein E_4, E_5, E_6, and R^{e4} have the values described herein. In some embodiments, R^e is (***b-vii***), wherein E_4 and R^{e4} have the values described herein. In some embodiments, R^e is (***b-viii***), wherein E_5, E_6, and R^{e4} have the values described herein. In some embodiments, R^e is



(*b-ix*)

wherein E_5, E_6, R^{e6}, R^{e7}, and R^{e8} have the values described herein.

[00150] In some embodiments, E_4 is S, O, or N(R^{n4}), wherein R^{n4} has the values described herein. In some embodiments, E_4 is S or O. In some embodiments, E_4 is S. In some embodiments, E_4 is O.

[00151] In some embodiments, R^{e4} is hydrogen, methyl, chloro, fluoro, bromo, iodo, cyano, or -CF_3. In some embodiments, R^{e4} is hydrogen, methyl, chloro, fluoro, cyano, or -CF_3. In some embodiments, R^{e4} is hydrogen, methyl, chloro, or fluoro. In some embodiments, R^{e4} is hydrogen or methyl. In some embodiments, R^{e4} is hydrogen.

[00152] In some embodiments, E_5 is N or C(R^{e5}), wherein R^{e5} has the values described herein. In some embodiments, E_5 is C(R^{e5}), wherein R^{e5} has the values described herein. In some embodiments, E_5 is N or C(H). In some embodiments, E_5 is C(H). In some embodiments, E_5 is N.

[00153] In some embodiments, R^{e5} is hydrogen, halogen, methyl, -SCH_3, -OCH_3, -CF_3, -OCF_3, -OCF_2H, or -C≡CH. In some embodiments, R^{e5} is hydrogen, halogen, methyl, -OCH_3, -CF_3, or -C≡CH. In some embodiments, R^{e5} is hydrogen or halogen. In some embodiments, R^{e5} is hydrogen, fluoro, or chloro. In some embodiments, R^{e5} is hydrogen, methyl, fluoro, or chloro. In some embodiments, R^{e5} is hydrogen.

[00154] In some embodiments, E_6 is N or C(H). In some embodiments, E_6 is N. In some embodiments, E_6 is C(H).

[00155] In some embodiments, R^{e6} is hydrogen, halogen, methyl, -SCH_3, -OCH_3, -CF_3, -OCF_3, -OCF_2H, or -C≡CH. In some embodiments, R^{e6} is hydrogen, halogen, methyl, -OCH_3, -CF_3, or -C≡CH. In some embodiments, R^{e6} is hydrogen or halogen. In some embodiments, R^{e6} is hydrogen, fluoro, or chloro. In some embodiments, R^{e6} is hydrogen, methyl, fluoro, or chloro. In some embodiments, R^{e6} is hydrogen.

[00156] In some embodiments, R^{e7} is hydrogen, halogen, methyl, -SCH_3, -OCH_3, -CF_3, -OCF_3, -OCF_2H, or -C≡CH. In some embodiments, R^{e7} is hydrogen, halogen, methyl, -OCH_3, -CF_3, or -C≡CH. In some embodiments, R^{e7} is hydrogen or halogen. In some embodiments, R^{e7} is hydrogen, fluoro, or chloro. In some embodiments, R^{e7} is hydrogen, methyl, fluoro, or chloro. In some embodiments, R^{e7} is hydrogen.

[00157] In some embodiments, R^{e8} is hydrogen, halogen, methyl, -SCH_3, -OCH_3, -CF_3, -OCF_3, -OCF_2H, or -C≡CH. In some embodiments, R^{e8} is hydrogen, halogen, methyl, -OCH_3, -CF_3, or -C≡CH. In some embodiments, R^{e8} is hydrogen or halogen. In some embodiments, R^{e8} is hydrogen, fluoro, or

chloro. In some embodiments, R^{e8} is hydrogen, methyl, fluoro, or chloro. In some embodiments, R^{e8} is hydrogen.

[00158] In some embodiments, each of R^{e5}, R^{e6}, R^{e7}, and R^{e8} is independently hydrogen, halogen, methyl, $-OCH_3$, $-CF_3$, or $-C\equiv CH$; wherein at least one of R^{e5}, R^{e6}, R^{e7}, and R^{e8} is hydrogen. In some embodiments, each of R^{e5}, R^{e6}, R^{e7}, and R^{e8} is independently hydrogen, halogen, methyl, $-OCH_3$, $-CF_3$, or $-C\equiv CH$; wherein at least two of R^{e5}, R^{e6}, R^{e7}, and R^{e8} are hydrogen.

[00159] In some embodiments, R^{e6} is hydrogen, fluoro, or chloro; R^{e7} is hydrogen, fluoro, or chloro; and R^{e8} is hydrogen, halogen, methyl, $-OCH_3$, or cyano; wherein at least one of R^{e6}, R^{e7}, and R^{e8} is hydrogen. In some embodiments, R^{e6} is hydrogen, fluoro, or chloro; R^{e7} is hydrogen, fluoro, or chloro; and R^{e8} is hydrogen, halogen, methyl, $-OCH_3$, or cyano; wherein at least two of R^{e6}, R^{e7}, and R^{e8} are hydrogen.

[00160] In some embodiments, R^R is furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, phenyl, naphthyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, imidazopyridyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, benzthiazolyl, benzothienyl, benzofuranyl, benzoxazolyl, benzodioxolyl, benzthiadiazolyl, 2,3-dihydrobenzofuranyl, 4H-furo[3,2-b]pyrrolyl, pyrazolopyrimidinyl, purinyl, quinolyl, isoquinolyl, tetrahydroquinolinyl, tetrahydronaphthyridinyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, tetrahydrofuranyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothienyl, indanyl, tetrahydroindazolyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, thiomorpholinyl, quinuclidinyl, phenanthridinyl, tetrahydronaphthyl, oxodihydropyridyl, indolinyl, benzodioxanyl, chromanyl, oxetanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, bicycloheptanyl, azabicyclooctanyl, oxabicyclooctanyl, bicyclononyl, bicyclooctanyl, or adamantyl. In some embodiments, R^R is furanyl, thienyl, phenyl, naphthyl, pyridyl, benzothienyl, benzofuranyl, cyclohexyl, or cyclohexenyl.

[00161] In some embodiments, Z_2 is hydrogen. In some embodiments, Z_2 is chloro and Z_1 is not hydrogen, halogen, methyl, or cyano.

[00162] In some embodiments, R^b is hydrogen or, together with the oxygen to which it is attached, forms a prodrug. In some embodiments, R^b is hydrogen or $-C(O)-R^{bx}$, wherein R^{bx} has the values described herein. In some embodiments, R^b is hydrogen. In some embodiments, R^b is $-C(O)-R^{bx}$, wherein R^{bx} has the values described herein.

[00163] In some embodiments, R^{bx} is C_{1-4} alkyl, $-CH(R^{by})-NH_2$, pyrrolidinyl, or $-L_b-OPO_3H_2$, wherein L_b and R^{by} have the values described herein. In some embodiments, R^{bx} is $-CH(R^{by})-NH_2$ wherein R^{by} has the values described herein. In some embodiments, R^{bx} is $-L_b-OPO_3H_2$, wherein L_b has the values described herein. In some embodiments, R^{bx} is C_{1-4} alkyl.

[00164] In some embodiments, R^{by} is C_{1-4} alkyl optionally substituted with hydroxyl, phenyl, phenolyl, imidazolyl, carboxyl, amino, guanidino, $-SCH_3$, $-C(O)NH_2$, or indolyl. In some embodiments, R^{by} is C_{1-4} alkyl optionally substituted with hydroxyl, phenyl, carboxyl, amino, or $-C(O)NH_2$. In some embodiments, R^{by} is C_{1-4} alkyl. In some embodiments, R^{by} is methyl, ethyl, isopropyl, propyl, butyl, or isobutyl. In some embodiments, R^{by} is methyl, ethyl, isopropyl, or isobutyl. In some embodiments, R^{by} is methyl. In some embodiments, R^{by} is ethyl. In some embodiments, R^{by} is isopropyl. In some embodiments, R^{by} is isobutyl.

[00165] In some embodiments, L_b is a bivalent linker chosen from C_{1-4} alkylene or $-(CH_2)_{n1}$-phenylene-$(CH_2)_{n2}$- where n1 is 0 or 1 and n2 is 1 or 2. In some embodiments, L_b is C_{1-4} alkylene. In some embodiments, L_b is C_{1-4} methylene. In some embodiments, L_b is C_{1-4} ethylene. In some embodiments, L_b is $-(CH_2)_{n1}$-phenylene-$(CH_2)_{n2}$- where n1 is 0 or 1 and n2 is 1 or 2. In some embodiments, L_b is -phenylene-$(CH_2)_{n2}$- where n2 is 1 or 2. In some embodiments, L_b is $-CH_2$-phenylene-$(CH_2)_{n2}$- where n2 is 1 or 2. In some embodiments, L_b is $-(CH_2)_{n1}$-phenylene-CH_2- where n1 is 0 or 1. In some embodiments, L_b is $-(CH_2)_{n1}$-phenylene-$(CH_2)_{n2}$- where n1 is 0 or 1 and n2 is 2.

[00166] In some embodiments, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following is/are true: Y is -O-; R^a is hydroxyl; $R^{a'}$ is hydrogen; R^c is hydrogen; X_1 is N; R^d is hydrogen; or X_3 is C(H). In some embodiments, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following is/are true: Y is -O-; R^a is hydrogen; $R^{a'}$ is hydrogen; R^c is hydrogen; X_1 is N; R^d is hydrogen; or X_3 is C(H).

[00167] In some embodiments, n is 1-5. In some embodiments, n is 1-4. In some embodiments, n is 1-3. In some embodiments, n is 1-2. In some embodiments, n is 1.

[00168] In some embodiments, each occurrence of R^2 is independently $-R^{2a}$, $-T_3$-R^{2d}, $-T_3$-R^{2a}, or $-V_2$-T_3-R^{2d}, wherein R^{2a}, T_3, R^{2d}, V_2 and T_3 have the values described herein. In some embodiments, each occurrence of R^2 is independently $-R^{2a}$ or T_3-R^{2a}, wherein R^{2a} and T_3 have the values described herein. In some embodiments, each occurrence of R^2 is independently $-R^{2a}$, wherein R^{2a} has the values described herein. In some embodiments, each occurrence of R^2 is independently halogen, $-R^{2c}$, $-N(R^{2b})_2$, $-OR^{2b}$, $-SR^{2c}$, C_{1-6} aliphatic or C_{1-6} fluoroaliphatic, wherein R^{2b} and R^{2c} have the values described herein.

[00169] In some embodiments, each occurrence of R^{2a} is independently halogen, $-CN$, $-NO_2$, $-R^{2c}$, $-N(R^{2b})_2$, $-OR^{2b}$, $-SR^{2c}$, $-S(O)R^{2c}$, $-S(O)_2R^{2c}$, $-C(O)R^{2b}$, $-C(O)OR^{2b}$, $-C(O)N(R^{2b})_2$, $-S(O)_2N(R^{2b})_2$, $-OC(O)N(R^{2b})_2$, $-N(R^{2e})C(O)R^{2b}$, $-N(R^{2e})SO_2R^{2c}$, $-N(R^{2e})C(O)OR^{2b}$, $-N(R^{2e})C(O)N(R^{2b})_2$, $-N(R^{2e})SO_2N(R^{2b})_2$, or $-Si(R^{2c})_3$, or a C_{1-6} aliphatic or C_{1-6} haloaliphatic, wherein R^{2b}, R^{2c}, and R^{2e} have the values described herein.

[00170] In some embodiments, each occurrence of R^{2b} is independently hydrogen or a group selected from C_{1-6} aliphatic, C_{1-6} haloaliphatic, 3- to 10-membered cycloaliphatic, 4- to 10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl having 1-5 heteroatoms independently selected

from nitrogen, oxygen, and sulfur, or two occurrences of R^{2b}, taken together with a nitrogen atom to which they are bound, form a 4- to -7-membered heterocyclyl having 0-1 additional heteroatoms selected from nitrogen, oxygen, and sulfur.

[00171] In some embodiments, each occurrence of R^{2c} is independently a group selected from C_1-C_6 aliphatic, C_1-C_6 haloaliphatic, 3- to 10-membered cycloaliphatic, 4- to 10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

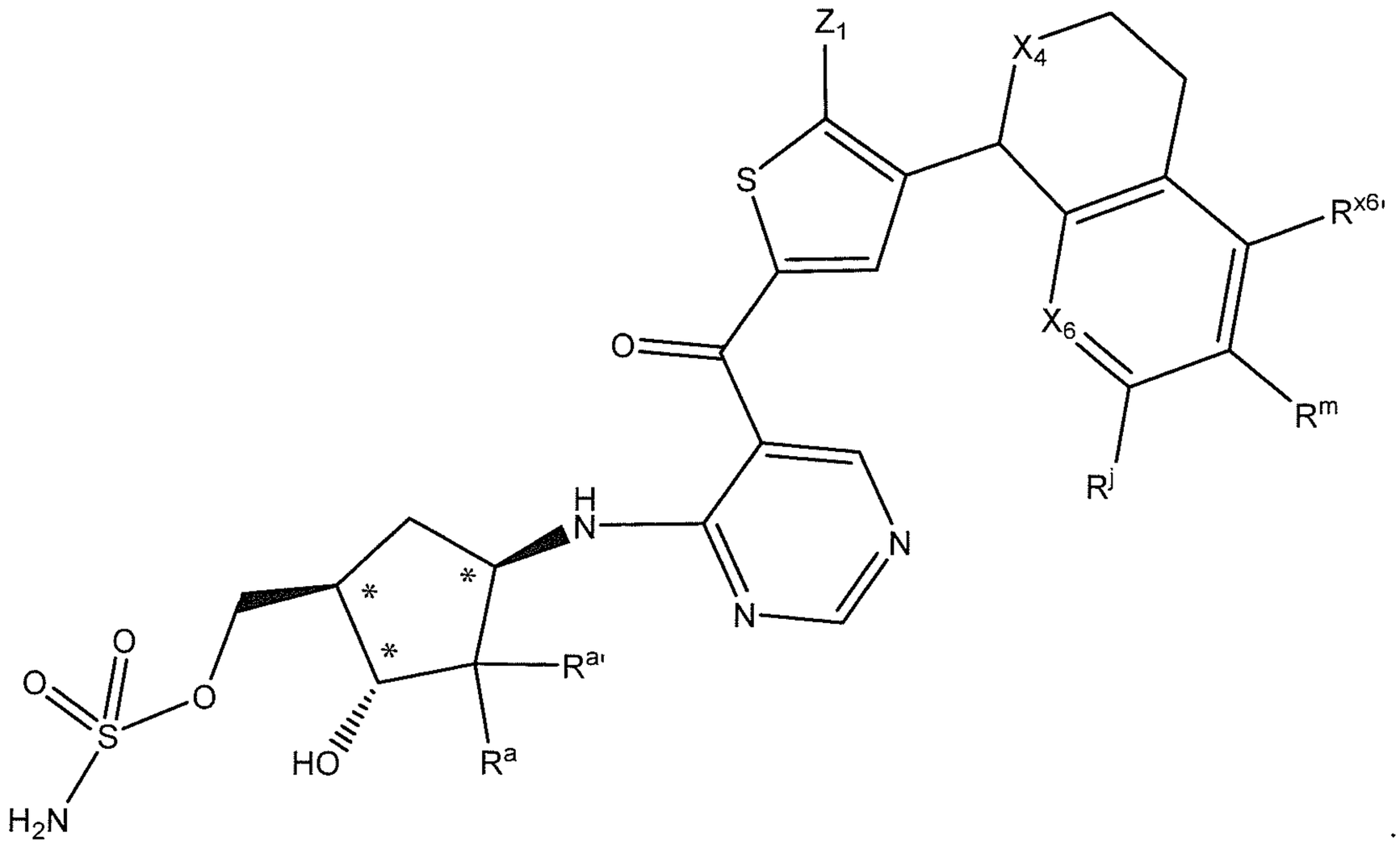
[00172] In some embodiments, each occurrence of R^{2d} is independently hydrogen or a group selected from 3- to 10-membered cycloaliphatic, 4- to 10-membered heterocyclyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur, 6- to 10-membered aryl, or 5- to 10-membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00173] In some embodiments, each occurrence of R^{2e} is independently hydrogen or a C_{1-6} aliphatic group.

[00174] In some embodiments, each occurrence of V_2 is independently $-N(R^{2e})-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{2e})-$, $-S(O)_2N(R^{2e})-$, $-OC(O)N(R^{2e})-$, $-N(R^{2e})C(O)-$, $-N(R^{2e})SO_2-$, $-N(R^{2e})C(O)O-$, $-N(R^{2e})C(O)N(R^{2e})-$, $-N(R^{2e})SO_2N(R^{2e})-$, $-OC(O)-$, or $-C(O)N(R^{2e})-O-$, wherein R^{2e} has the values described herein.

[00175] In some embodiments, each occurrence of T_3 is a C_{1-6} alkylene chain wherein the alkylene chain optionally is interrupted by $-N(R^4)-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-OC(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)SO_2-$, $-N(R^4)C(O)O-$, $-N(R^4)C(O)N(R^4)-$, $-N(R^4)S(O)_2N(R^4)-$, $-OC(O)-$, or $-C(O)N(R^4)-O-$ or wherein T_3 or a portion thereof optionally forms part of a 3- to 7-membered cycloaliphatic or 4- to 7-membered heterocyclyl, wherein R^4 is hydrogen or a C_{1-4} aliphatic group.

[00176] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***X-a***):



;

(*X-a*)

or a pharmaceutically acceptable salt thereof;

wherein:

stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry;

R^a is hydrogen and $R^{a'}$ is hydrogen; R^a is hydrogen and $R^{a'}$ is fluoro; R^a is fluoro and $R^{a'}$ is fluoro; or R^a is OH and $R^{a'}$ is hydrogen;

Z_1 is hydrogen, halogen, cyano, R^{z3}, -S-R^{z3}, -S(O)-R^{z3}, or -$S(O)_2$-R^{z3};

R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which may be substituted with one or more independently selected R^{z4};

R^{z4} is hydroxyl, halogen, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -$N(R^{z5})_2$, -$C(O)R^{z6}$, -$C(O)_2R^{z5}$, 5- or 6-membered cycloaliphatic or heterocyclyl, or a phenyl optionally substituted with one or more independently selected halogens;

each R^{z5} is independently hydrogen or C_{1-4} alkyl;

R^{z6} is C_{1-4} alkyl;

X_4 is O or $N(R^{n4})$;

R^{n4} is hydrogen or C_{1-4} alkyl;

X_6 is N or $C(R^{x6})$;

each of R^{x6}, $R^{x6'}$, R^j and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -$N(R^{z7})_2$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -CH_2-OR^{z7}, -CH_2NR^{z7}, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein at least one of R^{x6}, $R^{x6'}$, R^j and R^m is hydrogen; and

each R^{z7} is independently hydrogen or C_{1-4} alkyl.

[00177] In some such embodiments described directly above:

Z_1 is hydrogen, halogen, cyano, or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, C_{1-4} alkoxy, $-N(R^{z5})_2$, or phenyl optionally substituted with one more independently selected halogens;

X_4 is O or N(H);

X_6 is N or C(H);

$R^{x6'}$ is hydrogen;

R^m is hydrogen, fluoro or chloro; and

R^j is methyl, ethyl, isopropyl, hydrogen, fluoro, chloro, bromo, cyclopropyl, -C≡CH or $-CF_3$.

[00178] In some embodiments, the chemical entity of formula (***I***) is:

[(1R,2S,4R)-4-{[5-({4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

or a pharmaceutically acceptable salt thereof.

[00179] In some embodiments, the chemical entity of formula (***I***) is:

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

or a pharmaceutically acceptable salt thereof.

[00180] In some embodiments, a chemical entity is provided which is

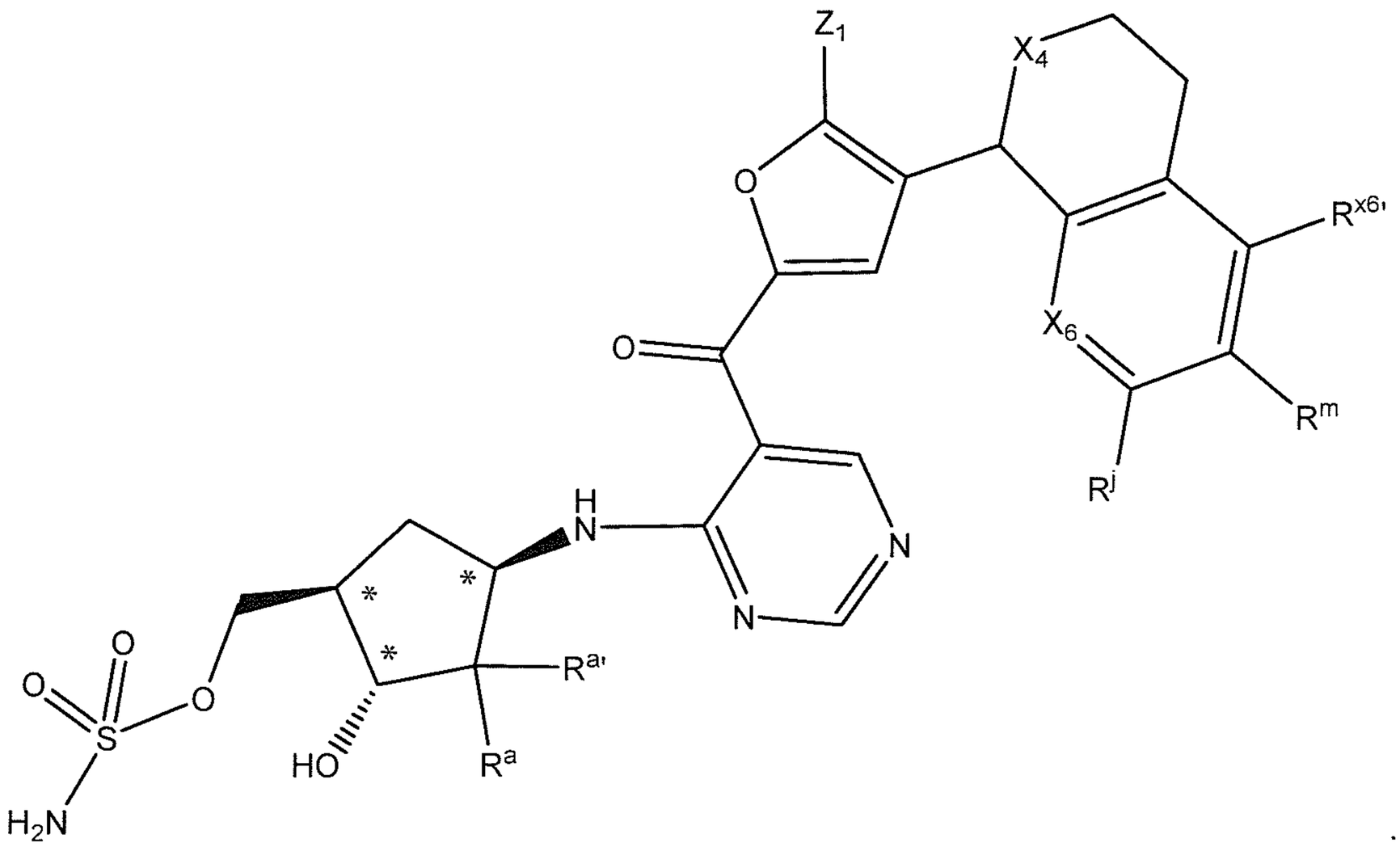
I-16a	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-18b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-22b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-248a	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-24a	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
I-251a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-252b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-253a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-

	yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-254b	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-255b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-256b	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-Dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-257b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-Chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-258a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
I-259a	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
I-261b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-263a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-264b	[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2R,3R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;
I-266b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-268b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

I-269a	[(1R,2S,4R)-4-{[5-({4-[(7S)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(7R)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-270b	{(1R,2S,4R)-4-[(5-{4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
I-271a	[(1R,2R,3R,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2R,3R,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;
I-277a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-282b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-285a	[(1R,2S,4R)-4-{[5-({4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-6a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-9a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

or a pharmaceutically acceptable salt thereof.

[00181] In some embodiments, the chemical entity of formula (***I***) is represented by formula (***X-b***):



(***X-b***)

or a pharmaceutically acceptable salt thereof;

wherein:

stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry;

R^a is hydrogen and $R^{a'}$ is hydrogen; R^a is hydrogen and $R^{a'}$ is fluoro; R^a is fluoro and $R^{a'}$ is fluoro; or R^a is OH and $R^{a'}$ is hydrogen;

Z_1 is hydrogen, halogen, cyano, R^{z3}, -S-R^{z3}, -S(O)-R^{z3}, or -$S(O)_2$-R^{z3};

R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which may be substituted with one or more independently selected R^{z4};

R^{z4} is hydroxyl, halogen, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -$N(R^{z5})_2$, -$C(O)R^{z6}$, -$C(O)_2R^{z5}$, 5- or 6-membered cycloaliphatic or heterocyclyl, or a phenyl optionally substituted with one or more independently selected halogens;

each R^{z5} is independently hydrogen or C_{1-4} alkyl;

R^{z6} is C_{1-4} alkyl;

X_4 is O or $N(R^{n4})$;

R^{n4} is hydrogen or C_{1-4} alkyl;

X_6 is N or $C(R^{x6})$;

each of R^{x6}, $R^{x6'}$, R^j and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -$N(R^{z7})_2$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -

CH_2-OR^{z7}, -$CH_2N(R^{z7})_2$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl, wherein at least one of R^{x6}, $R^{x6'}$, R^j and R^m is hydrogen; and

each R^{z7} is independently hydrogen or C_{1-4} alkyl.

[00182] In some such embodiments described directly above:

Z_1 is hydrogen, halogen, cyano, or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, C_{1-4} alkoxy, -$N(R^{z5})_2$, or phenyl optionally substituted with one more independently selected halogens;

X_4 is O or N(H);

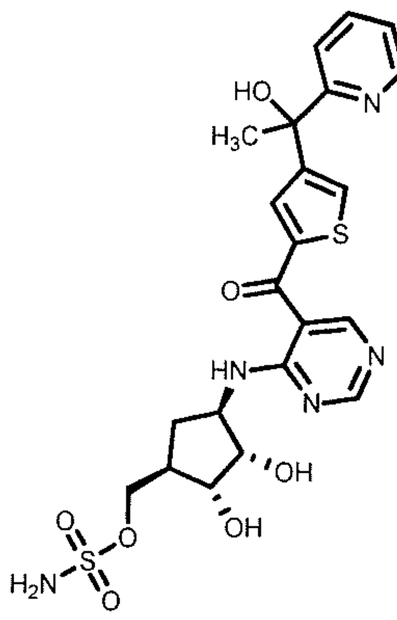
X_6 is N or C(H);

$R^{x6'}$ is hydrogen;

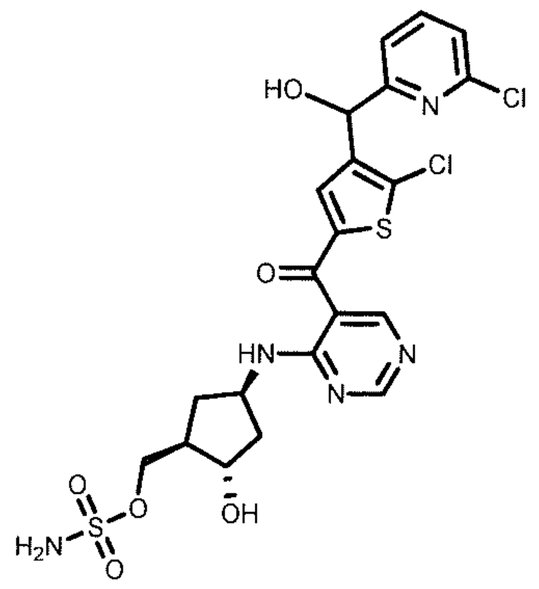
R^m is hydrogen, fluoro or chloro; and

R^j is methyl, ethyl, isopropyl, hydrogen, fluoro, chloro, bromo, cyclopropyl, -C≡CH or -CF_3.

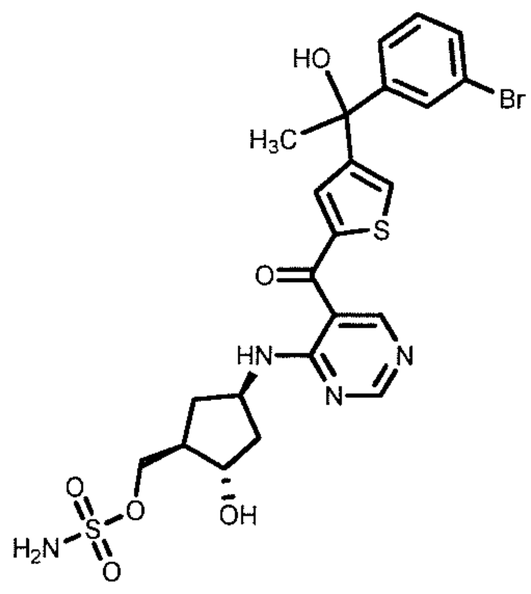
[00183] Representative examples of the chemical entities of formula (***I***) are shown below in Table 1.



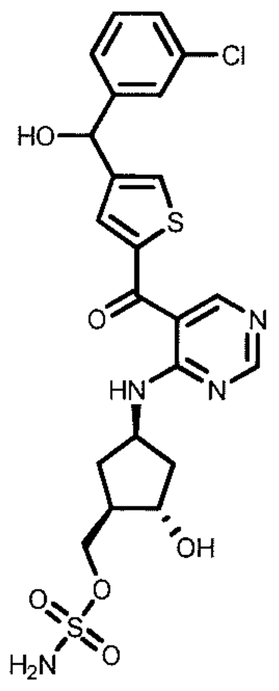
I-1
I-1a
I-1b



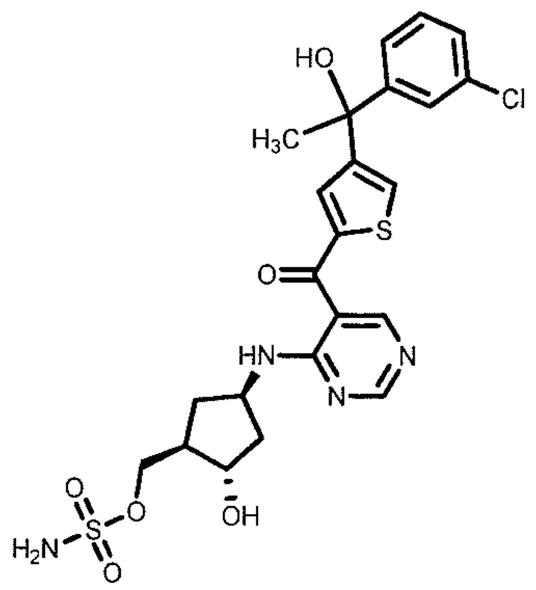
I-2
I-2a
I-2b



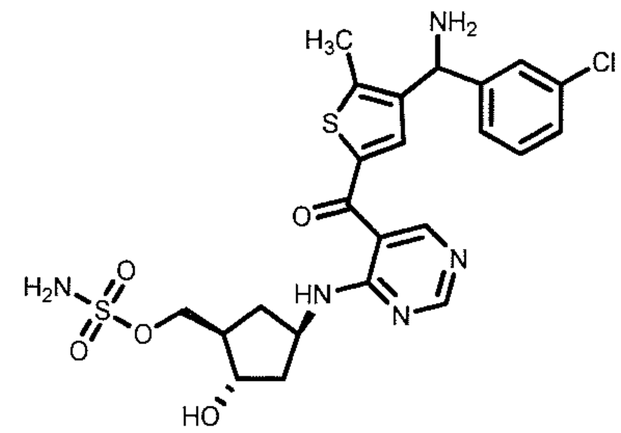
I-3
I-3a
I-3b



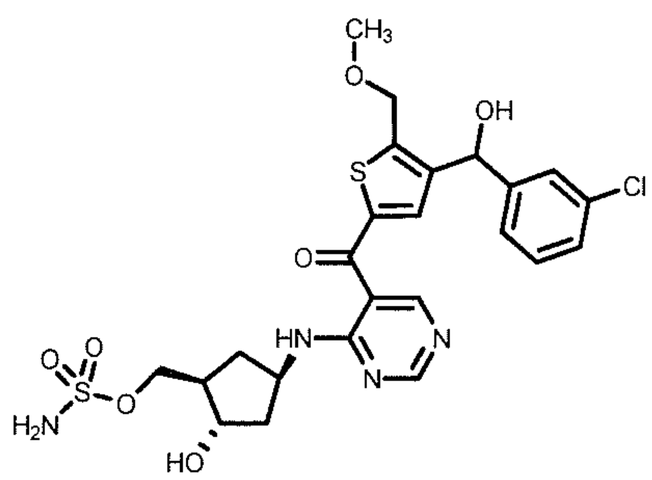
I-4
I-4a
I-4b



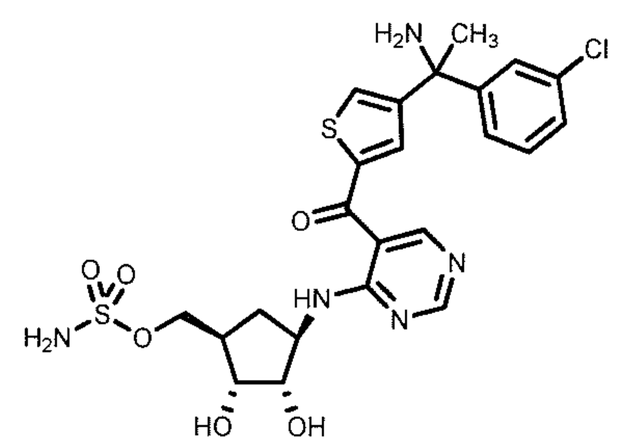
I-5
I-5a
I-5b



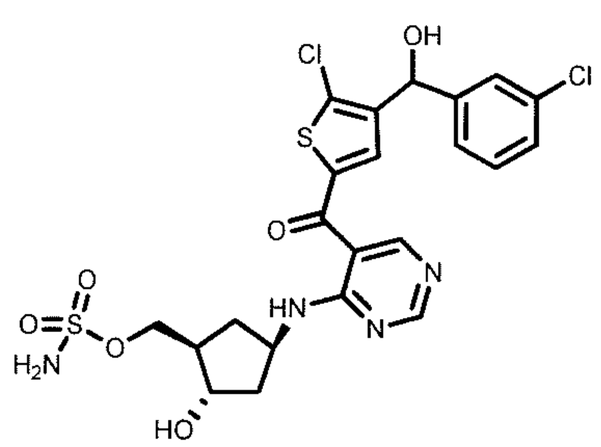
I-6
I-6a
I-6b



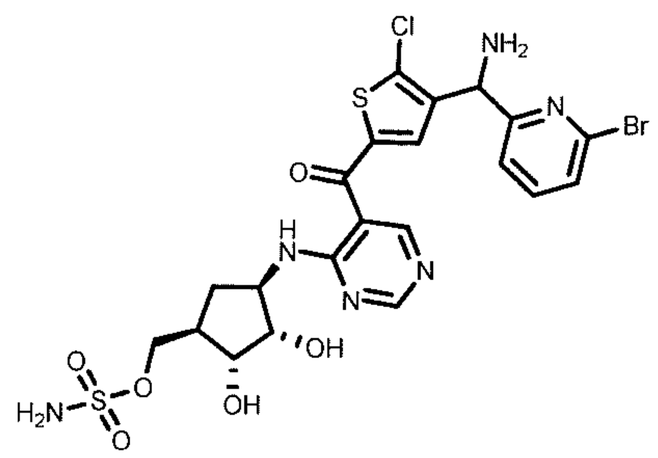
I-7
I-7a
I-7b



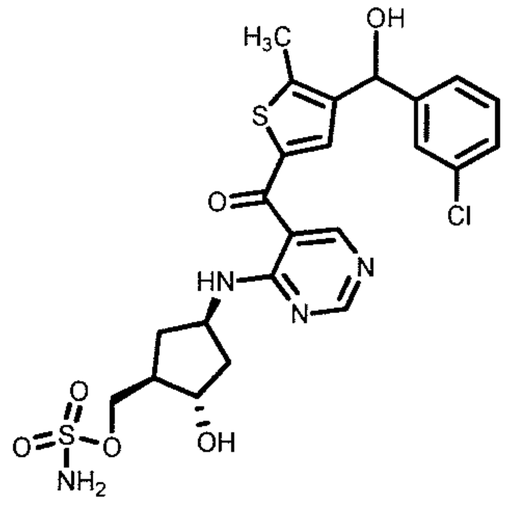
I-8
I-8a
I-8b

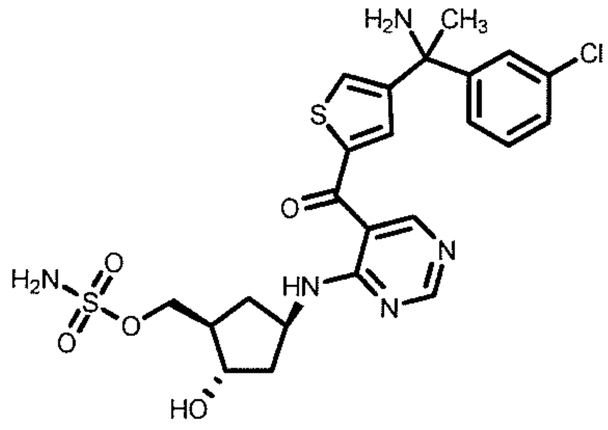


I-9
I-9a
I-9b

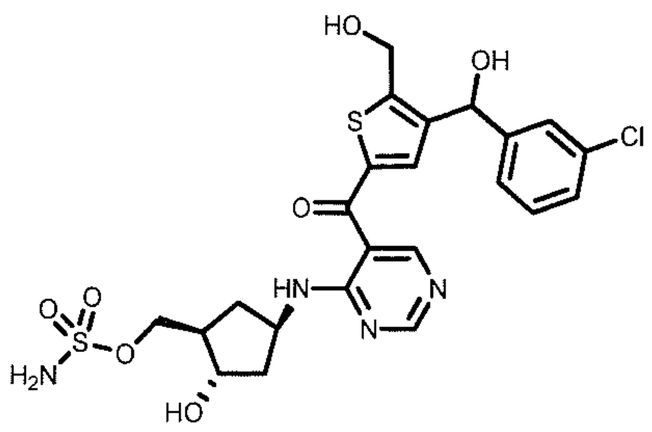


I-10
I-10a
I-10b



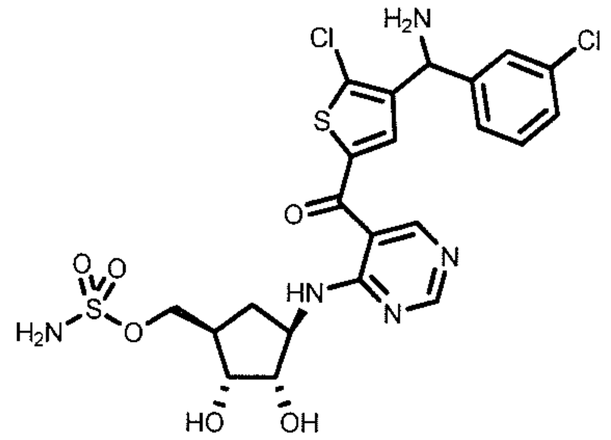


I-11
I-11a
I-11b

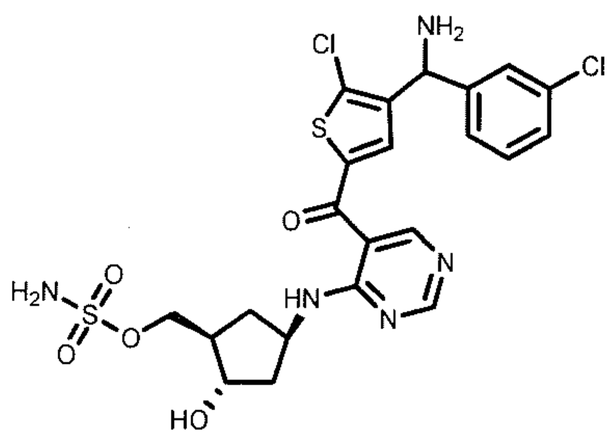


I-13

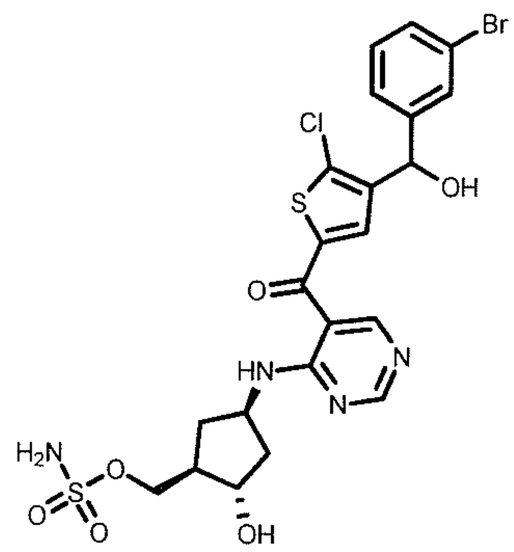
I-12
I-12a
I-12b



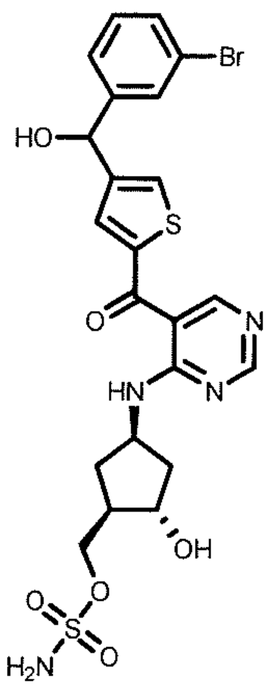
I-14a
I-14b



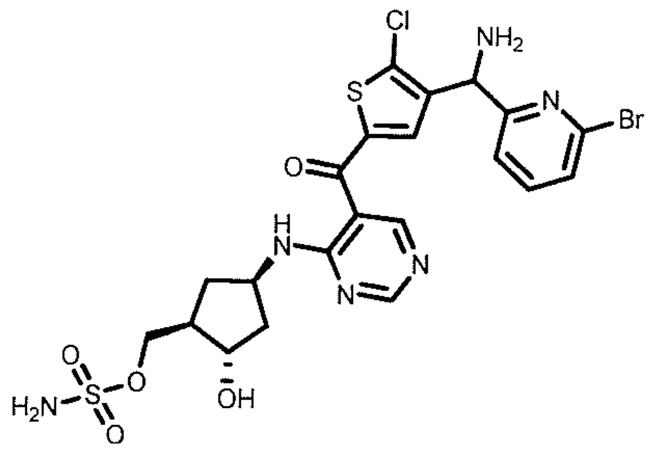
I-15
I-15a
I-15b



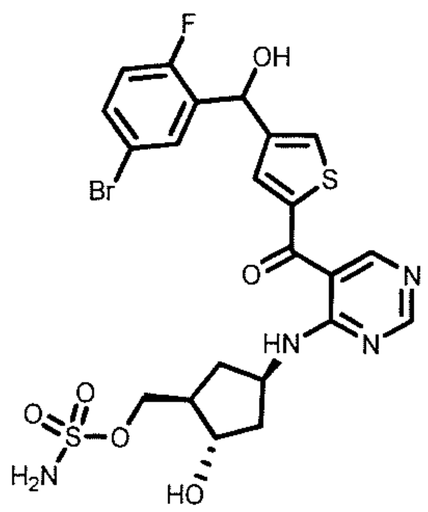
I-16a
I-16b



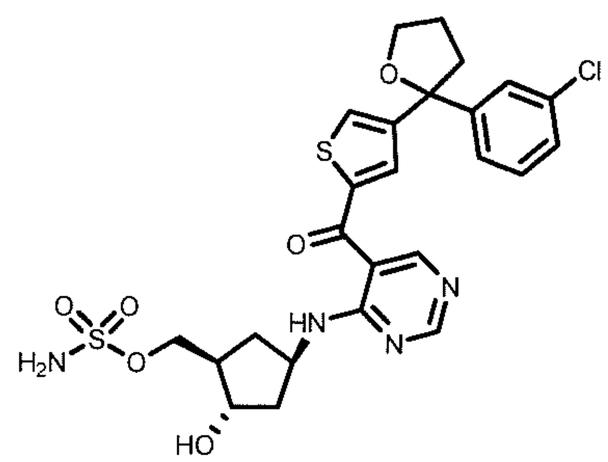
I-17



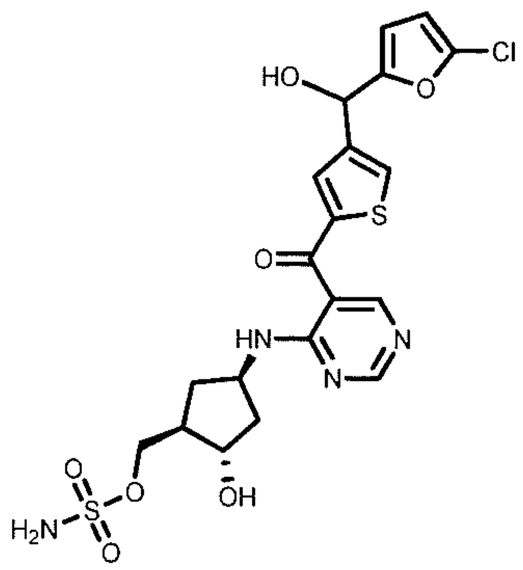
I-18
I-18a
I-18b



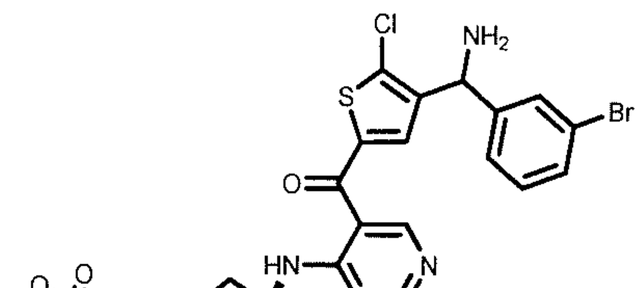
I-19
I-19a
I-19b



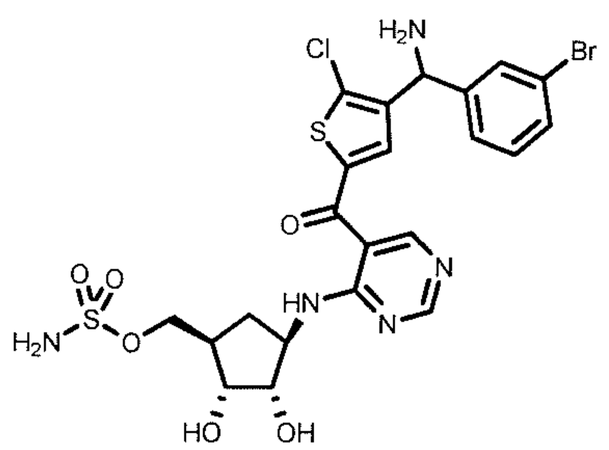
I-20a
I-20b



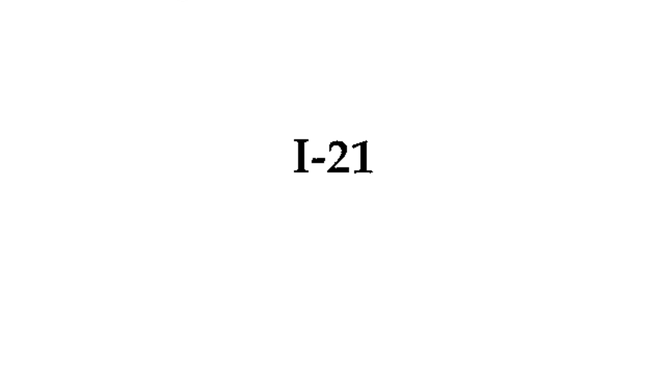
I-21



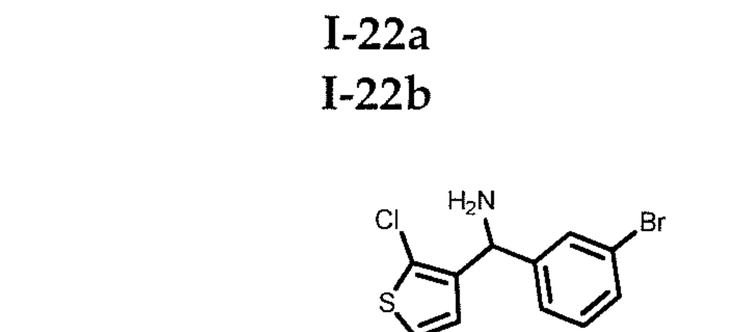
I-22
I-22a
I-22b



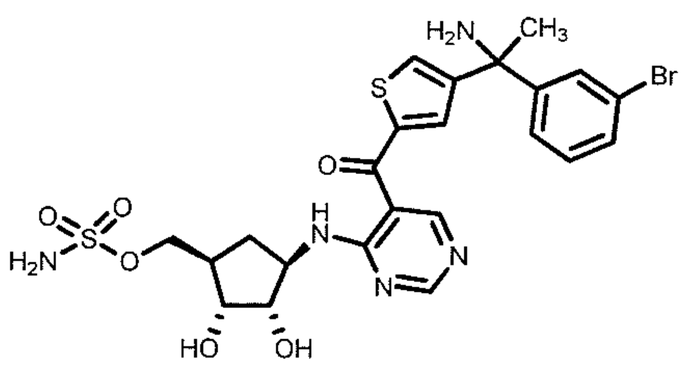
I-24a
I-24b



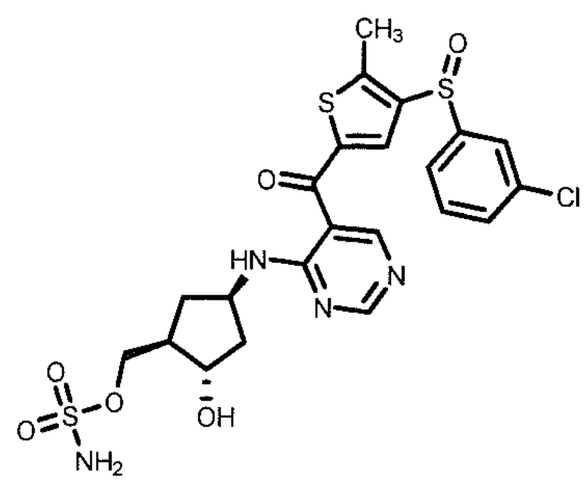
I-25
I-25a
I-25b



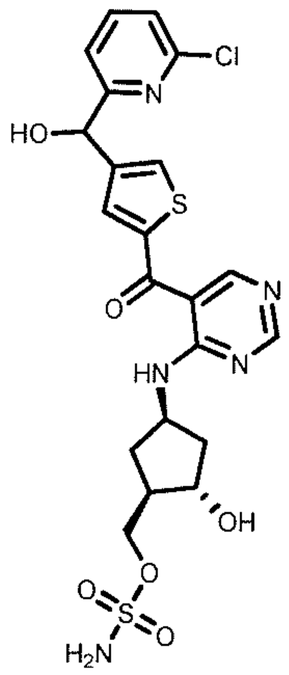
I-26



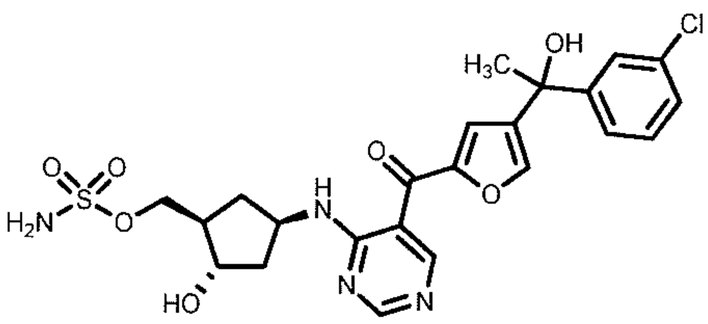
I-27a
I-27b



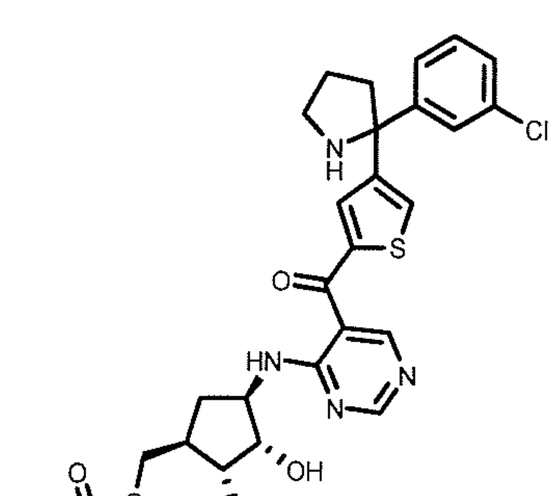
I-28
I-28a
I-28b



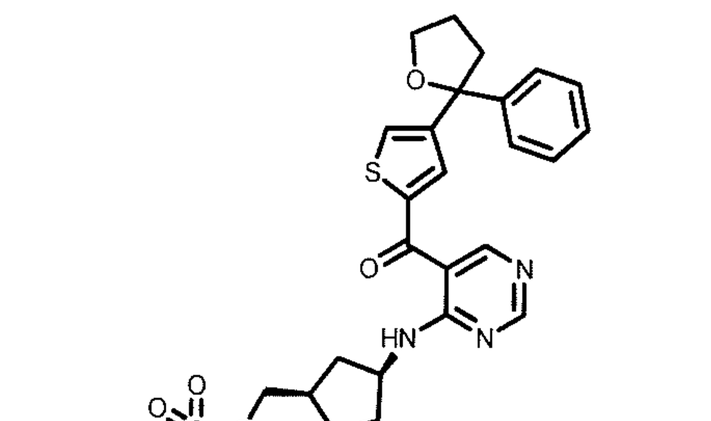
I-29
I-29a
I-29b



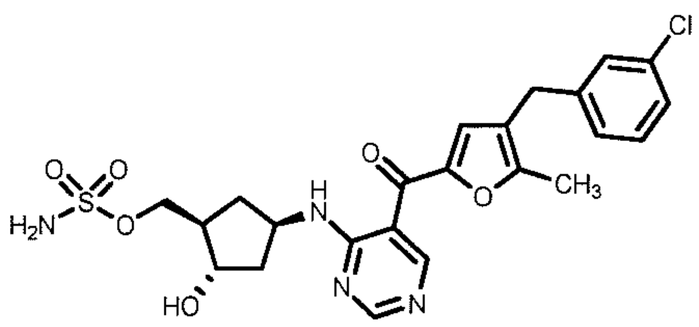
I-30
I-30a
I-30b



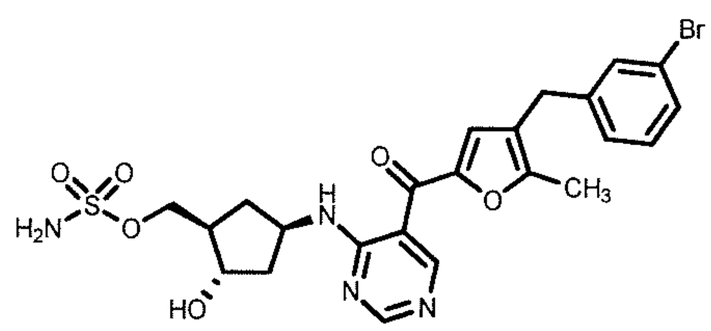
I-31



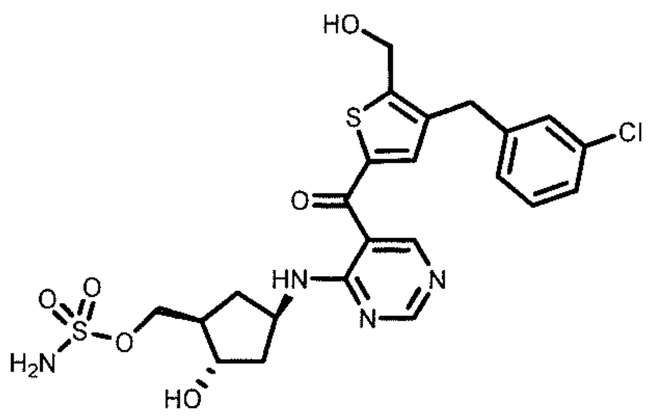
I-32
I-32a
I-32b



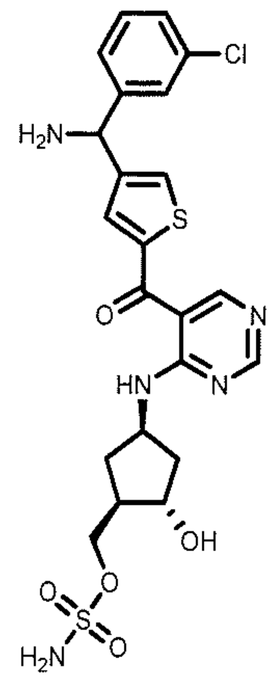
I-33



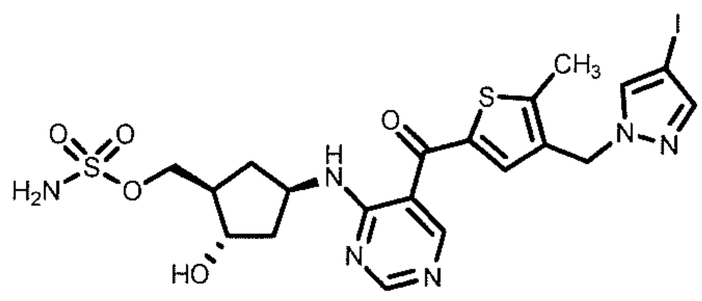
I-34



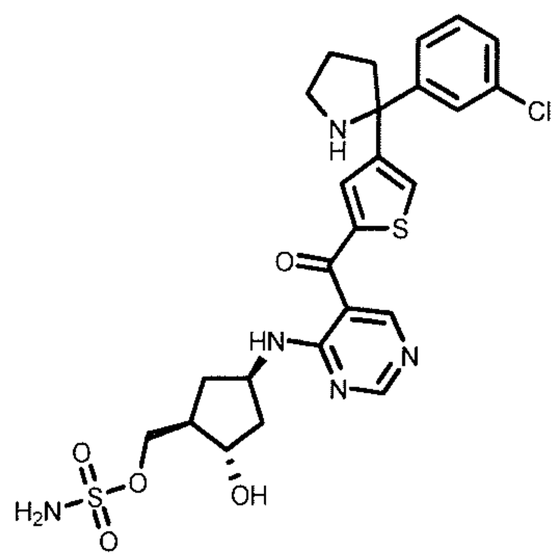
I-35



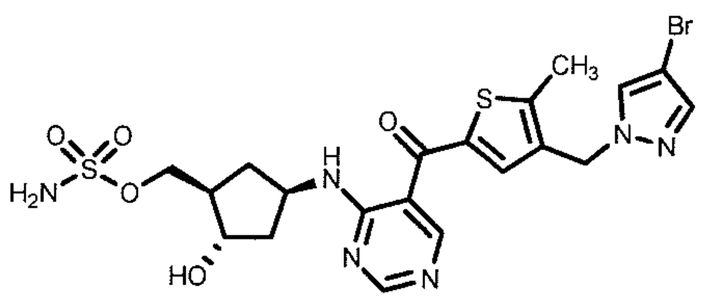
I-36
I-36a
I-36b



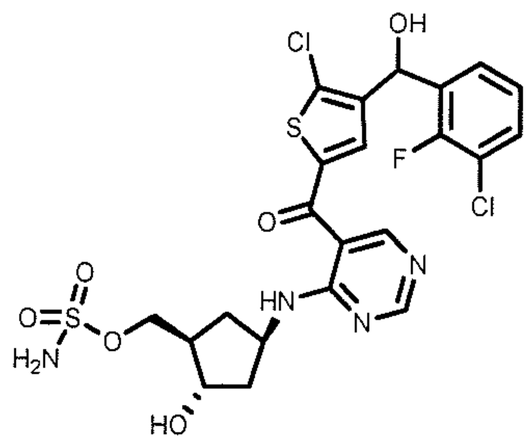
I-37



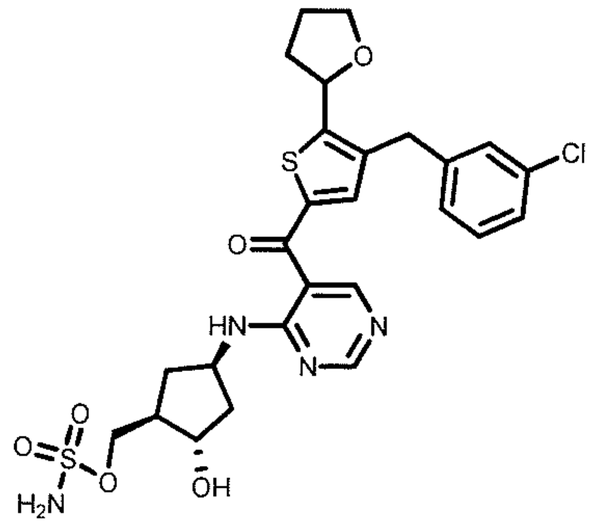
I-38
I-38a
I-38b



I-39



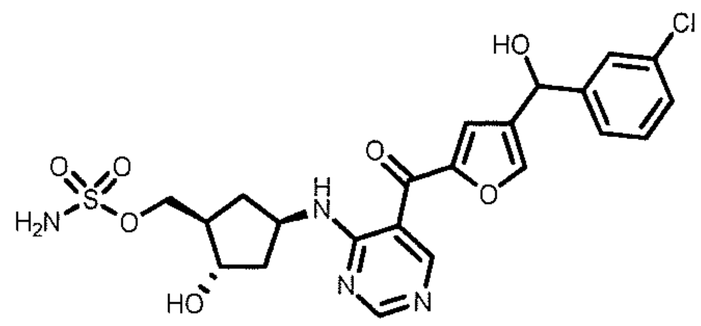
I-40



I-41

I-41a

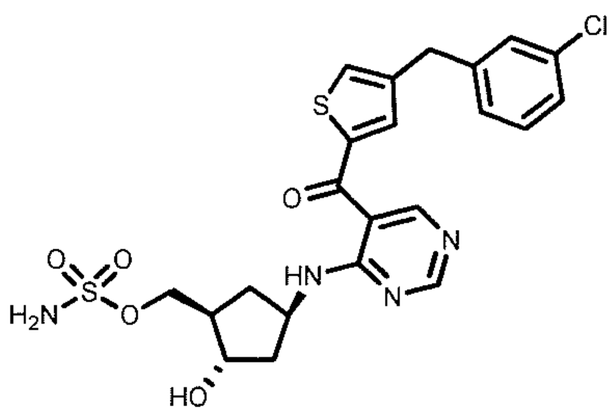
I-41b



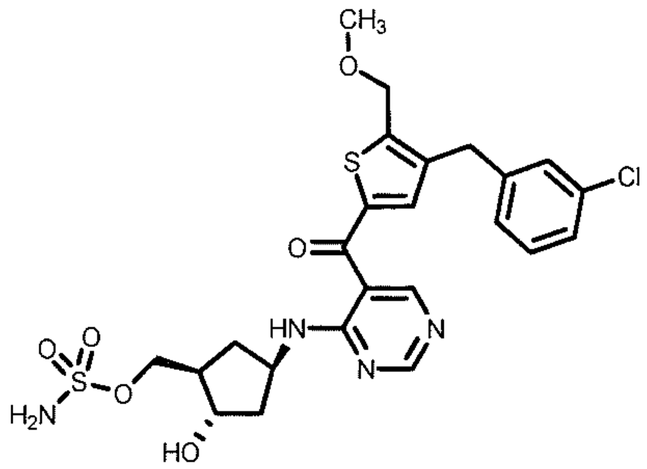
I-42

I-42a

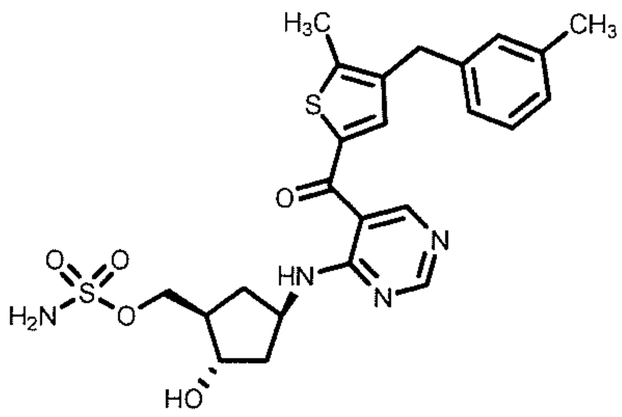
I-42b



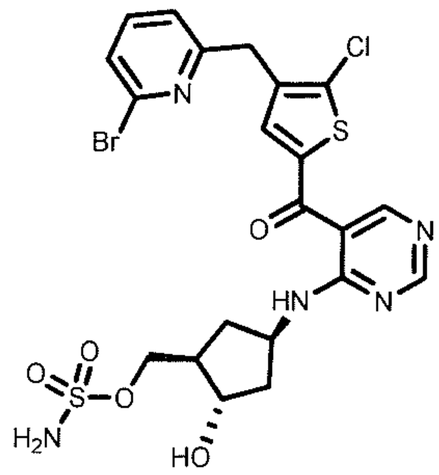
I-43



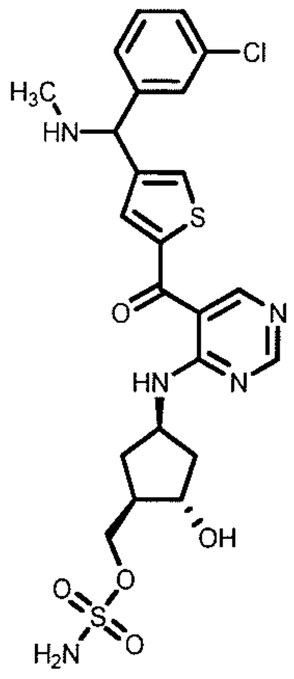
I-44



I-45



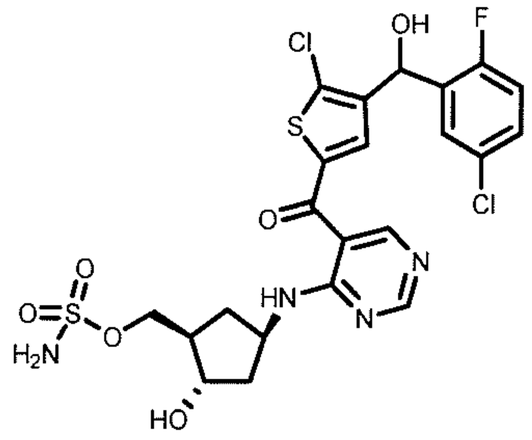
I-46



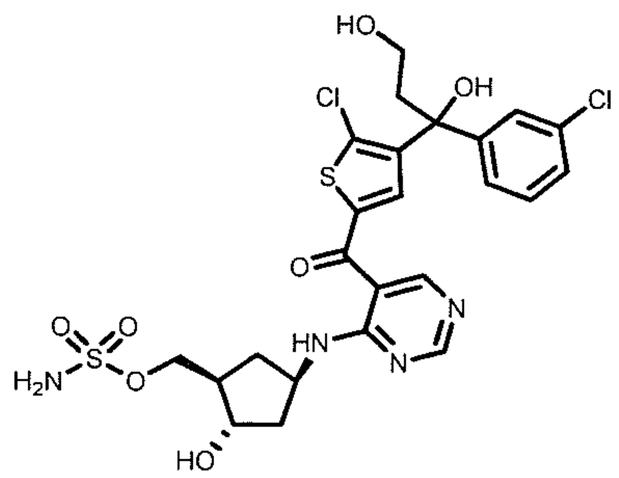
I-47

I-47a

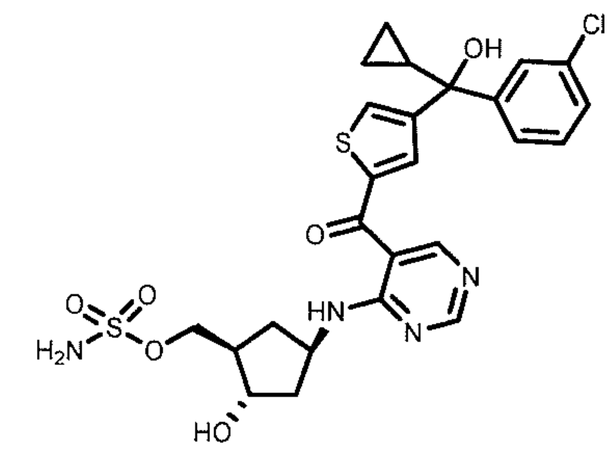
I-47b



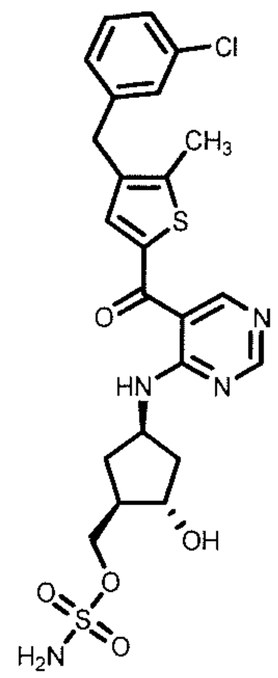
I-48



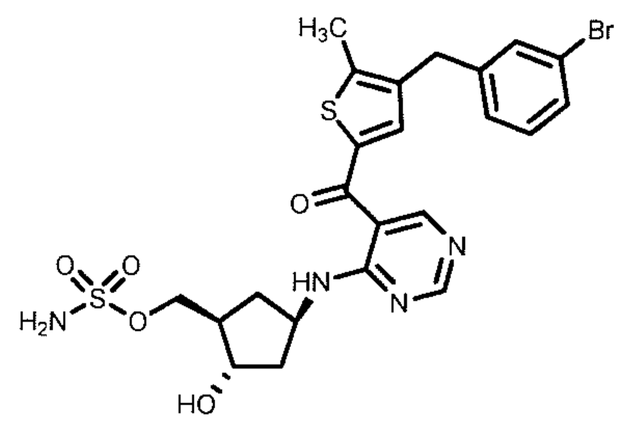
I-49



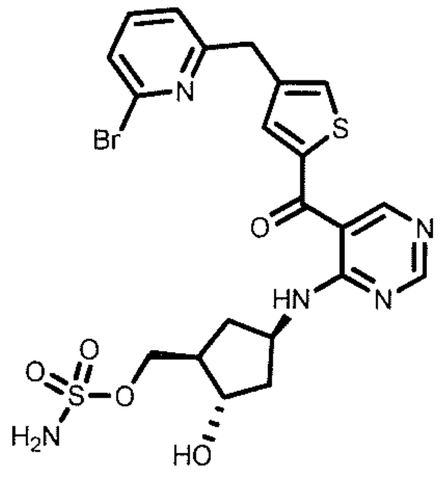
I-50



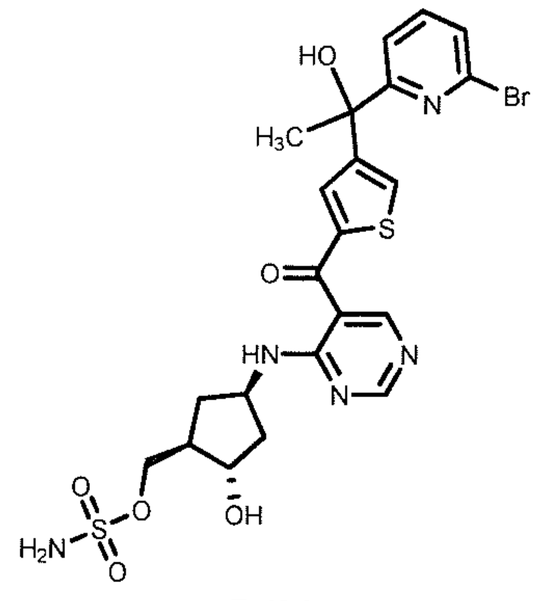
I-51



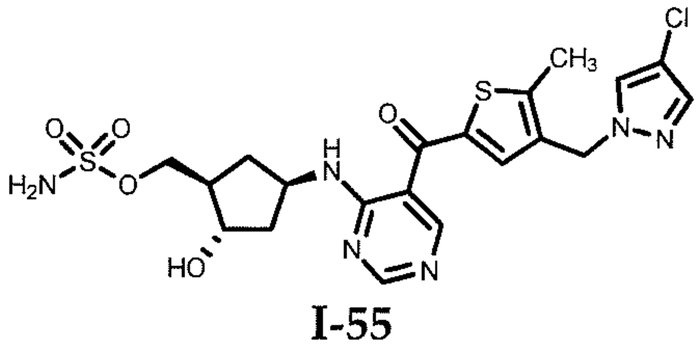
I-52



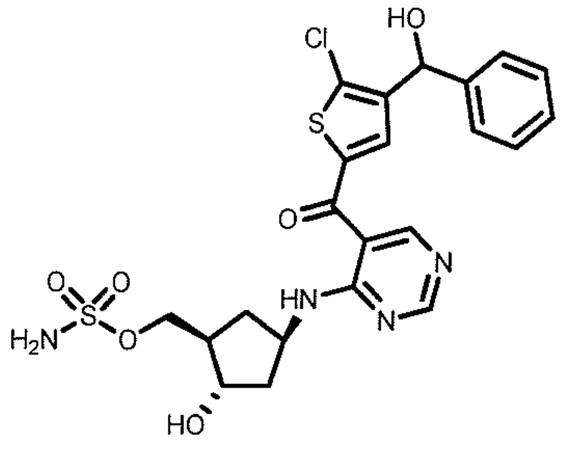
I-53



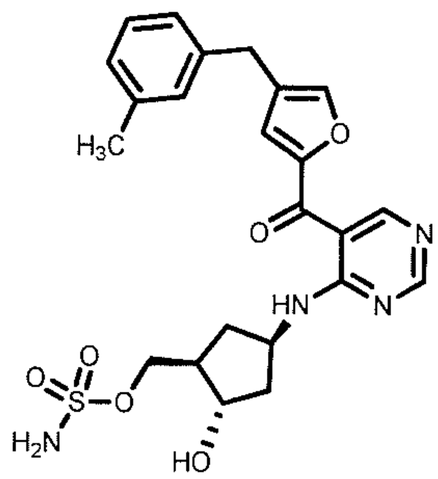
I-54



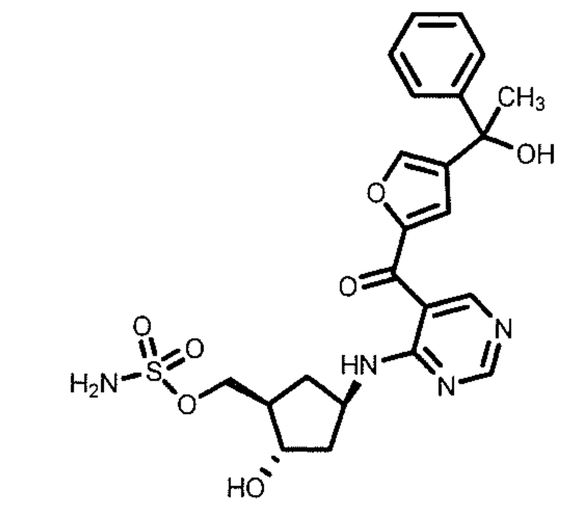
I-55



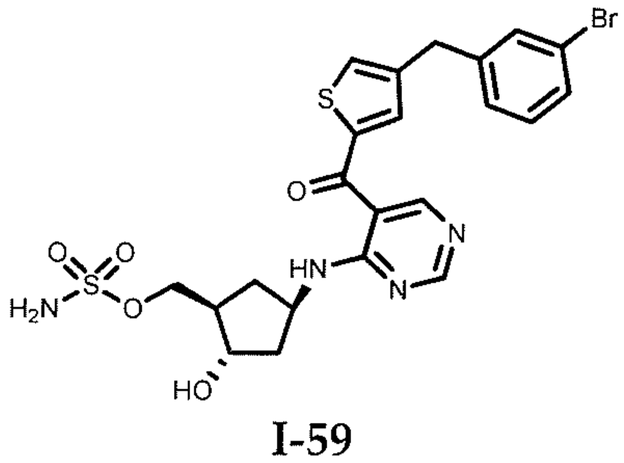
I-56



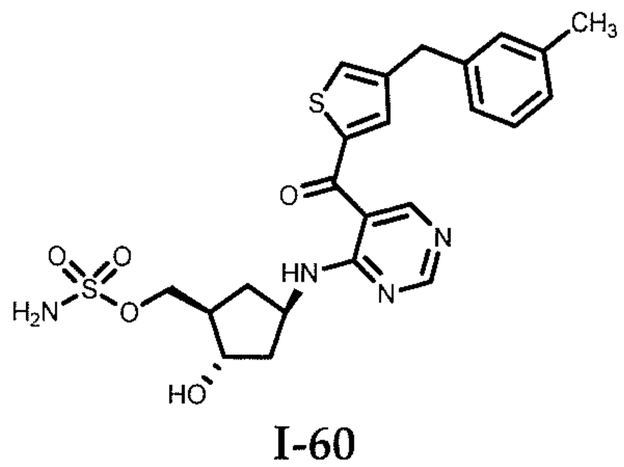
I-57



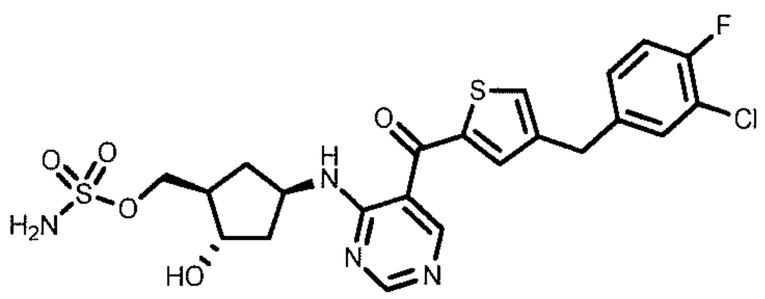
I-58
I-58a
I-58b



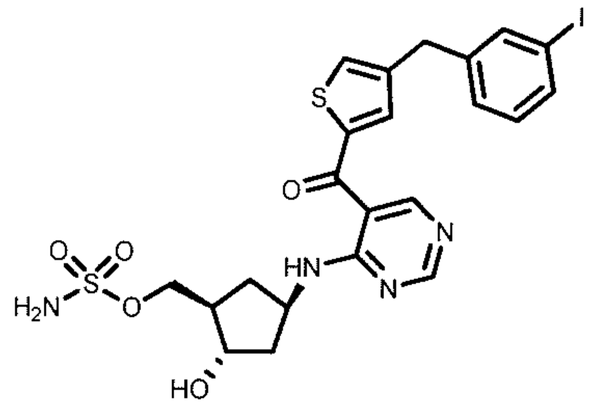
I-59



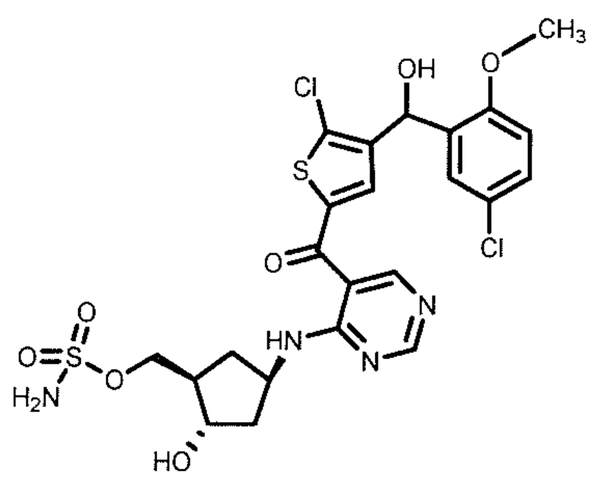
I-60



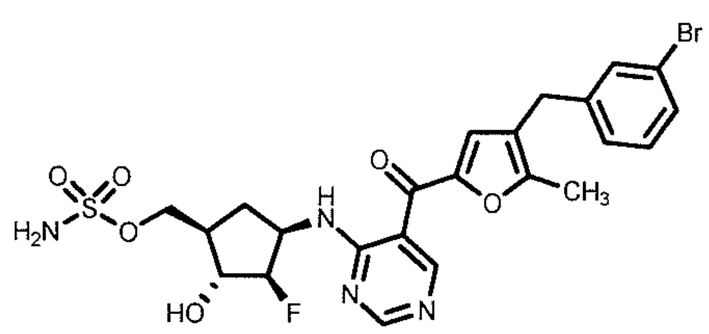
I-61



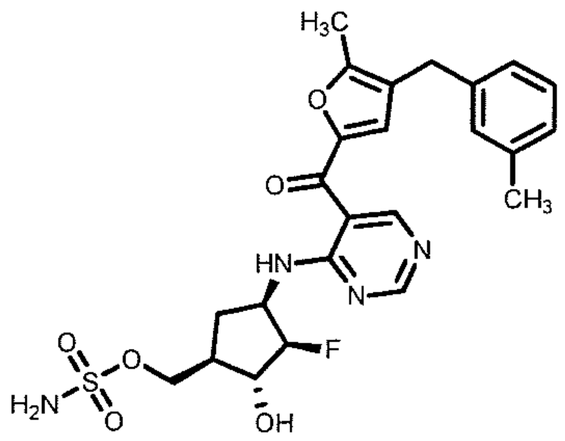
I-62



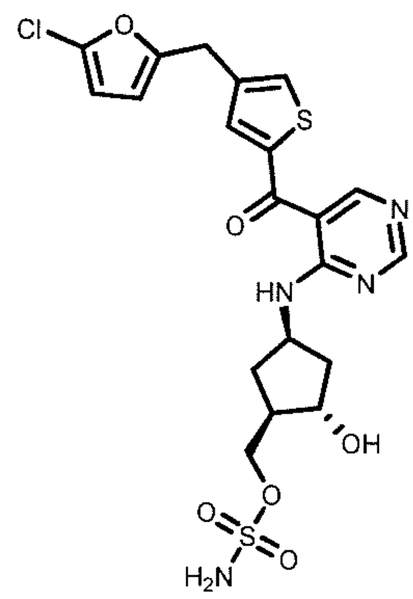
I-63



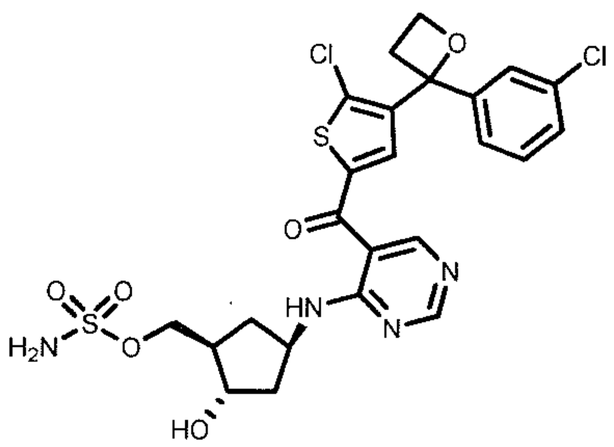
I-64



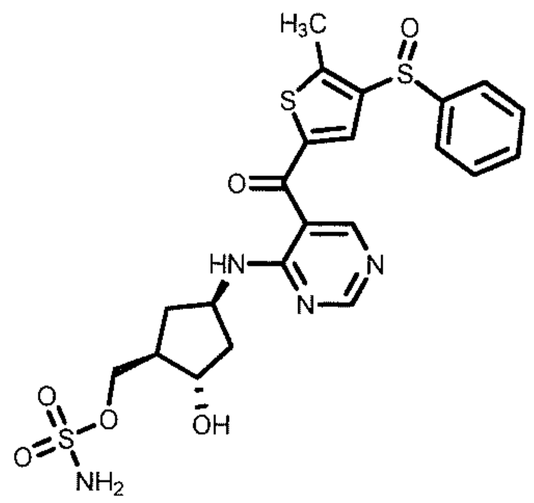
I-65



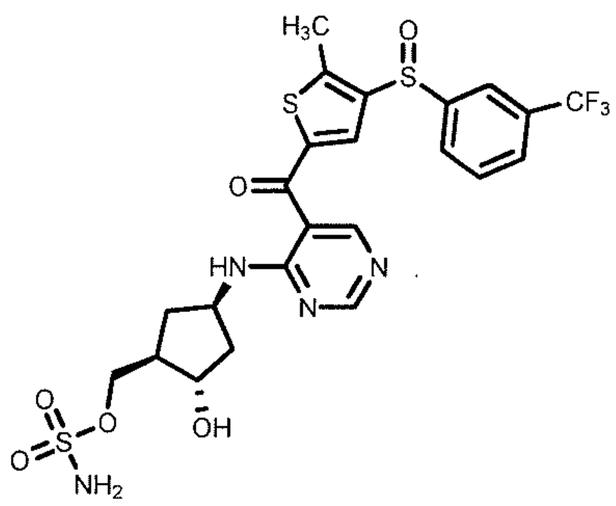
I-66



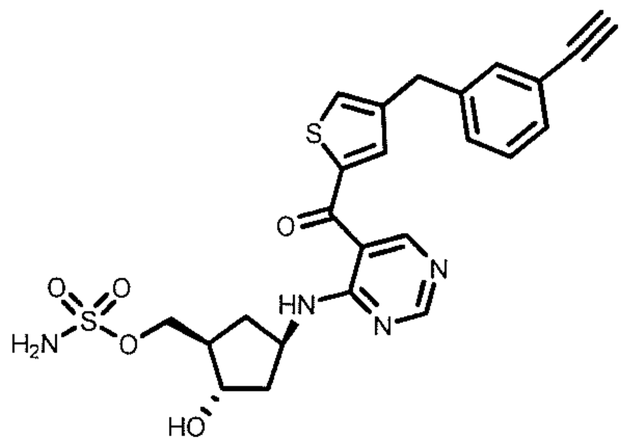
I-67



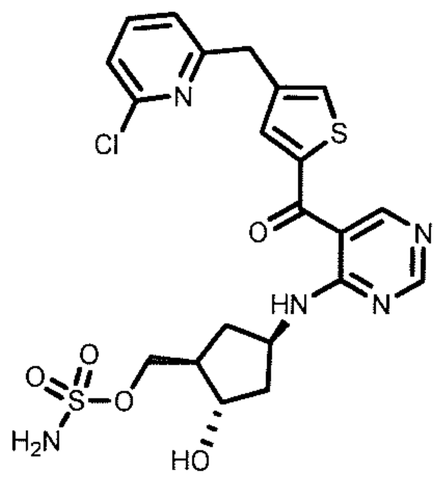
I-68



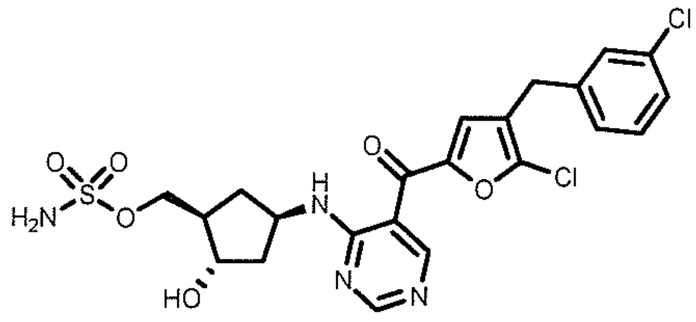
I-69



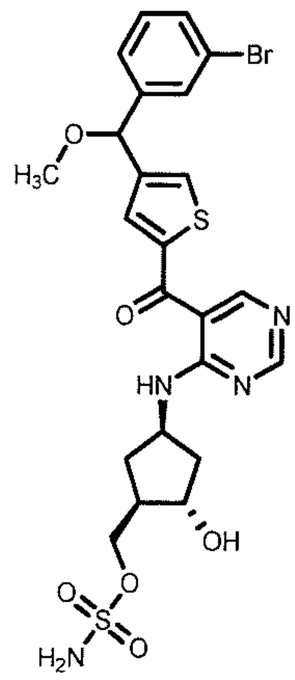
I-70



I-71

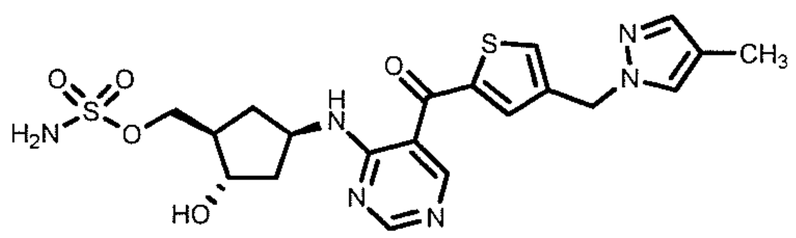


I-72

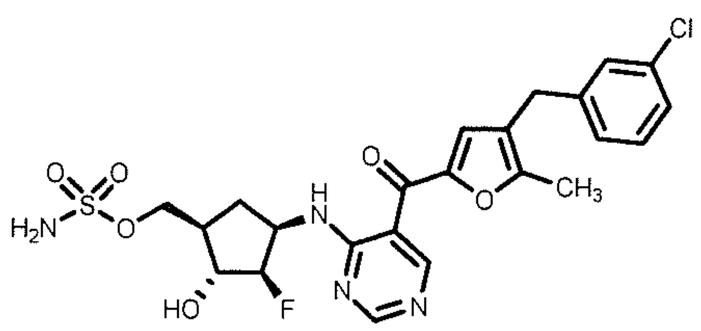


I-73a

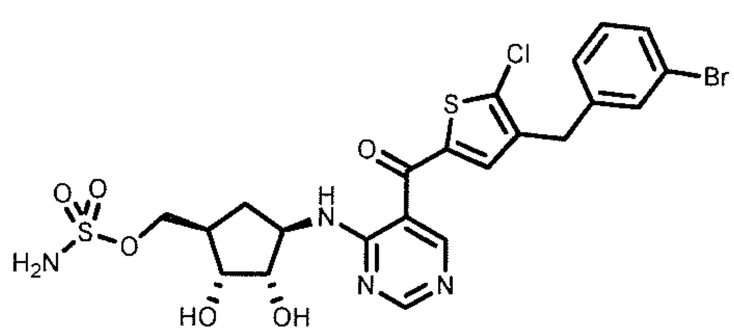
I-73b



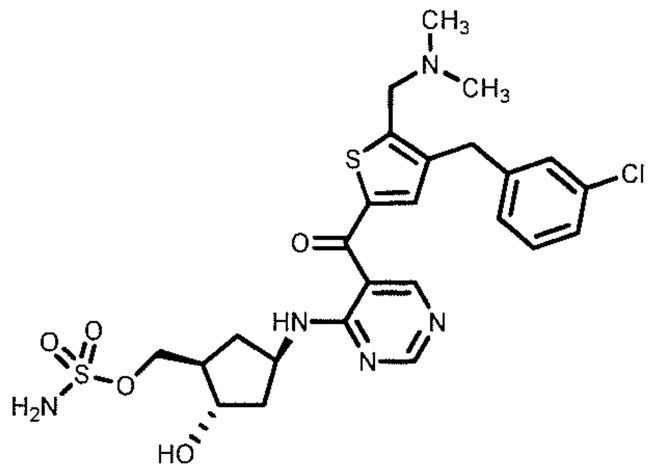
I-74



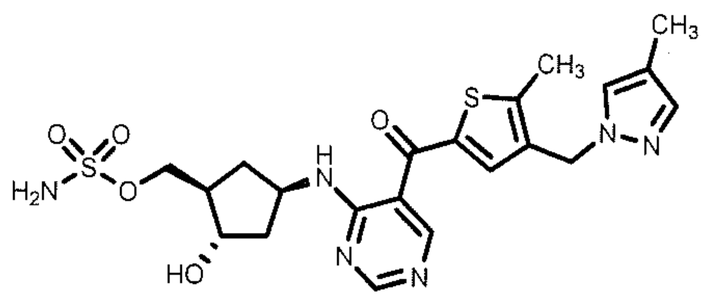
I-75



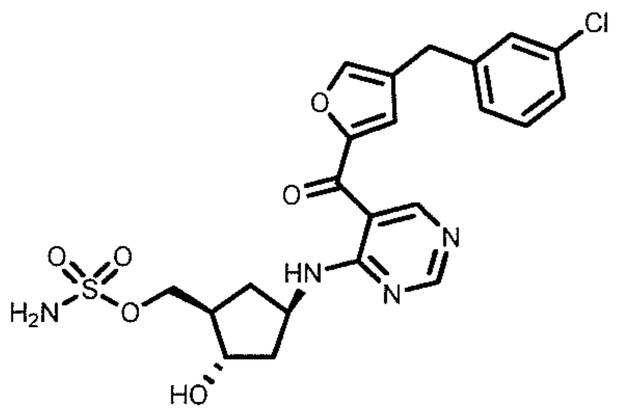
I-76



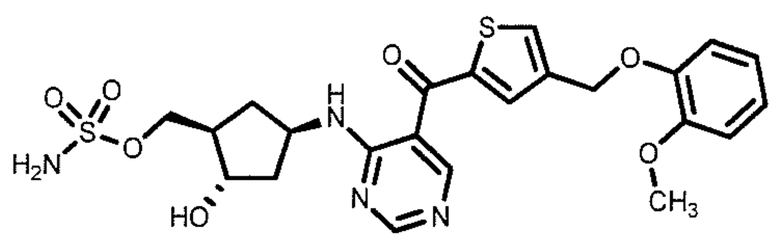
I-77



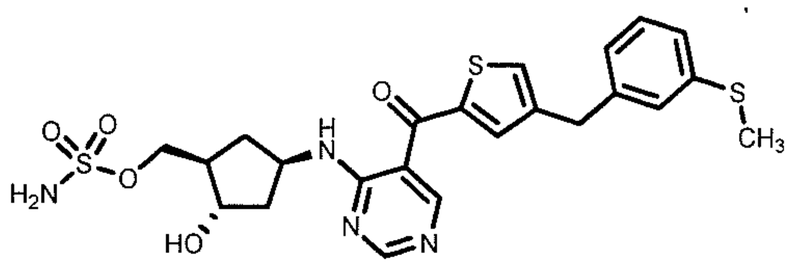
I-78



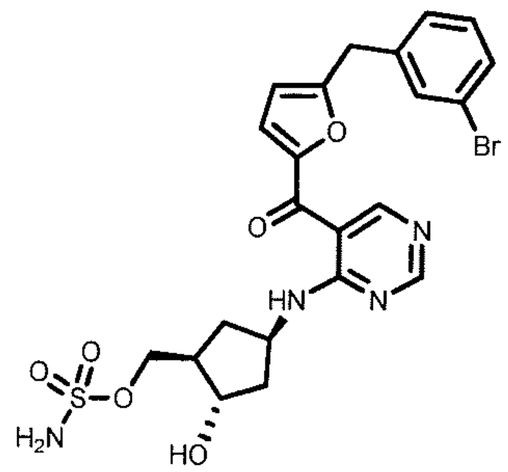
I-79



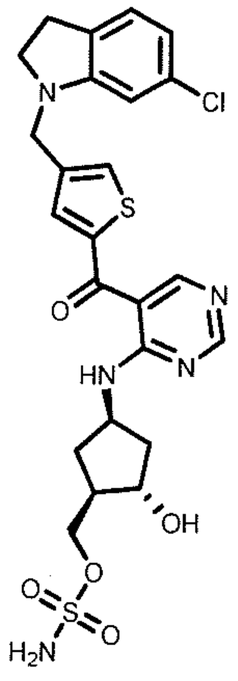
I-80



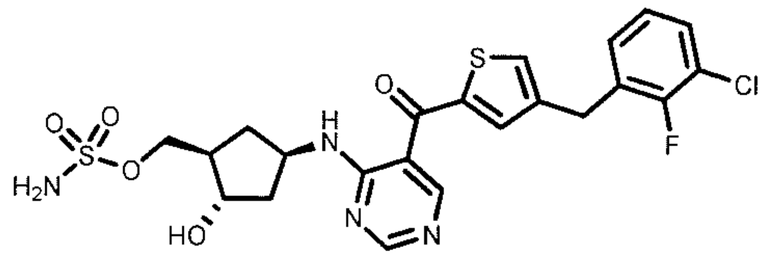
I-81



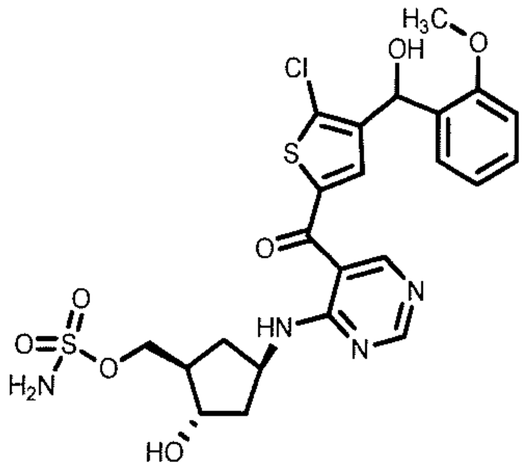
I-82



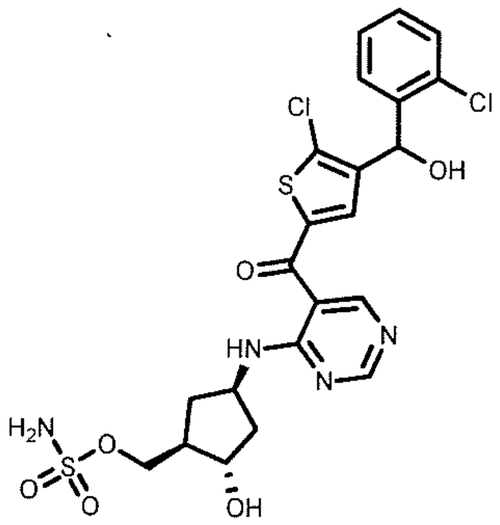
I-83



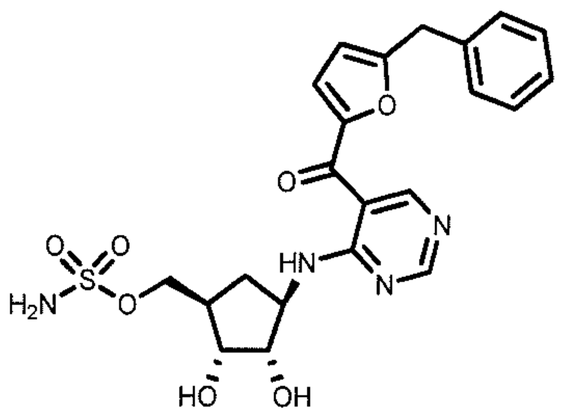
I-84



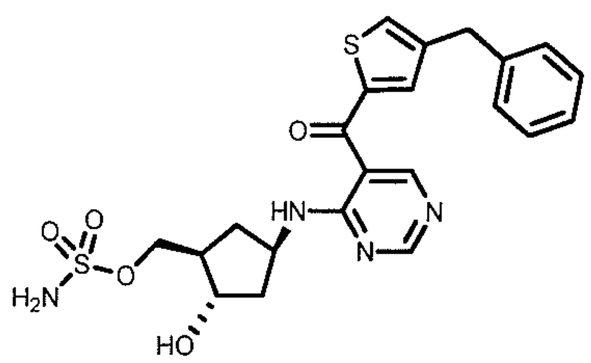
I-85



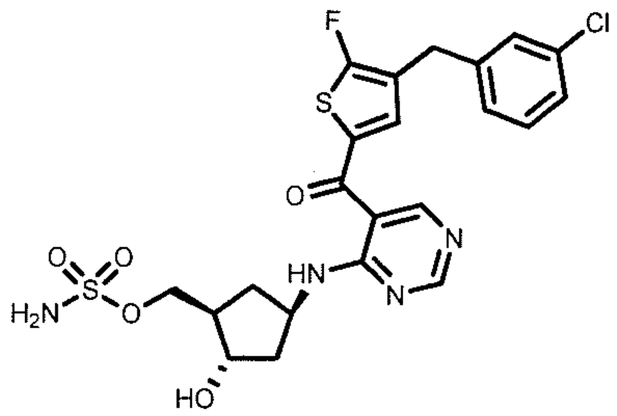
I-86



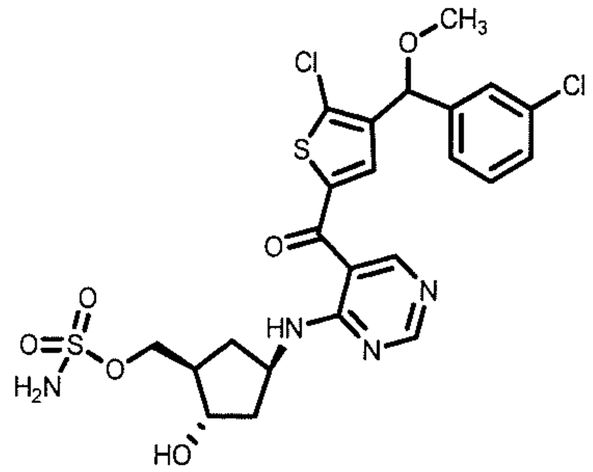
I-87



I-88



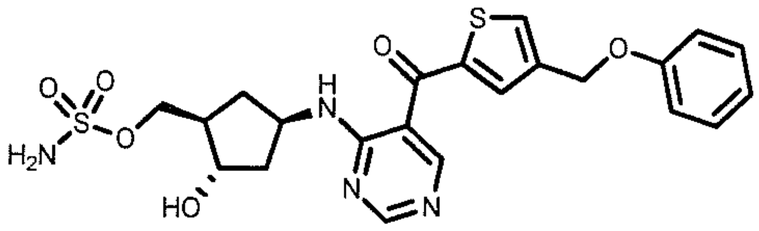
I-89



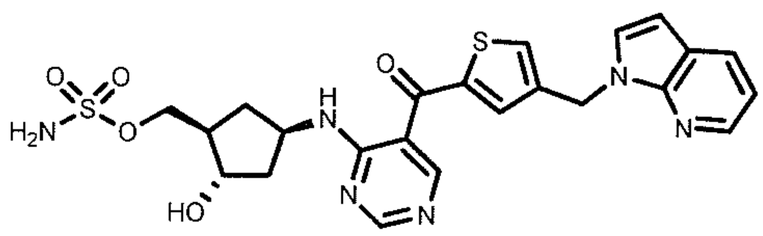
I-90

I-90a

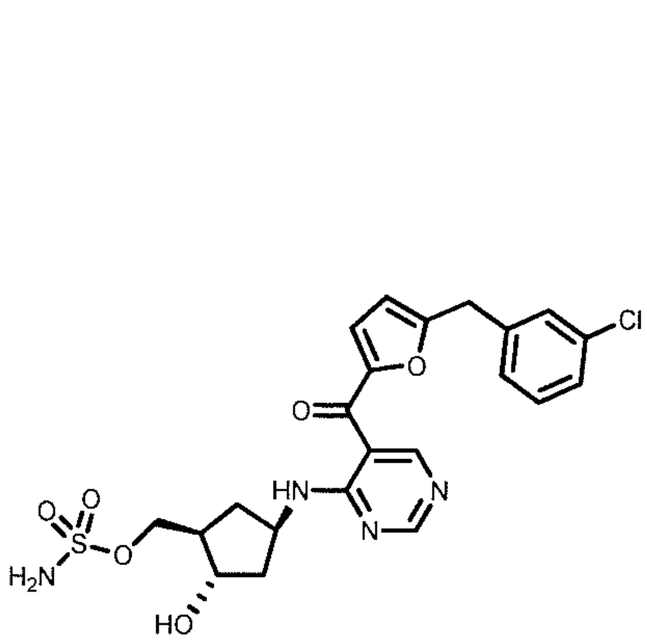
I-90b



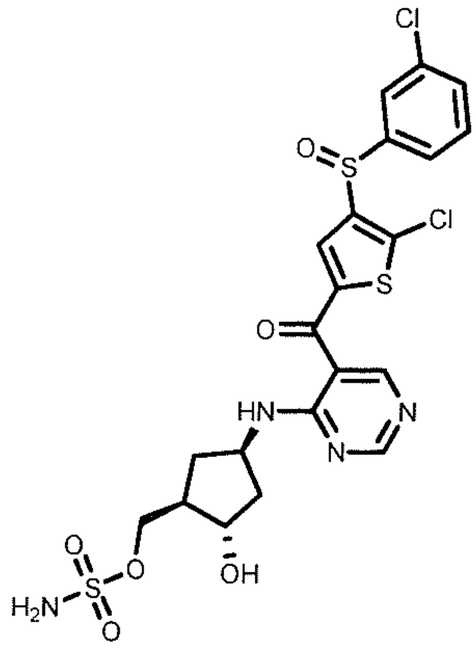
I-91



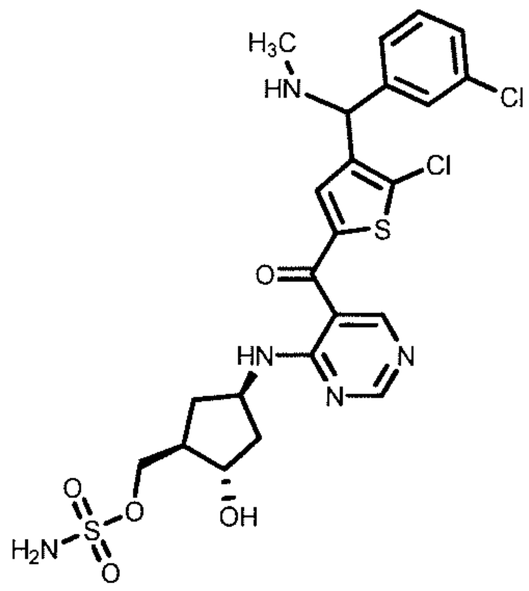
I-92



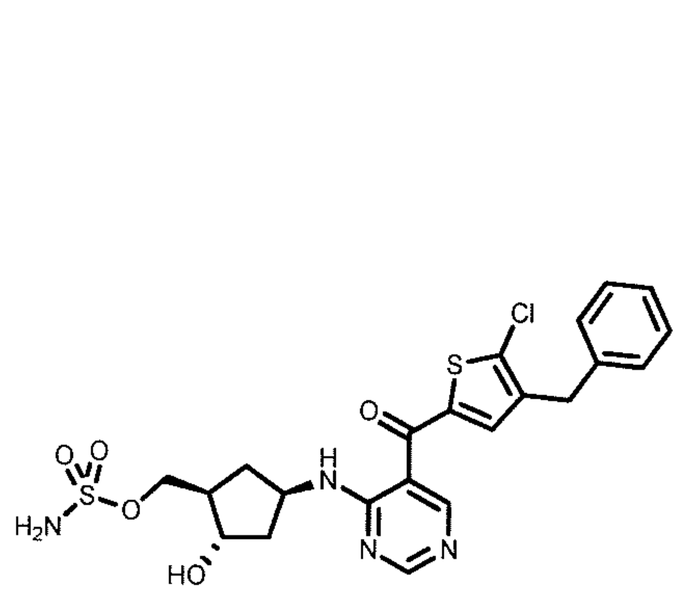
I-93



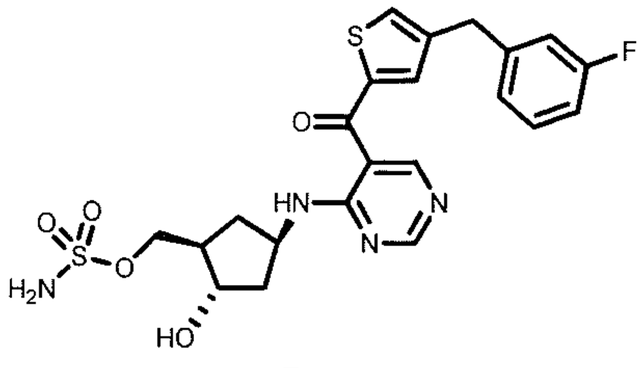
I-94



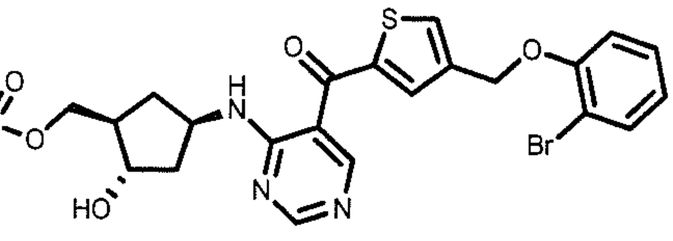
I-95



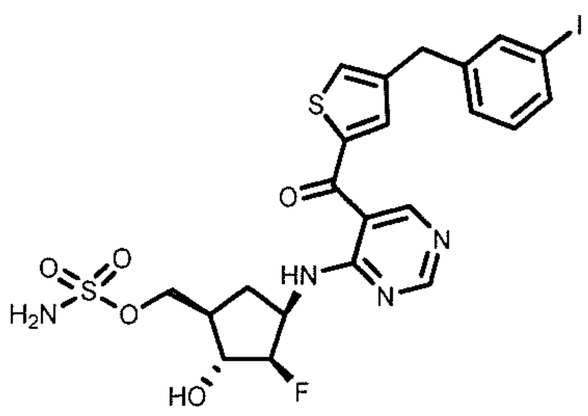
I-96



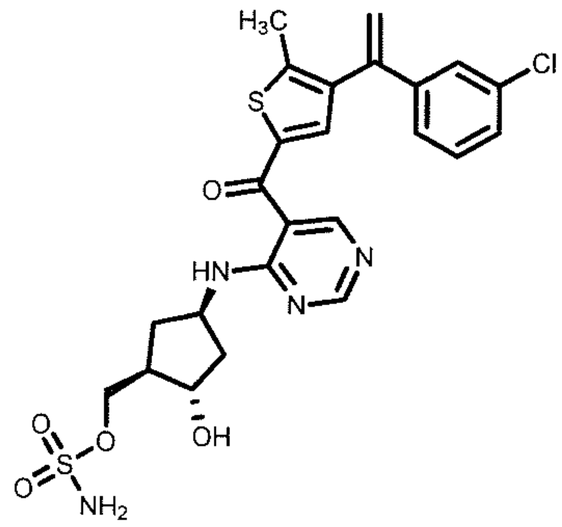
I-97



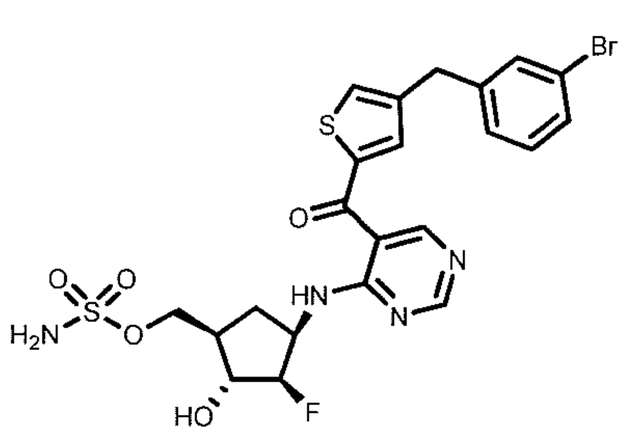
I-98



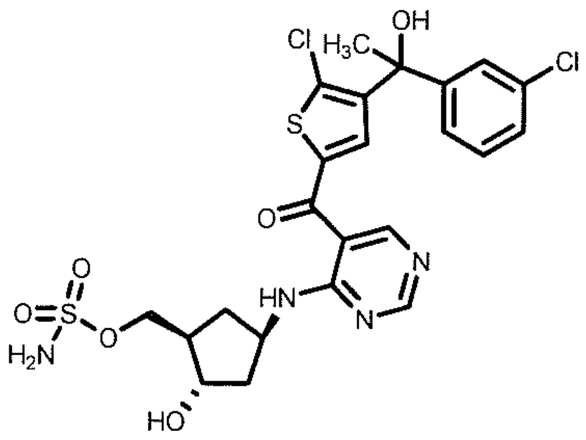
I-99



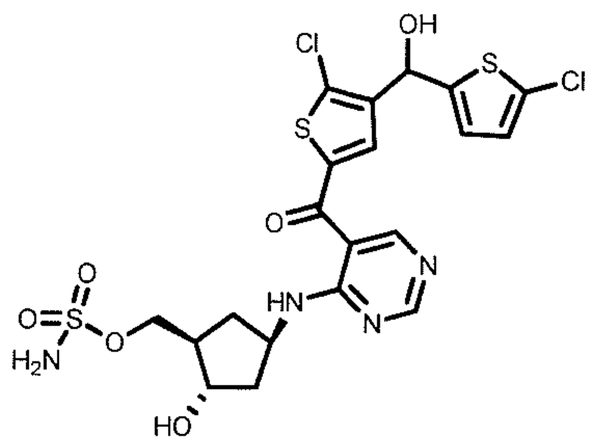
I-100



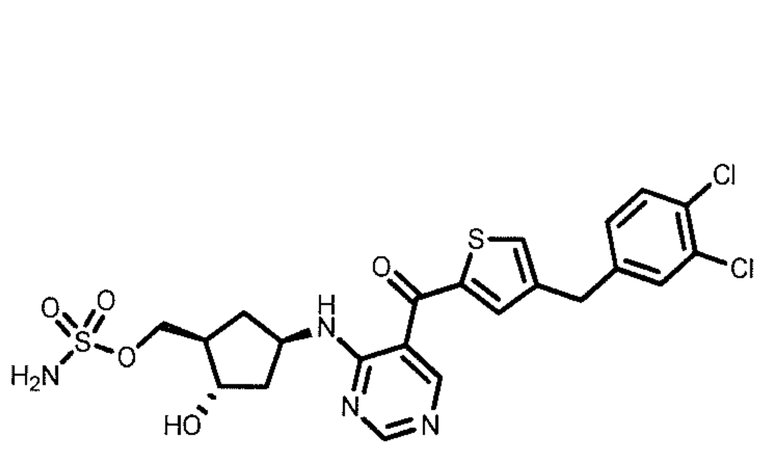
I-101



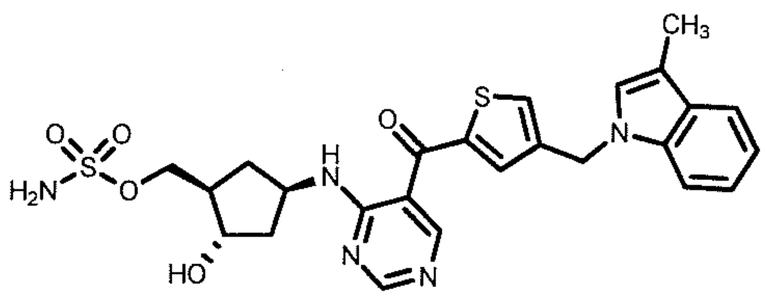
I-102
I-102a
I-102b

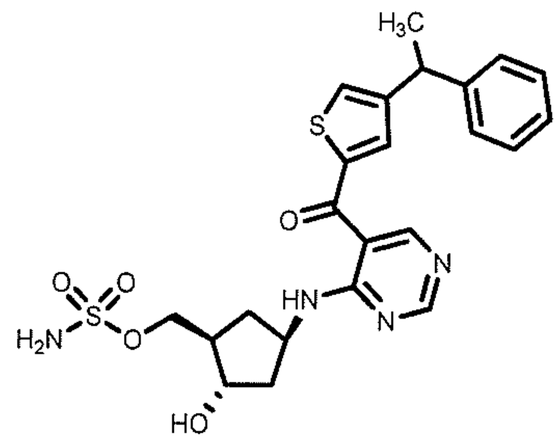


I-103

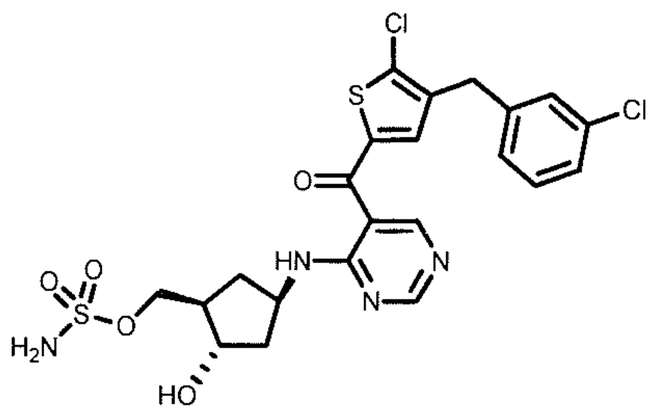


I-104





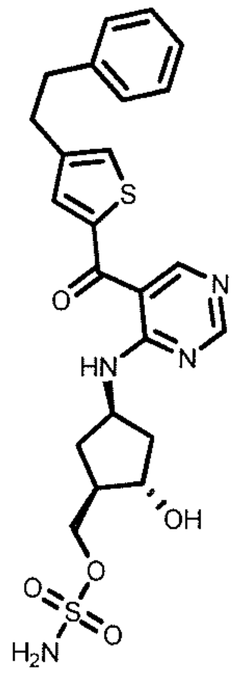
I-105



I-106

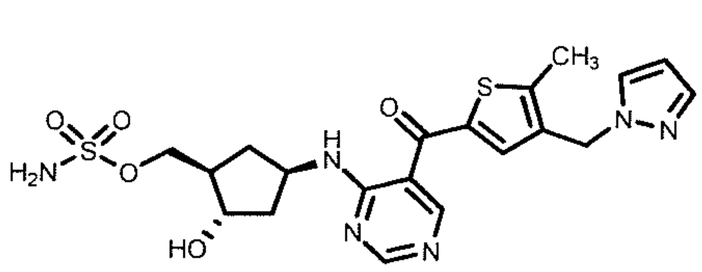
I-106a

I-106b

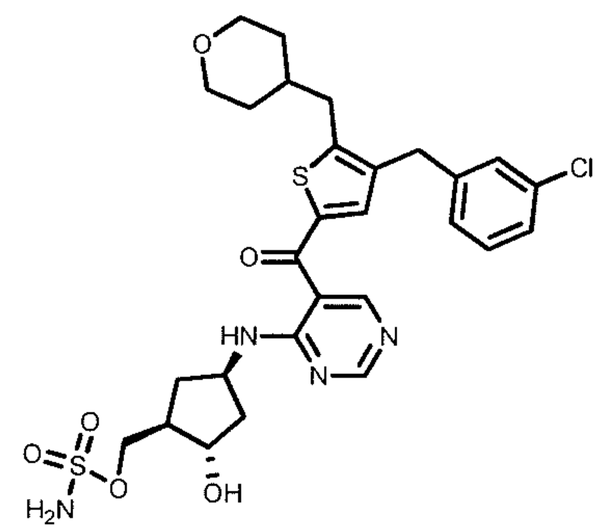


I-107

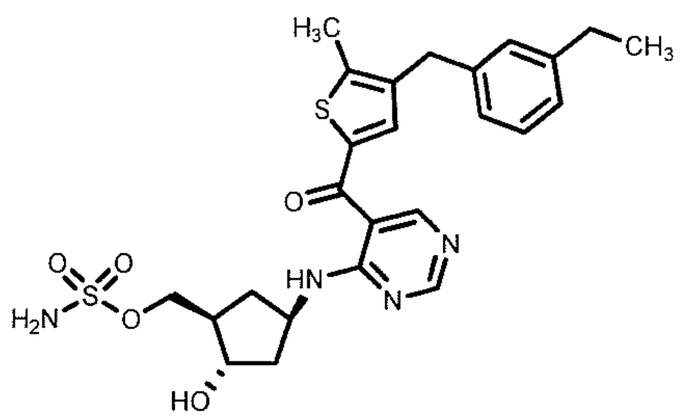
I-108



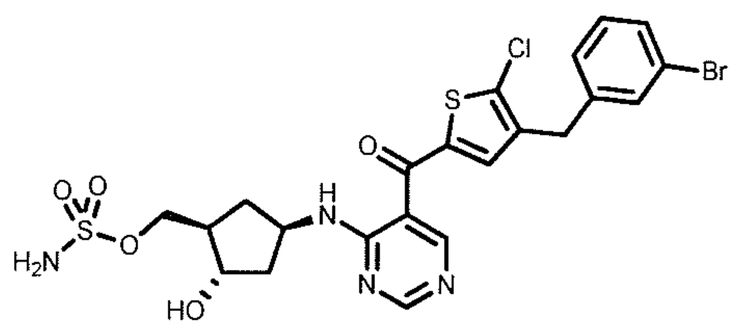
I-109



I-110



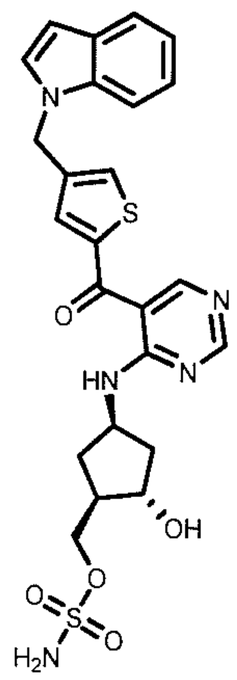
I-111



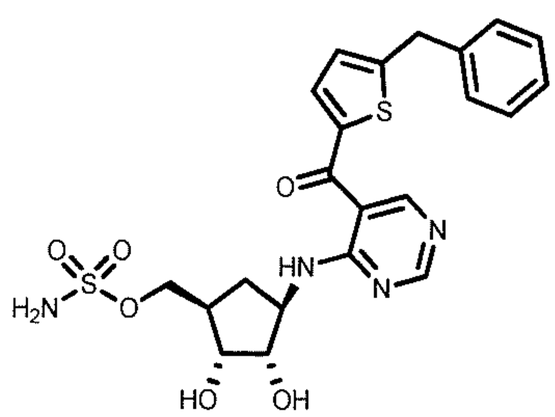
I-112



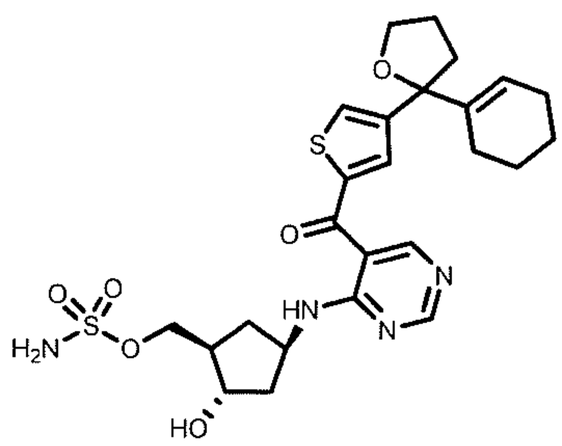
I-113



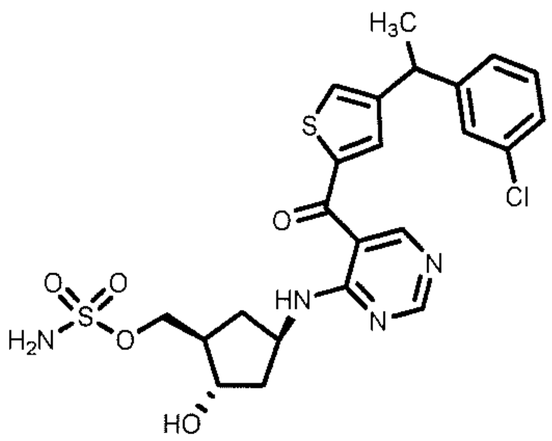
I-114



I-115



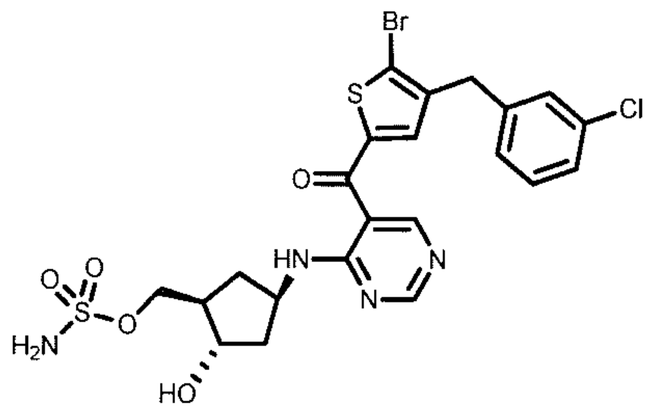
I-116



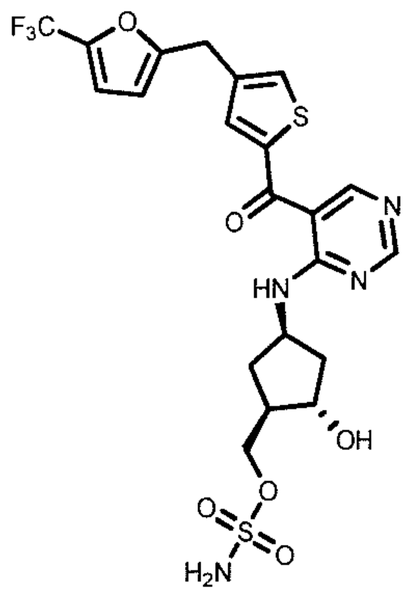
I-117

I-117a

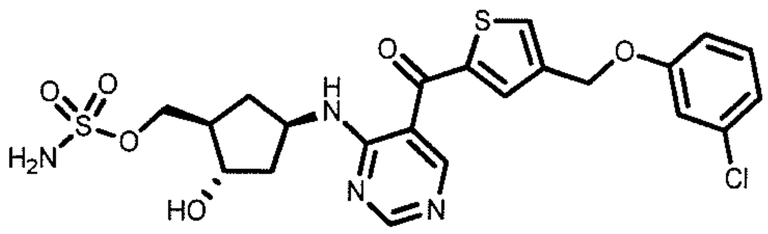
I-117b



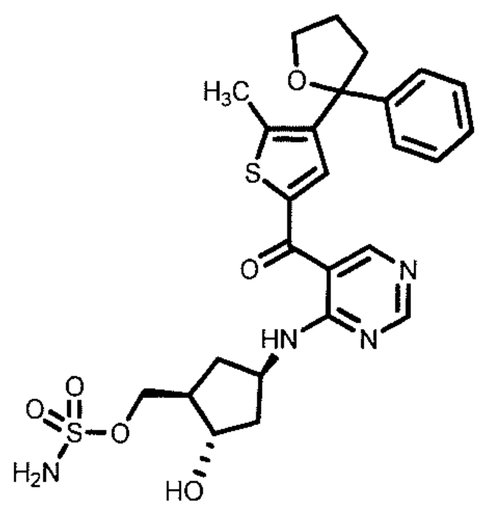
I-118



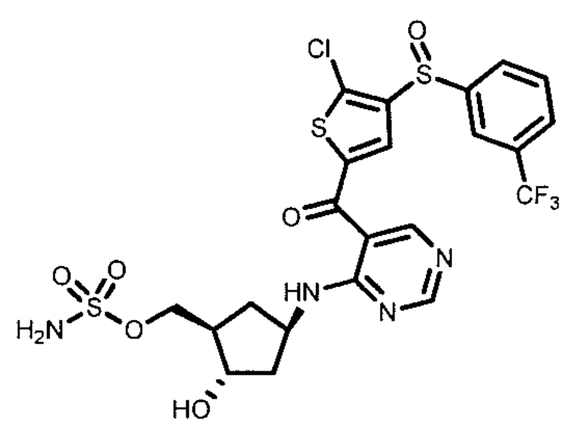
I-119



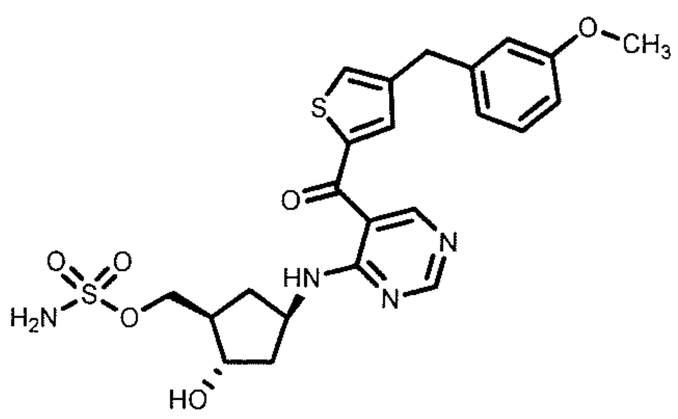
I-120



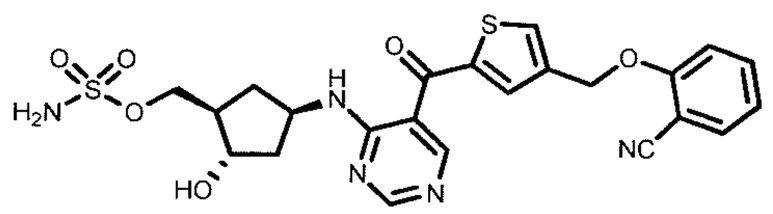
I-121



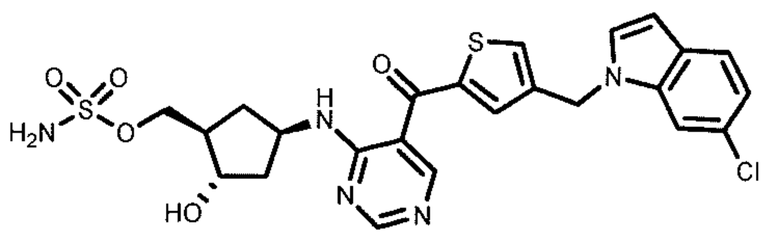
I-122



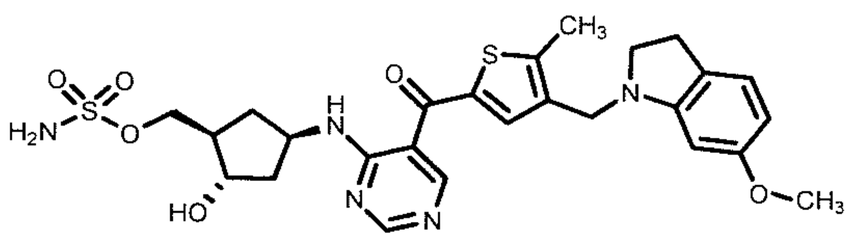
I-123



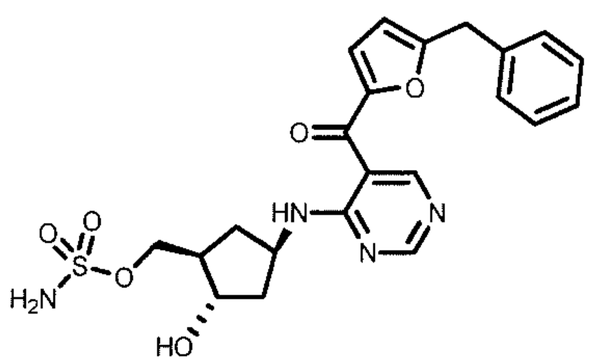
I-124



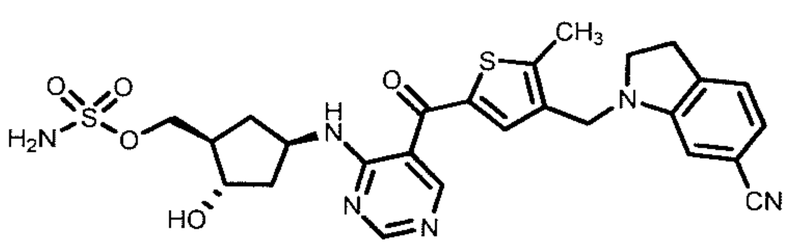
I-125



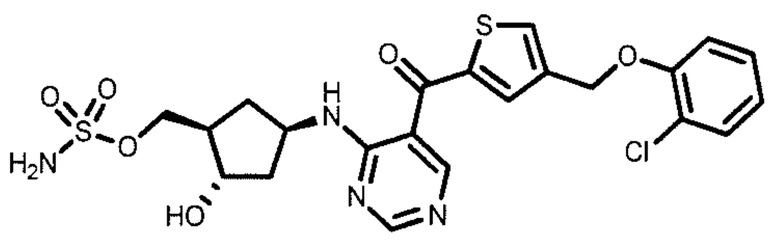
I-126



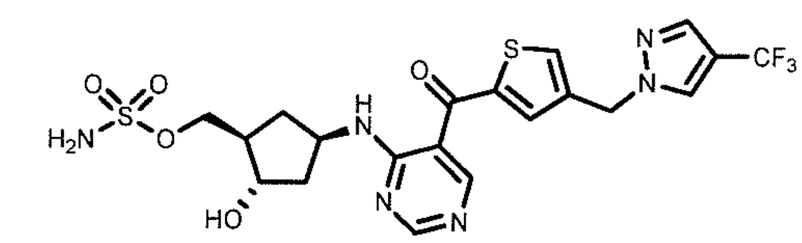
I-127



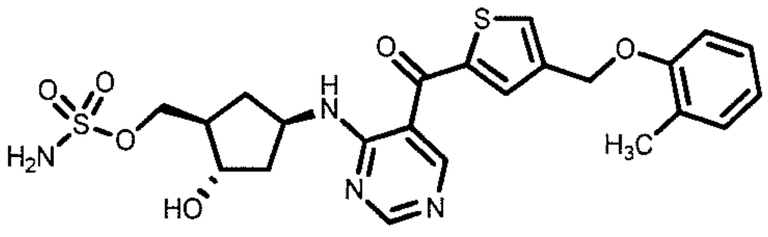
I-128



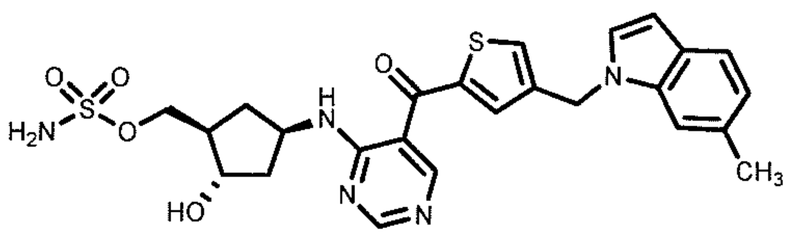
I-129



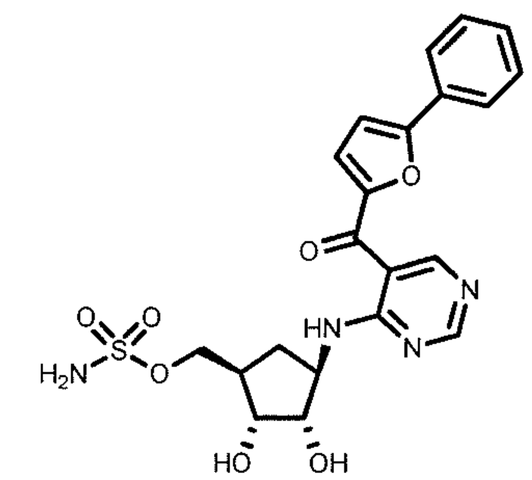
I-130



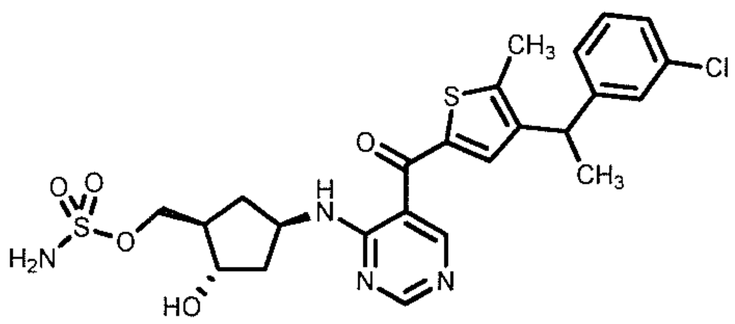
I-131



I-132



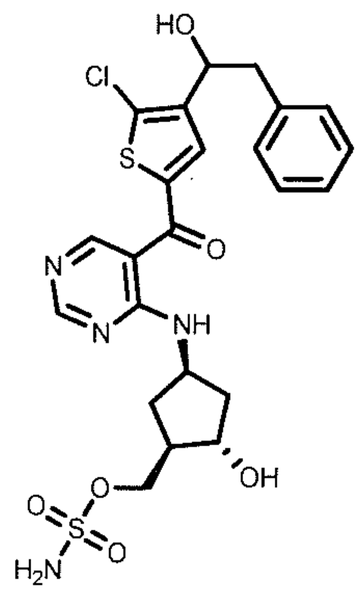
I-134



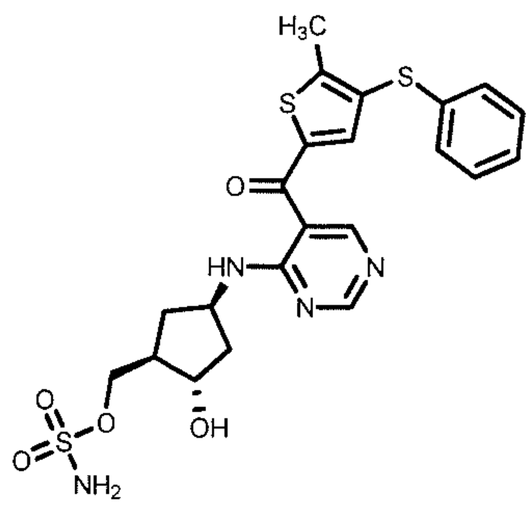
I-135

I-135a

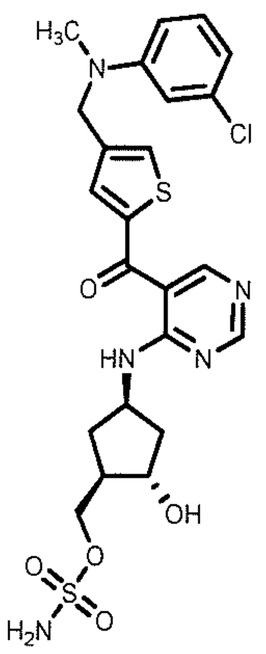
I-135b



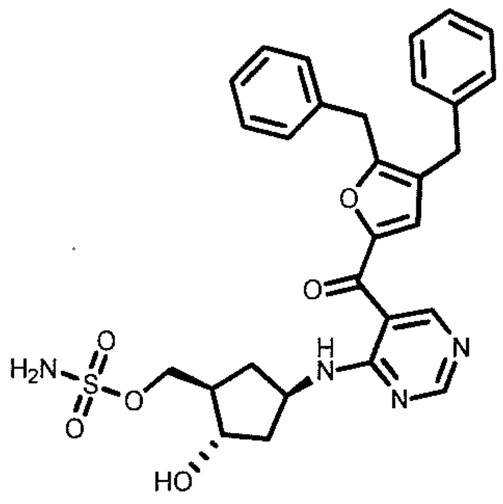
I-136



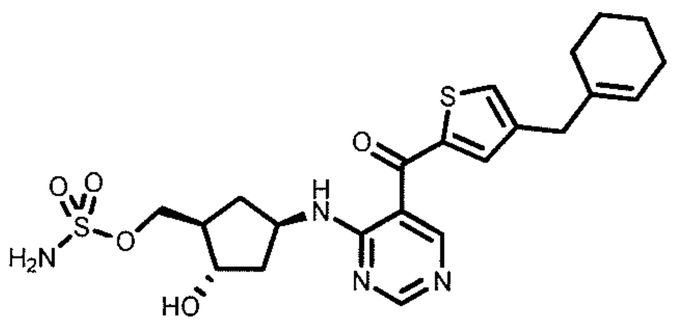
I-137



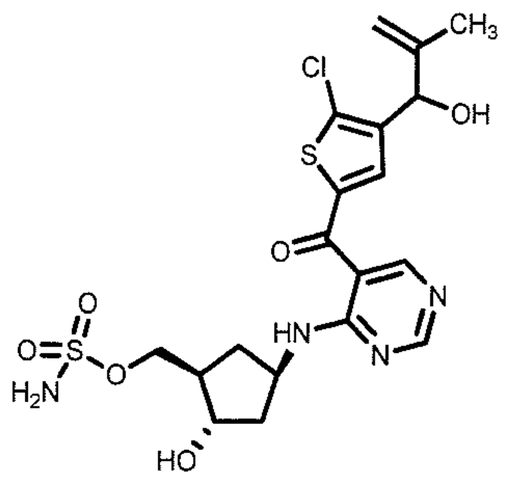
I-138



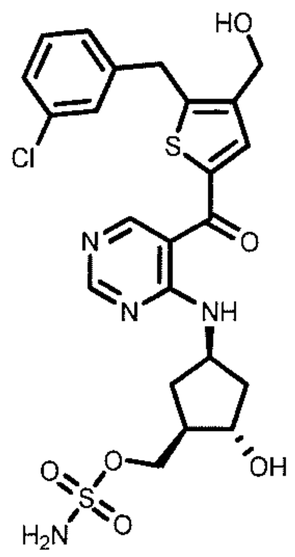
I-139



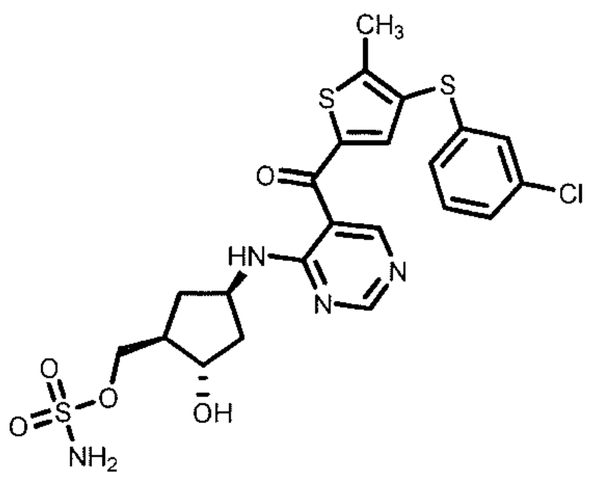
I-140



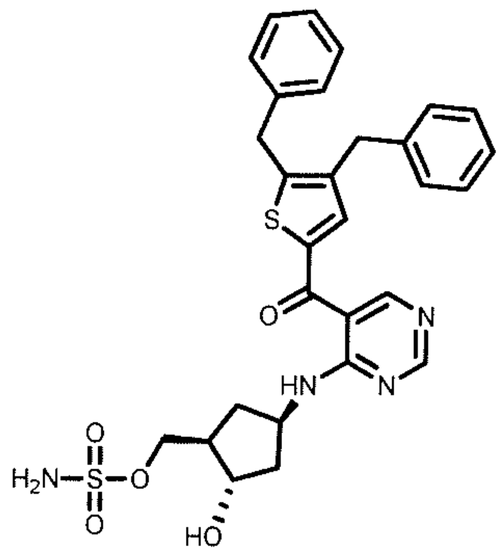
I-141



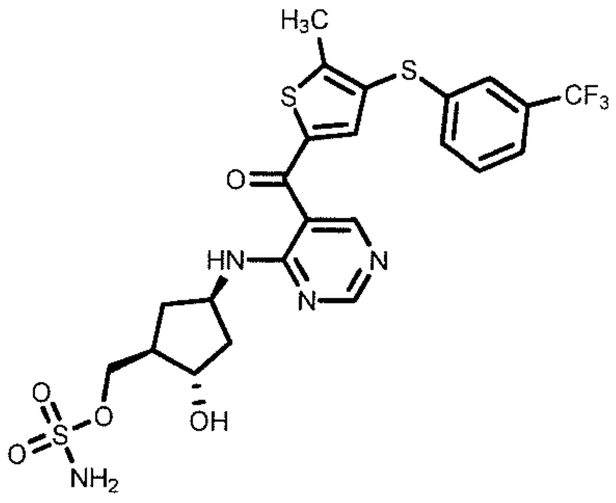
I-142



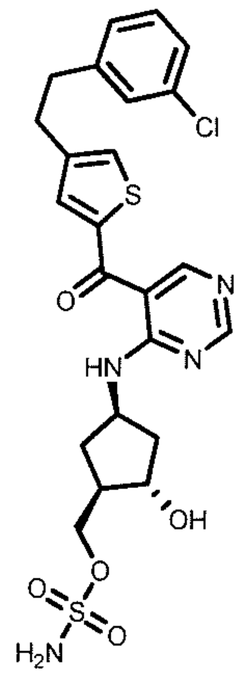
I-143



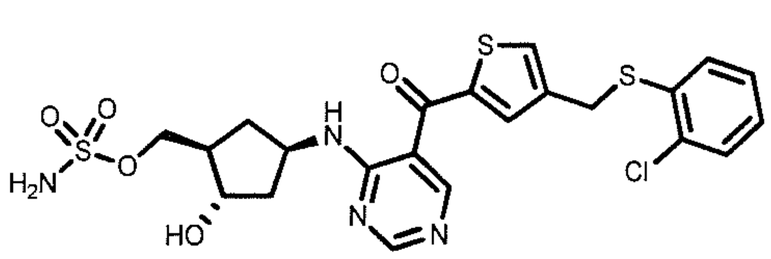
I-144



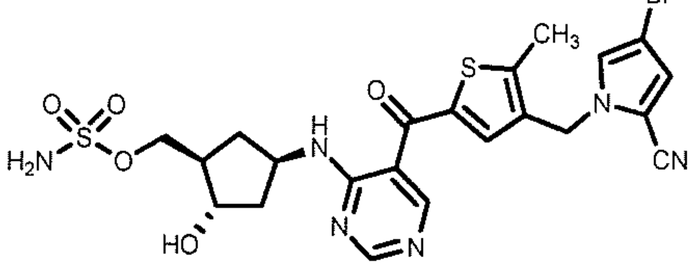
I-145



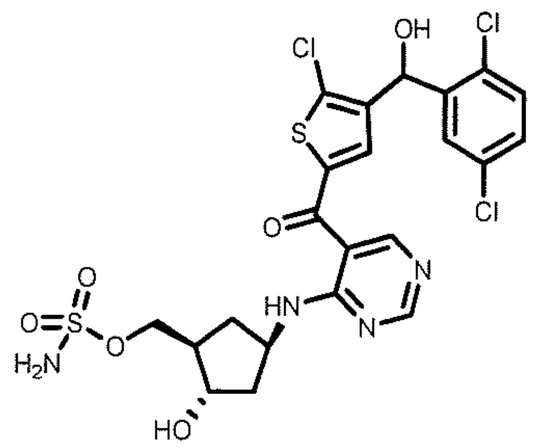
I-146



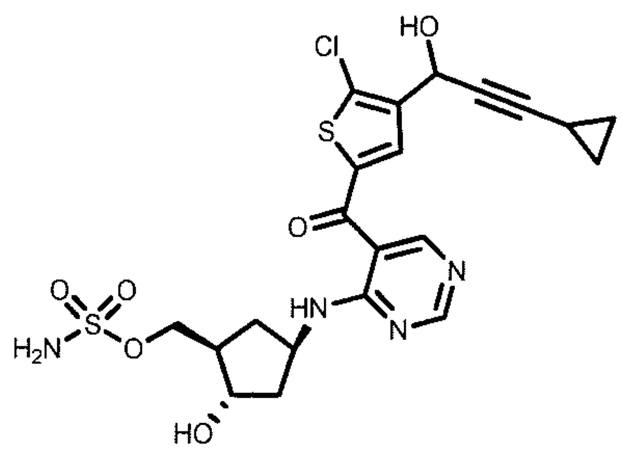
I-147



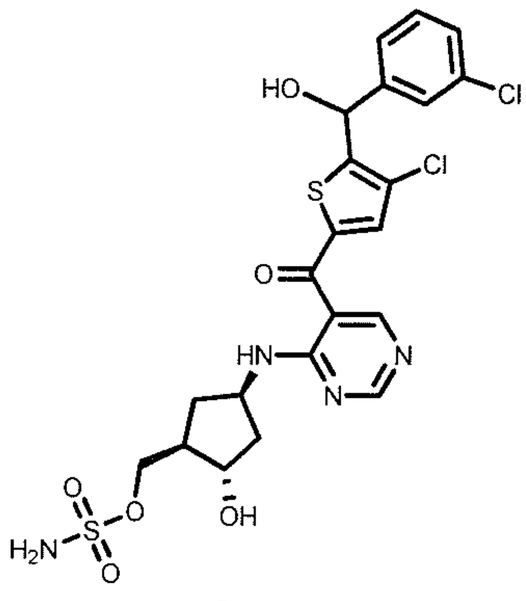
I-148



I-149



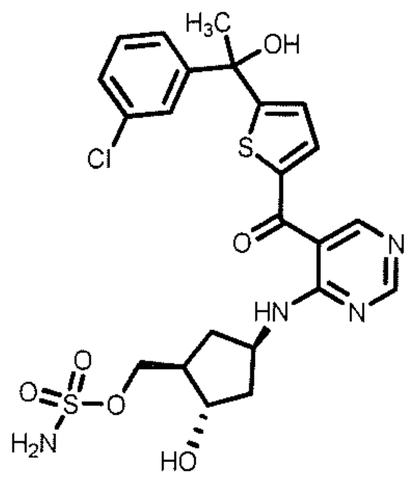
I-150



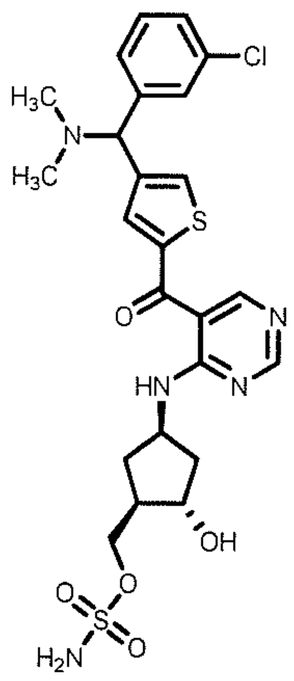
I-151

I-151a

I-151b



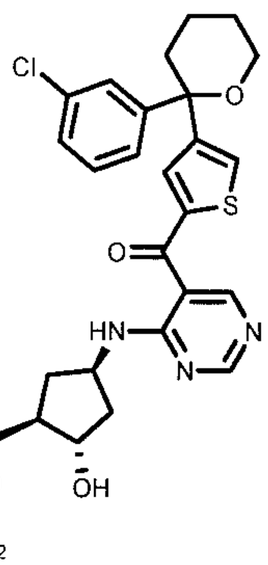
I-152



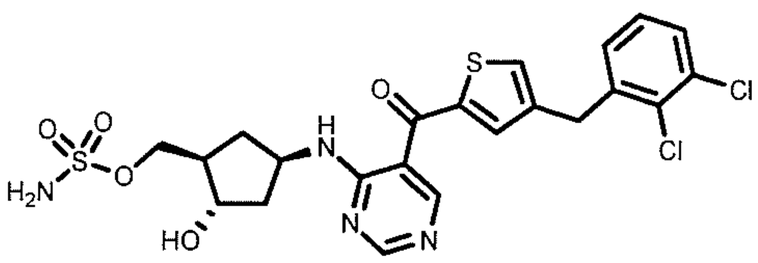
I-153

I-153a

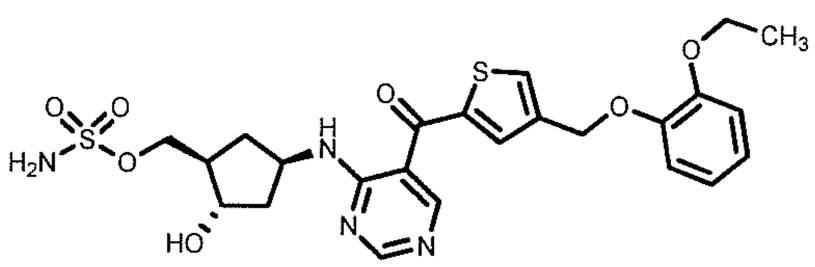
I-153b



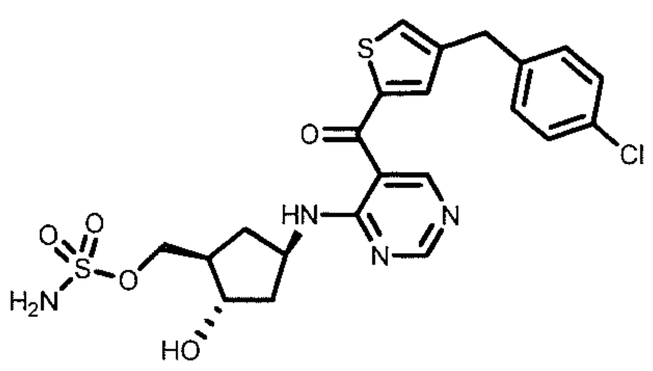
I-154



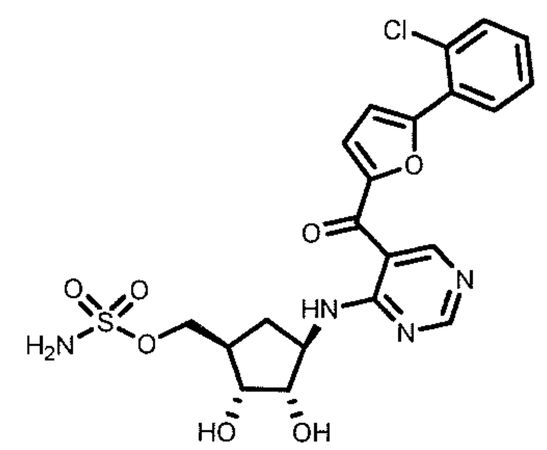
I-155



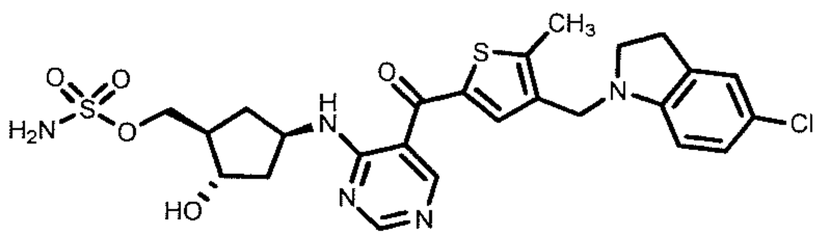
I-156



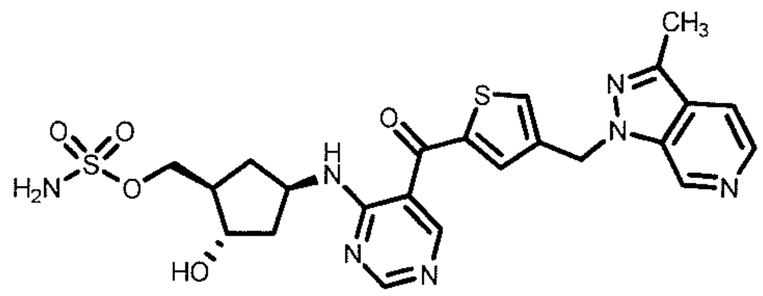
I-157



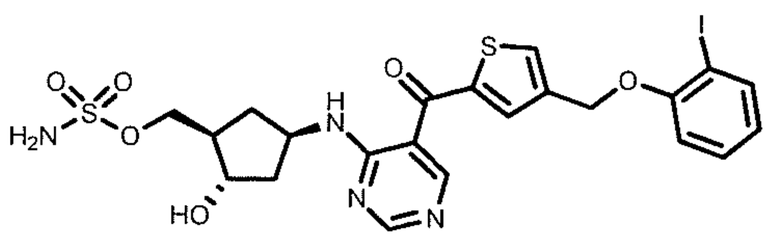
I-158



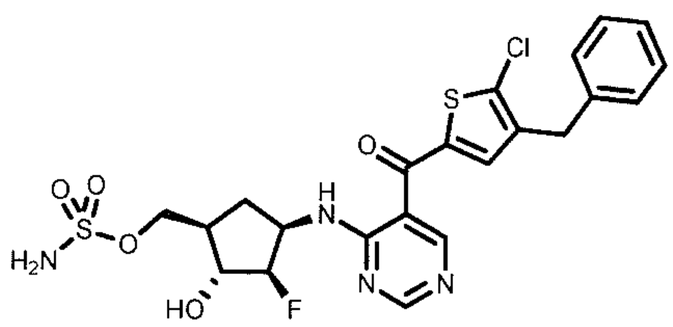
I-159



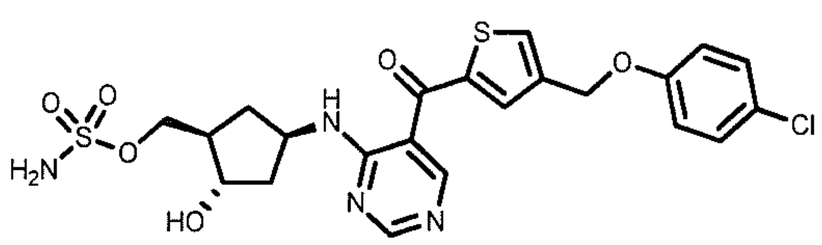
I-160



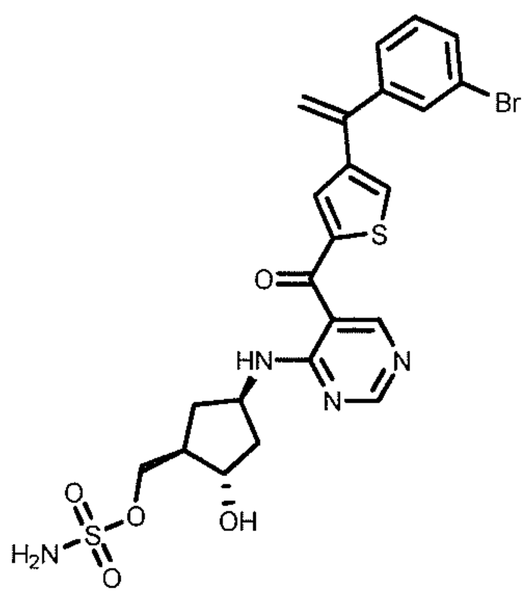
I-161



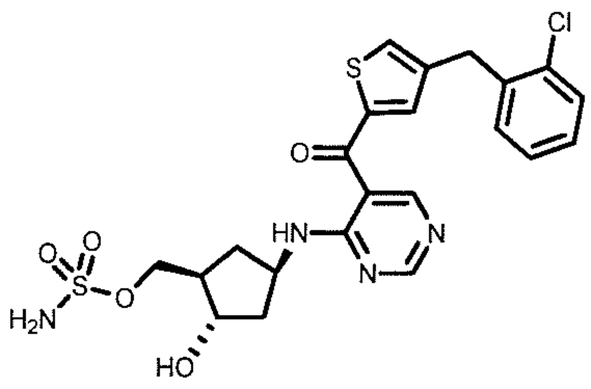
I-162



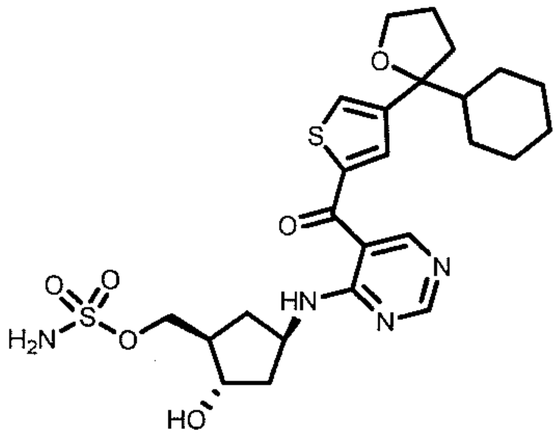
I-163



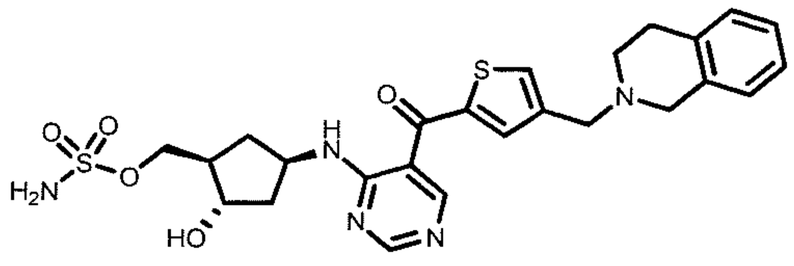
I-164



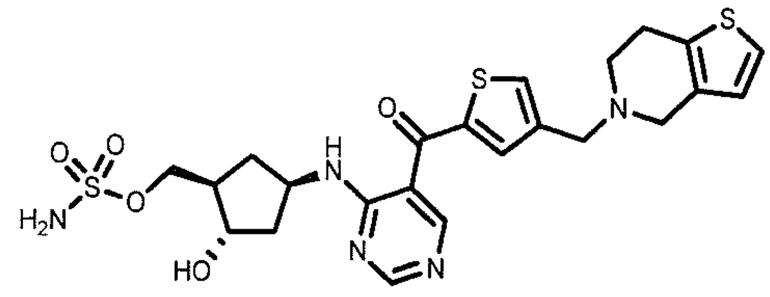
I-165



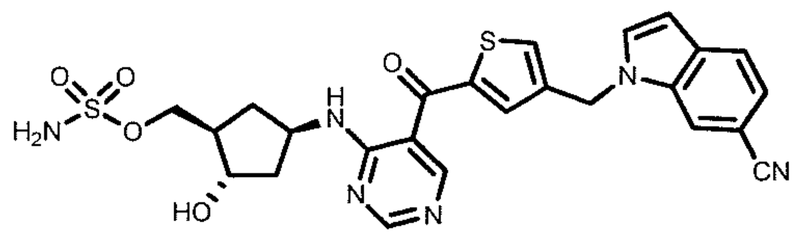
I-166



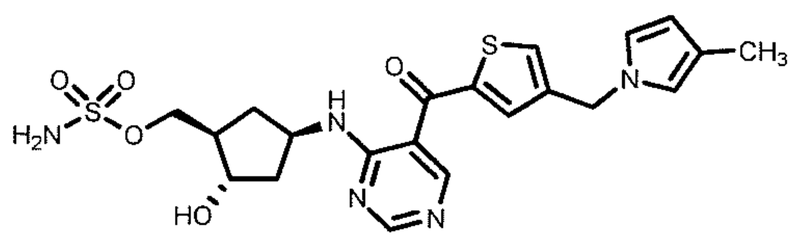
I-167



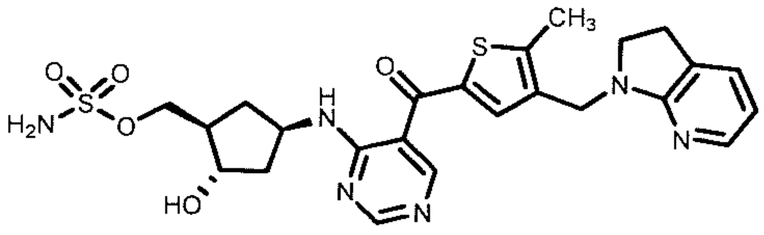
I-168



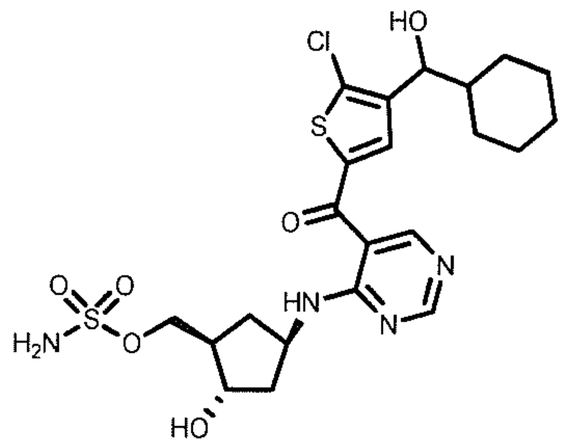
I-169



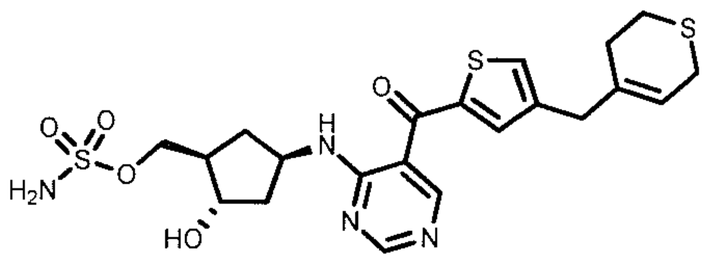
I-170



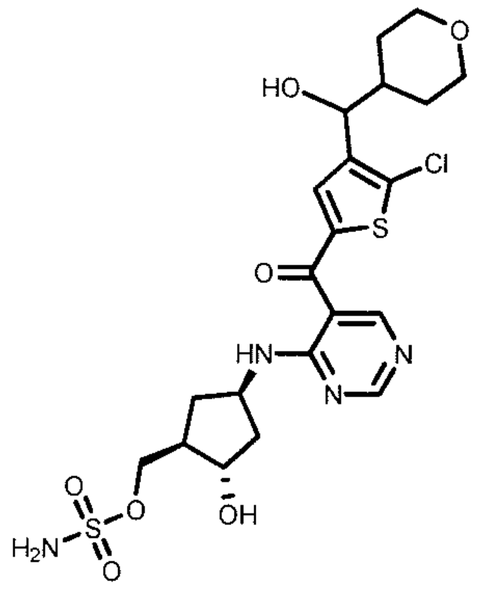
I-171



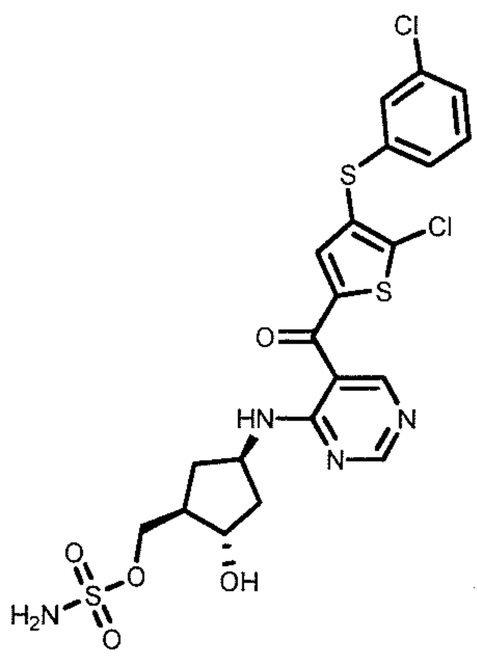
I-172



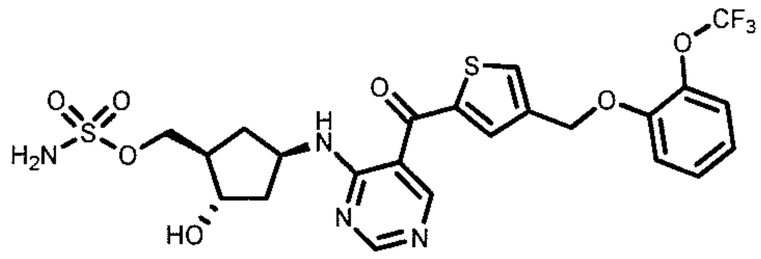
I-173



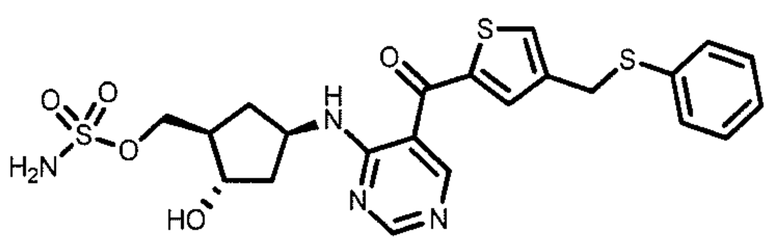
I-174



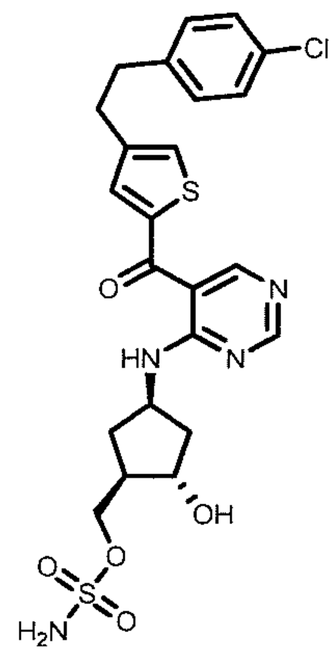
I-175



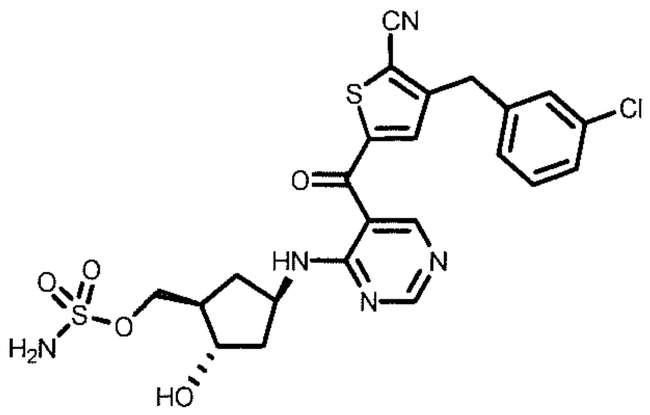
I-176



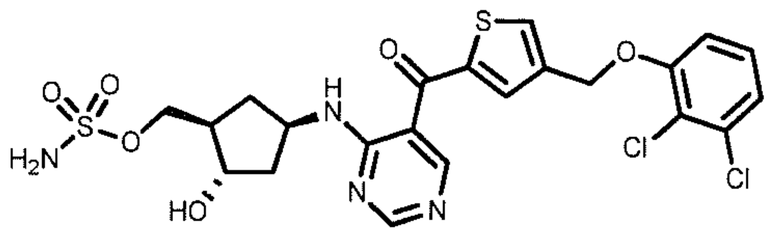
I-177



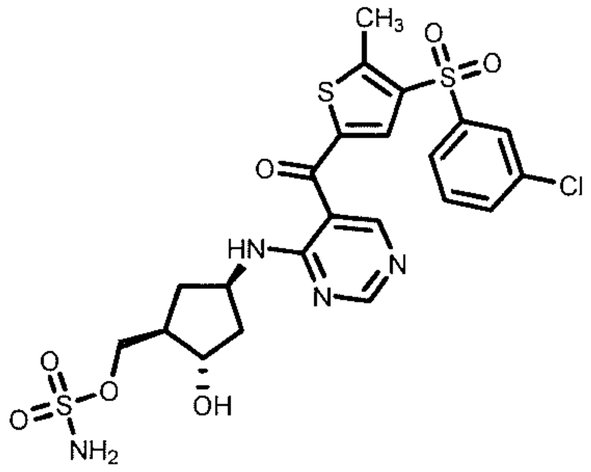
I-178



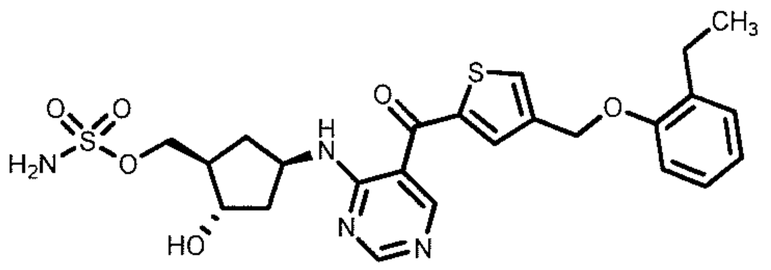
I-179



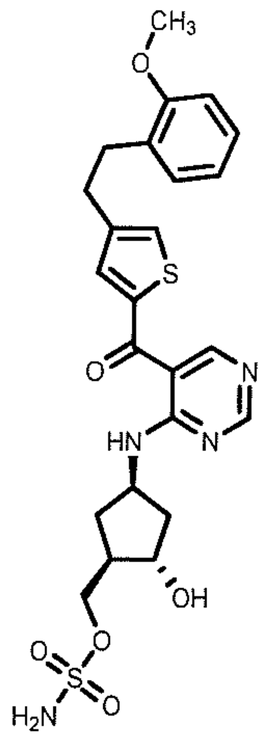
I-180



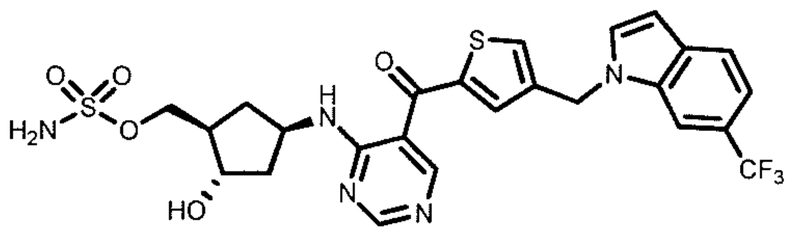
I-181



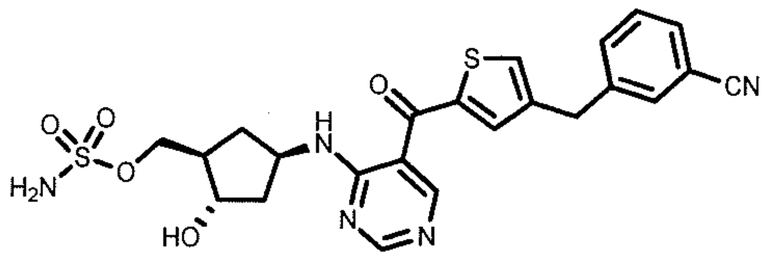
I-182



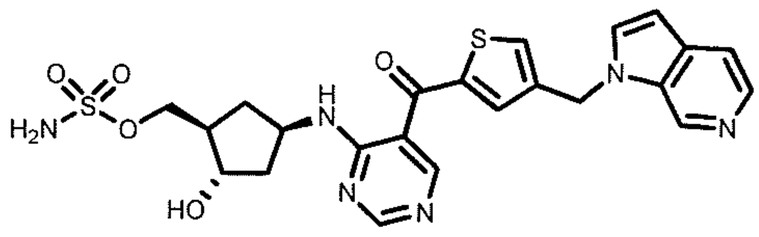
I-183



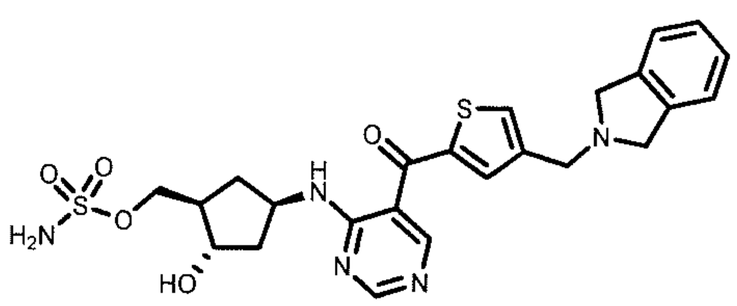
I-184



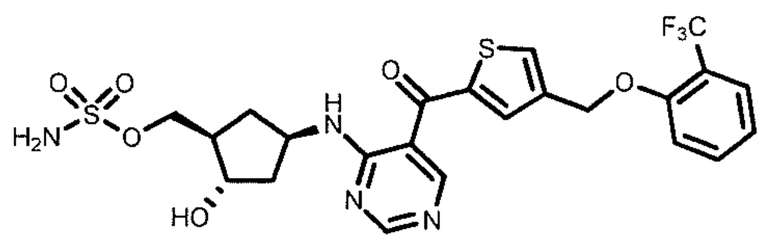
I-185



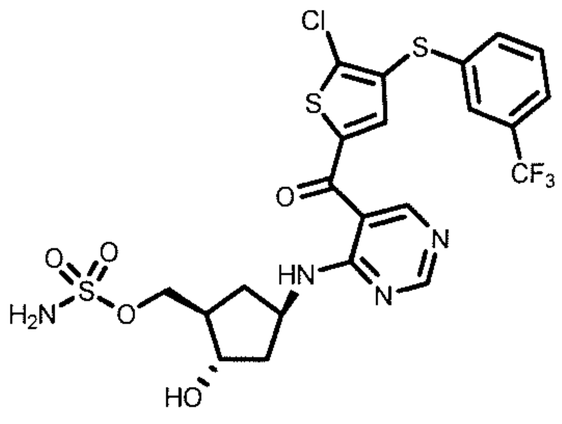
I-186



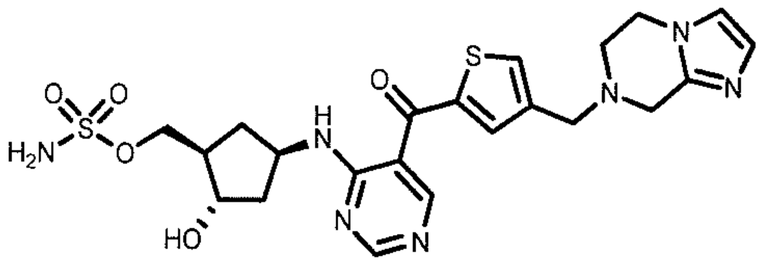
I-187



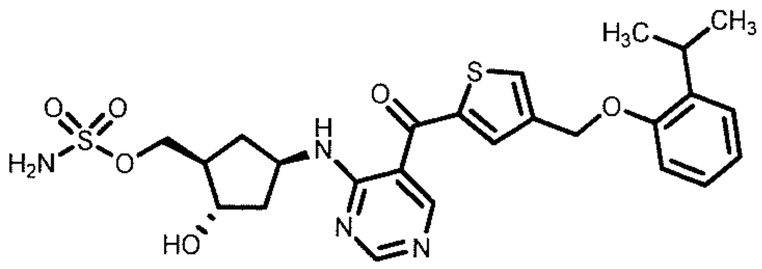
I-188



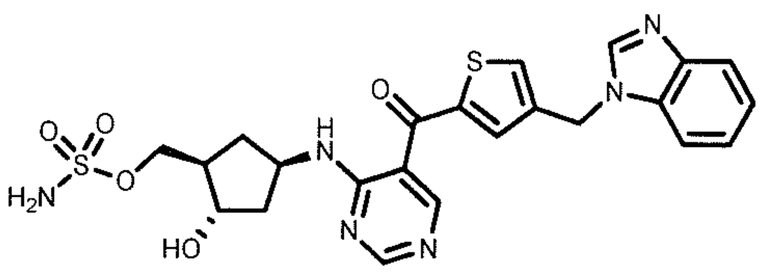
I-189



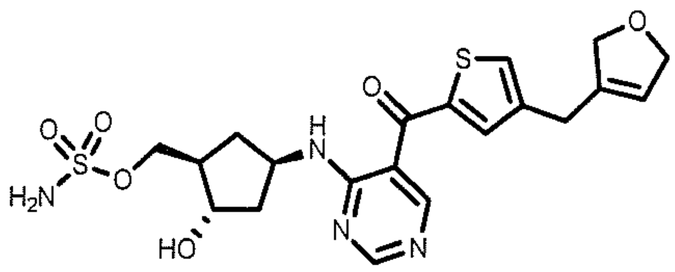
I-190



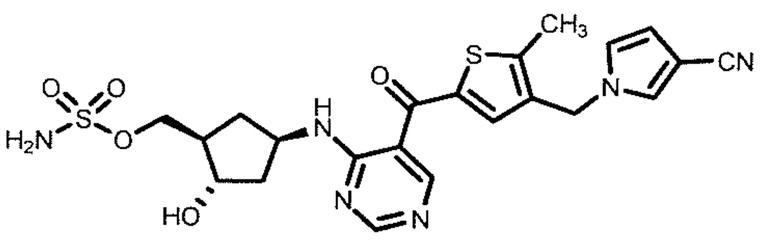
I-191



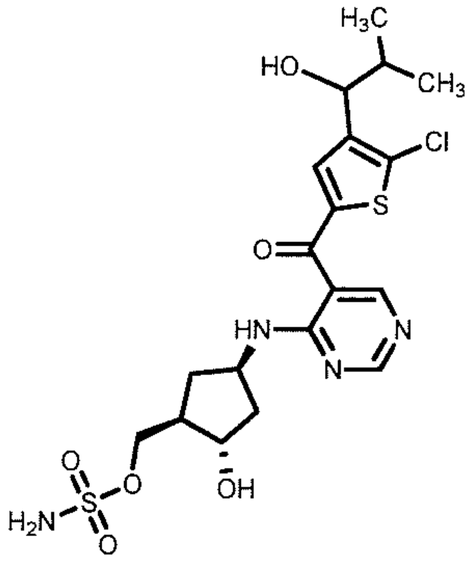
I-192



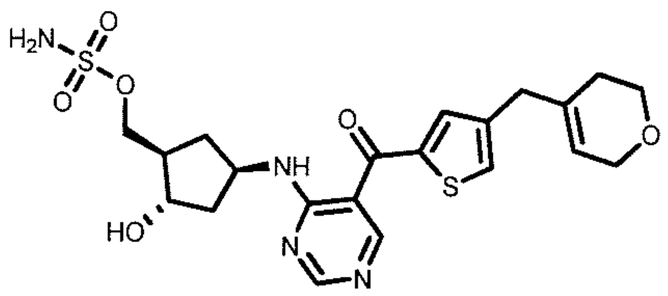
I-193



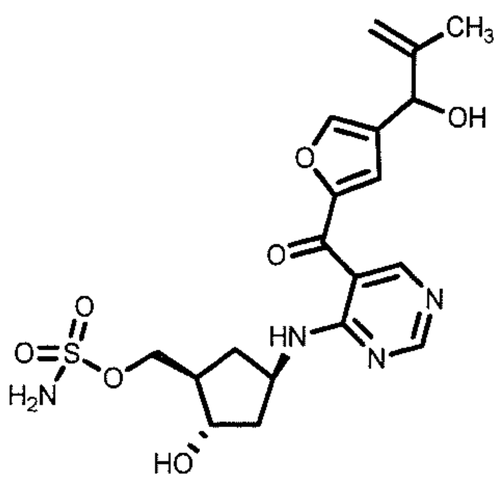
I-194



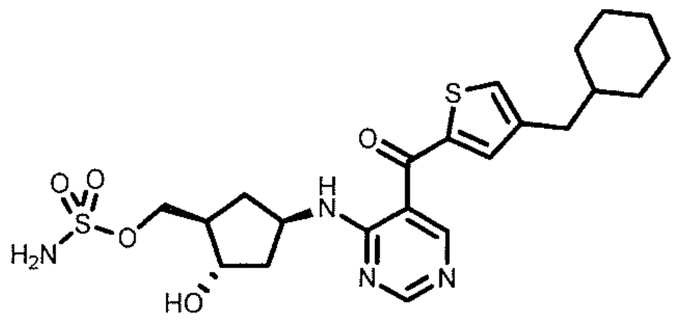
I-195



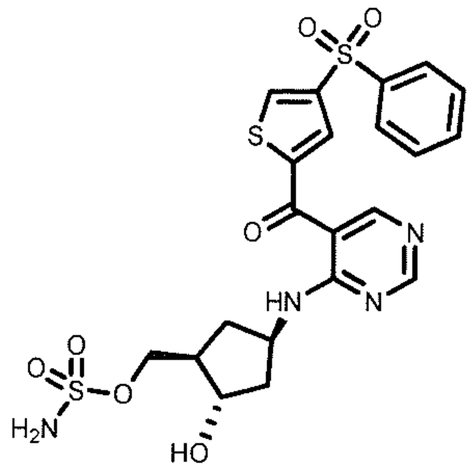
I-196



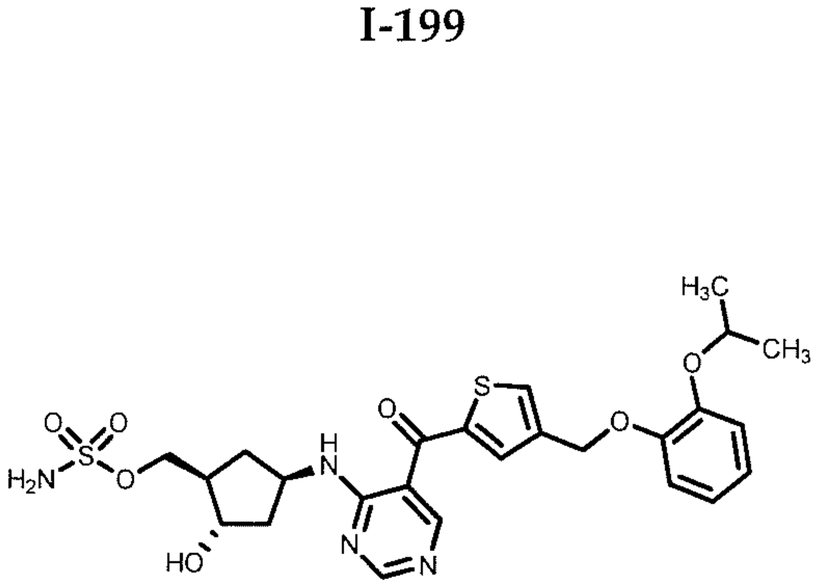
I-197



I-199

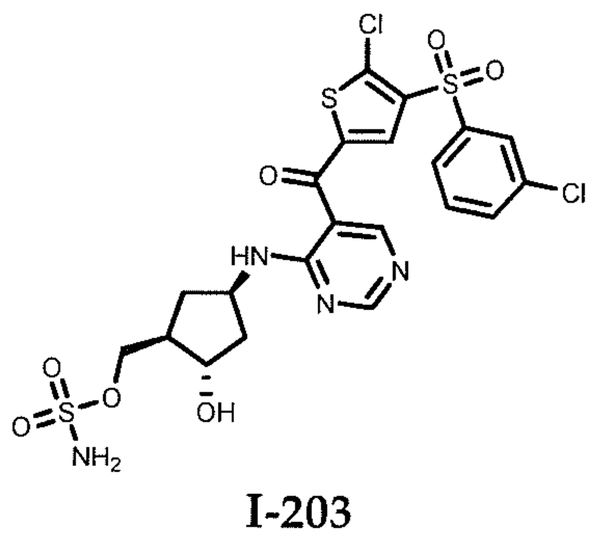


I-200

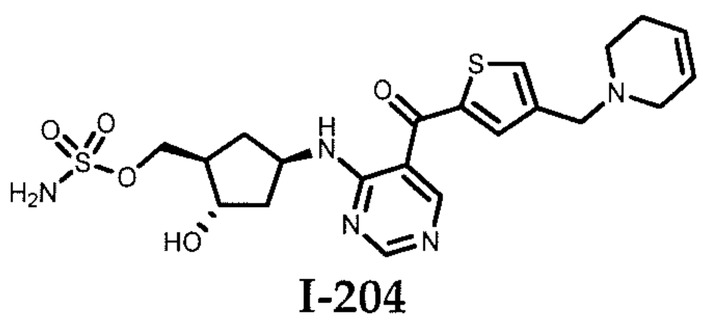


I-201

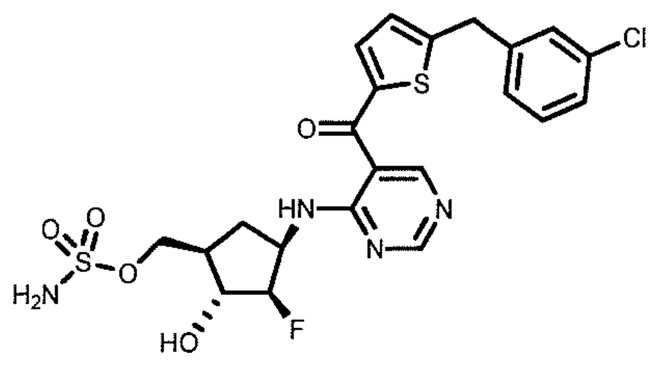
I-202



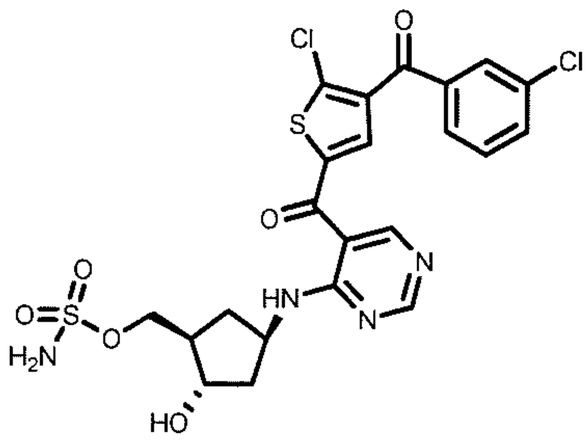
I-203



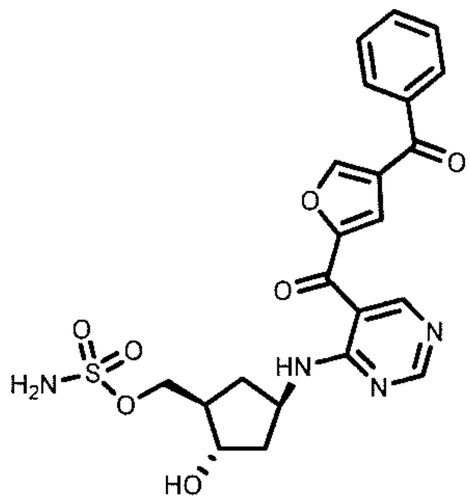
I-204



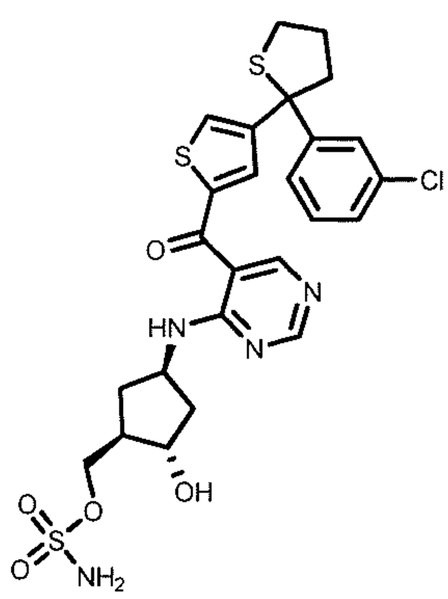
I-205



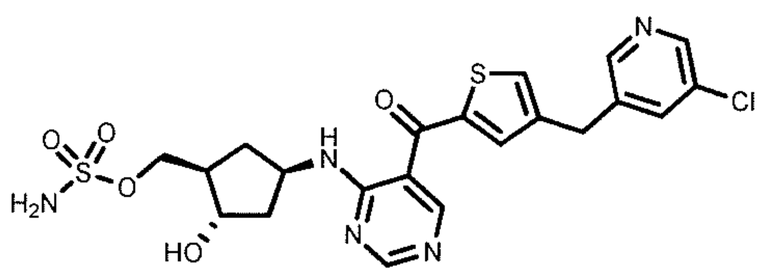
I-206



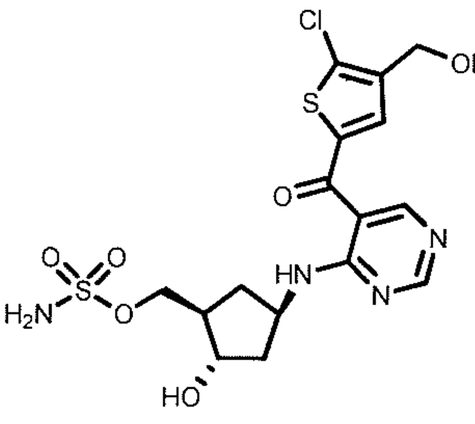
I-207



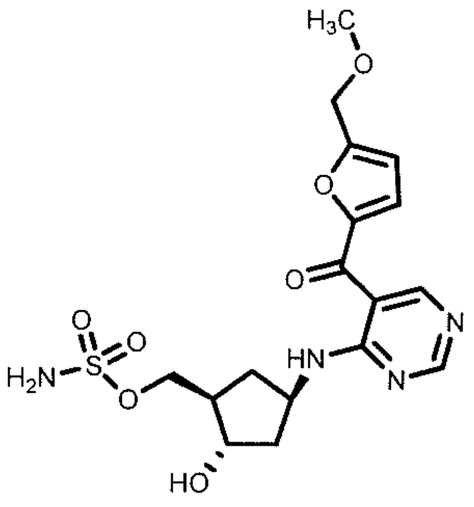
I-208



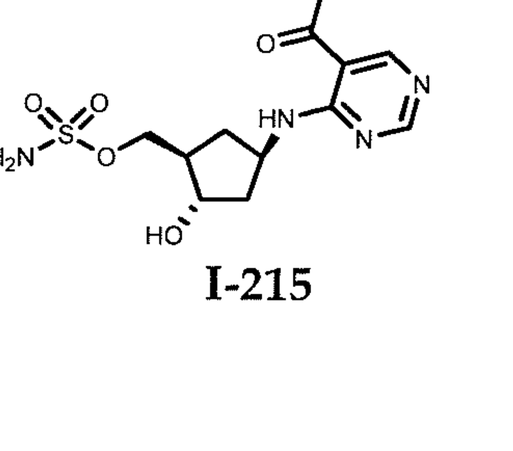
I-209



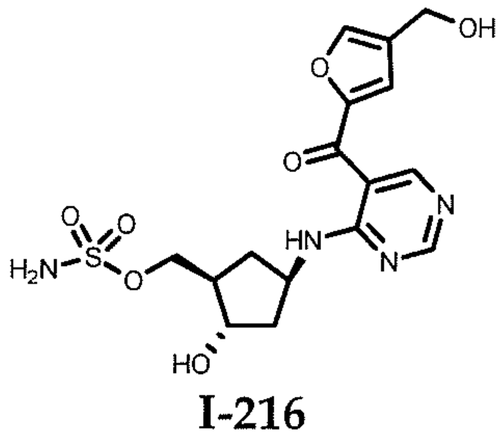
I-210



I-211

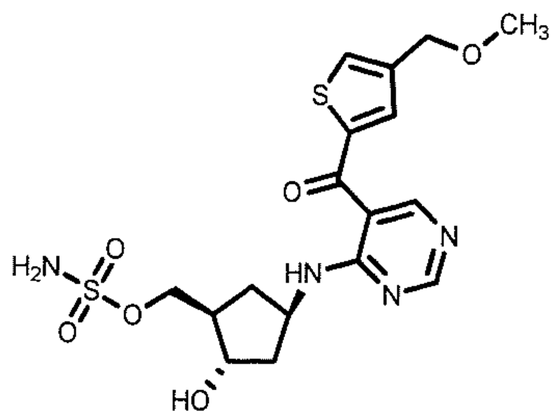


I-212

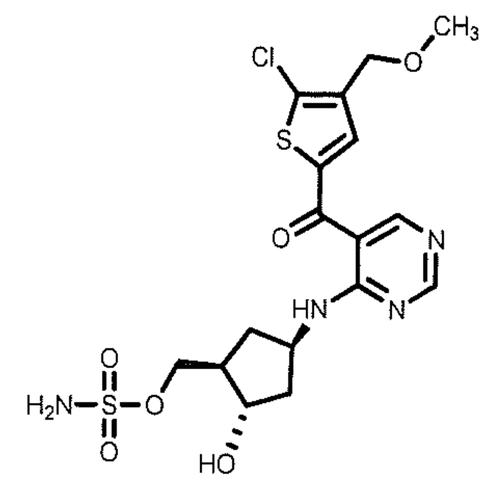


I-215

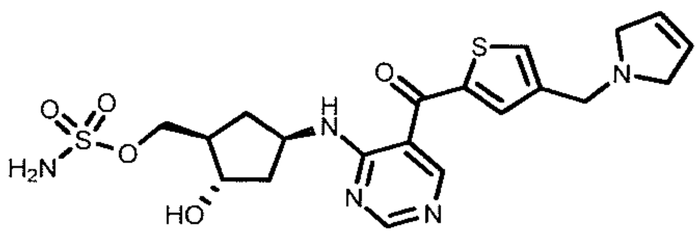
I-216



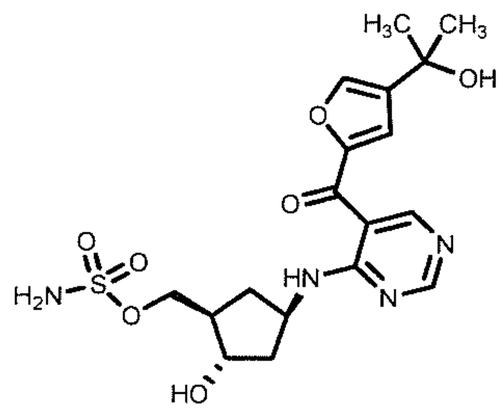
I-217



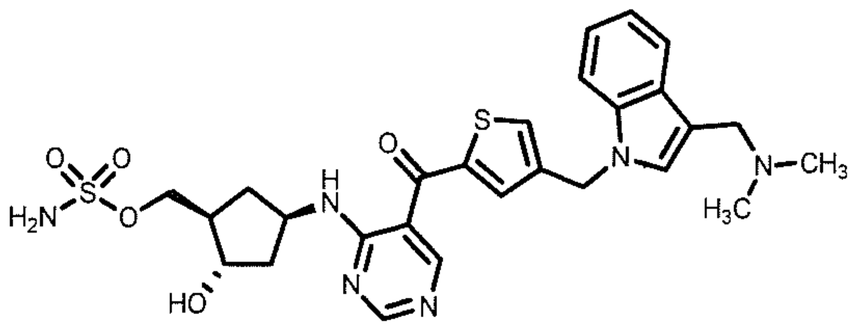
I-218



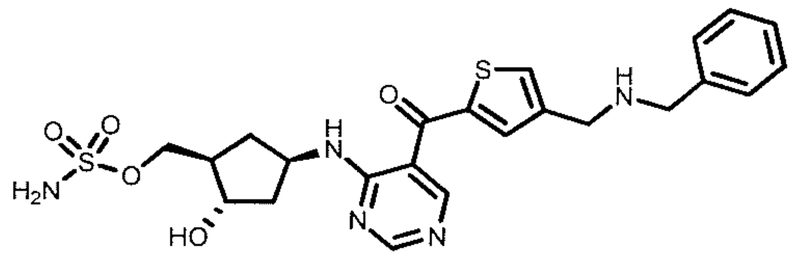
I-219



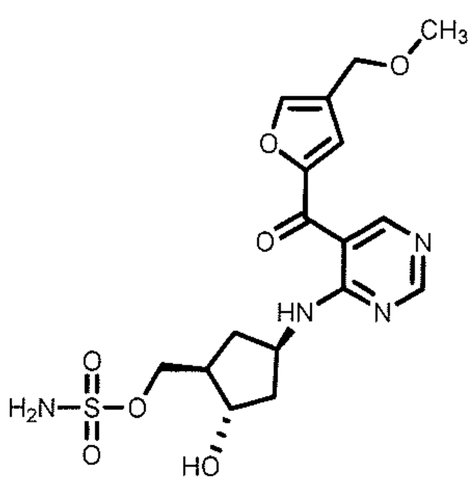
I-220



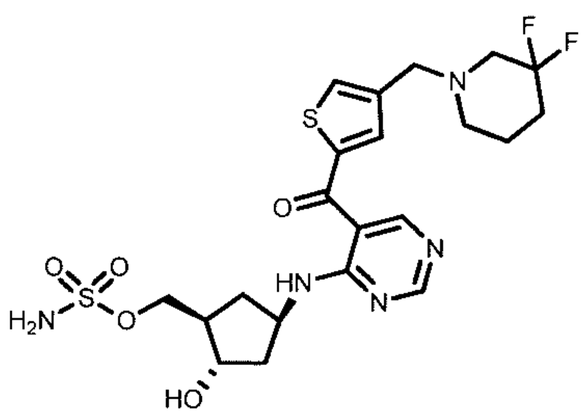
I-221



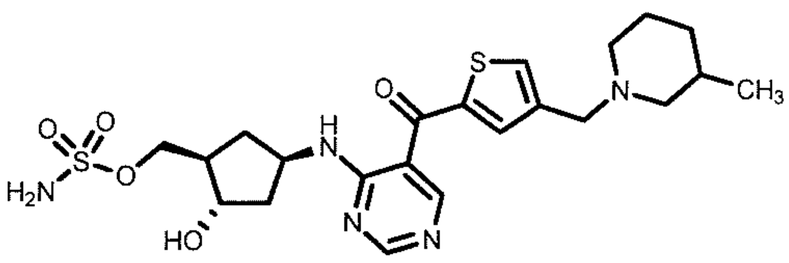
I-222



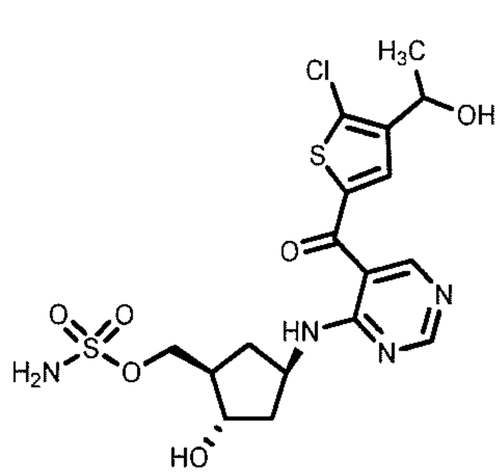
I-223



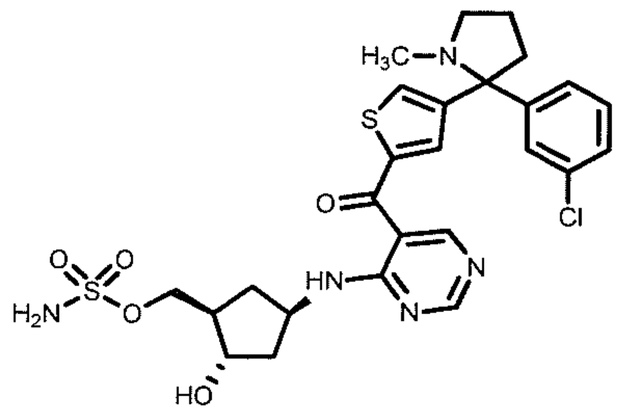
I-224



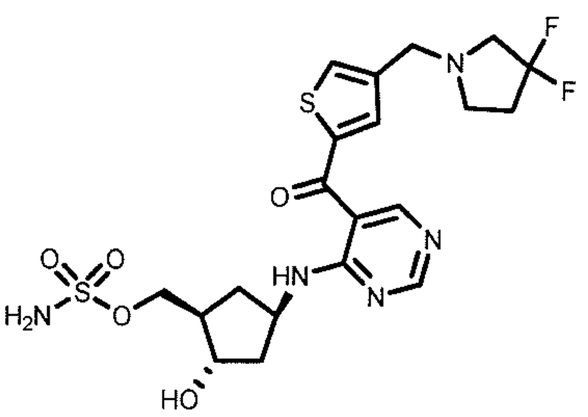
I-225



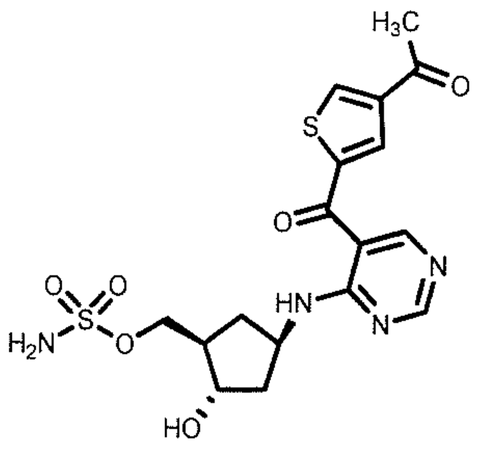
I-226



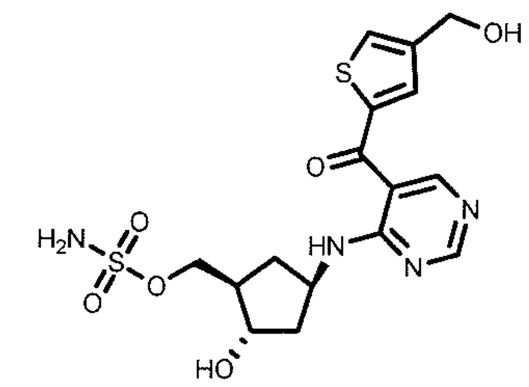
I-227



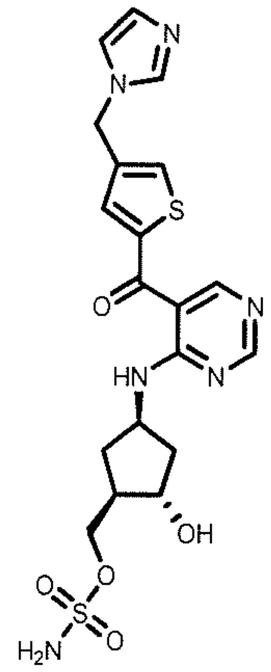
I-228



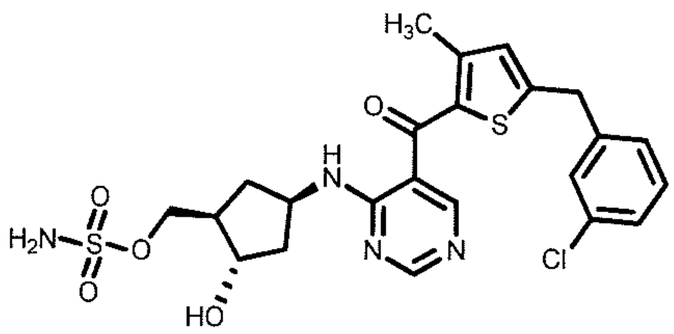
I-229



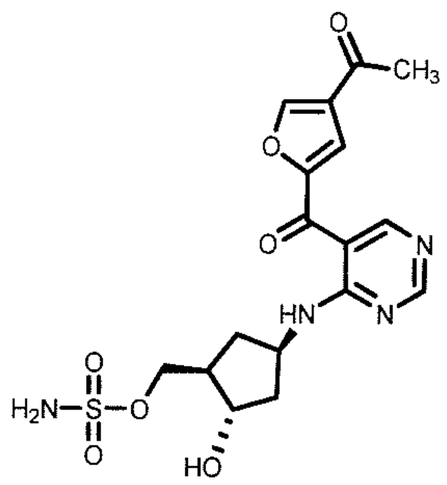
I-230



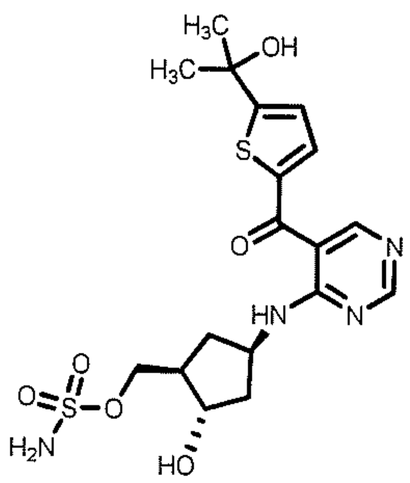
I-231



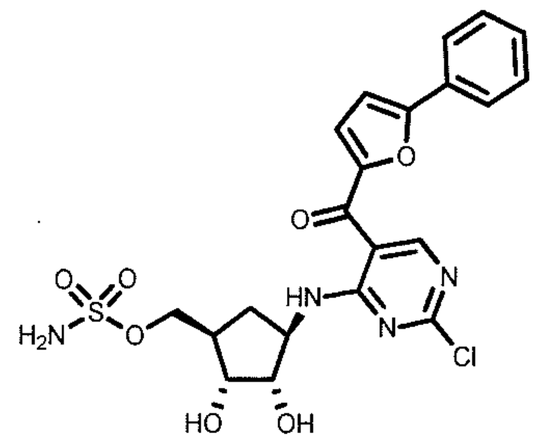
I-233



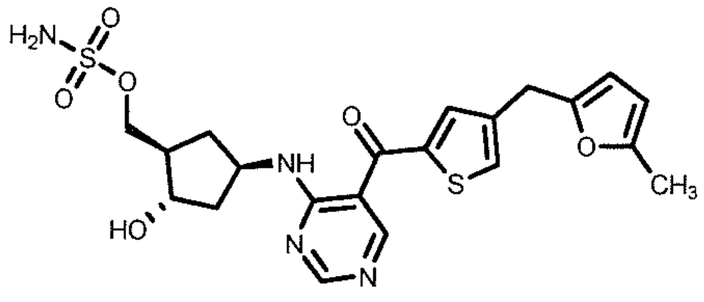
I-234



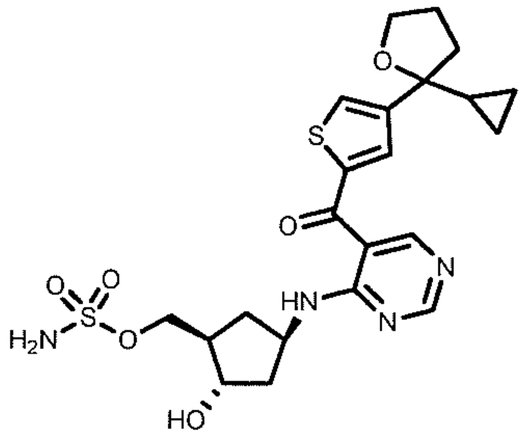
I-235



I-236



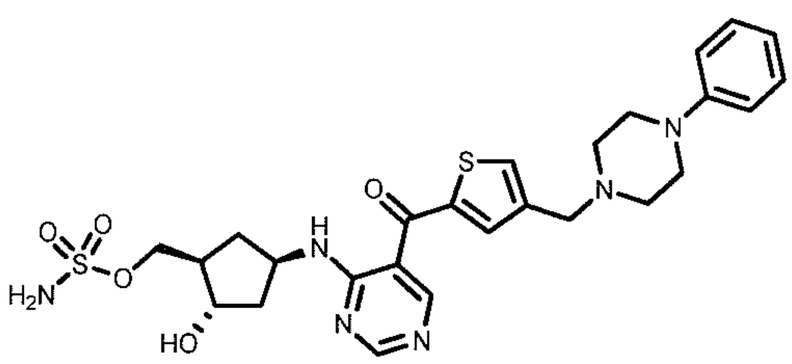
I-237



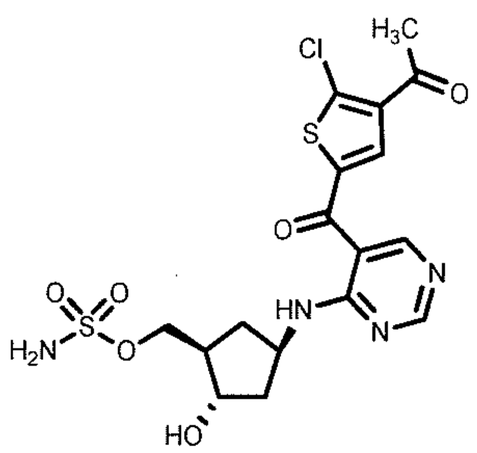
I-238

I-239

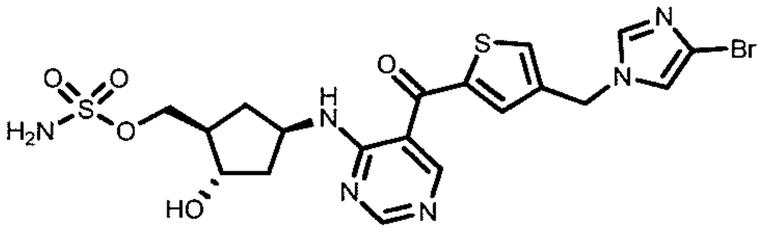
I-240



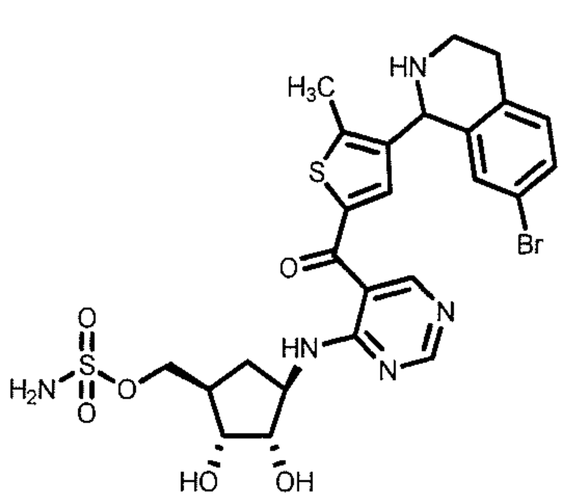
I-241



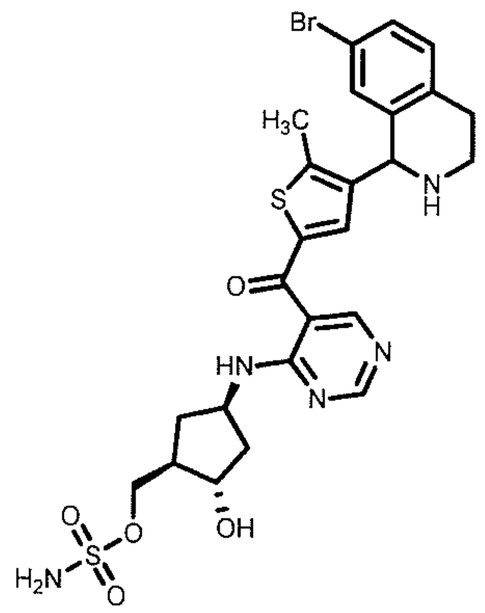
I-242



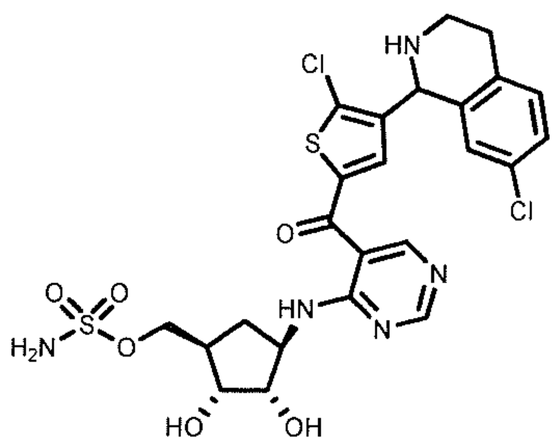
I-243



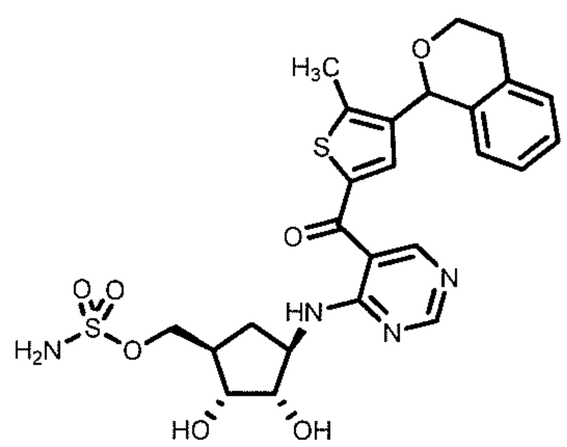
I-247a
I-247b



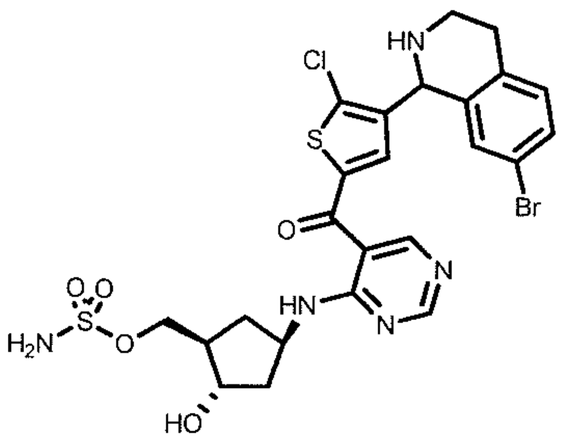
I-248a
I-248b



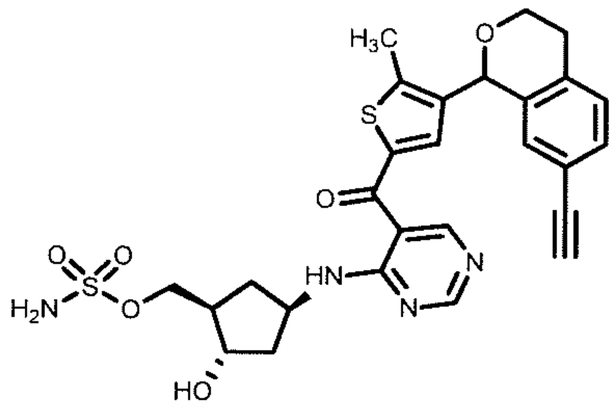
I-249a
I-249b



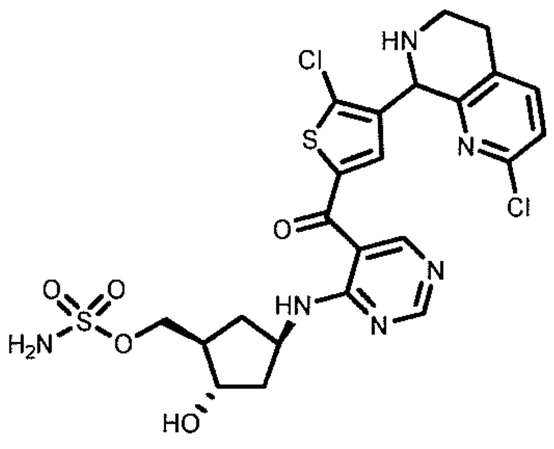
I-250
I-250a
I-250b

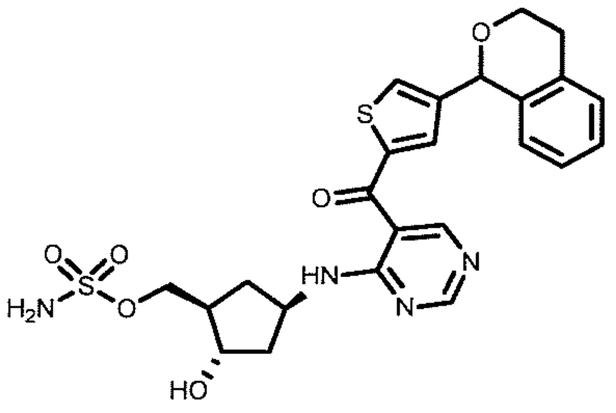


I-251
I-251a
I-251b

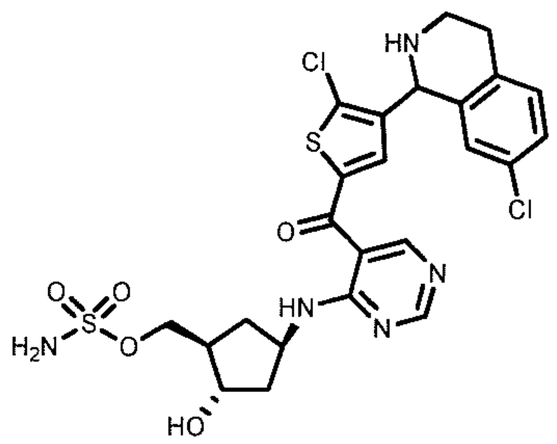


I-252
I-252a
I-252b

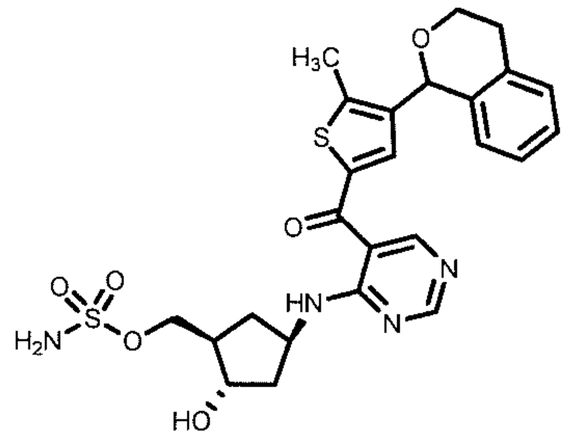




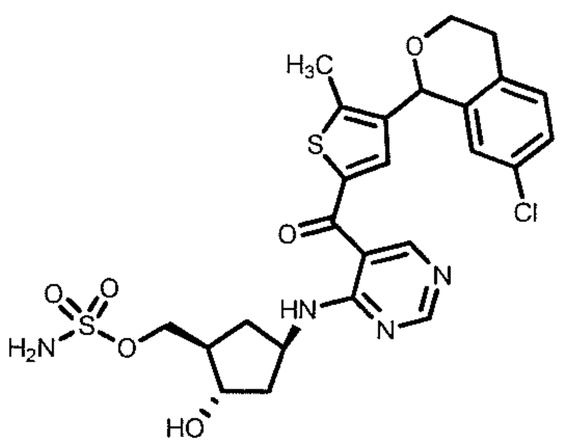
I-253
I-253a
I-253b



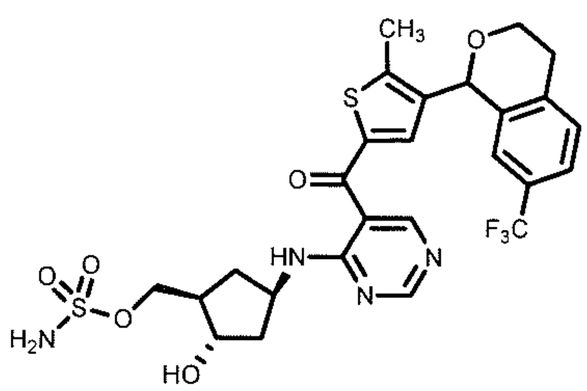
I-254
I-254a
I-254b



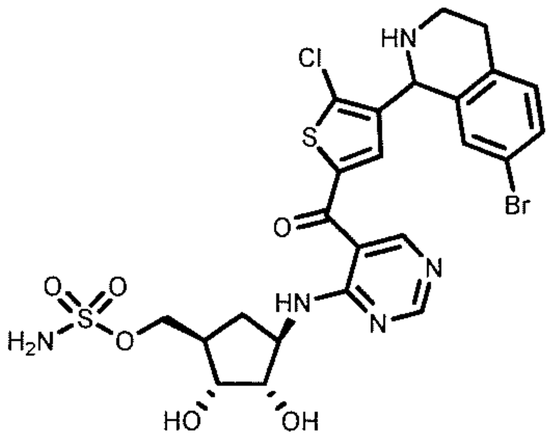
I-255a
I-255b



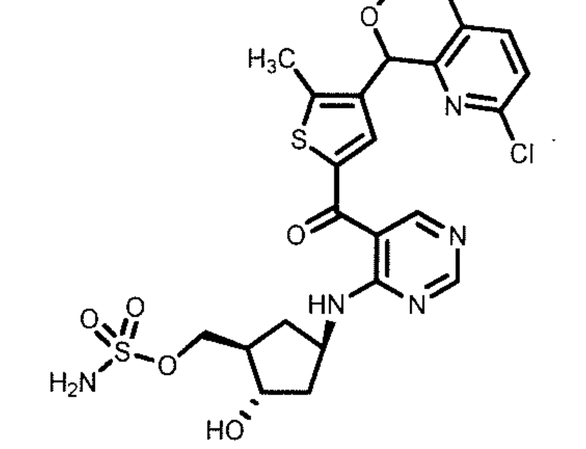
I-256
I-256a
I-256b



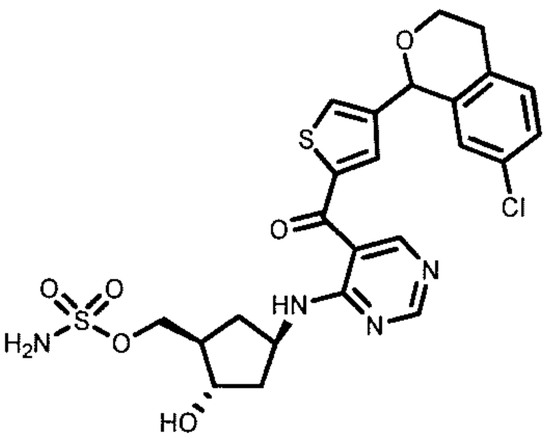
I-257
I-257a
I-257b



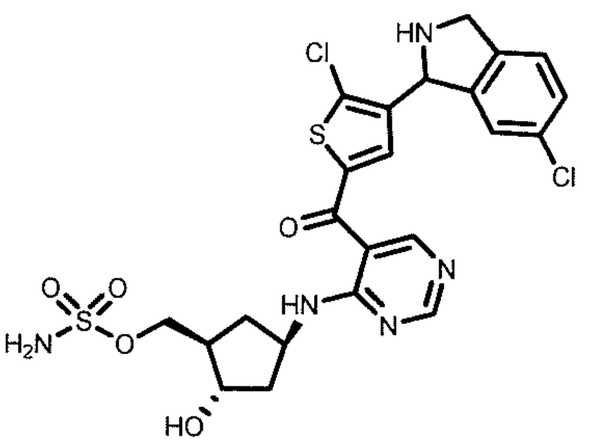
I-258
I-258a
I-258b



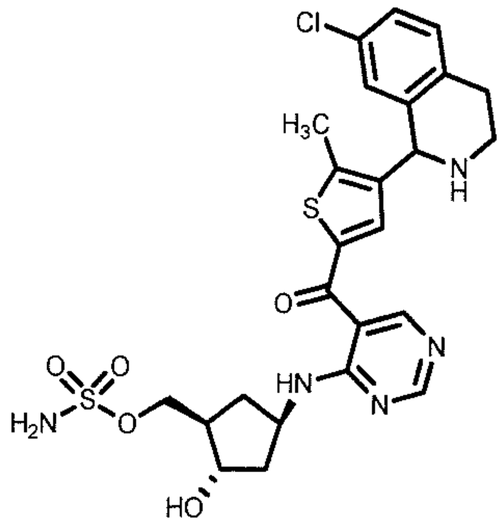
I-259
I-259a
I-259b



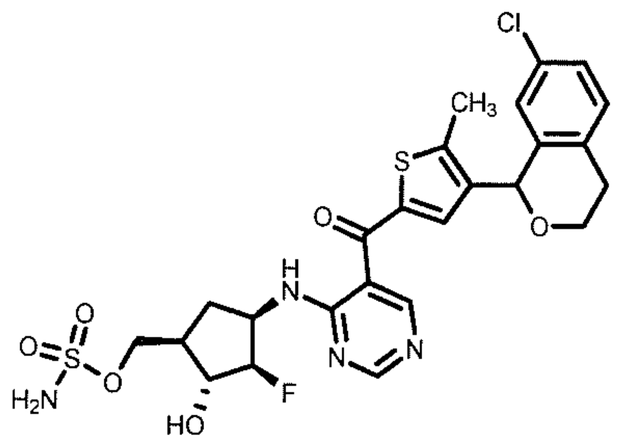
I-260
I-260a
I-260b



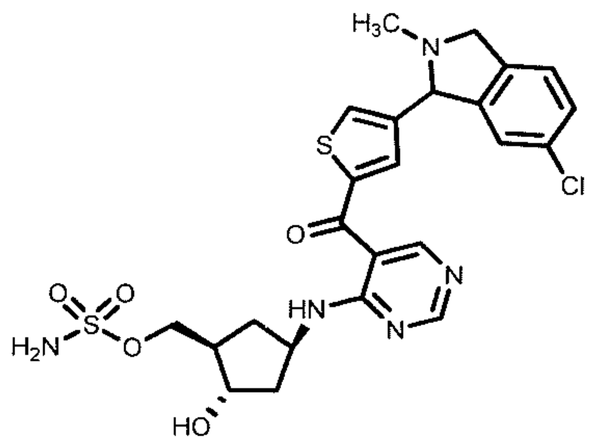
I-261
I-261a
I-261b



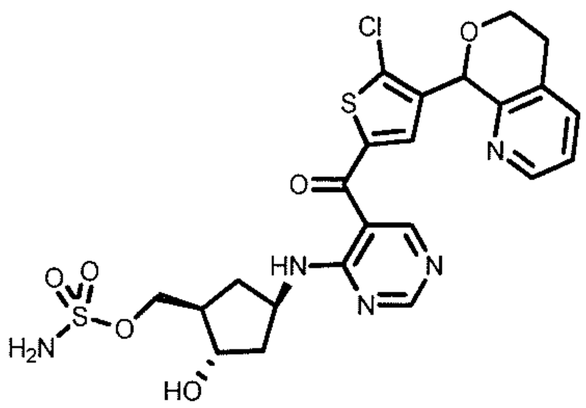
I-262
I-262a
I-262b



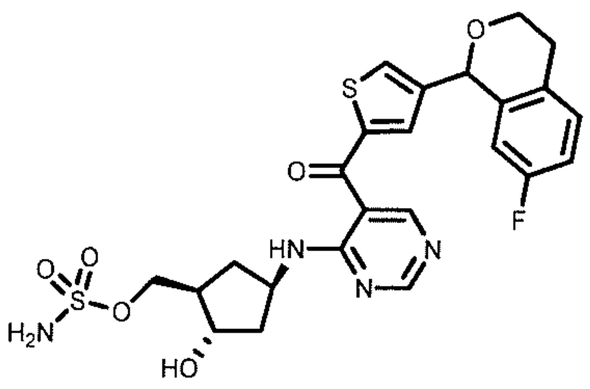
I-263a
I-263b



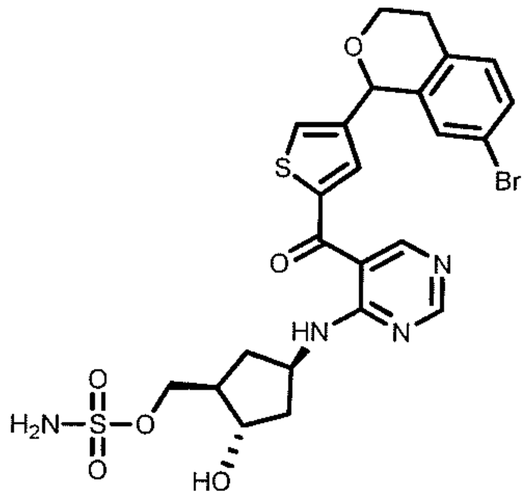
I-264
I-264a
I-264b



I-265
I-265a
I-265b

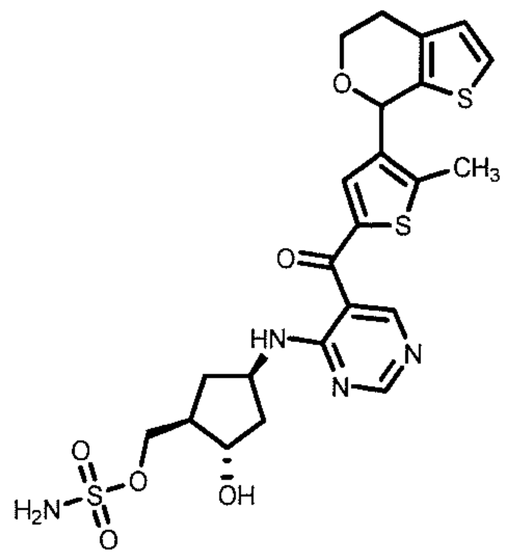


I-266
I-266a
I-266b

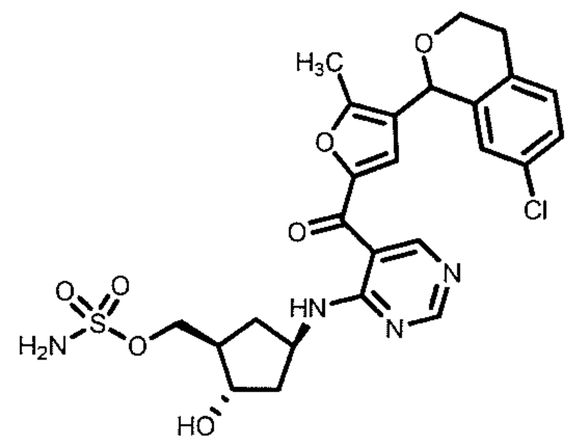


I-267
I-267a
I-267b

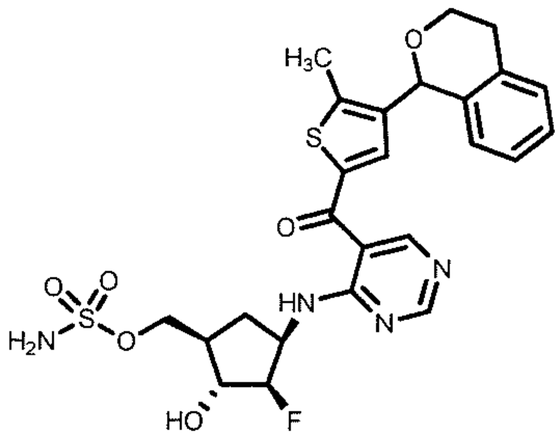
I-268
I-268a
I-268b



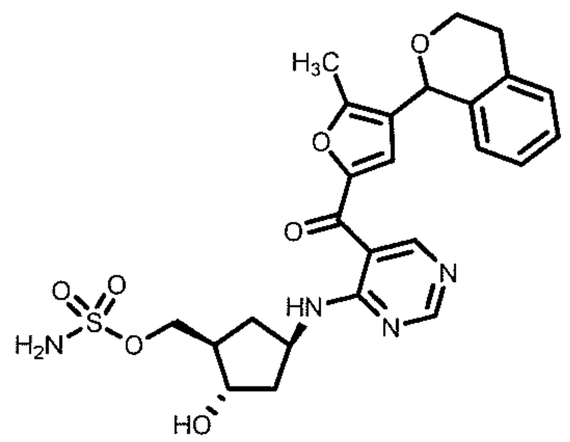
I-269
I-269a
I-269b



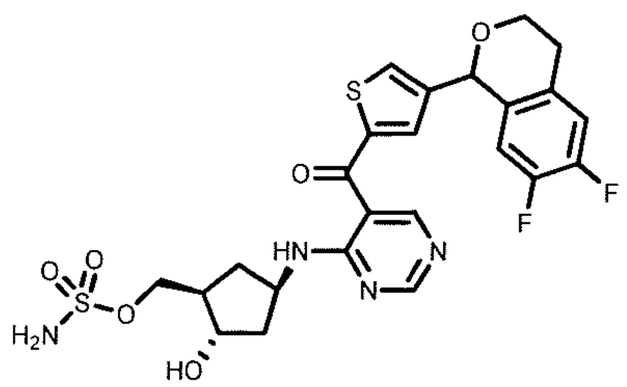
I-270
I-270a
I-270b



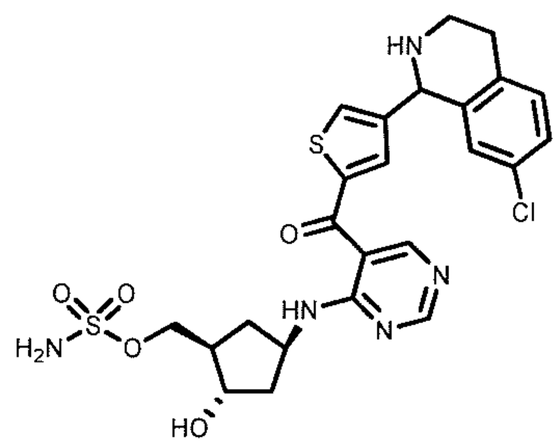
I-271a



I-272a
I-272b



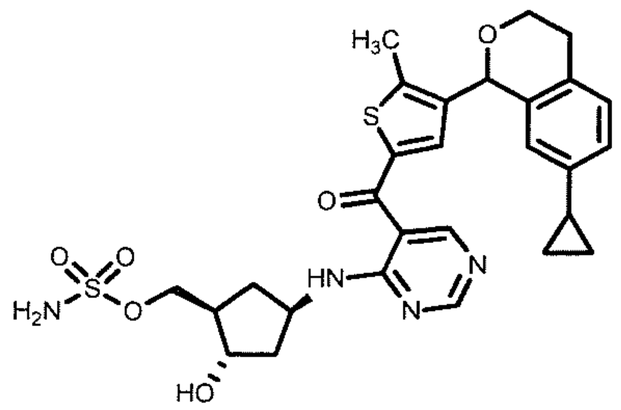
I-273 a



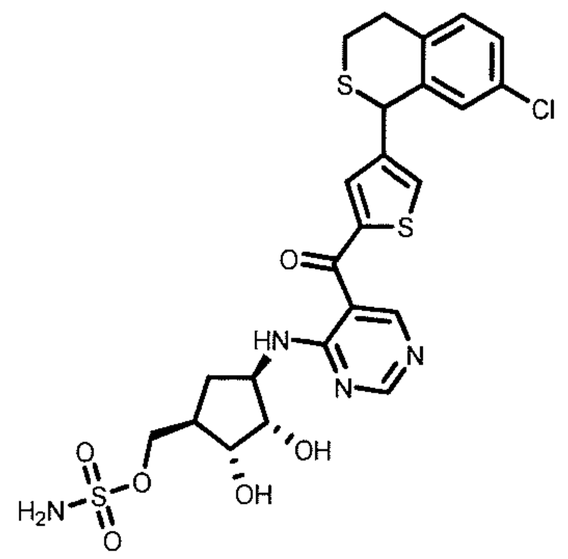
I-274
I-274a
I-274b

I-275

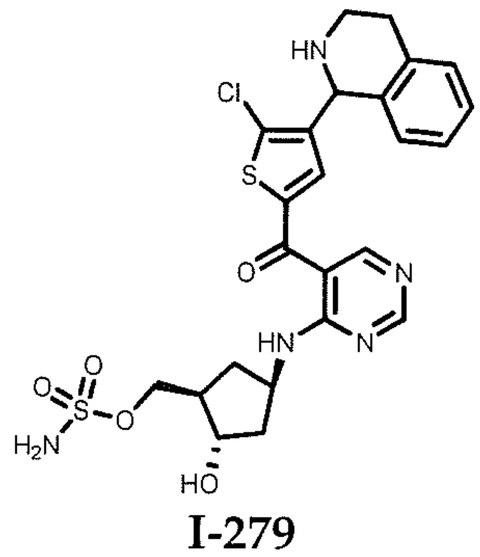
I-276
I-276a
I-276b



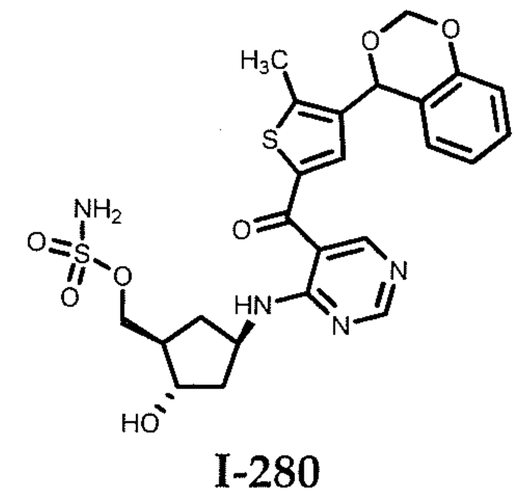
I-277
I-277a
I-277b



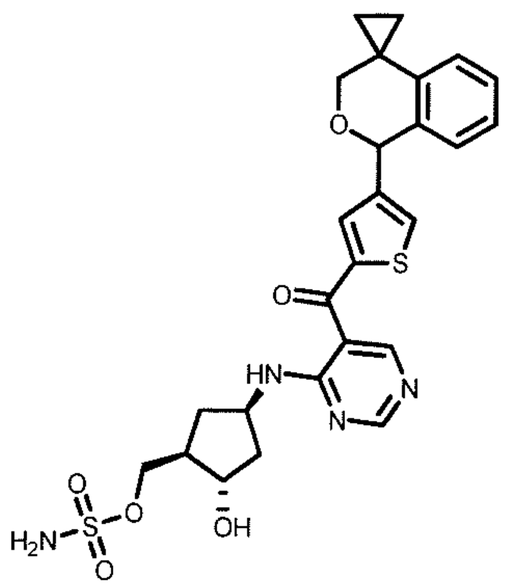
I-278
I-278a
I-278b



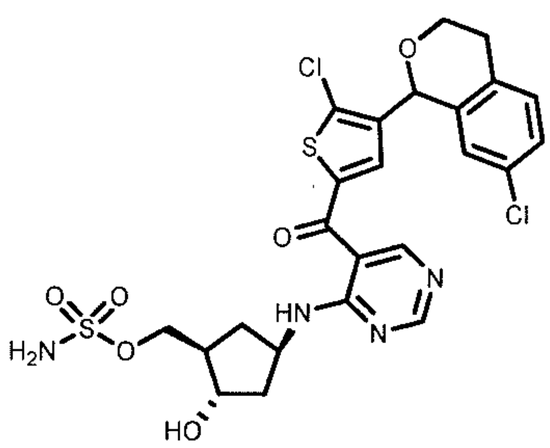
I-279
I-279a
I-279b



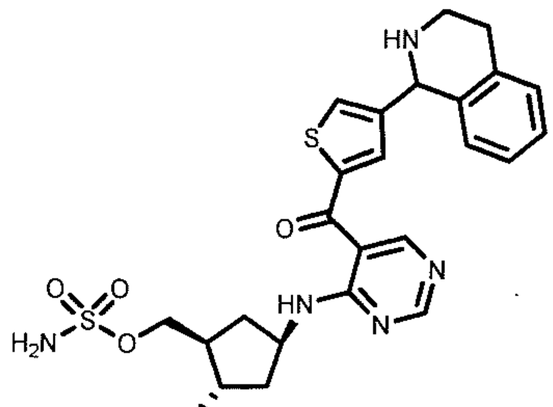
I-280
I-280a
I-280b



I-281
I-281a
I-281b



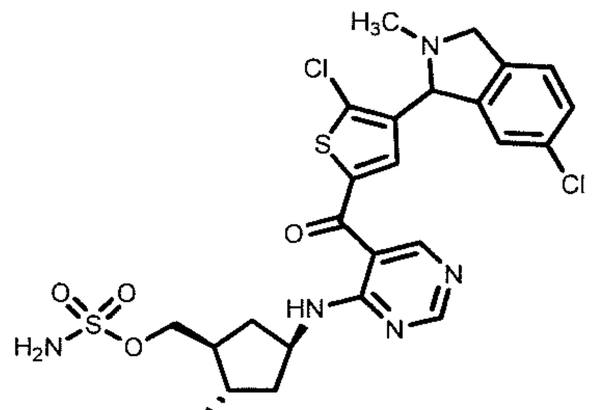
I-282
I-282a
I-282b



I-283

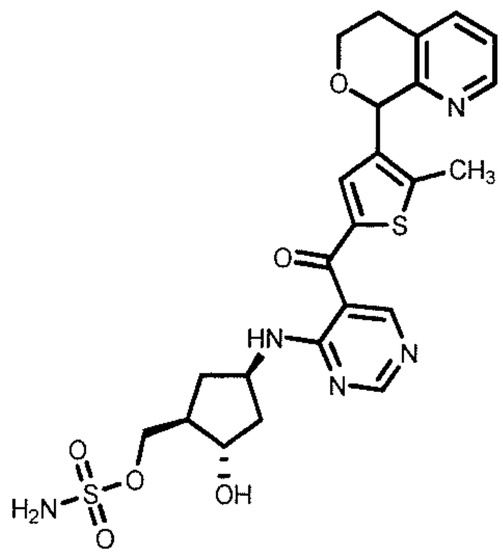
I-283a

I-283b



I-284a

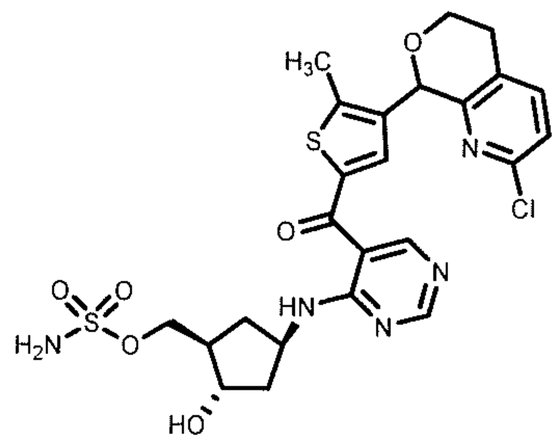
I-284b



I-285

I-285a

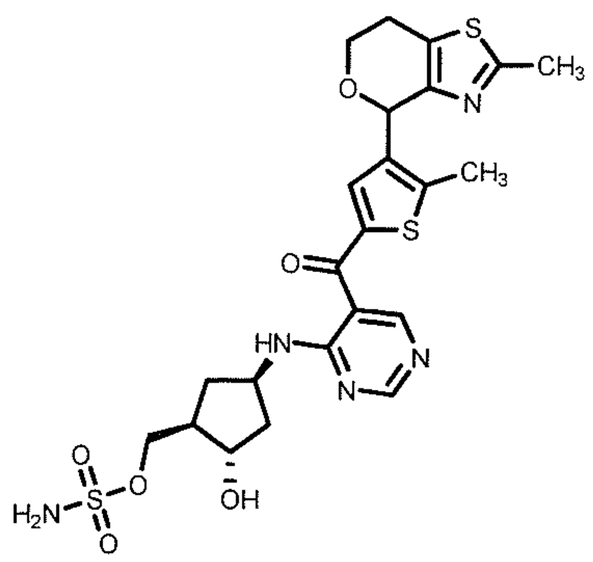
I-285b



I-286

I-286a

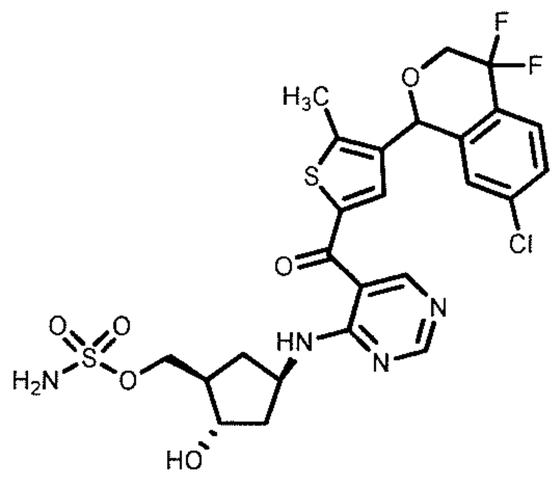
I-286b



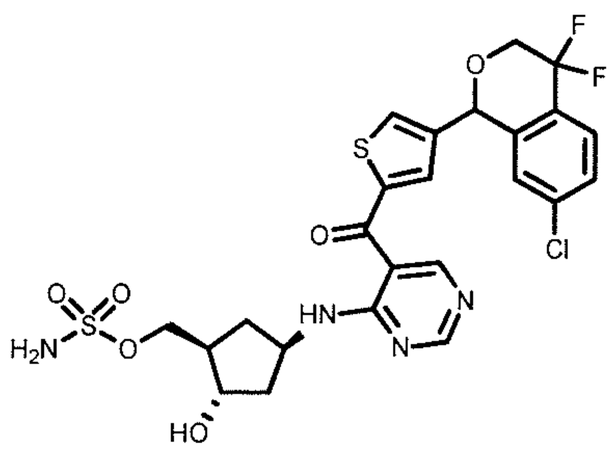
I-287

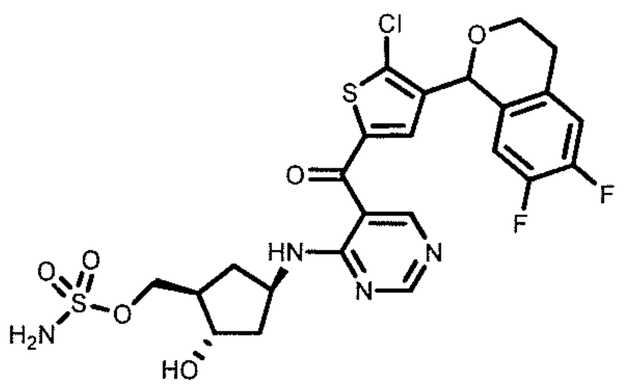
I-287a

I-287b



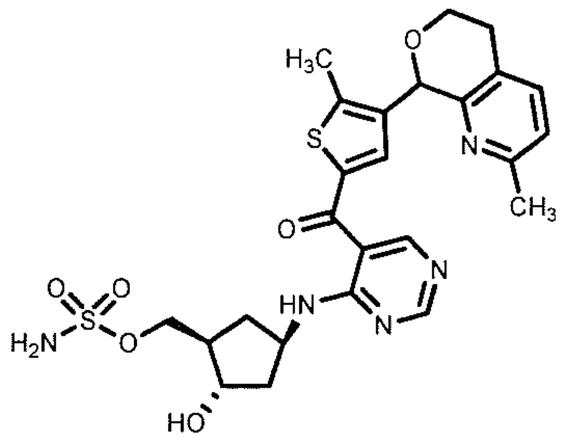
I-288



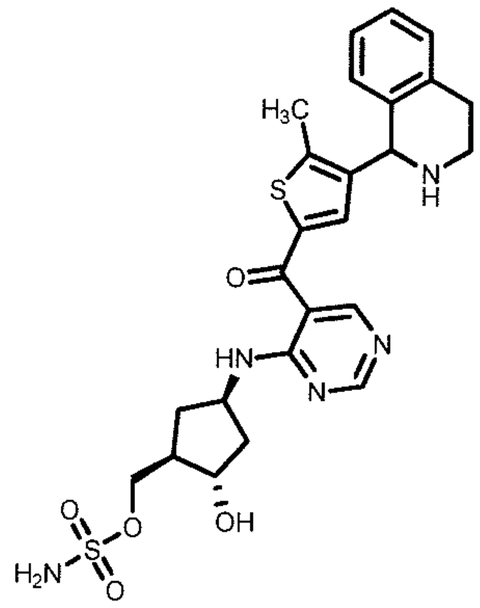


I-289
I-289a
I-289b

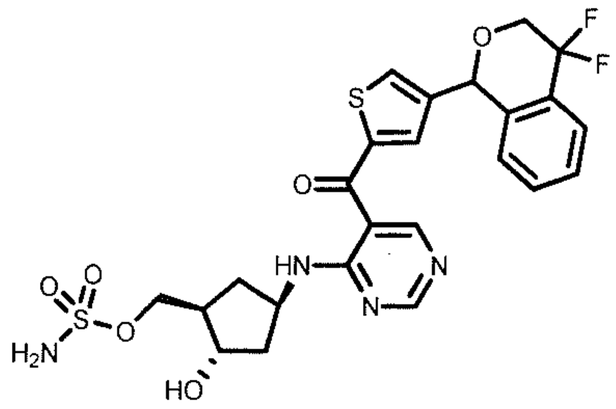
I-290a
I-290b



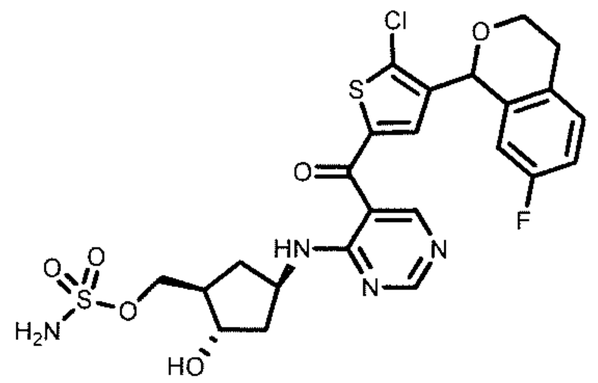
I-291
I-291a
I-291b



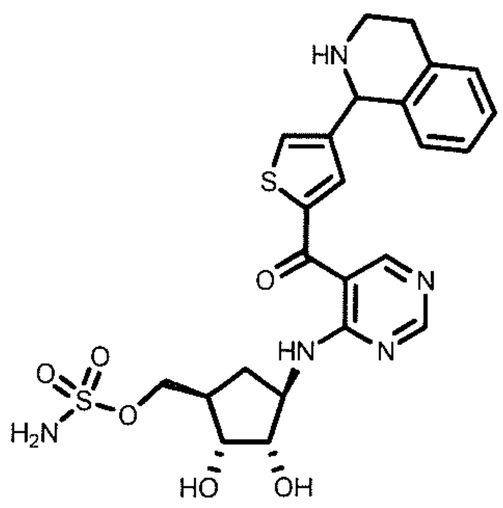
I-292a
I-292b



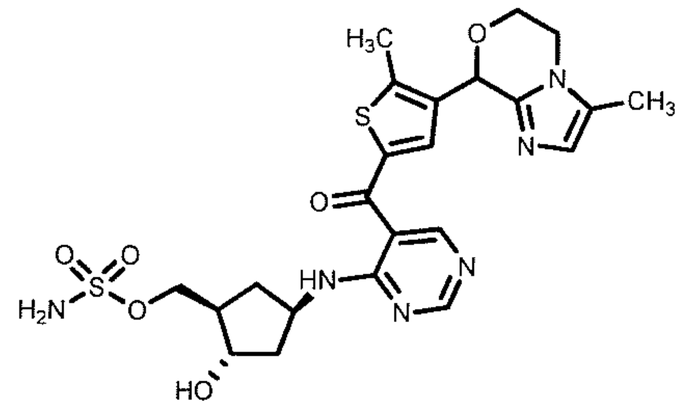
I-293
I-293a
I-293b



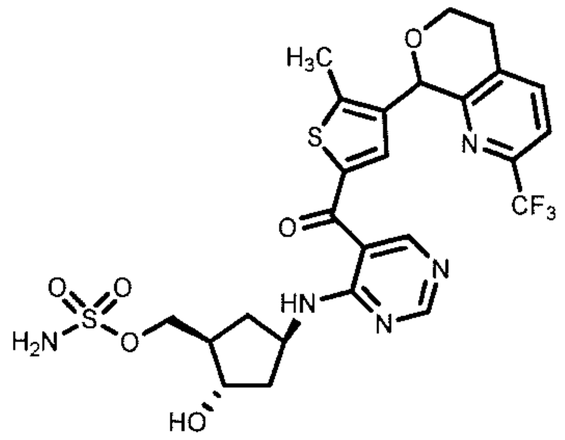
I-294
I-294a
I-294b



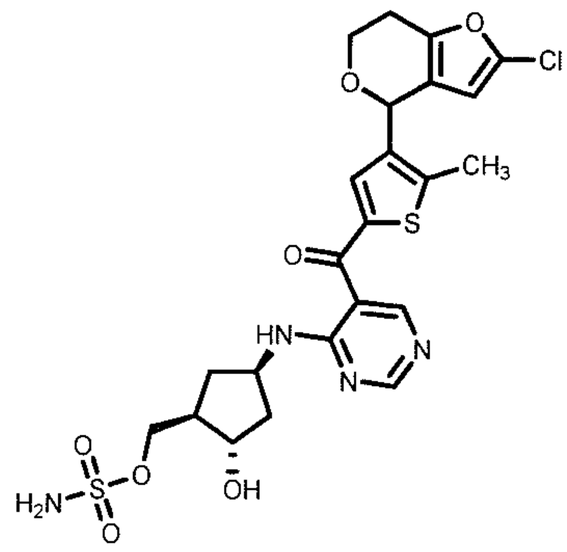
I-295



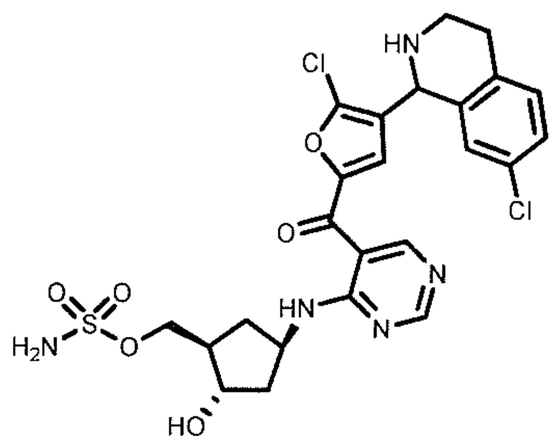
I-296



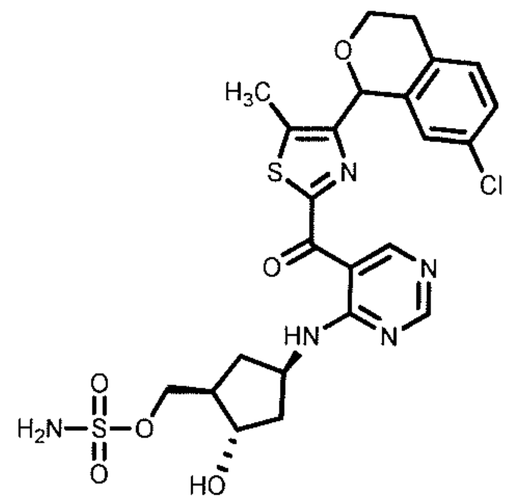
I-297
I-297a
I-297b



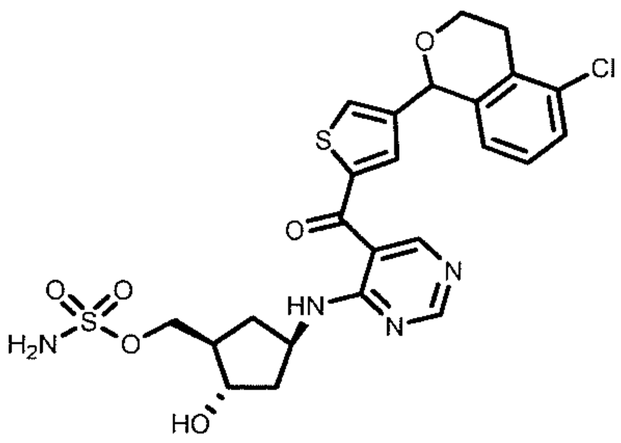
I-298
I-298a
I-298b



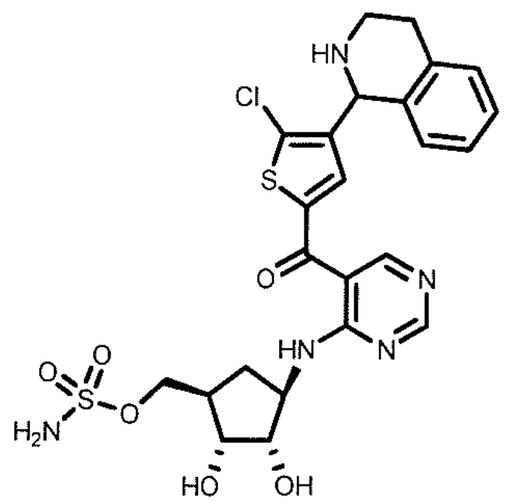
I-299
I-299a
I-299b



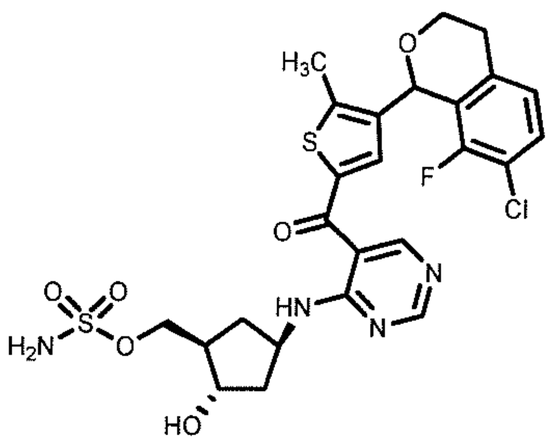
I-300a
I-300b



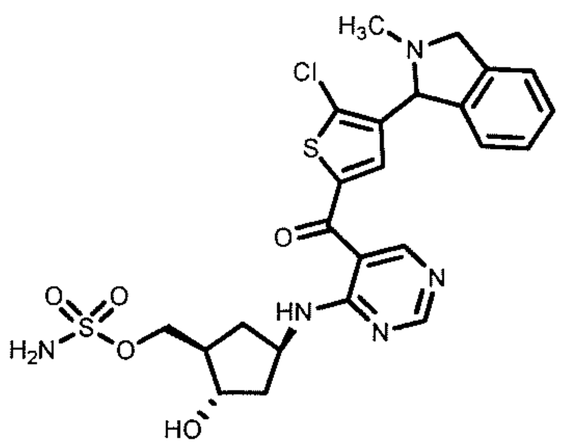
I-301
I-301a
I-301b



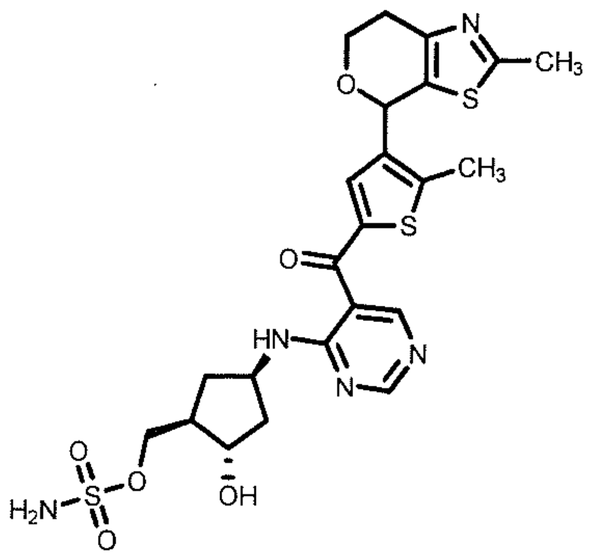
I-302



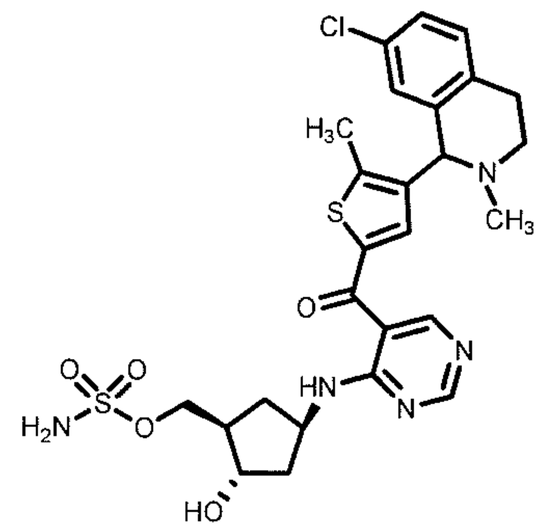
I-303



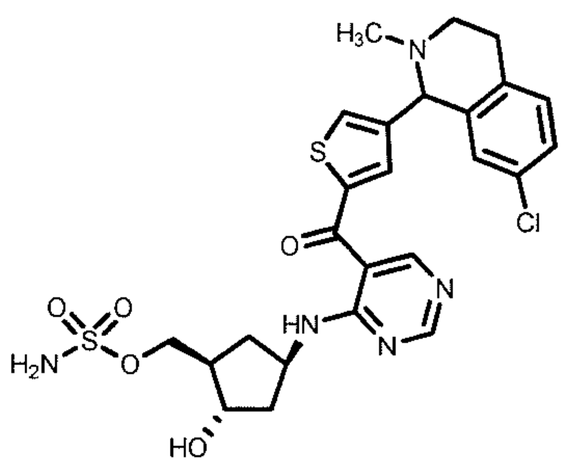
I-304



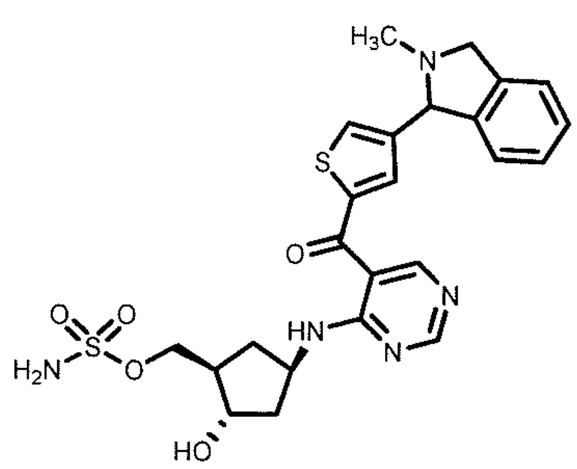
I-305
I-305a
I-305b



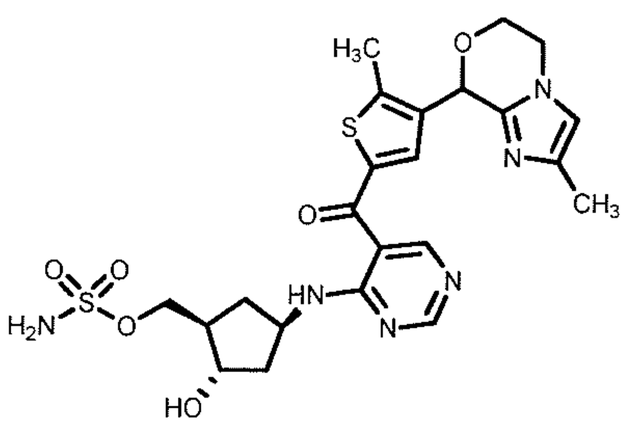
I-306



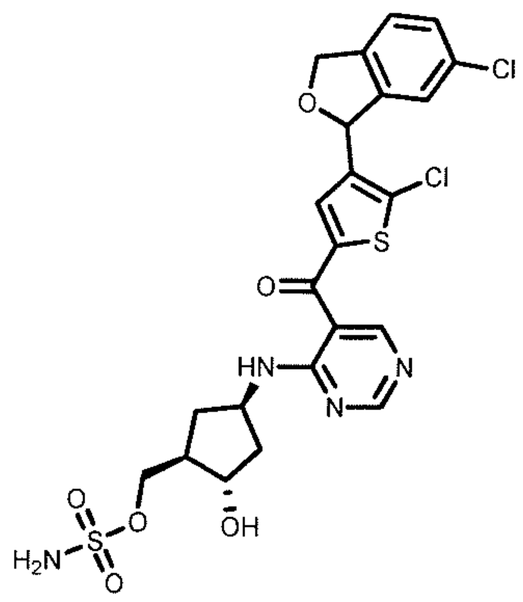
I-307
I-307a
I-307b



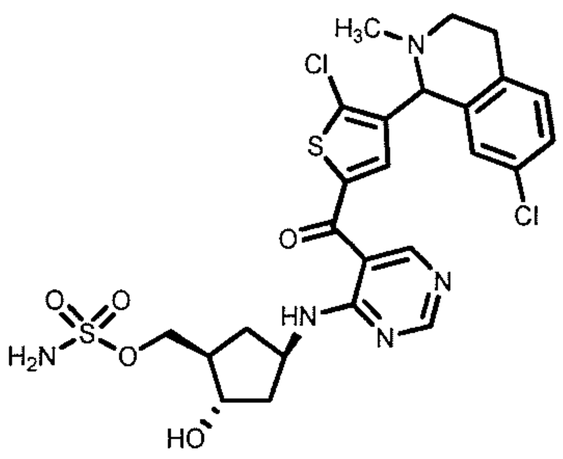
I-308



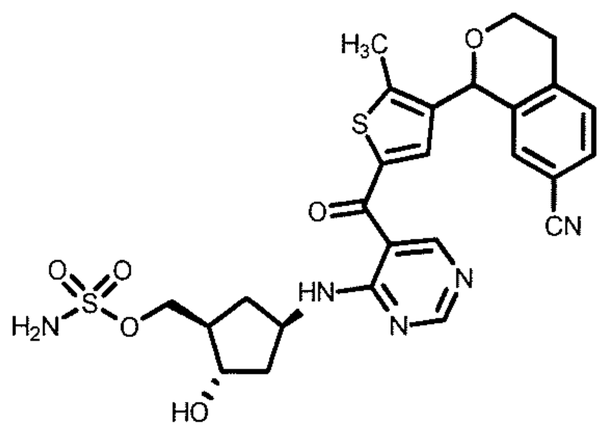
I-309



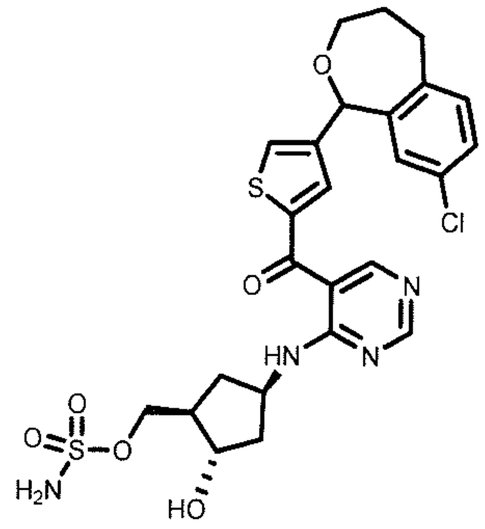
I-310
I-310a
I-310b



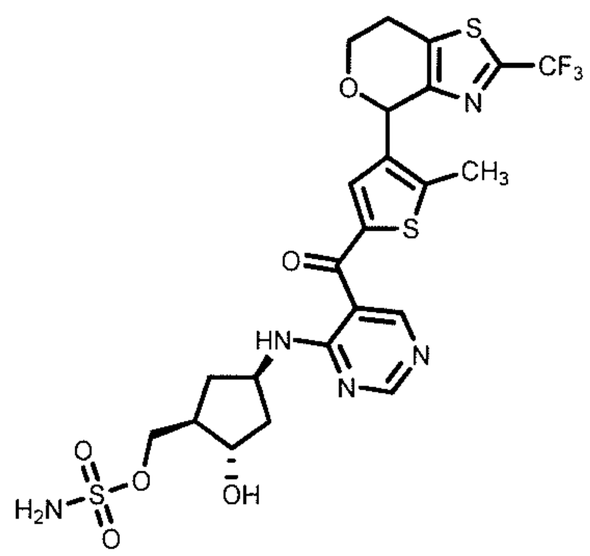
I-311a
I-311b



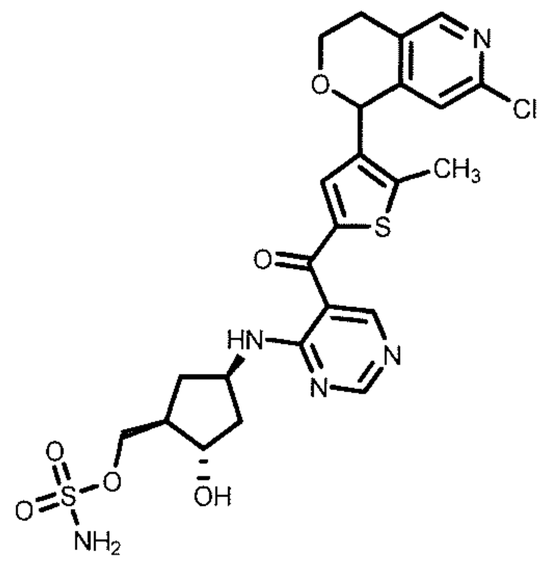
I-313



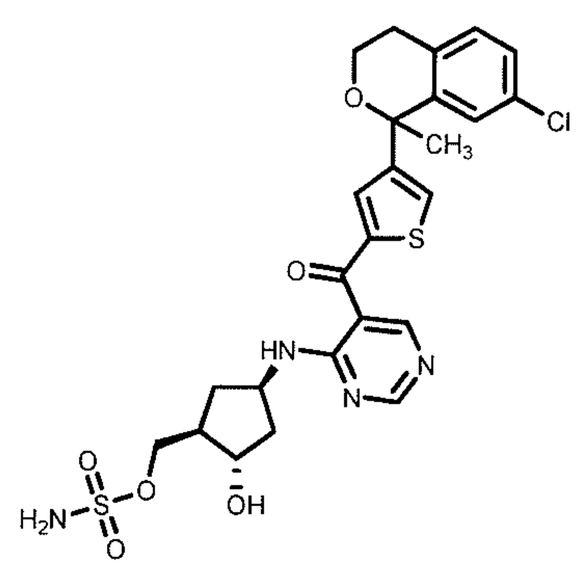
I-314
I-314a
I-314b



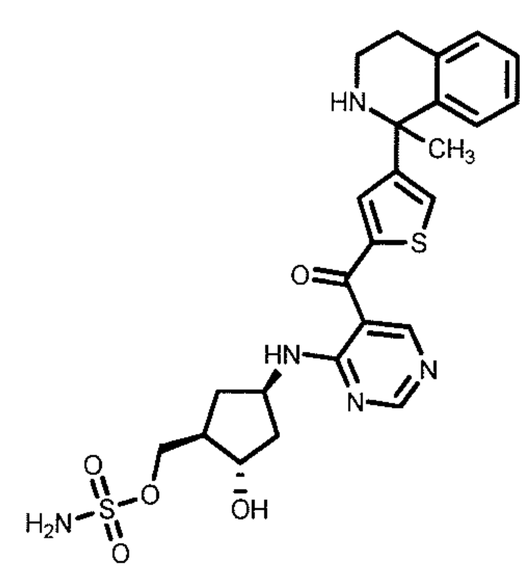
I-315



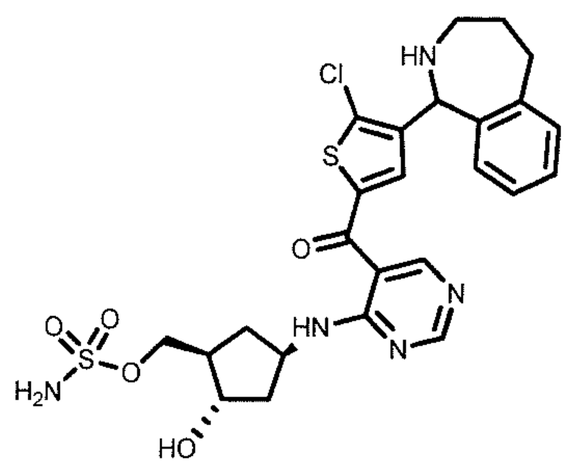
I-316



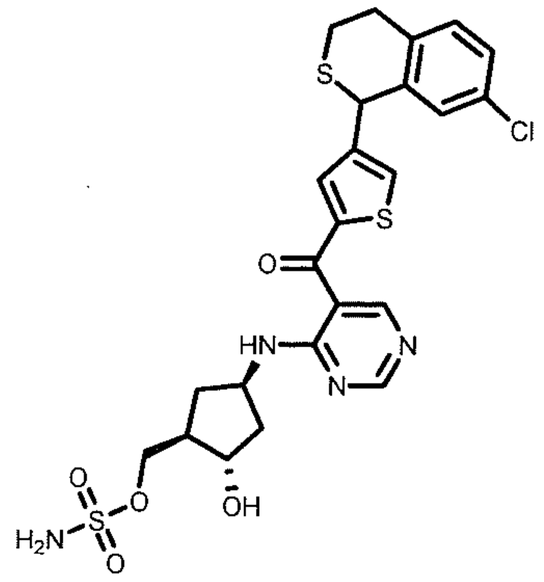
I-317



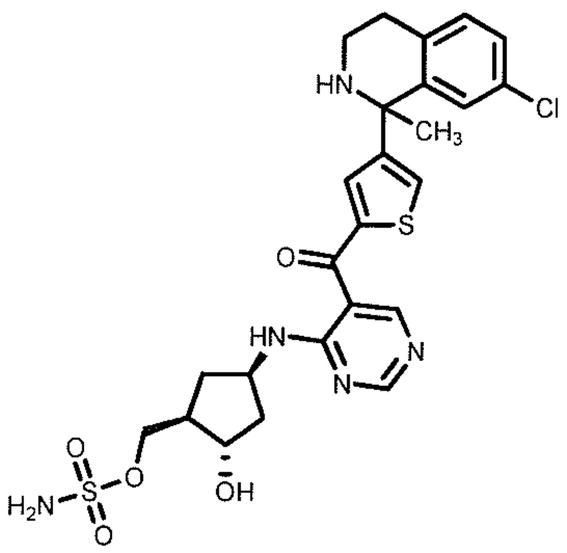
I-318



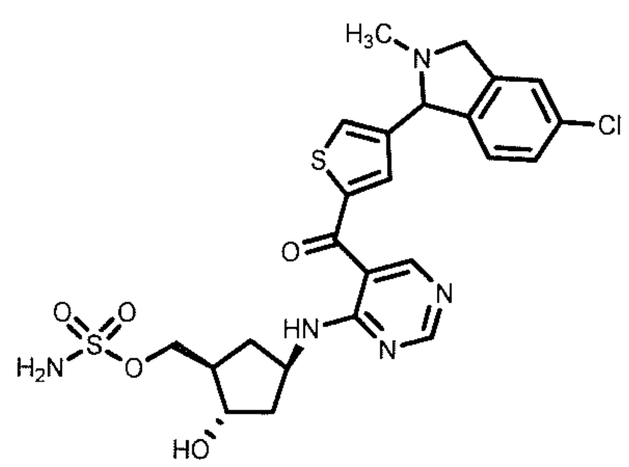
I-319



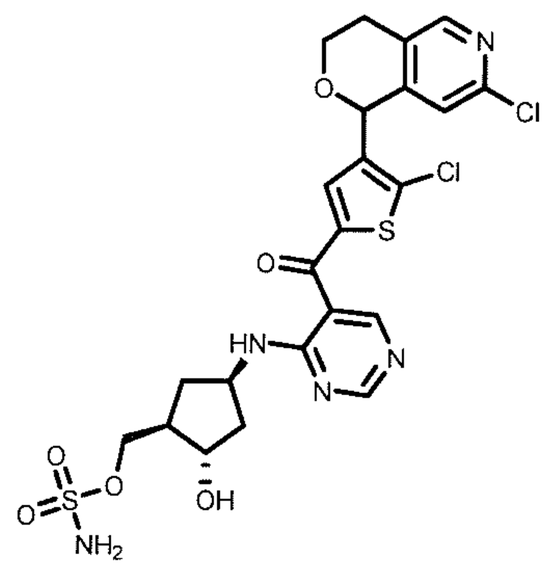
I-320
I-320a
I-320b



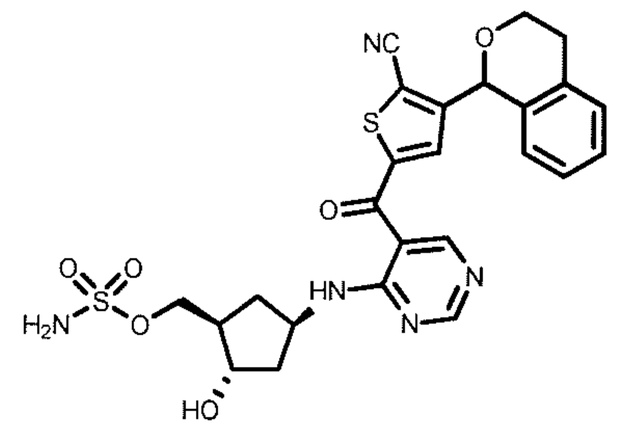
I-321



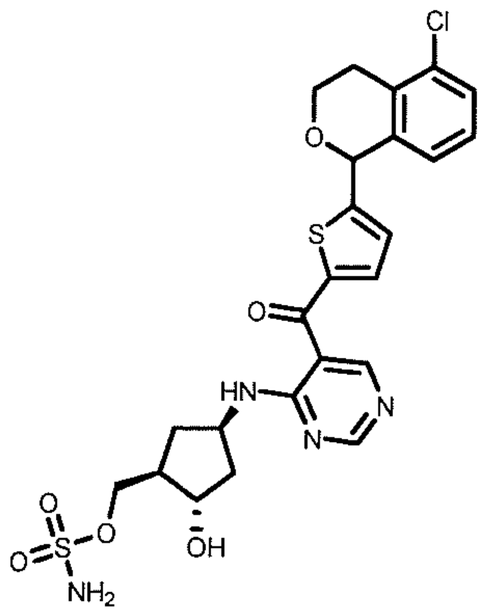
I-322



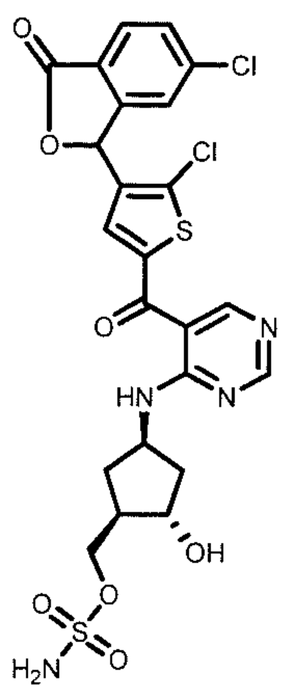
I-323



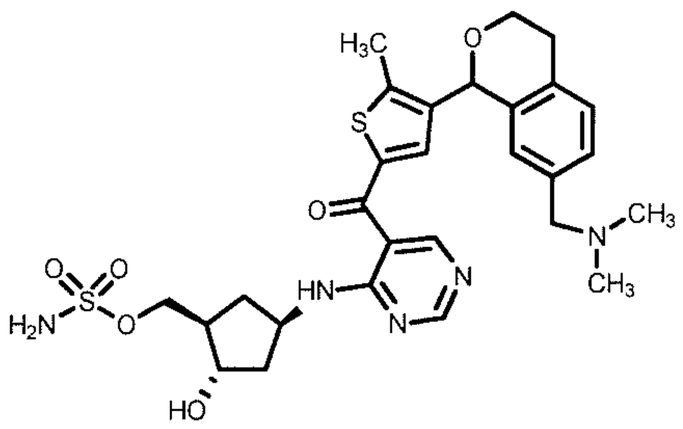
I-324



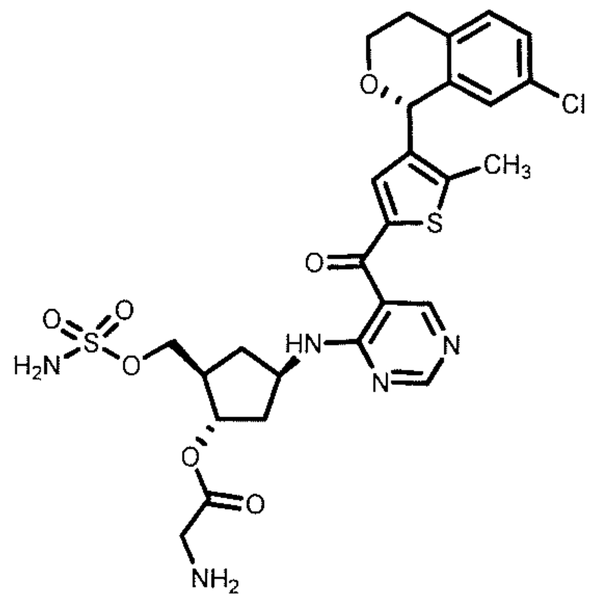
I-325



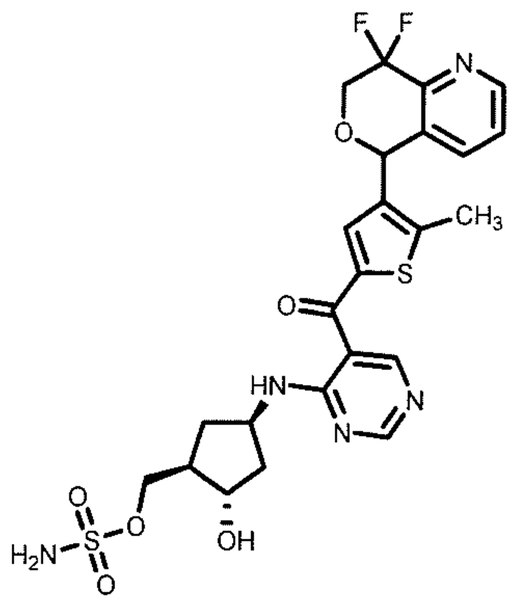
I-327



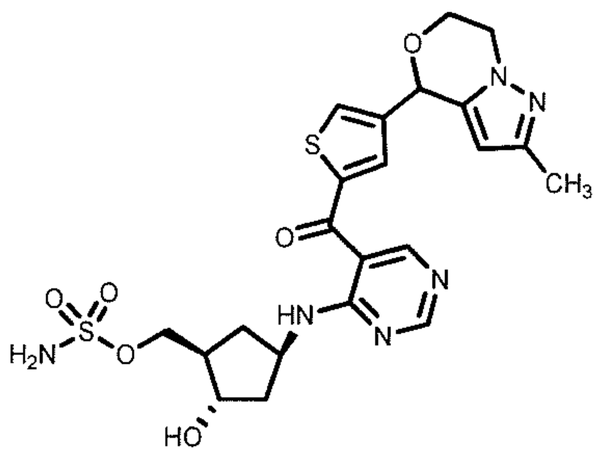
I-329



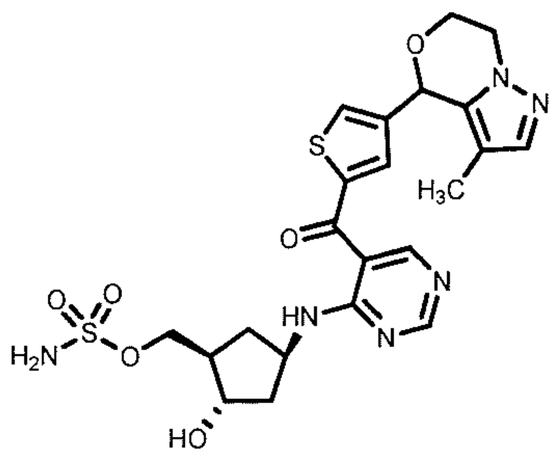
I-330



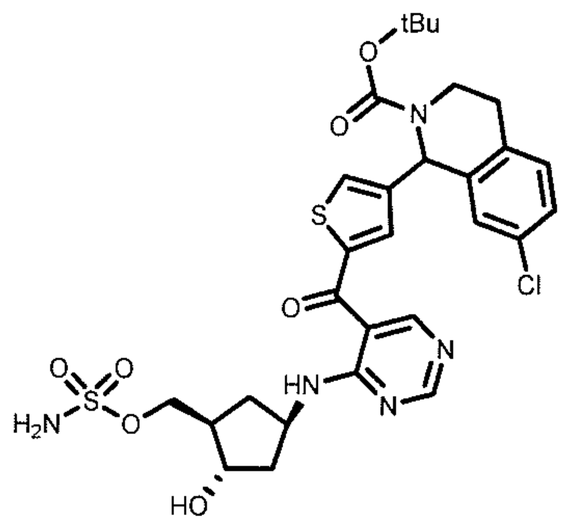
I-331



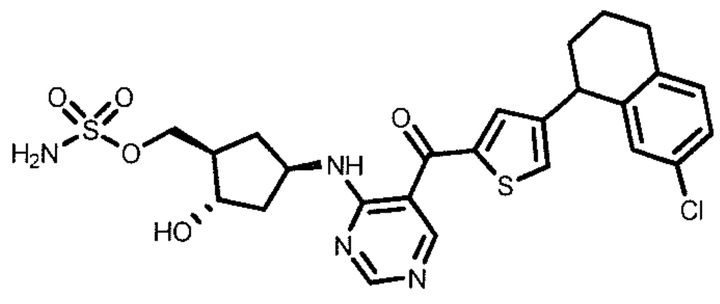
I-332



I-333



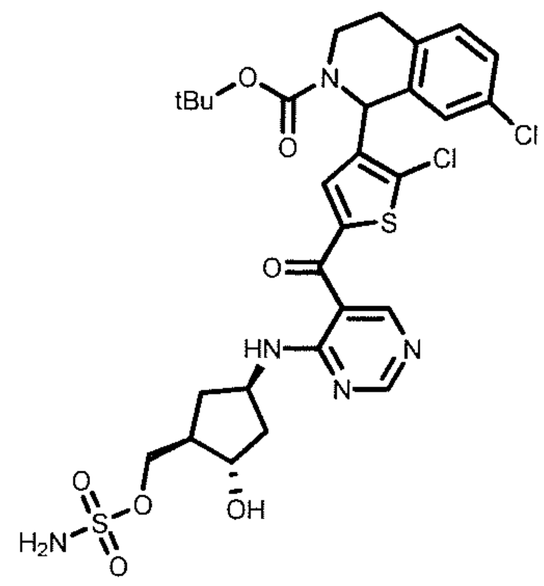
I-334



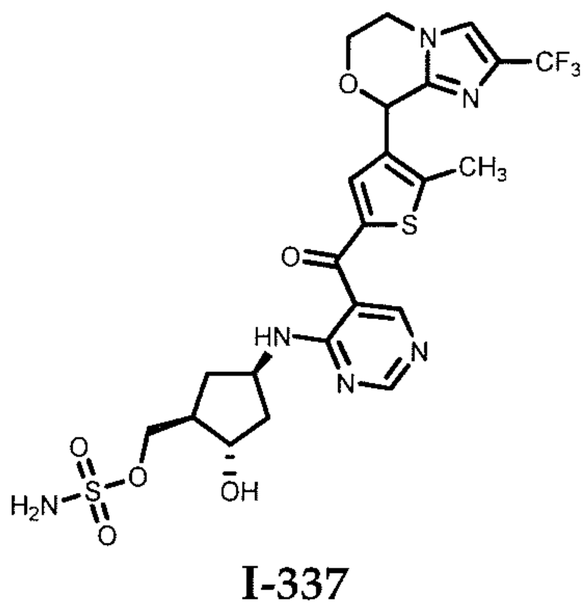
I-335

I-335a

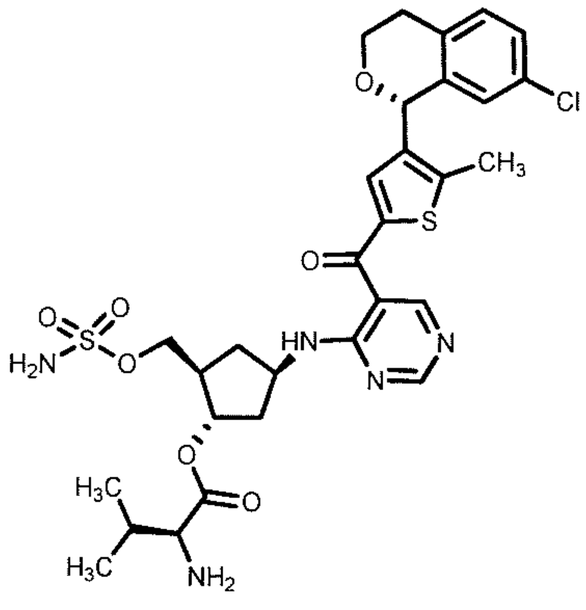
I-335b



I-336



I-337

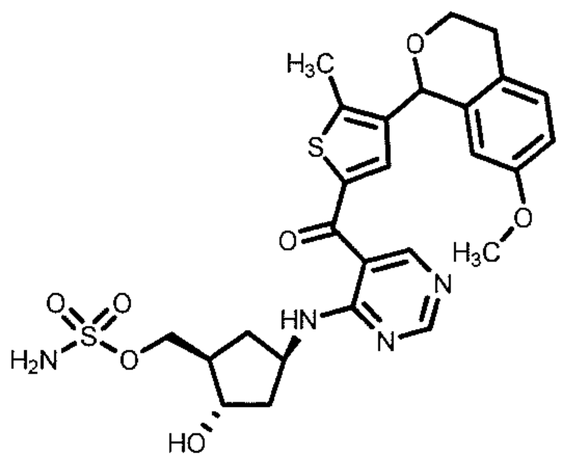


I-338

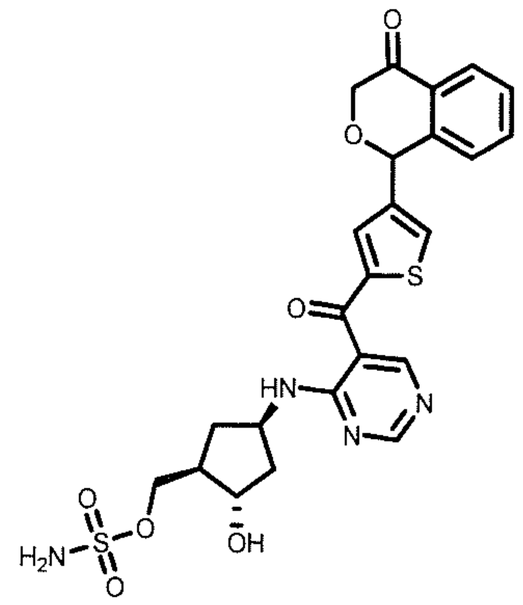
I-339

I-339a

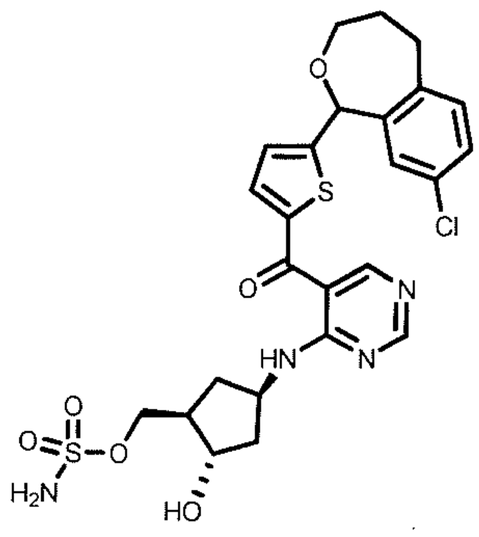
I-339b



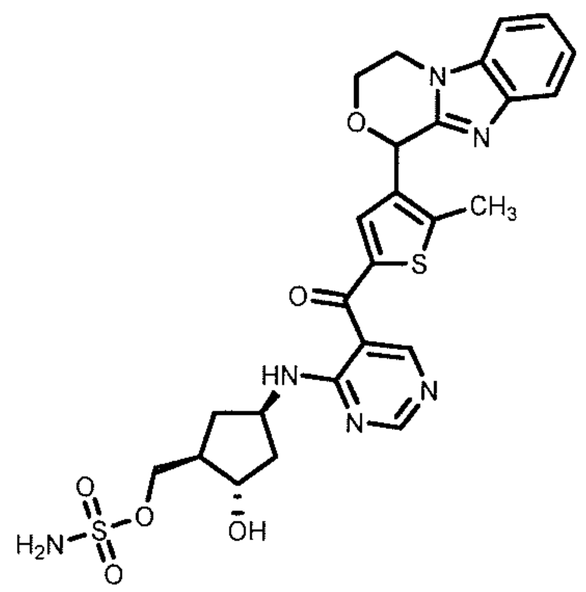
I-341



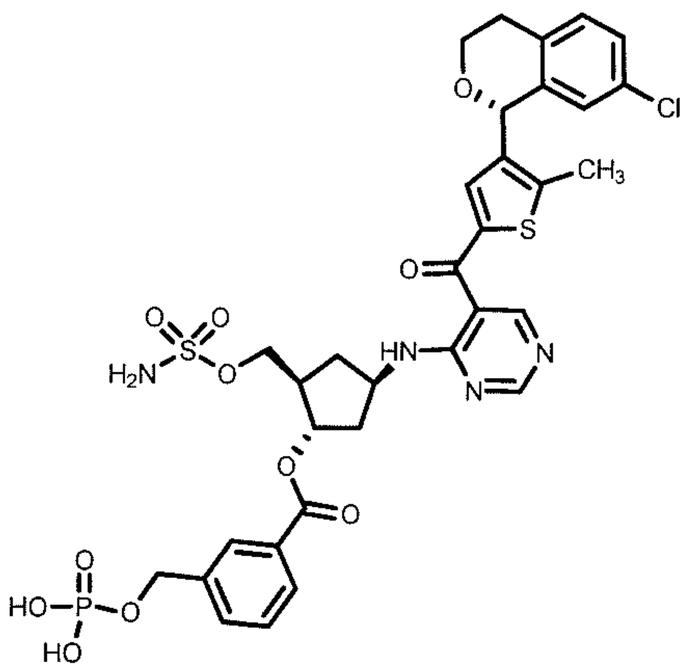
I-342



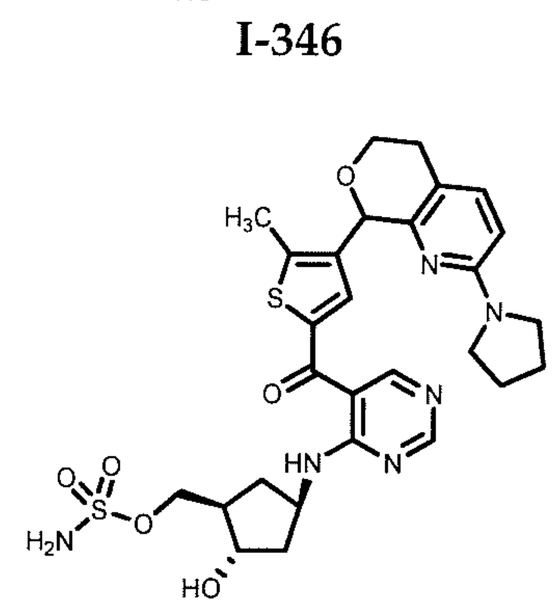
I-343a
I-343b



I-344

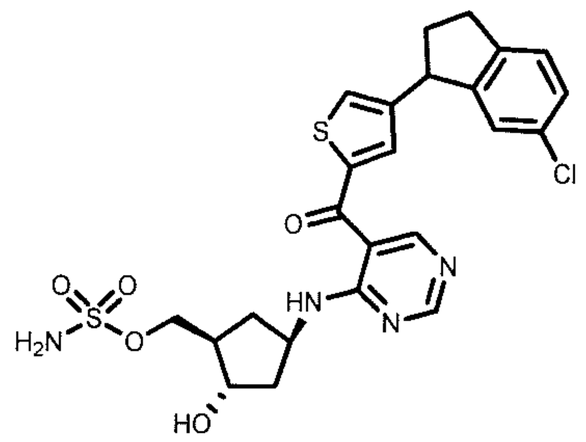


I-345

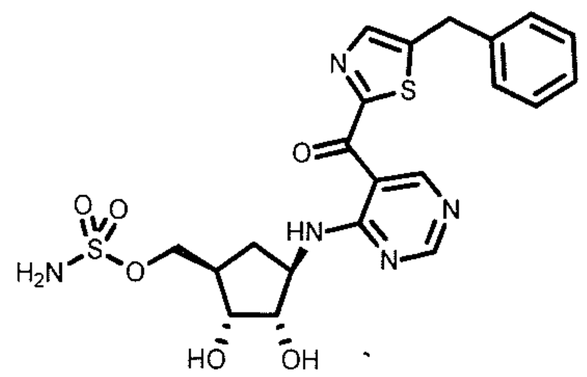


I-346

I-347



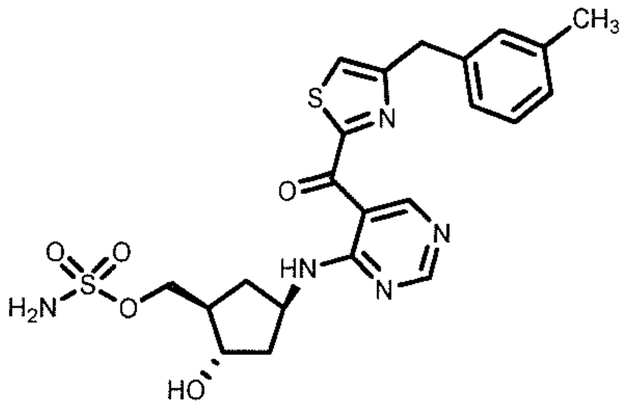
I-348



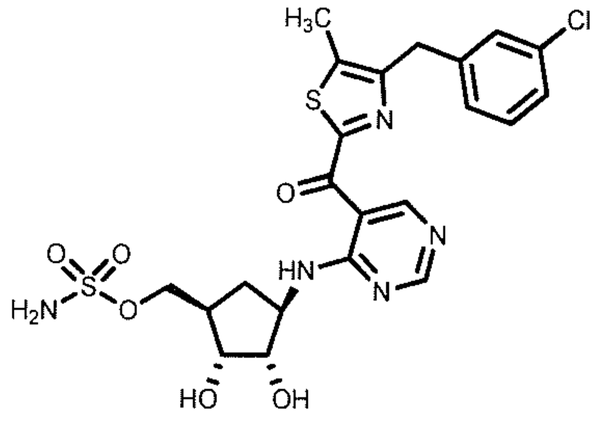
I-349

I-349a

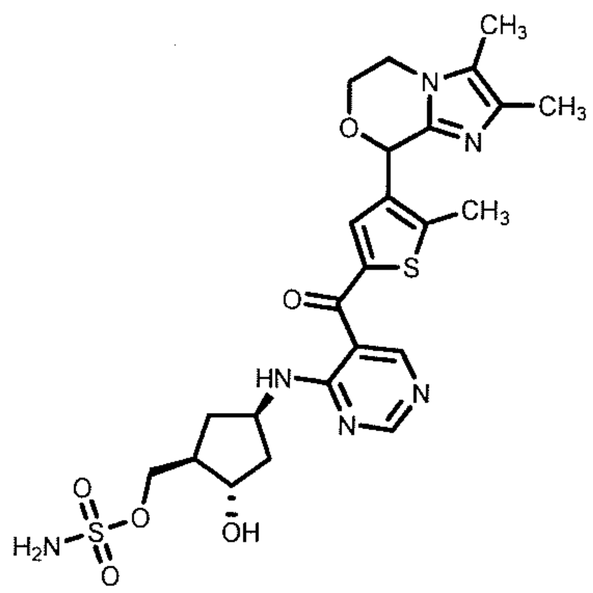
I-349b



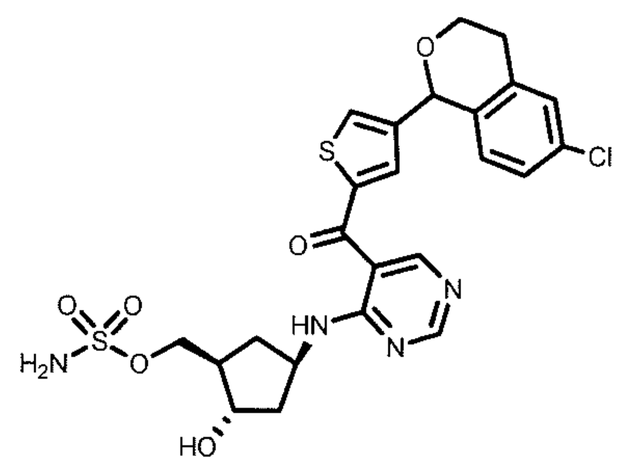
I-350



I-351



I-352

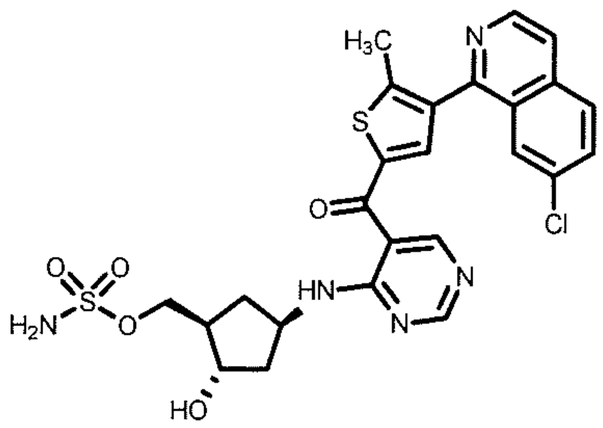


I-356

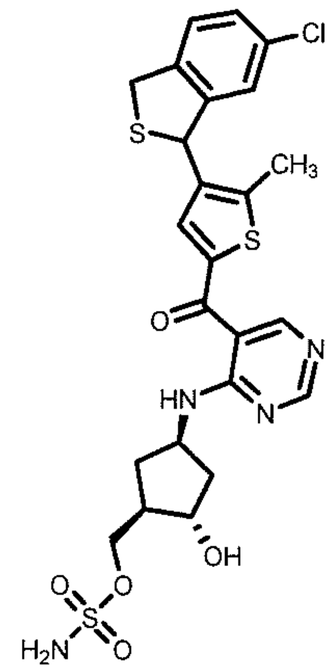
I-356a

I-356b

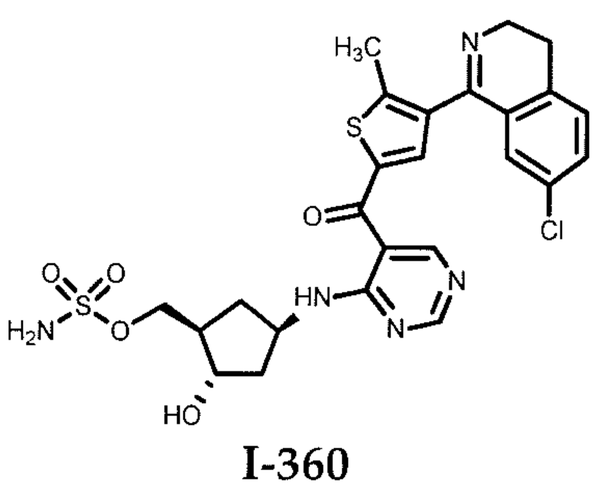
I-357



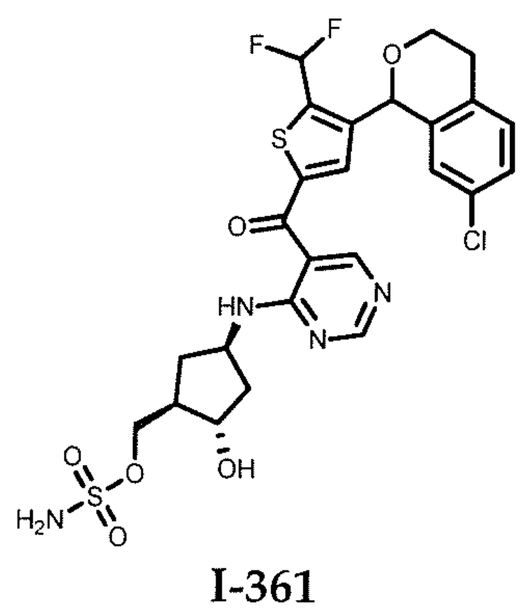
I-358



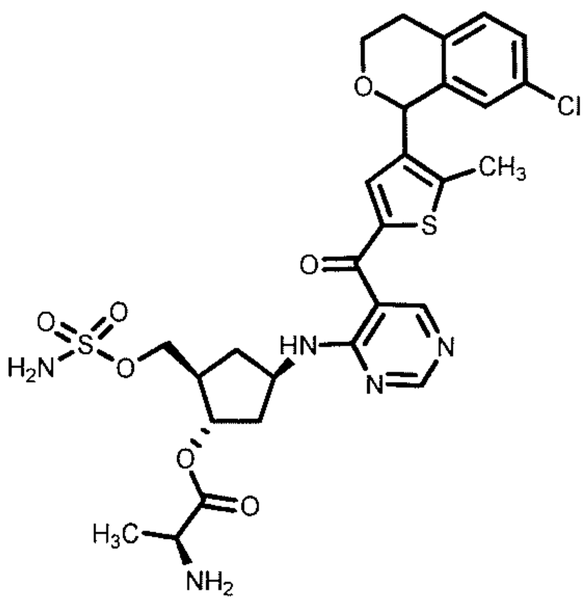
I-359a
I-359b



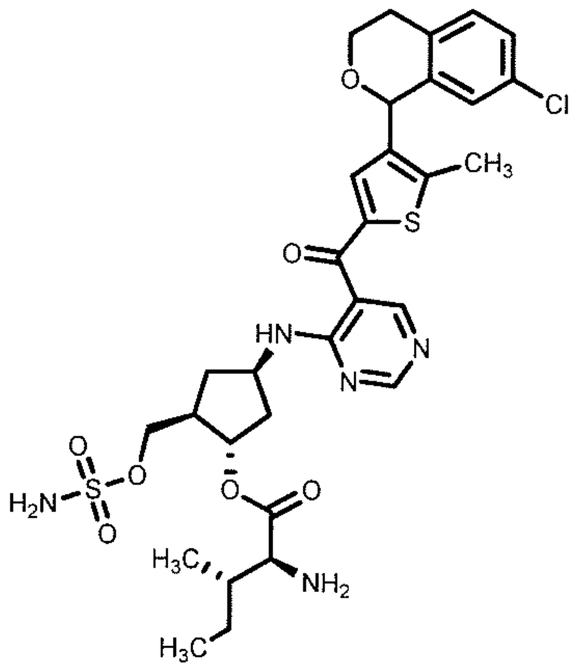
I-360



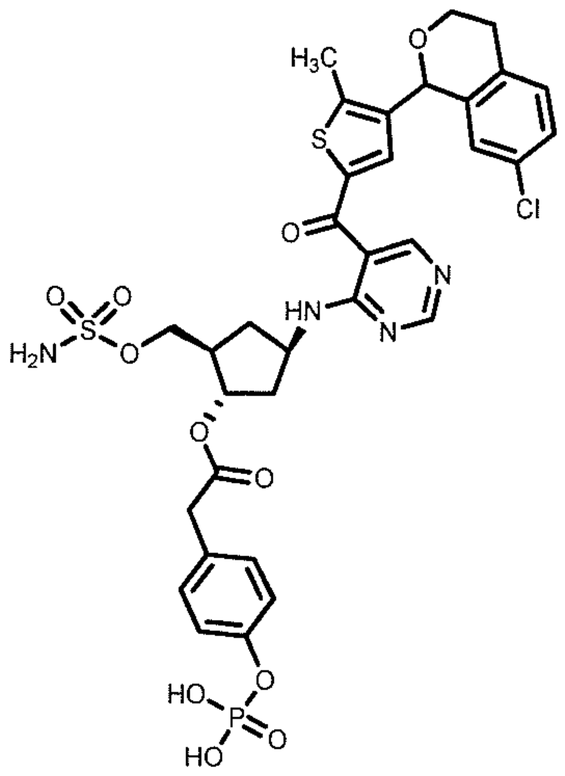
I-361



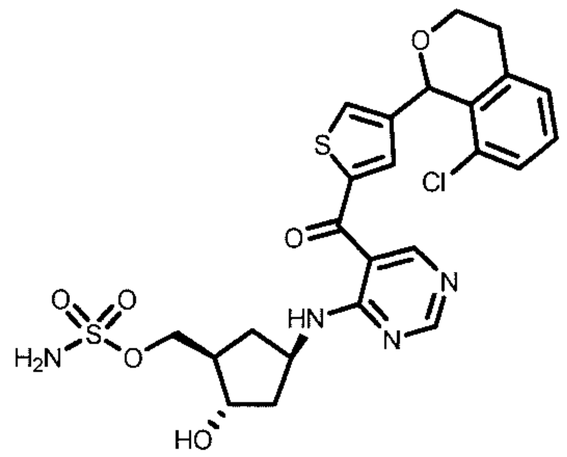
I-362



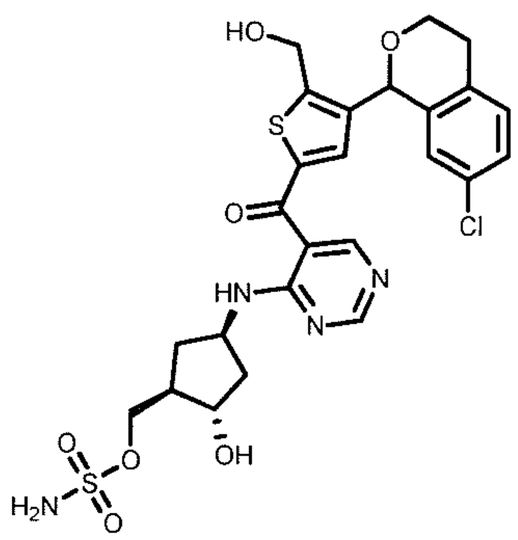
I-363



I-364



I-365



I-366

[00184] The chemical entities in Table 1 may also be identified by the following chemical names:

Compound No.	Name
I-1	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-1a	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-1b	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-2	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
	and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-2a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-2b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-3	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-3a	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-3b	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-4	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-4a	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-4b	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-5	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-5a	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-5b	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-6	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-6a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-6b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-7	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-7a	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-7b	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-8	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-8a	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or

Compound No.	Name
	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-8b	or
	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-9	and
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-9a	or
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-9b	or
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-10	and
	[(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-10a	or
	[(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-10b	or
	[(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-11	and
	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-11a	or
	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-11b	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-12	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-12a	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-12b	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-13	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-14a	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-14b	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-15	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-15a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-15b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-16a	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-16b	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-17	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-18	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-18a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-18b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-19	[(1R,2S,4R)-4-{[5-({4-[(R)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-19a	[(1R,2S,4R)-4-{[5-({4-[(R)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-19b	[(1R,2S,4R)-4-{[5-({4-[(R)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-20a	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
	or [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-20b	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-21	[(1R,2S,4R)-4-{[5-({4-[(S)-(5-chloro-2-furyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(R)-(5-chloro-2-furyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-22	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-22a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-22b	[(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-24a	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-24b	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-25	[(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-25a	[(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-25b	[(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-26	{(1R,2R,3S,4R)-4-[(5-{[4-(3-bromobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate
I-27a	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-bromophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-bromophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-27b	[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-bromophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-bromophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-28	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-28a	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-28b	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-29	[(1R,2S,4R)-4-{[5-({4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-29a	[(1R,2S,4R)-4-{[5-({4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-29b	[(1R,2S,4R)-4-{[5-({4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-30	{(1R,2S,4R)-4-[(5-{4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate and {(1R,2S,4R)-4-[(5-{4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-30a	{(1R,2S,4R)-4-[(5-{4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-30b	{(1R,2S,4R)-4-[(5-{4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-31	[(1R,2R,3S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-32	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2S)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2R)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-32a	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2S)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2R)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-32b	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2S)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2R)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-33	[(1R,2S,4R)-4-({5-[4-(3-chlorobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-34	[(1R,2S,4R)-4-({5-[4-(3-bromobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-35	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-36	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-36a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-36b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-37	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4-iodo-1H-pyrazol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-38	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-38a	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-38b	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-39	[(1R,2S,4R)-4-{[5-({4-[(4-bromo-1H-pyrazol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-40	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-41	[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2S)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2R)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-41a	[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2S)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2R)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-41b	[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2S)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2R)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-42	{(1R,2S,4R)-4-[(5-{4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate and {(1R,2S,4R)-4-[(5-{4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-42a	{(1R,2S,4R)-4-[(5-{4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-42b	{(1R,2S,4R)-4-[(5-{4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-43	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-44	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-(methoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-45	{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-methyl-4-(3-methylbenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-46	[(1R,2S,4R)-4-{[5-({4-[(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-47	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-47a	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-47b	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-48	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(5-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(5-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-49	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-(3-chlorophenyl)-1,3-dihydroxypropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-(3-chlorophenyl)-1,3-dihydroxypropyl]-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-50	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(cyclopropyl)hydroxymethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(cyclopropyl)hydroxymethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-51	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-52	{(1R,2S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-53	[(1R,2S,4R)-4-{[5-({4-[(6-bromopyridin-2-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-54	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-55	[(1R,2S,4R)-4-{[5-({4-[(4-chloro-1H-pyrazol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-56	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-hydroxy(phenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-hydroxy(phenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-57	[(1R,2S,4R)-2-hydroxy-4-({5-[4-(3-methylbenzyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-58	{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1S)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate and {(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1R)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-58a	{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1S)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate or {(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1R)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-58b	{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1S)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate or {(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1R)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-59	{(1R,2S,4R)-4-[(5-{[4-(3-bromobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-60	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-methylbenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-61	{(1R,2S,4R)-4-[(5-{[4-(3-chloro-4-fluorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-

Compound No.	Name
	yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-62	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-iodobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-63	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(5-chloro-2-methoxyphenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(5-chloro-2-methoxyphenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-64	[(1R,2R,3R,4R)-4-({5-[4-(3-bromobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
I-65	[(1R,2R,3R,4R)-3-fluoro-2-hydroxy-4-({5-[5-methyl-4-(3-methylbenzyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-66	[(1R,2S,4R)-4-{[5-({4-[(5-chloro-2-furyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-67	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(2R)-2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(2S)-2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-68	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(R)-phenylsulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(S)-phenylsulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-69	[(1R,2S,4R)-2-hydroxy-4-({5-[(5-methyl-4-{(R)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-({5-[(5-methyl-4-{(S)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-70	{(1R,2S,4R)-4-[(5-{[4-(3-ethynylbenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-71	[(1R,2S,4R)-4-{[5-({4-[(6-chloropyridin-2-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-72	[(1R,2S,4R)-4-({5-[5-chloro-4-(3-chlorobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-73a	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-73b	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-74	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4-methyl-1H-pyrazol-1-yl)methyl]-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-75	[(1R,2R,3R,4R)-4-({5-[4-(3-chlorobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
I-76	{(1R,2R,3S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-chloro-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate
I-77	[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-78	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4-methyl-1H-pyrazol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-79	[(1R,2S,4R)-4-({5-[4-(3-chlorobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-80	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-methoxyphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-81	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[3-(methylsulfanyl)benzyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-82	[(1R,2S,4R)-4-({5-[5-(3-bromobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-83	[(1R,2S,4R)-4-{[5-({4-[(6-chloro-2,3-dihydro-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-84	{(1R,2S,4R)-4-[(5-{[4-(3-chloro-2-fluorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-85	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-hydroxy(2-methoxyphenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-hydroxy(2-methoxyphenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-86	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(2-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(2-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-87	[(1R,2R,3S,4R)-4-{[5-(5-benzyl-2-furoyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-88	[(1R,2S,4R)-4-({5-[(4-benzyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-89	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-fluoro-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-90	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-90a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or

Compound No.	Name
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-90b	or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-91	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(phenoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-92	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-pyrrolo[2,3-b]pyridin-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-93	[(1R,2S,4R)-4-({5-[5-(3-chlorobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-94	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)sulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)sulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-95	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-96	[(1R,2S,4R)-4-({5-[(4-benzyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-97	{(1R,2S,4R)-4-[(5-{[4-(3-fluorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-98	[(1R,2S,4R)-4-{[5-({4-[(2-bromophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-99	{(1R,2R,3R,4R)-3-fluoro-2-hydroxy-4-[(5-{[4-(3-iodobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-100	[(1R,2S,4R)-4-{[5-({4-[1-(3-chlorophenyl)vinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-101	{(1R,2R,3R,4R)-4-[(5-{[4-(3-bromobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-3-fluoro-2-hydroxycyclopentyl}methyl sulfamate
I-102	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-102a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-102b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-103	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(5-chloro-2-thienyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(5-chloro-2-thienyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-104	{(1R,2S,4R)-4-[(5-{[4-(3,4-dichlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-105	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(3-methyl-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-106	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-106a	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-106b	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-107	{(1R,2S,4R)-4-[(5-{[5-chloro-4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-108	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(2-phenylethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-109	{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-methyl-4-(1H-pyrazol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-110	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-(tetrahydro-2H-pyran-4-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-111	{(1R,2S,4R)-4-[(5-{[4-(3-ethylbenzyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-112	{(1R,2S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-chloro-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-113	[(1R,2S,4R)-4-{[5-({4-[3-(difluoromethoxy)benzyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-114	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-indol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-115	[(1R,2R,3S,4R)-4-({5-[(5-benzyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2,3-dihydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-116	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-117	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-117a	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-117b	[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-118	{(1R,2S,4R)-4-[(5-{[5-bromo-4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-119	[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[5-(trifluoromethyl)-2-furyl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-120	[(1R,2S,4R)-4-{[5-({4-[(3-chlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-121	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(2S)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(2R)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-122	[(1R,2S,4R)-4-({5-[(5-chloro-4-{(R)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-({5-[(5-chloro-4-{(S)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-123	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-methoxybenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-124	[(1R,2S,4R)-4-{[5-({4-[(2-cyanophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-125	[(1R,2S,4R)-4-{[5-({4-[(6-chloro-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-126	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(6-methoxy-2,3-dihydro-1H-indol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-127	[(1R,2S,4R)-4-{[5-(5-benzyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-128	[(1R,2S,4R)-4-{[5-({4-[(6-cyano-2,3-dihydro-1H-indol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-129	[(1R,2S,4R)-4-{[5-({4-[(2-chlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-130	[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[4-(trifluoromethyl)-1H-pyrazol-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-131	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-methylphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-132	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(6-methyl-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-134	[(1R,2R,3S,4R)-2,3-dihydroxy-4-{[5-(5-phenyl-2-furoyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-135	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-135a	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-135b	[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-136	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxy-2-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxy-2-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-137	{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-methyl-4-(phenylsulfanyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-138	[(1R,2S,4R)-4-({5-[(4-{[(3-chlorophenyl)(methyl)amino]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-139	[(1R,2S,4R)-4-{[5-(4,5-dibenzyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-140	{(1R,2S,4R)-4-[(5-{[4-(cyclohex-1-en-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-141	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxy-2-methylprop-2-en-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxy-2-methylprop-2-en-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-142	{(1R,2S,4R)-4-[(5-{[5-(3-chlorobenzyl)-4-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-143	[(1R,2S,4R)-4-{[5-({4-[(3-chlorophenyl)sulfanyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-144	[(1R,2S,4R)-4-({5-[(4,5-dibenzyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-145	[(1R,2S,4R)-2-hydroxy-4-({5-[(5-methyl-4-{[3-(trifluoromethyl)phenyl]sulfanyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-146	[(1R,2S,4R)-4-{[5-({4-[2-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-147	[(1R,2S,4R)-4-({5-[(4-{[(2-chlorophenyl)sulfanyl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-148	[(1R,2S,4R)-4-{[5-({4-[(4-bromo-2-cyano-1H-pyrrol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-149	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(2,5-dichlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(2,5-dichlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-150	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-3-cyclopropyl-1-hydroxyprop-2-yn-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-3-cyclopropyl-1-hydroxyprop-2-yn-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-151	[(1R,2S,4R)-4-{[5-({4-chloro-5-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-chloro-5-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-151a	[(1R,2S,4R)-4-{[5-({4-chloro-5-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-chloro-5-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-151b	[(1R,2S,4R)-4-{[5-({4-chloro-5-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-chloro-5-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-152	[(1R,2S,4R)-4-{[5-({5-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-153	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and

Compound No.	Name
	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-153a	or
	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-153b	or
	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)tetrahydro-2H-pyran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-154	and
	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)tetrahydro-2H-pyran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-155	{(1R,2S,4R)-4-[(5-{[4-(2,3-dichlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-156	[(1R,2S,4R)-4-{[5-({4-[(2-ethoxyphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-157	{(1R,2S,4R)-4-[(5-{[4-(4-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-158	[(1R,2R,3S,4R)-4-({5-[5-(2-chlorophenyl)-2-furoyl]pyrimidin-4-yl}amino)-2,3-dihydroxycyclopentyl]methyl sulfamate
I-159	[(1R,2S,4R)-4-{[5-({4-[(5-chloro-2,3-dihydro-1H-indol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-160	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-161	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-iodophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-162	[(1R,2R,3R,4R)-4-({5-[(4-benzyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
I-163	[(1R,2S,4R)-4-{[5-({4-[(4-chlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-164	[(1R,2S,4R)-4-{[5-({4-[1-(3-bromophenyl)vinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-165	{(1R,2S,4R)-4-[(5-{[4-(2-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-cyclohexyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-166	and
	[(1R,2S,4R)-4-{[5-({4-[(2R)-2-cyclohexyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-167	{(1R,2S,4R)-4-[(5-{[4-(3,4-dihydroisoquinolin-2(1H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate

Compound No.	Name
I-168	{(1R,2S,4R)-4-[(5-{[4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-169	[(1R,2S,4R)-4-{[5-({4-[(6-cyano-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-170	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(3-methyl-1H-pyrrol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-171	{(1R,2S,4R)-4-[(5-{[4-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylmethyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-172	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-cyclohexyl(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-cyclohexyl(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-173	{(1R,2S,4R)-4-[(5-{[4-(3,6-dihydro-2H-thiopyran-4-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-174	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-hydroxy(tetrahydro-2H-pyran-4-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-hydroxy(tetrahydro-2H-pyran-4-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-175	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(3-chlorophenyl)sulfanyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-176	[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[2-(trifluoromethoxy)phenoxy]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-177	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(phenylsulfanyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-178	[(1R,2S,4R)-4-{[5-({4-[2-(4-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-179	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-cyano-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-180	[(1R,2S,4R)-4-{[5-({4-[(2,3-dichlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-181	[(1R,2S,4R)-4-{[5-({4-[(3-chlorophenyl)sulfonyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-182	[(1R,2S,4R)-4-{[5-({4-[(2-ethylphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-183	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[2-(2-methoxyphenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-184	[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[6-(trifluoromethyl)-1H-indol-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-185	{(1R,2S,4R)-4-[(5-{[4-(3-cyanobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-186	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-pyrrolo[2,3-c]pyridin-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-187	{(1R,2S,4R)-4-[(5-{[4-(1,3-dihydro-2H-isoindol-2-ylmethyl)-2-

Compound No.	Name
	thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-188	[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[2-(trifluoromethyl)phenoxy]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-189	[(1R,2S,4R)-4-({5-[(5-chloro-4-{[3-(trifluoromethyl)phenyl]sulfanyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-190	{(1R,2S,4R)-4-[(5-{[4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-191	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-isopropylphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-192	{(1R,2S,4R)-4-[(5-{[4-(1H-benzimidazol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-193	{(1R,2S,4R)-4-[(5-{[4-(2,5-dihydrofuran-3-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-194	[(1R,2S,4R)-4-{[5-({4-[(3-cyano-1H-pyrrol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-195	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxy-2-methylpropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxy-2-methylpropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-196	{(1R,2S,4R)-4-[(5-{[4-(3,6-dihydro-2H-pyran-4-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-197	{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1S)-1-hydroxy-2-methylprop-2-en-1-yl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate and {(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1R)-1-hydroxy-2-methylprop-2-en-1-yl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-199	{(1R,2S,4R)-4-[(5-{[4-(cyclohexylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-200	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(phenylsulfonyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-201	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-isopropoxyphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-202	{(1R,2R,3S,4R)-2,3-dihydroxy-4-[(5-{[5-(2-hydroxypropan-2-yl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-203	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(3-chlorophenyl)sulfonyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-204	{(1R,2S,4R)-4-[(5-{[4-(3,6-dihydropyridin-1(2H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-205	{(1R,2R,3R,4R)-4-[(5-{[5-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-3-fluoro-2-hydroxycyclopentyl}methyl sulfamate
I-206	[(1R,2S,4R)-2-hydroxy-4-({5-[5-(hydroxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate

Compound No.	Name
I-207	{(1R,2S,4R)-4-[(5-{[5-chloro-4-(3-chlorobenzoyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-208	[(1R,2S,4R)-4-{[5-(4-benzoyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-209	{(1R,2S,4R)-4-[(5-{[(2S)-2-(3-chlorophenyl)-2,3,4,5-tetrahydro-2,3'-bithiophen-5'-yl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate and {(1R,2S,4R)-4-[(5-{[(2R)-2-(3-chlorophenyl)-2,3,4,5-tetrahydro-2,3'-bithiophen-5'-yl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-210	[(1R,2S,4R)-4-{[5-({4-[(5-chloropyridin-3-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-211	{(1R,2S,4R)-4-[(5-{[5-chloro-4-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-212	[(1R,2S,4R)-2-hydroxy-4-({5-[5-(methoxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-215	[(1R,2S,4R)-4-({5-[(4-benzoyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-216	[(1R,2S,4R)-2-hydroxy-4-({5-[4-(hydroxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-217	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(methoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-218	{(1R,2S,4R)-4-[(5-{[5-chloro-4-(methoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-219	{(1R,2S,4R)-4-[(5-{[4-(2,5-dihydro-1H-pyrrol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-220	[(1R,2S,4R)-2-hydroxy-4-({5-[4-(2-hydroxypropan-2-yl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-221	{(1R,2S,4R)-4-[(5-{[4-({3-[(dimethylamino)methyl]-1H-indol-1-yl}methyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-222	[(1R,2S,4R)-4-{[5-({4-[(benzylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-223	[(1R,2S,4R)-2-hydroxy-4-({5-[4-(methoxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-224	[(1R,2S,4R)-4-{[5-({4-[(3,3-difluoropiperidin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-225	[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[(3R)-3-methylpiperidin-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[(3S)-3-methylpiperidin-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-226	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-227	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)-1-methylpyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)-1-methylpyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-228	[(1R,2S,4R)-4-{[5-({4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-229	[(1R,2S,4R)-4-({5-[(4-acetyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-230	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-231	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-imidazol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-233	{(1R,2S,4R)-4-[(5-{[5-(3-chlorobenzyl)-3-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-234	[(1R,2S,4R)-4-{[5-(4-acetyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-235	{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-(2-hydroxypropan-2-yl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-236	[(1R,2R,3S,4R)-4-{[2-chloro-5-(5-phenyl-2-furoyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-237	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(5-methyl-2-furyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-238	[(1R,2S,4R)-4-{[5-({4-[(2S)-2-cyclopropyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(2R)-2-cyclopropyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-239	[(1R,2S,4R)-2-hydroxy-4-({5-[5-(phenylsulfonyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate
I-240	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(2-hydroxypropan-2-yl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-241	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4-phenylpiperazin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-242	[(1R,2S,4R)-4-({5-[(4-acetyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-243	[(1R,2S,4R)-4-{[5-({4-[(4-bromo-1H-imidazol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-247a	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-247b	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-

Compound No.	Name
	2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-248a	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-248b	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-249a	[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-249b	[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-250	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-250a	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-250b	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-251	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-251a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-251b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-252	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-252a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-252b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-253	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-253a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-253b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-254	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-254a	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-254b	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
	or [(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-255a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-255b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-256	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-256a	[(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-256b	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-257	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-257a	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-257b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-258	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-258a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-258b	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-(trifluoromethyl)-3,4-dihydro-1H-

Compound No.	Name
	isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-259	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-259a	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-259b	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-260	[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-260a	[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-260b	[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-261	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-261a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-261b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-262	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-262a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-262b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-263a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-263b	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-264	[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2R,3R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
I-264a	[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2R,3R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
I-264b	[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2R,3R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-

Compound No.	Name
	2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-265	and [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-265a	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-265b	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-266	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-266a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-266b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-267	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-267a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-267b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-268	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-268a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-268b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-269	[(1R,2S,4R)-4-{[5-({4-[(7S)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(7R)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-269a	[(1R,2S,4R)-4-{[5-({4-[(7S)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(7R)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-269b	[(1R,2S,4R)-4-{[5-({4-[(7S)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(7R)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-270	{(1R,2S,4R)-4-[(5-{4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate and {(1R,2S,4R)-4-[(5-{4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-270a	{(1R,2S,4R)-4-[(5-{4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-270b	{(1R,2S,4R)-4-[(5-{4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-271a	[(1R,2R,3R,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or

Compound No.	Name
	[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate
I-272a	{(1R,2S,4R)-4-[(5-{4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-272b	{(1R,2S,4R)-4-[(5-{4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-273	[(1R,2S,4R)-4-{[5-({4-[(1R)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-274	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-274a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-274b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-275	[(1R,2S,4R)-4-{[5-({4-[(4S)-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(4R)-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-276	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-276a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-276b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-277	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-277a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-277b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-278	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-278a	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-278b	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-279	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-279a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-279b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-280	[(1R,2S,4R)-4-{[5-({4-[(4R)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(4S)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-280a	[(1R,2S,4R)-4-{[5-({4-[(4R)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(4S)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-280b	[(1R,2S,4R)-4-{[5-({4-[(4R)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(4S)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-281	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'R)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'S)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-281a	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'R)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'S)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-281b	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'R)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'S)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-282	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-282a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-282b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or

Compound No.	Name
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-283	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-283a	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-283b	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-284a	or
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-284b	or
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-285	and
	[(1R,2S,4R)-4-{[5-({4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-285a	or
	[(1R,2S,4R)-4-{[5-({4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-285b	or
	[(1R,2S,4R)-4-{[5-({4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-286	and
	[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl

Compound No.	Name
	sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-286a	or
	[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-286b	or
	[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-287	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-287a	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-287b	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-288	and
	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-289	and
	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-289a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-289b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-290a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-290b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-291	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-291a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-291b	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-292a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-292b	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-293	[(1R,2S,4R)-4-{[5-({4-[(1R)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and

Compound No.	Name
	[(1R,2S,4R)-4-{[5-({4-[(1S)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-293a	or
	[(1R,2S,4R)-4-{[5-({4-[(1S)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-293b	or
	[(1R,2S,4R)-4-{[5-({4-[(1S)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-294	and
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-294a	or
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-294b	or
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2R,3S,4R)-2,3-dihydroxy-4-{[5-({4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-295	and
	[(1R,2R,3S,4R)-2,3-dihydroxy-4-{[5-({4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-3-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-296	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-3-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-297	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-297a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-

Compound No.	Name
	yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-297b	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-298	[(1R,2S,4R)-4-{[5-({4-[(4R)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(4S)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-298a	[(1R,2S,4R)-4-{[5-({4-[(4R)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(4S)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-298b	[(1R,2S,4R)-4-{[5-({4-[(4R)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(4S)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-299	{(1R,2S,4R)-4-[(5-{5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate and {(1R,2S,4R)-4-[(5-{5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-299a	{(1R,2S,4R)-4-[(5-{5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-299b	{(1R,2S,4R)-4-[(5-{5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-300a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-300b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-1,3-

Compound No.	Name
	thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-301	[(1R,2S,4R)-4-{[5-({4-[(1R)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-301a	[(1R,2S,4R)-4-{[5-({4-[(1R)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-301b	[(1R,2S,4R)-4-{[5-({4-[(1R)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-302	[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate and [(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
I-303	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-8-fluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-8-fluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-304	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-305	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-305a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[4,3-

Compound No.	Name
	d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-305b	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-306	and
	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-307	and
	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-307a	or
	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-307b	or
	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-308	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-309	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-310	and
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate

Compound No.	Name
I-310a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-310b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-311a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-311b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-313	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyano-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyano-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-314	[(1R,2S,4R)-4-{[5-({4-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-314a	[(1R,2S,4R)-4-{[5-({4-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-314b	[(1R,2S,4R)-4-{[5-({4-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-315	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-(trifluoromethyl)-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and

Compound No.	Name
	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-(trifluoromethyl)-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-316	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-317	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-318	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-319	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-320	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-320a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-320b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-321	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-322	[(1R,2S,4R)-4-{[5-({4-[(1R)-5-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and

Compound No.	Name
	[(1R,2S,4R)-4-{[5-({4-[(1S)-5-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-323	and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-cyano-4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-324	and [(1R,2S,4R)-4-{[5-({5-cyano-4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-[(1R)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-325	and [(1R,2S,4R)-4-{[5-({5-[(1S)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-3-oxo-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-327	and [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-3-oxo-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-({5-[(4-{(1R)-7-[(dimethylamino)methyl]-3,4-dihydro-1H-isochromen-1-yl}-5-methyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-329	and [(1R,2S,4R)-4-({5-[(4-{(1S)-7-[(dimethylamino)methyl]-3,4-dihydro-1H-isochromen-1-yl}-5-methyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate
I-330	(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl aminoacetate
	[(1R,2S,4R)-4-{[5-({4-[(5R)-8,8-difluoro-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-331	and [(1R,2S,4R)-4-{[5-({4-[(5S)-8,8-difluoro-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4S)-2-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-332	and [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4R)-2-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-333	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4S)-3-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl

Compound No.	Name
	sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4R)-3-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-334	tert-butyl (1R)-7-chloro-1-(5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate and tert-butyl (1S)-7-chloro-1-(5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
I-335	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-335a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-335b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-336	tert-butyl (1R)-7-chloro-1-(2-chloro-5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate and tert-butyl (1S)-7-chloro-1-(2-chloro-5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
I-337	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(trifluoromethyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(trifluoromethyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-338	(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl (2S)-2-amino-3-methylbutanoate
I-339	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8S)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and

Compound No.	Name
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8R)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8S)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-339a	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8R)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8S)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-339b	or
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8R)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-7-methoxy-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-341	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-7-methoxy-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-4-oxo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-342	and
	[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-4-oxo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-343a	or
	[(1R,2S,4R)-4-{[5-({5-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({5-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-343b	or
	[(1R,2S,4R)-4-{[5-({5-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
	[(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazol-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-344	and
	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazol-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-345	(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl 3-[(phosphonooxy)methyl]benzoate
I-346	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-347	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-348	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(pyrrolidin-1-yl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate and [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(pyrrolidin-1-yl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate
I-349	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-349a	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-349b	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-350	[(1R,2R,3S,4R)-4-({5-[(5-benzyl-1,3-thiazol-2-yl)carbonyl]pyrimidin-4-yl}amino)-2,3-dihydroxycyclopentyl]methyl sulfamate
I-351	{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-methylbenzyl)-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate
I-352	{(1R,2R,3S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-methyl-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate
I-353	{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-methyl-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-354	{(1R,2R,3S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-methyl-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate
I-355	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-

Compound No.	Name
	yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-355a	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-355b	[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-356	[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-356a	[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-356b	[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-357	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-358	{(1R,2S,4R)-4-[(5-{[4-(7-chloroisoquinolin-1-yl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-359a	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-359b	[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-

Compound No.	Name
	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-360	{(1R,2S,4R)-4-[(5-{[4-(7-chloro-3,4-dihydroisoquinolin-1-yl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate
I-361	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(difluoromethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(difluoromethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-362	(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl (2S)-2-aminopropanoate
I-363	(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl (2S,3S)-2-amino-3-methylpentanoate
I-364	(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl [4-(phosphonooxy)phenyl]acetate
I-365	[(1R,2S,4R)-4-{[5-({4-[(1R)-8-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-8-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate
I-366	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl](methyl)amino}-2-hydroxycyclopentyl]methyl sulfamate and [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl](methyl)amino}-2-hydroxycyclopentyl]methyl sulfamate

[00185] It will be appreciated that the chemical entities of this disclosure may be derivatized at functional groups to provide prodrug derivatives which are capable of conversion back to the parent chemical entities *in vivo*. Examples of such prodrugs include the physiologically acceptable and metabolically labile derivatives. More specifically, the prodrug of the chemical entity of this disclosure is an ether or ester of the -OH group of the chemical entity. Prodrugs according to this disclosure include those in which R^b is -C(O)-R^{bx}, wherein R^{bx} has the values described herein, as discussed above. Furthermore, various approaches for providing prodrugs are known to those skilled in the art, as described in, e.g., Li et al., "Prodrugs of Nucleoside Analogues for Improved Oral Absorption and Tissue Targeting," *J. Pharm. Sci.* 97, 1109-34 (2008); Rautio et al., "Prodrugs: design

and clinical applications," *Nat. Rev. Drug Discovery* 7, 255-270 (2008); and Rautio, *Prodrugs and Targeted Delivery*, Wiley-VCH (2011) (ISBN-10: 3527326030).

[00186] As used herein, "crystalline" refers to a solid in which the constituent atoms, molecules, or ions are packed in a regularly ordered, repeating three-dimensional pattern having a highly regular chemical structure. In particular, a crystalline compound or salt might be produced as one or more crystalline forms. For the purposes of this application, the terms "crystalline form" and "polymorph" are synonymous; the terms distinguish between crystals that have different properties (e.g., different XRPD patterns, different DSC scan results). Pseudopolymorphs are typically different solvates of a material, and thus the properties of pseudopolymorphs differ from one another. Thus, each distinct polymorph and pseudopolymorph is considered to be a distinct crystalline form herein.

[00187] "Substantially crystalline" refers to compounds or salts that are at least a particular weight percent crystalline. In some embodiments, the compound or salt is substantially crystalline. Examples of a crystalline form or substantially crystalline form include a single crystalline form or a mixture of different crystalline forms. Particular weight percentages include 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% and 99.9%. In some embodiments, substantially crystalline refers to compounds or salts that are at least 70% crystalline. In some embodiments, substantially crystalline refers to compounds or salts that are at least 80% crystalline. In some embodiments, substantially crystalline refers to compounds or salts that are at least 85% crystalline. In some embodiments, substantially crystalline refers to compounds or salts that are at least 90% crystalline. In some embodiments, substantially crystalline refers to compounds or salts that are at least 95% crystalline.

[00188] The term "hydrate" includes, for example, hemihydrates, monohydrates, sesquihydrates, dihydrates, and trihydrates. In some embodiments, a hydrate, such as a sesquihydrate, may be prepared by crystallization of a chemical entity disclosed herein from ethanol/distilled water. In some embodiments, a hydrate may be prepared by crystallization of a chemical entity disclosed herein from aqueous 50 mM citrate buffer at about pH 4.5.

[00189] The term "seeding" refers to the addition of crystalline material to a solution or mixture to initiate crystallization.

[00190] Some embodiments are directed to compounds or salts wherein at least a particular percentage by weight of the compound or salt is crystalline. Some embodiments are directed to a compound or salt wherein at least a particular percentage by weight of the compound or salt is crystalline. Particular weight percentages include 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% and 99.9%. When a particular percentage by weight of the compound or salt is crystalline, the remainder of the compound or salt is the amorphous form of the compound or salt. When a particular percentage by weight of the compound or salt is a designated crystalline form, the remainder of the compound or

salt is some combination of the amorphous form of the compound or salt, and one or more crystalline forms of the compound or salt excluding the designated crystalline form.

[00191] When a crystalline form of a compound or salt is identified using one or more temperatures from a DSC profile (e.g., onset of endothermic transition, melt, etc.), each of the temperature values is understood to mean the given value ± 2 °C.

[00192] When a crystalline form of a compound or salt is identified using one or more peaks from a raman pattern expressed as cm^{-1}, it is understood to mean the given value ± 0.2 cm^{-1}, unless otherwise expressed.

[00193] *Solid state forms of I-257b.* Provided herein is an assortment of characterizing information, which is sufficient, but not all of which is necessary, to describe crystalline Form 1 anhydrous compound I-257 ("I-257b Form 1").

[00194] Figure 1 shows an X-ray powder diffraction (XRPD) pattern of Form 1 of compound I-257b obtained using Cu$K\alpha$ radiation. Peaks identified in Figure 1 include those listed in the table below.

Angle (2 Theta) °	Relative Intensity
7.0	2.7%
9.4	5.6%
10.2	7.5%
13.0	13.4%
14.5	62.5%
17.5	10.5%
18.2	15.4%
18.6	96.8%
19.1	29.0%
20.7	41.5%
21.4	23.8%
21.7	74.8%
22.6	53.9%
24.0	30.0%
24.8	19.1%
25.2	100.0%
25.8	27.2%
26.7	12.6%
27.0	5.9%
27.9	38.0%
29.1	2.7%

[00195] In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having a peak at 2θ angle 25.2°. In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 25.2° and 18.6°. In some embodiments, I-257b Form 1 is characterized by an

XRPD pattern having peaks at 2θ angles of 25.2°, 21.7°, 18.6°, and 14.5°. In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 25.2°, 21.7°, 18.6°, 14.5°, 22.6°, 20.7° and 27.9°. In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 25.2°, 21.7°, 18.6°, 14.5°, 22.6°, 20.7°, 27.9°, 24.0°, 19.1°, 25.8° and 21.4°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.1°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.2°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.3°. In some embodiments, I-257b Form 1 is characterized by an XRPD pattern substantially as shown in Figure 1.

[00196] In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 14.5 ± 0.3°, and having peaks at 2θ angles of 4.1°, 7.2°, and 10.7° relative to the reference peak. The term "reference peak" refers to a peak in the XRPD diffractogram that one skilled in the art considers as informing the polymorphic form of the material, *i.e.*, differentiated from instrument noise. By "relative" it is meant that the observed 2θ angle of each peak will be the sum of the 2θ angle of the reference peak and the relative 2θ angle of that peak. For example, if the reference peak has a 2θ angle of 14.2°, the relative peaks will have 2θ angles of 18.3°, 21.4°, and 24.9°; if the reference peak has a 2θ angle of 14.3°, the relative peaks will have 2θ angles of 18.4°, 21.5°, and 25.0°; if the reference peak has a 2θ angle of 14.4°, the relative peaks will have 2θ angles of 18.5°, 21.6°, and 25.1°; etc. In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 14.5 ± 0.3°, and having peaks at 2θ angles of 4.1°, 6.2°, 7.2°, 8.1°, 10.7°, and 13.4° relative to the reference peak. In some embodiments, I-257b Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 14.5 ± 0.3°, and having peaks at 2θ angles of 4.1°, 4.6°, 6.2°, 6.9°, 7.2°, 8.1°, 9.5°, 10.7°, 11.3°, and 13.4° relative to the reference peak. Any of the peaks that one skilled in the art considers as informing the polymorphic form of the material can serve as the reference peak and the relative peaks can then be calculated. For example, if the reference peak has a 2θ angle of 25.2°, then the relative peaks will have 2θ angles of -3.5°, -6.6°, and -10.7° relative to the reference peak.

[00197] In some embodiments, the chemical entity according to the disclosure is or comprises substantially crystalline I-257b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 70% by weight crystalline I-257b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 80% by weight crystalline I-257b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 90% by weight crystalline I-257b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 95% by weight crystalline I-257b Form 1.

[00198] FIG. 8 shows a differential scanning calorimetry (DSC) profile of I-257b Form 1. The DSC thermogram plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C/min. In some embodiments, I-257b Form 1 is characterized by a DSC profile substantially as shown in FIG. 8. FIG. 8 shows an endotherm event with onset of about 57.8

°C and peak at about 83.2 °C. FIG. 8 also shows an endotherm event with onset of about 135.0 °C and peak at about 143.8 °C. In some embodiments, I-257b Form 1 is characterized by a DSC profile having an endotherm event with onset of about 57.8 °C. In some embodiments, I-257b Form 1 is characterized by a DSC profile having an endotherm event with peak at about 83.2 °C. In some embodiments, I-257b Form 1 is characterized by a DSC profile having an endotherm event with onset of about 135.0 °C. In some embodiments, I-257b Form 1 is characterized by a DSC profile having an endotherm event with peak at about 143.8 °C.

[00199] FIG. 9 shows a thermal gravimetric analysis (TGA) profile of I-257b Form 1. The TGA thermogram plots the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C/min. FIG. 9 shows approximately 2.7 % weight loss to 79.5 °C. In some embodiments, I-257b Form 1 is characterized by a TGA profile substantially as shown in FIG. 9. In some embodiments, I-257b Form 1 is characterized by a TGA profile having about 2.7 % weight loss to 79.5°C.

[00200] FIG. 10 shows a raman pattern of I-257b Form 1 including data in the region of 500 cm^{-1} to 3000 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern substantially as shown in FIG. 10. FIG. 11 shows a raman pattern of I-257b Form 1 including data in the region of 200 cm^{-1} to 1600 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern substantially as shown in FIG. 11.

[00201] In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peak at 1450 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peak at 1572 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peak at 1422 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peak at 754 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peaks at 1450, 1572, 1422, and 754 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peaks at 1450, 1572, and 1422 cm^{-1}. In some embodiments, I-257b Form 1 is characterized by a raman pattern with a peaks at 1450 and 1572 cm^{-1}.

[00202] In some embodiments, I-257b Form 1 is characterized by at least one of the following features (I-i)-(I-v):

(I-i) an XRPD pattern having peaks at 2θ angles of 25.2°, 21.7°, 18.6°, and 14.5°;

(I-ii) a DSC profile substantially as shown in FIG. 8;

(I-iii) a TGA profile substantially as shown in FIG. 9;

(I-iv) a raman pattern substantially as shown in FIG. 10;

(I-v) a raman pattern substantially as shown in FIG. 11.

[00203] In some embodiments, I-257b Form 1 is characterized by at least two of the features (I-i)-(I-v). In some embodiments, I-257b Form 1 is characterized by at least three of the features (I-i)-(I-

v). In some embodiments, I-257b Form 1 is characterized by at least four of the features (I-i)-(I-v). In some embodiments, I-257b Form 1 is characterized by all five of the features (I-i)-(I-v).

[00204] *Solid state forms of I-263a.* Provided herein is an assortment of characterizing information, which is sufficient, but not all of which is necessary, to describe crystalline Form 1 anhydrous compound I-263a ("I-263a Form 1").

[00205] Figure 2 shows an X-ray powder diffraction (XRPD) pattern of Form 1 of compound I-263a obtained using Cu$K\alpha$ radiation. Peaks identified in Figure 2 include those listed in the table below.

Angle (2 Theta)	Relative Intensity
4.7	8.1%
7.1	11.7%
9.5	10.8%
9.7	13.1%
13.3	5.5%
14.1	9.0%
15.1	18.5%
16.3	13.7%
17.0	13.6%
17.7	6.6%
17.9	12.6%
18.2	12.0%
18.9	29.4%
19.5	37.2%
20.1	10.1%
20.5	9.2%
21.6	100.0%
22.6	7.2%
23.5	14.6%
24.6	6.1%
26.3	19.6%
27.2	21.2%
28.8	13.6%

[00206] In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having a peak at 2θ angle 21.6°. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.6° and 19.5°. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.6°, 19.5°, 18.9°, and 27.2°. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.6°, 19.5°, 18.9°, 27.2°, 26.3°, 15.1°, and 23.5°. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.6°, 19.5°, 18.9°, 27.2°, 26.3°, 15.1°, 23.5°, 16.3°, 17.0°, 28.8°,

and 9.7°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.1°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.2°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.3°. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern substantially as shown in Figure 2.

[00207] In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 18.9 ± 0.3°, and having peaks at 2θ angles of 0.6°, 2.7°, and 8.3° relative to the reference peak. The term "reference peak" refers to a peak in the XRPD diffractogram that one skilled in the art considers as informing the polymorphic form of the material, *i.e.*, differentiated from instrument noise. By "relative" it is meant that the observed 2θ angle of each peak will be the sum of the 2θ angle of the reference peak and the relative 2θ angle of that peak. For example, if the reference peak has a 2θ angle of 18.6°, the relative peaks will have 2θ angles of 19.2°, 21.3°, and 26.9°; if the reference peak has a 2θ angle of 18.7°, the relative peaks will have 2θ angles of 19.3°, 21.4°, and 27.0°; if the reference peak has a 2θ angle of 18.8°, the relative peaks will have 2θ angles of 19.4°, 21.5°, and 27.1°; etc. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 18.9 ± 0.3°, and having peaks at 2θ angles of -3.8°, 0.6°, 2.7°, 4.6°, 7.4°, and 8.3° relative to the reference peak. In some embodiments, I-263a Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 18.9 ± 0.3°, and having peaks at 2θ angles of -9.2°, -3.8°, -2.6°, -1.9°, 0.6°, 2.7°, 4.6°, 7.4°, and 8.3° and 9.9° relative to the reference peak. Any of the peaks that one skilled in the art considers as informing the polymorphic form of the material can serve as the reference peak and the relative peaks can then be calculated. For example, if the reference peak has a 2θ angle of 21.6°, then the relative peaks will have 2θ angles of -2.7°, -2.1°, and 5.6° relative to the reference peak.

[00208] In some embodiments, the chemical entity according to the disclosure is or comprises substantially crystalline I-263a Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 70% by weight crystalline I-263a Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 80% by weight crystalline I-263a Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 90% by weight crystalline I-263a Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 95% by weight crystalline I-263a Form 1.

[00209] FIG. 4 shows a differential scanning calorimetry (DSC) profile of I-263a Form 1. The DSC thermogram plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C/min. In some embodiments, I-263a Form 1 is characterized by a DSC profile substantially as shown in FIG. 4. FIG. 4 shows an endotherm event with onset of about 179.4 °C and peak at about 184.0 °C. FIG. 4 also shows an exotherm event with onset of about 279.0 °C and peak at about 282.4 °C. In some embodiments, I-263a Form 1 is characterized by a DSC profile having an endotherm event with onset of about 179.4 °C. In some embodiments, I-263a Form 1 is characterized by a DSC profile having an endotherm event with peak at about 184.0 °C. In some

embodiments, I-263a Form 1 is characterized by a DSC profile having an exotherm event with onset of about 279.0 °C. In some embodiments, I-263a Form 1 is characterized by a DSC profile having an exotherm event with peak at about 282.4 °C.

[00210] FIG. 5 shows a thermal gravimetric analysis (TGA) profile of I-263a Form 1. The TGA thermogram plots the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C/min. FIG. 5 shows approximately 0.9 % weight loss to 170.4°C. In some embodiments, I-263a Form 1 is characterized by a TGA profile substantially as shown in FIG. 5. In some embodiments, I-263a Form 1 is characterized by a TGA profile having about 0.9 % weight loss to 170.4°C.

[00211] FIG. 6 shows a raman pattern of I-263a Form 1 including data in the region of 500 cm^{-1} to 3000 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern substantially as shown in FIG. 6. FIG. 7 shows a raman pattern of I-263a Form 1 including data in the region of 200 cm^{-1} to 1600 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern substantially as shown in FIG. 7.

[00212] In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peak at 1441 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peak at 1604 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peak at 1583 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peak at 1381 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peaks at 1441, 1604, 1583, and 1381 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peaks at 1441, 1604, and 1583 cm^{-1}. In some embodiments, I-263a Form 1 is characterized by a raman pattern with a peaks at 1441 and 1604 cm^{-1}.

[00213] In some embodiments, I-263a Form 1 is characterized by at least one of the following features (I-i)-(I-v):

(I-i) an XRPD pattern having peaks at 2θ angles of 21.6°, 19.5°, 18.9°, and 27.2°;

(I-ii) a DSC profile substantially as shown in FIG. 4;

(I-iii) a TGA profile substantially as shown in FIG. 5;

(I-iv) a raman pattern substantially as shown in FIG. 6;

(I-v) a raman pattern substantially as shown in FIG. 7.

[00214] In some embodiments, I-263a Form 1 is characterized by at least two of the features (I-i)-(I-v). In some embodiments, I-263a Form 1 is characterized by at least three of the features (I-i)-(I-v). In some embodiments, I-263a Form 1 is characterized by at least four of the features (I-i)-(I-v). In some embodiments, I-263a Form 1 is characterized by all five of the features (I-i)-(I-v).

[00215] In some embodiments, the chemical entity I-263a is a hydrate. In some embodiments, the chemical entity I-263a is a sesquihydrate. In some embodiments, the chemical entity I-263a is a hydrate comprising between 2 and 3 equivalents of H_2O.

[00216] *I-263a Form 2.* Provided herein is an assortment of characterizing information, which is sufficient, but not all of which is necessary, to describe crystalline Form 2 sesquihydrate compound I-263a ("I-263a Form 2"). I-263a Form 2 may be prepared by crystallization of I-263a from a solvent system containing water (e.g., distilled water) and an organic solvent such as methanol, ethanol, isopropyl alcohol, acetonitrile, formamide, or 1,4-dioxane.

[00217] Figure 14 shows an X-ray powder diffraction (XRPD) pattern of I-263a Form 2 of obtained using Cu$K\alpha$ radiation. Peaks identified in Figure 14 include those listed in the table below.

Angle (2 Theta)	Relative Intensity
3.1	21.4%
9.4	6.2%
10.1	4.4%
10.9	12.7%
11.9	11.2%
13.0	32.8%
14.2	4.0%
15.5	5.9%
16.8	6.0%
17.9	7.3%
19.0	100.0%
19.5	4.4%
20.4	4.2%
21.1	10.2%
22.0	28.3%
22.4	12.2%
22.9	6.0%
24.0	9.4%
25.1	10.2%
26.2	11.6%
27.1	14.0%
31.4	6.3%

[00218] In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having a peak at 2θ angle 19.0°. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having peaks at 2θ angles of 19.0° and 13.0°. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having peaks at 2θ angles of 19.0°, 13.0°, 22.0° and 3.1°. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having peaks at 2θ angles of 19.0°, 13.0°, 22.0°, 3.1°, 27.1°, 10.9° and 22.4°. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having peaks at 2θ angles of 19.0°, 13.0°, 22.0°, 3.1°, 27.1°, 10.9°, 22.4°, 26.2°, 11.9°, 25.1° and 21.1°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.1°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.2°. In some embodiments, the

2θ angles given above have an error tolerance of ±0.3°. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern substantially as shown in Figure 14.

[00219] In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 3.1 ± 0.3°, and having peaks at 2θ angles of 9.9°, 15.9° and 18.9° relative to the reference peak. The term "reference peak" refers to a peak in the XRPD diffractogram that one skilled in the art considers as informing the polymorphic form of the material, *i.e.*, differentiated from instrument noise. By "relative" it is meant that the observed 2θ angle of each peak will be the sum of the 2θ angle of the reference peak and the relative 2θ angle of that peak. For example, if the reference peak has a 2θ angle of 2.8°, the relative peaks will have 2θ angles of 12.7°, 18.7° and 21.7°; if the reference peak has a 2θ angle of 2.9°, the relative peaks will have 2θ angles of 12.8°, 18.8° and 21.8°; if the reference peak has a 2θ angle of 3.0°, the relative peaks will have 2θ angles of 12.9°, 18.9° and 21.9°; etc. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 3.1 ± 0.3°, and having peaks at 2θ angles of 7.8°, 9.9°, 15.9°, 18.9°, 19.3° and 24.0° relative to the reference peak. In some embodiments, I-263a Form 2 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 3.1 ± 0.3°, and having peaks at 2θ angles of 7.8°, 8.8°, 9.9°, 15.9°, 18.0°, 18.9°, 19.3°, 22.0°, 23.1° and 24.0° relative to the reference peak. Any of the peaks that one skilled in the art considers as informing the polymorphic form of the material can serve as the reference peak and the relative peaks can then be calculated. For example, if the reference peak has a 2θ angle of 19.0°, then the relative peaks will have 2θ angles of -15.9°, -6.0° and 3.0° relative to the reference peak.

[00220] Karl Fischer measurements of I-263a Form 2 show a water content of about 4.8%. A thermal gravimetric analysis (TGA) profile of I-263a Form 2 can show that the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C/min, is approximately 5 % weight loss to 50.7°C. The TGA profile can also show that the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C/min, is approximately 10.1 % weight loss to 252.8°C. A differential scanning calorimetry (DSC) profile of I-263a Form 2 can show the following regarding the heat flow as a function of temperature from a sample of I-263a Form 2, the temperature rate change being about 10 °C/min. In some embodiments, I-263a Form 2 is characterized by an endotherm event with a peak at about 47.7 °C. In some embodiments, I-263a Form 2 is characterized by an endotherm event with a peak at about 60.7 °C. In some embodiments, I-263a Form 2 is characterized by an endotherm event with a peak at about 73.8 °C. In some embodiments, I-263a Form 2 is characterized by an exotherm event with a peak at about 132.9 °C. In some embodiments, I-263a Form 2 is characterized by an exotherm event with a peak at about 149.3 °C.

[00221] In some embodiments, I-263a Form 2 is characterized by at least one of the following features (I-i)-(I-iv):

(I-i) an XRPD pattern having peaks at 2θ angles of 3.1°, 13.0°, 19.0°, and 22.0° as shown in FIG. 14;

(I-ii) a DSC profile characterized by at least two of an endotherm event with a peak at about 47.7 °C, an endotherm event with a peak at about 60.7 °C, an endotherm event with a peak at about 73.8 °C, an exotherm event with a peak at about 132.9 °C, and an exotherm event with a peak at about 149.3 °C;

(I-iii) a TGA profile characterized by at least one of approximately 5 % weight loss to 50.7°C and approximately 10.1 % weight loss to 252.8°C

(I-iv) a water content of about 4.8% according to Karl Fischer measurements.

[00222] In some embodiments, I-263a Form 2 is characterized by at least two of the features (I-i)-(I-iv). In some embodiments, I-263a Form 2 is characterized by at least three of the features (I-i)-(I-iv). In some embodiments, I-263a Form 2 is characterized by all four of the features (I-i)-(I-iv).

[00223] *I-263a Form 3.* Provided herein is an assortment of characterizing information, which is sufficient, but not all of which is necessary, to describe crystalline Form 3 hydrate compound I-263a ("I-263a Form 3"). I-263a Form 3 may be prepared by crystallization of I-263a from aqueous 50 mM citrate buffer at about pH 4.5.

[00224] Figure 15 shows an X-ray powder diffraction (XRPD) pattern of I-263a Form 3 of obtained using Cu$K\alpha$ radiation. Peaks identified in Figure 15 include those listed in the table below.

Angle (2 Theta)	**Relative Intensity**
9.0	14.0%
9.9	19.8%
12.4	23.2%
14.6	14.9%
15.6	100.0%
16.2	55.0%
17.1	18.8%
17.8	24.1%
18.0	44.1%
18.3	21.9%
19.2	35.0%
19.4	27.0%
20.0	39.3%
20.3	26.7%
20.7	26.3%
21.3	18.4%
21.8	25.6%
22.3	29.2%
23.1	31.4%
23.9	15.4%
24.9	17.9%

25.4	25.6%
27.2	13.2%

[00225] In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having a peak at 2θ angle 15.6°. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having peaks at 2θ angles of 15.6° and 16.2°. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having peaks at 2θ angles of 15.6°, 16.2°, 18.0° and 20.0°. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having peaks at 2θ angles of 15.6°, 16.2°, 18.0°, 19.2°, 20.0°, 22.3°, and 23.1°. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having peaks at 2θ angles of 15.6°, 16.2°, 18.0°, 19.2°, 20.0°, 22.3°, 23.1°, 20.3°, 20.7°, 21.8°, and 25.4°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.1°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.2°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.3°. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern substantially as shown in Figure 14.

[00226] In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 15.6 ± 0.3°, and having peaks at 2θ angles of 0.6°, 2.4° and 4.4° relative to the reference peak. The term "reference peak" refers to a peak in the XRPD diffractogram that one skilled in the art considers as informing the polymorphic form of the material, *i.e.*, differentiated from instrument noise. By "relative" it is meant that the observed 2θ angle of each peak will be the sum of the 2θ angle of the reference peak and the relative 2θ angle of that peak. For example, if the reference peak has a 2θ angle of 15.3°, the relative peaks will have 2θ angles of 15.9°, 17.7° and 19.7°; if the reference peak has a 2θ angle of 15.4°, the relative peaks will have 2θ angles of 16.0°, 17.8° and 19.8°; if the reference peak has a 2θ angle of 15.5°, the relative peaks will have 2θ angles of 16.1°, 17.9° and 19.9°; etc. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 15.6 ± 0.3°, and having peaks at 2θ angles of 0.6°, 2.4°, 3.6°, 4.4°, 6.7°, and 7.5° relative to the reference peak. In some embodiments, I-263a Form 3 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 15.6 ± 0.3°, and having peaks at 2θ angles of 0.6°, 2.4°, 3.6°, 4.4°, 4.7°, 5.1°, 6.2°, 6.7°, 7.5°, and 9.8° relative to the reference peak. Any of the peaks that one skilled in the art considers as informing the polymorphic form of the material can serve as the reference peak and the relative peaks can then be calculated. For example, if the reference peak has a 2θ angle of 18.0°, then the relative peaks will have 2θ angles of -2.4°, -1.8° and 2.0° relative to the reference peak.

[00227] FIG. 16 shows a thermal gravimetric analysis (TGA) profile of I-263a Form 3. The TGA thermogram plots the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C/min. FIG. 16 shows approximately 7.6 % weight loss to 110.3°C. FIG. 16 also shows approximately 15.2 % weight loss to 237.8°C. In some embodiments, I-263a Form 3 is characterized by a TGA profile substantially as shown in Figure 16. In some

embodiments, I-263a Form 3 is characterized by a TGA profile showing approximately 7.6 % weight loss to 110.3°C. In some embodiments, I-263a Form 3 is characterized by a TGA profile showing approximately 15.2 % weight loss to 237.8°C. The weight loss of approximately 7.6 % to 110.3°C shown in the TGA profile is consistent with a water content of about 2 to about 3 molar equivalents of H_2O.

[00228] FIG. 17 shows a differential scanning calorimetry (DSC) profile of I-263a Form 3. The DSC thermogram plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C/min. In some embodiments, I-263a Form 3 is characterized by a DSC profile substantially as shown in FIG. 17. FIG. 17 shows an endotherm event with onset of about 50.1 °C and peak at about 72.3 °C. FIG. 4 also shows an exotherm event with onset of about 148.0 °C and peak at about 164.3 °C. In some embodiments, I-263a Form 3 is characterized by a DSC profile having an endotherm event with onset of about 50.1 °C. In some embodiments, I-263a Form 3 is characterized by a DSC profile having an endotherm event with peak at about 72.3 °C. In some embodiments, I-263a Form 3 is characterized by a DSC profile having an exotherm event with onset of about 148.0 °C. In some embodiments, I-263a Form 3 is characterized by a DSC profile having an exotherm event with peak at about 164.3 °C.

[00229] In some embodiments, I-263a Form 3 of compound I-101 is characterized by at least one of the following features (I-i)-(I-iii):

(I-i) an XRPD pattern having peaks at 2θ angles of 15.6°, 16.2°, 18.0°, and 20.0° as shown in FIGURE 15;

(I-ii) a DSC profile substantially as shown in FIGURE 17;

(I-iii) a TGA profile substantially as shown in FIGURE 16.

[00230] In some embodiments, I-263a Form 3 is characterized by at least two of the features (I-i)-(I-iii). In some embodiments, I-263a Form 3 is characterized by all three of the features (I-i)-(I-iii).

[00231] *Solid state forms of I-256b.* Provided herein is an assortment of characterizing information, which is sufficient, but not all of which is necessary, to describe crystalline Form 1 anhydrous compound I-256b ("I-256b Form 1").

[00232] Figure 3 shows an X-ray powder diffraction (XRPD) pattern of Form 1 of compound I-256b obtained using Cu$K\alpha$ radiation. Peaks identified in Figure 3 include those listed in the table below.

Angle (2 Theta)	Relative Intensity
11.9	10.1%
14.8	9.9%
15.5	15.4%
16.3	37.4%
17.5	28.3%
18.7	34.8%

18.9	44.0%
19.7	20.2%
20.1	45.9%
20.6	30.0%
21.1	100.0%
21.8	15.1%
22.8	55.5%
23.3	32.1%
24.1	23.8%
25.8	10.2%
26.2	10.3%
27.0	38.3%
27.5	23.6%
27.8	19.6%
28.8	5.4%

[00233] In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having a peak at 2θ angle 21.1°. In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.1° and 22.8°. In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.1°, 22.8°, 20.1°, and 18.9°. In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.1°, 22.8°, 20.1°, 18.9°, 27.0°, 16.3°, and 18.7°. In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having peaks at 2θ angles of 21.1°, 22.8°, 20.1°, 18.9°, 27.0°, 16.3°, 18.7°, 23.3°, 17.5°, 24.1°, and 27.5°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.1°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.2°. In some embodiments, the 2θ angles given above have an error tolerance of ±0.3°. In some embodiments, I-256b Form 1 is characterized by an XRPD pattern substantially as shown in Figure 3.

[00234] In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 18.9 ± 0.3°, and having peaks at 2θ angles of 1.2°, 2.2°, and 3.9° relative to the reference peak. The term "reference peak" refers to a peak in the XRPD diffractogram that one skilled in the art considers as informing the polymorphic form of the material, *i.e.*, differentiated from instrument noise. By "relative" it is meant that the observed 2θ angle of each peak will be the sum of the 2θ angle of the reference peak and the relative 2θ angle of that peak. For example, if the reference peak has a 2θ angle of 18.6°, the relative peaks will have 2θ angles of 19.8°, 20.8°, and 22.5°; if the reference peak has a 2θ angle of 18.7°, the relative peaks will have 2θ angles of 19.9°, 20.9°, and 22.6°; if the reference peak has a 2θ angle of 18.8°, the relative peaks will have 2θ angles of 20.0°, 21.0°, and 22.7°; etc. In some embodiments, I-256b Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of 18.9 ± 0.3°, and having peaks at 2θ angles of -2.6°, -0.2°, 1.2°, 2.2°, 3.9°, and 8.1° relative to the reference peak. In some embodiments, I-256b

Form 1 is characterized by an XRPD pattern having a reference peak with a 2θ angle of ± 0.3°, and having peaks at 2θ angles of -2.6°, -1.4°, -0.2°, 1.2°, 2.2°, 3.9°, 4.4°, 5.2°, 8.1°, and 8.6° relative to the reference peak. Any of the peaks that one skilled in the art considers as informing the polymorphic form of the material can serve as the reference peak and the relative peaks can then be calculated. For example, if the reference peak has a 2θ angle of 21.1°, then the relative peaks will have 2θ angles of -2.2°, -1.0°, and 1.7° relative to the reference peak.

[00235] In some embodiments, the chemical entity according to the disclosure is or comprises substantially crystalline I-256b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 70% by weight crystalline I-256b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 80% by weight crystalline I-256b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 90% by weight crystalline I-256b Form 1. In some embodiments, the chemical entity according to the disclosure comprises at least 95% by weight crystalline I-256b Form 1.

[00236] FIG. 12 shows a differential scanning calorimetry (DSC) profile of I-256b Form 1. The DSC thermogram plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C/min. In some embodiments, I-256b Form 1 is characterized by a DSC profile substantially as shown in FIG. 12. FIG. 12 shows an endotherm event with onset of about 157.7 °C and peak at about 163.9 °C. FIG. 12 also shows an exotherm event with onset of about 167.1 °C and peak at about 172.6 °C. In some embodiments, I-256b Form 1 is characterized by a DSC profile having an endotherm event with onset of about 157.7 °C. In some embodiments, I-256b Form 1 is characterized by a DSC profile having an endotherm event with peak at about 163.9 °C. In some embodiments, I-256b Form 1 is characterized by a DSC profile having an exotherm event with onset of about 167.1 °C. In some embodiments, I-256b Form 1 is characterized by a DSC profile having an exotherm event with peak at about 172.6 °C.

[00237] FIG. 13 shows a thermal gravimetric analysis (TGA) profile of I-256b Form 1. The TGA thermogram plots the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C/min. FIG. 13 shows approximately 0.3 % weight loss to 141.3°C. In some embodiments, I-256b Form 1 is characterized by a TGA profile substantially as shown in FIG. 13. In some embodiments, I-256b Form 1 is characterized by a TGA profile having about 0.3 % weight loss to 141.3°C.

[00238] In some embodiments, I-256b Form 1 is characterized by at least one of the following features (I-i)-(I-iii):

(I-i) an XRPD pattern having peaks at 2θ angles of 21.1°, 22.8°, 20.1°, and 18.9°;

(I-ii) a DSC profile substantially as shown in FIG. 12;

(I-iii) a TGA profile substantially as shown in FIG. 13.

[00239] In some embodiments, I-256b Form 1 is characterized by at least two of the features (I-i)-(I-iii). In some embodiments, I-256b Form 1 is characterized by at least three of the features (I-i)-(I-v). In some embodiments, I-256b Form 1 is characterized by at least four of the features (I-i)-(I-v). In some embodiments, I-256b Form 1 is characterized by all three of the features (I-i)-(I-iii).

[00240] As discussed above, the present disclosure provides chemical entities that are useful as inhibitors of SAE, and thus the present chemical entities can be useful for treating proliferative, inflammatory, cardiovascular and neurodegenerative disorders.

[00241] The chemical entities and pharmaceutical compositions of the present disclosure can be useful for the treatment of cancer. As used herein, the term "cancer" refers to a cellular disorder characterized by uncontrolled or disregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term "cancer" includes, but is not limited to, solid tumors and bloodborne tumors (hematologic malignancies). The term "cancer" encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term "cancer" further encompasses primary and metastatic cancers.

[00242] In some embodiments, therefore, the present disclosure provides the chemical entity of formula (***I***), or a pharmaceutically acceptable salt thereof, for use in treating cancer. In some embodiments, the present disclosure provides a pharmaceutical composition (as described herein) for the treatment of cancer comprising the chemical entity of formula (***I***), or a pharmaceutically acceptable salt thereof. In some embodiments, the present disclosure provides the use of the chemical entity of formula (***I***), or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition (as described herein) for the treatment of cancer. In some embodiments, the present disclosure provides the use of an effective amount of the chemical entity of formula (***I***), or a pharmaceutically acceptable salt thereof, for the treatment of cancer. In some embodiments, the present disclosure provides the chemical entity of formula (***I***), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in treating cancer.

[00243] Non-limiting examples of solid tumors that can be treated with the disclosed inhibitors include pancreatic cancer; bladder cancer including invasive bladder cancer; colorectal cancer; thyroid cancer, gastric cancer, breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; liver cancer including e.g. hepatocellular cancer and intrahepatic bile duct; lung and bronchus cancer, including non-small cell lung cancer (NSCLC), squamous lung cancer, brochioloalveolar carcinoma (BAC), adenocarcinoma of the lung, and small cell lung cancer (SCLC); ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; uterine cancer including e.g. uterine corpus and uterine cervix; endometrial cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck, nasopharyngeal caner, oral cavity and pharynx; melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain cancer, including, e.g., glioma/glioblastoma,

anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; neuroendocrine, including metastatic neuroendocrine tumors; bone cancer; and soft tissue sarcoma.

[00244] Non-limiting examples of hematologic malignancies that can be treated with the disclosed inhibitors include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL); T-cell lymphoma; multiple myeloma (MM); amyloidosis; Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); small lymphocytic lymphoma (SLL); marginal zone lymphoma; smoldering multiple myeloma; and myeloproliferative syndromes.

[00245] In some embodiments, chemical entities of the present disclosure are suitable for the treatment of breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia or acute lymphoblastic leukemia. In some embodiments, chemical entities of the present disclosure are suitable for the treatment of NHL. In some embodiments, chemical entities of the present disclosure are suitable for the treatment of indolent NHL. In some embodiments, chemical entities of the present disclosure are suitable for the treatment of follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma or marginal zone lymphoma. In some embodiments, chemical entities of the present disclosure are suitable for the treatment of diffuse large B-cell lymphoma (DLBCL) or chronic lymphocytic lymphoma (CLL). In some embodiments, chemical entities of the present disclosure are suitable for the treatment of multiple myeloma. In some embodiments, chemical entities of the present disclosure are suitable for the treatment of ALL, AML, or MDS.

[00246] In other embodiments, chemical entities of the present disclosure are suitable for the treatment of inflammatory, cardiovascular and neurodegenerative disorders including, but not limited to, allergies/anaphylaxis, acute and/or chronic inflammation, rheumatoid arthritis, autoimmunity disorders, thrombosis, hypertension, cardiac hypertrophy, heart failure, Huntington's disease and Alzheimers.

[00247] Accordingly, in another aspect of the present disclosure, pharmaceutical compositions are provided, wherein these compositions comprise any of the chemical entities as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00248] It will also be appreciated that certain of the chemical entities of present disclosure can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present disclosure, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other

adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a chemical entity as otherwise described herein, or a metabolite or residue thereof.

[00249] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this disclosure that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of SAE.

[00250] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19. The chemical entities of this disclosure include pharmaceutically acceptable salts, such as those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. The present disclosure also envisions the quaternization of any basic nitrogen-containing groups of the chemical entities disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00251] As described above, the pharmaceutically acceptable compositions of the present disclosure additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid

binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the chemical entities of the present disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of the present disclosure. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers; alumina; aluminum stearate; lecithin; serum proteins, such as human serum albumin; buffer substances such as phosphates (including but not limited to phosphate buffer solutions), glycine, sorbic acid, or potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids; water; salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts; colloidal silica; magnesium trisilicate; polyvinyl pyrrolidone; polyacrylates; waxes; polyethylene-polyoxypropylene-block polymers; wool fat; sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; glycols such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; and non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate. Additionally, coloring agents; releasing agents; coating agents; sweetening, flavoring and perfuming agents; preservatives; and antioxidants can also be present in the composition, according to the judgment of the formulator. In some embodiments, pharmaceutically acceptable compositions of the disclosure comprise a compound of Formula (I) (5 mg/mL); β-Cyclodextrin Sulfobutyl Ethers, Sodium Salts (Captisol®) (Ligand Pharmaceuticals Inc) (10% w/v); the composition being adjusted to a pH of 2 +/- 0.2 using 25 mM HCl and H_3PO_4; and Water for injection (q.s. to a fill volume, e.g., 5 mL or 10 mL). In some embodiments, pharmaceutically acceptable compositions of the disclosure comprise a compound of Formula (I) (10 mg/mL); β-Cyclodextrin Sulfobutyl Ethers, Sodium Salts (Captisol®) (Ligand Pharmaceuticals Inc) (10% w/v); the composition being adjusted to a pH of 2 +/- 0.2 using 50mM H_3PO_4; and Water for injection (q.s. to a fill volume, e.g 10 mL).

[00252] In yet another aspect, a method for treating a proliferative, inflammatory, cardiovascular or neurodegenerative disorder is provided comprising administering an effective amount of a chemical entity, or a pharmaceutical composition to a subject in need thereof. In certain embodiments of the present disclosure an "effective amount" of the chemical entity or pharmaceutical

composition is that amount effective for treating a proliferative, inflammatory, infectious, neurological or cardiovascular disorder, or is that amount effective for treating cancer. In other embodiments, an "effective amount" of a chemical entity is an amount which inhibits binding of SAE.

[00253] The chemical entities and compositions, according to the method of the present disclosure, may be administered using any amount and any route of administration effective for treating the disease. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The chemical entities of the present disclosure are frequently formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the chemical entities and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disease being treated and the severity of the disease; the activity of the specific chemical entity employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific chemical entity employed; the duration of the treatment; drugs used in combination or coincidental with the specific chemical entity employed, and like factors well known in the medical arts. The term "patient," as used herein, means an animal, for instance a mammal, such as a human.

[00254] The pharmaceutically acceptable compositions of the present disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, lotions, salves, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the chemical entities of the present disclosure may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg, for instance from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00255] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active chemical entities, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (for instance, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions

can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00256] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00257] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00258] In order to prolong the effect of a chemical entity of the present disclosure, it is often desirable to slow the absorption of the chemical entity from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the chemical entity then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered chemical entity form is accomplished by dissolving or suspending the chemical entity in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the chemical entity in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of chemical entity to polymer and the nature of the particular polymer employed, the rate of chemical entity release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the chemical entity in liposomes or microemulsions that are compatible with body tissues.

[00259] Compositions for rectal or vaginal administration are, for instance, suppositories which can be prepared by mixing the chemical entities of the present disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active chemical entity.

[00260] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active chemical entity is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders

such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00261] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or for instance, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00262] The active chemical entities can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active chemical entity may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or for instance, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00263] Dosage forms for topical or transdermal administration of a chemical entity of the present disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of the present disclosure. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a chemical entity to the body. Such dosage forms

can be made by dissolving or dispensing the chemical entity in the proper medium. Absorption enhancers can also be used to increase the flux of the chemical entity across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the chemical entity in a polymer matrix or gel.

[00264] In some embodiments, a chemical entity of the present disclosure or a pharmaceutical composition thereof is administered in conjunction with an anticancer agent. As used herein, the term "anticancer agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer. Combination therapy includes administration of the therapeutic agents concurrently or sequentially. Alternatively, the therapeutic agents can be combined into one composition which is administered to the patient.

[00265] In one embodiment, the chemical entities of the present disclosure are used in combination with other therapeutic agents. In some embodiments, the additional therapeutic agent is selected from other inhibitors of SAE. In other embodiments, a chemical entity of the present disclosure is administered in conjunction with a therapeutic agent selected from the group consisting of cytotoxic agents, radiotherapy, and immunotherapy. In some embodiments, the chemical entities of the present disclosure can be used in combination with a chemotherapeutic regimen for the treatment of relapsed/refractory non-Hodgkin's lymphoma including DLBCL and CLL. Chemotherapeutic regimens include, but are not limited to R-ICE (rituximab, ifosfamide, carboplatin and etoposide), R-DHAP (rituximab, dexamethasone, high-dose cytarabine and cisplatin), and R-GDP (rituximab, gemcitabine, cisplatin and dexamethasone). It is understood that other combinations may be undertaken while remaining within the scope of the invention.

[00266] Those additional agents may be administered separately from a provided combination therapy, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a chemical entity of the present disclosure. If administered as part of a combination therapy, the two therapeutic agents may be submitted simultaneously, sequentially, or intermittently. Combination therapy can be used for any of the therapeutic indications described herein. In some embodiments, the combination therapy is for the treatment of a proliferative disorder (e.g., cancer) in a patient. In some embodiments, the proliferative disorder is breast cancer, lung cancer, ovarian cancer, multiple myeloma, acute myeloid leukemia or acute lymphoblastic leukemia.

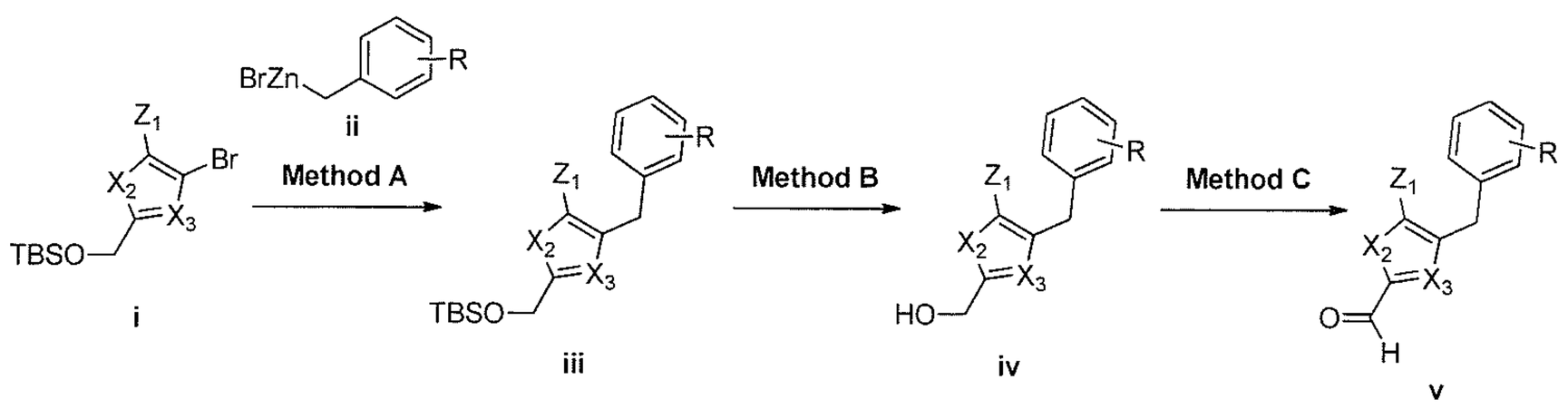
[00267] Another aspect of the present disclosure relates to inhibiting SAE activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a chemical entity of formula (***I***), or a composition comprising said chemical entity. The term "biological sample," as used herein, generally includes *in vivo*, *in vitro*, and *ex vivo* materials, and also includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00268] Still another aspect of the present disclosure is to provide a kit comprising separate containers in a single package, wherein a compound disclosed herein or a pharmaceutical composition and/or salt thereof is provided in combination with one or more pharmaceutically acceptable carriers for use in treating one or more disorders, symptoms and diseases where SAE plays a role.

General Synthetic Methods and Intermediates

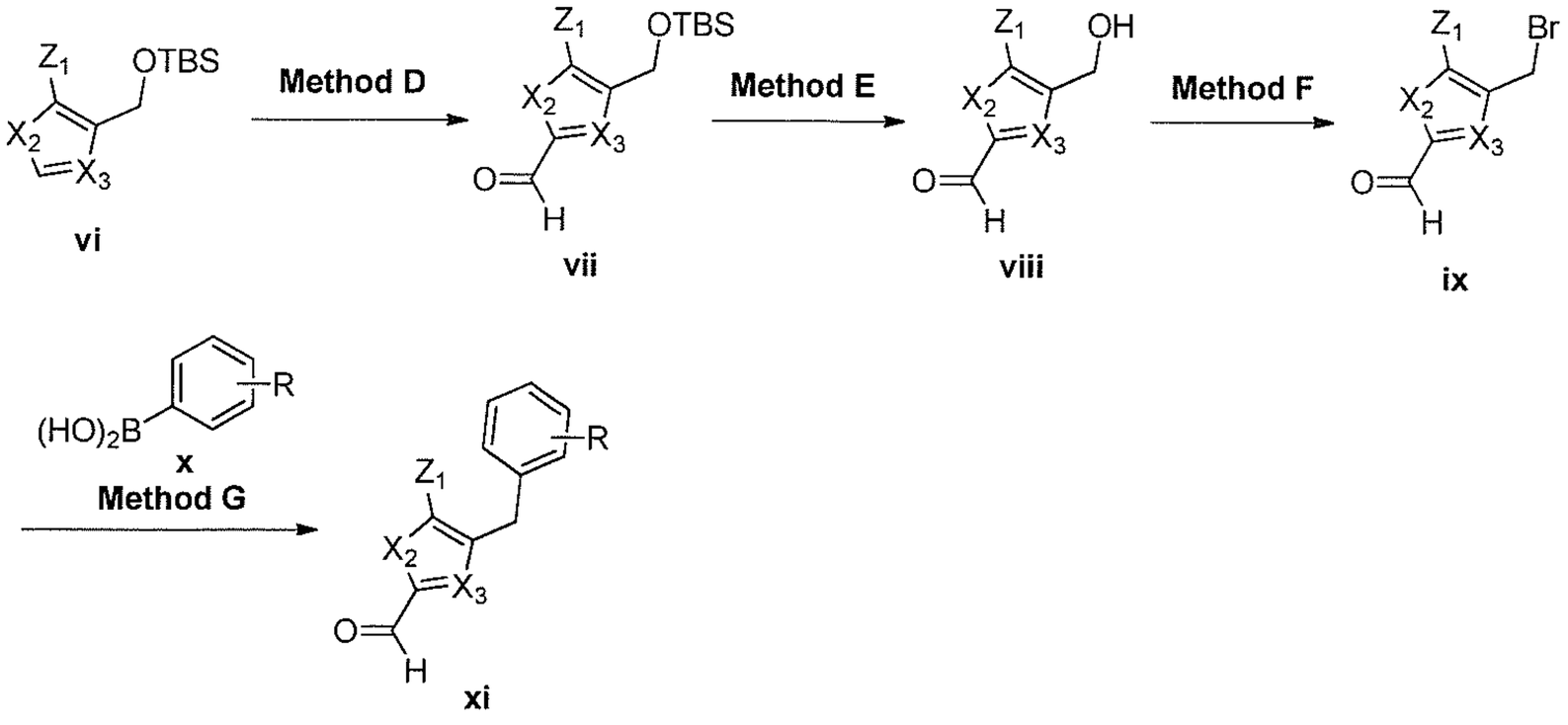
[00269] The chemical entities of the present disclosure can be prepared by one of ordinary skill in the art in light of the present disclosure and knowledge in the art, and / or by reference to the schemes shown below and the synthetic examples. Exemplary synthetic routes are set forth in Schemes below and in the Examples.

Scheme 1: General method for the preparation of aldehyde v



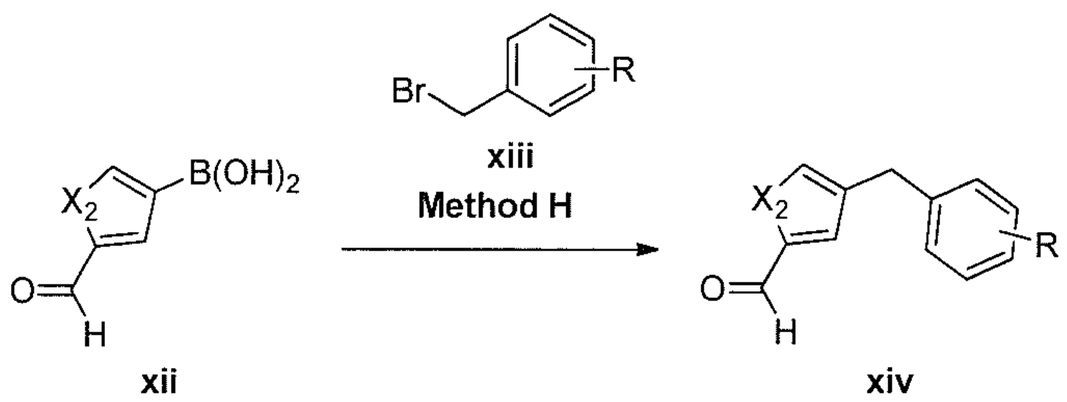
[00270] Scheme 1 depicts the synthesis of aldehydes **v**. Conversion of **i** to the compound **iii** is accomplished by a palladium mediated coupling reaction with an organozinc reagent **ii** in suitable solvent, such as 1,4-dioxane or THF at elevated temperature or microwave irradiation (Method A). Deprotection of TBS group of **iii** is effected by treatment with TBAF or acid, such as aq. HCl or TFA (Method B). Further treatment with an oxidation reagent, such as MnO_2 or Dess-Martin periodinane, in DCM affords the aldehyde **v** (method C).

Scheme 2: General method for the preparation of aldehyde xi



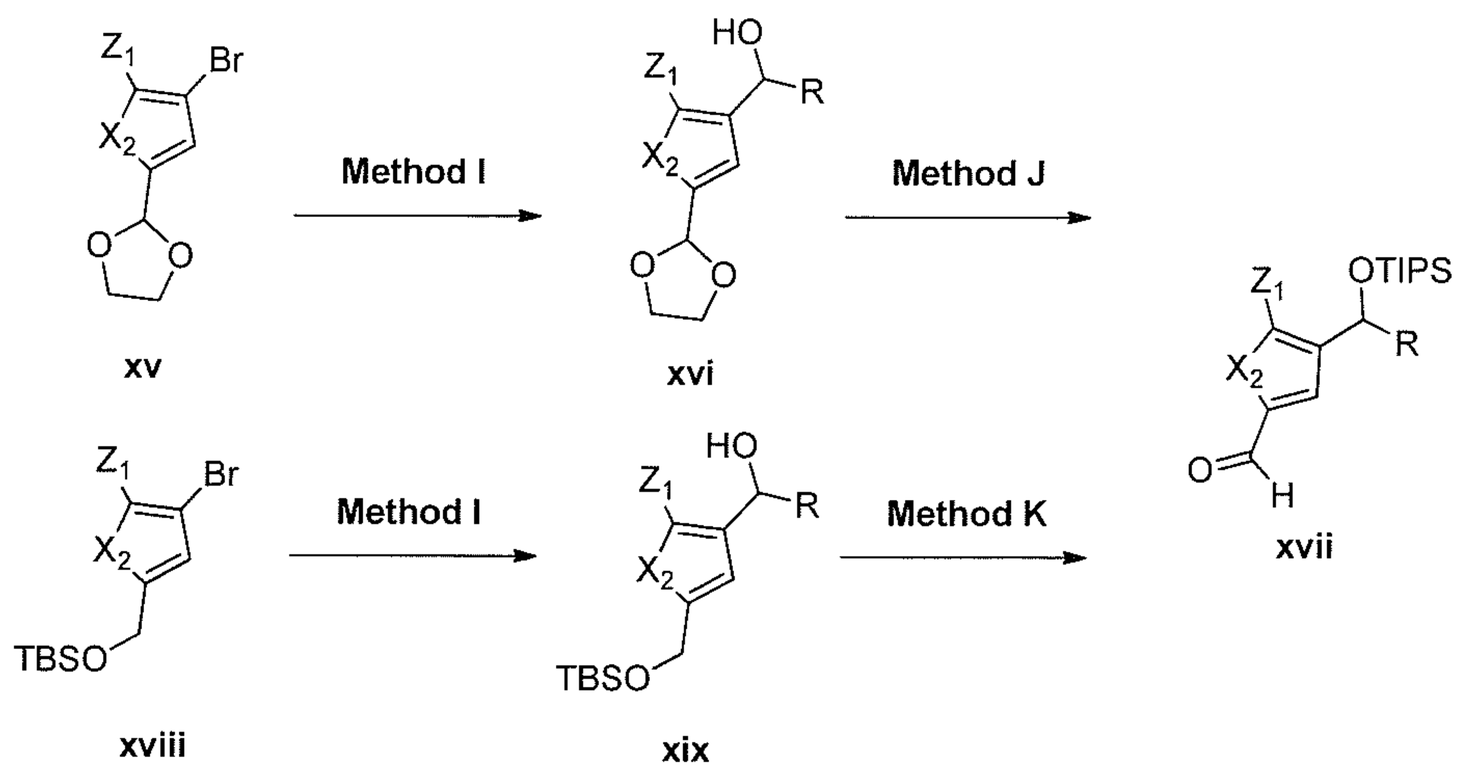
[00271] Scheme 2 depicts the synthesis of aldehydes **xi**. Formylation of the appropriate heteroaryl **vi** in the presence of alkyl lithium, such as *n*-BuLi or *t*-BuLi, and DMF in THF at cold temperature gives aldehydes **vii** (Method D), that are then deprotected with TBAF or acid, such as aq. HCl or TFA, to afford compounds of formula **viii** (Method E). Formation of the methylene bromide is achieved using a suitable reagent, for example PPh_3 and CBr_4 in DCM to afford halides of formula **ix** (Method F). Halides **ix** can be subjected to a coupling reaction with boronic acid derivatives **x** under suitable conditions, for example $Pd(PPh_3)_4$, K_2CO_3 in a suitable solvent, such as a dioxane-water mixture at elevated temperature or microwave irradiation, to give compounds of formula **xi** (Method G).

Scheme 3: General method for the preparation of aldehyde xiv



[00272] Scheme 3 depicts the synthesis of aldehydes **xiv**. The appropriate boronic acid derivatives **xii** can be coupled with alkyl or aryl halides, such as benzyl bromide under standard Suzuki coupling conditions, such as $Pd(PPh_3)_4$, Na_2CO_3, dioxane/water, elevated temperature or microwave irradiation to give compounds of formula **xiv** (Method H).

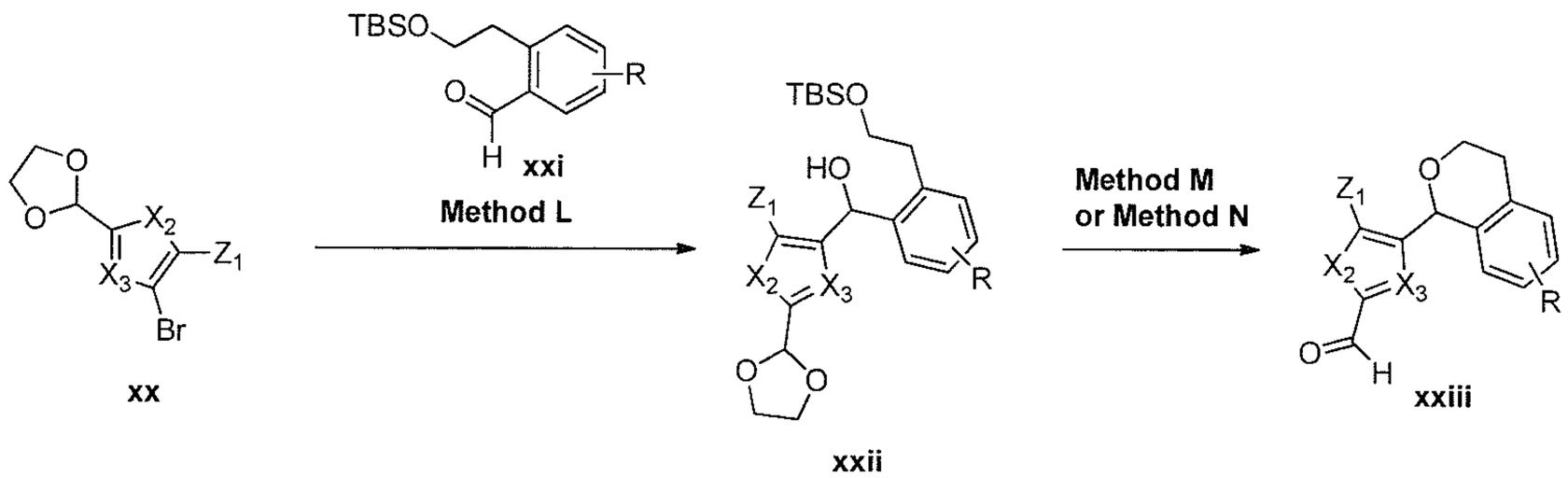
Scheme 4: General method for the preparation of aldehyde xvii



[00273] Scheme 4 depicts the synthesis of aldehydes **xvii**. Lithiation of appropriate heteroaryl bromides **xv** using alkyl lithium, such as n-BuLi or t-BuLi, and addition of suitable aldehydes or ketones gives the alcohols **xvi** (Method I). Protection of the alcohol, such as with a TIPS or TBS group followed by cleavage of the acetal group using acidic conditions, such as aq. HCl/THF or

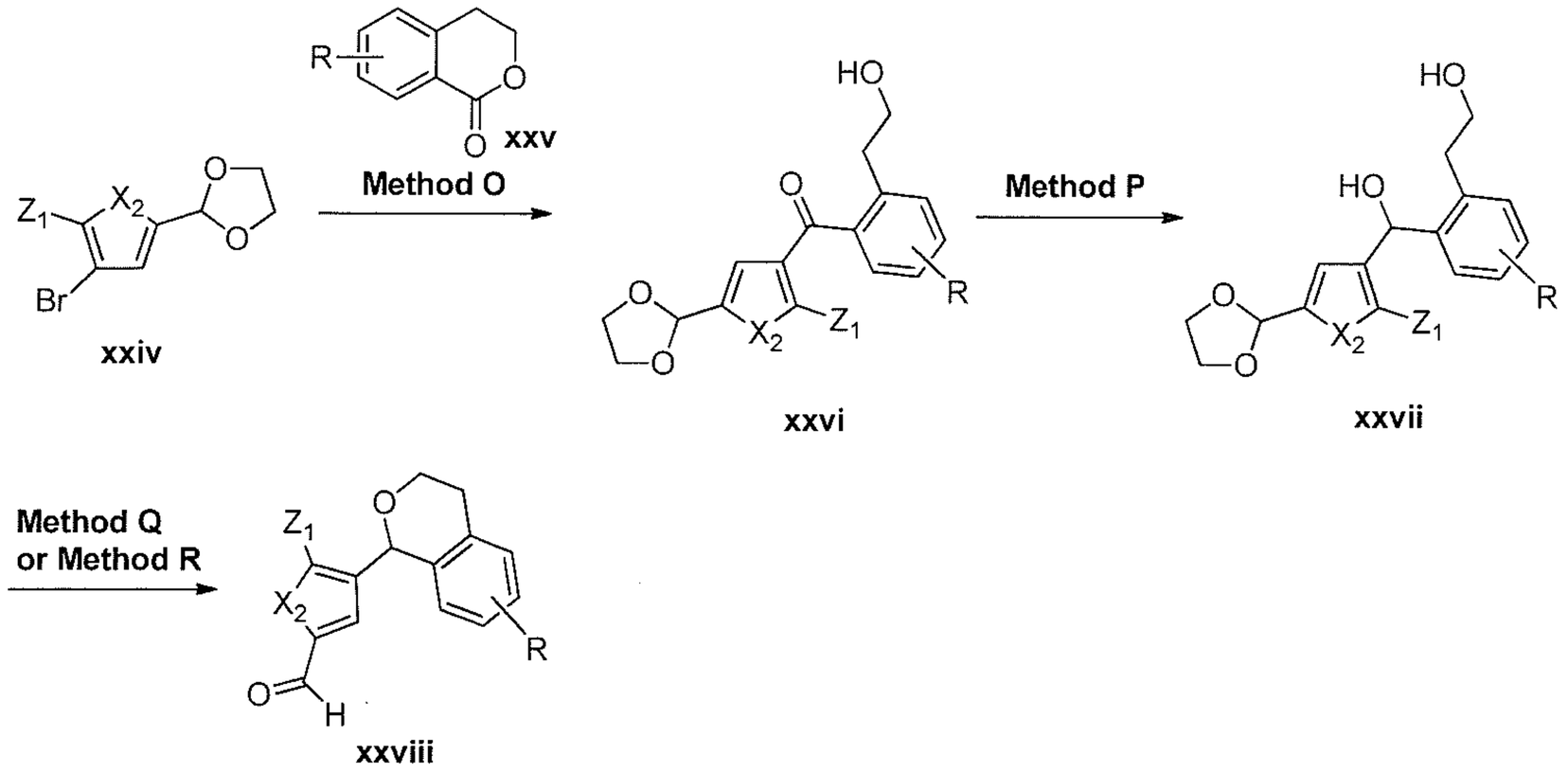
Dowex resin, in suitable solvent, such as acetone, gives the aldehydes **xvii** (Method J). Alternatively, silyl ethers **xviii** are lithiated in an analogous fashion and reacted with suitable aldehydes or ketones to give alcohols **xix**. Protection followed by selective deprotection of the primary silyl ether with mild acidic conditions, such as 1% HCl in ethanol followed by an oxidation using Dess-Martin periodinane or MnO_2 in suitable solvent, such as DCM, gives the aldehydes **xvii** (Method K).

Scheme 5: General method for the preparation of isochroman substituted aldehyde xxiii



[00274] Scheme 5 depicts the synthesis of aldehydes **xxiii** substituted with an isochroman ring. Lithiation of an appropriate bromide **xx** using alkyl lithium, such as n-BuLi or t-BuLi followed by addition of an aldehydes **xxi** gives the alcohols **xxii** (Method L). Under acidic conditions, such as aq. HCl/THF or TFA/water, cyclization and deprotection occur to form the aldehyde **xxiii** (Method M). Alternatively, deprotection of the primary silyl ethers, followed by activation of the primary alcohols, such as conversion to the iodide or mesylate, facilitates cyclization using Ag_2O or base such as NaH in suitable solvent, such as Et_2O or DMF. Deprotection of the acetals yields aldehydes **xxiii** (Method N).

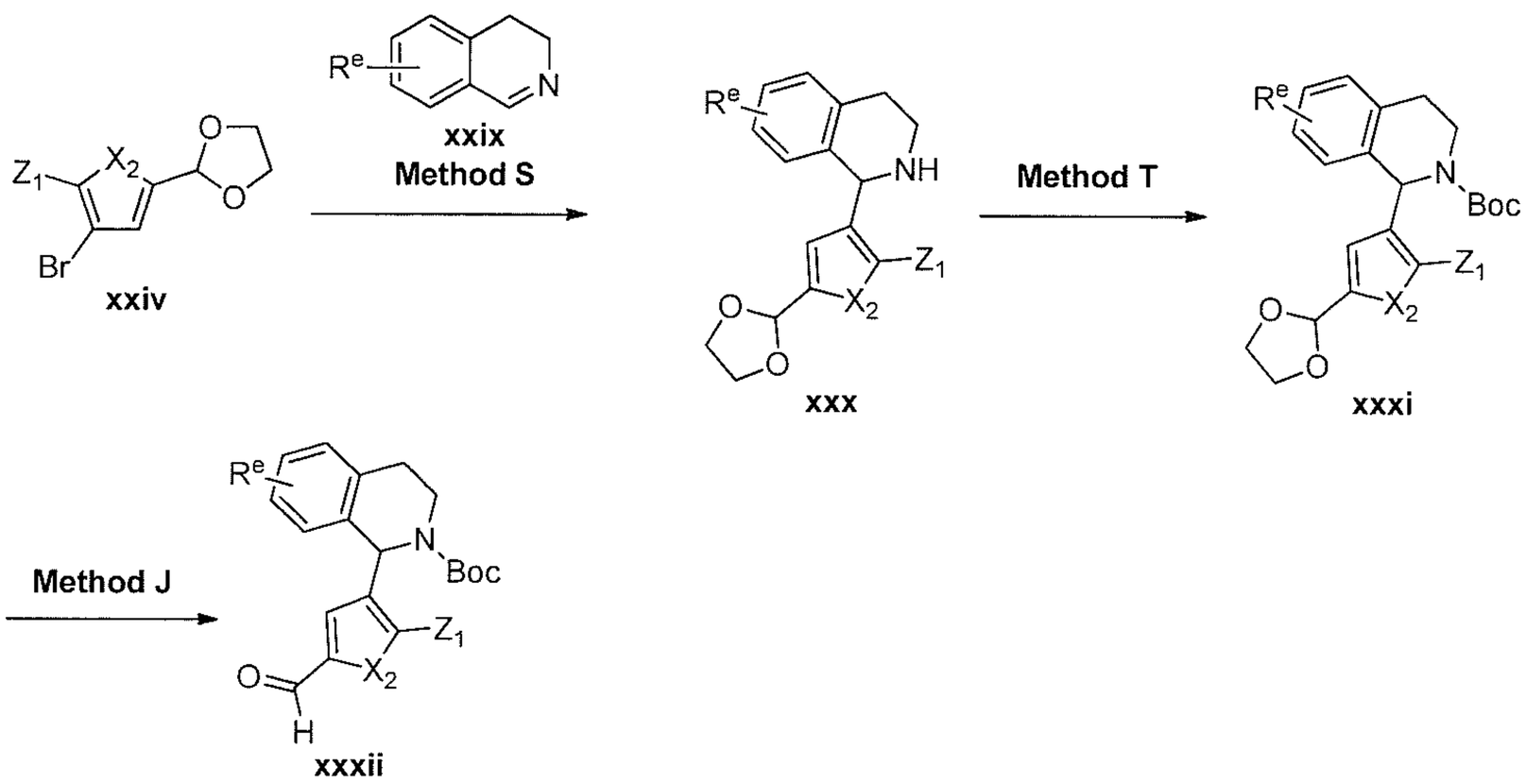
Scheme 6: General method for the preparation of isochroman substituted aldehydes xxviii



[00275] Scheme 3b depicts an alternative synthesis of aldehydes **xxviii** substituted with an isochroman ring. Lithiation of an appropriate bromide using alkyl lithium, such as n-BuLi or t-BuLi, at cold temperature followed by addition of lactones **xxv** gives the ketones **xxvi** (Method O). Reduction of the ketone by reducing agent, such as $NaBH_4$ in a suitable solvent, such as THF,

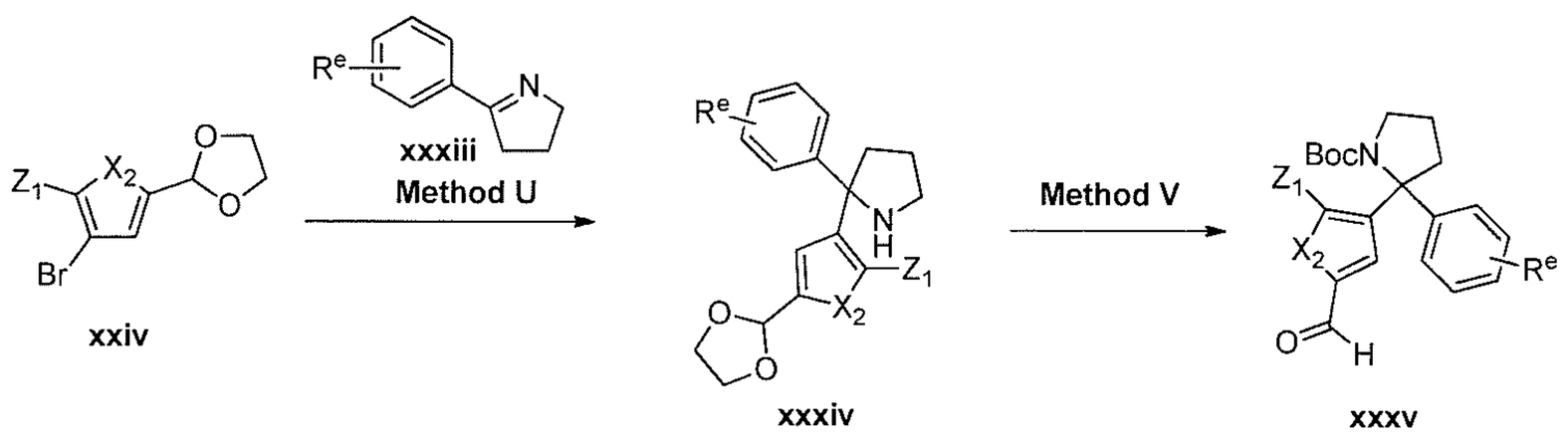
provides alcohols **xxvii** (Method P). Under acidic conditions, such as aq. HCl/THF or TFA/water cyclization and deprotection occur to form the aldehyde **xxviii** (Method Q). Alternatively, activation of the primary alcohols, such as conversion to the iodide or mesylate facilitates cyclization using Ag_2O or base such as NaH in suitable solvent, such as Et_2O or DMF. Deprotection of the acetals under acidic condition, such as aq. HCl/THF or TFA/water yields aldehydes **xxviii** (Method R).

Scheme 7: General method for the preparation of tetrahydroisoquinoline substituted aldehyde xxxii



[00276] Scheme 4 depicts the synthesis of aldehydes **xxxii**, substituted with a tetrahydroisoquinoline ring. Lithiation of an appropriate heteroaryl bromide using alkyl lithium, such as n-BuLi or t-BuLi at cold temperature and addition of dihydroisoquinolines (imine) **xxix** in the presence of Lewis acid, such as BF_3 Et_2O complex, gives the tetrahydroisoquinolines **xxx** (Method S). Protection of amines under general conditions, such as $(Boc)_2O$/DMAP in acetonitrile, affords carbamates **xxxi** (Method T). Cleavage of the acetal group using acidic conditions, such as aq. HCl/THF or Dowex resin in suitable solvent, such as acetone, gives the aldehydes **xxxii** (Method J).

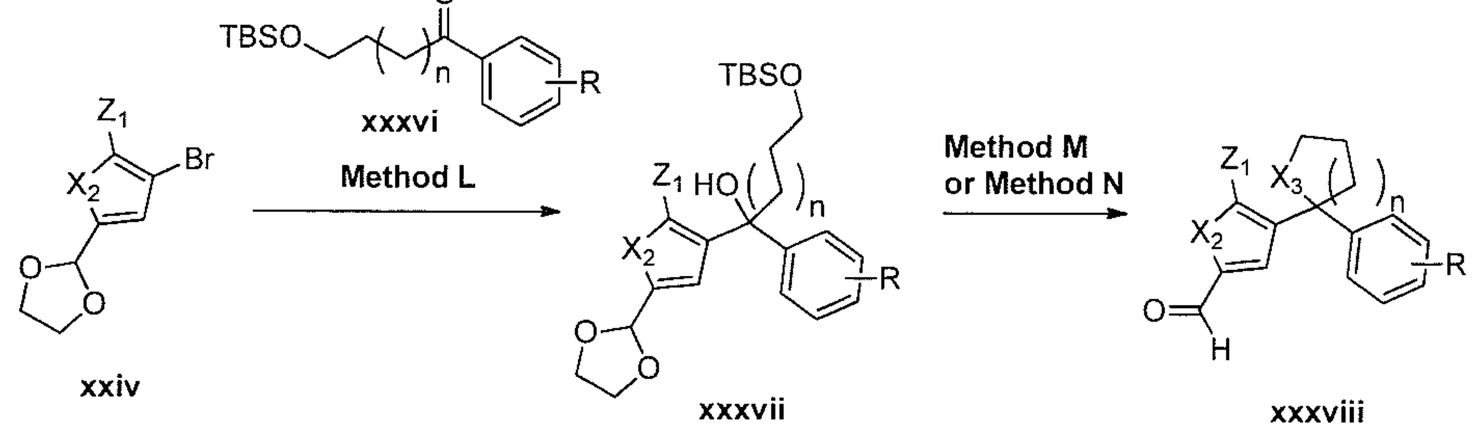
Scheme 8: General method for the preparation of pyrrolidine substituted aldehyde xxxv



[00277] Scheme 8 depicts the synthesis of aldehydes substituted with a pyrrolidine ring. Lithiation of an appropriate bromides using alkyl lithium, such as n-BuLi or t-BuLi, at cold temperature and addition of a dihydropyrrolidines (imine) **xxxiii** gives the pyrrolidine intermediates **xxxiv** (Method U). Acetals **xxxiv** are treated under acidic conditions, such as aq. HCl/acetone or

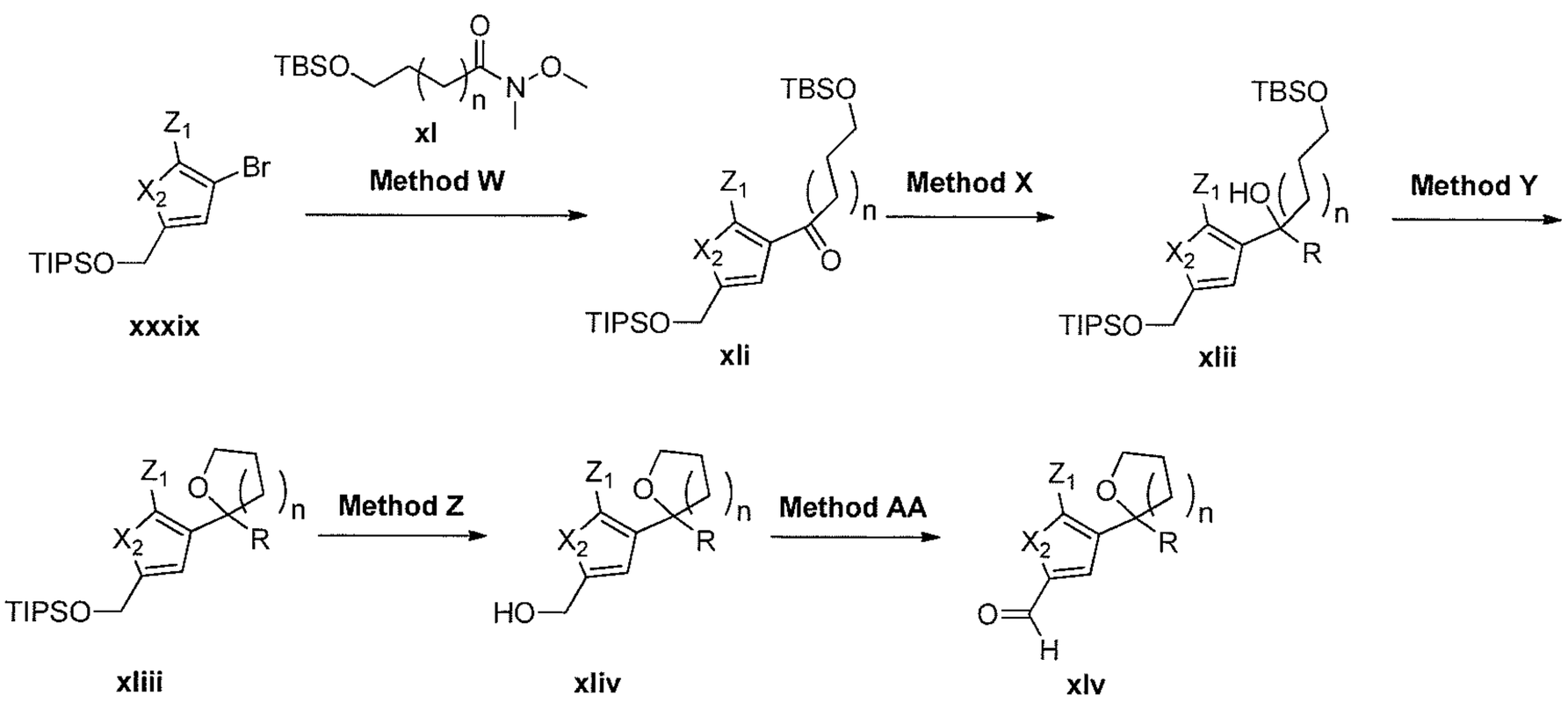
Dowex/acetone followed by protection of amines under usual conditions, such as $(Boc)_2O$, DMAP in suitable solvent, such as acetonitrile, gives the aldehydes **xxxv** (Method V).

Scheme 9: General method for the preparation of thiophene and furan aldehydes xxxviii



[00278] Scheme 9 depicts the synthesis of aldehydes **xxxviii**. Alcohols **xxxvii** can be prepared by appropriate bromides **xxiv** and phenyl ketone derivatives **xxxvi** under an analogous reaction condition described in scheme 5 (Method L). Under acidic conditions, such as aq. HCl/THF or TFA/water, cyclization and deprotection occur to form the aldehydes **xxxviii** (Method M). Alternatively, deprotection of the primary silyl ethers, followed by activation of the primary alcohols, such as conversion to the iodide or mesylate, facilitates cyclization using Ag_2O or base such as NaH in suitable solvent, such as Et_2O or DMF. Deprotection of the acetals under acidic conditions, such as aq. HCl/acetone or Dowex/acetone, yields aldehydes **xxxviii** (Method N). Alternatively, a trityl sulfur group instead of the TBS ether group provides corresponding aldehyde **xxxviii**.

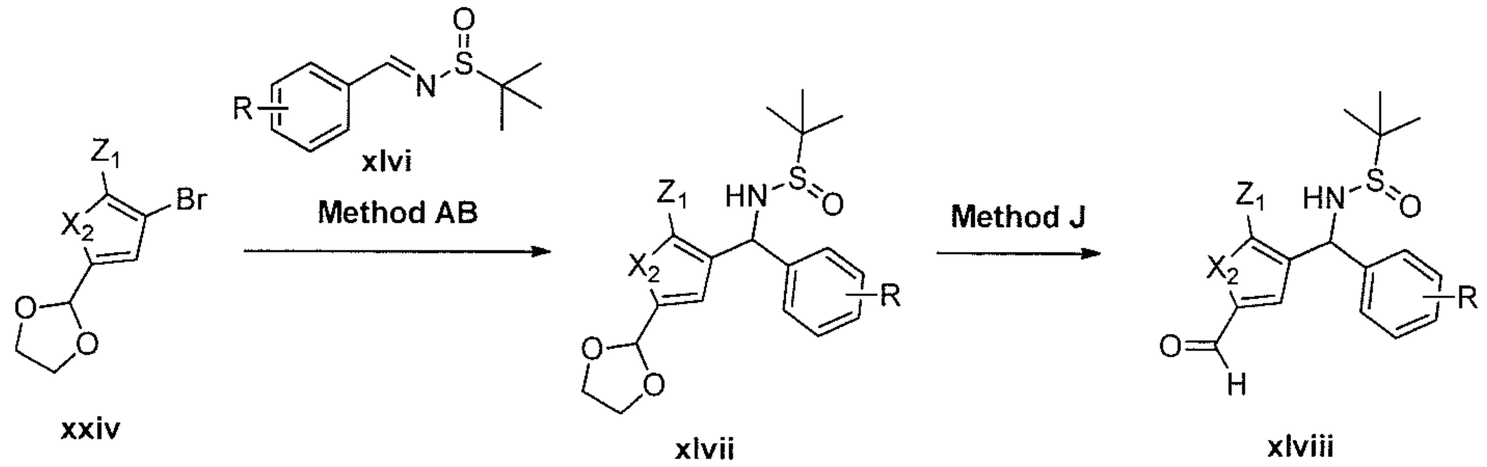
Scheme 10: General method for the preparation of aldehydes xlv



[00279] Scheme 10 depicts the synthesis of aldehydes **xlv**. Lithiation of appropriate bromides **xxxix** using alkyl lithium, such as n-BuLi or t-BuLi, at cold temperature and addition of Weinreb amides **xl** gives corresponding ketones **xli** (Method W). Subjecting the ketones **xli** to alkylation with appropriate Grignard reagents or alkyl lithium reagents in suitable solvent, such as THF, at cold temperature gives alcohols **xlii** (Method X). Deprotection of TBS group followed by internal

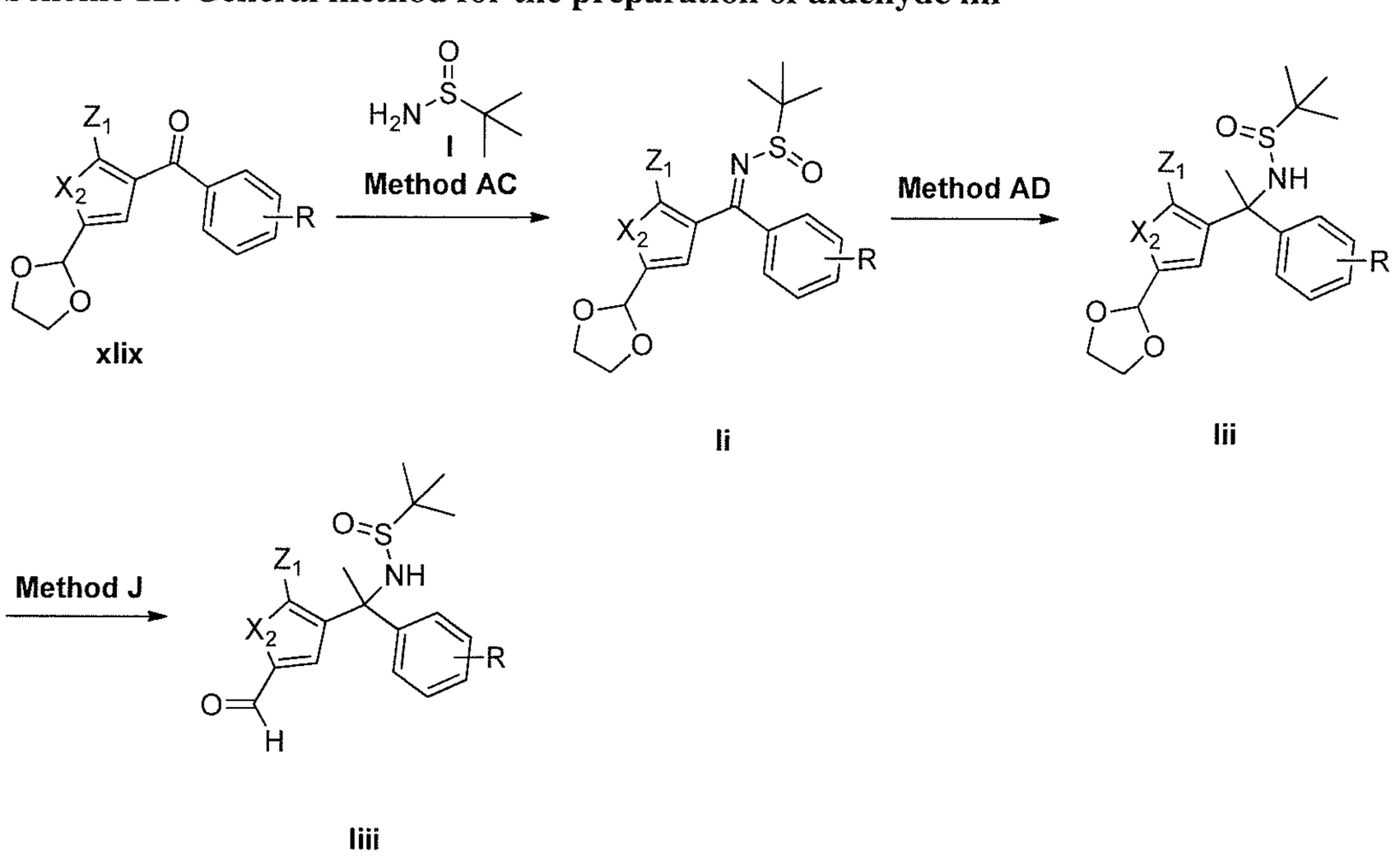
cyclization under acidic conditions, such as 1% HCl in ethanol, affords tetrahydrofuran derivatives **xliii** (Method Y) and then deprotection of TIPS group using TBAF or acid, such as aq. HCl/ THF or TFA/ water (Method Z), followed by oxidation by MnO_2 or Dess-Martin periodinane in suitable solvent, such as DCM, provides the aldehydes **xlv** (Method AA).

Scheme 11: General method for the preparation of aldehydes xlviii



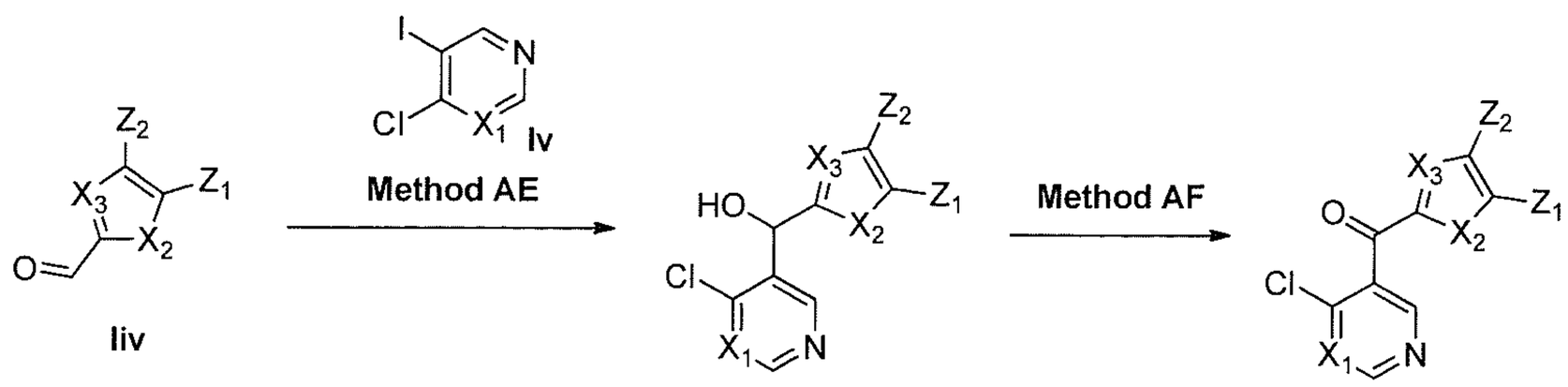
[00280] Scheme 11 depicts the synthesis of aldehydes **xlviii**. Lithiation of appropriate bromides **xxiv** using alkyl lithium, such as n-BuLi or t-BuLi, at cold temperature and addition of sulfonamides **xlvi** gives the compounds of formula **xlvii** (Method AB). Deprotection of the acetal group under conditions analogous to those described in Scheme 5 gives the aldehydes **xlviii** (Method J).

Scheme 12: General method for the preparation of aldehyde liii



[00281] Scheme 12 depicts the synthesis of aldehydes **liii**. Condensation of an appropriate ketone **xlix** and 2-methylpropane-2-sulfinamide **l** using Lewis acid, such as $Ti(OEt)_4$ in suitable solvent, such as THF, gives the intermediates **li**. The compounds **li** are treated with MeLi at cold temperature to afford compounds of formula **lii**, and deprotection of acetal group under conditions analogous to those described in Scheme 5 gives the aldehydes **liii** (Method J).

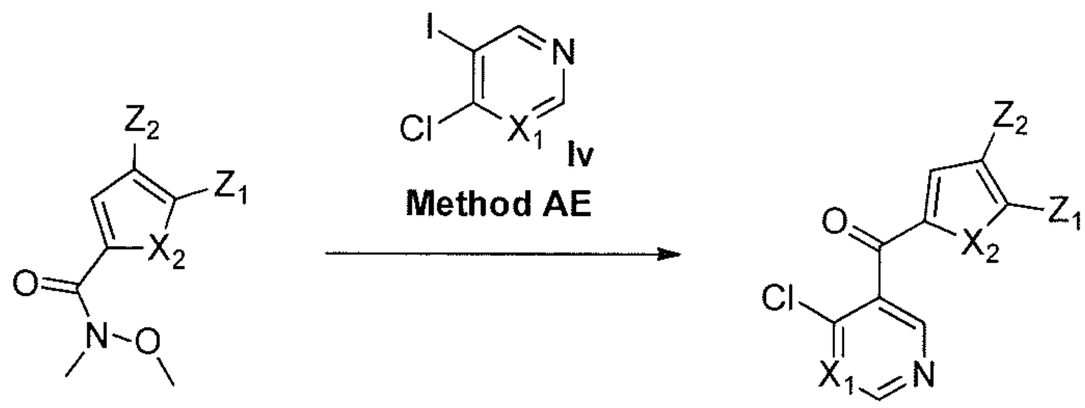
Scheme 13: General method for the preparation of diaryl ketones lvii



lvi lvii

[00282] Scheme 13 depicts the synthesis of diaryl ketone intermediates **lvii**. Lithiation of bis-halogenated pyrimidines or pyridines **lv** can be followed by addition of the aldehydes **liv** to give diaryl alcohols **lvi** (Method AE). Oxidation for example with MnO_2 or Dess-Martin periodinane provides diarylketones **lvii** (Method AF).

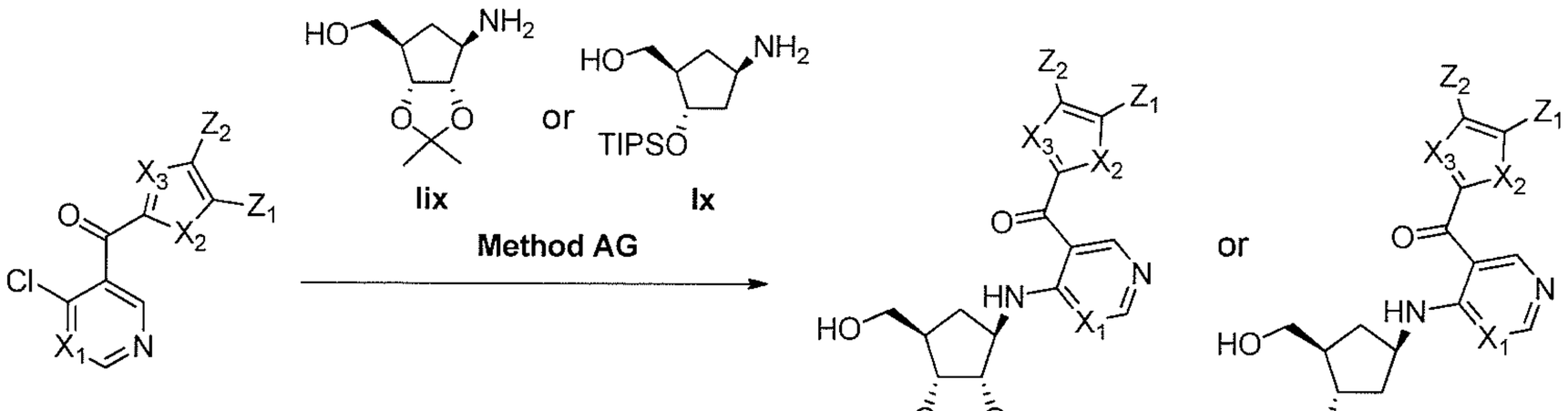
Scheme 14: General method for the preparation of diaryl ketones lix



lix

[00283] Scheme 14 depicts that the diarylketones **lix** can also be accessed by reaction of Weinreb amides **lviii** with bis-halogenated pyrimidines or pyridines **lv** (method AE).

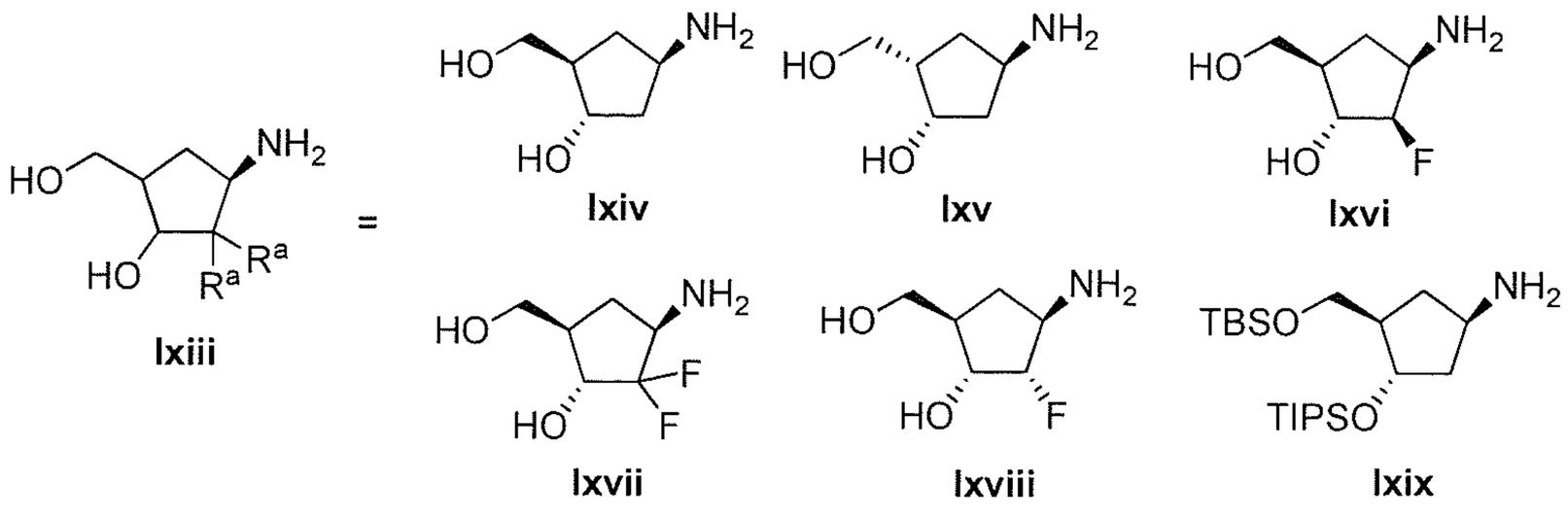
Scheme 15: General method for the synthesis of keto arylamines lxi and lxii



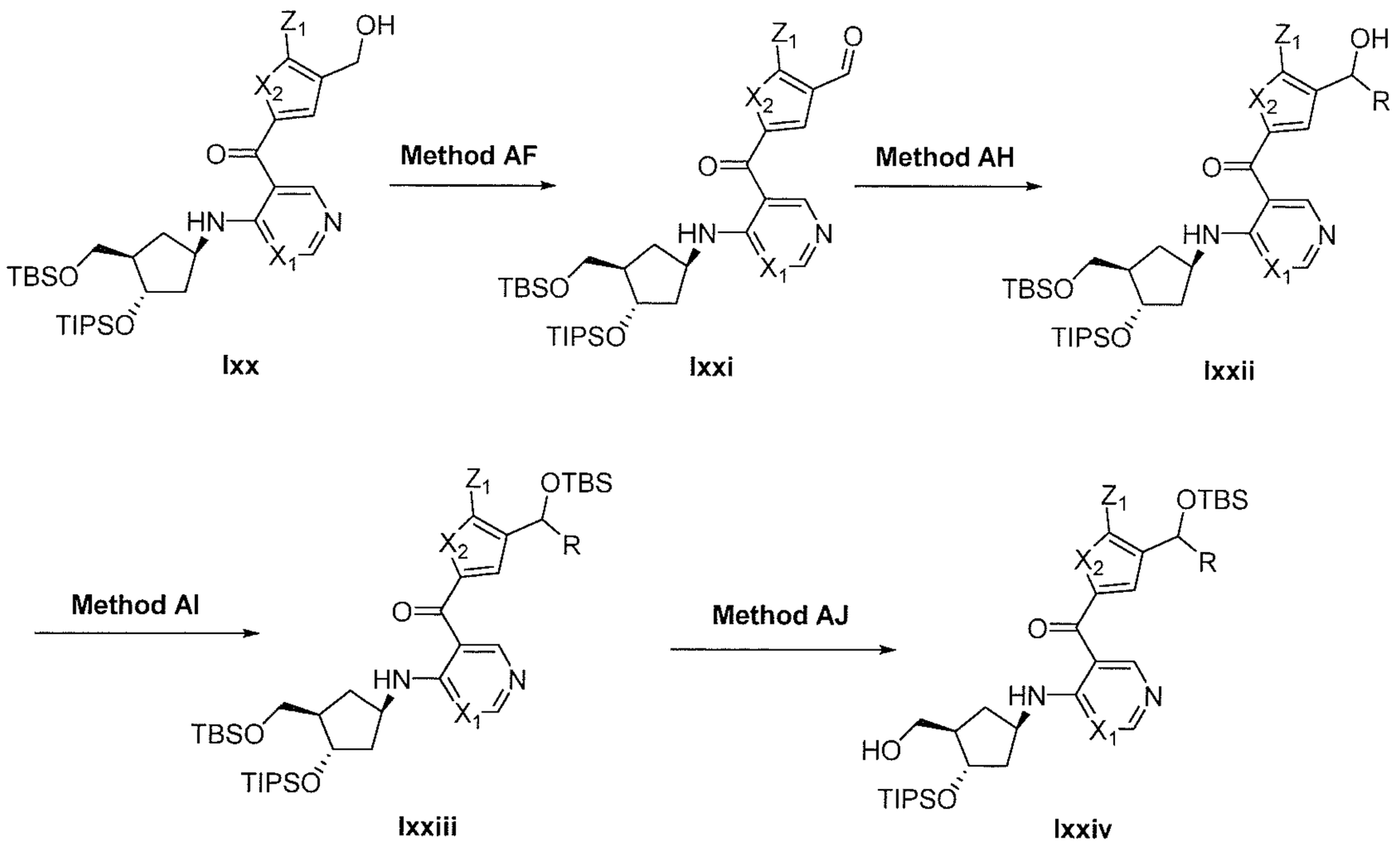
[00284] Scheme 15 shows a synthetic route for the preparation of compounds of formula **lxi** and **lxii**. Diaryl ketones **lvii** can be treated with an appropriate amines, such as (1R,2S,3R,4R)-1-amino-2,3-(isopropylidenyl)dihydroxy-4-hydroxymethyl cyclopentane **lix** (prepared according to Claiborne, C.F. et al; PCT Application Publication WO 2008/019124) or **lx** in the presence of a suitable base, such as K_2CO_3, DIEA or TEA in a polar solvent, such as iPrOH, PrOH, nBuOH or DMF (Method AG).

[00285] Alternative amines can be used in this reaction (Method AG, scheme 15) such as those shown by the general formula **lxiii** and represented by **lxiv** through **lxix** in Diagram A below. Salts of the amine, such as the hydrochloride, can usually be used in this reaction with the appropriate equivalents of base. For amine **lxiv** see: Ober, M. et al. *J. Am. Chem. Soc.* **2005**, *127*, 18143-18149; for **lxv** see: Armitage, I. et al. US Patent Application Publication 2009/0036678; for **lxvi**, **lxvii**, **lxix** see: Biggadike, K. at al. *J. Chem. Soc. Perkin Trans.* **1988**, *3*, 549-554; Borthwick, A.D. et al. *J. Med. Chem.* **1990**, *33*, 179-186.

Diagram A



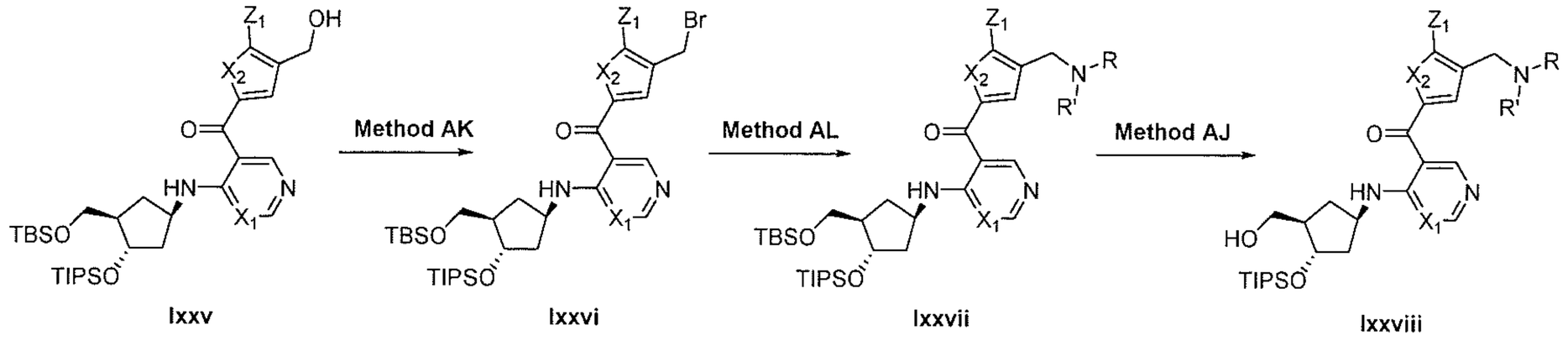
Scheme 16: General method for the preparation of ketoaryl intermediates lxxiv



[00286] Scheme 16 depicts the synthesis of di-aryl ketone intermediates **lxxiv**. The alcohol intermediates **lxx** can be oxidized to the aldehydes **lxxi** (Method AF). The aldehydes **lxxi** can be reacted with appropriate Grignard reagents or organolithium reagents to give compounds of formula **lxxii** (Method AH). A suitable protection, such as TBS or TIPS group under general conditions

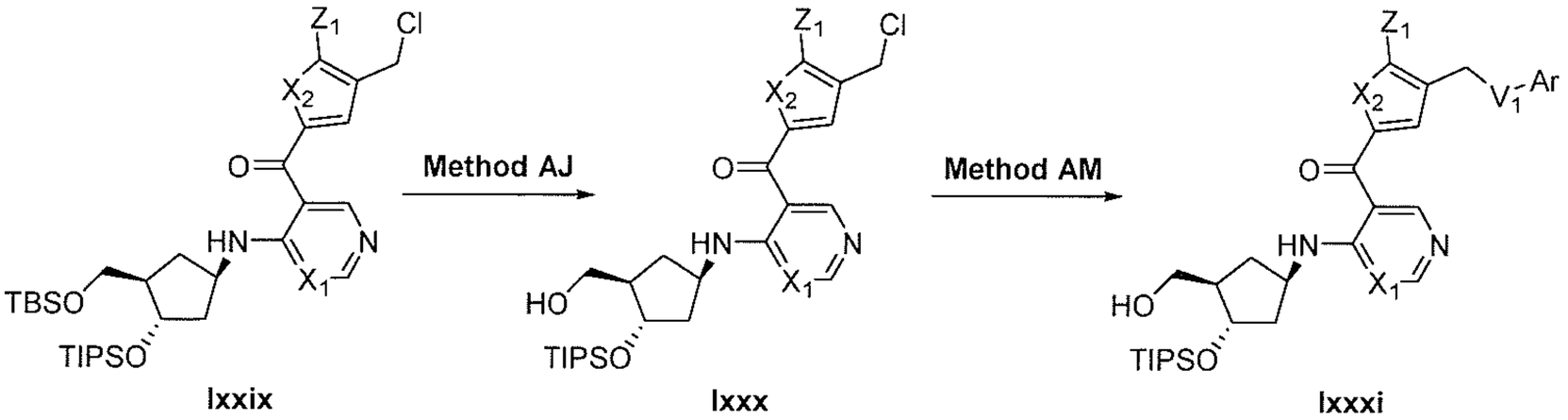
(Method AI) and deprotection of the primary TBS ether under mild acidic conditions, such as 1% aq.HCl in ethanol, at cold temperature gives compounds of formula **lxxiv** (Method AJ).

Scheme 17: General method for the preparation of ketoaryl intermediates lxxviii



[00287] Scheme 17 depicts the synthesis of keto aryl intermediates **lxxviii**. The alcohol intermediates **lxxv** are activated, for example by conversion to the bromide or chloride under standard conditions, such as PPh_3 with CBr_4 or CCl_4 in suitable solvent, such as DCM, to give intermediate alkyl halides **lxxvi** (Method AK) and reacted with an appropriate amines in the presence of base, such as DIEA or Et_3N to give amine derivatives **lxxvii** (Method AL). Additional nucleophiles may also be employed. For example, the bromide may be reacted with an alcohol or alkoxide to give ethers. The nitrogen nucleophile may be part of an aromatic ring, for example a pyrrole, imidazole, or indole. A suitable protection/deprotection strategy such as that shown at method AJ in scheme 16 gives the intermediates **lxxviii**.

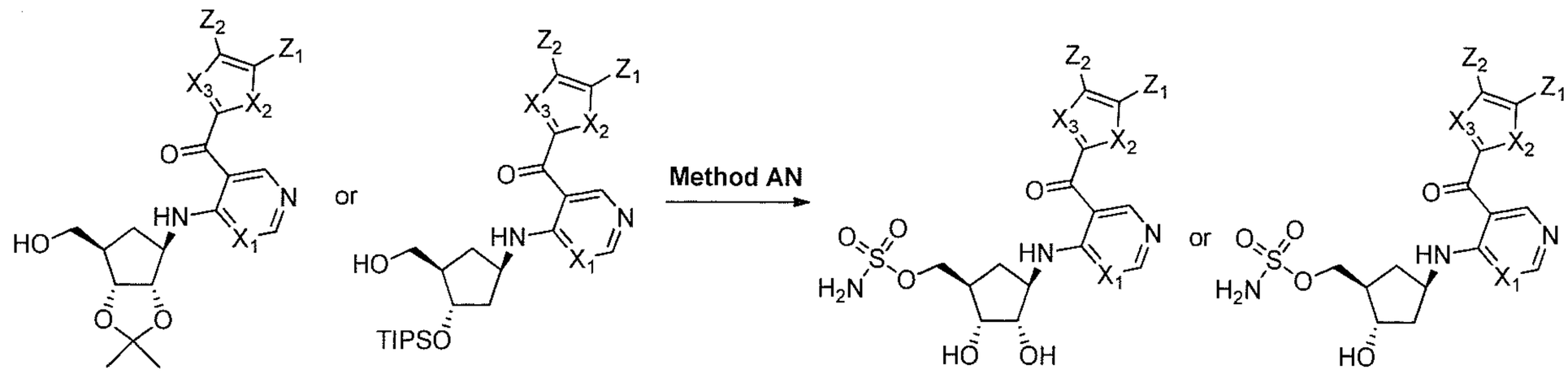
Scheme 18: General method for the preparation of ketoaryl intermediates lxxxi



[00288] Scheme 18 depicts the synthesis of keto aryl intermediates **lxxxi** where V_1 is S or O. The alcohol is activated, for example by conversion to the bromide or chloride, and reacted with appropriate alcohol or thiol derivatives, such as optionally substituted phenols or benzenethiols, to give ether or thio ether intermediates **lxxxi**.

[00289]

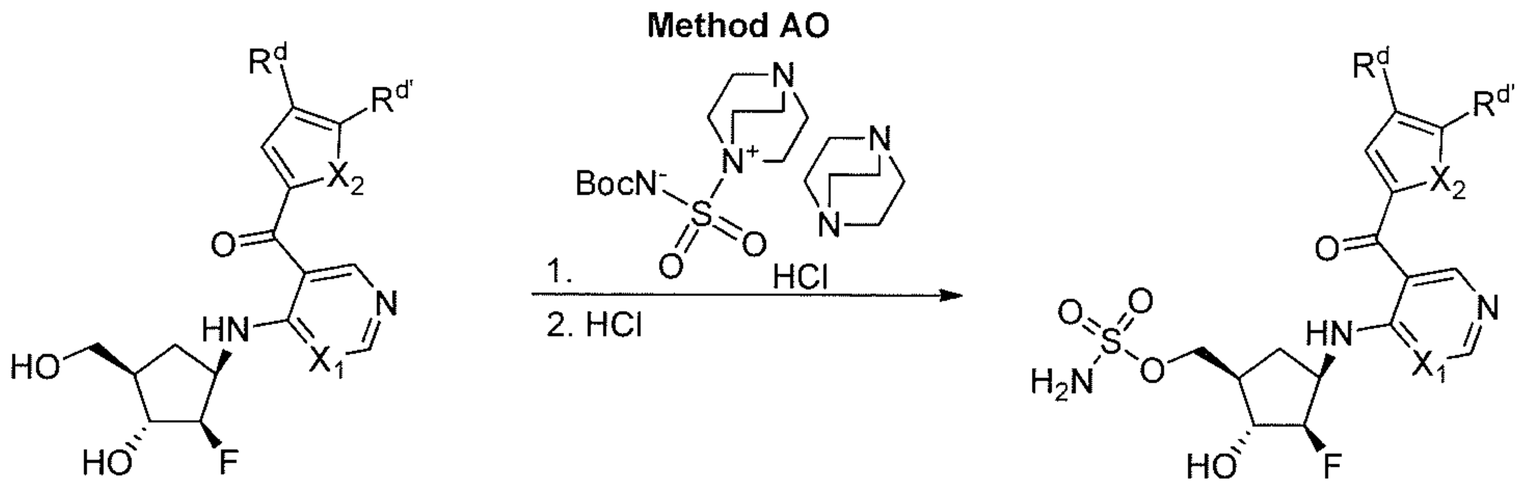
Scheme 19: General method for the preparation of sulfamate derivatives of the keto arylamines



lxxxii lxxxiii lxxxiv lxxxv

Scheme 19 illustrates the syntheses of compounds with general structure **lxxxiv** and **lxxxv**. A two-step sequence consisting of sulfamation and deprotection completes the synthesis of ketopyrimidines (ketopyridines) **lxxxiv** and **lxxxv**. The acetonide can be removed under acidic conditions, such as aq. HCl/THF or TFA/water, and the silyl group can be removed under acidic conditions, such as aq. HCl/THF H_3PO_4/acetonitrile or TFA/water, or by using an appropriate fluoride source, such as TBAF or TASF. If using a bis protected diol such as **lxix** the silyl group (TBS) can be selectively removed from the primary alcohol (e.g. mild acidic conditions at reduced temperature, such as 1% HCl in EtOH at 4 °C) prior to sulfamation. When using amines with unprotected alcohols, such as **lxiv** through **lxviii**, a suitable protecting group strategy can be employed to give the desired sulfamate. For example, protection of the free alcohols can be accomplished by prolonged treatment with TBSCl in DMF, which is then subjected to selective deprotection of the primary silyl group with mild acid at reduced temperature. Subsequent sulfamation and deprotection provides the desired sulfamate.

Scheme 20: Procedure for selective sulfamation



lxxxvi lxxxvii

[00290] A selective sulfamation procedure can also be employed such as shown in scheme 11. The procedure employs a modified Burgess reagent (Armitage, I. et al. *Org. Lett.* **2012**, *14*, 2626-2629) followed by treatment with acid to deprotect the sulfamate (Method AO).

Preparation of Exemplary Chemical Entities

[00291] Definitions

AA	LCMS method using ammonium acetate
ACN	acetonitrile

aq	aqueous
Boc	*tert*-butoxycarbonyl
BPR	back pressure regulator
C	Celsius
CBS	Corey-Bakshi-Shibata
DCM	methylene chloride
DEA	diethylamine
DIAD	diisopropyl azodicarboxylate
DIBAl-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	N,N-dimethyl-4-aminopyridine
DME	dimethyl ether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
FA	LCMS method using formic acid
FR	flow rate
h	hour(s)
HPLC	high performance liquid chromatography
IC_{50}	inhibitory concentration 50%
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminium hydride
LCMS	liquid chromatography mass spectrometry
LC	liquid chromatography
m/z	mass to charge
min	minute(s)
NBS	N-bromosuccinimide

NCS	N-chlorosuccinimide
NMM	N-methylmorpholine
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
PPh_3	Triphenylphosphine
PPTS	pyridinium *p*-toluenesulfonate
psi	pounds per square inch
PTSA	*p*-toluenesulfonic acid
Rf	retention factor
rt	room temperature
SFC	supercritical fluid chromatography
STAB	sodium triacetoxyborohydride
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

[00292] Analytical Methods

[00293] NMR conditions: ^{1}H NMR spectra are run on a 400 MHz Bruker unless otherwise stated.

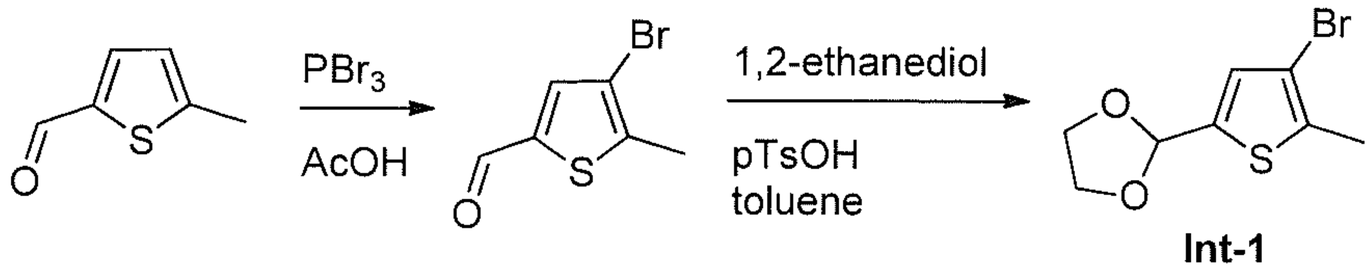
LCMS conditions:

[00294] LCMS spectra are recorded on a Hewlett-Packard HP1100 or Agilent 1100 Series LC system connected to a Micromass mass spectromteter using reverse phase C18 columns. Various gradients and run times are selected in order to best characterize the compounds. Mobile phases are based on ACN/water gradients and contain either 0.1% formic acid (methods indicated FA) or

10 mM ammonium acetate (methods indicated AA). One example of a solvent gradient that is used is 100% mobile phase A (mobile phase A = 99% water + 1% ACN + 0.1% formic acid) to 100% mobile phase B (mobile phase B = 95% ACN + 5% water + 0.1% formic acid) at a flow rate of 1 mL/min for a 16.5 min e.

[00295] One of ordinary skill in the art will recognize that modifications of the gradient, column length, and flow rate are possible and that some conditions may be more suitable for compound characterization than others, depending on the chemical species being analyzed.

Example 1: 2-(4-Bromo-5-methyl-2-thienyl)-1,3-dioxolane Int-1



Int-1

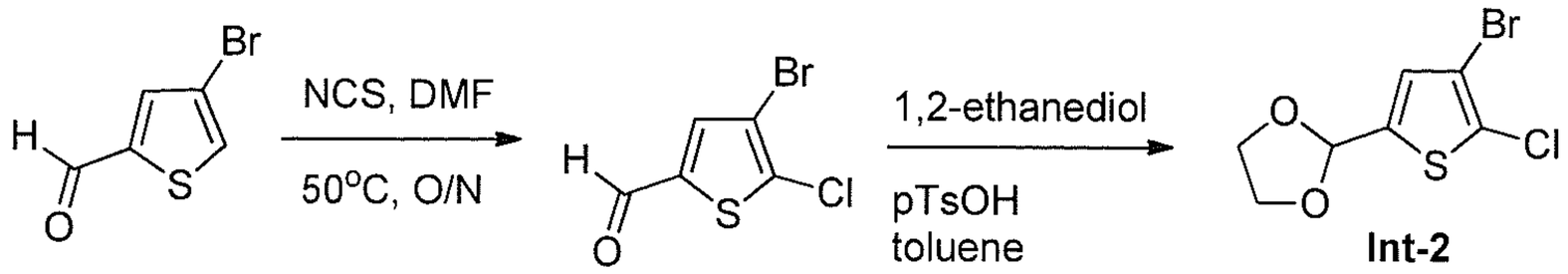
Step 1: 4-Bromo-5-methyl-2-thiophenecarbaldehyde

[00296] A 1000mL round bottom flask was charged with 5-methyl-2-thiophenecarboxaldehyde (15 g, 120 mmol) and acetic acid (200 mL, 4000 mmol). Added pyridinium tribromide (48.5 g, 137 mmol). Heated in a 40 °C oil bath for 24 h. Reaction mixture was cooled to rt and poured into water (1L). Layers were separated, and the aqueous layer was extracted three times with EtOAc. Combined organics were washed with saturated $NaHCO_3$ and then brine. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. Subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound as a white solid (yield = 11.44g). ^{1}H NMR (400 MHz, Acetone-d6) δ 9.87 (s, 1H), 7.88 (s, 1H), 2.52 (s, 3H).

Step 2: 2-(4-Bromo-5-methyl-2-thienyl)-1,3-dioxolane

[00297] To a round bottom flask was added 4-bromo-5-methyl-2-thiophenecarbaldehyde (4.23 g, 20.6 mmol), 1,2-ethanediol (7.80 mL, 1.40E2 mmol), p-toluenesulfonic acid monohydrate (0.39 g, 2.1 mmol), and 100 ml toluene . The resulting reaction mixture was heated at reflux with a Dean-Stark trap overnight. The mixture was cooled to rt. EtOAc was added and the mixture was washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (hexanes/EtOAc=9/1 as eluent) to give 4.2g of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.99 (s, 1H), 6.02 (s, 1H), 4.15 – 4.09 (m, 2H), 4.06 – 3.99 (m, 2H), 2.40 (s, 3H).

Example 2: 2-(4-Bromo-5-chloro-2-thienyl)-1,3-dioxolane Int-2



Int-2

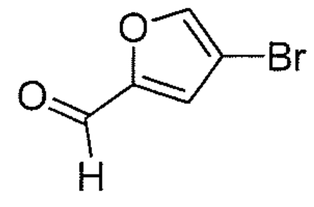
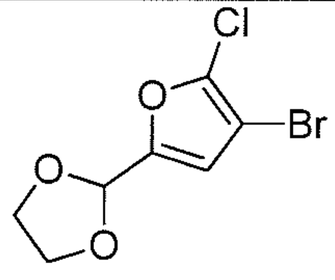
Step 1: 4-bromo-5-chlorothiophene-2-carbaldehyde

[00298] To a solution of 4-bromothiophene-2-carbaldehyde (20 g, 100 mmol) in DMF (49 mL, 630 mmol) was added N-chlorosuccinimide (21 g, 160 mmol), in portions. The reaction mixture was stirred at 50 °C overnight. The resulting solution was cooled to rt and then poured onto 500mL of ice water (a light pink precipitate formed). The precipitate was collected via vacuum filtration and then dried in a vacuum oven to give 19.35 g of the title compound as a light tan solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.79 (s, 1H), 7.62 (s, 1H).

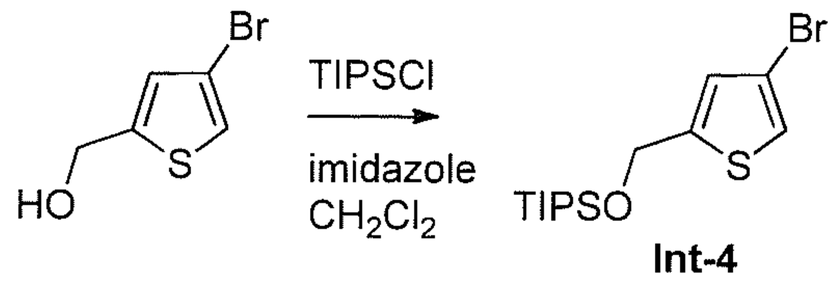
Step 2: 2-(4-Bromo-5-chloro-2-thienyl)-1,3-dioxolane

[00299] To a solution of 4-bromo-5-chlorothiophene-2-carbaldehyde (19.35 g, 85.81 mmol) in toluene (300 mL, 2000 mmol) was added 1,2-ethanediol (23.9 mL, 429 mmol) and p-toluenesulfonic acid monohydrate (0.816 g, 4.29 mmol). The reaction mixture was fitted with a Dean-Stark trap, stirred at reflux overnight under argon gas. The reaction was quenched with water (300mL), extracted with EtOAc (3x150mL), washed with brine, dried over magnesium sulfate, filtered and concentrated to give ~28 g of crude product as a brown oil. The product was purified by flash chromatography (330g column, DCM loaded) with 0-10% EtOAc in hexanes over 20 min to give 21.25 g of the title compound as an amber oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.99 (d, J = 0.5 Hz, 1H), 6.02 (s, 1H), 4.15 – 4.07 (m, 2H), 4.07 – 3.99 (m, 2H).

[00300] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Starting material	Product (Int #)	NMR Data
	 **Int-3**	^{1}H NMR (400 MHz, Chloroform-d) δ 6.53 (s, 1H), 5.87 (s, 1H), 4.17 – 4.07 (m, 2H), 4.07 – 3.97 (m, 2H).

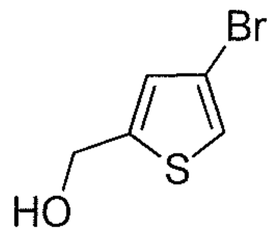
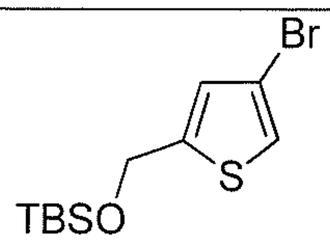
Example 3: [(4-Bromo-2-thienyl)methoxy](triisopropyl)silane Int-4



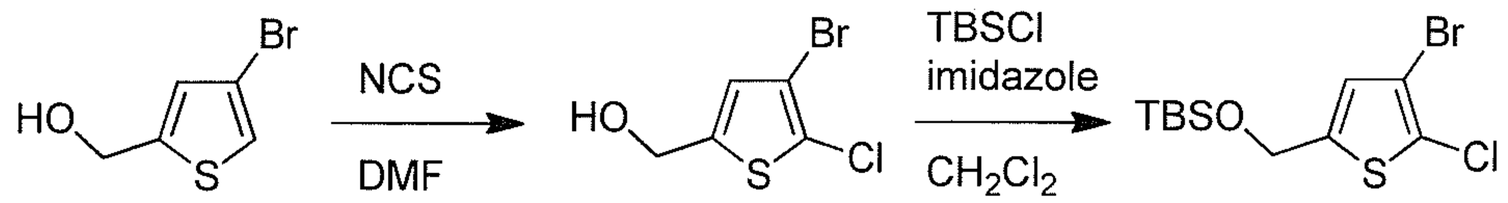
Int-4

[00301] To a solution of (4-bromo-2-thienyl)methanol (9.11 g, 47.2 mmol) in DCM (200 mL, 4000 mmol) was added 1H-imidazole (4.82 g, 70.8 mmol) followed by triisopropylsilyl chloride (12.5 mL, 59.0 mmol) at rt, and the reaction was stirred overnight. The reaction was quenched by addition of water (150 mL) and extracted with DCM (50 mLx2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was loaded onto the column as a solution in hexanes. Chromatography was performed (330 g column, 0-5% EtOAc:hexanes over 40 min) to afford the title compound. yield = 15.6 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.14 (s, 1H), 6.84 (s, 1H), 4.95 (s, 2H), 1.26 – 1.04 (m, 21H).

[00302] The compound listed in the table below was prepared in an analogous fashion to that described above, using TBSCl instead of TIPSCl:

Starting material	Product (Int #)	NMR Data
	 **Int-5**	^{1}H NMR (400 MHz, Chloroform-d) δ 7.02 (d, J = 1.4 Hz, 1H), 6.73 – 6.70 (m, 1H), 4.72 (d, J = 0.9 Hz, 2H), 0.82 (s, 9H), -0.00 (s, 6H)..

Example 4: [(4-Bromo-5-chloro-2-thienyl)methoxy](tert-butyl)dimethylsilane Int-6



Int-6

Step 1: (4-Bromo-5-chloro-2-thienyl)methanol

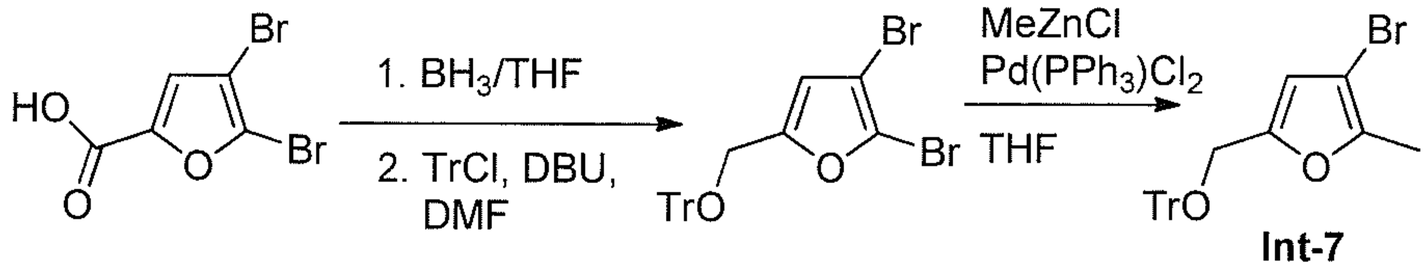
[00303] To a solution of (4-bromo-2-thienyl)methanol (5.00 g, 25.9 mmol) in DMF (10.0 mL) was added N-chlorosuccinimide (4.15 g, 31.1 mmol), and the reaction was heated at 60 °C for 3h. Reaction was allowed to cool to rt and stirred for14h. The reaction was concentrated in vacuo. To the residue was added Et_2O and the suspension was filtered. The filtrate was concentrated and then purified by ISCO silica gel column chromatography (120 g, eluting with 15% EtOAc in

hexanes, 70mL/min flow) to give 4.08g of the title compound as a colorless solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.84 (s, 1H), 4.76 (d, J = 6.0 Hz, 2H), 1.86 (t, J = 6.1 Hz, 1H).

Step 2: [(4-Bromo-5-chloro-2-thienyl)methoxy](tert-butyl)dimethylsilane

[00304] To a solution of (4-bromo-5-chloro-2-thienyl)methanol (3.50 g, 15.4 mmol) in DCM (48.3 mL) was added 1H-imidazole (1.57 g, 23.1 mmol) followed by TBSCl (2.55 g, 16.9 mmol) at rt, and the mixture was stirred for 2h. The reaction was quenched by addition of water (100mL) and extracted with hexane (100 mLx2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue as purified by ISCO silica gel column chromatography (120 g, eluting with 0% EtOAc in hexane for 3min then gradient to 5% EtOAc in hexane over 10min, 50mL/min flow) to give 5.01g of the title compound as colorless solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.60 (t, J = 1.0 Hz, 1H), 4.65 (d, J = 1.1 Hz, 2H), 0.82 (s, 9H), -0.00 (s, 6H).

Example 5: 3-Bromo-2-methyl-5-[(trityloxy)methyl]furan Int-7



Int-7

Step 1: (4,5-Dibromo-2-furyl)methanol

[00305] To a solution of 4,5-dibromo-2-furoic acid (10.0 g, 37.0 mmol) in THF (174.8 mL, 2154 mmol) was slowly added 1.0 M of borane in THF (52.4 mL, 52.4 mmol) as gas evolved. Toward the end of the addition of borane the reaction mixture progressed from a clear solution to a white cloudy mixture. When bubbling ceased a reflux condenser was attached and the resulting reaction mixture was heated at 80 °C overnight. Over the first hour of heating, cloudy mixture progressed to a clear, pink solution. Reaction was cooled to rt and quenched via addition of saturated aqueous $NaHCO_3$ (care, gas evolution) . Reaction mixture was transferred to a separatory funnel and diluted with Et_2O (200 mL). Layers were separated, and the aqueous layer was extracted 1 x Et_2O (40 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography was performed (220 g column, 0-30% EtOAc:hexanes as eluent) to afford the title compound. Yield = 7.25 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.41 (s, 1H), 4.59 (s, 2H).

Step 2: 2,3-Dibromo-5-[(trityloxy)methyl]furan

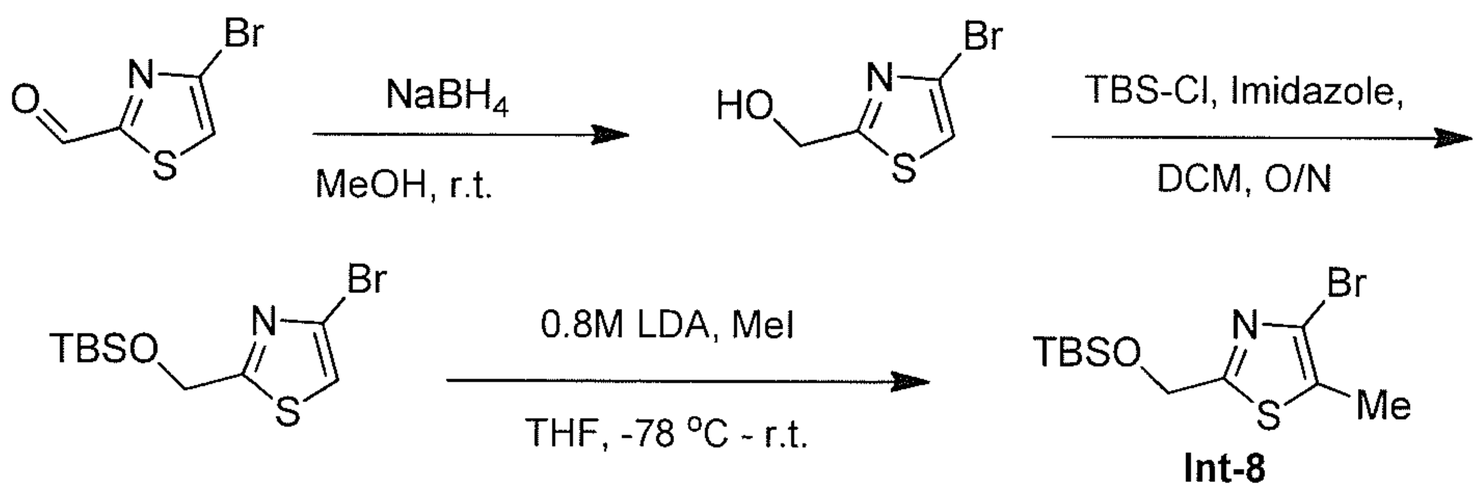
[00306] To a solution of (4,5-dibromo-2-furyl)methanol (10.5 g, 41.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (18.4 mL, 123 mmol) in DMF (41.0 mL, 5.30E2 mmol) was added triphenylmethyl chloride (28.6 g, 102 mmol). The resulting mixture was stirred at rt overnight. Reaction mixture was partitioned between water (200 mL) and EtOAc (500 mL). Layers were separated, and the aqueous layer was extracted 2 x EtOAc (100 mL each). Combined

organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was adsorbed to Celite (75 mL) for dry-loading onto the column. Chromatography was performed (330 g column, 0-8% EtOAc:hexanes as eluent) to afford the title compound. yield = 19.5 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 – 7.45 (m, 6H), 7.39 – 7.24 (m, 9H), 6.32 (s, 1H), 4.07 (d, J = 0.6 Hz, 2H).

Step 3: 3-Bromo-2-methyl-5-[(trityloxy)methyl]furan

[00307] To a solution of 2,3-dibromo-5-[(trityloxy)methyl]furan (9.5 g, 19 mmol) in THF (110 mL, 1400 mmol) was added 2.00 M of methylzinc chloride in THF (38.14 mL, 76.27 mmol) and the mixture was purged with vacuum/argonargon. Bis(triphenylphosphine)palladium(II) chloride (1.338 g, 1.907 mmol) was then added and the resulting mixture was stirred overnight at rt. Reaction mixture was filtered through Celite, and the filtrate was then concentrated in vacuo. The crude residue was adsorbed to Celite (100 mL) for dry-loading onto the column. Chromatography was performed (0-5% EtOAc:hexanes as eluent, 220 g column) afforded the title compound. Yield = 5.06 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 – 7.45 (m, 6H), 7.37 – 7.30 (m, 6H), 7.28 – 7.23 (m, 3H), 6.23 (s, 1H), 4.02 (s, 2H), 2.31 (s, 3H).

Example 6: 4-Bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-5-methyl-1,3-thiazole Int-8



Int-8

Step 1: (4-Bromo-thiazol-2-yl)-methanol

[00308] To a solution of 4-bromo-2-formylthiazole (4.00 g, 20.8 mmol) in methanol (60.0 mL, 1480 mmol) was slowly added sodium tetrahydroborate (0.946 g, 25.0 mmol), and the reaction was stirred at rt for 20 min. The reaction was concentrated in vacuo, diluted with EtOAc, and washed with water 2x and then brine 1x. Organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatograpy (40g column, 20% - 50% EtOAc in hexanes over 30min) to give a light yellow oil. Yield = 3.28 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 (s, 1H), 4.95 (d, J = 6.2 Hz, 2H), 2.76 (t, J = 6.2 Hz, 1H). LCMS (FA): 196.0 m/z (M + 1).

Step 2: 4-Bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole

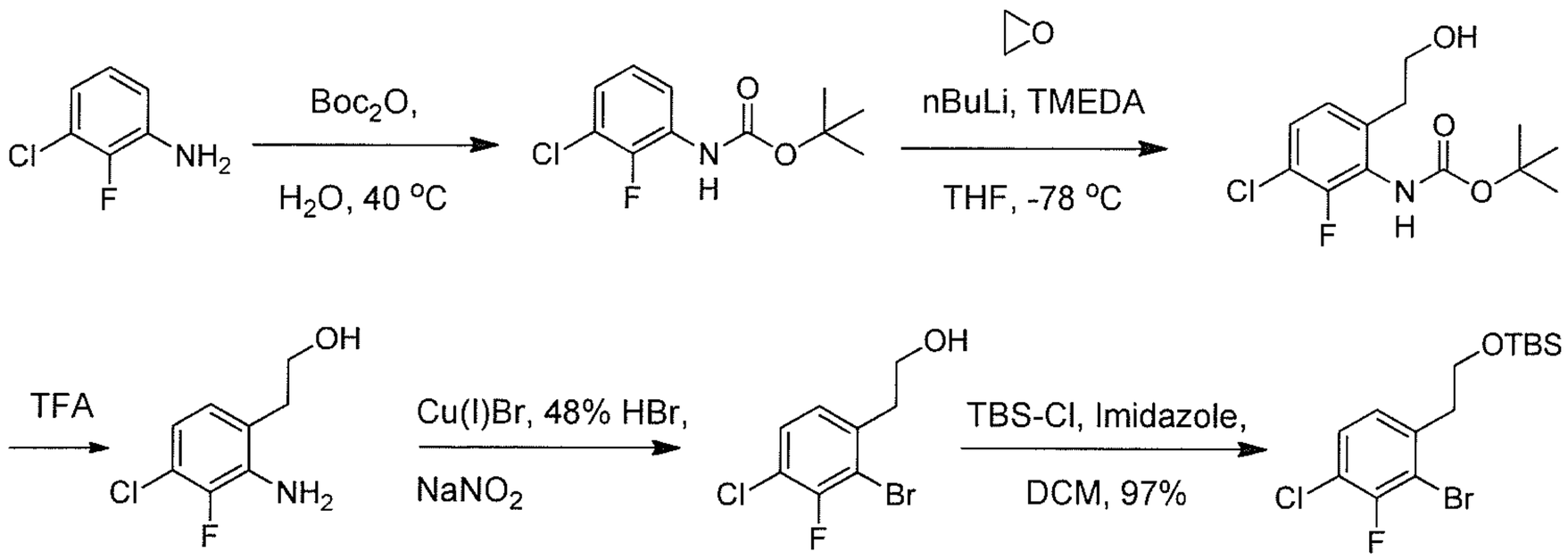
[00309] (4-Bromo-thiazol-2-yl)-methanol (3.28 g, 16.9 mmol), DCM (32.8 mL, 512 mmol), tert-butyldimethylsilyl chloride (3.18 g, 21.1 mmol), 1H-imidazole (2.88 g, 42.2 mmol) and N,N-

dimethylaminopyridine (103 mg, 0.845 mmol) were combined in a 250 mL round-bottom flask at rt and stirred overnight. The reaction was diluted with EtOAc and water, and the organic layer was washed 1x water, 2x saturated NH_4Cl and 1x brine. The organic layer was then dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (40g ISCO, 4% EtOAc in hexanes isocratic) to give the title compound as a clear colorless oil. Yield = 5.09 g. ^1H NMR (400 MHz, Chloroform-d) δ 7.17 (s, 1H), 4.94 (s, 2H), 0.95 (s, 9H), 0.13 (s, 6H).

Step 3: 4-Bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-5-methyl-1,3-thiazole

[00310] A solution of 4-bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole (0.500 g, 1.62 mmol) in THF (1.50 mL, 18.5 mmol) was cooled to -78 °C. 0.8 M of lithium diisopropylamide in THF (2.25 mL, 1.80 mmol) was added dropwise at -78 °C. The reaction became a yellow color upon addition. The reaction was allowed to stir for 30min under an atmosphere of argon at -78 °C. Methyl iodide (0.500 mL, 8.03 mmol) was added, and the reaction was stirred at -78 °C for 30min then allowed to warm to rt. The reaction was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was washed 2x with saturated NH_4Cl and 1x brine and then dried over Na_2SO_4, filtered and concentrated in vacuo. The material was purified via column chromatography (24g ISCO 1% EtOAc in hexanes isocratic) to give a clear colorless oil. Yield = 452 mg. ^1H NMR (400 MHz, Methanol-d4) δ 4.85 (s, 2H), 2.38 (s, 3H), 0.96 (s, 9H), 0.15 (s, 6H). LCMS (FA): 324.4 m/z (M + 1).

Example 7: [2-(2-Bromo-4-chloro-3-fluorophenyl)ethoxy](tert-butyl)dimethylsilane Int-9



Int-9

Step 1: tert-Butyl (3-chloro-2-fluorophenyl)carbamate

[00311] 2-Fluoro-3-chloroaniline (3.00 g, 0.0206 mol), di-tert-butyldicarbonate (9.44 g, 0.0433 mol), THF (46.3 mL, 0.571 mol), N,N-dimethylaminopyridine (252 mg, 0.00206 mol) were combined in a 250mL round-bottom flask with vigorous stirring and heated at rt overnight. The reaction was diluted with EtOAc, and then washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (0.5% EtOAC in hexanes isocratic

eluent, 80g ISCO column, 50 mL/min) to give 3.40g (67%) of the product as a clear colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.06 – 7.97 (m, 1H), 7.07 – 6.98 (m, 2H), 6.70 (s, 1H), 1.53 (s, 9H)

Step 2: tert-Butyl [3-chloro-2-fluoro-6-(2-hydroxyethyl)phenyl]carbamate

[00312] A solution of tert-butyl (3-chloro-2-fluorophenyl)carbamate (1.58 g, 6.43 mmol) was dissolved in THF (20.0 mL, 246 mmol) was cooled to -78 °C under an atmosphere of argon . N,N,N',N'-tetramethylethylenediamine (2.27 mL, 15.0 mmol) was added followed by 1.40 M of sec-butyllithium in cyclohexane(10.4 mL, 14.5 mmol) and the solution turned a light yellow color. The reaction was warmed to 0 °C and then immediately cooled back to -78 °C. Separately, ethylene oxide (1.61 mL, 32.2 mmol) was condensed at 0 °C and transferred via cannula to the reaction. The reaction was stirred at -78 °C for 30min then warmed to rt. The reaction was quenched with saturated NH_4Cl, extracted 2x with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (80g ISCO, 10% - 50% EtOAc in hexanes) to give 0.852g (45%) of the product as an off-white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.19 (m, 1H), 6.96 (dd, J = 8.4, 1.4 Hz, 1H), 6.81 (s, 1H), 3.90 (q, J = 5.7 Hz, 2H), 2.87 (t, J = 5.8 Hz, 2H), 1.96 (t, J = 4.4 Hz, 1H), 1.50 (s, 9H).

Step 3: 2-(2-Amino-4-chloro-3-fluorophenyl)ethanol

[00313] Tert-butyl [3-chloro-2-fluoro-6-(2-hydroxyethyl)phenyl]carbamate (0.752 g, 2.60 mmol) was weighed into a 50mL round-bottom flask. To the flask was added TFA (4.00 mL, 51.9 mmol), at which point gas evolved. Once gas evolution ceased, the reaction was quenched with saturated $NaHCO_3$ and extracted 2x with DCM. The combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was loaded onto a 40g Gold ISCO column eluting with 50% EtOAc in hexanes isocratic to give 0.421g (86%) of the product as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.80 – 6.72 (m, 2H), 3.92 (t, J = 5.9 Hz, 2H), 2.81 (t, J = 5.9 Hz, 2H).

Step 4: 2-(2-Bromo-4-chloro-3-fluorophenyl)ethanol

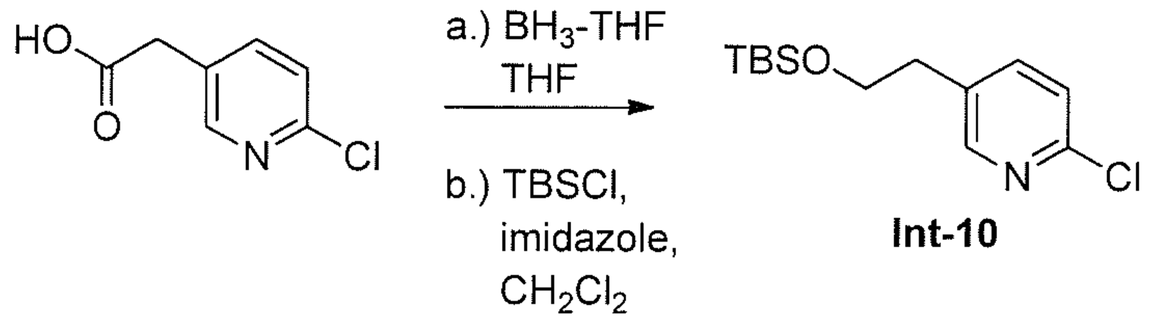
[00314] A 100 mL round bottom flask was charged with [2-(2-amino-4-chloro-3-fluorophenyl)ethanol (0.420 g, 2.22 mmol) and 8.90 M of hydrobromic acid in water (3.61 mL, 32.2 mmol), and the mixture was cooled in an ice bath. To this was added an ice-cooled solution of sodium nitrite (0.153 g, 2.22 mmol) in ~1mL water dropwise. A brown solution resulted. In a separate flask, copper(I) bromide (0.318 g, 2.22 mmol) and 8.90 M of hydrobromic acid in water(0.723 mL, 6.43 mmol) were combined and cooled in an ice bath. The second solution was added to the first via rapid, dropwise addition and the mixture was warmed to rt. Reaction was quenched with water, and the aqueous mixture was extracted 3x with DCM. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (24g Gold ISCO, 30% EtOAc in hexanes isocratic 25mL/min) to give 0.442g

(79%) of the product as yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.58 – 7.51 (m, 1H), 7.24 (dd, J = 8.4, 1.5 Hz, 1H), 4.77 (t, J = 5.3 Hz, 1H), 3.65 – 3.55 (m, 2H), 2.89 (t, J = 6.8 Hz, 2H).

Step 5: [2-(2-Bromo-4-chloro-3-fluorophenyl)ethoxy](tert-butyl)dimethylsilane

[00315] To a solution of 2-(2-bromo-4-chloro-3-fluorophenyl)ethanol (0.442 g, 1.74 mmol) in DCM (4.78 mL, 74.6 mmol) was added 1H-imidazole (0.308 g, 4.52 mmol) followed by tert-butyldimethylsilyl chloride (0.309 g, 2.05 mmol). The reaction was stirred for 30 min at rt. The reaction was quenched with water, the layers were separated, and the aqueous layer was extracted 2x with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (40g ISCO, 0-10% EtOAc in hexanes over 20min) to give 0.620g (97%) of a clear colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.29 – 7.23 (m, 1H), 7.02 (dd, J = 8.3, 1.4 Hz, 1H), 3.81 (t, J = 6.7 Hz, 2H), 2.98 (t, J = 6.6 Hz, 2H), 0.86 (s, 9H), -0.02 (s, 6H).

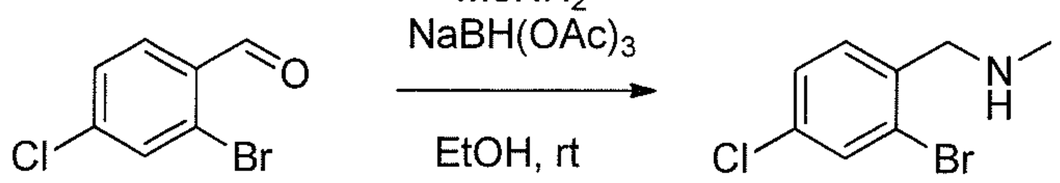
Example 8: 5-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-2-chloropyridine Int-10



Int-10

[00316] This compound was prepared in an analogous fashion to that described in **Example 11**, Step 1, beginning with (2-chloropyridyl)-5-acetic acid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.33 (d, J = 2.2 Hz, 1H), 7.80 (dd, J = 8.2, 2.5 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 3.85 (t, J = 6.2 Hz, 2H), 2.83 (t, J = 6.2 Hz, 2H), 0.87 (s, 9H), -0.00 (s, 6H).

Example 9: 1-(2-Bromo-4-chlorophenyl)-N-methylmethanamine Int-11

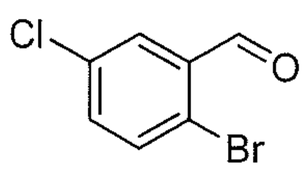
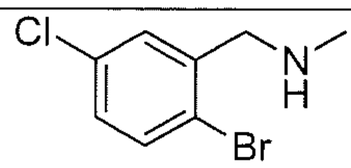
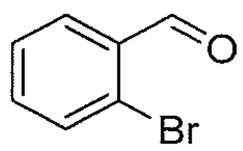
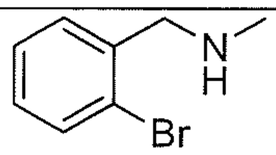


Int-11

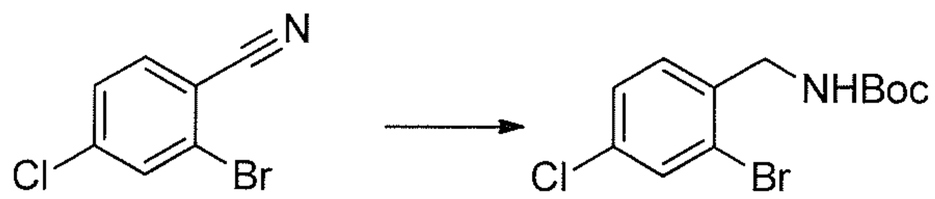
[00317] To a solution of 2-bromo-4-chlorobenzaldehyde (3.00 g, 13.7 mmol) in ethanol (10.0 mL, 171 mmol) was added 8.4 M of methylamine in ethanol (3.27 mL, 27.3 mmol) and the mixture was stirred for 4h at rt. The mixture was cooled at 0 °C and sodium triacetoxyborohydride (3.04 g, 14.4 mmol) was added portion wise. The reaction was stirred for 1h. The reaction was concentrated in vacuo, and then 1N NaOH (200mL) was added to the residue and the mixture was extracted with DCM (200mLx3). The combined organic layers were dried over Na_2SO_4, filtered,

and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (40g, eluting with 5% MeOH in DCM for 5min then gradient to 10% MeOH in DCM over 15min, 40mL/min flow) to give 2.5 g of the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.71 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.3, 2.1 Hz, 1H), 2.29 (s, 3H), 2.22 (s, 1H).

[00318] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Starting material	**Product (Int #)**
	 **Int-12**
	 **Int-13**

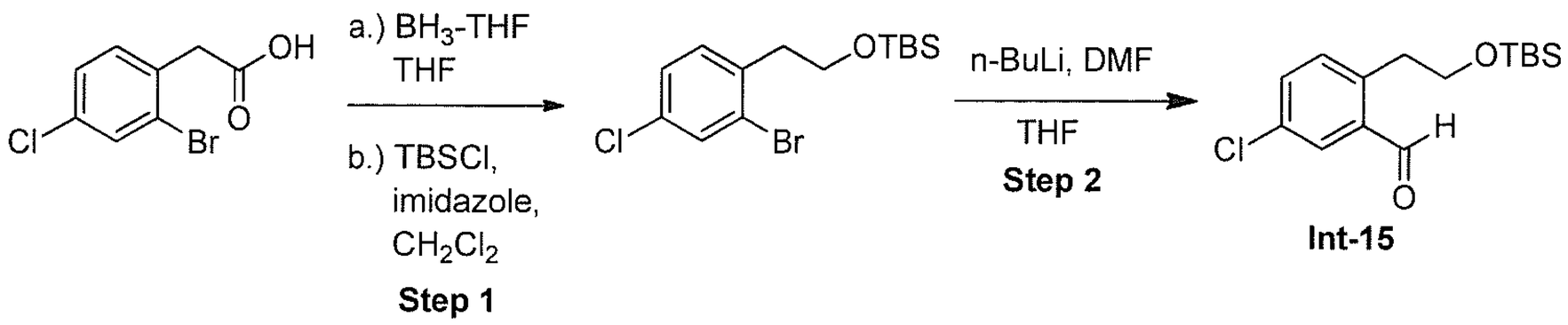
Example 10: tert-Butyl (2-bromo-4-chlorobenzyl)carbamate Int-14



Int-14

[00319] In a microwave vial, a solution of 2-bromo-4-chlorobenzonitrile (1.0 g, 4.6 mmol) in toluene (6.00 mL, 56.3 mmol) was purged with argon and sealed with a septum. To the solution was added 1,1,3,3-tetramethyldisiloxane (0.816 mL, 4.62 mmol) followed by titanium tetraisopropoxide (1.36 mL, 4.62 mmol) at rt, and the mixture was stirred at 60 °C for 24 h. The reaction was cooled to rt and quenched by addition of 1N HCl. The mixture was washed with EtOAc (x2). The water layer was basified by addition of 3N NaOH until pH ~10 and extracted with DCM (x3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in CH_3CN (3.00 mL, 57.4 mmol) and di-tert-butyldicarbonate (1.01 g, 4.62 mmol) was added. Some colorless precipitates were observed. To the mixture was added triethylamine (0.9658 mL, 6.930 mmol) and the suspension turned to a clear solution. After 30min, the mixture was concentrated in vacuo and the residue was purified by ISCO silica gel column chromatography (24g, eluting with 5% EtOAc in Hexane, 40mL/min flow) to give the title compound as colorless solid. Yield 404mg (27%).

Example 11: 2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-5-chlorobenzaldehyde Int-15



Step 1: [2-(2-Bromo-4-chlorophenyl)ethoxy](tert-butyl)dimethylsilane

[00320] To a solution of (2-bromo-4-chlorophenyl)acetic acid (25.0 g, 100 mmol in THF (400 mL, 5000 mmol) was added slowly 1.0 M of borane in THF (120.2 mL, 120.2 mmol) at rt. When bubbling ceased the resulting reaction mixture was heated at 60 °C overnight. Reaction was quenched via slow careful addition of 1.0 M of HCl in water (300 mL, 300 mmol). THF was removed in vacuo and the resulting residue was partitioned between Et_2O and water. Layers were separated, and the aqueous layer was extracted 2 x Et_2O. The combined organic solvents were dried, filtered and concentrated in vacuo. Crude yield: 23.1 g.

To a solution of the crude alcohol produced above (23.5 g, 99.8 mmol) in DCM (435.2 mL, 6789 mmol) was added 1H-imidazole (11.89 g, 174.6 mmol) followed by tert-butyldimethylsilyl chloride (22.56 g, 149.7 mmol) at rt, and the reaction was stirred for 24h. The reaction was quenched by addition of water (250 mL) and extracted with DCM (3x). The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (750g, Hexanes then 0-10% EtOAc/Hexanes over 50 min) to afford the title compound. Yield: 23.9 g (69% - 2 steps). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (d, J = 1.3 Hz, 1H), 7.23 (d, J = 1.9 Hz, 2H), 3.83 (t, J = 6.7 Hz, 2H), 2.96 (t, J = 6.7 Hz, 2H), 0.89 (s, 9H), -0.00 (s, 6H).

Step 2: Reaction conditions A (as depicted in Example 11): 2-(2-{[tert-Butyl(dimethyl)silyl]oxy}-ethyl)-5-chlorobenzaldehyde

[00321] A solution of [2-(2-bromo-4-chlorophenyl)ethoxy](tert-butyl)dimethylsilane (15.5 g, 44.3 mmol) in THF (197 mL, 2430 mmol) was cooled to -78 C, at which point was added 2.50 M of *n*-BuLi in hexane (24.8 mL, 62.0 mmol). After stirring for 5 min, DMF (5.15 mL, 66.5 mmol) was added, and the reaction mixture was stirred at -78 °C for 10 min. The reaction was quenched by adding saturated aq. NH_4Cl (150 mL) and then was warmed to rt. Reaction mixture was further diluted with water (60 mL, enough for complete dissolution of white solid). THF was removed in vacuo. Aqueous residue was diluted with Et_2O (300 mL), the layers were separated, and the aqueous layer was extracted 2 x Et_2O (70 mL each). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was loaded onto the column as a solution in hexane. Chromatography was performed (330 g column, 0-20% EtOAc:hexanes over 50 min) to afford the title compound. Yield = 12.7 g (96%). ^{1}H NMR (400 MHz, Chloroform-d)

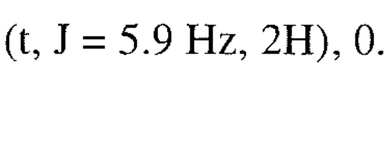
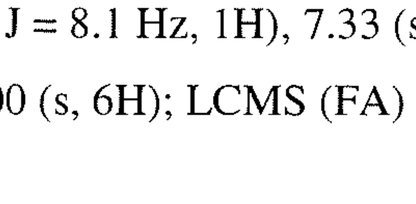
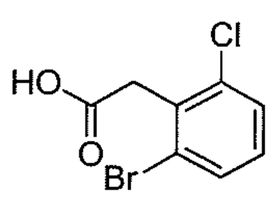
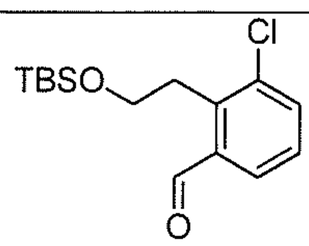
δ 10.25 (s, 1H), 7.83 (d, J = 2.3 Hz, 1H), 7.50 – 7.45 (m, 1H), 3.83 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 6.2 Hz, 2H), 0.81 (s, 9H), -0.09 (s, 6H).

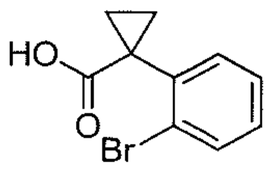
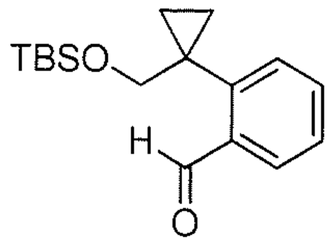
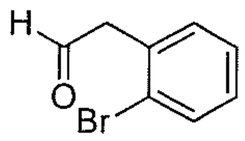
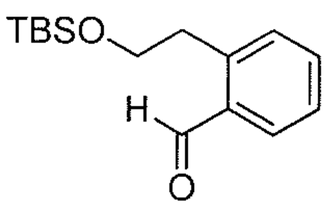
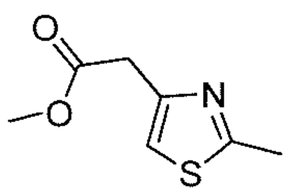
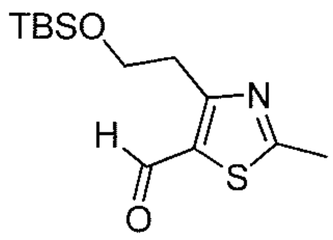
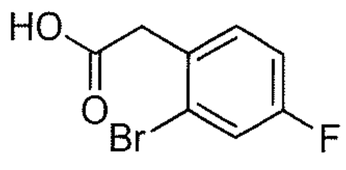
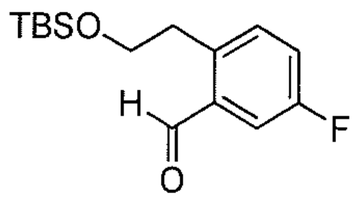
Alternative conditions for Step 2: Reaction conditions B (e.g., Entry 8, below):

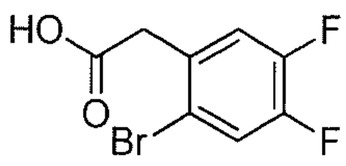
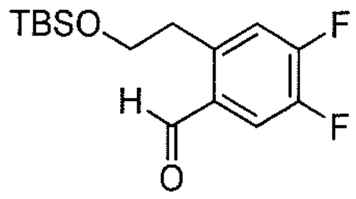
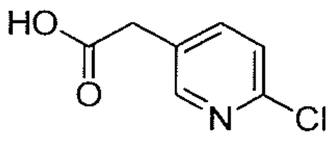
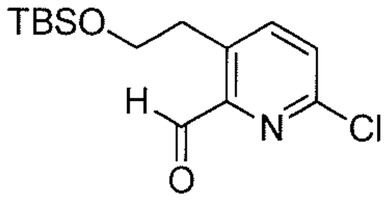
3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-6-chloropyridine-2-carbaldehyde

[00322] To a 0 °C cooled solution of N,N-dimethylaminoethanol (4.430 mL, 44.08 mmol) in hexane (25.0 mL, 191 mmol) was added a 2.5 M solution of *n*-BuLi in hexane(36.7 mL, 91.7 mmol), dropwise over 30 min via syringe. The reaction mixture was stirred at 0 °C then cooled to -78 °C. To the resulting mixture was added a solution of 5-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-2-chloropyridine (4.00 g, 14.7 mmol) in hexane (25.0 mL, 191 mmol), dropwise over 15 min, via syringe. The reaction mixture was stirred at -78 °C for 1 hour followed by addition of a solution of DMF (5.13 mL, 66.2 mmol) in THF (26 mL, 320 mmol), dropwise over 15 min, via syringe. The resulting solution was stirred at -78 °C for 1 hour then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give 6.655 g of crude product as a brown oil. The crude material was purified by ISCO silica gel chromatography eluting with 0-5% EtOAc in hexanes to give 2.439 g of the title compound (55%). ^{1}H NMR (400 MHz, Chloroform-d) δ 10.15 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 3.91 (t, J = 5.9 Hz, 2H), 3.32 (t, J = 5.9 Hz, 2H), 0.89 (s, 9H), -0.00 (s, 6H); LCMS (FA) M+1 300.1.

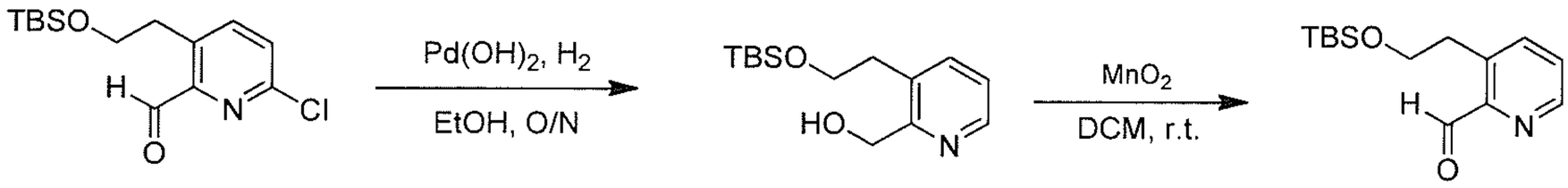
[00323] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the appropriate starting materials:

Entry	Starting material	Reaction conditions for Step 2	Product (Int #)	NMR Data
1		A	 **Int-16**	^{1}H NMR (400 MHz, DMSO-d6) δ 10.31 (s, 1H), 8.12 (d, J = 1.4 Hz, 1H), 7.96 (dd, J = 8.1, 1.6 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 3.82 (t, J = 6.1 Hz, 2H), 3.34 – 3.26 (m, 2H), 0.74 (s, 9H), -0.15 (s, 6H).
2		A		^{1}H NMR (400 MHz, Chloroform-d) δ 10.47 (s, 1H), 7.91 (dd, J = 7.7, 1.3 Hz,

			Int-17	1H), 7.71 (dd, J = 7.9, 1.3 Hz, 1H), 7.47 – 7.38 (m, 1H), 4.00 – 3.94 (m, 2H), 3.58 – 3.50 (m, 2H), 0.89 (s, 9H), -0.00 (s, 6H).
3		**A**	 **Int-18**	^{1}H NMR (400 MHz, Chloroform-d) δ 10.75 (d, J = 0.7 Hz, 1H), 7.90 (dd, J = 7.8, 1.0 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.39 – 7.32 (m, 1H), 3.65 (s, 2H), 1.04 – 0.99 (m, 2H), 0.90 – 0.85 (m, 2H), 0.78 (s, 9H), -0.16 (s, 6H).
4		**A**	 **Int-19**	^{1}H NMR (400 MHz, Chloroform-d) δ 10.38 (s, 1H), 7.94 (dd, J = 7.7, 1.2 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.50 – 7.44 (m, 1H), 7.40 (d, J = 7.6 Hz, 1H), 3.94 (t, J = 6.4 Hz, 2H), 3.34 (t, J = 6.4 Hz, 2H), 0.91 (s, 9H), -0.00 (s, 6H).
5		**A**	 **Int-20**	^{1}H NMR (400 MHz, Chloroform-d) δ 10.08 (s, 1H), 4.07 – 3.99 (m, 2H), 3.31 (t, J = 5.9 Hz, 2H), 2.82 (s, 3H), 0.88 (s, 9H), 0.00 (s, 6H).
6		**A**	 **Int-21**	N/A

7		A	 **Int-22**	N/A
8		B	 **Int-23**	^{1}H NMR (400 MHz, Chloroform-d) δ 10.15 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 3.91 (t, J = 5.9 Hz, 2H), 3.32 (t, J = 5.9 Hz, 2H), 0.89 (s, 9H), -0.00 (s, 6H)

Example 12: 3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)pyridine- 2-carbaldehyde Int-24



Int-23 Int-24

Step 1: [3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)pyridin-2-yl]methanol

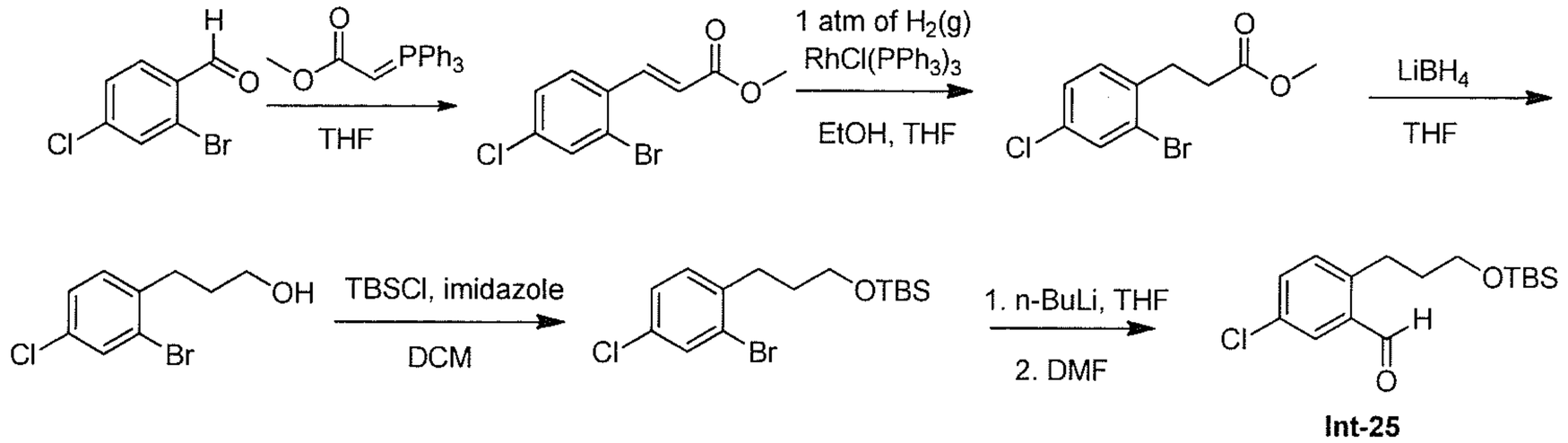
[00324] To a solution of 3-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-6-chloropyridine-2-carbaldehyde (**Int-23**, 2.299 g, 7.667 mmol) in ethanol (75.4 mL, 1290 mmol) was added $NaHCO_3$ (2.576 g, 30.67 mmol) and Pearlman's catalyst (palladium hydroxide on carbon)(10:90, palladium hydroxide:methane, 0.538 g, 0.383 mmol). The resulting mixture was purged with hydrogen gas, and then stirred at rt under a balloon of hydrogen gas for 15 h. The reaction mixture was filtered over a pad of Celite and the filtrate was concentrated to give crude product as a grey residue. The crude material was purified by ISCO silica gel chromatography eluting with 0-5% MeOH in DCM to give 1.955 g of the title compound (95%) as a clear oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.54 – 8.49 (m, 1H), 7.66 – 7.54 (m, 1H), 7.31 – 7.22 (m, 1H), 4.84 (s, 2H), 3.87 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 0.88 (s, 9H), -0.00 (s, 6H); LCMS (FA) M+1 268.2

Step 2: 3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)pyridine-2-carbaldehyde

[00325] To a solution of [3-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)pyridin-2-yl]methanol (1.995 g, 7.460 mmol) in DCM (71.5 mL, 1120 mmol) was added MnO_2 (6.49 g, 74.7 mmol). The reaction mixture was stirred at rt for 20 h then filtered over a pad of Celite. The resulting filtrate was concentrated to give 2.421 g of crude product. The crude material was purified by ISCO silica gel chromatography eluting with 0-20% EtOAc in hexanes to give 1.308 g of the title compound (66%) as a clear oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.28 (d, J = 0.5 Hz, 1H), 8.83 – 8.64

(m, 1H), 7.91 – 7.72 (m, 1H), 7.55 – 7.44 (m, 1H), 3.95 (t, J = 6.1 Hz, 2H), 3.37 (t, J = 6.1 Hz, 2H), 0.90 (s, 9H), -0.00 (s, 6H); LCMS (FA) M+1 266.2.

Example 13: 2-(3-{[tert-Butyl(dimethyl)silyl]oxy}propyl)-5-chlorobenzaldehyde Int-25



Step 1: Methyl (2E)-3-(2-bromo-4-chlorophenyl)acrylate

[00326] To a flask was added 2-bromo-4-chlorobenzaldehyde (3.00 g, 0.0137 mol) dissolved in THF (40 mL, 0.5 mol). The solution was cooled to 0 °C and (carbomethoxymethylene)triphenylphosphorane (5.26 g, 0.0157 mol) was added. The resulting mixture was stirred at 0 °C for 30 min and overnight at RT. Celite was then added to the reaction followed by concentration to dryness. The residue was solid loaded and purified by ISCO silica gel chromatography (80g column, eluting with 0-30-50% EtOAc/Hex. over 25 min) to give 3.15 g (84%) of the title compound as a 2:1 mixture of trans and cis. LCMS (FA): m/z = 275.2 (M+H).

Step 2: Methyl 3-(2-bromo-4-chlorophenyl)propanoate

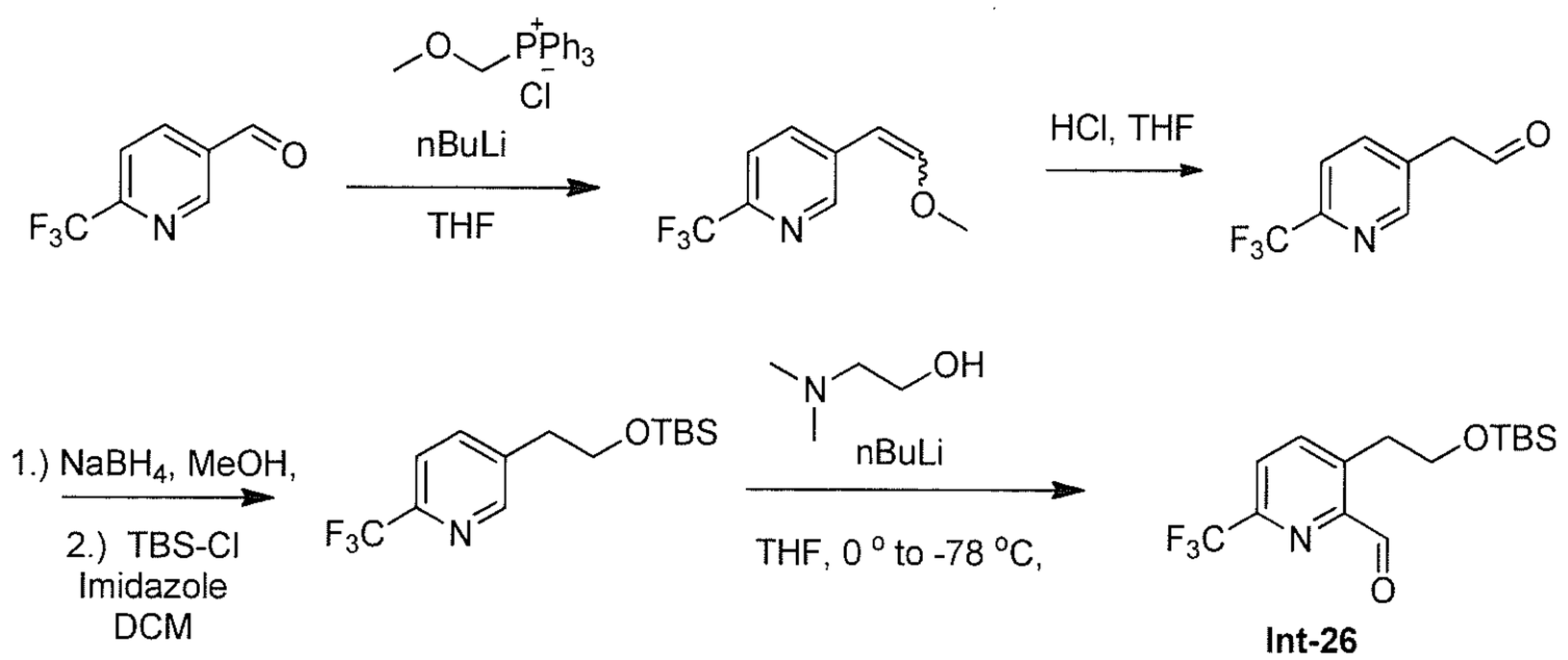
[00327] Into a 1-neck round-bottom flask was added methyl (2E)-3-(2-bromo-4-chlorophenyl)acrylate (1.78 g, 6.46 mmol) dissolved in ethanol (20.0 mL, 342 mmol) and THF (10.0 mL, 123 mmol). Tris(triphenylphosphine)rhodium(I) chloride (0.598 g, 0.646 mmol) was added and the mixture was purged with a H_2 gas balloon (3X). The resulting mixture was then stirred at rt over the weekend under a balloon of H_2 gas. The balloon was removed and the mixture was flushed with argon. Celite was then added to the reaction mixture and concentrated to dryness. The residue was solid loaded and purified by ISCO silica gel chromatography (40 g column, eluting with 0-30-50% EtOAc/Hex. over 20 min) to give 1.62 g (90%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 (d, J = 1.9 Hz, 1H), 7.24 – 7.17 (m, 2H), 3.68 (s, 3H), 3.04 (t, J = 7.7 Hz, 2H), 2.63 (t, J = 7.7 Hz, 2H).

Steps 3 and 4: 2-(3-{[tert-Butyl(dimethyl)silyl]oxy}propyl)-5-chlorobenzaldehyde

[00328] These steps were performed in analogous fashion to **Example 11**, using $LiBH_4$ instead of BH3/THF in Step 1, and using Reaction Conditions A in Step 2. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.27 (s, 1H), 7.81 (d, J = 2.3 Hz, 1H), 7.46 (dd, J = 8.2, 2.3 Hz, 1H), 7.25 – 7.22 (m, 1H), 3.64 (t, J = 6.0 Hz, 2H), 3.11 – 3.04 (m, 2H), 1.86 – 1.76 (m, 2H), 0.91 (d, J = 2.6

Hz, 9H), 0.06 (s, 6H).

Example 14: 3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-6-(trifluoromethyl)pyridine-2-carbaldehyde Int-26



Int-26

Step 1: 5-[(E)-2-Methoxyvinyl]-2-(trifluoromethyl)pyridine and 5-[(Z)-2-methoxyvinyl]-2-(trifluoromethyl)pyridine

[00329] (Methoxymethyl)triphenylphosphonium chloride (11.7 g, 34.3 mmol) was placed in a 250ml two-neck round bottom flask under an atmosphere of argon. THF (1.00e2 ml, 1230 mmol) was added and the suspension was cooled at -78 °C. 2.5 M of *n*-BuLi in hexane (12.8 ml, 32.0 mmol) was added drop wise. The reaction turned an orange color but remained a suspension. The reaction was warmed at 0 °C and turned a dark orange color and presented as a solution which was stirred at 0 °C for 30 min under an atmosphere of argon. 5-formyl-2-(trifluoromethyl)pyridine (4.00 g, 22.8 mmol) in THF (10.0 ml, 123 mmol) was added dropwise quickly to the solution at 0 °c. The reaction was stirred for 30min at 0 °C under an atmosphere of argon. The reaction was warmed to rt and quenched. TLC (10% EtOAc in hexanes) showed no starting material remaining with a major spot just above it. The reaction was quenched with water and saturated NH_4Cl. The reaction was extracted 3x with DCM. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was loaded with DCM onto a 220g gold isco column (10% EtOAc in hexanes isocratic 100ml/min) to give the product as a 1:1 mixture of the title products as a yellow oil. LCMS (FA) 203.9 (m + 1).

Step 2: [6-(Trifluoromethyl)pyridin-3-yl]acetaldehyde

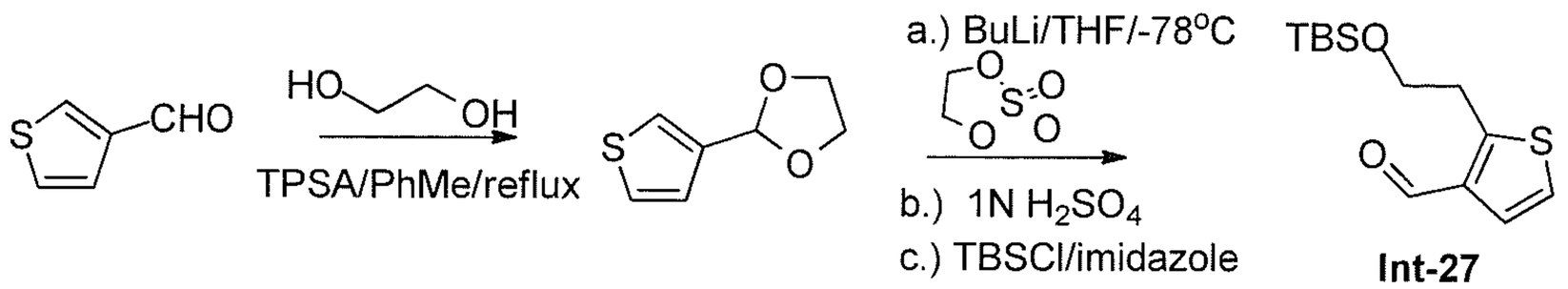
[00330] To a solution of 5-[(Z)-2-methoxyvinyl]-2-(trifluoromethyl)pyridine (1.30 g, 6.4 mmol) and 5-[(E)-2-methoxyvinyl]-2-(trifluoromethyl)pyridine (1.30g, 6.4 mmol) in THF (100 mL, 1000 mmol) was added 1N HCl. The reaction was stirred overnight. The reaction was basified by addition of saturated $NaHCO_3$ and the mixture was extraction with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via column chromatography (80g ISCO, 30% EtOAc in hexanes isocratic) to give the

title compound as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.85 (s, 1H), 8.59 (s, 1H), 7.79 – 7.66 (m, 2H), 3.88 (s, 2H).

Steps 3 and 4: 3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-6-(trifluoromethyl)pyridine-2-carbaldehyde

[00331] These steps were performed in analogous fashion to **Example 11**, using $NaBH_4$ instead of BH_3/THF in Step 1, and using Reaction Conditions B in Step 2. LCMS (FA) 335.2 (M + 1)

Example 15: 2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)thiophene- 3-carbaldehyde Int-27



Int-27

Step 1: 3-Thiophenecarboxaldehyde ethylene acetal

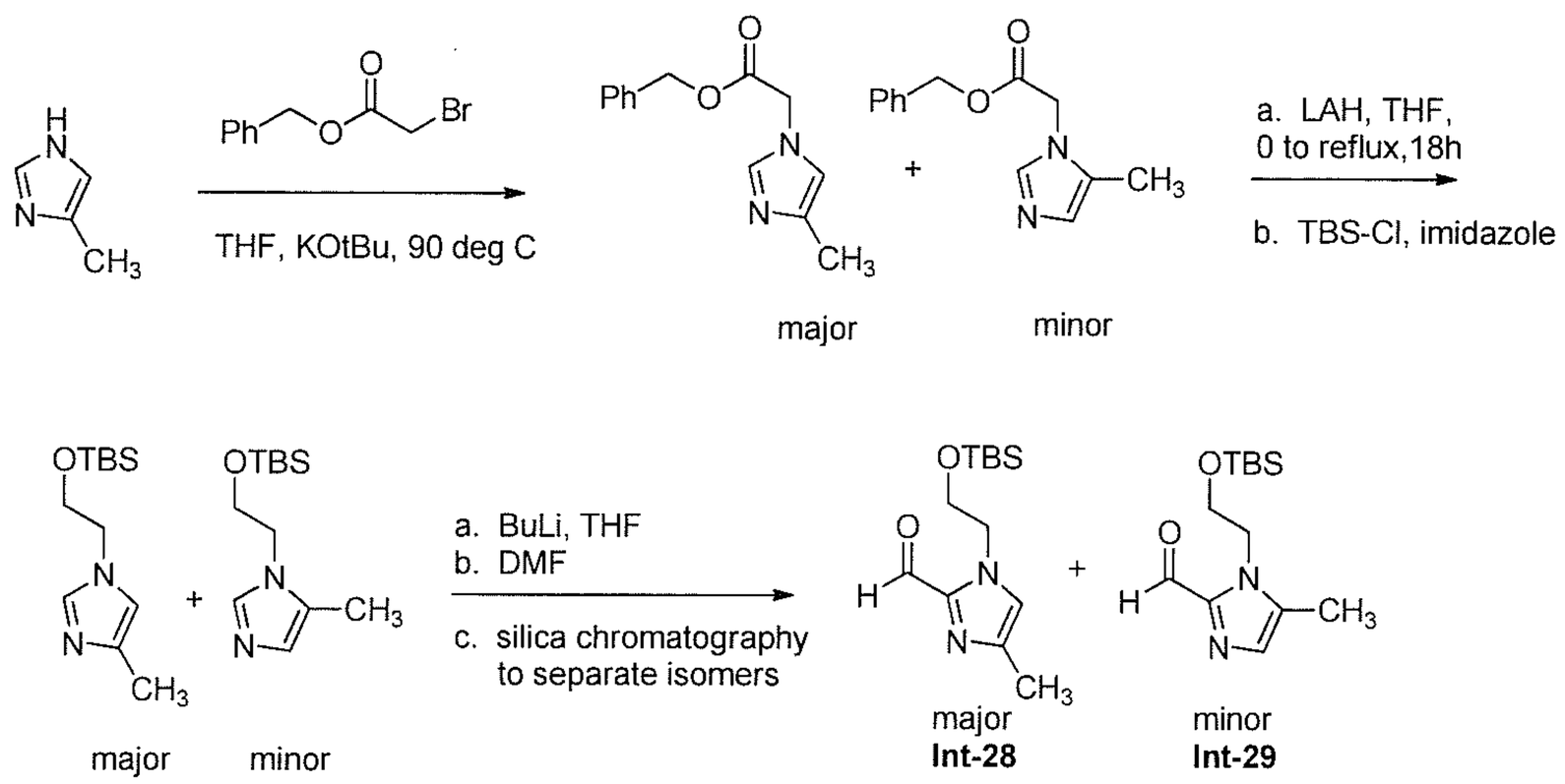
[00332] 3-Thiophenecarboxaldehyde (5.8341 g, 52.020 mmol) and 1,2-ethanediol (9.6863 g, 156.06 mmol) were added to toluene (180 mL, 1700 mmol), then toluenesulfonic acid (0.35832 g, 2.0808 mmol) was added to the solution. The reaction was stirred at reflux for 24 hrs. The reaction mixture was then cooled to rt and washed with 3 x 40 ml water. The organic layer was concentrated to yield 7.34g (90%) of the title compound as a crude oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 (ddd, J = 3.0, 1.2, 0.6 Hz, 1H), 7.34 (dd, J = 5.0, 3.0 Hz, 1H), 7.18 (dd, J = 5.0, 1.2 Hz, 1H), 5.93 (s, 1H), 4.15 – 4.10 (m, 2H), 4.07 – 4.01 (m, 2H).

Step 2: 2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)thiophene-3-carbaldehyde

[00333] A solution of 3-thiophenecarboxaldehyde ethylene acetal (4.33 g, 27.7 mmol) in THF (130.0 mL, 1603 mmol) was cooled to -78 °C, at which point 2.50 M of *n*-BuLi in hexane (17.74 mL, 44.35 mmol) was added. A solution of ethylenesulfate (3.7846 g, 30.492 mmol) in THF (10.0 mL, 123 mmol) was added solution and the reaction was stirred for 30 min at -78 °C. The reaction was concentrated to ~20% of the original volume in vacuo, and then a solution of 6 ml 98% H_2SO_4 in 30ml water was added to the mixture. This mixture was then stirred at 75 °C overnight. The solution was added slowly to 150 ml saturated $NaHCO_3$ aqueous solution to neutralize and then extracted with 3 x 50 ml DCM. The combined organic layers were concentrated to dryness, and the residue was dissolved into DCM (100 mL, 2000 mmol), to which were added 1H-imidazole (3.774 g, 55.44 mmol) and tert-butyldimethylsilyl chloride (5.013 g, 33.26 mmol). The reaction was stirred for 30 min, and poured into 60ml water. The aqueous was extracted with 2 x 40 mL DCM. The combined organic layers were concentrated in vacuo and purified by flash column (80g, eluent was 0-25% EtOAc in hexane over 15min) to afford 3.102g (41%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.04 (s, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.15 (dd, J = 5.4, 0.5 Hz, 1H), 3.89 (t, J = 6.0 Hz, 2H), 3.40 (t, J = 6.0 Hz, 2H), 0.88 (s, 9H), -0.00 (s,

6H).

Example 16: 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-methyl-1H-imidazole-2-carbaldehyde (Int-28) and 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-5-methyl-1H-imidazole-2-carbaldehyde (Int-29)



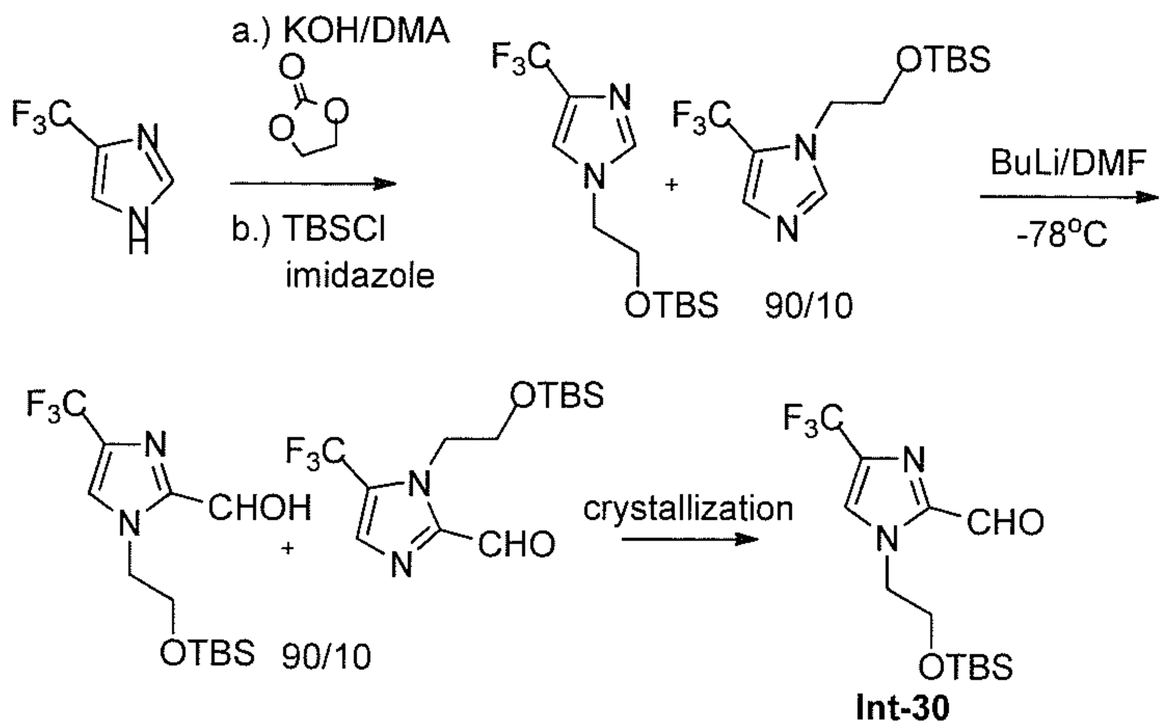
Step 1: Benzyl (4-methyl-1H-imidazol-1-yl)acetate and Benzyl (5-methyl-1H-imidazol-1-yl)acetate

[00334] An oven-dried 500 mL 2-neck round bottom flask under nitrogen was charged with 4-methylimidazole (2.00 g, 24.4 mmol) and 2-methyltetrahydrofuran (10 mL), then placed in a 70 °C oil bath. Added 1.00 M of potassium tert-butoxide in THF (26.8 mL, 26.8 mmol) in a stream. Added benzyl 2-bromoacetate (4.25 mL, 26.8 mmol) in a single portion. After 30min quenched by adding ice. Poured into saturated $NaHCO_3$; extracted three times with EtOAc; washed combined organic portions with brine; dried with anhydrous sodium sulfate; filtered, and concentrated in vacuo. An oil remained. Residue was subjected to ISCO chromatography eluting with a DCM / MeOH gradient to afford a brown oil (2.06 g). LCMS indicates this substance is a mixture of the title compounds. Used as is in next step. LCMS: (AA) M+1 231.1

Steps 2 and 3: 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-methyl-1H-imidazole-2-carbaldehyde and 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-5-methyl-1H-imidazole-2-carbaldehyde

[00335] These steps were performed in analogous fashion to **Example 11**, using lithium tetrahydroaluminate instead of BH_3/THF in Step 1, and using Reaction Conditions A in Step 2. Major isomer: ^{1}H NMR (400 MHz, Chloroform-d) δ 9.74 (s, 1H), 6.98 (s, 1H), 4.48 – 4.43 (m, 2H), 3.88 – 3.84 (m, 2H), 2.29 (s, 3H), 0.83 (s, 9H), -0.09 (s, 6H).

Example 17: 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde Int-30



Step 1: 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-(trifluoromethyl)-1H-imidazole (A) and 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-5-(trifluoromethyl)-1H-imidazole

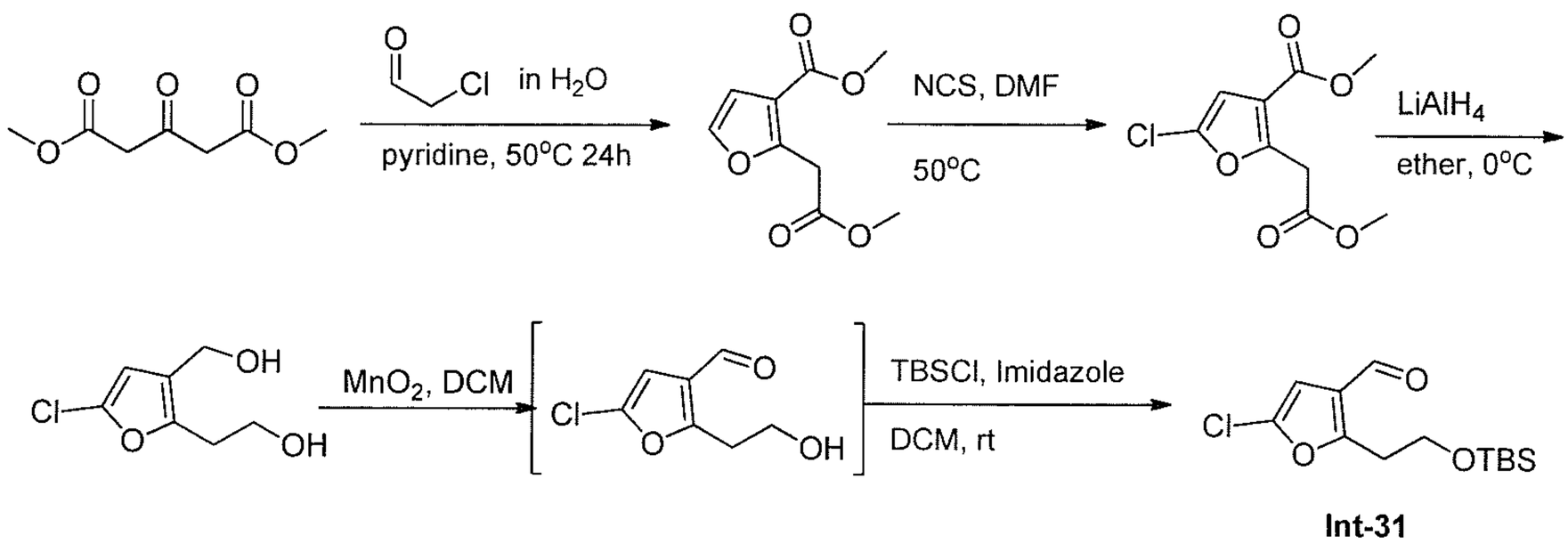
[00336] To a solution of 4-(trifluoromethyl)-1H-imidazole (6.233 g, 45.80 mmol) in N,N-dimethylacetamide (30.0 mL, 323 mmol) was added ethylene carbonate (4.840 g, 54.97 mmol) and potassium hydroxide (0.2570 g, 4.580 mmol). The reaction was heated at 160 °C for 2 hrs, and then cooled to 0 °C. To the cooled mixture were added DCM (80.0 mL, 1250 mmol) and 1H-imidazole (6.237 g, 91.61 mmol), and then tert-butyldimethylsilyl chloride (8.975 g, 59.55 mmol) was added slowly to the solution. The reaction was stirred at rt for an additional 2 h. The mixture was then poured into 150 ml water, and extracted with 2 x 50 ml DCM. Concentrated the organic layers in vacuo, and purified by flash column (80g). The products contained regio isomers (A/B=90/10 by NMR) which couldn't be separated by chromatography. Total recovery of mixture: 9.70g (72%) as an oil. The product was used as is in the next step.

Step 2: 1-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-4-(trifluoromethyl)-1H-imidazole-2-carbaldehyde

[00337] The 90:10 mixture of 1-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-4-(trifluoromethyl)-1H-imidazole (9.50 g, 32.3 mmol) and 1-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-5-(trifluoromethyl)-1H-imidazole (0.95 g, 3.2 mmol) isolated above was dissolved into THF (150.0 mL, 1849 mmol), and the solution was cooled to -78 °C. 2.50 M of *n*-BuLi in hexane (20.65 mL, 51.63 mmol) was added to the solution at -78 °C over 15 min, and then DMF (7.784 g, 106.5 mmol) was added to the solution. The reaction was stirred for 30 min, at which point acetic acid (3.670 mL, 64.54 mmol) was added and the mixture was allowed to warm to rt. The solution was poured into 200ml water and extracted 3 x 150ml EtOAc. The organic layers were combined and concentrated, and then purified by ISCO column (80g, eluent was 0-35% EtOAc in hexane over 15 min) to afford 7.35g crude product which contained a 90:10 mixture of regioisomers. The crude product was the crystallized from 30% DCM in hexane to afford 3.452g (33%) of the title

compound as a single regioisomer. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.92 (d, J = 0.9 Hz, 1H), 7.63 (s, 1H), 4.69 – 4.57 (m, 2H), 4.04 – 3.91 (m, 2H), 0.90 (s, 9H), -0.00 (s, 6H). LCMS (AA) M+1 323

Example 18: 2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-5-chloro- 3-furaldehyde Int-31



Int-31

Step 1: Methyl 3-(methoxycarbonyl)-2-furanacetate

[00338] (Methyl 3-(methoxycarbonyl)-2-furanacetate was prepared according to the procedure reported in M. Tada, *et al.* Chem Pharm. Bull. 42(10), 2167-2169, 1994. A solution of 50% chloroacetaldehyde in water (4.64 mL, 36.5 mmol) was added dropwise to a solution of dimethyl 1,3-acetonedicarboxylate (5.00 g, 28.7 mmol) in pyridine (10.0 mL, 124 mmol) with stirring at rt. A slight exotherm was observed. The orange solution was then heated at 50°C under argon for 18 h. The reaction was cooled to rt and partitioned between water and EtOAc. The organic layer was washed sequentially with 1N HCl, saturated aqueous $NaHCO_3$, 1N NaOH and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0 to 25% EtOAc in hexane) to give 3.386 g (60%) of product as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 1.9 Hz, 1H), 4.08 (s, 2H), 3.83 (s, 3H), 3.73 (s, 3H); LCMS (AA): (M+H) 199.1

Step 2: Methyl 5-chloro-2-(2-methoxy-2-oxoethyl)-3-furoate

[00339] In a 100mL round bottom flask equipped with reflux condenser, a solution of methyl 3-(methoxycarbonyl)-2-furanacetate (2.3280 g, 11.747 mmol) and N-chlorosuccinimide (1.57 g, 11.7 mmol) in DMF (23.6 mL) was stirred at 50 °C for 2 h. N-chlorosuccinimide (1.57 g, 11.7 mmol) was added and the reaction was stirred at 50 °C for 1.5 h. The reaction was quenched with water, extracted with EtOAc, washed with saturated Na_2SO_3, brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0 to 15% EtOAc in hexane) to obtain 2.062 g (75%) of product as a colorless oil.^{1}H NMR (400 MHz, Chloroform-d) δ 6.48 (s, 1H), 4.04 (s, 2H), 3.82 (s, 3H), 3.74 (s, 3H); LCMS (AA): (M+H) 233.0/235.0

Step 3: 2-[5-Chloro-3-(hydroxymethyl)-2-furyl]ethanol

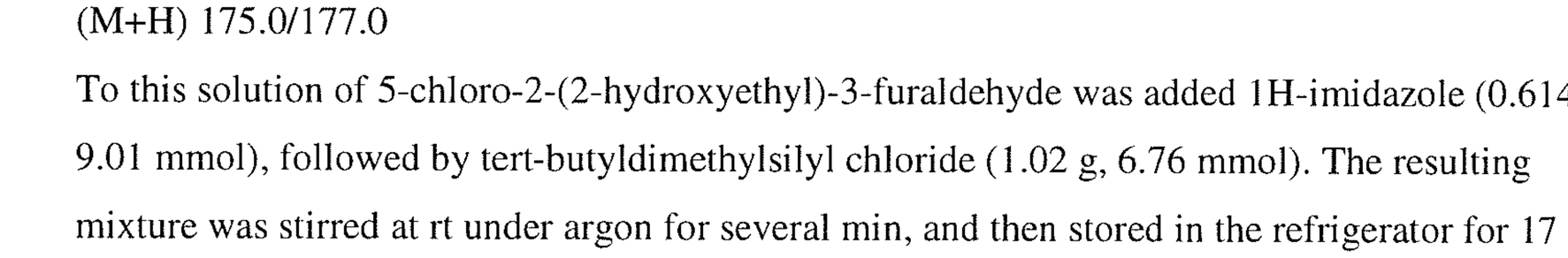
[00340] To a solution of methyl 5-chloro-2-(2-methoxy-2-oxoethyl)-3-furoate (2.048 g, 8.804 mmol) in ether (7.931 mL) at 0 °C under argon was added 1.0 M of lithium tetrahydroaluminate in THF (26.50 mL, 26.50 mmol). The reaction was stirred for 3 h at rt. Then the reaction was cooled to 0 °C and quenched with water and 1N HCl. The layers were separated, and the aqueous layer was extracted with EtOAc (2x), and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0 to10% MeOH in DCM, monitored by TLC with UV and KMnO4 stain) to obtain 1.009 g (65%) of product as a brown oil.^{1}H NMR (400 MHz, Chloroform-d) δ 6.14 (s, 1H), 4.42 (s, 2H), 3.83 (t, J = 5.6 Hz, 2H), 2.89 (t, J = 5.7 Hz, 2H), 2.22 (s, 2H); LCMS (AA): (M-OH) 159.0

Step 4: 2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)-5-chloro-3-furaldehyde

[00341] To a solution of 2-[5-chloro-3-(hydroxymethyl)-2-furyl]ethanol (0.796 g, 4.51 mmol) in DCM (167 mL) was added MnO_2 (3.92 g, 45.1 mmol) at rt, and the mixture was stirred for 2 h. MnO_2 (3.92 g, 45.1 mmol) was added and the mixture was stirred at rt for 2.5 h. The mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate was transferred to a 500 mL round bottom flask, and the volume of solvent was reduced until ~100 mL remained to provide a solution of 5-chloro-2-(2-hydroxyethyl)-3-furaldehyde. LCMS (AA): (M+H) 175.0/177.0

To this solution of 5-chloro-2-(2-hydroxyethyl)-3-furaldehyde was added 1H-imidazole (0.614 g, 9.01 mmol), followed by tert-butyldimethylsilyl chloride (1.02 g, 6.76 mmol). The resulting mixture was stirred at rt under argon for several min, and then stored in the refrigerator for 17 h. The reaction mixture was diluted with water and extracted with EtOAc (2X). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude oil was purified by silica gel column chromatography (0 to 10% EtOAc in hexane) to obtain 513 mg (39%) of 2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)-5-chloro-3-furaldehyde as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.85 (s, 1H), 6.49 (s, 1H), 3.89 (t, J = 6.0 Hz, 2H), 3.11 (t, J = 6.0 Hz, 2H), 0.83 (s, 9H), -0.03 (s, 6H); LCMS (AA): (M+H) 289.1/291.1

Example 19: 5-Chloro-2-{2-[(4-methoxybenzyl)sulfanyl]ethyl}benzaldehyde Int-32



Int-32

Step 1: 2-Bromo-1-(2-bromoethyl)-4-chlorobenzene

[00342] 2-(2-bromo-4-chlorophenyl)ethanol (1.97 g, 8.36 mmol) and carbon tetrabromide (3.61 g, 10.9 mmol) were dissolved into DCM (30.0 mL, 468 mmol), then triphenylphosphine (3.29 g,

12.5 mmol) was added at rt. The reaction was stirred at rt for 2 hrs. To the reaction mixture was added 100 mL hexane with stirring, at which point a precipitate formed that was removed by filtration. The filtrate was concentrated and purified by flash column (80g column, 100% hexane as eluent) to provide 1.92g (77%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 – 7.41 (s, 1H), 7.23 – 7.15 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 3.49 (t, J = 7.3 Hz, 2H), 3.18 (t, J = 7.3 Hz, 2H).

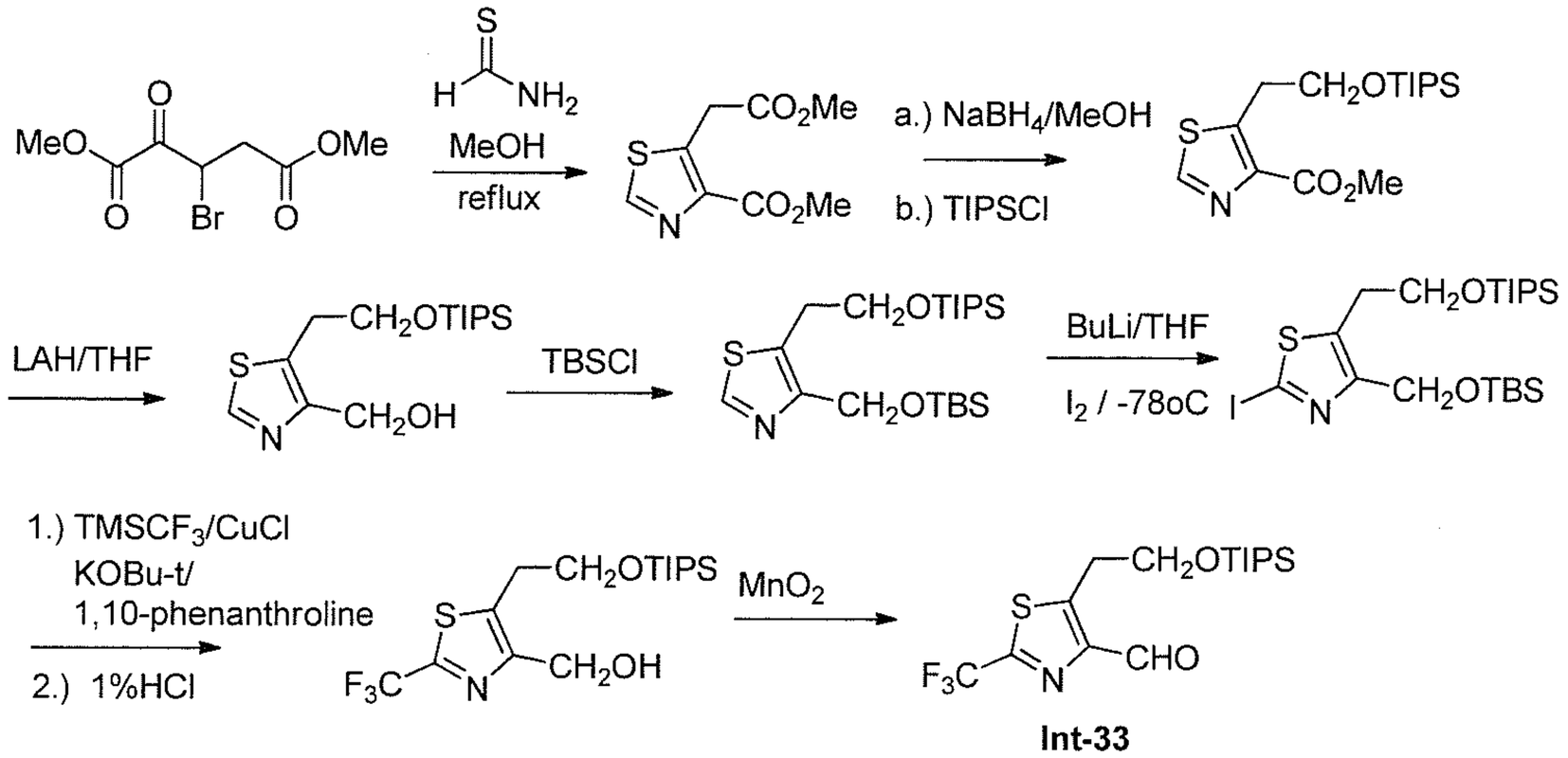
Step 2: 2-Bromo-4-chloro-1-{2-[(4-methoxybenzyl)sulfanyl]ethyl}benzene4-({[2-(2-bromo-4-chlorophenyl)ethyl]sulfanyl}methyl)phenyl methyl ether

[00343] To a solution of 2-bromo-1-(2-bromoethyl)-4-chlorobenzene (2.47 g, 8.28 mmol) and p-methoxy-α-toluenethiol (1.3262 mL, 9.5190 mmol) in dimethyl sulfoxide (6.00 mL, 84.5 mmol) was added potassium carbonate (2.2880 g, 16.555 mmol) and the reaction was stirred at rt for 72 h. The reaction was quenched by pouring into 40ml water, the layers were separated, and the aqueous layer was extracted 2 x 15ml DCM. The combined organic layers were concentrated and purified by flash column (80g, eluent 0-15% EtOAc in hexane for 15 min) to give 1.95g (64%) of title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 (s, 1H), 7.23 – 7.13 (m, 3H), 7.06 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 3.75 (s, 3H), 3.64 (s, 2H), 2.93 – 2.79 (t, J = 7.3 Hz, 2H), 2.65 – 2.51 (t, J = 7.3 Hz, 2H).

Step 3: 5-Chloro-2-{2-[(4-methoxybenzyl)sulfanyl]ethyl}benzaldehyde

[00344] A solution of 2-bromo-4-chloro-1-{2-[(4-methoxybenzyl)sulfanyl]ethyl}benzene4-({[2-(2-bromo-4-chlorophenyl)ethyl]sulfanyl}methyl)phenyl methyl ether (1.102 g, 2.964 mmol) in THF (40.0 mL, 493 mmol) was cooled to -78 °C. 2.50 M of *n*-BuLi in hexane (2.016 mL, 5.040 mmol) was added and the mixture was stirred at -78 °C for 10 min. DMF (1.148 mL, 14.82 mmol) was then added and the mixture was stirred at -78 °C for 5 min. The mixture warmed to rt over 10 min and then the solution was poured into 30 ml brine. The layers were separated, and the aqueous layer was extracted 3 x 40ml EtOAc. The combined organic layers were concentrated and the residue was chromatographed (hexane/EtOAc=3/1 as eluent) to give 0.4572g (48%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.17 (s, 1H), 7.79 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.6 Hz, 3H), 6.86 (d, J = 7.9 Hz, 2H), 3.84 – 3.78 (s, 3H), 3.69 (s, 2H), 3.22 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H).

Example 20: 2-(Trifluoromethyl)-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole-4-carbaldehyde Int-33



Step 1: Methyl 5-(2-methoxy-2-oxoethyl)-1,3-thiazole-4-carboxylate

[00345] To a solution of dimethyl 3-bromo-2-oxopentanedioate (7.52 g, 29.7 mmol) in methanol (100 mL, 2000 mmol) was added methanethioamide (2.72 g, 44.6 mmol). The reaction was stirred at reflux for 2 hrs. The reaction mixture was concentrated in vacuo, then 25 ml THF was added to the residue. 40 ml hexane was added to the solution with stirring, at which point mixture was filtered and the filtrate was concentrated and purified by flash column (80g, eluent was 30-90% EtOAc in hexane for 20min) to afford 4.18g (65%) of title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.73 (s, 1H), 4.37 (s, 2H), 3.95 (s, 3H), 3.77 (s, 3H).

Step 2: Methyl 5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole-4-carboxylate

[00346] To a 0 °C solution of methyl 5-(2-methoxy-2-oxoethyl)-1,3-thiazole-4-carboxylate (1.45 g, 7.75 mmol) and 2,6-lutidine (1.347 mL, 11.63 mmol) in DCM (60.0 mL, 936 mmol) was added triisopropylsilyl triflate (2.293 mL, 8.531 mmol) and the mixture was stirred at rt overnight. The reaction was quenched by addition of saturated NH_4Cl (50mL), and then the resulting mixture was extracted with DCM (70 mLx3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (eluent was 0-50% EtOAc in hexane) to afford 1.553g (51%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.66 (s, 1H), 3.96 (s, 3H), 3.95 (t, 2H), 3.57 – 3.52 (t, 2H).

Step 3: (5-{2-[(Triisopropylsilyl)oxy]ethyl}-1,3-thiazol-4-yl)methanol

[00347] To a solution of methyl 5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole-4-carboxylate (1.70 g, 4.95 mmol) in THF (60.0 mL, 7.40E2 mmol) was added lithium tetrahydroaluminate (0.2817 g, 7.422 mmol) slowly at 0 °C. The reaction was stirred at 0 °C for 30 min, and then allowed to warm to rt with stirring for 2hrs. The solution was poured slowly into a mixture of 80 ml water and 5 ml acetic acid with stirring. The layers were separated, and the aqueous layer was extracted with 3 x 70 ml EtOAc. The organic layer was concentrated and purified by flash column (40g, eluent was 0-90% EtOAc in hexane) to afford the title compound (0.8090g, 52%). ^{1}H NMR (400

MHz, Chloroform-d) δ 8.62 (s, 1H), 3.95 (m, J = 10.1, 4.2 Hz, 5H), 3.51 (t, J = 5.6 Hz, 2H), 1.08 – 0.94 (m, 21H).

Step 4: 4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole

[00348] To a round bottom flask was added (5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazol-4-yl)methanol (0.8090 g, 2.564 mmol), 1H-imidazole (0.5236 g, 7.691 mmol), 60 ml DCM, and tert-butyldimethylsilyl chloride (0.6183 g, 4.102 mmol) . The resulting reaction mixture was stirred at rt for 4 hrs. The mixture was concentrated in vacuo, and the residue was suspended in EtOAc. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed (40g column, 0-30% EtOAc in hexane) to provide 0.8043g (73%) of the title compound as an oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.48 (s, 1H), 4.74 (s, 2H), 3.80 (t, J = 6.2 Hz, 2H), 3.04 (t, J = 6.2 Hz, 2H), 0.98 – 0.93 (m, 21H), 0.81 (s, 9H), 0.00 (s, 6H)..

Step 5: 4-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-iodo-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole

[00349] A solution of 4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole (0.4320 g, 1.005 mmol) into THF (20.0 mL, 246 mmol) was cooled to -78 °C. 2.50 M of *n*-BuLi in hexane (1.206 mL, 3.015 mmol) was added followed by a solution of iodine (0.3316 g, 1.307 mmol) in 2 ml THF and the reaction was stirred for 30 min at -78 °C. A solution of acetic acid (0.1811 g, 3.015 mmol) in 1ml THF was added to the reaction, and then the solvent was removed in vacuo. The residue was purified by flash column (24g column, eluent was 0-10% EtOAc in hexane) to provide 0.4210g (75%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.70 (s, 2H), 3.76 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 1.00 – 0.95 (m, 21H), 0.81 (s, 9H), -0.00 (s, 6H).

Step 6: [2-(Trifluoromethyl)-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazol-4-yl]methanol

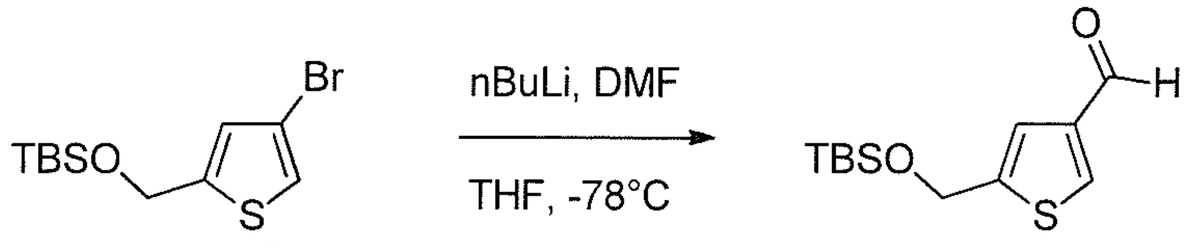
[00350] Potassium tert-butoxide (0.4258 g, 3.794 mmol), o-phenanthroline (0.6837 g, 3.794 mmol) and cuprous monochloride (0.3756 g, 3.794 mmol) were added to a 100ml flask which was dried by heat gun. The flask was sealed with a rubber stopper and purged with vacuum and then backfilled with argon. DMF (8.00 mL, 103 mmol) was added to the flask and the mixture was stirred at rt for 30 min, at which point (trifluoromethyl)trimethylsilane (0.5929 mL, 3.794 mmol) was added and the reaction was stirred for 30 min at rt. Next, a solution of 4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-iodo-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole (0.4217 g, 0.7588 mmol) in 2 ml DMF was added to the mixture, and the reaction was stirred at 50 °C for 1hr. The reaction was poured into 100ml water, the layers were separated, and the aqueous layer was extracted 3 x 50ml DCM. The combined organic layers were concentrated in vacuo. The resulting residue was dissolved into 30 ml 1% HCl methanol solution, and the reaction was stirred at rt for 30 min. The solution was then poured into 60 ml saturated NaCl, the layers were separated, and the aqueous layer was extracted 3 x 40 ml DCM. The combined organic layers were concentrated in vacuo and the resulting residue was purified by flash column (24g column,

eluent was 0-20% EtOAc in hexane) to provide 0.1732g (60%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.67 (d, J = 5.7 Hz, 2H), 3.82 (t, J = 5.7 Hz, 2H), 3.04 (t, J = 5.7 Hz, 2H), 1.04 – 0.84 (m, 21H). LCMS (AA) M+1 384.

Step 7: 2-(Trifluoromethyl)-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazole-4-carbaldehyde

[00351] To a solution of [2-(trifluoromethyl)-5-{2-[(triisopropylsilyl)oxy]ethyl}-1,3-thiazol-4-yl]methanol (0.2297 g, 0.5989 mmol) was in DCM (40.0 mL, 624 mmol) was added MnO_2 (0.6248 g, 7.187 mmol) and the resulting mixture was stirred at rt overnight. Reaction was not complete, so MnO_2 (0.2083 g, 2.396 mmol) was added and the reaction was stirred for an additional 8 hrs at rt. The mixture was filtered, and the filtrate was concentrated in vacuo to provide the title compound (137 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 10.11 (s, 1H), 3.89 (t, J = 5.4 Hz, 2H), 3.48 (t, J = 5.3 Hz, 2H), 1.06 – 0.93 (m, 21H).

Example 21: 5-({[tert-Butyl(dimethyl)silyl]oxy}methyl)thiophene-3-carbaldehyde Int-34

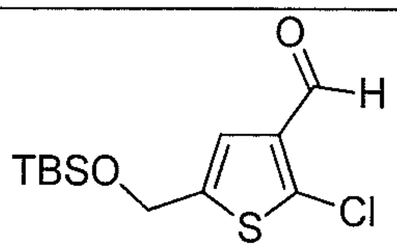
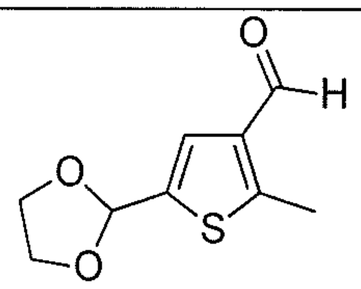


Int-5 **Int-34**

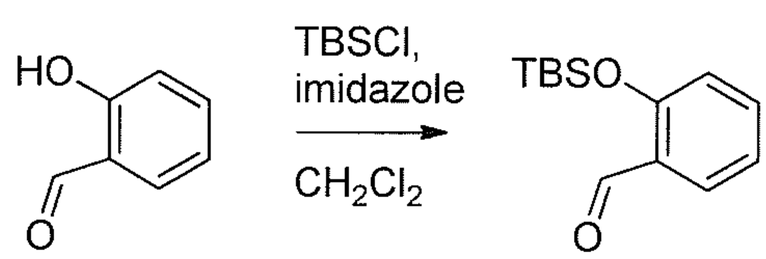
[00352] A heat-gun dried 250mL round bottom flask was charged with 2.50 M of *n*-BuLi in hexane(8.590 mL, 21.48 mmol) and THF (30.0 mL, 3.70E2 mmol) and cooled to -78 °C. **Int-5** (6.00 g, 19.5 mmol) was next added (neat) and the solution was stirred for 5 min at -78 °C. To the mixture was then added DMF (2.268 mL, 29.28 mmol) quickly dropwise and the reaction was stirred for 10 min at -78 °C. The reaction was quenched by addition of water (80 mL) and extracted with EtOAc (80 mLx3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was loaded onto the column as a solution in hexane. Chromatography was performed (220 g column, 0-10% EtOAc:hexanes as eluent) to afford 1 minor peak and then the major title product peak. Yield = 1.95 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.72 (s, 1H), 7.90 (d, J = 1.2 Hz, 1H), 7.20 (s, 1H), 4.78 – 4.73 (m, 2H), 0.82 (s, 9H), -0.00 (s, 6H).

[00353] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Entry	**Starting material**	**Product (Int #)**	**NMR Data**

1	Int-6	 Int-35	^{1}H NMR (400 MHz, Chloroform-d) δ 9.86 (s, 1H), 6.99 (s, 1H), 4.67 (d, J = 1.0 Hz, 2H), 0.82 (s, 9H), -0.00 (s, 6H).
2	Int-1	 Int-36	^{1}H NMR (400 MHz, DMSO-d6) δ 9.95 (s, 1H), 7.43 (s, 1H), 6.00 (s, 1H), 4.06 – 3.99 (m, 2H), 3.99 – 3.91 (m, 2H), 2.76 (s, 3H).

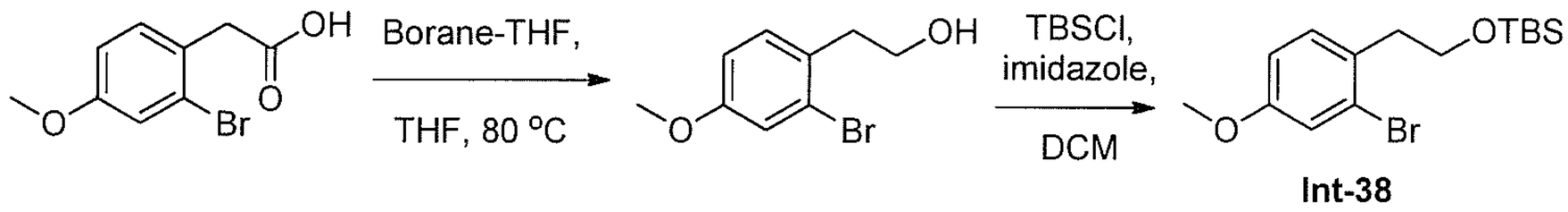
Example 22: 2-{[tert-Butyl(dimethyl)silyl]oxy}benzaldehyde Int-37



Int-37

[00354] To a solution of 2-hydroxybenzaldehyde (2.62 mL, 24.6 mmol) in DCM (30 mL, 400 mmol) were added 1H-imidazole (5.02 g, 73.7 mmol) and tert-butyldimethylsilyl chloride (5.55 g, 36.8 mmol). The thick slurry was then stirred overnight at RT. Quenched with water (20 mL) and diluted with additional DCM (40 mL). Layers were separated, and the aqueous layer was extracted 2 x DCM (40 mL each). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was adsorbed to Celite (50 mL) for dry-loading. Chromatography was performed (80 g column, 0-5% EtOAc:hexanes) to afford one major peak. Yield = 5.2 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.41 (s, 1H), 7.75 (dd, J = 7.8, 1.8 Hz, 1H), 7.46 – 7.34 (m, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 0.96 (s, 9H), 0.22 (s, 6H).

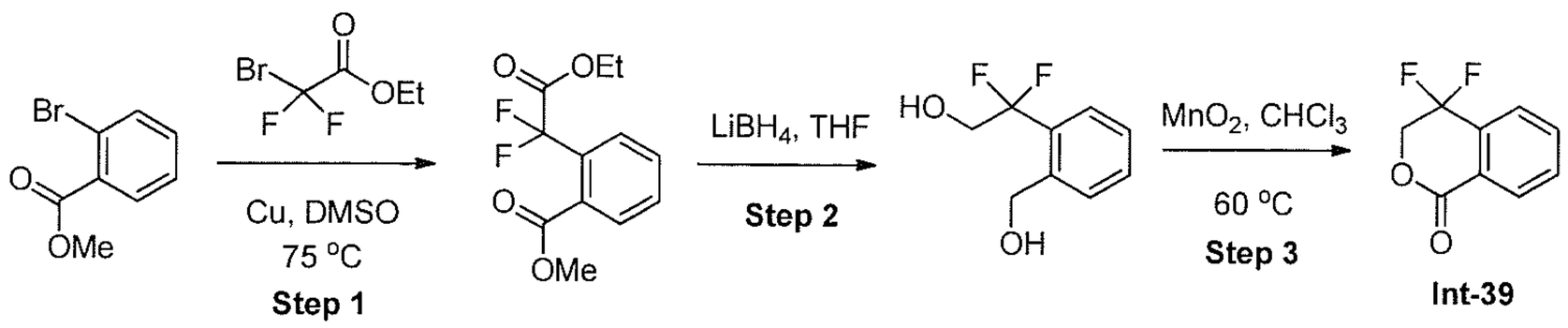
Example 23: [2-(2-Bromo-4-methoxyphenyl)ethoxy](tert-butyl)dimethylsilane Int-38



Int-38

[00355] This sequence was performed in an analogous fashion to that described in Step 1 of **Example 11**, beginning with 2-bromo-4-methoxyphenylacetic acid as starting material. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 6.80 (dd, J = 8.5, 2.6 Hz, 1H), 3.82 – 3.76 (m, 5H), 2.92 (t, J = 7.1 Hz, 2H), 0.88 (s, 9H), -0.00 (s, 6H).

Example 24: 4,4-Difluoro-3,4-dihydro-1H-isochromen-1-one Int-39



Step 1: Methyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate

[00356] To a solution of methyl 2-iodobenzoate (1.12 mL, 7.63 mmol) in dimethyl sulfoxide (33.4 mL, 4.70E2 mmol) was added ethyl bromodifluoroacetate (1.475 mL, 11.45 mmol) followed by activated copper (1.455 g, 22.90 mmol) at rt. After the reaction vessel was purged with argon, the reaction was heated at 75 °C for 14h. After cooling to room temp, the reaction was quenched by addition of 1N KH_2PO_4 solution (200 mL) and the mixture was stirred for 30 min. Mixture was transferred to a separatory funnel and diluted with EtOAc (600 mL) The lower, aqueous layer contained a blue suspended solid, and the upper, organic layer contained a yellow suspended solid. Layers were separated and the EtOAc layer (containing the yellow solid) was filtered. The filtrate was washed 2 x water and 1 x brine, then dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was loaded onto the column as a solution in hexane, with a small amount of DCM for complete solubility. Chromatography was performed (80 g column, 0-25% EtOAc:hexanes over 35 min) to afford 2 very minor byproduct peaks and then the major title compound peak. Yield = 1.75 g. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H).

Step 2: 2,2-Difluoro-2-[2-(hydroxymethyl)phenyl]ethanol.

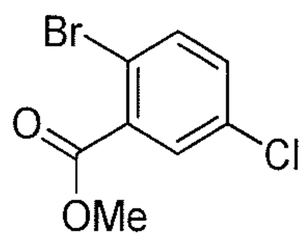
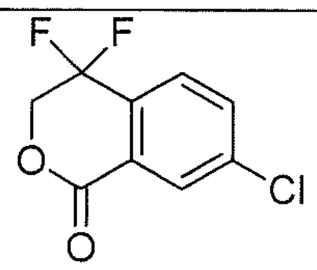
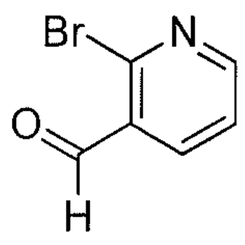
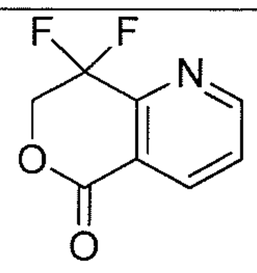
[00357] To a solution of methyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (1.75 g, 6.78 mmol) in THF (79.2 mL, 977 mmol) was added 2.00 M of lithium borohydride in THF(10.2 mL, 20.3 mmol) and the mixture was stirred in the fridge (~4 °C) overnight. The reaction was carefully quenched by addition of saturated $NaHCO_3$ (30 mL). Reaction mixture was then diluted with and EtOAc (80 mL). Layers were separated, and the aqueous layer was extracted 2 x EtOAc (40 mL each). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was loaded onto the column as a solution in DCM. Chromatography was performed (40 g column, 0-50% EtOAc:hexanes over 25 min) to afford one major compound. Yield = 909 mg. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 (d, J = 7.9 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 4.87 (s, 2H), 4.10 (t, J = 13.4 Hz, 2H), 2.36 (s, 1H), 2.07 (s, 1H). LC/MS (FA): M+Na = 211.

Step 3: 4,4-Difluoro-3,4-dihydro-1H-isochromen-1-one

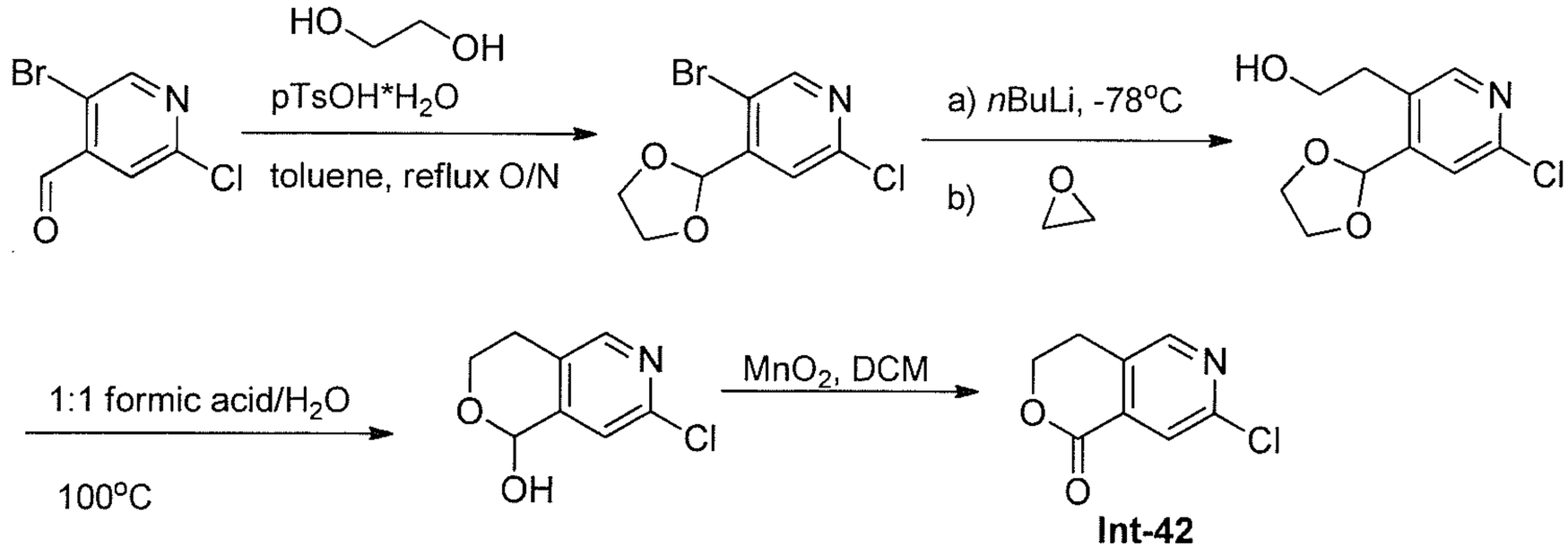
[00358] To a solution of 2,2-difluoro-2-[2-(hydroxymethyl)phenyl]ethanol (0.905 g, 4.81 mmol) in chloroform (60.13 mL, 751.6 mmol) was added MnO_2 (5.284 g, 60.78 mmol) at rt, and the

mixture was stirred for 18h at 50 °C. After cooling to room temp, the reaction was filtered through a Celite pad and the residual solid was rinsed with EtOAc several times. The filtrate was concentrated in vacuo to afford the title compound Yield = 642 mg. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 (d, J = 7.7 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.73 (t, J = 7.4 Hz, 1H), 4.71 (t, J = 10.7 Hz, 2H). LC/MS (FA): M+H = 185.

[00359] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the appropriate starting materials:

Entry	Starting material	Product (Int #)	NMR Data
1		 **Int-40**	^{1}H NMR (400 MHz, DMSO-d6) δ 8.08 – 8.05 (m, 1H), 8.02 (dd, J = 8.3, 2.2 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 5.00 (t, J = 11.6 Hz, 2H)
2		 **Int-41**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.03 (dd, J = 4.8, 1.7 Hz, 1H), 8.51 (dq, J = 8.0, 1.3 Hz, 1H), 7.77 – 7.65 (m, 1H), 4.80 (t, J = 11.0 Hz, 2H)

Example 25: 7-Chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-one Int-42



Step 1: 5-Bromo-2-chloro-4-(1,3-dioxolan-2-yl)pyridine

[00360] To a solution of 5-bromo-2-chloropyridine-4-carboxaldehyde (5.235 g, 23.75 mmol) and1,2-ethanediol (6.62 mL, 119 mmol) in toluene (36.0 mL) was added p-toluenesulfonic acid monohydrate (0.226 g, 1.19 mmol). The reaction flask was fitted with a Dean-Stark trap (which

was fitted with a reflux condenser), and the reaction mixture was stirred at reflux under argon for 17 h. The reaction was cooled to rt, diluted with EtOAc, and transferred to a separatory funnel. The mixture was washed with saturated $NaHCO_3$ (2x) and brine, then dried over Na_2SO_4, filtered, and concentrated. The dark brown oil was purified by silica gel column chromatography (0 to 15% EtOAc in hexanes) to give 6.00 g (96%) of product as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.65 (s, 1H), 7.58 (s, 1H), 5.95 (s, 1H), 4.13 – 3.97 (m, 4H); LCMS: (AA) M+1 264.0/266.0

Step 2: 2-[6-Chloro-4-(1,3-dioxolan-2-yl)pyridin-3-yl]ethanol

[00361] 5-bromo-2-chloro-4-(1,3-dioxolan-2-yl)pyridine (5.60 g, 21.2 mmol) was dissolved in THF (35.29 mL) under argon, and the resulting yellow solution was cooled to -78°C. To the mixture was added dropwise 2.50 M of *n*-BuLi in hexanes (11.85 mL, 29.64 mmol), keeping the internal temperature less than -70 °C. The resulting brown mixture was stirred for 1 hour at -78 °C, at which point 2.50 M of ethylene oxide in THF (12.70 mL, 31.76 mmol) was added dropwise via syringe. The reaction was stirred for 5 min, and then boron trifluoride etherate (4.829 mL, 38.11 mmol) was added dropwise, keeping the temperature below -70 °C. The reaction was stirred at -78°C for 1hour. The reaction was quenched by addition of saturated $NaHCO_3$ (26 mL) and brine (26 mL), and the reaction was allowed to warm up to rt. The layers were separated, and the aqueous layer was extracted with EtOAc (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The yellow oil was purified by silica gel column chromatography (0 to 100% EtOAc in hexane) to afford 0.973 g (20%) of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.30 (s, 1H), 7.44 (s, 1H), 6.01 (s, 1H), 4.75 (t, J = 5.2 Hz, 1H), 4.09 – 3.95 (m, 4H), 3.64 – 3.56 (m, 2H), 2.85 (t, J = 6.6 Hz, 2H); LCMS: (AA) M+1 230.0/232.0

Step 3: 7-Chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-ol

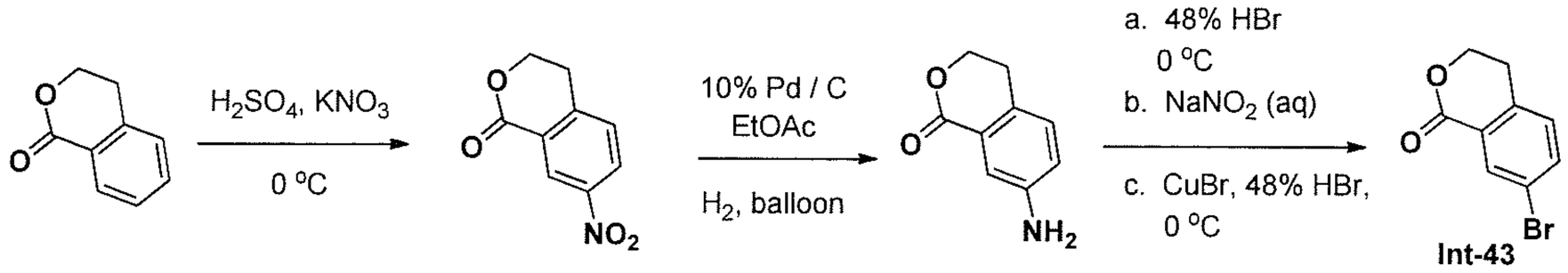
[00362] A solution of 2-[6-chloro-4-(1,3-dioxolan-2-yl)pyridin-3-yl]ethanol (972.0 mg, 4.232 mmol) in formic acid (14.53 mL, 385.1 mmol) and water (14.49 mL, 804.1 mmol) was stirred at 100°C for 3 h. The reaction was cooled to rt, diluted with EtOAc, transferred to separatory funnel and washed with saturated $NaHCO_3$ (2x) and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford 719 mg (82%) crude title compound as a beige solid, which was used in the next step without purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.26 (s, 1H), 7.31 (s, 1H), 7.09 (d, J = 6.3 Hz, 1H), 5.76 (d, J = 6.3 Hz, 1H), 4.06 – 3.97 (m, 1H), 3.89 – 3.82 (m, 1H), 2.79 – 2.71 (m, 2H); LCMS: (AA) M+1 186.1/188.1

Step 4: 7-Chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-one

[00363] To a solution of 7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-ol (708.0 mg, 3.814 mmol) in DCM (141.3 mL) was added MnO_2 (3.32 g, 38.1 mmol), and the mixture was stirred at rt for 23 h. The reaction was filtered through a pad of Celite, and the filter cake was washed with EtOAc. The filtrate was concentrated in vacuo to give 572 mg (82%) of the title compound as a yellow

solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.62 – 8.58 (m, 1H), 7.83 (s, 1H), 4.59 (t, J = 6.0 Hz, 2H), 3.10 (t, J = 6.0 Hz, 2H); LCMS: (AA) M+1 184.0/186.0

Example 26: 7-Bromo-3,4-dihydro-1H-isochromen-1-one Int-43



Step 1: 7-Nitro-3,4-dihydro-1H-isochromen-1-one

[00364] A 3-neck 1L round bottom flask was charged with 18.4 M sulfuric acid in water (55.6 mL, 1020 mmol) and cooled to 0 °C . Isochroman-1-one (20.00 g, 135.0 mmol) was added dropwise over 30 min, keeping the internal temperature less than +5 °C . A solution of potassium nitrate (13.8 g, 136 mmol) in 18.4 M sulfuric acid in water(77.8 mL, 1430 mmol) was added dropwise over 100 min, keeping the internal temperature less than or equal to 0 °C. The mixture was warmed to rt and poured onto ice and water to afford a white precipitate. This heterogeneous mixture was stirred at rt, and then the white solid product was isolated by vacuum filtration. The filter cake was allowed dry by pulling vacuum through it over the weekend, and then purified by ISCO chromatography eluting with a hexanes / EtOAc gradient to afford the title compound as a white solid, 18g (70%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.28 – 8.19 (m, 1H), 7.70 – 7.60 (m, 1H), 7.20 – 7.11 (m, 1H), 4.60 – 4.46 (m, 2H), 3.08 – 2.96 (m, 2H).

Step 2: 7-Amino-3,4-dihydro-1H-isochromen-1-one

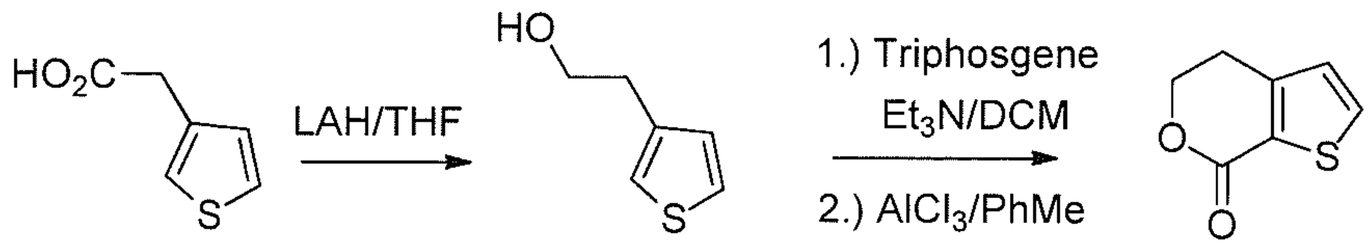
[00365] A 1L round bottom flask was charged with 7-nitro-3,4-dihydro-1H-isochromen-1-one (12.24 g, 63.37 mmol) and EtOAc (250 mL). To this solution was added 10% palladium on carbon (1.00 g), and the reaction mixture was stirred under balloon pressure of hydrogen for 18h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford a white solid which was used as is in the following step.

Step 3: 7-Bromo-3,4-dihydro-1H-isochromen-1-one

[00366] A 1L round bottom flask was charged with 7-amino-3,4-dihydro-1H-isochromen-1-one (13.40 g, 82.12 mmol) and 8.90 M of hydrobromic acid in water (134 mL, 1190 mmol), and the resulting mixture was cooled in an ice bath. To this white suspension was added an ice cooled solution of sodium nitrite (5.66 g, 82.1 mmol) in ~2mL water dropwise keeping the internal temperature less than +5 °C . In a separate flask, copper(I) bromide (11.8 g, 82.1 mmol) and 8.90 M hydrobromic acid in water(26.8 mL, 238 mmol) were combined and cooled in an ice bath, at which point this solution was rapidly added to the first solution . The reaction mixture was allowed to warm to rt, and then ~1L water was added. The resulting tan precipitate was isolated

by vacuum filtration and dried under vacuum overnight. The solid was then subjected to ISCO chromatography eluting with a hexanes / EtOAc gradient to afford a pale brown solid, 12.91g (69%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.29 – 8.17 (m, 1H), 7.73 – 7.57 (m, 1H), 7.19 – 7.11 (m, 1H), 4.61 – 4.44 (m, 2H), 3.09 – 2.95 (m, 2H).

Example 27: 4,5-Dihydro-7H-thieno[2,3-c]pyran-7-one Int-44



Int-44

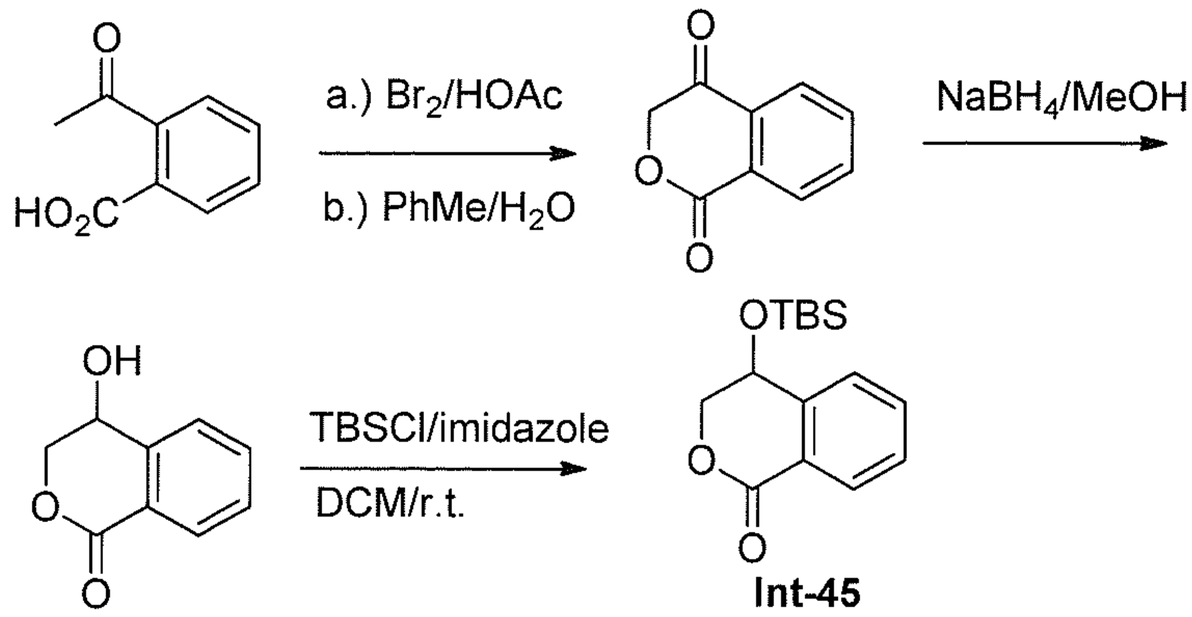
Step 1: 2-(3-Thienyl)ethanol

[00367] A solution of thiophene-3-acetic acid (4.982 g, 35.04 mmol) in THF (120 mL, 1500 mmol) was cooled to 0 °C, and lithium tetrahydroaluminate (1.596 g, 42.05 mmol) was added slowly over 15 min. The reaction was allowed to warm to rt and stirred for 2hrs. The reaction was quenched via addition of water (5 mL) and EtOAc (10ml). The mixture was filtered, and the filter cake was washed with 30ml EtOAc. The filtrate was concentrated in vacuo to afford the title compound (3.59 g). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.31 (dd, J = 4.9, 3.0 Hz, 1H), 7.11 – 7.05 (m, 1H), 7.05 – 6.97 (m, 1H), 3.87 (t, J = 6.4 Hz, 2H), 2.92 (t, J = 6.4 Hz, 2H), 1.71 (s, 1H).

Step 2: 4,5-Dihydro-7H-thieno[2,3-c]pyran-7-one

[00368] A solution of 2-(3-thienyl)ethanol (2.18 g, 17.0 mmol) in DCM (60.0 mL, 936 mmol) was cooled to 0 °C, then triphosgene (3.2801 g, 11.054 mmol) was added and the reaction was stirred for 15 min at 0 °C. N,N-diisopropylethylamine (4.4431 mL, 25.508 mmol) was added dropwise to the solution over 15 min, and the resulting mixture was warmed to rt and stirred for 1hr. The solution was poured into 80 ml 1N HCl solution, the layers were separated, and the aqueous layer was extracted 2 x 60ml DCM. The combined organic layers were concentrated in vacuo to afford crude intermediate chloroformate (3.18g), which was dissolved into toluene (50.0 mL, 469 mmol) and cooled to 0 °C. Aluminum trichloride (3.4013 g, 25.508 mmol) was added to this solution at 0 °C and the resulting mixture was warmed to rt and stirred for 1hr. The reaction was quenched via addition of a solution of sodium potassium tartrate tetrahydrate (28.796 g, 102.03 mmol) in 150 ml water. The layers were separated, and the aqueous layer was extracted 3 x 60 ml EtOAc. The combined organic layers were concentrated in vacuo and purified by flash column (80g column, eluent was 0-70% EtOAc) to afford the title compound as brown solid (1.124g, 43%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (d, J = 5.0 Hz, 1H), 7.02 (d, J = 5.0 Hz, 1H), 4.66 – 4.50 (m, 2H), 3.04 (t, J = 6.2 Hz, 2H).

Example 28: 4-{[tert-Butyl(dimethyl)silyl]oxy}-3,4-dihydro-1H-isochromen- 1-one Int-45



Step 1: 1H-Isochromene-1,4(3H)-dione

[00369] To a solution of 2-acetylbenzoic acid (8.458 g, 51.52 mmol) in acetic acid (50.0 mL, 879 mmol) was added 30 ml of 33% HBr in acetic acid. Bromine (8.646 g, 54.10 mmol) was next added to the solution, and the reaction was heated to 40 °C with stirring for 30 min. The reaction mixture was poured into 300 ml water, the layers were separated, and the aqueous layer was extracted with 3 x 100ml DCM. Combined the organic layers and concentrated in vacuo to yield crude intermediate, which was dissolved in 25 ml acetic acid, 130ml toluene and 30 ml water. The resulting mixture was stirred at reflux overnight. The reaction was cooled to rt, and the layers were separated. The organic layer was concentrated in vacuo and purified by flash column (120g column, eluent 0-55% EtOAc in hexane)to afford 5.24g (63%) of title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.36 – 8.28 (m, 1H), 8.17 – 8.07 (m, 1H), 7.95 – 7.79 (m, 2H), 5.16 (s, 2H).

Step 2: 4-Hydroxy-3,4-dihydro-1H-isochromen-1-one

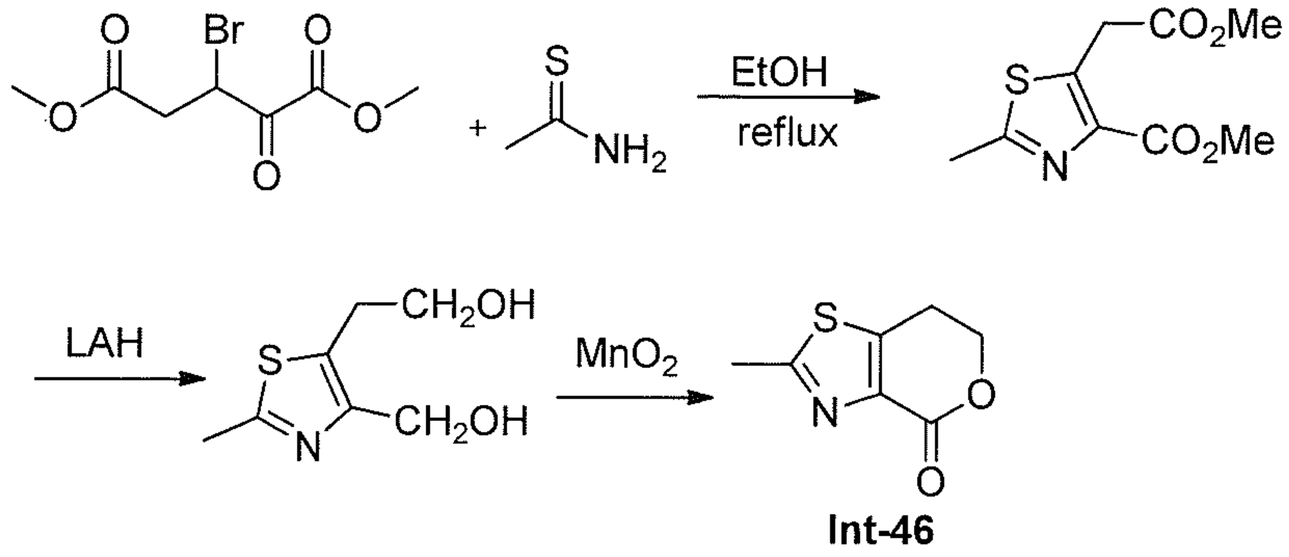
[00370] A solution of 1H-isochromene-1,4(3H)-dione (3.05 g, 18.8 mmol) in methanol (60.0 mL, 1480 mmol), was cooled to 0 °C, and sodium tetrahydroborate (1.067 g, 28.22 mmol) was added. The reaction was allowed to warm to rt and stirred for 60 min. The mixture was poured into 200 ml water, the layers were separated, and the aqueous layer was extracted 3 x 60 ml DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo to yield 2.69g (87%) the title compound. LCMS (AA) M+1 165

Step 3: 4-{[tert-Butyl(dimethyl)silyl]oxy}-3,4-dihydro-1H-isochromen-1-one

[00371] To a round bottom flask was added 4-hydroxy-3,4-dihydro-1H-isochromen-1-one (0.3052 g, 1.859 mmol), 1H-imidazole (0.5063 g, 7.437 mmol), 60 ml DCM, and tert-butyldimethylsilyl chloride (0.8406 g, 5.578 mmol) . The resulting reaction mixture was stirred at rt for 4hrs. The mixture was concentrated in vacuo, and the residue was suspended in EtOAc. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed (100% hexanes as eluent) to provide the title compound (0.5812g, 90%) as an oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 (dd, J = 8.1, 1.3 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.39 – 7.31 (m, 2H), 4.91 (dd, J = 8.5, 4.4 Hz, 1H), 4.33 (dd, J = 10.8, 4.4 Hz, 1H), 4.18 (dd, J = 10.8,

8.5 Hz, 1H), 0.84 (s, 9H), 0.07 (d, J = 8.8 Hz, 6H).

Example 29: 2-Methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-one Int-46



Int-46

Step 1: Methyl 5-(2-methoxy-2-oxoethyl)-2-methyl-1,3-thiazole-4-carboxylate

[00372] To a solution of methyl 3-bromo-2-oxopentanedioate (23 g, 73 mmol) in methanol (250.0 mL, 6172 mmol) was added ethanethioamide (10.65 g, 141.8 mmol). The mixture was stirred at reflux for 2 hrs, and then cooled to rt. The volatiles were removed in vacuo and the residue was suspended in 25ml THF and 40 ml hexane with stirring. The solid (ethanethioamide) was filtered and the filtrate was concentrated and purified by flash column (120g column, eluent was 0-70% EtOAc in hexane) to provide 10.01g (60%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.27 (s, 2H), 3.90 (s, 3H), 3.72 (d, J = 2.2 Hz, 3H), 2.69 (s, 3H).

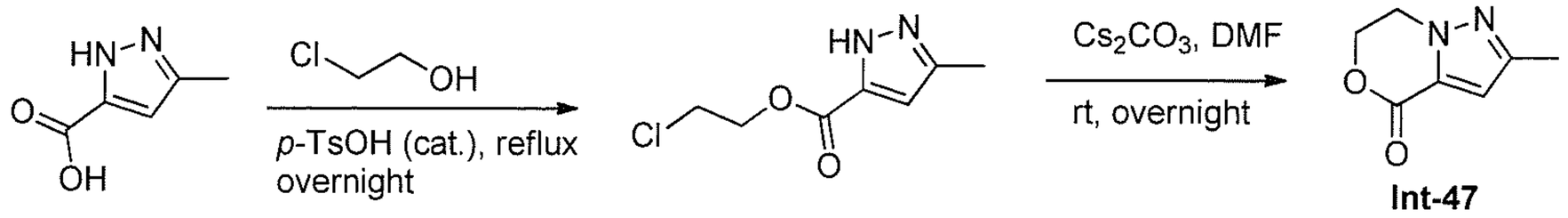
Step 2: 2-[4-(Hydroxymethyl)-2-methyl-1,3-thiazol-5-yl]ethanol

[00373] To a solution of ethyl 5-(2-methoxy-2-oxoethyl)-2-methyl-1,3-thiazole-4-carboxylate (1.79 g, 7.81 mmol) in THF (50.0 mL, 616 mmol) was added lithium tetrahydroaluminate (0.5927 g, 15.62 mmol) and the mixture was stirred for 20 min. Reaction was quenched by addition of 2 ml water, the solid was filtered and the filter cake was washed with 30 ml methanol. The filtrate was concentrated and purified by flash column (40g column, eluent 0-20% methanol in EtOAc) to provide 0.7121g (53%) of the title compound.^{1}H NMR (400 MHz, Chloroform-d) δ 4.61 (s, 2H), 3.79 (t, J = 5.8 Hz, 2H), 3.03 (t, J = 5.8 Hz, 2H), 2.63 (s, 3H).

Step 3: 2-Methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4- one

[00374] To a solution of 2-[4-(hydroxymethyl)-2-methyl-1,3-thiazol-5-yl]ethanol (0.09262 g, 0.5346 mmol) in DCM (10.0 mL, 156 mmol) was added MnO_2 (1.859 g, 21.39 mmol) and the reaction was stirred at rt overnight. The solid was filtered, and the filtrate was concentrated in vacuo and purified by flash column (24g column, eluent was 0-60% EtOAc in hexanes) to provide 0.0244g (27%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.54 (t, J = 6.1 Hz, 2H), 3.13 (t, J = 6.1 Hz, 2H), 2.67 (s, 3H).

Example 30: 2-Methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin- 4-one Int-47



Int-47

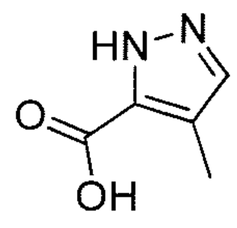
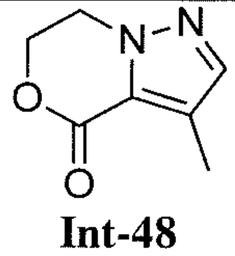
Step 1: 2-Chloroethyl 3-methyl-1H-pyrazole-5-carboxylate

[00375] To a solution of 3-methyl-5-pyrazolecarboxylicacid (1.00 g, 7.93 mmol) in 2-chloroethanol (7.97 mL) was added p-toluenesulfonic acid monohydrate (603 mg, 3.17 mmol) and the reaction mixture was heated to 115 °C with stirring overnight. The mixture was cooled to rt and the solvent was removed in vacuo. The residue was diluted with EtOAc and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography (0 to 80% EtOAc in hexanes) to give 728 mg (49%) of the title product as a colorless solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 10.56 (s, 1H), 6.64 (s, 1H), 4.56 (t, J = 5.9 Hz, 2H), 3.79 (t, J = 5.9 Hz, 2H), 2.37 (s, 3H); LCMS (FA): m/z = 189.0 (M+H).

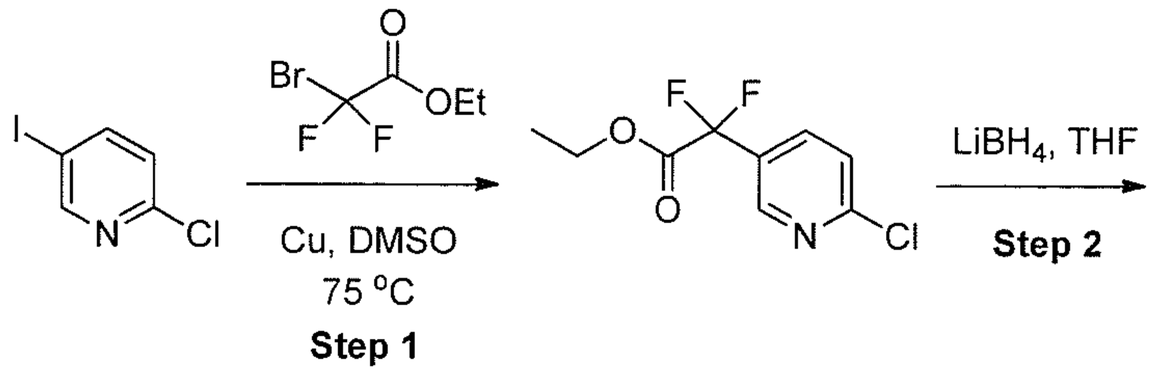
Step 2: 2-Methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin- 4-one

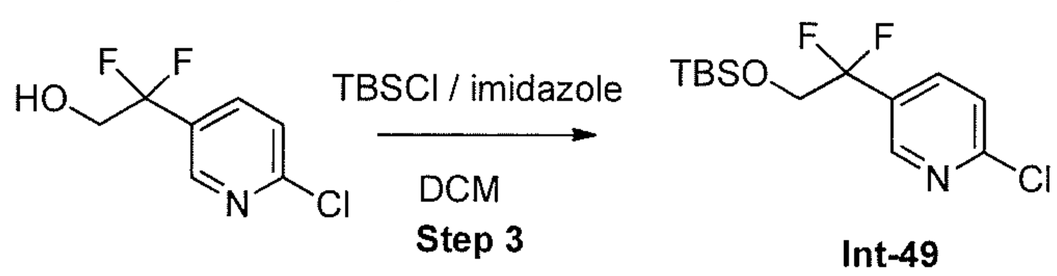
[00376] To a solution of 2-chloroethyl 5-methyl-1H-pyrazole-3-carboxylate (690 mg, 3.66 mmol) in DMF (2.34 mL) was added Cs_2CO_3 (1.79 g, 5.49 mmol) and the reaction was stirred at rt overnight. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (0 to 100% EtOAc in hexanes) to provide 299 mg (54%) of the title product as a colorless solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.77 (s, 1H), 4.71 – 4.66 (m, 2H), 4.42 – 4.36 (m, 2H), 2.34 (s, 3H); LCMS (FA): m/z = 153.1(M+H).

[00377] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Starting material	Product (Int #)	NMR Data
	 Int-48	^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 (s, 1H), 4.70-4.60 (m, 1H), 4.40-4.30 (m, 1H), 2.30 (s, 3H).

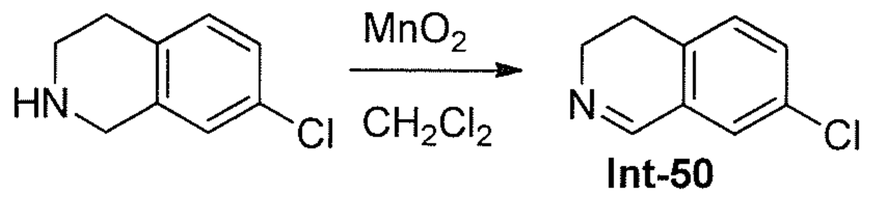
Example 31: 5-(2-{[tert-Butyl(dimethyl)silyl]oxy}-1,1-difluoroethyl)-2-chloropyridine Int-49





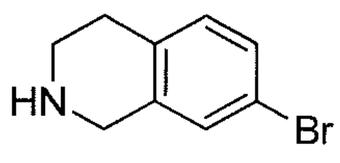
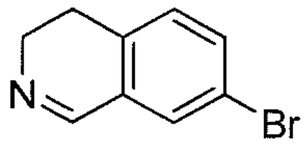
[00378] Steps 1 and 2 were performed in an analogous fashion to that described in **Example 24**, steps 1 and 2. Step 3 was performed in an analogous fashion to that described in **Example 4**, step 2. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.54 (d, J = 1.7 Hz, 1H), 7.78 (dd, J = 8.3, 2.5 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 3.98 (t, J = 11.8 Hz, 2H), 0.84 (s, 9H), 0.02 (s, 6H).

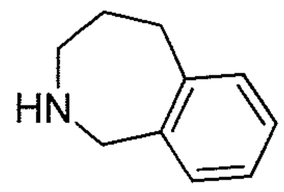
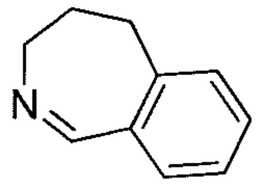
Example 32: 7-Chloro-3,4-dihydroisoquinoline Int-50



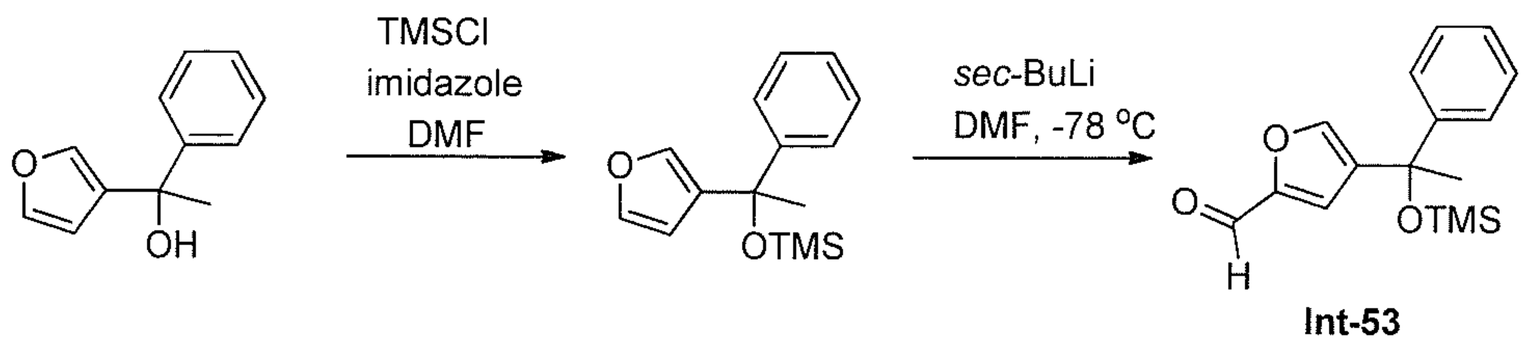
[00379] To a solution of 7-chloro-1,2,3,4-tetrahydro-isoquinoline (1.15 g, 6.86 mmol) in DCM (70.0 mL, 1090 mmol) was added MnO_2 (5.96 g, 68.6 mmol) at rt, and the mixture was stirred for 16h. The reaction was filtered through a Celite pad and the residual solid was rinsed with DCM several times. The filtrate was concentrated in vacuo and the residue was purified by ISCO silica gel column chromatography (40g, eluting with 50% EtOAc in DCM, 50mL/min flow) to give 915 mg of the title compound as colorless solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (t, J = 2.1 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.46 (dd, J = 8.0, 2.3 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 3.70 – 3.63 (m, 2H), 2.71 – 2.65 (m, 2H).

[00380] The compounds listed in the table below was prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Starting material	Product (Int #)	NMR Data
	 Int-51	^{1}H NMR (400 MHz, Chloroform-d) δ 8.30 (t, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.0, 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 3.87 – 3.73 (m, 2H), 2.80 – 2.64 (m, 2H).

	 **Int-52**	^{1}H NMR (400 MHz, Chloroform-d) δ 8.52 (s, 1H), 7.38 – 7.31 (m, 3H), 7.26 – 7.22 (m, 1H), 3.64 (t, J = 5.6 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 2.35 – 2.24 (m, 2H).

Example 33: **rac-4-{1-Phenyl-1-[(trimethylsilyl)oxy]ethyl}-2-furaldehyde Int-53**



Int-53

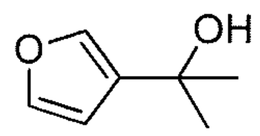
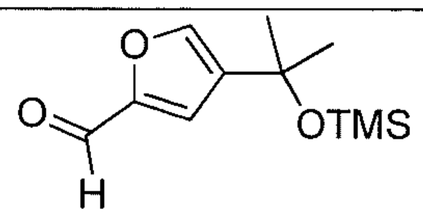
Step 1: rac-1-(3-Furyl)-1-phenylethoxy](trimethyl)silane.

[00381] 1-(3-Furyl)-1-phenylethanol (1.53 g, 8.13 mmol) was dissolved in DMF (8.62 mL) and the solution was cooled to 0 °C. Imidazole (1.66 g, 24.4 mmol) and TMSCl (1.55 mL, 12.2 mmol) were added. The reaction was allowed to warm to rt and stirred for 1 hour. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to afford 2.11 g (99%) of the title product as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.38 (m, 2H), 7.34 – 7.27 (m, 4H), 7.24 – 7.17 (m, 1H), 6.22 – 6.16 (m, 1H), 1.86 (s, 3H), 0.04 (s, 9H).

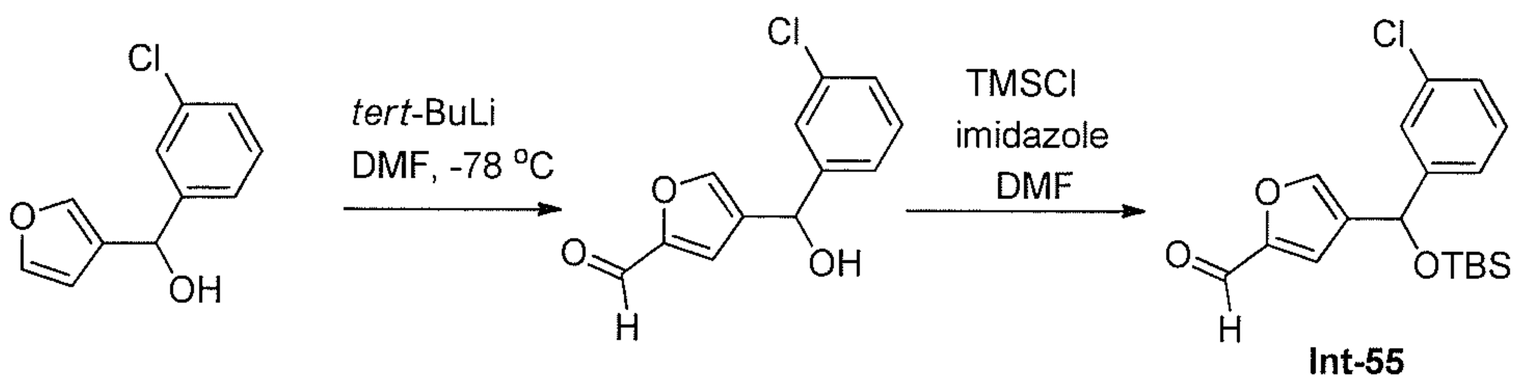
Step 2: rac-4-{1-Phenyl-1-[(trimethylsilyl)oxy]ethyl}-2-furaldehyde.

[00382] [1-(3-Furyl)-1-phenylethoxy](trimethyl)silane (1.32 g, 5.07 mmol) was dissolved in THF (23.3 mL), and then cooled at -78 °C. 1.40 M of *sec*-BuLi in cyclohexane (4.71 mL, 6.59 mmol) was added to the solution at -78 °C. After 30 min, DMF (1.18 mL, 15.2 mmol) was added to the solution and the resulting mixture was stirred for 10 min. The reaction was quenched by adding saturated aqueous NH_4Cl, warmed to rt and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 10% EtOAc in hexanes as eluent) to give 1.02 g (70%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.56 (s, 1H), 7.58 – 7.54 (m, 1H), 7.42 – 7.37 (m, 2H), 7.35 – 7.29 (m, 2H), 7.25 – 7.22 (m, 1H), 7.04 – 7.02 (m, 1H), 1.92 (s, 3H), 0.04 (s, 9H).

[00383] The compounds listed in the table below was prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Starting material	Product / Int-No.	Characterization Data
	 **Int-54**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.62 (s, 1H), 7.53 (s, 1H), 7.19 (d, *J* = 0.8 Hz, 1H), 1.56 (s, 6H), 0.10 (s, 9H).^{1}H NMR

Example 34**: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-2-furaldehyde Int-55**



Int-55

Step 1: rac-4-[(3-Chlorophenyl)(hydroxy)methyl]-2-furaldehyde.

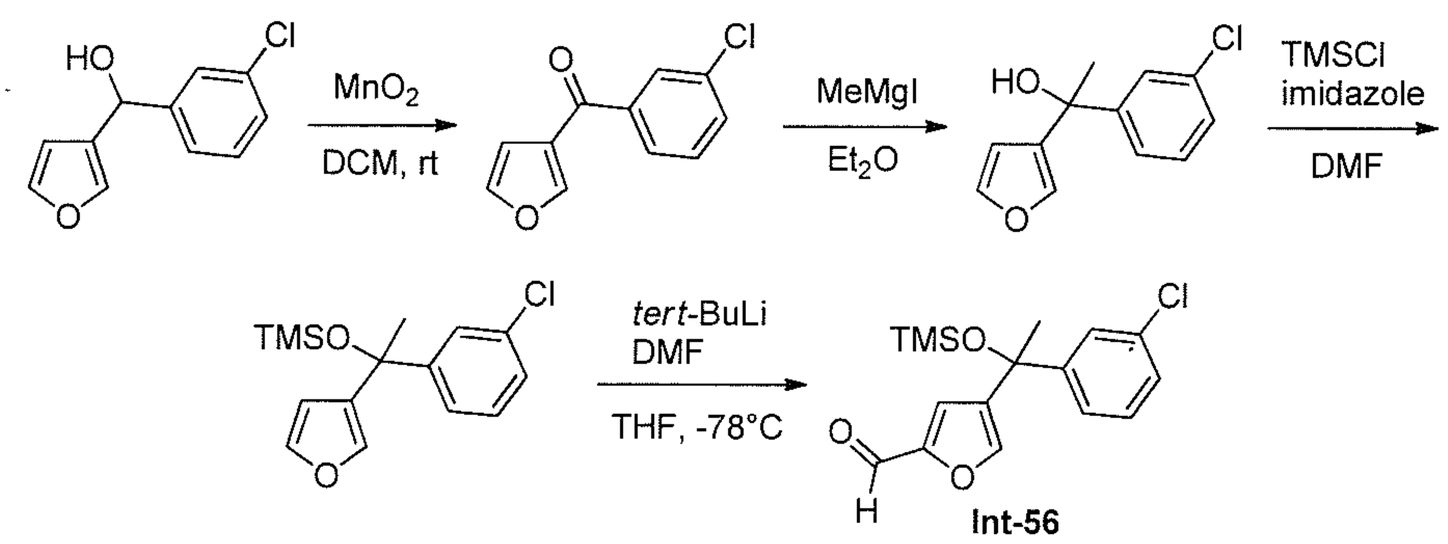
[00384] To a solution of rac-(3-chlorophenyl)(3-furyl)methanol (2.00 g, 9.58 mmol) in Et_2O (40.0 mL) was added 1.70 M of *tert*-BuLi in pentane (14.1 mL, 24.0 mmol) at -78 °C. After stirring at -78 °C for 30 min, DMF (1.11 mL, 14.4 mmol) was added to the mixture. Then, the reaction mixture was warmed to 0 °C and stirred for 1 hour. The reaction mixture was poured into saturated aqueous NH_4Cl at rt and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% - 30% EtOAc in hexanes as eluent) to give 862 mg (38%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (d, *J* = 0.6 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.42 – 7.36 (m, 1H), 7.34 – 7.24 (m, 3H), 7.15 – 7.08 (m, 1H), 5.79 (s, 1H), 2.57 – 2.38 (br s, 1H).

Step 2: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-2-furaldehyde.

[00385] To a solution of rac-4-[(3-chlorophenyl)(hydroxy)methyl]-2-furaldehyde (550 mg, 2.32 mmol) in DMF (10.0 mL) were added imidazole (396 mg, 5.81 mmol) and TBSCl (420 mg, 2.78 mmol) at rt. After overnight, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography

(0% - 10% EtOAc in hexanes as eluent) to give 478 mg (59%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.57 (d, *J* = 0.6 Hz, 1H), 7.53 (d, *J* = 0.8 Hz, 1H), 7.35 (t, *J* = 1.7 Hz, 1H), 7.31 – 7.21 (m, 3H), 7.07 – 7.03 (m, 1H), 5.69 (s, 1H), 0.91 (s, 9H), 0.06 (s, 3H), -0.01 (s, 3H).

Example 35: **rac-4-{1-(3-Chlorophenyl)-1-[(trimethylsilyl)oxy]ethyl}-2-furaldehyde Int-56**



Step 1: (3-Chlorophenyl)(3-furyl)methanone.

[00386] To a solution of rac-(3-chlorophenyl)(3-furyl)methanol (1.81 g, 8.68 mmol) in DCM (30.0 mL) was added MnO_2 (11.3 g, 130 mmol) at rt. After stirring overnight, the reaction mixture was filtered through a Celite pad, and washed with DCM. The filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 1.60 g (90%) of the title compound as a white powder. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 1.4, 0.8 Hz, 1H), 7.83 (t, *J* = 1.7 Hz, 1H), 7.73 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 6.90 (dd, *J* = 1.9, 0.8 Hz, 1H).

Step 2: rac-1-(3-Chlorophenyl)-1-(3-furyl)ethanol.

[00387] To a solution of (3-chlorophenyl)(3-furyl)methanone (1.60 g, 7.74 mmol) in Et_2O (30 mL) was added 3.0 M of MeMgI in Et_2O (3.87 mL, 11.6 mmol) at 0 °C. After stirring at 0 °C for 1 hour, the reaction mixture was poured into saturated aqueous NH_4Cl at rt and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% - 30% EtOAc in hexanes as eluent) to give 1.48 g (86%) of the title compound as a pale red oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.47 (m, 1H), 7.39 – 7.37 (m, 1H), 7.35 – 7.30 (m, 2H), 7.29 – 7.21 (m, 2H), 6.35 – 6.24 (m, 1H), 2.15 – 2.07 (br s, 1H), 1.85 (s, 3H).

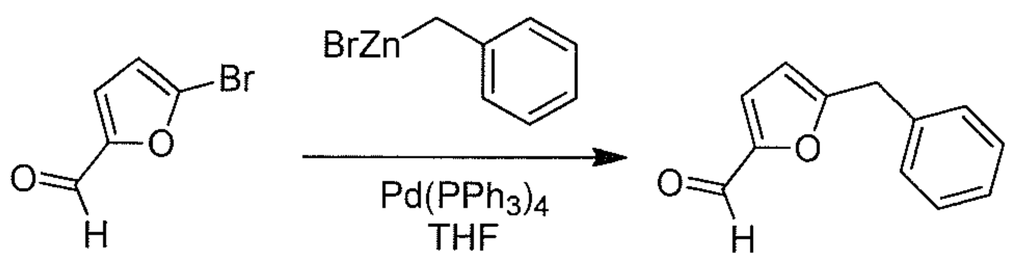
Step 3: rac-[1-(3-Chlorophenyl)-1-(3-furyl)ethoxy](trimethyl)silane.

[00388] To a solution of rac-1-(3-chlorophenyl)-1-(3-furyl)ethanol (1.48 g, 6.65 mmol) in DMF (20.0 mL) were added imidazole (1.13 g, 16.6 mmol) and TMSCl (1.01 mL, 7.98 mmol) at rt. After stirring overnight, the reaction mixture was poured into saturated aqueous $NaHCO_3$ at rt and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (100% hexanes as eluent) to give 1.65 g (84%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.40 (m, 1H), 7.37 – 7.34 (m, 1H), 7.34 – 7.31 (m, 1H), 7.27 – 7.16 (m, 3H), 6.20 – 6.12 (m, 1H), 1.84 (s, 3H), 0.05 (s, 9H).

Step 4: rac-4-{1-(3-Chlorophenyl)-1-[(trimethylsilyl)oxy]ethyl}-2-furaldehyde.

[00389] To a solution of rac-[1-(3-chlorophenyl)-1-(3-furyl)ethoxy](trimethyl)silane (1.64 g, 5.56 mmol) in Et_2O (20.0 mL) was added 1.70 M of *tert*-BuLi in pentane (4.91 mL, 8.34 mmol) at -78 °C. After stirring at -78 °C for 30 min, DMF (0.65 mL, 8.34 mmol) was added to the mixture. Then, the reaction mixture was allowed to warm to 0 °C and stirred for 1 hour. The reaction mixture was poured into saturated aqueous NH_4Cl at rt and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 549 mg (31%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.60 – 7.56 (m, 1H), 7.42 – 7.37 (m, 1H), 7.26 – 7.20 (m, 3H), 7.02 (d, J = 0.9 Hz, 1H), 1.90 (s, 3H), 0.06 (s, 9H).

Example 36**: 5-Benzyl-2-furaldehyde Int-57**



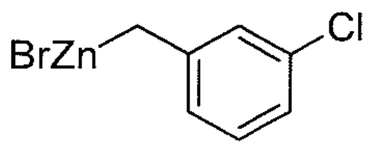
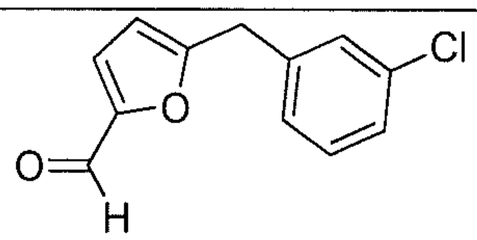
Int-57

Step 1: 5-Benzyl-2-furaldehyde.

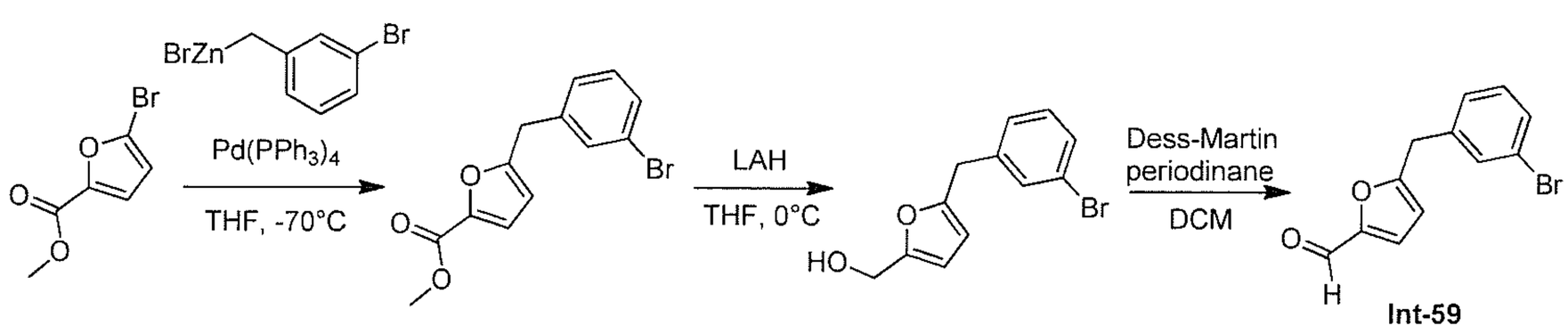
[00390] A solution of 5-bromo-2-furaldehyde (1.00 g, 5.72 mmol) and $Pd(PPh_3)_4$ (132 mg, 0.11 mmol) in THF (35.7 mL) was degassed with argon gas. 0.50 M of benzylzinc bromide in THF (14.3 mL, 7.14 mmol) was added, and the reaction mixture was then stirred at 70 °C for 2 h. The solution was concentrated to remove the solvent and diluted with EtOAc. The organic layer was washed with 1M HCl, saturated $NaHCO_3$, and brine. The resulting solution was dried over $MgSO_4$, filtered and then concentrated in vacuo. The crude material was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 554 mg of the title

compound (52%) as an orange residue. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (s, 1H), 7.48 (d, J = 3.5 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.32 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 4.12 (s, 2H). LCMS (FA): m/z=187.2 (M+H).

[00391] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the corresponding starting materials:

Grignard reagent	Product / Int No.	Characterization Data
	 **Int-58**	LCMS (FA): m/z = 221.3 (M+H).

Example 37**: 5-(3-Bromobenzyl)-2-furaldehyde Int-59**



Step 1: Methyl 5-(3-bromobenzyl)-2-furoate.

[00392] A microwave reaction tube was charged with methyl 5-bromofuran-2-carboxylate (775 mg, 3.78 mmol) and $Pd(PPh_3)_4$ (218 mg, 0.19 mmol). The flask was sealed and purged with argon for 5 min, and then THF (10.0 mL) was added to the reaction vessel. 0.5 M of 3-bromobenzylzincbromide in THF (8.32 mL, 4.16 mmol) was then added to the solution and the reaction was heated at 70 °C for 1 day. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 0.60 g (54%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.36 (m, 2H), 7.20 – 7.16 (m, 2H), 7.10 (d, J = 3.4 Hz, 1H), 6.11 (d, J = 3.4 Hz, 1H), 4.01 (s, 2H), 3.88 (s, 3H).

Step 2: [5-(3-Bromobenzyl)-2-furyl]methanol

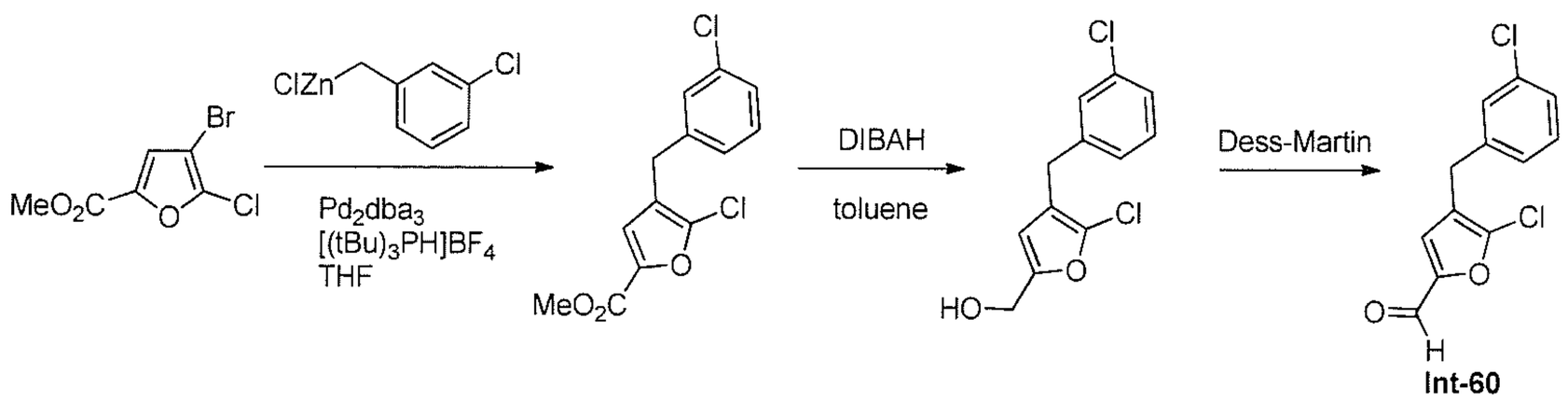
[00393] To a round bottom flask was added methyl 5-(3-bromobenzyl)-2-furoate (733 mg, 2.48 mmol) in THF (8.00 mL) and cooled at 0 °C. 1.0 M of lithium tetrahydroaluminate in Et_2O (3.23

mL, 3.23 mmol) was then added slowly and the resulting mixture was stirred at 0 °C for 2 h. Added 1mL of water slowly to quench reaction mixture, then added solid Na_2SO_4. The mixture was stirred at rt for 1 hour and then filtered through a pad of Celite. The filtrate was concentrated to dryness and no further purification was done to give 610 mg of crude title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.37 (m, 1H), 7.32 – 7.28 (m, 1H), 7.25 – 7.21 (m, 2H), 7.18 – 7.15 (m, 1H), 6.22 – 6.17 (m, 1H), 5.98 – 5.91 (m, 1H), 4.56 (s, 2H), 3.94 (d, *J* = 13.7 Hz, 2H).

Step 3: 5-(3-Bromobenzyl)-2-furaldehyde

[00394] Into a round bottom flask was added crude [5-(3-bromobenzyl)-2-furyl]methanol (609 mg, 2.28 mmol) dissolved in DCM (10.0 mL). Dess-Martin periodinane (1.16 g, 2.74 mmol) was added and the resulting reaction mixture was stirred at rt for 1 hour. The reaction was then quenched by the addition of saturated $Na_2S_2O_3$ and extracted with DCM (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 167 mg (28%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.56 (s, 1H), 7.43 – 7.37 (m, 2H), 7.23 – 7.14 (m, 3H), 6.22 (d, *J* = 3.5 Hz, 1H), 4.03 (s, 2H).

Example 38: **5-Chloro-4-(3-chlorobenzyl)-2-furaldehyde Int-60**



Int-60

Step 1: Methyl 5-chloro-4-(3-chlorobenzyl)-2-furoate.

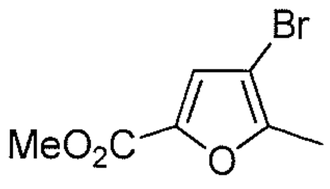
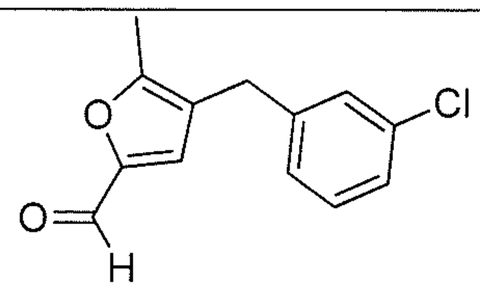
[00395] To a solution of methyl 4-bromo-5-chloro-2-furoate (1.20 g, 5.01 mmol) in THF (20.0 mL), degassed with nitrogen gas) were added $Pd_2(dba)_3$ (184 mg, 0.20 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (116 mg, 0.40 mmol) at rt. After stirring at rt for 10 min, 0.5 M of 3-chlorobenzylzinc chloride in THF (15.0 mL, 7.52 mmol) was added to the mixture. After stirring at rt for 4 h, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 628 mg (44%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 –7.21 (m, 2H), 7.20 – 7.16 (m, 1H), 7.11 –7.06 (m, 1H), 7.01 (s, 1H), 3.89 (s, 3H), 3.74 (s, 2H).

Step 2: [5-Chloro-4-(3-chlorobenzyl)-2-furyl]methanol.

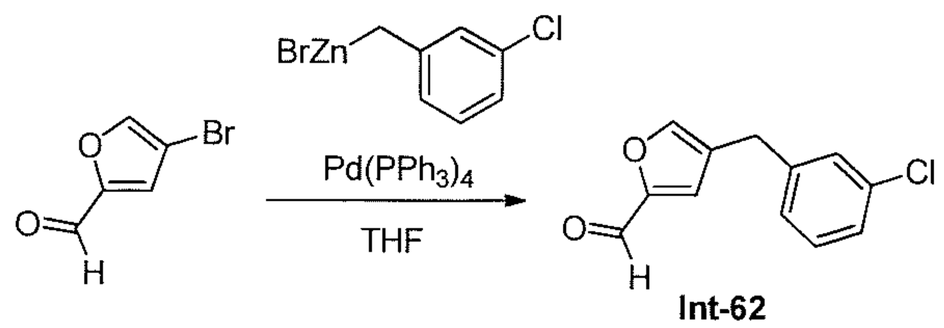
[00396] To a solution of methyl 5-chloro-4-(3-chlorobenzyl)-2-furoate (700 mg, 2.46 mmol) in toluene (10.0 mL) was added 1.0 M of DIBAL-H in toluene (6.14 mL, 6.14 mmol) at -78 °C. After stirring at -78 °C for 30 min, the reaction mixture was poured into saturated aqueous Rochelle's salt at rt and EtOAc was added to the mixture. The resulting mixture was vigorously stirred at rt for 1 hour. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 528.2 mg (84%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.17 (m, 3H), 7.12 – 7.07 (m, 1H), 6.15 (s, 1H), 4.52 (d, *J* = 0.5 Hz, 2H), 3.68 (s, 2H), 1.93 – 1.81 (br s, 1H).

Step 3: 5-Chloro-4-(3-chlorobenzyl)-2-furaldehyde.

[00397] To a solution of [5-chloro-4-(3-chlorobenzyl)-2-furyl]methanol (510 mg, 1.98 mmol) in DCM (10.0 mL) was added MnO_2 (2.59 g, 29.8 mmol) at rt. After stirring at rt overnight, the mixture was filtered through a Celite pad and washed with DCM. The filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 332 mg (66%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.51 (s, 1H), 7.32 –7.23 (m, 2H), 7.22 –7.16 (m, 1H), 7.13 –7.08 (m, 1H), 7.06 (s, 1H), 3.78 (s, 2H).

Starting material	Product / Int No.	Characterization Data
	 **Int-61**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.46 (s, 1H), 7.26 – 7.18 (m, 2H), 7.14 – 7.11 (m, 1H), 7.03 (dt, *J* = 7.0, 1.7 Hz, 1H), 6.98 (s, 1H), 3.72 (s, 2H), 2.36 (s, 3H).

Example 39**: 4-(3-Chlorobenzyl)-2-furaldehyde Int-62**

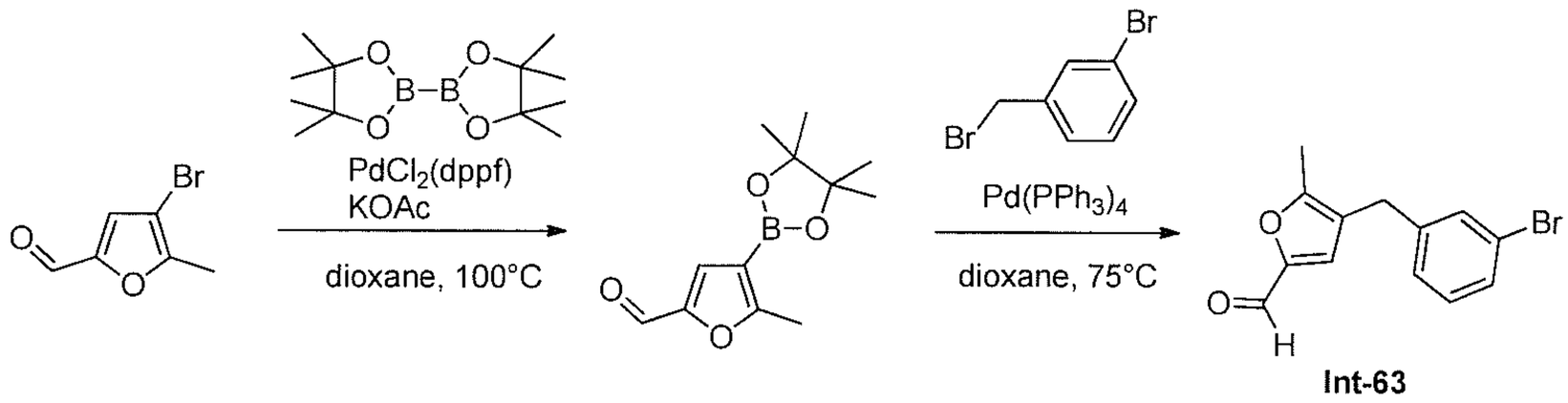


Int-62

Step 1: 4-(3-Chlorobenzyl)-2-furaldehyde.

[00398] A 20 mL of microwave vessel was charged with 4-bromo-2-furaldehyde (500 mg, 2.86 mmol), $Pd_2(dba)_3$ (52.3 mg, 0.06 mmol), and tri-*tert*-butylphosphonium tetrafluoroborate (33.2 mg, 0.11 mmol). THF (2.0 mL) was added to the mixture and the reaction vessel was purged with argon followed by sealing with a cap. After the mixture was stirred for 5 min at rt, 0.5 M of 3-chlorobenzylzinc chloride in THF (7.43 mL, 3.72 mmol) was added to the mixture and then the resulting mixture was heated at 50 °C for 1 hour. The reaction was cooled to rt and diluted with EtOAc. The organic layer was washed with water and brine. After drying over Na_2SO_4, the mixture was filtered through a glass frit funnel and the filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 135 mg (20 %) of the title compound.

Example 40: **4-(3-Bromobenzyl)-5-methyl-2-furaldehyde Int-63**



Int-63

Step 1: 5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furaldehyde.

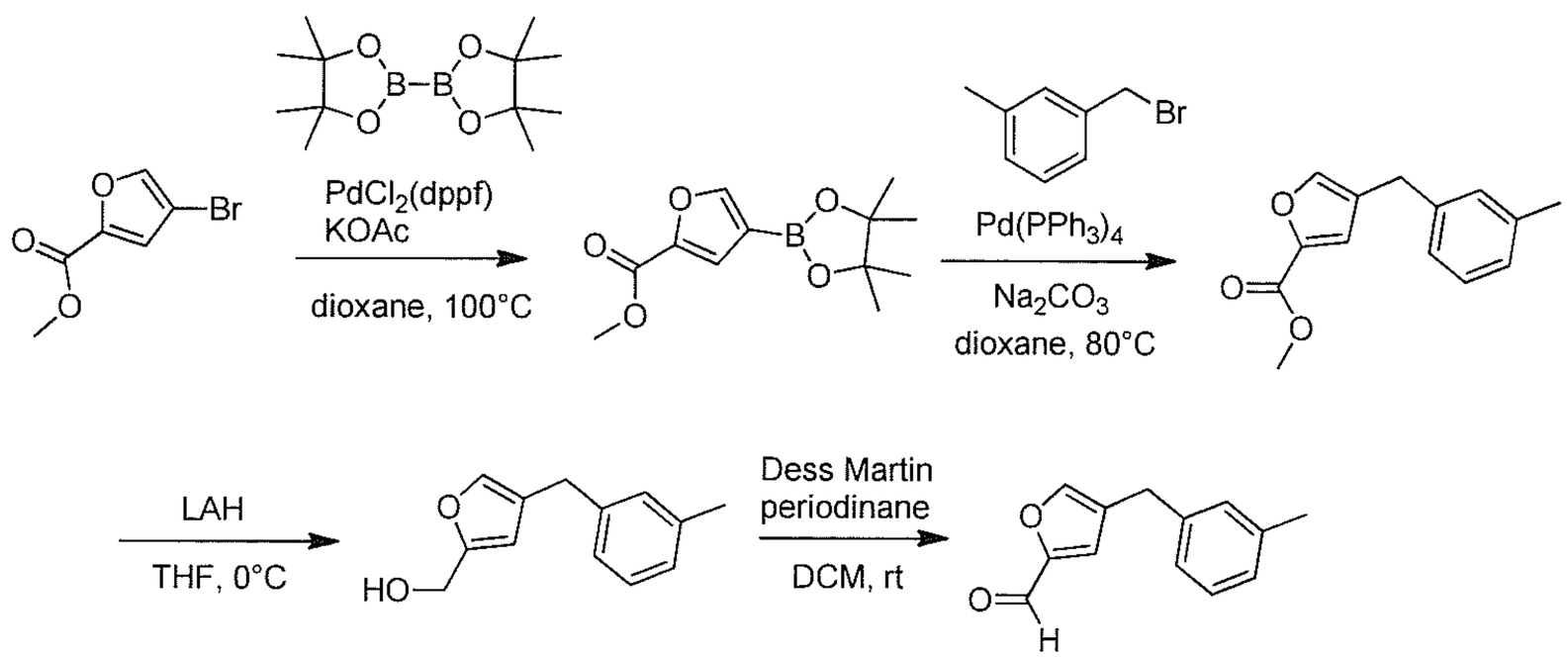
[00399] To a solution of 4-bromo-5-methyl-2-furaldehyde (880 mg, 4.66 mmol) in 1,4-dioxane (15.0 mL) were added bis(pinacolato)diborom (1.54 g, 6.05 mmol), potassium acetate (1.37 g, 13.9 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (192 mg, 0.23 mmol) at rt. After stirring at 100 °C overnight, the reaction mixture was poured into water at rt and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in EtOAc and then activated charcoal was added to the mixture, and stirred for 15 min at rt. The mixture was filtered through a Celite pad, and washed with EtOAc. The filtrate was concentrated in vacuo to give 1.94 g of crude title compound. LCMS (FA): m/z = 237.2 (M+H).

Step 2: 4-(3-Bromobenzyl)-5-methyl-2-furaldehyde.

[00400] To a solution of crude 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furaldehyde (1.09 g, 4.66 mmol) in 1,4-dioxane (40.0 mL) and water (10.0 mL) were added 3-bromobenzyl bromide (1.28 g, 5.12 mmol), $Pd(PPh_3)_4$ (538 mg, 0.47 mmol) and Na_2CO_3 (1.48 g, 13.9 mmol) at rt. After stirring at 75 °C overnight, the reaction mixture was poured into water at

rt and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (0% - 20% EtOAc in hexanes as eluent) to give 291 mg (22%) of the title product as a brown oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.46 (s, 1H), 7.40 – 7.33 (m, 1H), 7.29 (t, *J* = 1.6 Hz, 1H), 7.22 – 7.13 (m, 1H), 7.13 – 7.04 (m, 1H), 6.98 (s, 1H), 3.72 (s, 2H), 2.37 (s, 3H).

Example 41: **4-(3-Methylbenzyl)-2-furaldehyde Int-64**



Int-64

Step 1: Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furoate.

[00401] Methyl 4-bromofuran-2-carboxylate (1.00 g, 4.88 mmol), bis(pinacolato)diboron (1.61 g, 6.3 mmol), and potassium acetate (1.44 g, 14.6 mmol) were weighed into a microwave vial and 1,4-dioxane (15.0 mL) was added to the vial. The mixture was purged with argon and to this suspension was added [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (201 mg, 0.24 mmol). The reaction mixture was heated at 100 °C overnight in an oil bath. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO basic alumina column chromatography (0% - 10% MeOH in DCM as eluent) to give the title compound. LCMS (FA): *m/z* = 253.1 (M+H).

Step 2: Methyl 4-(3-methylbenzyl)-2-furoate.

[00402] 1-Bromomethyl-3-methylbenzene (110 mg, 0.60 mmol) and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-furoate (600 mg, 2.38 mmol) were weighed into a microwave vial with a stirbar. 1,4-Dioxane (5.0 mL) and water (1.30 mL, 72.2 mmol) were added followed by Na_2CO_3 (189 mg, 1.78 mmol). The mixture was purged with argon and $Pd(PPh_3)_4$ (68.8 mg, 0.06 mmol) was added. The resulting reaction mixture was heated to 80 °C and stirred overnight. The reaction was quenched with water and extracted with EtOAc (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue

was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 130 mg (95%) of the title compound. LCMS (FA): *m/z* = 231.0 (M+H).

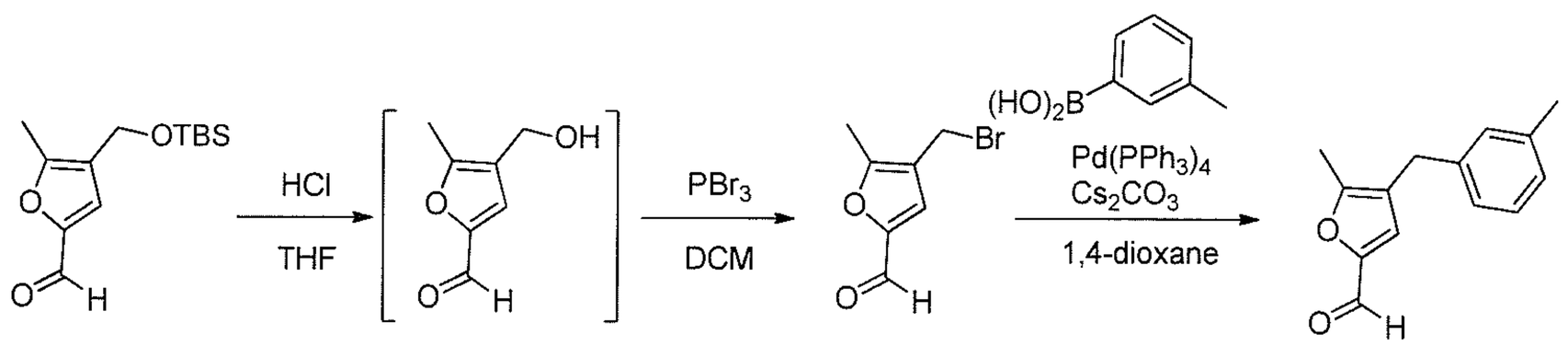
Step 3: [4-(3-Methylbenzyl)-2-furyl]methanol.

[00403] To a round bottom flask was added methyl 4-(3-methylbenzyl)-2-furoate (283 mg, 1.23 mmol) in THF (4.0 mL) and cooled at 0 °C. 1.0 M of lithium tetrahydroaluminate in Et_2O (1.60 mL, 1.60 mmol) was then added slowly and the resulting mixture was stirred at 0 °C for 1 hour. Added 1mL of water slowly to quench reaction mixture, then added solid Na_2SO_4. The mixture was stirred at rt for 1 hour and then filtered through a pad of Celite. The filtrate was concentrated to dryness and no further purification was done to give 230 mg (93%) of crude title compound. LCMS (FA): *m/z* = 203.5 (M+H).

Step 4: 4-(3-Methylbenzyl)-2-furaldehyde.

[00404] Into a 1-neck round-bottom flask was added crude [4-(3-methylbenzyl)-2-furyl]methanol (230 mg, 1.14 mmol) dissolved in DCM (5.0 mL). Dess-Martin periodinane (579 mg, 1.37 mmol) was then added and the resulting reaction mixture was stirred at rt for 1 hour. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ and extracted with DCM (x3). The combined organic layers were then washed with saturated $NaHCO_3$, water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 129 mg (57%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (s, 1H), 7.47 (s, 1H), 7.24 – 7.18 (m, 1H), 7.10 – 7.04 (m, 2H), 7.03 – 6.97 (m, 2H), 3.78 (s, 2H), 2.33 (s, 3H).

Example 42: **5-Methyl-4-(3-methylbenzyl)-2-furaldehyde Int-65**



Int-65

Step 1: 4-(Bromomethyl)-5-methyl-2-furaldehyde.

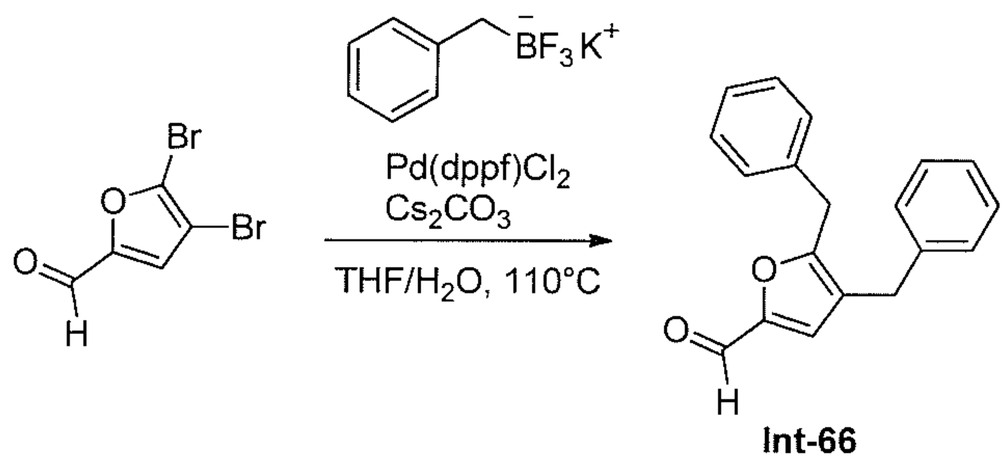
[00405] To a round bottom flask was added 4-({[tert-butyl(dimethyl)silyl]oxy}methyl)-5-methyl-2-furaldehyde (0.56 g, 2.2 mmol), THF (3 mL), and 4 M HCl in 1,4-dioxane (2 mL) . The resulting reaction mixture was stirred at rt 2 h. The mixture was concentrated in vacuo. To the residue was added DCM (5 mL) and PBr_3 (0.29 mL, 3.08 mmol) at rt and the mixture was stirred for 20 min. The reaction was quenched by addition of water and the resulting mixture was extracted with DCM. After concentration in vacuo, the residue was purified by ISCO column chromatography

(30 % EtOAc in hexanes as eluent) to give 0.19 g (42%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.42 (s, 1H), 7.12 (s, 1H), 4.24 (s, 2H), 2.32 (s, 3H).

Step 2: 5-Methyl-4-(3-methylbenzyl)-2-furaldehyde.

[00406] 4-(Bromomethyl)-5-methyl-2-furaldehyde (0.52 g, 2.6 mmol) and m-tolylboronic acid (696 mg, 5.12 mmol) were weighed into a microwave vial with stir bar. 1,4-Dioxane (12.0 mL) and water (2.00 mL) were added to the reaction vessel. Then Cs_2CO_3 (2.92g, 8.96 mmol) and $Pd(PPh_3)_4$ (444 mg, 0.38 mmol) was added and the reaction mixture was then heated to 130 °C in microwaver for 25 min. The mixture was filtered through Celite and the filtred was concentrated in vacuo. The residue was purified by ISCO column chromatography (30% EtOAc in hexanes as eluent) to give 268 mg (49%) of the title compound. LCMS (FA): *m/z* =215.2 (M+H).

Example 43**: 4,5-Dibenzyl-2-furaldehyde Int-66**

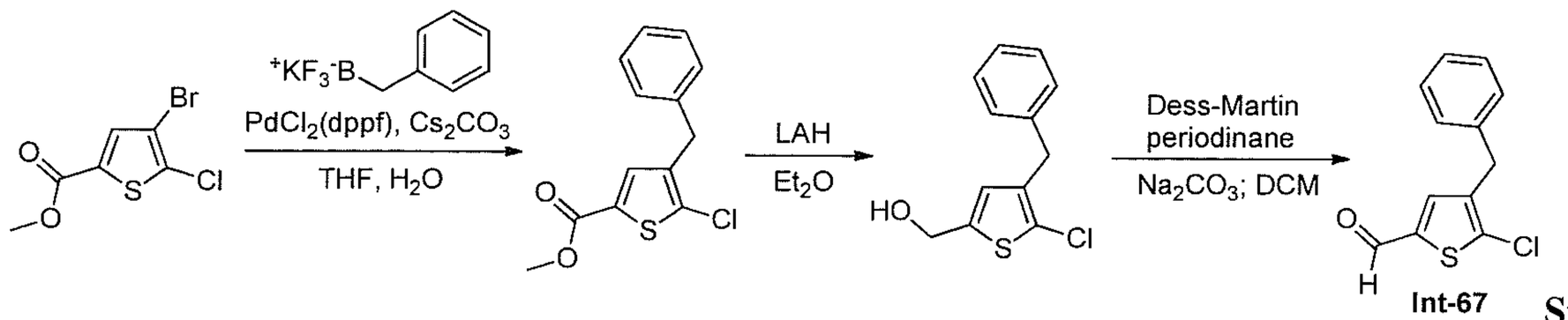


Int-66

Step 1: 4,5-Dibenzyl-2-furaldehyde

[00407] A sealable reaction vessel was charged with 4,5-dibromo-2-furaldehyde (1.00 g, 3.94 mmol), benzyltrifluoroborate potassium salt (1.95 g, 9.85 mmol), Cs_2CO_3 (3.89 g, 11.9 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (648 mg, 0.79 mmol). The contents were dissolved in THF (48 mL) and water (4.7 mL, 260 mmol), and a stir bar was added. The vessel was sealed and the resulting solution was stirred at 80 °C overnight, and then the reaction was stirred for 8 h at 110 °C. Reaction mixture was filtered through Celite pad, and the filtrate was partitioned between water (30 mL) and EtOAc (100 mL). Layers were separated, and the aqueous layer was extracted with EtOAc (100 mL x2). The combined organic layers were washed brine, then dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude residue was purified by ISCO column chromatography (0% - 15% EtOAc in hexanes as eluent) to afford 141 mg (13%) of the title compound. LCMS (FA): *m/z* = 277.5 (M+H).

Example 44**: 4-Benzyl-5-chlorothiophene-2-carbaldehyde. Int-67**



Step 1: Methyl 4-benzyl-5-chlorothiophene-2-carboxylate.

[00408] A microwave vial was charged with a stirbar, methyl 4-bromo-5-chlorothiophene-2-carboxylate (0.10 g, 0.39 mmol), Benzyltrifluoroborate potassium salt (94.0 mg, 0.47 mmol), Cs_2CO_3 (0.39 g, 1.18 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)dichloride (64.4 mg, 78.3 umol). The mixture was sealed under an atmosphere of argon. THF (4.7 mL) and water (0.47 mL, 26 mmol) were then added and the resulting solution stirred at 75 °C for 16 h. The reaction was concentrated. The crude pdt was purified on ISCO column chromatography (0% - 5% EtOAC/hexanes as eluent) to give the title compound (yield = 74 mg). LCMS (FA): *m/z* = 267.0 (M+1)

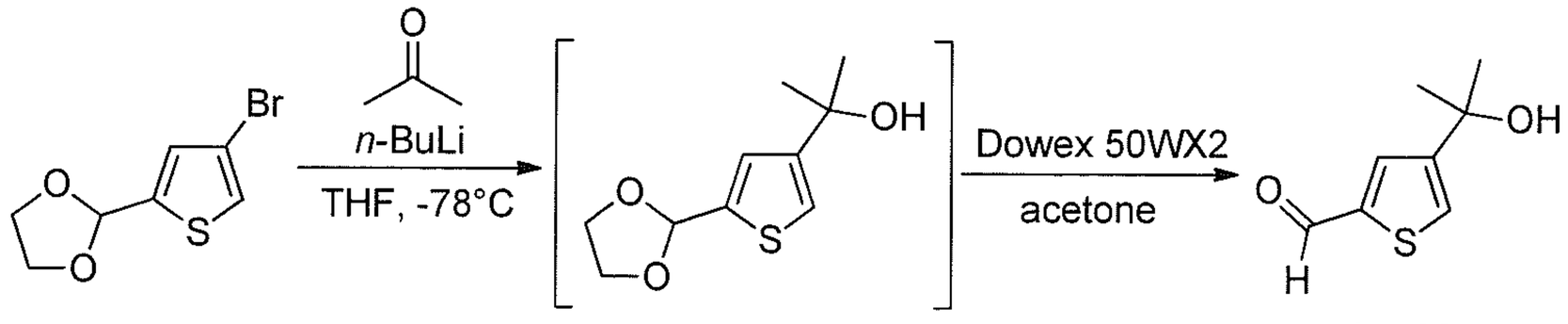
Step 2: (4-Benzyl-5-chloro-2-thienyl)methanol.

[00409] 1.0 M of lithium tetrahydroaluminate in THF (0.55 mL, 0.55 mmol) was added to an ice-bath cooled solution of methyl 4-benzyl-5-chlorothiophene-2-carboxylate (0.10 g, 0.37 mmol) in Et_2O (3.5 mL). The resulting solution was stirred at 0 °C for 45 min. The reaction was quenched with water (~1 mL) at 0 °C. Na_2SO_4 dodecahydrate (~2g) was added along with ~15 mL EtOAc and the mixture allowed to warm to rt and the mixture was stirred for 2 h. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was concentrated. Crude product was purified on ISCO column chromatography (0% - 20% EtOAc/hexanes as eluent) to give the title compound (yield = 80 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 6.60 (s, 1H), 4.64 (s, 2H), 3.88 (s, 2H), 1.82 (s, 1H).

Step 3: 4-Benzyl-5-chlorothiophene-2-carbaldehyde.

[00410] (4-Benzyl-5-chloro-2-thienyl)methanol (0.21 g, 0.88 mmol) was dissolved in DCM (15.3 mL), then Dess-Martin periodinane (0.45 g, 1.1 mmol) was added to this solution. The reaction was allowed to stir at rt for 1 hour. The reaction was concentrated and the crude material purified on ISCO column chromatography (0% - 10% EtOAC/hexanes as eluent) to give the title compound (yield = 190 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.68 (s, 1H), 7.38 – 7.30 (m, 3H), 7.29 – 7.23 (m, 1H), 7.23 – 7.17 (m, 2H), 3.96 (s, 2H).

Example 45**: 4-(2-Hydroxypropan-2-yl)thiophene-2-carbaldehyde. Int-68**

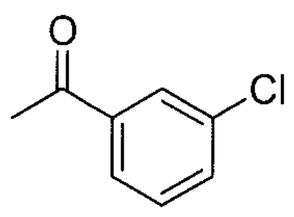
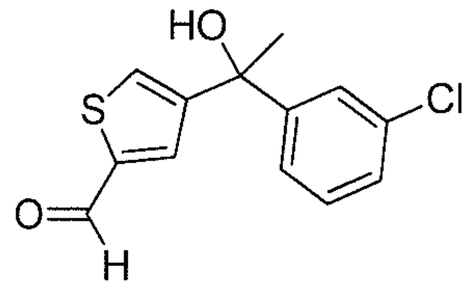
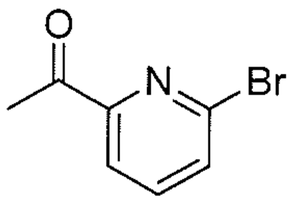
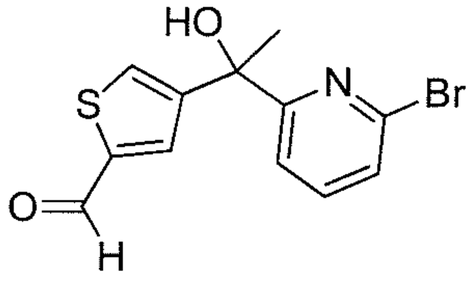


Int-68

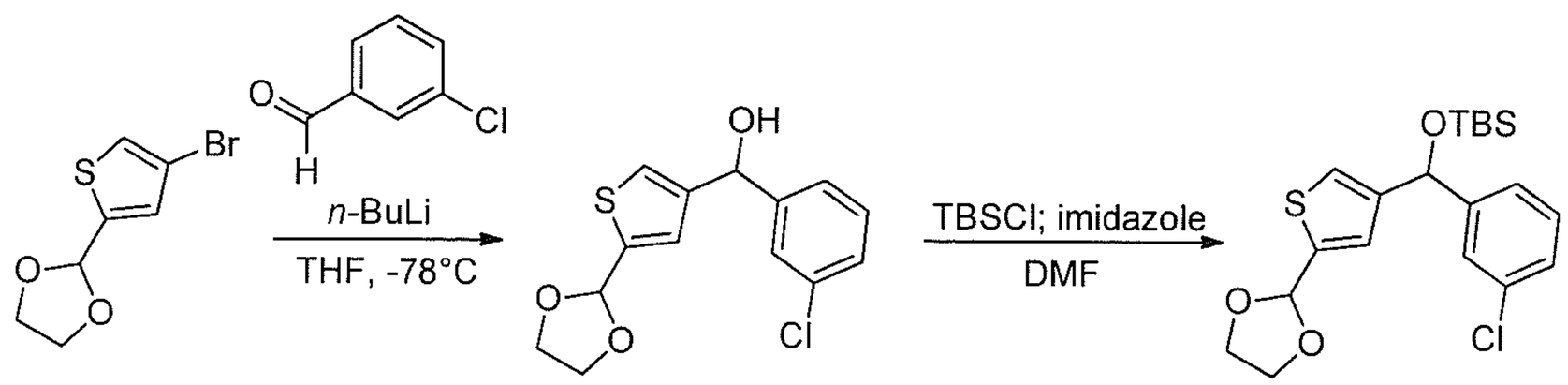
Step 1: 4-(2-Hydroxypropan-2-yl)thiophene-2-carbaldehyde.

[00411] To a round bottom flask was added THF (50 mL) and 2.5 M *n*-BuLi in hexane (3.1 mL, 7.66 mmol) at -78 °C. 2-(4-Bromothiophen-2-yl)-1,3-dioxolane (1.50 g, 6.38 mmol) in 5 mL THF was added and the mixture was stirred for 30 seconds. To the mixture was added acetone (2.00 mL, 27.2 mmol) and the reaction was stirred at -78 °C for 10 min. The reaction was quenched by addition of saturated NH_4Cl was added and the reaction was warmed to rt. The mixture was extracted with EtOAc (x2) and the combined organic layers were washed with brine, dried under $MgSO_4$, filtered, and concentrated in vacuo. To the residue was added 40 ml of acetone and 3g of Dowex 50WX2-200 ion-exchange resin and the mixture was stirred for 2 h at rt. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc in hexanes as eluent) to give 0.76g (70%) of the title compound. LCMS (FA): *m/z* = 171.1 (M+1).

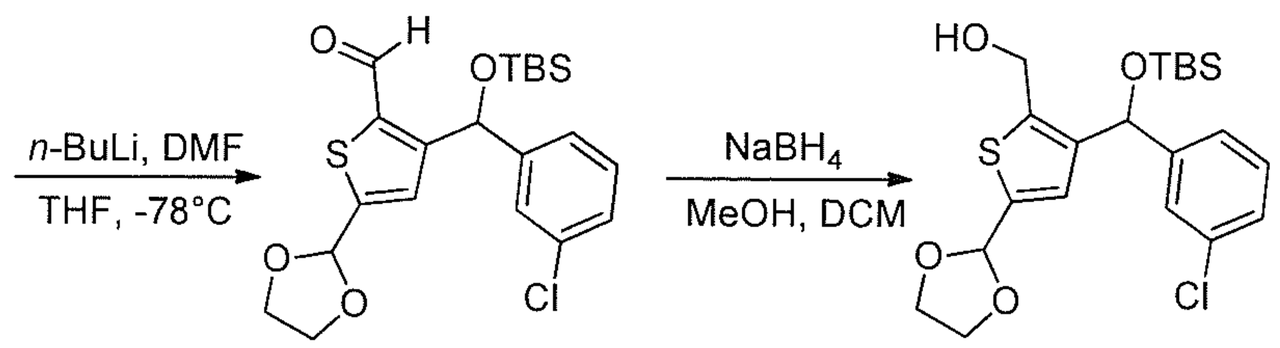
[00412] The compounds listed in the table below were prepared using similar methods to that described above starting from the listed starting materials.

Starting ketone	Product / Int No.	Characterization Data
	 **Int-69**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.80 (d, *J* = 1.2 Hz, 1H), 7.62 (dt, *J* = 2.7, 1.5 Hz, 2H), 7.47 – 7.44 (m, 1H), 7.30 – 7.23 (m, 3H), 2.68 – 2.30 (br s, 1H), 1.94 (s, 3H).^{1}H NMR
	 **Int-70**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (d, *J* = 1.2 Hz, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.69 (t, *J* = 1.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.43 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.28 (dd, *J* = 7.7, 0.7 Hz, 1H), 2.05 – 1.95 (br s, 1H), 1.92 (s, 3H).^{1}H NMR

Example 46**: rac-(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol Int-71 and rac-{3-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(1,3-dioxolan-2-yl)-2-thienyl}methanol Int-72**



Int-71



Int-72

Step 1: rac-(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol.

[00413] To a -78 °C cooled solution of 2.50 M of *n*-BuLi in hexane (4.08 mL, 10.2 mmol) in THF (40 mL) was added a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (2.00 g, 8.50 mmol) in THF (4 mL) dropwise. Immediately after addition was complete 3-chlorobenzaldehyde (0.97 mL, 8.50 mmol) was added dropwise (~2 min) as a solution in THF (4 mL). The resulting mixture was allowed to stir 30 min at -78 °C. The reaction was quenched with water before warming all the way to rt. The mixture was extracted with EtOAc (2x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by ISCO column chromatography eluting with 0% - 30% EtOAc in hexanes to give 1.7 g (67%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 (s, 1H), 7.35 – 7.24 (m, 4H), 7.21 (s, 1H), 7.06 (s, 1H), 6.04 (s, 1H), 5.82 (d, J = 3.6 Hz, 1H), 4.21 – 3.94 (m, 4H).

Step 2: rac-*tert*-Butyl{(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methoxy}dimethylsilane.

[00414] To a solution of (3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol (3.02 g, 10.2 mmol) in DMF (106 mL) was added TBSCl (4.60 g, 30.5 mmol) and 1H-imidazole (2.08 g, 30.5 mmol). The reaction mixture was stirred at 50 °C for 4 h. The mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with 10% aqueous LiCl, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 4.15 g (99%) of the title compound as a clear oil. LCMS (FA): *m/z* = 411.4 (M+1).

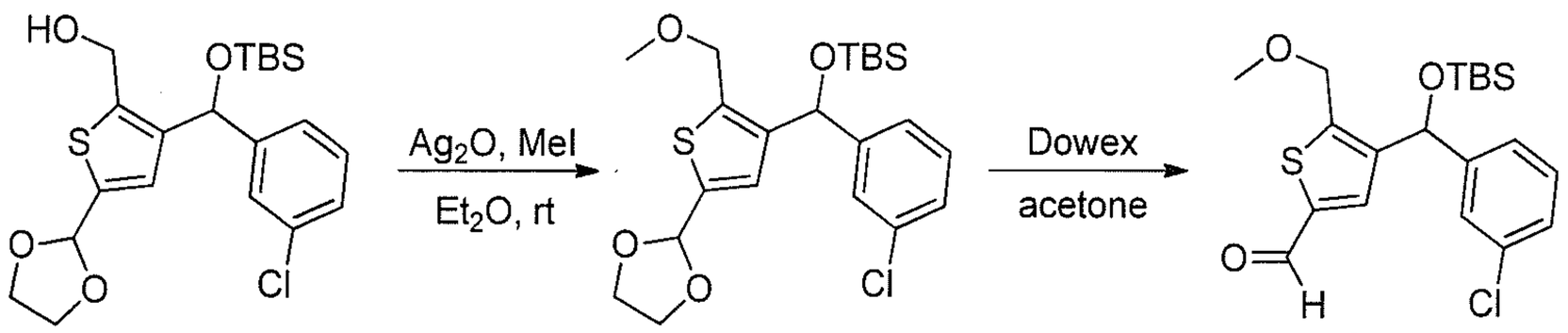
Step 3: rac-3-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(1,3-dioxolan-2-yl)thiophene-2-carbaldehyde.

[00415] To a -78 °C cooled solution of 2.50 M of *n*-BuLi in hexane (0.46 mL, 1.14 mmol) and THF (3.00 mL) was a solution of *tert*-butyl{(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methoxy}dimethylsilane (234 mg, 0.57 mmol) in THF (2.0 mL). The reaction mixture was stirred at -78 °C for 15 min. A solution of DMF (88.2 uL, 1.14 mmol) in THF (1.0 mL) was added dropwise and then stirred for an additional 1 hour. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 141 mg (56%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.41 (s, 1H), 7.53 (s, 1H), 7.48 – 7.39 (m, 3H), 7.41 – 7.32 (m, 2H), 6.58 (s, 1H), 6.11 (s, 1H), 4.09 – 3.92 (m, 4H), 0.90 (s, 9H), 0.08 – -0.04 (m, 6H). LCMS (FA): *m/z* = 439.5 (M+1).

Step 4: rac-{3-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(1,3-dioxolan-2-yl)-2-thienyl}methanol.

[00416] To a 0 °C cooled solution of 3-[{[*tert*-butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(1,3-dioxolan-2-yl)thiophene-2-carbaldehyde (141 mg, 0.32 mmol) in MeOH (1.5 mL) and DCM (1.5 mL) was added $NaBH_4$ (18.2 mg, 0.48 mmol). The reaction mixture was stirred at rt overnight and then concentrated to remove the solvent. The resulting residue was diluted with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography eluting with 0% - 25% EtOAc in hexanes to give 100 mg (71%) of the title compound. LCMS (FA): *m/z* = 441.5 (M+1).

Example 47**: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(methoxymethyl)thiophene-2-carbaldehyde Int-73**



Int-72 **Int-73**

Step 1: rac-*tert*-Butyl{(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-(methoxymethyl)-3-thienyl]methoxy}dimethylsilane

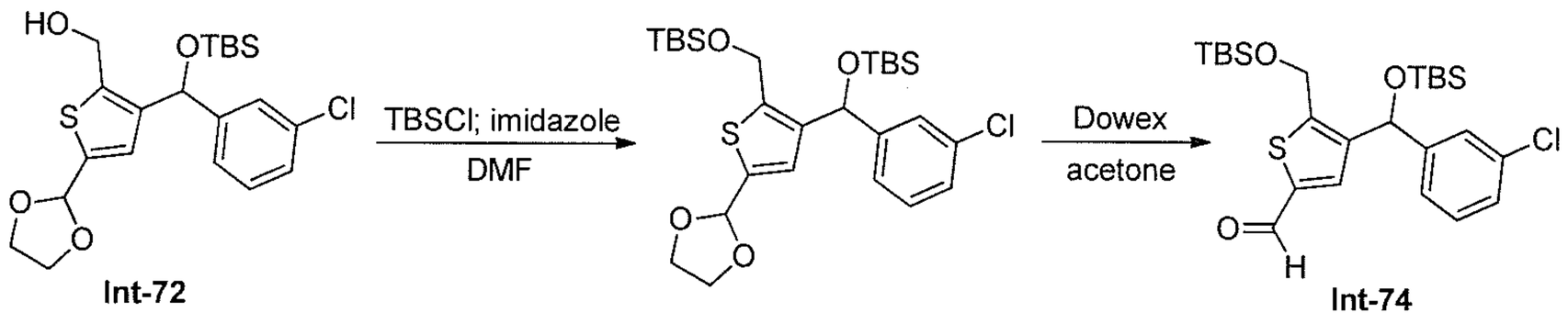
[00417] To a solution of **Int-72** (480 mg, 1.09 mmol) in Et_2O (10 mL) was added Ag_2O (630 mg, 2.72 mmol) and MeI (2.71 mL, 43.5 mmol). The resulting mixture was stirred at rt for 5 days, and then filtered over a pad of Celite. The filtrate was concentrated in vacuo. The crude material was

purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 371 mg (75%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.52 – 7.32 (m, 4H), 7.16 – 6.91 (m, 1H), 6.41 – 6.12 (m, 1H), 6.04 – 5.99 (m, 1H), 4.74 – 4.51 (m, 2H), 4.17 – 3.92 (m, 4H), 3.40 – 3.35 (m, 3H), 0.94 (s, 9H), 0.12 – -0.03 (m, 6H); LCMS (FA) M+1 455.5

Step 2: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(methoxymethyl)thiophene-2-carbaldehyde.

[00418] To a solution of *tert*-butyl{(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-(methoxymethyl)-3-thienyl]methoxy}dimethylsilane (371 mg, 0.82 mmol) in acetone (10.8 mL) was added 380 mg of DOWEX 50WX2-200 (H). The resulting mixture was stirred at rt for 2 h and then filtered. The filtrate was concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 283 mg (84%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.41 – 9.84 (m, 1H), 8.02 – 7.22 (m, 5H), 6.61 – 6.03 (m, 1H), 4.82 – 4.61 (m, 2H), 3.40 – 3.28 (m, 3H), 0.95 – 0.83 (m, 9H), 0.09 – -0.04 (m, 6H). LCMS (FA): *m/z* = 411.4 (M+1).

Example 48**: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-({[tert-butyl(dimethyl)silyl]oxy}methyl)thiophene-2-carbaldehyde Int-74**



Step 1: rac-*tert*-Butyl({3-[{[*tert*-butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(1,3-dioxolan-2-yl)-2-thienyl}methoxy)dimethylsilane

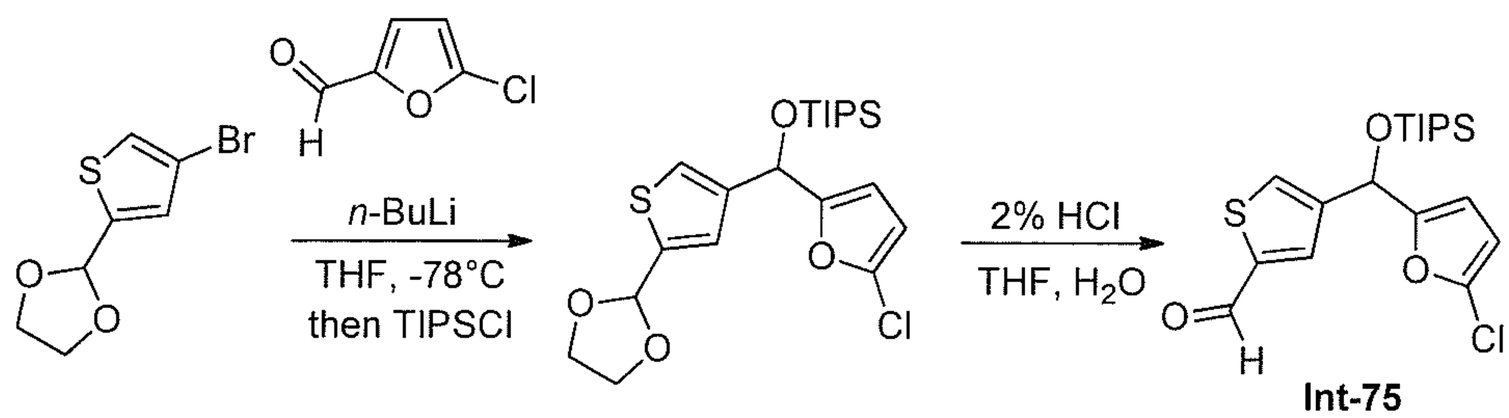
[00419] To a solution of **Int-72** (648 mg, 1.47 mmol) in DMF (15 mL) was added TBSCl (664 mg, 4.41 mmol) and 1H-imidazole (300 mg, 4.41 mmol). The reaction mixture was stirred at rt for 17 h then quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, washed with 10% aqueous LiCl, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 5% EtOAc in hexanes to give 373 mg (46%) of the title compound. LCMS (FA): *m/z* = 555.6 (M+1).

Step 2: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)thiophene-2-carbaldehyde.

[00420] To a solution of *tert*-butyl({3-[{[*tert*-butyl(dimethyl)silyl]oxy}(3-chlorophenyl)methyl]-5-(1,3-dioxolan-2-yl)-2-thienyl}methoxy)dimethylsilane (373 mg, 0.67 mmol) in acetone (8.9 mL)

was added 380 mg of DOWEX 50WX2-200 (H). The resulting mixture was stirred at rt for 2 h and then filtered. The filtrate was concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 289 mg (84%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.76 (s, 1H), 7.88 (s, 1H), 7.40 – 7.24 (m, 4H), 5.98 (s, 1H), 4.86 (s, 2H), 0.83 (d, J = 0.9 Hz, 16H), 0.04 – -0.02 (m, 6H), -0.03 – -0.11 (m, 6H). LCMS (FA): *m/z* = 511.6 (M+1).

Example 49**: rac-4-{(5-Chloro-2-furyl)[(triisopropylsilyl)oxy]methyl}thiophene-2-carbaldehyde. Int-75**



Step 1: rac-{(5-Chloro-2-furyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methoxy}(triisopropyl)silane.

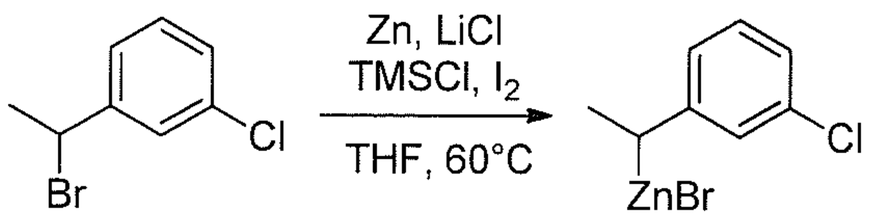
[00421] 2.50 M of *n*-BuLi in hexane (2.68 mL, 6.69 mmol) was added dropwise via syringe into THF (40 mL) at -78 °C. 2-(4-Bromothiophen-2-yl)-1,3-dioxolane (1.05 g, 4.46 mmol) was added to the solution at -78 °C, and then 5-chloro-2-furaldehyde (582 mg, 4.46 mmol) was added to the solution at once at -78 °C. The reaction was stirred at -78 °C for 15 min. To the mixture was TIPSCl (1.72 g, 8.92 mmol) was added to this solution and the resulting mixture was warmed to rt followed by refluxing for 4 h. The solution was poured into 60ml water and the mixture was extracted with EtOAc (50 ml x 2). The combined organic layers were concentrated in vacuo. The residue was purified by ISCOcolumn chromatography (0% - 30% EtOAc in hexanes as eluent) to give 1.51g (76%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (s, 1H), 7.12 (s, 1H), 6.12 (d, 1H), 6.07 (s, 1H), 6.06 (d, *J* = 3.3 Hz, 1H), 5.83 (s, 1H), 4.20 – 4.11 (m, 2H), 4.07 – 3.98 (m, 2H), 1.07 (s, 21H).

Step 2: rac-4-{(5-Chloro-2-furyl)[(triisopropylsilyl)oxy]methyl}thiophene-2-carbaldehyde.

[00422] To a solution of {(5-chloro-2-furyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methoxy}(triisopropyl)silane (1.96 g, 4.43 mmol) in THF (20.0 mL) was added water (1.00 mL, 55.5 mmol) followed by 20 ml 2% HCl in THF solution at rt. The reaction was stirred for 15 min at same temperature. The solution was poured into the solution of 30 ml saturated $NaHCO_3$ solution and 30ml water solution. The mixture was extracted with EtOAc (50 ml x2). The combined organic layers were concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 1.18g (67%) of the title

compound as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 7.66 (d, *J* = 3.3 Hz, 1H), 7.65 – 7.62 (s, 1H), 6.09 (s, 1H), 6.00 (d, *J* = 3.3 Hz, 1H), 5.80 (s, 1H), 1.03 – 0.89 (m, 21H).

Example 50**: rac-Bromo[1-(3-chlorophenyl)ethyl]zinc. Int-76**

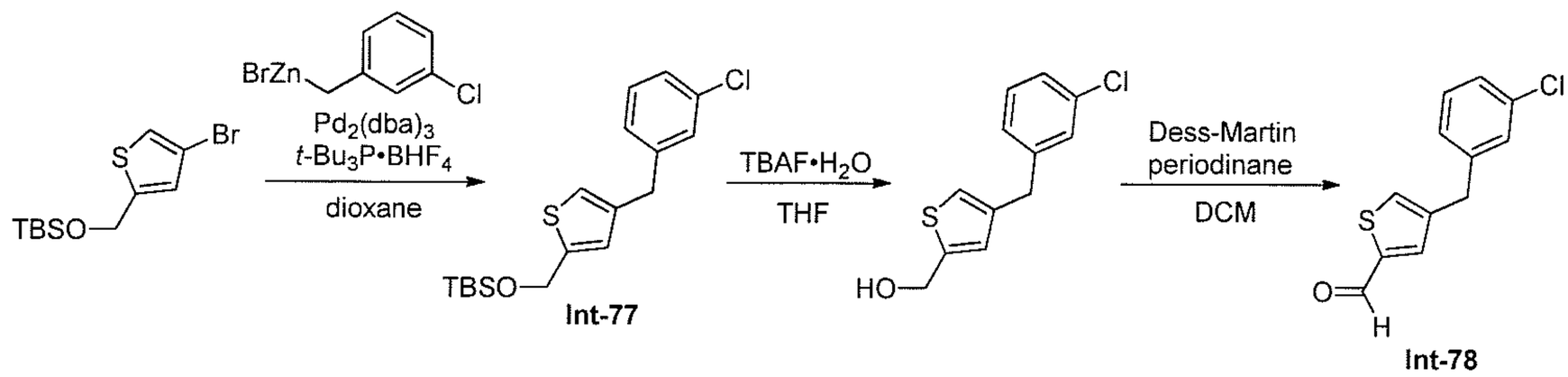


Int-76

Step 1: rac-Bromo[1-(3-chlorophenyl)ethyl]zinc.

[00423] Lithium chloride (0.39 g, 9.11 mmol) was added to an oven-dried 50mL 2-neck round bottom flask under an atmosphere of argon. The vessel was evacuated under high vacuum and heated with a heat gun for 10 min and backfilled with argon after cooling to rt. Zinc powder (0.596 g, 9.11 mmol) was added. The vessel was heated with a heat gun under high vac for 10 min and backfilled with argon after cooling to rt. THF (4.6 mL) was added followed by 1,2-dibromoethane (20 uL, 0.2 mmol). The reaction was heated at 60 °C for 20 min. TMSCl (5.78 uL, 45.6 umol) and iodine (5.78 mg, 22.8 umol) in THF (0.5 mL) were added to the vessel via syringe and the reaction was heated for 20 min at 60 °C. 1-(1-Bromoethyl)-3-chlorobenzene (1.00 g, 4.56 mmol) was added and the reaction was heated at 50 °C for 2 h. TLC showed no starting material remaining and a new less polar spot. An additional 5 mL of THF was added. This solution of Int-76 in the next reaction without further purification.

Example 51**: *tert*-Butyl{[4-(3-chlorobenzyl)-2-thienyl]methoxy}dimethylsilane Int-77, and 4-(3-chlorobenzyl)thiophene-2-carbaldehyde Int-78**



Step1: *tert*-Butyl{[4-(3-chlorobenzyl)-2-thienyl]methoxy}dimethylsilane.

[00424] A 20mL of microwave vessel was charged with ((4-bromothiophen-2-yl)methoxy)(*tert*-butyl)dimethylsilane (425 mg, 1.38 mmol), $Pd_2(dba)_3$ (25.3 mg, 0.03 mmol), and tri-*tert*-butylphosphonium tetrafluoroborate (16.1 mg, 0.06 mmol). To the mixture was added THF (18.2

mL) and the reaction vessel was purged with argon followed by sealing with a cap. After the mixture was stirred for 5 min at rt, 0.5 M of 3-chlorobenzylzinc chloride in THF solution (3.18 mL, 1.59 mmol) was added to the mixture. The reaction was heated at 50 °C for 1 hour. The reaction was cooled to rt and diluted with EtOAc. The organic layer was filtered through a Celite pad and the filtrate was washed with water followed by brine. The EtOAc layer was filtered and the filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (5% EtOAc in hexanes as eluent) to give 475mg (92%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 – 7.17 (m, 4H), 7.12 (s, 1H), 6.80 (s, 1H), 4.77 (s, 2H), 3.88 (s, 2H), 0.86 (s, 9H), 0.04 (s, 6H).

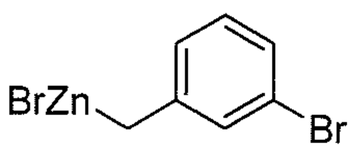
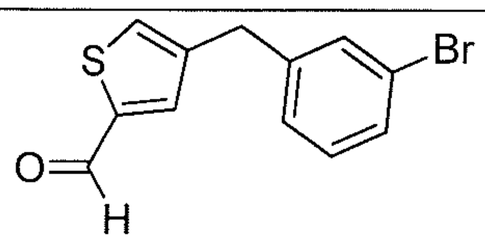
Step 2: [4-(3-Chlorobenzyl)-2-thienyl]methanol.

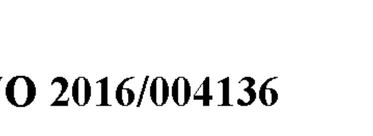
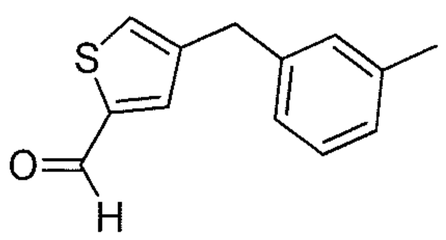
[00425] To a solution of *tert*-butyl{[4-(3-chlorobenzyl)-2-thienyl]methoxy}dimethylsilane (1.68 g, 4.76 mmol) in THF (15.0 mL) was added TBAF hydrate (1.87 g, 7.14 mmol) at rt and the reaction was stirred overnight. The mixture was concentrated in vacuo and the residue was purified by ISCO column chromatography (40% EtOAc in hexanes as eluent) to give 0.82 g (72%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.06 (m, 3H), 7.02 – 6.94 (m, 1H), 6.82 – 6.77 (m, 1H), 6.69 (s, 1H), 4.66 (s, 2H), 3.79 (s, 2H).

Step 3: 4-(3-Chlorobenzyl)thiophene-2-carbaldehyde.

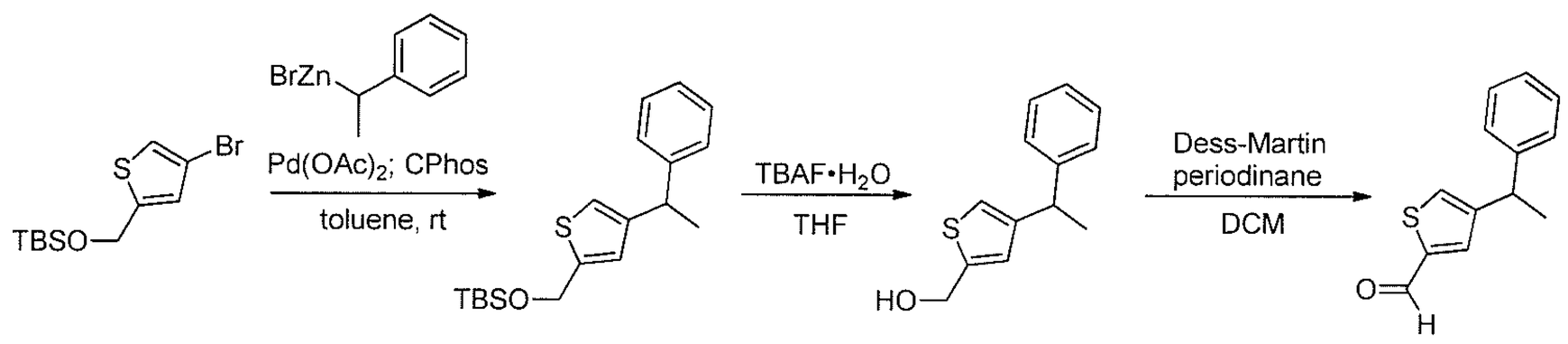
[00426] To a solution of [4-(3-chlorobenzyl)-2-thienyl]methanol (0.82 g, 3.4 mmol) in DCM (30.0 mL) was added Dess-Martin periodinane (1.53 g, 3.61 mmol) at rt and the reaction was stirred for 2 h. The mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 0.80g (98%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) d 9.82 (s, 1H), 7.55 (s, 1H), 7.38 (s, 1H), 7.28 – 7.17 (m, 3H), 7.09 (dt, J = 7.2, 1.6 Hz, 1H), 3.96 (s, 2H).

[00427] The compounds listed in the table below were prepared in a similar fashion to that described above starting from the listed starting materials. The following alternative conditions can be employed in the described reaction steps. Step 1: $Pd(PPh_3)_4$, THF at 70°C instead of $Pd_2(dba)_3$ with tri-*tert*-butylphosphonium tetrafluoroborate, THF at 50°C.

Step 1 zinc reagent	**Step 1 condition**	**Product / Int No.**	**Characterization Data**
	**$Pd(PPh_3)_4$ THF; 70°C**	 **Int-79**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (d, J = 1.1 Hz, 1H), 7.55 (d, J = 1.2 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.35 (s, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.7

			Hz, 1H), 3.97 (s, 2H). LCMS (FA): *m/z* = 282.9 (M+1).
	**$Pd(PPh_3)_4$ THF; 70°C**	 **Int-80**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (d, *J* = 1.1 Hz, 1H), 7.56 (d, *J* = 1.2 Hz, 1H), 7.38 (s, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.03 – 6.97 (m, 2H), 3.95 (s, 2H), 2.33 (s, 3H). LCMS (FA): *m/z* = 217.1 (M+1).

Example 52**: rac-4-(1-Phenylethyl)thiophene-2-carbaldehyde. Int-81**



Int-81

Step 1: rac-*tert*-Butyl(dimethyl){[4-(1-phenylethyl)-2-thienyl]methoxy}silane.

[00428] ((4-Bromothiophen-2-yl)methoxy)(*tert*-butyl)dimethylsilane (135 mg, 0.439 mmol), $Pd(OAc)_2$ (7.1 mg, 0.032 mmol) and 2-dicyclohexylphosphino-2',6'-bis(*N,N*-dimethylamino)biphenyl (21.2 mg, 48.6 umol) were added to a microwave reaction vial. The vial was purged with argon and toluene (1.00 mL) was added. To the dark red solution at rt was added 0.5 M of alpha-methylbenzylzinc bromide in THF (1.32 mL, 0.66 mmol) dropwise over 30 min and the reaction was stirred for 1 hour. The reaction was quenched with 0.5 M HCl and diluted with water and EtOAc. The layers were separated and the aqueous layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via ISCO column chromatography (2% isocratic EtOAc in hexanes as eluent) to give the title compound as clear colorless oil (yield = 134 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 2H), 7.22 – 7.18 (m, 3H), 6.86 – 6.84 (m, 1H), 6.69 – 6.66 (m, 1H), 4.78 (d, *J* = 0.9 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Step 2: rac-[4-(1-Phenylethyl)-2-thienyl]methanol.

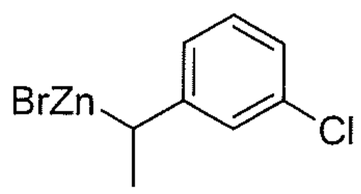
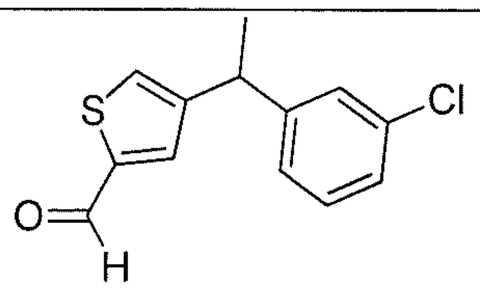
[00429] *tert*-Butyl(dimethyl){[4-(1-phenylethyl)-2-thienyl]methoxy}silane (134 mg, 0.40 mmol), THF (4.0 mL) and TBAF hydrate (225 mg, 0.81 mmol) were combined in a 100 mL round-bottom flask and the reaction was stirred for 10 min. The reaction was concentrated in vacuo and purified via ISCO column chromatography (20% EtOAc in hexanes isocratic as eluent) to give the title compound as colorless oil (yield = 90 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.26

(m, 2H), 7.24 – 7.14 (m, 3H), 6.92 (s, 1H), 6.78 (s, 1H), 4.74 (s, 2H), 4.09 (q, J = 7.2 Hz, 1H), 1.61 (d, J = 7.2 Hz, 3H).

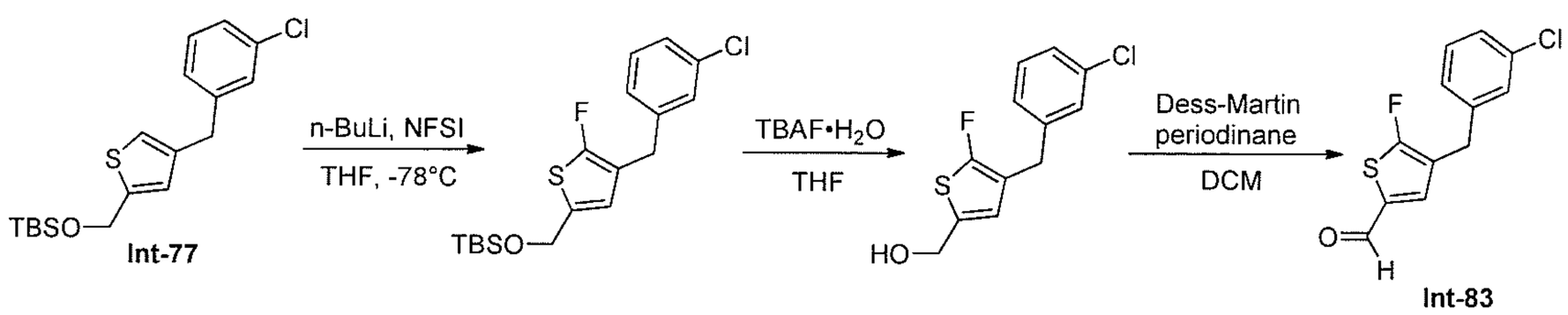
Step 3: rac-4-(1-Phenylethyl)thiophene-2-carbaldehyde.

[00430] To a solution of [4-(1-phenylethyl)-2-thienyl]methanol (132 mg, 0.61 mmol) in DCM (12 mL) was added Dess-Martin periodinane (385 mg, 0.91 mmol) at rt and the mixture was stirred for 30 min. The reaction was quenched by addition of saturated $NaHCO_3$ (50 mL) and extracted with DCM (50 mLx2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (5% EtOAc in hexanes as eluent) to give the title compound as a colorless oil (yield = 98 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (d, J = 1.1 Hz, 1H), 7.55 (d, J = 1.3 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.25 – 7.16 (m, 3H), 4.17 (q, J = 7.1 Hz, 1H), 1.66 (d, J = 7.2 Hz, 3H).

[00431] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Step 1 zinc reagent	Product / Int No.	Characterization Data
 **Int-40**	 **Int-82**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (d, J = 1.1 Hz, 1H), 7.53 (d, J = 1.3 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.29 – 7.19 (m, 2H), 7.19 – 7.16 (m, 1H), 7.10 – 7.05 (m, 1H), 4.15 (q, J = 7.2 Hz, 1H), 1.65 (d, J = 7.2 Hz, 3H).

Example 53: **4-(3-Chlorobenzyl)-5-fluorothiophene-2-carbaldehyde Int-83**



Step 1: *tert*-Butyl{[4-(3-chlorobenzyl)-5-fluoro-2-thienyl]methoxy}dimethylsilane.

[00432] *tert*-Butyl{[4-(3-chlorobenzyl)-2-thienyl]methoxy}dimethylsilane (Int-77, 380 mg, 1.08 mmol) in a 100mL 2-neck round bottom flask was dissolved in THF (20.0 mL) under atmosphere of argon, and the solution was cooled at -78 °C. To the solution was added dropwise 2.50 M of *n*-BuLi in hexane (0.65 mL, 1.62 mmol) and the light orange solution was stirred for 30min at -78 °C. To the solution was added dropwise a solution of *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (509 mg, 1.62 mmol) in THF (4.0 mL) at -78 °C, and the

reaction was stirred for 30min. The reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with hexane (60 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0.5% EtOAc in hexanes as eluent) to give 283mg (67%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (t, J = 7.9 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.58 (d, J = 4.0 Hz, 1H), 4.68 (d, J = 2.1 Hz, 2H), 3.81 (s, 2H), 0.85 (s, 9H), 0.04 (s, 6H).

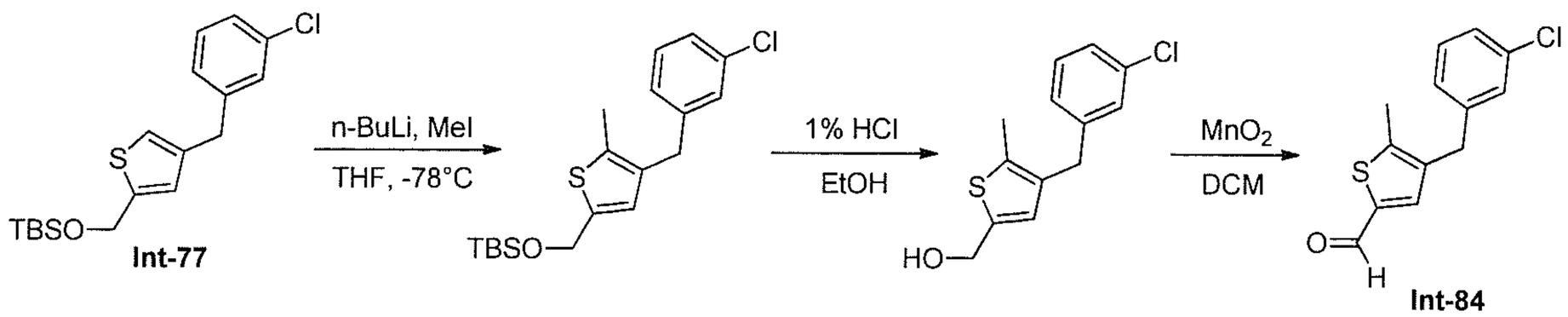
Step 2: [4-(3-Chlorobenzyl)-5-fluoro-2-thienyl]methanol.

[00433] *tert*-Butyl{[4-(3-chlorobenzyl)-5-fluoro-2-thienyl]methoxy}dimethylsilane (283 mg, 0.76 mmol) in THF (10.0 mL, 123 mmol) was added a solution of TBAF hydrate (320 mg, 1.14 mmol) in THF (2.0 mL) at rt, and the mixture was stirred for 30 min. The reaction was quenched by addition of water (80 mL) and extracted with EtOAc (80 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (FA, 45% to 80% CH_3CN in water, UV: 232). The product fractions were combined and concentrated in vacuo to remove organic solvent. The residual water layer was added 20 mL of saturated $NaHCO_3$ and then the mixture was extracted with EtOAc (60 mLx3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 185mg (95%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 – 7.30 (m, 1H), 7.30 – 7.24 (m, 2H), 7.18 (d, J = 7.5 Hz, 1H), 6.54 (d, J = 4.0 Hz, 1H), 5.46 (t, J = 5.8 Hz, 1H), 4.48 – 4.41 (m, 2H), 3.80 (s, 2H).

Step 3: 4-(3-Chlorobenzyl)-5-fluorothiophene-2-carbaldehyde.

[00434] To a solution of [4-(3-chlorobenzyl)-5-fluoro-2-thienyl]methanol (180 mg, 0.70 mmol) in DCM (10.0 mL, 156 mmol) was added Dess-Martin periodinane (446 mg, 1.05 mmol) at rt, and the reaction was stirred for 30 min. The reaction was quenched by addition of saturated $NaHCO_3$ (60 mL) and extracted with DCM (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (5% - 10% EtOAc in hexanes as eluent) to give 125mg (70%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (d, J = 4.4 Hz, 1H), 7.79 (d, J = 4.5 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.31 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 7.3 Hz, 1H), 3.95 (s, 2H).

Example 54**: 4-(3-Chlorobenzyl)-5-methylthiophene-2-carbaldehyde. Int-84**



Step 1: *tert*-Butyl{[4-(3-chlorobenzyl)-5-methyl-2-thienyl]methoxy}dimethylsilane.

[00435] Int-77 (0.67 g, 1.90 mmol) was dissolved into THF (10.0 mL), and then cooled down at -78 °C. 2.50 M of *n*-BuLi in hexane (6.08 mL, 15.2 mmol) was added dropwise via syringe to this solution at -78 °C and the mixture was stirred for 30 min. To the mixture was added methyl iodide (1.18 mL, 19.0 mmol) and the reaction was stirred at -78 °C for 30 min. The reaction was quenched by addition of 30 ml water at -78 °C and the mixture was warmed at rt. The resulting mixture was extracted with DCM (30 ml x2). The organic layers were combined and concentrated in vacuo to yield 574 mg (82%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.12 – 7.08 (m, 2H), 7.03 (s, 1H), 6.94 (d, J = 7.1 Hz, 1H), 6.45 (s, 1H), 4.66 (s, 2H), 3.71 (s, 2H), 2.26 (s, 3H), 0.83 (s, 9H), -0.00 (s, 6H).

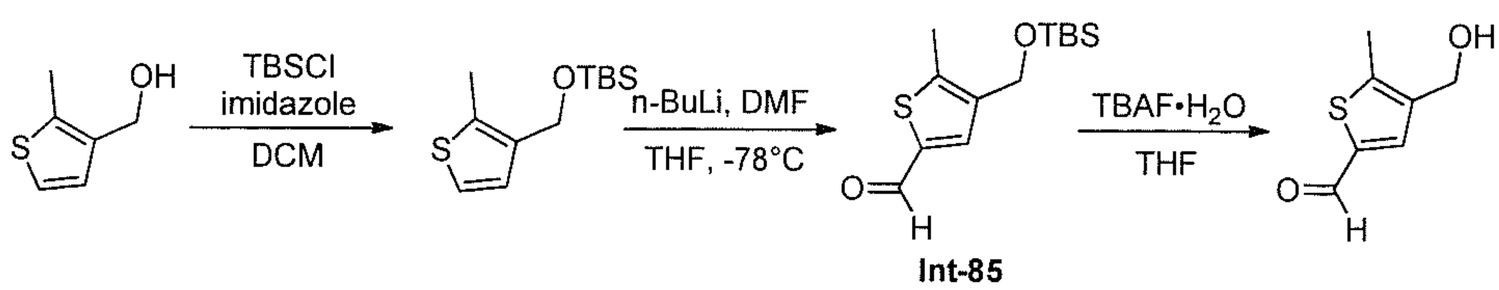
Step 2: [4-(3-Chlorobenzyl)-5-methyl-2-thienyl]methanol.

[00436] *tert*-Butyl{[4-(3-chlorobenzyl)-5-methyl-2-thienyl]methoxy}dimethylsilane (0.62 g, 1.69 mmol) was dissolved into 20 ml 1% HCl in EtOH solution and the mixture was stirred at rt for 30 min. The solution was poured into 30 ml saturated $NaHCO_3$ solution and the mixture was extracted with DCM (30 ml x2). The combined organics were concentrated in vacuo and the mixture was purified by ISCO column chromatography (0% - 60% EtOAc in hexanes as eluent) to give 332.5 mg (78%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.17 (m, 2H), 7.14 (s, 1H), 7.05 (dd, *J* = 7.1, 1.7 Hz, 1H), 6.65 (s, 1H), 4.71 (s, 2H), 3.82 (s, 2H), 2.39 (s, 3H).

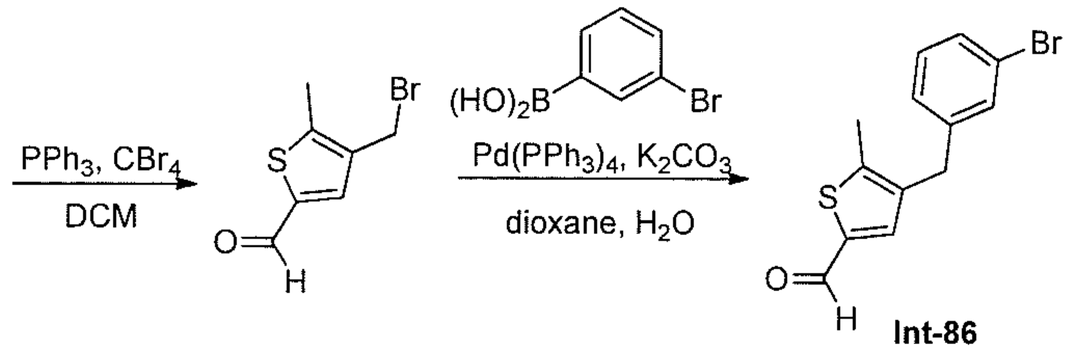
Step 3: 4-(3-Chlorobenzyl)-5-methylthiophene-2-carbaldehyde.

[00437] To a solution of [4-(3-chlorobenzyl)-5-methyl-2-thienyl]methanol (324.2 mg, 1.28 mmol) in DCM (40.0 mL) was added MnO_2 (1.67 g, 19.2 mmol) and the mixture was stirred at rt for 6 h. The reaction mixture was filtered through a Celite pad and the filter cake was washed with DCM several times. The filtrate was concentrated in vacuo to yield 289.2 mg (90%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 7.42 (s, 1H), 7.30 – 7.19 (m, 2H), 7.14 (s, 1H), 7.11 – 7.00 (m, 1H), 3.90 (s, 2H), 2.48 (s, 3H).

Example 55**: 4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-5-methylthiophene-2-carbaldehyde Int-85, and 4-(3-bromobenzyl)-5-methylthiophene-2-carbaldehyde Int-86**



Int-85



Int-86

Step 1: *tert*-Butyl(dimethyl)[(2-methyl-3-thienyl)methoxy]silane.

[00438] To a solution of (2-methyl-3-thienyl)methanol (2.6 g, 20.0 mmol) in DCM (64.2 mL) was added 1H-imidazole (2.07 g, 30.4 mmol) followed by TBSCl (3.21 g, 21.3 mmol) at rt, and the mixture was stirred for 6 h. The reaction was quenched by addition of water (50mL) and then mixture was extracted with EtOAc (1x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified on ISCO column chromatography (0% - 25% EtOAc in hexanes as eluent) to give 4.44 g (90%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 (d, *J* = 5.2 Hz, 1H), 6.96 (d, *J* = 5.2 Hz, 1H), 4.63 (s, 2H), 2.40 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H).

Step 2: 4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-5-methylthiophene-2-carbaldehyde.

[00439] *tert*-Butyl(dimethyl)[(2-methyl-3-thienyl)methoxy]silane (1.0 g, 4.10 mmol) was weighed into a 250mL 2-neck round bottom flask and the reaction vessel was purged with argon. The content was dissolved in THF (20.0 mL) and the solution was cooled at -78 °C. To this solution was added dropwise 2.50 M of *n*-BuLi in hexane (1.73 mL, 4.33 mmol) and the mixture was stirred for 30 min. Then DMF (0.48 mL, 6.19 mmol) was added dropwise to the mixture at -78 °C. The reaction was stirred for 30 min. The reaction was quenched by addition of saturated NH_4Cl (80 mL) and extracted with EtOAc (80 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (5% EtOAc in hexanes as eluent) to give 888 mg of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 (s, 1H), 7.64 (s, 1H), 4.62 (s, 2H), 2.47 (s, 3H), 1.55 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H).

Step 3: 4-(Hydroxymethyl)-5-methylthiophene-2-carbaldehyde.

[00440] To a solution of 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-5-methylthiophene-2-carbaldehyde (850.0 mg, 3.143 mmol) in THF (20.0 mL) was added TBAF monohydrate (966 mg, 3.46 mmol) at rt, and the mixture was stirred for 30 min. The reaction was quenched by addition of water (60 mL) and extracted with EtOAc (60 mLx3). The combined organic layers

were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (50% EtOAc in hexanes as eluent) to give 395mg (81%) of the title compound as colorless oil. LCMS (FA): *m/z* = 156.9 (M+H).

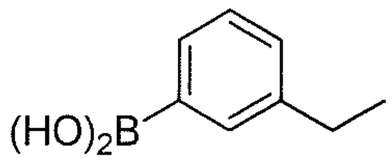
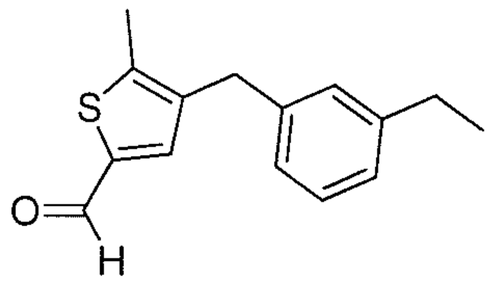
Step 4: 4-(Bromomethyl)-5-methylthiophene-2-carbaldehyde.

[00441] 4-(hydroxymethyl)-5-methylthiophene-2-carbaldehyde (316 mg, 2.02 mmol) in DCM (31.6 mL) was added PPh_3 (689.8 mg, 2.63 mmol) followed by CBr_4 (805 mg, 2.43 mmol) at rt, and the mixture was stirred for 1 hour. The reaction was concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 365mg (82%) of the title compound as light yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 (s, 1H), 7.66 (s, 1H), 4.44 (s, 2H), 2.54 (s, 3H).

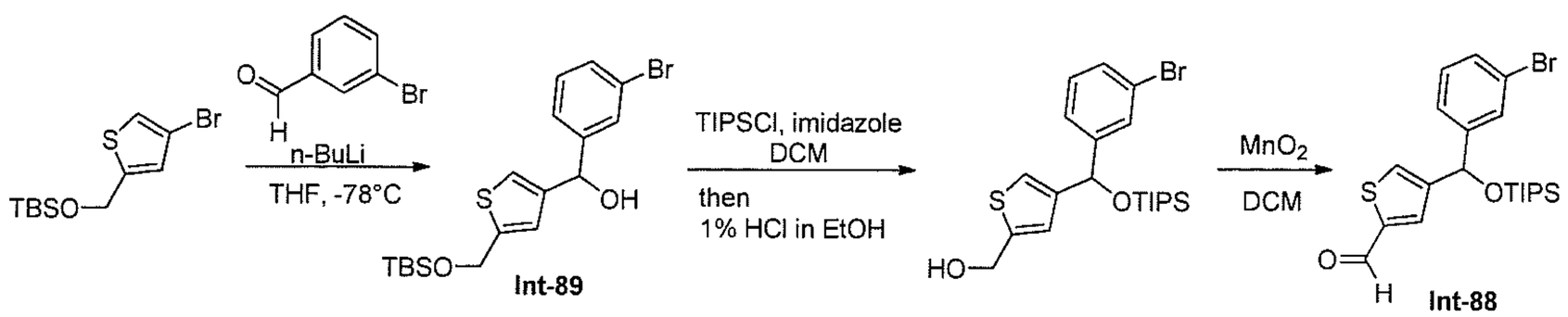
Step 5: 4-(3-Bromobenzyl)-5-methylthiophene-2-carbaldehyde.

[00442] A microwave reaction vial was charged with 4-(bromomethyl)-5-methylthiophene-2-carbaldehyde (95.0 mg, 0.43 mmol), 3-bromophenylboronicacid (87.1 mg, 0.43 mmol), K_2CO_3 (0.18 g, 1.30 mmol), and $Pd(PPh_3)_4$ (25.0 mg, 0.02 mmol). The contents were dissolved in 1,4-dioxane (2.0 mL) followed by addition of water (0.5 mL), and the vial was sealed with cap under atmosphere of argon. The reaction was heated at 80 °C for 1 hour. The reaction was cooled at rt and transferred into a separatory funnel with EtOAc and water. The mixture was extracted with EtOAc (x3) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 92mg of the title compound as light yellow oil. LCMS (FA): *m/z* = 296.9 (M+H).

[00443] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Step 5 boronic acid	Compound Name / Int No.	Characterization Data
	 **Int-87**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.41 (s, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.01 – 6.92 (m, 2H), 3.88 (s, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.47 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H). LCMS (FA): *m/z* = 245.1 (M+1).

Example 56: **rac-4-{(3-Bromophenyl)[(triisopropylsilyl)oxy]methyl}thiophene-2-carbaldehyde Int-88**



Step 1: rac-(3-Bromophenyl)[5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]methanol. Int-89

[00444] 2.50 M of *n*-BuLi in hexane (5.99 mL, 15.0 mmol) was dissolved into THF (75.0 mL) at -78 °C, then ((4-bromothiophen-2-yl)methoxy)(tert-butyl)dimethylsilane (3.83 g, 12.5 mmol) was added to this solution at -78 °C and the mixture was stirred for 2 min. 3-Bromobenzaldehyde (2.42 g, 13.1 mmol) was added to the solution at -78 °C and the reaction was stirred at -78 °C for 15 min. The solution was poured into 100ml of 5g acetic acid in water solution and the resulting mixture was extracted with DCM (70 ml x2). The combined organic layers were concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 15% EtOAc in hexanes as eluent) to give 4.05g (79%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (s,, 1H), 7.33 (d, *J* = 7.3, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.04 – 6.98 (s, 1H), 6.69 (s,, 1H), 5.69 (s, 1H), 4.72 (s, 2H), 0.83 (s,, 9H), 0.01 (s, 6H).

Step 2: rac-(4-{(3-Bromophenyl)[(triisopropylsilyl)oxy]methyl}-2-thienyl)methanol.

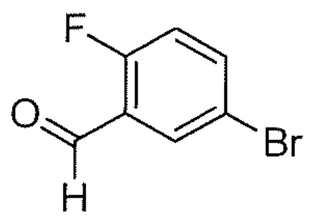
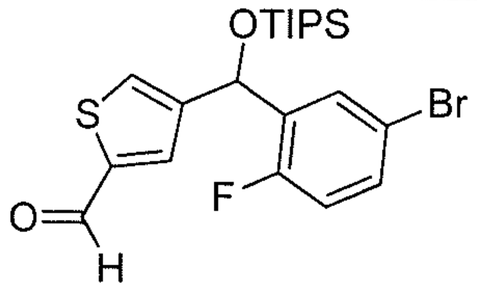
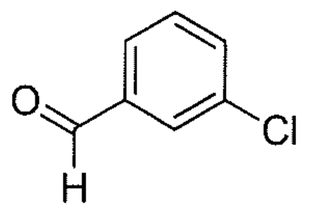
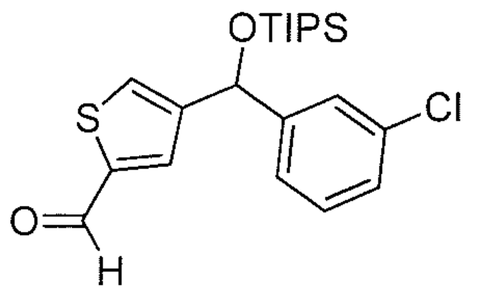
[00445] rac-(3-Bromophenyl)[5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]methanol (1.32 g, 3.19 mmol) and 1H-imidazole (3.26 g, 47.9 mmol) was dissolved in DCM (20.0 mL), then TIPSCl (6.16 g, 31.9 mmol) was added to this solution at rt. The solvent was removed by evaporation. The neat reaction mixture was heated at 80 °C for 2 h. The reaction was quenched by addition of 30 ml water and the mixture was extracted with DCM (10 ml x2). The combined organic layers were concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 8% EtOAc in hexanes as eluent) provide the disilylated intermediate. The mixture was dissolved in 30 mL of 1% HCl in EtOH solution and the resulting mixture was stirred for 15 min at rt. The reaction was quenched by addition of saturated $NaHCO_3$ (30mL) and the mixture was extracted with DCM (30mLx2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 0.50g (34%) of the title compound. LCMS (FA): *m/z* = 455.0 (M+1).

Step 3: rac-4-{(3-Bromophenyl)[(triisopropylsilyl)oxy]methyl}thiophene-2-carbaldehyde.

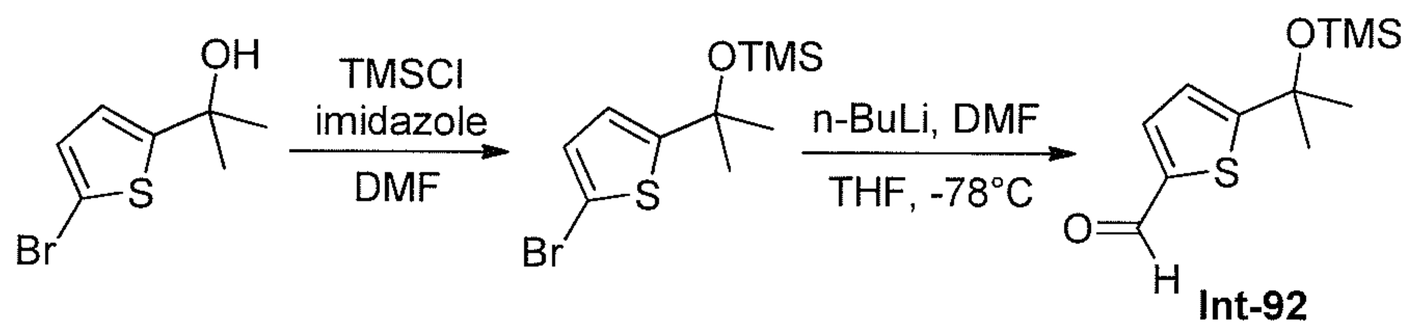
[00446] rac-(4-{(3-Bromophenyl)[(triisopropylsilyl)oxy]methyl}-2-thienyl)methanol (0.50 g, 1.10 mmol) was dissolved into DCM (30.0 mL), then MnO_2 (1.43 g, 16.5 mmol) was added to this solution. The reaction was sirred at rt overnight. The mixture was filtered through a Celite pad

and washed with DCM. The filtrate was concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 20% EtOAc in hexanes as eluent) to give 201.3 mg (40%) of the title compound as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (d, *J* = 1.3 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.65 – 7.59 (m, 1H), 7.59 – 7.54 (m, 1H), 7.42 – 7.37 (m, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 5.87 (s, 1H), 1.19 – 0.95 (m, 21H).

[00447] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the listed starting material:

Step 1 aldehyde	Compound Name / No.	Characterization Data
	 **Int-90**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (d, *J* = 1.1 Hz, 1H), 7.76 (dd, *J* = 6.3, 2.5 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.34 (ddd, *J* = 8.6, 4.6, 2.6 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.20 (s, 1H), 1.22 – 1.07 (m, 3H), 1.04 – 0.95 (m, 18H).^{1}H NMR
	 **Int-91**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.82 (d, *J* = 1.2 Hz, 1H), 7.65 (q, *J* = 1.3 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.40 (s, 1H), 7.30 – 7.26 (m, 2H), 7.23 (ddt, *J* = 6.6, 4.5, 2.6 Hz, 1H), 5.86 (s, 1H), 1.16 – 1.05 (m, 3H), 1.04 – 0.96 (m, 18H).^{1}H NMR

Example 57: **5-{2-[(Trimethylsilyl)oxy]propan-2-yl}thiophene-2-carbaldehyde. Int-92**



Int-92

Step 1: {[2-(5-Bromo-2-thienyl)propan-2-yl]oxy}(trimethyl)silane.

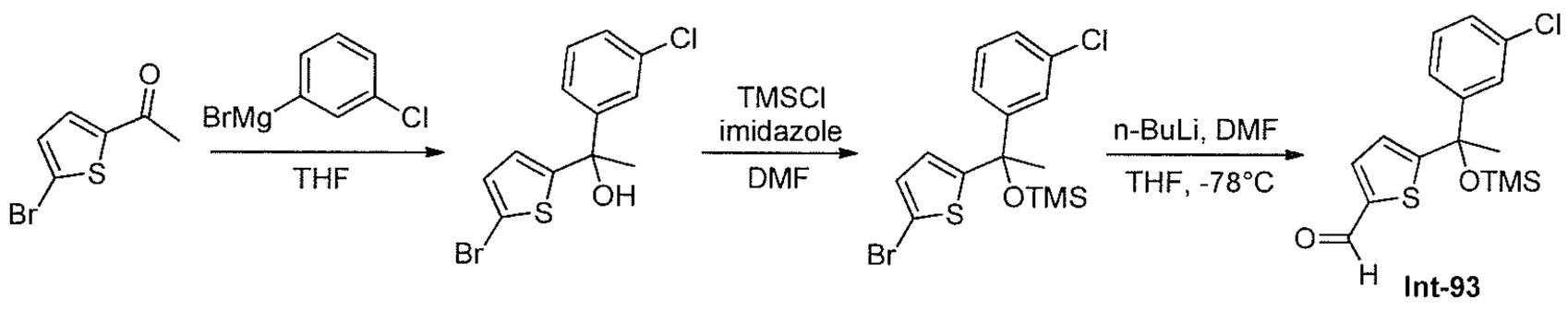
[00448] To a solution of 2-(5-bromo-2-thienyl)propan-2-ol (821 mg, 3.71 mmol) in DMF (14.0 mL) was added 1H-imidazole (758 mg, 11.1 mmol) and TMSCl (0.71 mL, 5.57 mmol) at rt and the reaction was stirred overnight. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ at rt and extracted with EtOAc (3x). The combined organic layers were washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 835 mg (77%) of the title

compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.84 (d, *J* = 3.8 Hz, 1H), 6.57 (d, *J* = 3.8 Hz, 1H), 1.61 (s, 6H), 0.11 (s, 9H).

Step 2: 5-{2-[(Trimethylsilyl)oxy]propan-2-yl}thiophene-2-carbaldehyde.

[00449] Into a round-bottom flask cooled at -78 °C was added 2.50 M of *n*-BuLi in hexane (1.25 mL, 3.13 mmol). To the *n*-BuLi solution was added quickly dropwise a solution of {[2-(5-bromo-2-thienyl)propan-2-yl]oxy}(trimethyl)silane (835 mg, 2.85 mmol) in THF (9.0 mL) and the mixture was stirred for 5 min at -78 °C. To the mixture was added quickly dropwise a solution of DMF (0.33 mL, 4.27 mmol) in THF (2.0 mL) and the reaction was stirred for 30 min. The reaction was then quenched with water and extracted with EtOAc (3x). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 494 mg (72%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (s, 1H), 7.60 (d, *J* = 3.9 Hz, 1H), 6.94 (d, *J* = 3.9 Hz, 1H), 1.66 (s, 6H), 0.14 (s, 9H).

Example 58: **rac-5-{1-(3-Chlorophenyl)-1-[(trimethylsilyl)oxy]ethyl}thiophene-2-carbaldehyde Int-93**



Step 1: rac-1-(5-Bromo-2-thienyl)-1-(3-chlorophenyl)ethanol.

[00450] Into a round-bottom flask was added 2-bromo-5-acetylthiophene (1.00 g, 4.88 mmol) dissolved in THF (10.0 mL). The mixture was cooled to 0 °C and a 0.5 M solution of 3-chlorophenylmagnesium bromide in THF (19.5 mL, 9.75 mmol) was added dropwise over 30 min. The mixture was then stirred at 0 °C for 1 hour, warmed to rt and stirred overnight. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3x). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 1.20 g (78%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.48 (m, 1H), 7.36 – 7.32 (m, 1H), 7.28 – 7.26 (m, 2H), 6.88 (d, *J* = 3.8 Hz, 1H), 6.65 (d, *J* = 3.8 Hz, 1H), 2.36 (s, 1H), 1.96 (s, 3H).

Step 2: rac-[1-(5-Bromo-2-thienyl)-1-(3-chlorophenyl)ethoxy](trimethyl)silane.

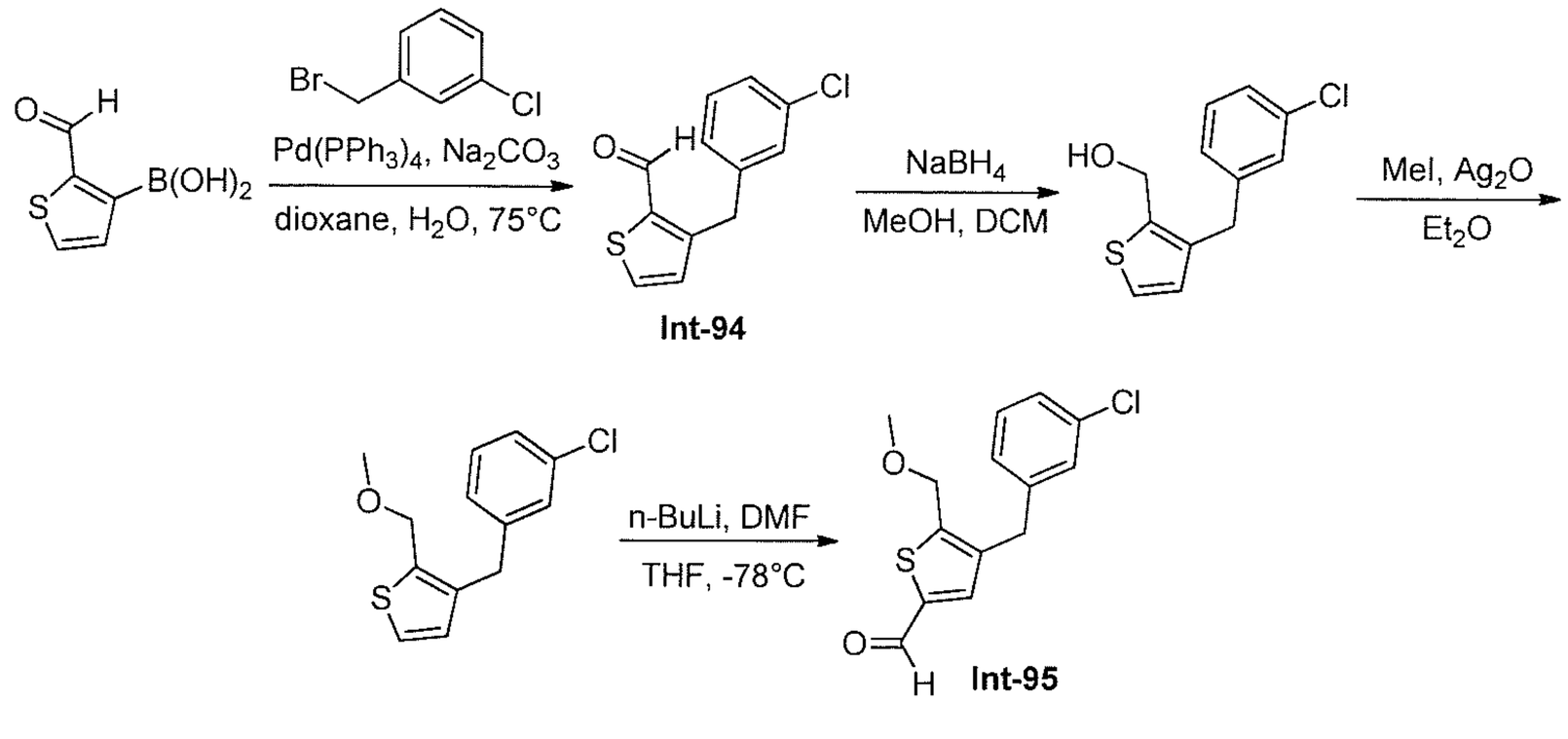
[00451] To a solution of rac-1-(5-bromo-2-thienyl)-1-(3-chlorophenyl)ethanol (590 mg, 1.86 mmol) in DMF (7.0 mL) was added 1H-imidazole (379 mg, 5.57 mmol) and TMSCl (0.35 mL, 2.79 mmol)

at rt. The reaction was then stirred at rt for 2 h. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (3x). The organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 523 mg (72%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.41 (m, 1H), 7.29 – 7.26 (m, 1H), 7.23 – 7.20 (m, 2H), 6.84 (d, *J* = 3.8 Hz, 1H), 6.58 (d, *J* = 3.8 Hz, 1H), 1.95 (s, 3H), 0.08 (s, 9H).

Step 3: rac-5-{1-(3-Chlorophenyl)-1-[(trimethylsilyl)oxy]ethyl}thiophene-2-carbaldehyde.

[00452] Into a round-bottom flask cooled at -78 °C 2.50 M of *n*-BuLi in hexane (0.59 mL, 1.48 mmol) was added. To the *n*-BuLi solution was added quickly dropwise a solution of rac-[1-(5-bromo-2-thienyl)-1-(3-chlorophenyl)ethoxy](trimethyl)silane (523 mg, 1.34 mmol) in THF (4.00 mL) and the mixture was stirred for 5 min at -78 °C. To the mixture was added quickly dropwise a solution of DMF (0.16 mL, 2.01 mmol) in THF (1.00 mL) and the reaction was stirred for 10 min. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 362 mg (80%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (s, 1H), 7.57 (d, *J* = 3.9 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.33 – 7.28 (m, 1H), 7.25 – 7.21 (m, 2H), 6.87 (d, *J* = 3.9 Hz, 1H), 2.03 (s, 3H), 0.08 (s, 9H).

Example 59: **3-(3-Chlorobenzyl)thiophene-2-carbaldehyde Int-94 and 4-(3-Chlorobenzyl)-5-(methoxymethyl)thiophene-2-carbaldehyde Int-95**



Step 1: 3-(3-Chlorobenzyl)thiophene-2-carbaldehyde

[00453] To a degassed solution of 2-formyl-3-thiopheneboronic acid (3.05 g, 19.5 mmol), 1-(bromomethyl)-3-chlorobenzene (2.82 mL, 21.5 mmol), and Na_2CO_3 (6.21 g, 58.6 mmol) in 1,4-dioxane (60 mL) and water (15 mL, 830 mmol) was added $Pd(PPh_3)_4$ (2.26 g, 1.95 mmol). The

reaction mixture was stirred 75 °C for 15 h and then quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, washed with brine, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 3.86 g (84%) of the title compound as a tan oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.18 (d, J = 1.0 Hz, 1H), 8.03 (d, J = 4.9 Hz, 1H), 7.43 – 7.20 (m, 4H), 7.15 (d, J = 5.0 Hz, 1H), 4.38 (s, 2H). LCMS (FA): *m/z* = 237.3 (M+1).

Step 2: [3-(3-Chlorobenzyl)-2-thienyl]methanol

[00454] To a 0 °C stirred solution of 3-(3-chlorobenzyl)thiophene-2-carbaldehyde (3.54 g, 15.0 mmol) in MeOH (50 mL) and DCM (50 mL, 800 mmol) was added $NaBH_4$ (848 mg, 22.4 mmol). The reaction mixture was stirred at 0 °C for 15 h, then quenched with water and concentrated to remove the solvent. The resulting aqueous layer was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 3.34 g (94%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.37 – 7.11 (m, 5H), 6.82 (d, J = 5.1 Hz, 1H), 5.42 (t, J = 5.5 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 3.91 (s, 2H).

Step 3: [3-(3-Chlorobenzyl)-2-thienyl]methyl methyl ether3-(3-chlorobenzyl)-2-(methoxymethyl)thiophene

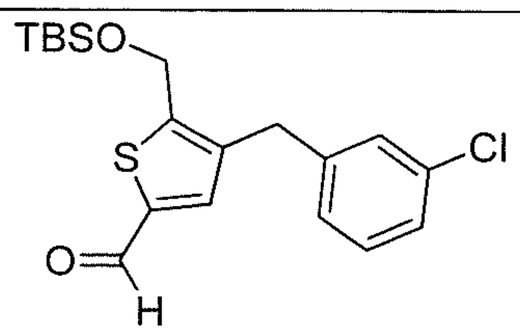
[00455] To a solution of [3-(3-chlorobenzyl)-2-thienyl]methanol (979 mg, 4.10 mmol) in Et_2O (26 mL) was added MeI (10.2 mL, 164 mmol) and Ag_2O (2.38 g, 10.2 mmol). The reaction was stirred at rt for 16 h and then filtered over a pad of Celite. The resulting filtrate was concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 450 mg (44%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.24 – 7.16 (m, 4H), 7.04 – 6.99 (m, 1H), 6.82 – 6.78 (m, 1H), 4.57 (s, 2H), 3.96 (s, 2H), 3.40 (s, 3H).

Step 4: 4-(3-Chlorobenzyl)-5-(methoxymethyl)thiophene-2-carbaldehyde

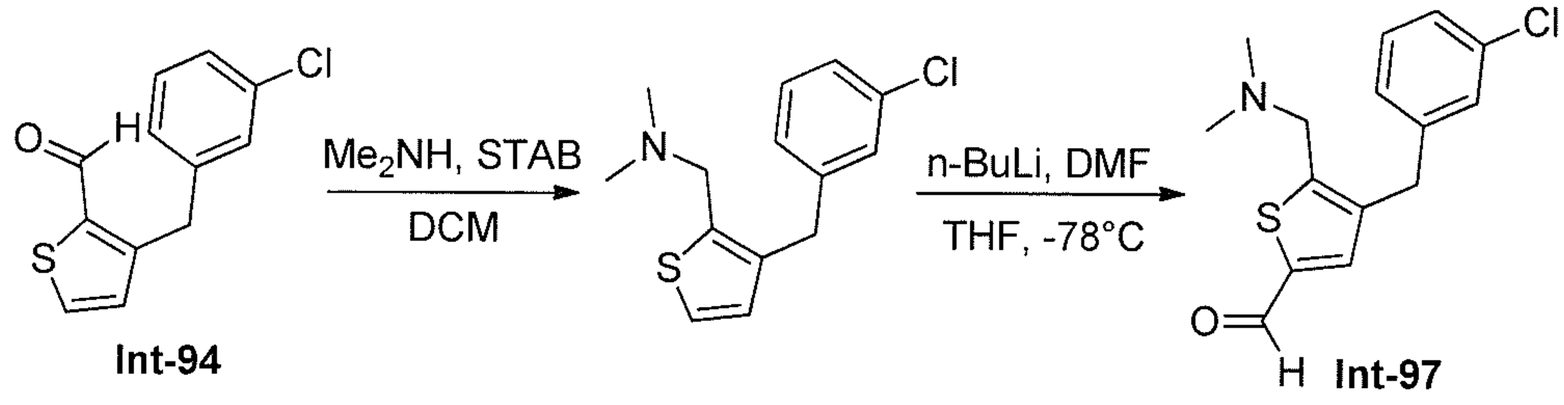
[00456] To a -78 °C cooled solution of [3-(3-chlorobenzyl)-2-thienyl]methyl methyl ether3-(3-chlorobenzyl)-2-(methoxymethyl)thiophene (541 mg, 2.14 mmol) in THF (15.0 mL) was added a 2.50 M solution of *n*-BuLi in hexane (1.71 mL, 4.28 mmol), dropwise, via syringe. The resulting mixture was stirred for 30 min followed by addition of DMF (1.66 mL, 21.4 mmol), dropwise, via syringe. The reaction was allowed to stir at -78 °C for an additional 30 min and then quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, washed with brine, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 15% EtOAc in hexanes to give 305 mg (51%) of the title compound as a light brown oil. ^{1}H NMR (400 MHz, Chloroform-d) δ

9.82 (s, 1H), 7.46 (s, 1H), 7.35 – 7.20 (m, 3H), 7.17 (s, 1H), 7.06 (d, J = 6.6 Hz, 1H), 4.60 (s, 2H), 3.96 (s, 2H), 3.45 (s, 3H). LCMS (FA): *m/z* = 281.4 (M+1).

[00457] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Step 3 reaction reagents	**Compound Name / No.**	**Characterization Data**
TBSCl, imidazole DMF	 **Int-96**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.74 (s, 1H), 7.38 – 7.25 (m, 3H), 7.21 (d, *J* = 7.4 Hz, 1H), 4.91 (s, 2H), 3.94 (s, 2H), 0.89 (s, 9H), 0.08 (s, 6H).^{1}H NMR

Example 60: **4-(3-Chlorobenzyl)-5-[(dimethylamino)methyl]thiophene-2-carbaldehyde Int-97**



Int-94 **Int-97**

Step 1: 1-[3-(3-Chlorobenzyl)-2-thienyl]-N,N-dimethylmethanamine

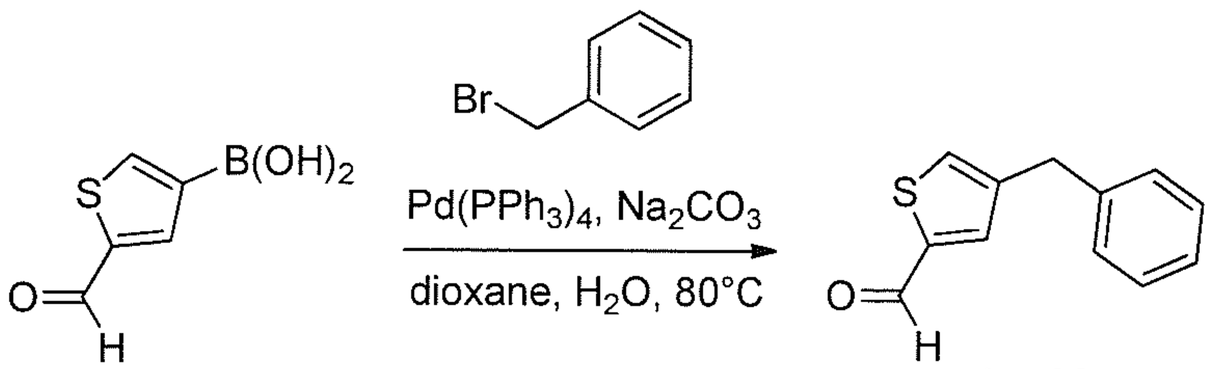
[00458] To a solution of Int-94 (415 mg, 1.75 mmol) in MeOH (12.3 mL) was added a 2.0 M solution of Me_2NH in MeOH (1.75 mL, 3.51 mmol) and sodium triacetoxyborohydride (743 mg, 3.51 mmol). The reaction mixture was stirred at rt for 24 h and then concentrated to remove the solvent. The residue was diluted in water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 50% EtOAc in hexanes to give 357 mg (77%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.37 – 7.28 (m, 2H), 7.27 – 7.20 (m, 2H), 7.15 (d, J = 7.6 Hz, 1H), 6.83 (d, J = 5.1 Hz, 1H), 3.93 (s, 2H), 3.54 (s, 2H), 2.16 (s, 6H). LCMS (FA): *m/z* = 266.3 (M+1).

Step 2: 4-(3-Chlorobenzyl)-5-[(dimethylamino)methyl]thiophene-2-carbaldehyde.

[00459] To a -78 °C cooled solution of 1-[3-(3-chlorobenzyl)-2-thienyl]-N,N-dimethylmethanamine (357 mg, 1.34 mmol) in THF (12.6 mL) was added a 2.50 M solution of *n*-BuLi in hexane (1.07 mL, 2.69 mmol), dropwise, via syringe. The reaction was allowed to stir at -78 °C for 20 min followed by addition of a solution of DMF (0.21 mL, 2.69 mmol) in THF (3 mL), dropwise, via

syringe. After 30 min, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 5% MeOH in DCM to give 270 mg (69%) of the title compound as a light yellow oil. LCMS (FA): *m/z* = 295.9 (M+1).

Example 61: **4-Benzylthiophene-2-carbaldehyde Int-98**

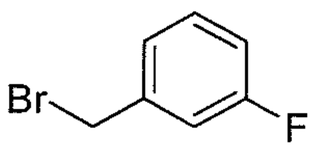
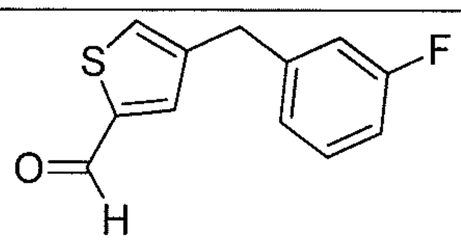


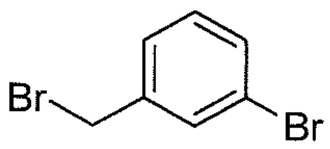
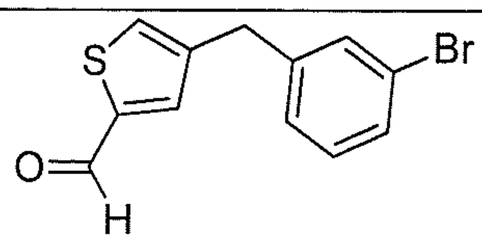
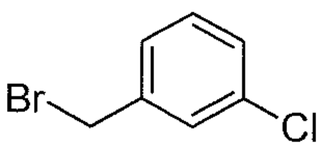
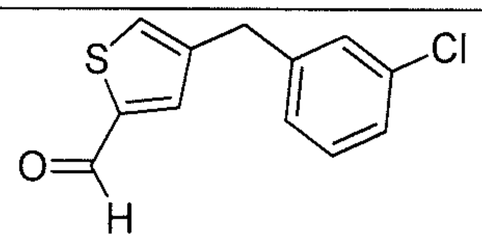
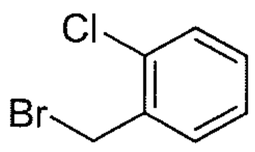
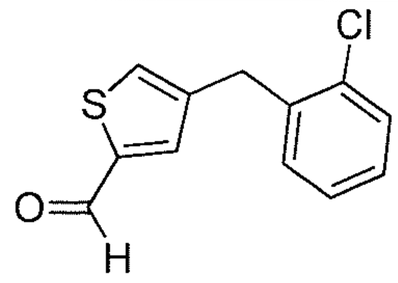
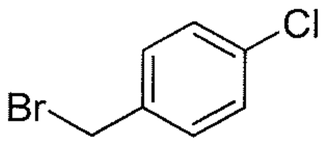
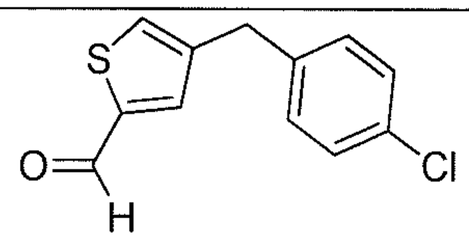
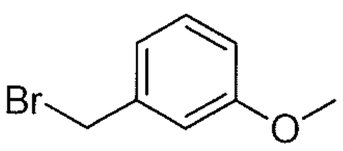
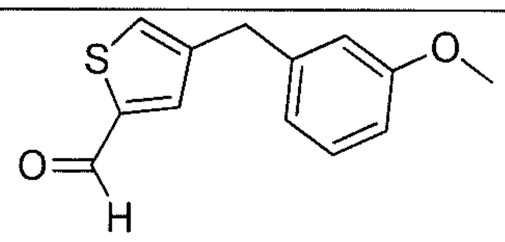
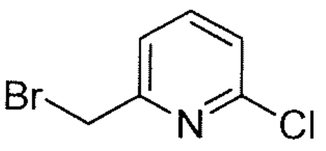
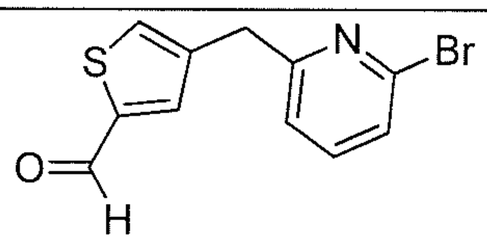
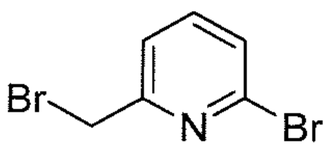
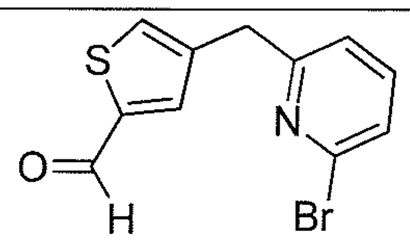
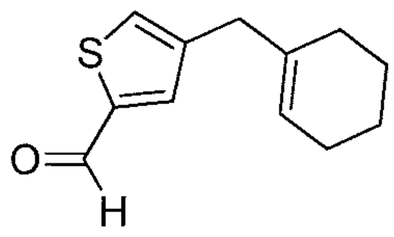
Int-98

Step 1: 4-Benzylthiophene-2-carbaldehyde.

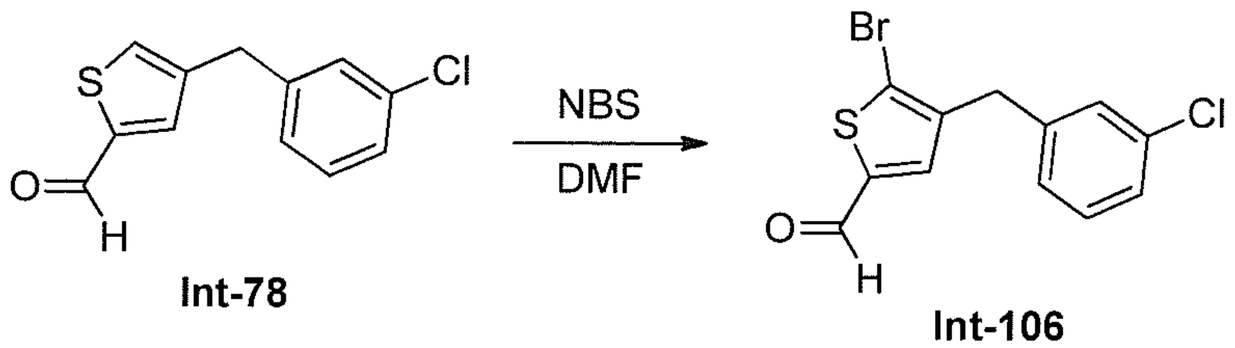
[00460] To a degassed solution of 2-formyl-4-thiopheneboronicacid (509 mg, 3.26 mmol), benzyl bromide (558 mg, 3.26 mmol), and Na_2CO_3 (692 mg, 6.53 mmol) in 1,4-dioxane (24.4 mL) was added $Pd(PPh_3)_4$ (377 mg, 0.33 mmol). The reaction mixture was stirred at 80 °C for 3 h then quenched with water and extracted with EtOAc. The combined organic layers were dried over Mg_2SO_4, filtered and concentrated in vacuo the crude material was purified by ISCO column chromatography eluting with 0% - 10% EtOAc in hexanes to give 377 mg (57%) of the title compound as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.86 (d, J = 1.2 Hz, 1H), 7.84 (d, J = 6.1 Hz, 2H), 7.38 – 7.18 (m, 5H), 4.00 (s, 2H). LCMS (FA): *m/z* = 203.0 (M+1).

[00461] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the appropriate starting materials. The following alternative conditions could be employed in the described reaction steps. Condition A: $Pd(PPh_3)_4$, Na_2CO_3, dioxane, water, 80°C, B: $Pd(PPh_3)_4$, K_2CO_3, dioxane, water, 80°C, C: $PdCl_2(dppf)$, Cs_2CO_3, dioxane, water, 60°C, D: $Pd(PPh_3)_4$, Cs_2CO_3, dioxane, water, 75°C, E: $PdCl_2(dppf)$, Cs_2CO_3, THF, water, 70°C.

Alkyl bromide	Reaction Condition	Compound Name / No.	Characterization Data
	A	 **Int-99**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (d, *J* = 1.3 Hz, 1H), 7.89 – 7.84 (m, 2H), 7.35 (td, *J* = 8.1, 6.3 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.04 (td, *J* = 8.6, 8.2, 2.5 Hz, 1H), 4.02 (s, 2H).^{1}H NMR

	**A**	 **Int-79**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (d, *J* = 1.2 Hz, 1H), 7.55 (d, *J* = 1.2 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 3.97 (s, 2H).^{1}H NMR
	**A**	 **Int-78**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (d, *J* = 1.0 Hz, 1H), 7.87 (s, 2H), 7.39 – 7.31 (m, 2H), 7.31 – 7.22 (m, 2H), 4.01 (s, 2H).^{1}H NMR
	**A**	 **Int-100**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (d, *J* = 1.3 Hz, 1H), 7.86 – 7.78 (m, 2H), 7.49 – 7.38 (m, 2H), 7.36 – 7.26 (m, 2H), 4.10 (s, 2H).^{1}H NMR
	**A**	 **Int-101**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (d, *J* = 1.2 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 2H), 7.42 – 7.33 (m, 2H), 7.32 – 7.25 (m, 2H), 3.99 (s, 2H).^{1}H NMR
	**B**	 **Int-102**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (d, *J* = 0.9 Hz, 1H), 7.56 (s, 1H), 7.39 (s, 1H), 7.26 – 7.21 (m, 1H), 6.83 – 6.75 (m, 2H), 6.73 (s, 1H), 3.97 (s, 2H), 3.79 (s, 3H). LCMS (FA): *m/z* = 233.1 (M+1).
	**C**	 **Int-103**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 1.1 Hz, 1H), 7.67 (d, *J* = 1.1 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.52 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 4.15 (s, 2H).^{1}H NMR
	**D**	 **Int-104**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 1.0 Hz, 1H), 7.66 (d, *J* = 1.1 Hz, 1H), 7.52 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 4.15 (s, 2H).^{1}H NMR
	**E**	 **Int-105**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 1.1 Hz, 1H), 7.58 (d, *J* = 1.1 Hz, 1H), 7.38 (s, 1H), 5.51 – 5.46 (m, 1H), 3.25 (s, 2H), 2.08 – 1.97 (m, 2H), 1.92 – 1.82 (m, 2H), 1.68 – 1.49 (m, 4H). LCMS (FA): *m/z* = 207.1 (M+1).

Example 62**: 5-Bromo-4-(3-chlorobenzyl)thiophene-2-carbaldehyde Int-106**

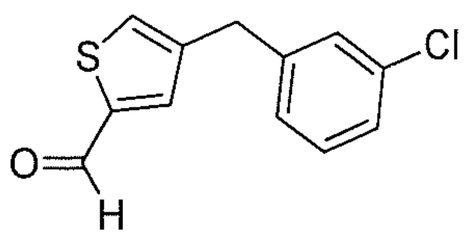
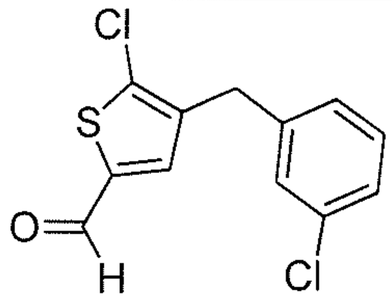
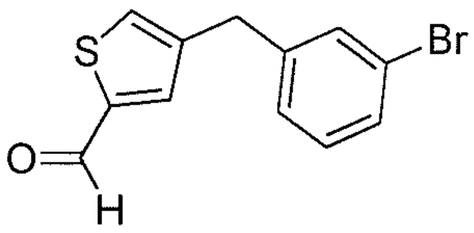
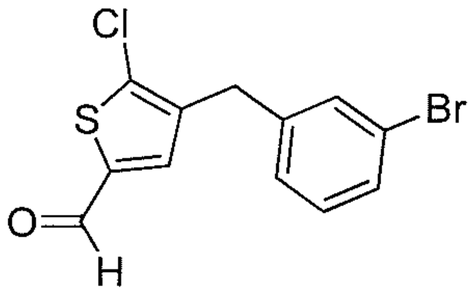
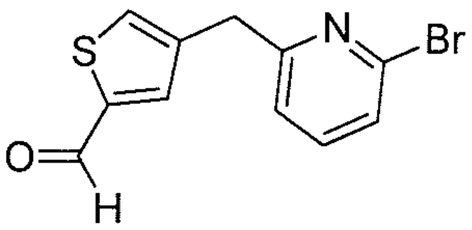
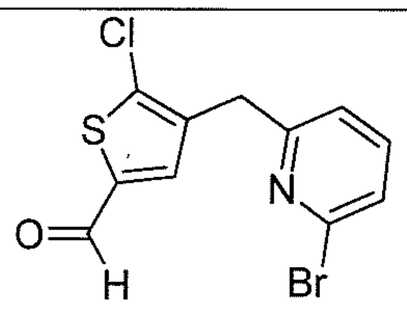


Int-78 **Int-106**

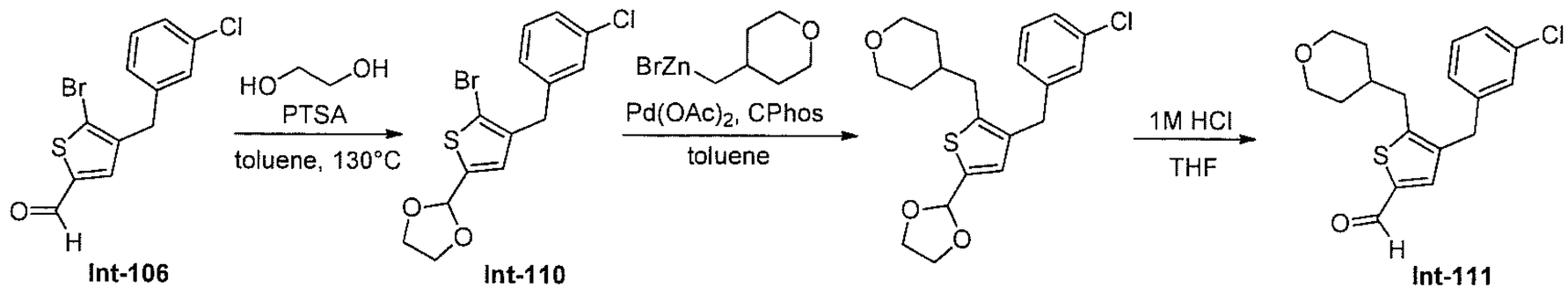
Step 1: 5-Bromo-4-(3-chlorobenzyl)thiophene-2-carbaldehyde.

[00462] To a solution of Int-78 (637 mg, 2.69 mmol) and NBS (718 mg, 4.04 mmol) in DMF (27 mL). The reaction mixture was stirred at 50 °C for 15 h and then quenched with water and extracted with EtOAc. The combined organic layers were washed with 10% aqueous LiCl, dried over $MgSO_4$, filtered and concentrated in vacuo and the crude material was purified by ISCO column chromatography eluting with 0% - 25% EtOAc in hexanes to give 289 mg (34%) of title compound as a clear oil. LCMS (FA): *m/z* = 317.0 (M+1).

[00463] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the appropriate starting materials. The following alternative conditions could be employed in the described reaction steps. Step 1: NCS instead of NBS halogenation.

Starting material	Step 1 reagent	Compound Name / No.	Characterization Data
 **Int-78**	**NCS**	 **Int-107**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.89 (s, 1H), 7.40 – 7.29 (m, 3H), 7.24 – 7.19 (m, 1H), 4.00 (s, 2H).^{1}H NMR
 **Int-79**	**NCS**	 **Int-108**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.71 (s, 1H), 7.42 – 7.32 (m, 3H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 3.93 (s, 2H). LCMS (FA): *m/z* = 317.1 (M+1).
 **Int-103**	**NCS**	 **Int-109**	LCMS (FA): *m/z* = 318.1 (M+1).

Example 63: **2-[5-Bromo-4-(3-chlorobenzyl)-2-thienyl]-1,3-dioxolane Int-110 and 4-(3-Chlorobenzyl)-5-(tetrahydro-2H-pyran-4-ylmethyl)thiophene-2-carbaldehyde Int-111**



Step 1: 2-[5-Bromo-4-(3-chlorobenzyl)-2-thienyl]-1,3-dioxolane.

[00464] A 1 L round bottom flask under nitrogen was charged with Int-106 (1.70 g, 5.39 mmol), toluene (20 mL), 1,2-ethanediol (1.50 mL, 26.9 mmol), and p-toluenesulfonic acid monohydrate (51.2 mg, 0.27 mmol). Attached a Dean-Stark Trap and a condenser and heated to reflux overnight. The reaction mixture was allowed to cool to rt and quenched with water. The solution was extracted with EtOAc (25mLx3). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to ISCO column chromatographyl (0% - 30% EtOAc in hexanes as eluent) to give 1.8g (93%) of the title compound as an amber oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.15 (m, 3H), 7.09 – 7.04 (m, 1H), 6.75 (s, 1H), 5.95 (s, 1H), 4.11 – 4.03 (m, 2H), 4.01 – 3.93 (m, 2H), 3.85 (s, 2H).

Step 2: 4-{[3-(3-Chlorobenzyl)-5-(1,3-dioxolan-2-yl)-2-thienyl]methyl}tetrahydro-2H-pyran

[00465] A 100 mL 2-neck round bottom flask was charged with zinc powder (548 mg, 8.38 mmol) and the reaction vessel was purged with argon. DMA (6mL) was added into the flask and iodine (36 mg, 0.14 mmol) was added to the suspension. The resulting mixture was stirred until the red color of iodine had faded. To the mixture was added 4-bromomethyltetrahydropyran (1 g, 6 mmol) and the mixture was allowed to stirr for 12 h at 70 °C. After cooling to rt, the gray solution was passed through Acrodisc R filter and this 1.0M solution was carried on the next reaction without purification.

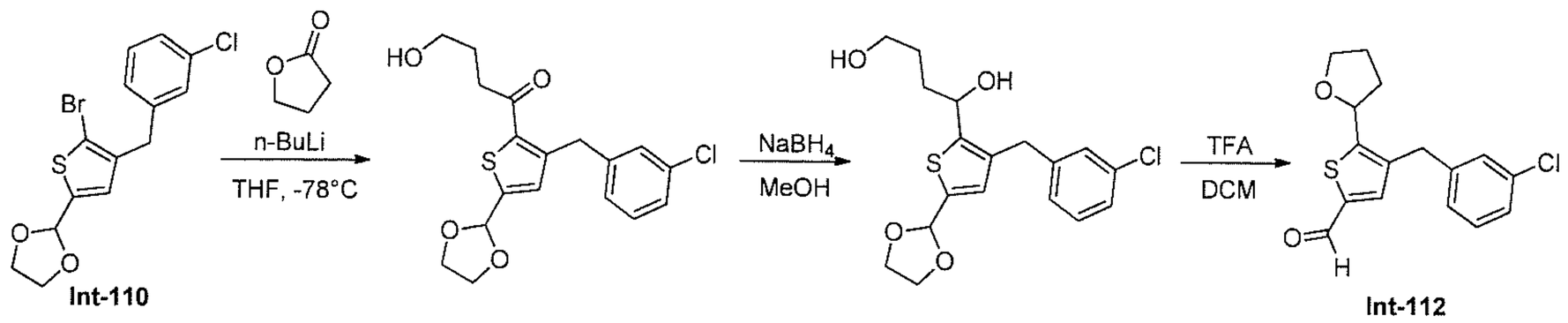
[00466] A 20mL of microwave vessel was charged with 2-[5-bromo-4-(3-chlorobenzyl)-2-thienyl]-1,3-dioxolane (500 mg, 1 mmol)), $Pd(OAc)_2$ (15.6 mg, 0.07 mmol) and 2-dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl (60.7 mg, 0.14 mmol). To the mixture was added toluene (4.26 mL) followed by the addition of 1.0M [(tetrahydro-2H-pyran-4-yl)methyl]zinc(II) bromide in DMA solution (2.78 mL, 2.78 mmol) dropwise over 30 min. Upon addition of the solution turned a deep red color and the reaction vessel was purged with argon followed by sealing with a cap. The reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched with 0.5M HCl and diluted with water and EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 40% EtOAc in hexanes as eluent) to give 186 mg (40%) of the

title compound as an orange color oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.16 (m, 2H), 7.09 (s, 1H), 6.99 (d, *J* = 6.7 Hz, 1H), 6.79 (s, 1H), 5.95 (s, 1H), 4.15 – 4.09 (m, 2H), 4.01 – 3.96 (m, 2H), 3.92 (dd, *J* = 12.0, 5.0 Hz, 2H), 3.82 (s, 2H), 3.29 (t, 2H), 2.66 (d, *J* = 7.1 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.56 (s, 1H), 1.30 – 1.23 (m, 2H).

Step 3: 4-(3-Chlorobenzyl)-5-(tetrahydro-2H-pyran-4-ylmethyl)thiophene-2-carbaldehyde.

[00467] To a solution of 4-{[3-(3-Chlorobenzyl)-5-(1,3-dioxolan-2-yl)-2-thienyl]methyl}tetrahydro-2H-pyran (170 mg, 0.45 mmol) in THF (3.0 mL) was added 1.0 M of HCl in water (1.21 mL) at rt. After 2 h, the reaction mixture was basified with saturated $NaHCO_3$, extracted with EtOAc (50mLx2). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by ISCO column chromatography (0% - 40% EtOAc in hexanes as eluent) to give 128 mg (85%) of the title compound as a pale yellow oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.81 (s, 1H), 7.46 (s, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.28 (s, 1H), 7.16 (s, 1H), 7.07 (d, *J* = 6.7 Hz, 1H), 3.99 (dd, *J* = 11.4, 3.7 Hz, 2H), 3.95 (s, 2H), 3.37 (t, *J* = 11.1 Hz, 2H), 2.80 (d, *J* = 7.2 Hz, 2H), 2.10 (s, 1H), 1.67 (d, *J* = 13.1 Hz, 2H), 1.37 (dd, *J* = 12.5, 4.1 Hz, 2H).

Example 64**: rac-4-(3-Chlorobenzyl)-5-(tetrahydrofuran-2-yl)thiophene-2-carbaldehyde. Int-112**



Step 1: 1-[3-(3-Chlorobenzyl)-5-(1,3-dioxolan-2-yl)-2-thienyl]-4-hydroxybutan-1-one.

[00468] To a stirred solution of Int-110 (120 mg, 0.33 mmol) in dry Et_2O (3 mL) 1.6 M of *n*-BuLi in hexane (0.25 mL, 0.40 mmol) was added dropwise at -78 °C. The solution was stirred for 30 min at -78 °C. The solution of γ-butyrolactone (40 mg, 0.5 mmol) in Et_2O (0.5 mL) was added slowly and stirred for 15 min at -78 °C. The solution was allowed to rt and stirred 1 hour. The solution was quenched with saturated NH_4Cl aq. (5 mL) solution and was extracted with EtOAc (2x20 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 80% EtOAc in hexanes as eluent) to give 75 mg (61%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 (s, 1H), 7.25 – 7.23 (m, 2H), 7.18 – 7.11 (m, 1H), 6.95 (s, 1H), 6.07 (s, 1H), 4.38 (s, 2H), 4.18 – 4.15 (m, 2H), 4.11 – 4.04 (m, 2H), 3.77 (t, *J* = 5.3 Hz, 2H), 3.06 (t, *J* = 6.9 Hz, 2H), 2.04 (q, *J* = 6.5 Hz, 2H).

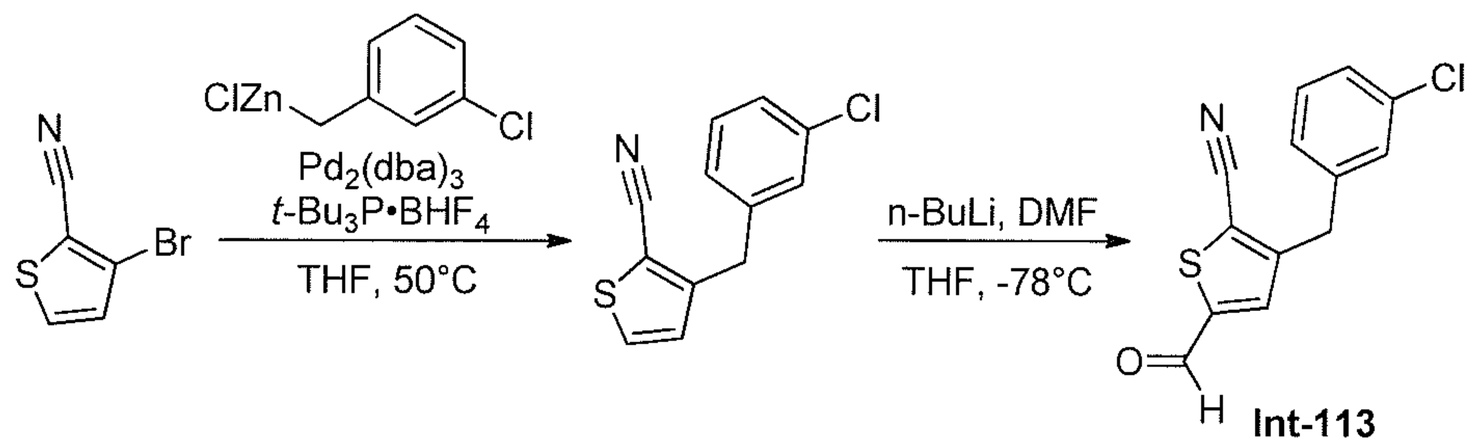
Step 2: rac-1-[3-(3-Chlorobenzyl)-5-(1,3-dioxolan-2-yl)-2-thienyl]butane-1,4-diol.

[00469] To a solution of 1-[3-(3-chlorobenzyl)-5-(1,3-dioxolan-2-yl)-2-thienyl]- 4-hydroxybutan- 1-one (50 mg, 0.1 mmol) in MeOH (5 mL) was added $NaBH_4$ (6.19 mg, 0.16 mmol) at 0 °C and the reaction was stirred for 2 h at 0 °C. The reaction mixture was quenched by addition of saturated $NaHCO_3$ (5mL) and extracted with EtOAc (10mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 100% EtOAc in hexanes as eluent) to give 40 mg (80%) of the title compound. LCMS (FA): *m/z* = 369.5 (M+1).

Step 3: rac-4-(3-Chlorobenzyl)-5-(tetrahydrofuran-2-yl)thiophene-2-carbaldehyde.

[00470] rac-1-[3-(3-chlorobenzyl)-5-(1,3-dioxolan-2-yl)-2-thienyl]butane-1,4-diol (815 mg, 2.21 mmol) was dissolved into DCM (5.1 mL), then TFA (18 mL, 230 mmol) was added to this solution with stirring at rt. The reaction mixture was stirred at rt for 2 h, and quenched with water, and extracted with DCM (10mLx2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 35% EtOAc in hexanes as eluent) to give 681 mg (92%) of the title compound as a pink oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.89 (s, 1H), 7.54 (s, 1H), 7.42 – 7.33 (m, 3H), 7.15 (dd, *J* = 6.4, 2.0 Hz, 1H), 5.31 (t, *J* = 7.0 Hz, 1H), 4.29 – 4.21 (m, 2H), 4.06 – 4.00 (m, 2H), 2.46 – 2.37 (m, 1H), 2.28 – 2.09 (m, 2H), 1.98 – 1.88 (m, 1H).

Example 65**: 3-(3-Chlorobenzyl)-5-formylthiophene-2-carbonitrile Int-113**



Int-113

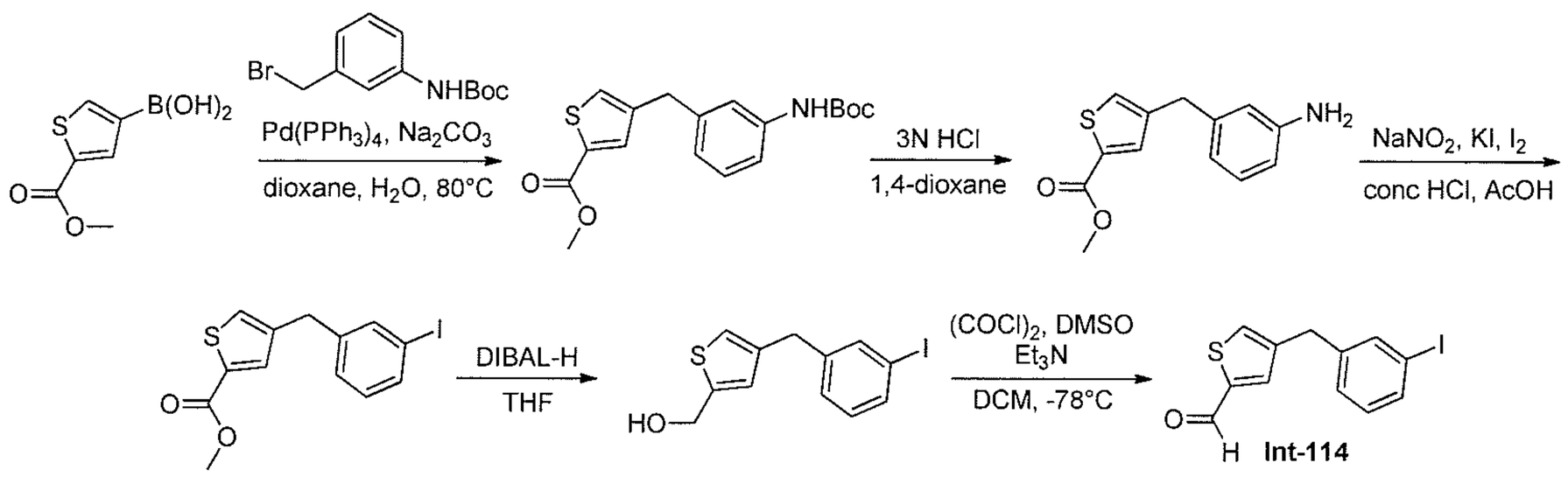
Step 1: 3-(3-Chlorobenzyl)thiophene-2-carbonitrile.

[00471] To a solution of 3-bromothiophene-2-carbonitrile (419 mg, 2.23 mmol) in THF (10.0 mL) was added $Pd_2(dba)_3$ (41 mg, 0.05 mmol), tri-t-butylphosphonium tetrafluoroborate (25 mg, 0.09 mmol). The reaction mixture was stirred at 50 °C for 24 h then quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography (0% - 10% EtOAc in hexanes as eluent) to give 225 mg (43%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.83 – 7.73 (m, 1H), 7.38 – 7.13 (m, 4H), 7.12 – 7.02 (m, 1H), 4.15 (s, 2H)

Step 2: 3-(3-Chlorobenzyl)-5-formylthiophene-2-carbonitrile.

[00472] To a -78 °C cooled solution of 3-(3-chlorobenzyl)thiophene-2-carbonitrile (150 mg, 0.64 mmol) in THF (6.04 mL) was added a 2.50 M solution of *n*-BuLi in hexane (0.39 mL, 0.96 mmol) dropwise, via syringe. The reaction mixture was allowed to stir for 20 min followed by addition of a solution of DMF (0.10 mL, 1.28 mmol) in THF (2 mL), dropwise, via syringe. The resulting mixture was stirred for an additional 1 hour then quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified by ISCO column chromatography (0% - 10% EtOAc in hexanes as eluent) to give 84 mg (50%) of the title compound as a white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 10.76 (s, 1H), 8.81 (s, 1H), 8.29 – 8.13 (m, 3H), 8.07 (d, J = 7.4 Hz, 1H), 4.14 (s, 2H).

Example 66**: 4-(3-Iodobenzyl)thiophene-2-carbaldehyde. Int-114**



Step 1: Methyl 4-{3-[(tert-butoxycarbonyl)amino]benzyl}thiophene-2-carboxylate.

[00473] A threaded 250mL round bottom flask was charged with 5-(methoxycarbonyl)thiophene-3-boronic acid (1.9 g, 10 mmol), tert-butyl [3-(bromomethyl)phenyl]carbamate (3.00 g, 10.5 mmol), Na_2CO_3 (3.33 g, 31.4 mmol), 1,4-dioxane (89.2 mL), and water (22.8 mL). The mixture was degassed with nitrogen for 15 min. To the mixture was added $Pd(PPh_3)_4$ (1.21 g, 1.05 mmol) and the reaction vessel was sealed. The reaction was heated in an 85 °C oil bath for 18 h. The mixture was concentrated in vacuo to remove dioxane followed by addition of water. The resulting mixture was extracted three times with EtOAc and then the combined organic poritons were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to give the title compound as a yellow solid, 2.25g, (62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.56 (m, 1H), 7.25 – 7.17 (m, 3H), 7.17 – 7.15 (m, 1H), 6.88 – 6.82 (m, 1H), 6.44 (s, 1H), 3.92 – 3.91 (m, 2H), 3.85 (s, 3H), 1.51 (s, 9H).

Step 2: Methyl 4-(3-aminobenzyl)thiophene-2-carboxylate.

[00474] A 100mL round bottom flask was charged with methyl 4-{3-[(tert-butoxycarbonyl)amino]benzyl}thiophene-2-carboxylate (3.28 g, 9.44 mmol) and EtOAc (20 mL) and the solution was cooled in an ice bath. To the solution was added 4 M HCl in 1,4-dioxane (20 mL) and the mixture was stirred at rt for 18 h. The reaction was poured into saturated $NaHCO_3$ and then the mixture was extracted three times with EtOAc, washed combined organic portions with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexanes / EtOAc gradient to give the title compound as yellow oil, 2.20g, (94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.56 (m, 1H), 7.18 – 7.15 (m, 1H), 7.12 – 7.05 (m, 1H), 6.62 – 6.57 (m, 1H), 6.57 – 6.53 (m, 1H), 6.51 – 6.47 (m, 1H), 3.89 – 3.80 (m, 5H), 3.62 (s, 2H).

Step 3: Methyl 4-(3-iodobenzyl)thiophene-2-carboxylate.

[00475] A 50mL round bottom flask was charged with methyl 4-(3-aminobenzyl)thiophene-2-carboxylate (2.20 g, 8.90 mmol), acetic acid (4.4 mL), and 12 M HCl in water (1.8 mL). To this mixture was added dropwise a solution of sodium nitrite (0.65 g, 9.4 mmol) in water (3.1 mL) keeping the internal temperature below 10 °C and the mixture was stirred for 20 min with cooling. To the mixture was added dropwise a solution of KI (1.77 g, 10.6 mmol) and I_2 (1.32 g, 5.21 mmol) in water (1.8 mL), and the reaction was stirred for 30 min. The resulting mixture was transferred to a sepratory funnel and 10% sodium bisulfite solution was added. The mixture was extracted three times with EtOAc and the combined organic portions were washed with brine, dried organic layer with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexanes / EtOAc gradient to give the title compound as colorless oil, 1.35g (42%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.53 (m, 3H), 7.18 – 7.12 (m, 2H), 7.07 – 7.01 (m, 1H), 3.89 (s, 2H), 3.86 (s, 3H).

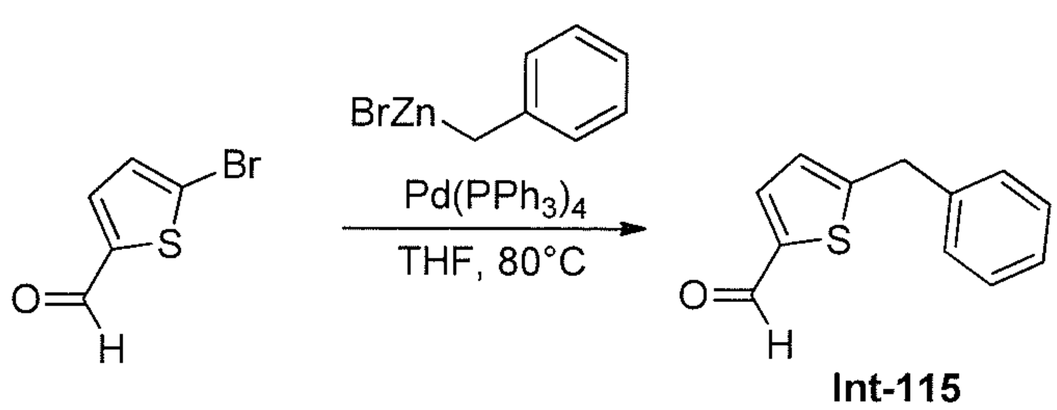
Step 4: [4-(3-Iodobenzyl)-2-thienyl]methanol.

[00476] A 500 mL round bottom flask under nitrogen was charged with methyl 4-(3-iodobenzyl)thiophene-2-carboxylate (1.35 g, 3.77 mmol) and THF (87 mL). The solution was cooled to -65 °C and then 1.0 M of DIBAL-H in toluene (15 mL) was added dropwise to the solution keeping the internal temperature below -60 °C. The reaction was stirred 1 hour at -60 °C followed by stirring for 3 h at -40 °C. The reaction was quenched by adding a 10% solution of Rochelle's Salt and the mixture was extracted three times with EtOAc. The combined organic portions were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to give the title compound as a colorless oil, 1.24g (94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.52 (m, 2H), 7.18 – 7.13 (m, 1H), 7.06 – 7.00 (m, 1H), 6.90 – 6.86 (m, 1H), 6.80 – 6.76 (m, 1H), 4.80 – 4.70 (m, 2H), 3.85 (s, 2H).

Step 5: 4-(3-Iodobenzyl)thiophene-2-carbaldehyde.

[00477] A 100mL round bottom flask under nitrogen was charged with DCM (9.4 mL) and oxalyl chloride (0.35 mL, 4.13 mmol) and the solution was cooled to -60 °C. To the solution was added dimethyl sulfoxide (0.64 mL, 9.01 mmol) dropwise and the mixture was stirred for 5 min. To the mixture was added a solution of [4-(3-iodobenzyl)-2-thienyl]methanol (1.24 g, 3.76 mmol) in DCM (4.8 mL) in a slow stream and the resulting mixture was stirred 10 min with cooling. To the reaction was added triethylamine (2.62 mL, 18.8 mmol) at -60 °C and the mixture was warmed slowly to rt. The resulting mixture was poured into saturated $NaHCO_3$ and extracted three times with DCM. The combined organic portions were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to give the title compound as pale, 1.22g (99%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.94 – 9.78 (m, 1H), 7.62 – 7.52 (m, 3H), 7.40 – 7.36 (m, 1H), 7.18 – 7.13 (m, 1H), 7.09 – 7.03 (m, 1H), 3.94 (s, 2H).

Example 67**: 5-Benzyl-thiophene-2-carbaldehyde. Int-115**

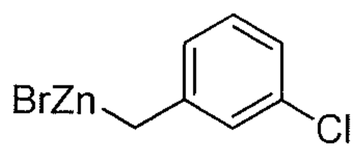
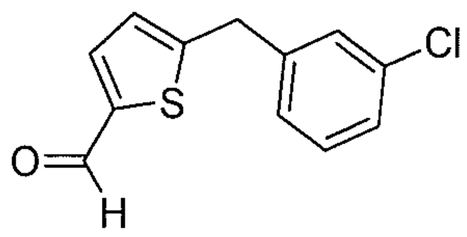


Int-115

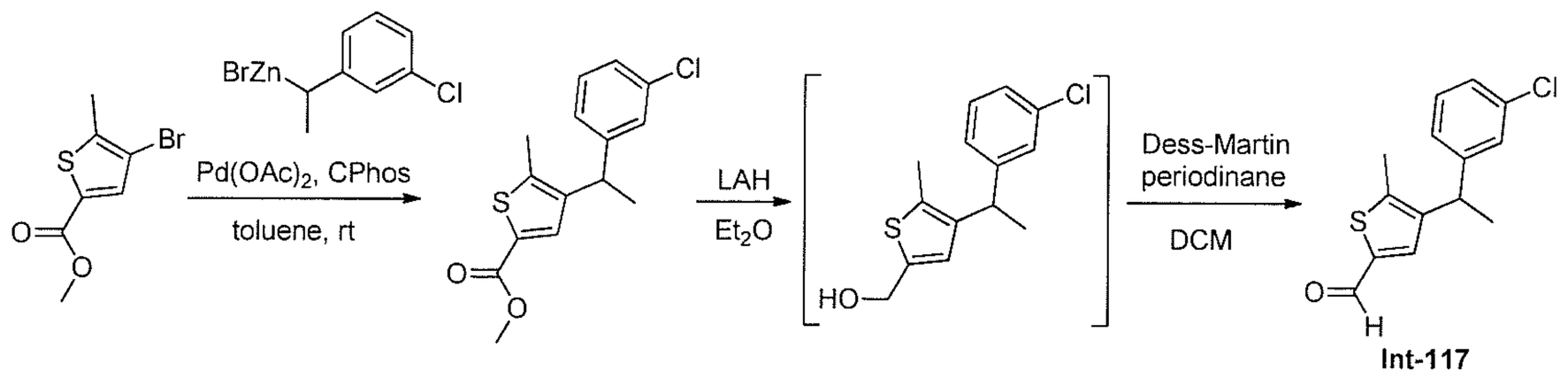
Step 1: 5-Benzyl-thiophene-2-carbaldehyde

[00478] 5-Bromo-2-thiophenecarboxaldehyde (500 mg, 2.62 mmol) and $Pd(PPh_3)_4$ (75.6 mg, 0.07 mmol) were weighed into a microwave tube and THF (5 mL) was added to the tube. The solution was stirred for 15 min under atmosphere of argon. To the mixture was added 0.50 M of benzylzinc bromide in THF (7.85 mL, 3.93 mmol), and the mixture was heated at 70 °C for 1 hour. The reaction was cooled to rt and concentrated in vacuo. To the residue was added EtOAc (100mL) and the organic layer was washed with 1N HCl (50mL) followed by saturated $NaHCO_3$ (50mL) and then brine (50mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 319mg (54%) of the title compound as a yellow oil. LCMS (AA): *m/z* = 203.4 (M+H).

[00479] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Step 1 zinc reagent	Compound Name / No.	Characterization Data
	 **Int-116**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.82 (s, 1H), 7.88 (d, J = 3.8 Hz, 1H), 7.40 (q, J = 1.6 Hz, 1H), 7.36 (d, J = 7.4 Hz, 1H), 7.32 (dt, J = 8.0, 1.5 Hz, 1H), 7.28 (dd, J = 7.3, 1.6 Hz, 1H), 7.16 (d, J = 3.8 Hz, 1H), 4.27 (s, 2H). LCMS (FA): m/z = 237.4 (M+H)

Example 68**: 4-[1-(3-Chlorophenyl)ethyl]-5-methylthiophene-2-carbaldehyde Int-117**



Int-117

Step 1: rac-Methyl 4-[1-(3-chlorophenyl)ethyl]-5-methylthiophene-2-carboxylate.

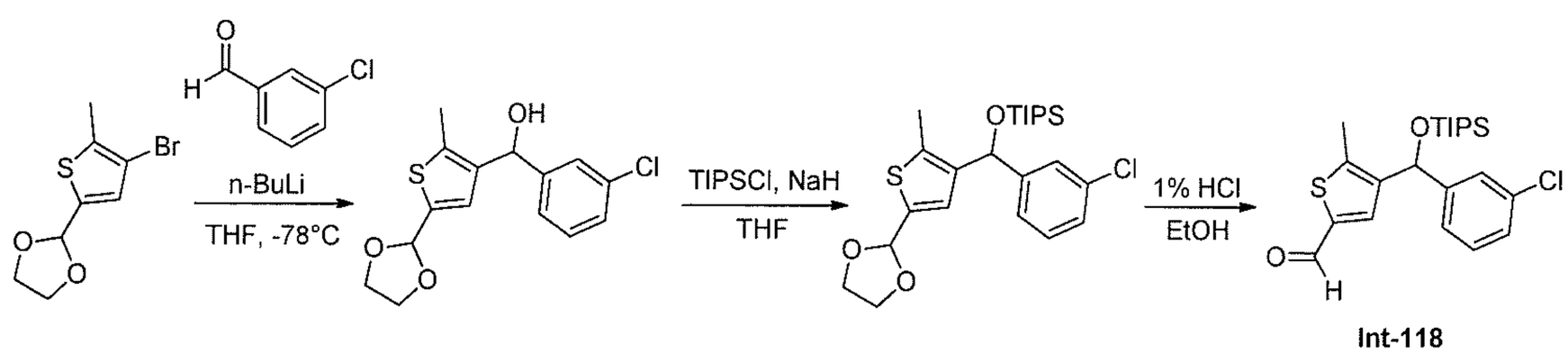
[00480] Methyl 4-bromo-5-methylthiophene-2-carboxylate (400 mg, 2.0 mmol), $Pd(OAc)_2$ (14.6 mg, 0.07 mmol) and 2-dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl (56.7 mg, 0.13 mmol) were added to a microwave reaction vial. The vial was purged with argon and toluene (4.2 mL) was added. To the dark red solution at 0 °C , 0.50 M of bromo[1-(3-chlorophenyl)ethyl]zinc in THF (4.0 mL, 2.00 mmol) was added dropwise over 10 min. The reaction was allowed to warm to rt and stir for 14 h. The reaction was quenched with 1 M HCl and diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined org layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound (yield = 442 mg). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.63 (s, 1H), 7.24 – 7.14 (m, 2H), 7.14 – 7.11 (m, 1H), 7.03 (d, J = 7.3 Hz, 1H), 4.09 (q, J = 7.2 Hz, 1H), 3.85 (s, 3H), 2.32 (s, 3H). LCMS (FA): m/z = 295.2 (M+H).

Step 2: rac-4-[1-(3-Chlorophenyl)ethyl]-5-methylthiophene-2-carbaldehyde.

[00481] 1.0 M of lithium tetrahydroaluminate in THF (1.46 mL, 1.46 mmol) was added to an ice-bath cooled solution of methyl 4-[1-(3-chlorophenyl)ethyl]-5-methylthiophene-2-carboxylate (0.43 g, 1.40 mmol) in Et_2O (8.5 mL). The resulting solution was stirred at 0 °C for 15min. The reaction was quenched with water (~1 mL) at 0 °C. Na_2SO_4 decahydrate (~1g) was added along with 20

mL EtOAc and the mixture allowed to warm to rt. The mixture was stirred for 2 h, filtered and the filter cake was washed with EtOAc. The filtrate was concentrated to yield 0.37g (95%) of alcohol product. This compound was dissolved in DCM (20 mL), and then Dess-Martin periodinane (0.71 g, 1.70 mmol) was added to the solution. The reaction was allowed to stir at rt for 30 min. The reaction was concentrated and the crude material purified on ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound (yield = 227 mg).

Example 69**: rac-4-{(3-Chlorophenyl)[(triisopropylsilyl)oxy]methyl}-5-methylthiophene-2-carbaldehyde. Int-118**



Int-118

Step 1: rac-(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methanol.

[00482] A 100mL 2-neck round bottom flask was charged with THF (60 mL) then the flask was purged with argon, and was cooled at -78 °C. To the THF, 2.50 M of *n*-BuLi in hexane (5.40 mL, 13.5 mmol) was added dropwise via syringe and the mixture was stirred for 10 min at -78 °C. 2-(4-bromo-5-methyl-2-thienyl)-1,3-dioxolane (2.69 g, 10.8 mmol) was added dropwise at -78 °C. The solution was stirred for 30 min at -78 °C. 3-chlorobenzaldehyde (1.23 mL, 10.8 mmol) was added to the solution at once at -78 °C and stirred for 15 min. The reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 2.3 g (68%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.14 – 7.06 (m, 4H), 6.79 (s, 1H), 5.81 (s, 1H), 5.70 (s, 1H), 4.00 – 3.91 (m, 3H), 3.88 – 3.77 (m, 2H), 2.32 (s, 4H).

Step 2: rac-{(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methoxy}(triisopropyl)silane.

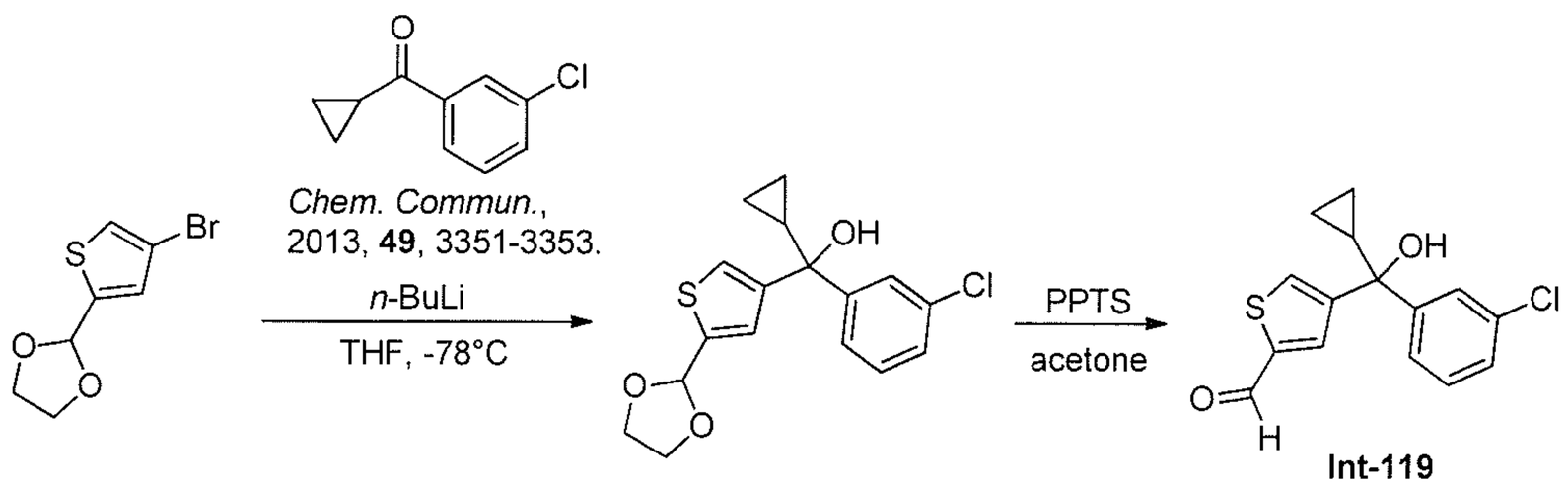
[00483] rac-(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methanol (927 mg, 2.98 mmol) was dissolved in THF (30.6 mL), then 60% NaH in mineral oil (329 mg, 13.7 mmol) was added to this solution. The solution was stirred at 40 °C for 30 min. TIPSCl (1.45 mL, 6.86 mmol) was added and the reaction mixture stirred at rt overnight. The solution was poured into 30 mL saturated NH_4Cl solution. The solution was extracted with EtOAc (30 mLx2). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was

purified by ISCO column chromatography (10% - 25% EtOAc in hexanes as eluent) to give 1.39 g (100%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 – 7.02 (m, 4H), 6.96 (s, 1H), 5.87 (s, 1H), 5.72 (s, 1H), 4.00 – 3.94 (m, 2H), 3.90 – 3.85 (m, 2H), 2.33 (s, 3H), 1.00 – 0.93 (m, 21H).

Step 3: rac-4-{(3-Chlorophenyl)[(triisopropylsilyl)oxy]methyl}-5-methylthiophene-2-carbaldehyde.

[00484] rac-{(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methoxy}(triisopropyl)silane (1.6 g, 3.4 mmol) was dissolved in 1% HCl in EtOH (20 mL) and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with water, extracted with DCM (20 ml x2). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was purified by ISCO column chromatography (28% - 30% EtOAc in hexanes as eluent) to give 1.4 g (97%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.67 (s, 1H), 7.63 (s, 1H), 7.21 – 7.03 (m, 4H), 5.75 (s, 1H), 2.40 (s, 3H), 1.06 – 0.92 (m, 21H).

Example 70: **rac-4-[(3-Chlorophenyl)(cyclopropyl)hydroxymethyl]thiophene-2-carbaldehyde Int-119**



Step 1: rac-(3-Chlorophenyl)(cyclopropyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol

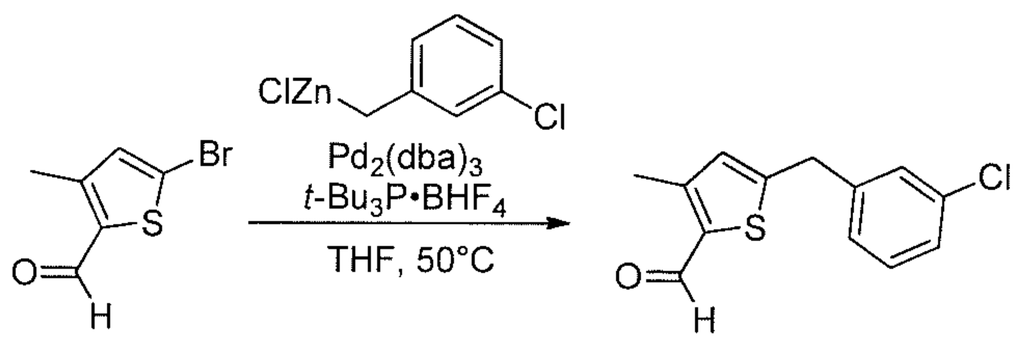
[00485] A 2-neck 250mL round bottom flask under nitrogen was charged with THF (100 mL). To the solution was added 2.50 M of *n*-BuLi in hexane (9.2 mL, 23 mmol) at -78 °C followed by addition of a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (4.15 g, 17.7 mmol) in THF (10 mL). After 5 min, a solution of 3-chlorophenyl cyclopropyl ketone (3.35 g, 18.5 mmol) in THF (10 mL) was added to the mixture in a single portion, and the reaction was allowed to stir for 30 min. The reaction mixture was quenched by adding saturated NH_4Cl and the resulting mixture was warmed to rt. The mixture was extracted with EtOAc (x3) and the combined organic portions were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO column chromatgraphy eluting using a hexane / EtOAc gradient to give the title compound as pale solid, 3.72g (63%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.46 (m, 1H), 7.34 – 7.31 (m, 1H), 7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 2H), 7.03 – 7.00 (m, 1H), 5.99

(s, 1H), 4.19 – 3.94 (m, 4H), 1.85 (s, 1H), 1.63 – 1.54 (m, 1H), 0.69 – 0.61 (m, 1H), 0.55 – 0.45 (m, 3H).

Step 2: rac-4-[(3-Chlorophenyl)(cyclopropyl)hydroxymethyl]thiophene-2-carbaldehyde.

[00486] A 100mL round bottom flask under nitrogen was charged with rac-(3-chlorophenyl)(cyclopropyl) [5-(1,3-dioxolan-2-yl)-3-thienyl]methanol (250 mg, 0.74 mmol), acetone (5.45 mL), and water (1.34 mL). To the mixture was added PPTS (373 mg, 1.48 mmol) and the reaction was allowed to stir for 2 h at rt. The reaction was poured into water and extracted with EtOAc (x3). The combined organic portions were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to give the title compund as colorless oil, 195mg (90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 – 9.81 (m, 1H), 7.75 – 7.71 (m, 1H), 7.64 – 7.59 (m, 1H), 7.51 – 7.47 (m, 1H), 7.35 – 7.24 (m, 3H), 2.04 (s, 1H), 1.65 – 1.54 (m, 1H), 0.73 – 0.44 (m, 4H).

Example 71**: 5-(3-Chlorobenzyl)-3-methylthiophene-2-carbaldehyde. Int-120**

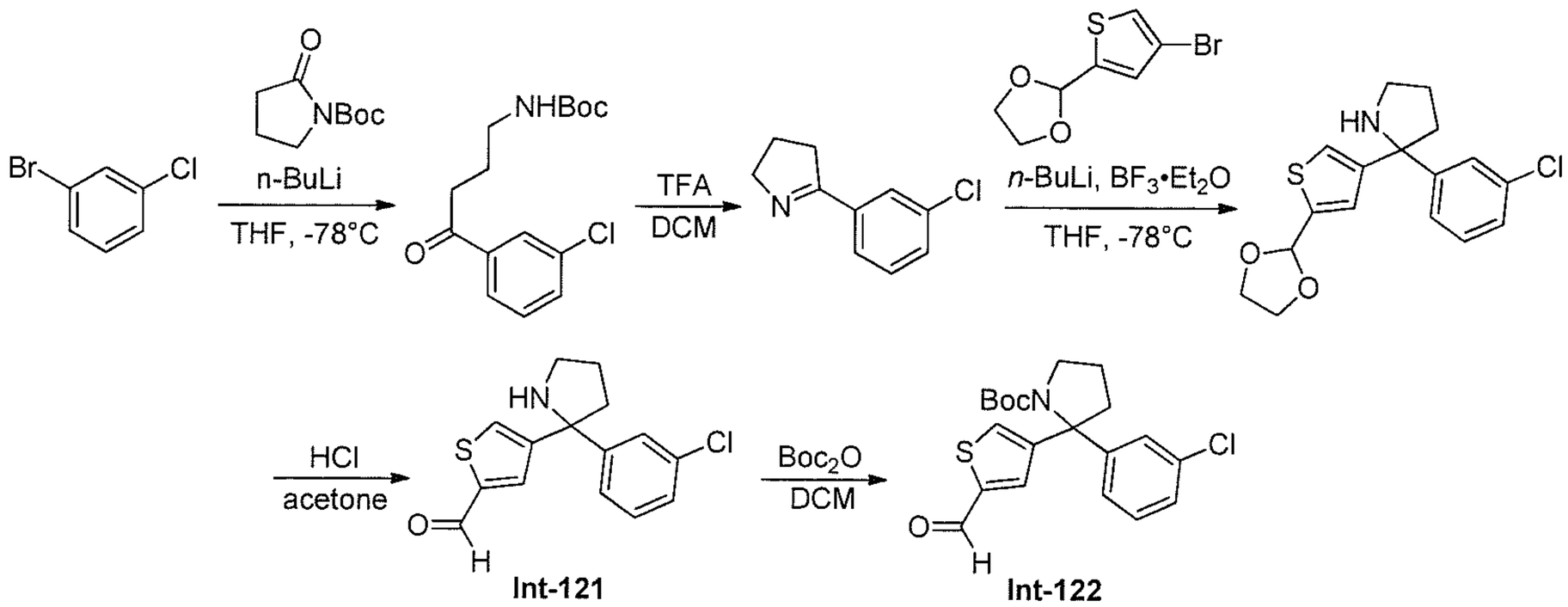


Int-120

Step 1: 5-(3-Chlorobenzyl)-3-methylthiophene-2-carbaldehyde

[00487] A 20mL of microwave vessel was charged with 5-bromo-3-methylthiophene-2-carbaldehyde (680 mg, 3.32 mmol), Pd_2dba_3 (60.8 mg, 66.3 umol), and tri-tert-butylphosphonium tetrafluoroborate (38.5 mg, 0.13 mmol). To the mixture was added THF (4.0 mL) and the reaction vessel was purged with argon followed by sealing with a cap. After the mixture was stirred for 5 min at rt, 0.5 M of 3-chlorobenzylzinc chloride in THF solution (8.62 mL, 4.31 mmol) was added to the mixture and then the resulting mixture was heated at 50 °C for 1 hour. The reaction was cooled to rt and diluted with EtOAc. The organic layer was washed with water (50mL) followed by brine. After drying over Na_2SO_4, the mixture was filtered through a glass frit funnel and the filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (0% -15% EtOAc in hexanes as eluent) to give 184 mg (22%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.96 (s, 1H), 7.65 (s, 1H), 7.49 – 7.40 (m, 1H), 7.27 (t, 1H), 7.25 (d, J = 4.6 Hz, 1H), 7.14 (d, J = 4.5 Hz, 1H), 6.69 (s, 1H), 4.10 (s, 2H), 2.52 (s, 3H).

Example 72: **rac-4-[2-(3-Chlorophenyl)pyrrolidin-2-yl]thiophene-2-carbaldehyde Int-121 and rac-tert-butyl 2-(3-Chlorophenyl)-2-(5-formyl-3-thienyl)pyrrolidine-1-carboxylate Int-122**



Step 1: *tert*-Butyl [4-(3-chlorophenyl)-4-oxobutyl]carbamate.

[00488] A 500mL 2-neck round bottom flask under nitrogen was charged with THF (192.0 mL) and cooled at -78°C. To the solution was added 2.50 M of *n*-BuLi in hexane (30.6 mL, 76.6 mmol) followed by a solution of 3-chlorobromobenzene (11.3 g, 58.9 mmol) in THF (10 mL). To the mixture was added immediately a solution of 1-(*tert*-butoxycarbonyl)-2-pyrrolidine (12.0 g, 64.8 mmol) in THF (10 mL). After 15 min, the reaction was quenched by slow addition of saturated $NaHCO_3$ and the resulting mixture was warmed to rt. The mixture was extracted with EtOAc (x3) and the combined organics were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO column chromatography eluting with a hexane / EtOAc gradient to give the title compound as yellow oil, 15.54g (89%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.90 (m, 1H), 7.85 – 7.79 (m, 1H), 7.56 – 7.50 (m, 1H), 7.43 – 7.37 (m, 1H), 4.62 (s, 1H), 3.26 – 3.17 (m, 2H), 3.05 – 2.97 (m, 2H), 1.99 – 1.88 (m, 2H), 1.43 – 1.41 (m, 9H).

Step 2: 5-(3-Chlorophenyl)-3,4-dihydro-2H-pyrrole.

[00489] A 500mL round bottom flask was charged with *tert*-butyl [4-(3-chlorophenyl)-4-oxobutyl]carbamate (15.6 g, 52.3 mmol) and DCM (26 mL). To the solution was added TFA (48.3 mL, 627.4 mmol). After 1 hour, the reaction was poured into water and the mixture was extracted with DCM (x3). The combined organics were washed with saturated $NaHCO_3$ then brine; dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO column chromatography eluting with a hexane / EtOAc to give the title compound as white solid, 4.93g (53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.81 (m, 1H), 7.74 – 7.67 (m, 1H), 7.42 – 7.37 (m, 1H), 7.37 – 7.31 (m, 1H), 4.10 – 4.01 (m, 2H), 2.98 – 2.84 (m, 2H), 2.13 – 1.98 (m, 2H).

Step 3: rac-2-(3-Chlorophenyl)-2-[5-(1,3-dioxolan-2-yl)-3-thienyl]pyrrolidine.

[00490] To a solution of 5-(3-chlorophenyl)-3,4-dihydro-2H-pyrrole (5.90 g, 32.8 mmol) in THF (100 mL) was added boron trifluoride diethyl ether complex (4.5 mL, 36.1 mmol) at -78 °C and the mixture was stirred for 30 min. A separate reaction vessel was charged with THF (300 mL), cooled to -78 °C, 2.50 M of *n*-BuLi in hexane (22.3 mL, 55.8 mmol) was added followed by a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (10.8 g, 46.0 mmol) in THF (10 mL) and the mixture was stirred for 5 min. To the mixture was added a previously prepared solution via cannula at -78 °C, and the mixture was allowed to stir at -40 °C for 1 hour. The reaction was quenched by addition of saturated $NaHCO_3$, and the resulting mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO column chromatography eluting with a hexane / EtOAc gradient to give the title compound as brown foam oil, 7.09g (64%). LCMS (FA): *m/z* = 336.1 (M+H).

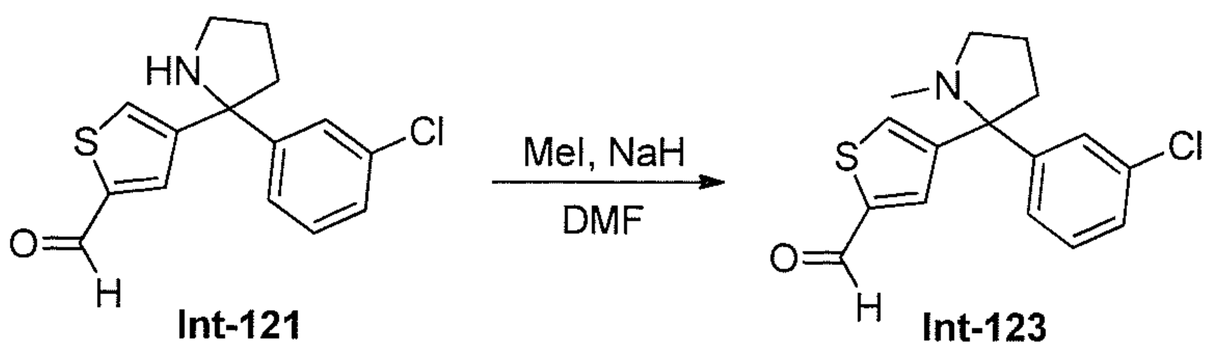
Step 4: rac-4-[2-(3-Chlorophenyl)pyrrolidin-2-yl]thiophene-2-carbaldehyde.

[00491] To a solution of rac-2-(3-chlorophenyl)-2-[5-(1,3-dioxolan-2-yl)-3-thienyl] pyrrolidine (7.09 g, 21.1 mmol) in acetone (100 mL) was added a solution of 12 M of HCl in water (2 mL) and the reaction was allowed to stir at rt 6 h. The reaction was poured into saturated $NaHCO_3$ and the mixture was extracted with DCM (x3). The combined organic portions were dried with $MgSO_4$, filtered, and concentrated in vacuo. Residue was subjected to ISCO column chromatography eluting with a hexane / EtOAc gradient to give the title compound as orange oil, 4.15g (67%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.81 (s, 1H), 7.64 – 7.58 (m, 2H), 7.52 – 7.46 (m, 1H), 7.34 – 7.29 (m, 1H), 7.25 – 7.22 (m, 1H), 7.22 – 7.18 (m, 1H), 3.18 – 3.01 (m, 2H), 2.50 – 2.27 (m, 2H), 2.01 – 1.80 (m, 3H).

Step 5: rac-*tert*-Butyl 2-(3-chlorophenyl)-2-(5-formyl-3-thienyl)pyrrolidine-1-carboxylate.

[00492] A 100mL round bottom flask under nitrogen was charged with rac-4-[2-(3-chlorophenyl)pyrrolidin -2-yl]thiophene-2-carbaldehyde (4.15 g, 14.2 mmol), DCM (69.6 mLm), N,N-dimethylaminopyridine (0.08 mg, 0.7 mmol), and Boc_2O (4.66 g, 21.3 mmol). After 18 h at rt, the reaction was concentrated in vacuo. Residue was subjected to ISCO column chromatography eluting with a hexane / EtOAc gradient to give the title compound as white foam, 2.83g (51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.93 – 9.85 (m, 1H), 7.83 – 7.68 (m, 1H), 7.68 – 7.50 (m, 1H), 7.36 – 7.11 (m, 4H), 3.92 – 3.80 (m, 2H), 2.77 – 2.45 (m, 2H), 2.03 – 1.79 (m, 2H), 1.55 – 1.27 (m, 9H).

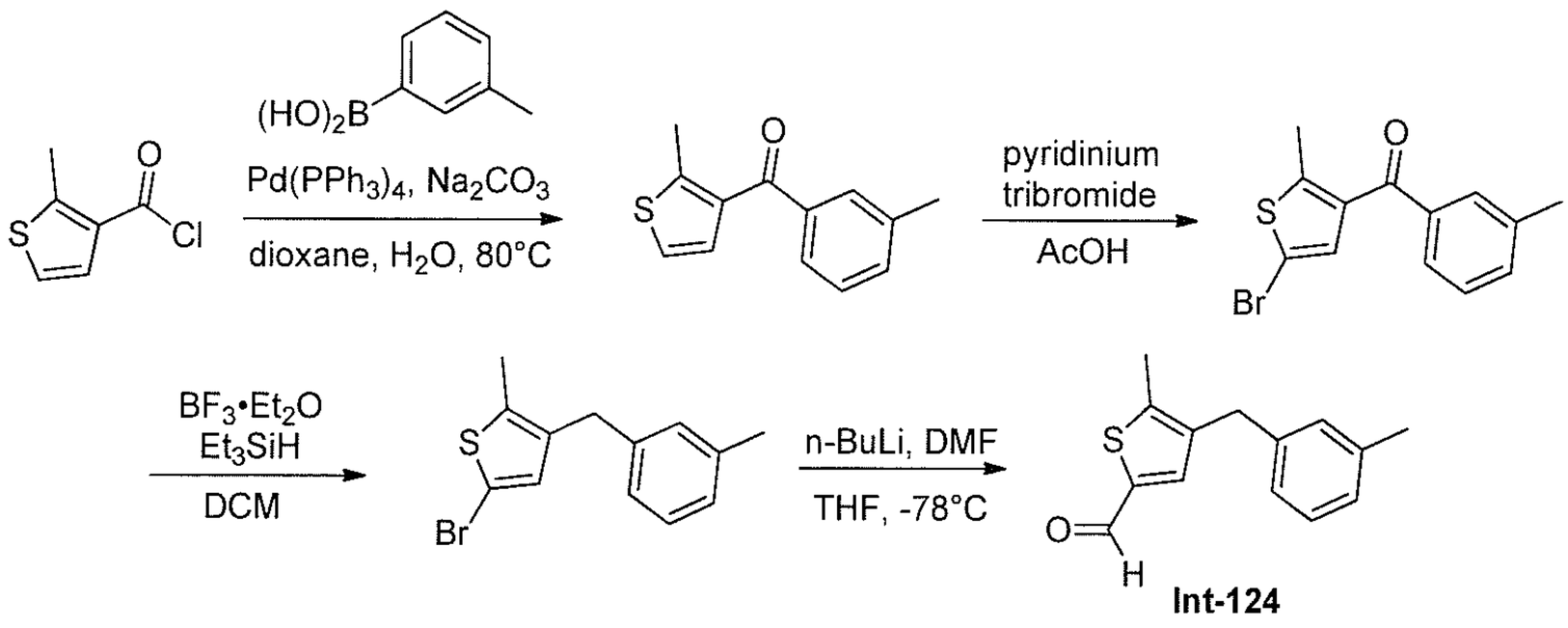
Example 73**: rac-4-[2-(3-Chlorophenyl)-1-methylpyrrolidin-2-yl]thiophene-2-carbaldehyde. Int-123**



Step 1: rac-4-[2-(3-Chlorophenyl)-1-methylpyrrolidin-2-yl]thiophene-2-carbaldehyde.

[00493] An oven-dried 100mL round bottom flask under nitrogen was charged with DMF (10 mL) and 60% NaH in mineral oil (228 mg, 5.69 mmol) and the mixture was cooled at 0 °C. To the mixture was added a solution of Int-121 (664 mg, 2.28 mmol) in DMF (5 mL) and the reaction was stirred for 30 min. To the mixture was added MeI (0.43 mL, 6.83 mmol) and the reaction was stirred for 1 hour at rt. The reaction mixture was poured onto ice and saturated $NaHCO_3$ was added to the mixture. The mixture was extracted EtOAc (x3), and the combined organic portions were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to ISCO column chromatography eluting with a hexane / EtOAc gradient to give the title compound as a pale oil, 133 mg (20%). ^{1}H NMR (400 MHz, Methanol-*d4*) δ 9.88 – 9.80 (m, 1H), 7.76 – 7.69 (m, 1H), 7.62 – 7.55 (m, 1H), 7.39 – 7.35 (m, 1H), 7.34 – 7.24 (m, 2H), 7.22 – 7.17 (m, 1H), 3.06 – 2.96 (m, 1H), 2.63 – 2.45 (m, 2H), 2.22 – 2.11 (m, 1H), 2.08 (s, 3H), 2.06 – 1.94 (m, 2H).

Example 74**: 5-Methyl-4-(3-methylbenzyl)thiophene-2-carbaldehyde. Int-124**



Step 1: (3-Methylphenyl)(2-methyl-3-thienyl)methanone.

[00494] A microwave tube was charged with m-tolylboronic acid (231 mg, 1.70 mmol), Cs_2CO_3 (830 mg, 2.55 mmol), and $Pd(PPh_3)_4$ (58.9 mg, 0.05 mmol). These contents were suspended with toluene (5mL) followed by addition of 2-methylthiophene-3-carbonyl chloride (300 mg, 1.87 mmol) at rt. The reaction vessel was purged with argon and then sealed with cap. The reaction was heated at 100 °C with oil-bath for 30 min. The reaction was cooled to rt and transferred into a separatory funnel. The mixture was diluted with EtOAc (70mL) and the organic layer was

washed with water (50mL) followed by brine. The EtOAc layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (3% EtOAc in Hexanes as eluent) to give 220mg (60%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (s, 1H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.13 (d, *J* = 5.3 Hz, 1H), 7.04 (d, *J* = 5.3 Hz, 1H), 2.65 (s, 3H), 2.41 (s, 3H).

Step 2: (5-Bromo-2-methyl-3-thienyl)(3-methylphenyl)methanone.

[00495] To a solution of (3-methylphenyl)(2-methyl-3-thienyl)methanone (410 mg, 1.90 mmol) in acetic acid (2.0 mL) was added pyridinium tribromide (1.52 g, 4.74 mmol) at rt, and the reaction was heated at 50 °C for 2 h. The reaction was cooled at rt and poured into water (100 mL). The mixture was extracted with EtOAc (100 mL x2). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL) followed by $Na_2S_2O_3$ solution and then brine. The EtOAc layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (5% EtOAc in hexanes as eluent) to give 529 mg (85%) of the title compound as a light yellow sticky oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (s, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.32 (m, 2H), 7.08 (s, 1H), 2.57 (s, 3H), 2.42 (s, 3H).

Step 3: 5-Bromo-2-methyl-3-(3-methylbenzyl)thiophene.

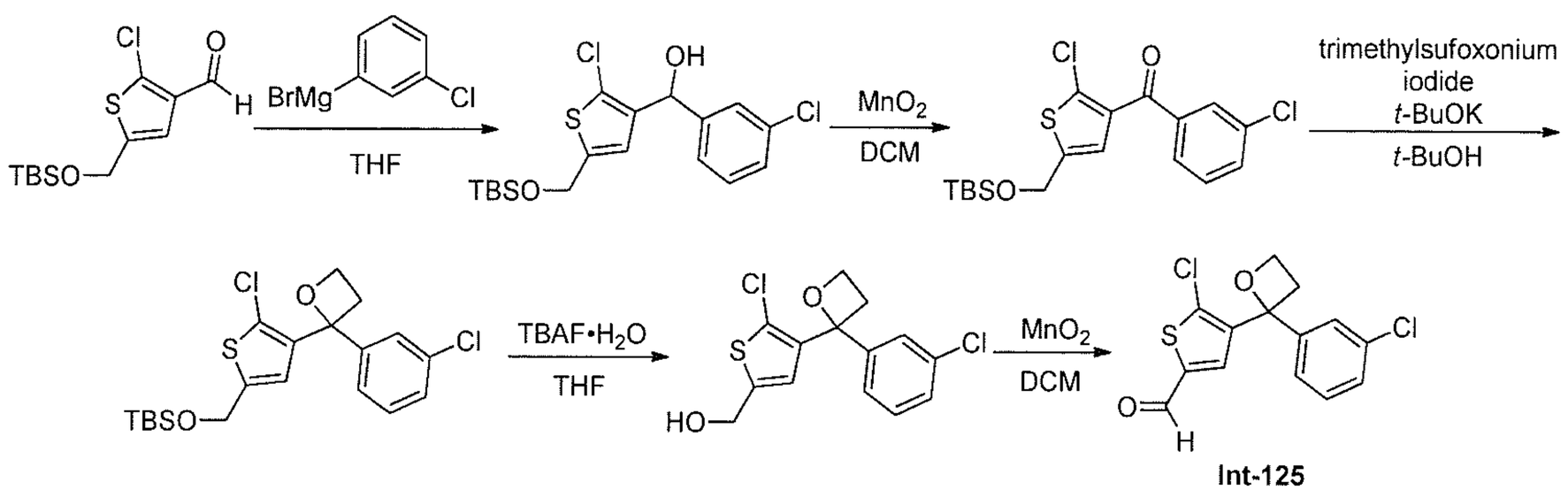
[00496] (5-Bromo-2-methyl-3-thienyl)(3-methylphenyl)methanone (520 mg, 1.60 mmol) in a 100mL round botton flask was dissolved in CH_3CN (5.0 mL) and DCM (5.0 mL) under atmosphere of argon and the mixture was cooled to 0 °C. To this solution was added triethylsilane (0.76 mL, 4.76 mmol) followed by boron trifluoride etherate (0.60 mL, 4.76 mmol), and the reaction was stirred for 14 h at 0 °C to room temp. The reaction was quenched by slow addition of K_2CO_3 aqueous solution (50mL) and extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (100% hexane as eluent) to give 447 mg (90%) of the title compound as a colorless oil.^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.97 – 6.88 (m, 2H), 6.66 (s, 1H), 3.77 (s, 2H), 2.33 (s, 2H), 2.32 (s, 3H).

Step 4: 5-Methyl-4-(3-methylbenzyl)thiophene-2-carbaldehyde.

[00497] 5-Bromo-2-methyl-3-(3-methylbenzyl)thiophene (235 mg, 0.75 mmol) was weighed into a 100mL 2-neck round bottom flask and the reaction vessel was purged with argon. The content was dissolved in THF (12.0 mL) and the solution was cooled at -78 °C. To the solution was added dropwise 2.50 M of *n*-BuLi in hexane (0.69 mL, 1.71 mmol) at -78 °C, and the mixture was stirred for 30 min. To the mixture was added DMF (0.13 mL, 1.67 mmol) at -78 °C, and the resulting mixture was stirred for 15 min. The reaction was quenched by addition of saturated NH_4Cl (50mL) and extracted with EtOAc (50 mL x3). The combined organic layers were washed

with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (5% EtOAc in hexanes as eluent) to give 151 mg (87%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.41 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 3.86 (s, 2H), 2.47 (s, 3H), 2.33 (s, 3H).

Example 75: **rac-5-Chloro-4-[2-(3-chlorophenyl)oxetan-2-yl]thiophene-2-carbaldehyde. Int-125**



Step 1: rac-[5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl](3-chlorophenyl)methanol.

[00498] To a solution of 5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chlorothiophene-3-carbaldehyde (1.00 g, 3.44 mmol) in THF (20.0 mL) and the solution was cooled at 0 °C. To the solution was added dropwise 0.50 M of 3-chlorophenylmagnesium bromide in THF (8.25 mL, 4.13 mmol), and the reaction was stirred for 30 min at rt. The reaction was quenched by addition of saturated NH_4Cl (100mL) and extracted with EtOAc (100 mLx3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 1.35g (97%) of the title compound as light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 1H), 7.26 (d, *J* = 4.1 Hz, 3H), 6.66 (s, 1H), 5.94 (s, 1H), 4.71 (d, *J* = 0.9 Hz, 2H), 2.57 – 1.90 (br s, 1H), 0.90 (s, 9H), 0.07 (s, 6H).

Step 2: [5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl](3-chlorophenyl)methanone.

[00499] To a solution of rac-[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl](3-chlorophenyl)methanol (1.35 g, 3.35 mmol) in DCM (50.0 mL) was added MnO_2 (2.91 g, 33.5 mmol) at rt, and the reaction was stirred for 21 h. The reaction was filtered through a Celite pad and the residual filter cake was rinsed with DCM several times. The filtrate was concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 5% EtOAc in hexanes as eluent) to give 742mg (55%) of the title compound as colorless oil. ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 7.79 (t, *J* = 1.8 Hz, 1H), 7.69 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 6.91 (s, 1H), 4.80 (d, *J* = 1.0 Hz, 2H), 0.94 (s, 9H), 0.12 (s, 6H).

Step 3: rac-*tert*-Butyl({5-chloro-4-[2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}methoxy)dimethylsilane.

[00500] A 20mL microwave reaction tube was charged with Trimethylsufoxonium iodide (576 mg, 2.62) and *t*-BuOK (294 mg, 2.62 mmol) and then the reaction tube was purged with argon followed by sealed with cap. To the reaction vessel was added *t*-BuOH (3.0 mL) and the mixture was stirred for 30 min at 50 °C. To the white suspension was added a solution of [5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl](3-chlorophenyl)methanone (300 mg, 0.75 mmol) in t-BuOH (4.5 mL, 47.0 mmol) at 50 °C, and the resulting mixture was stirred for 44 h. The reaction was quenched by addition of water (60 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (2% EtOAc in hexanes as eluent) to give 195 mg (61%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (t, *J* = 1.8 Hz, 1H), 7.35 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.24 (dt, *J* = 7.8, 1.7 Hz, 1H), 6.78 (s, 1H), 4.74 (s, 2H), 4.69 – 4.63 (m, 2H), 3.54 – 3.44 (m, 1H), 3.14 – 3.03 (m, 1H), 0.91 (s, 9H), 0.09 (d, *J* = 1.8 Hz, 6H).

Step 4: rac-{5-Chloro-4-[2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}methanol.

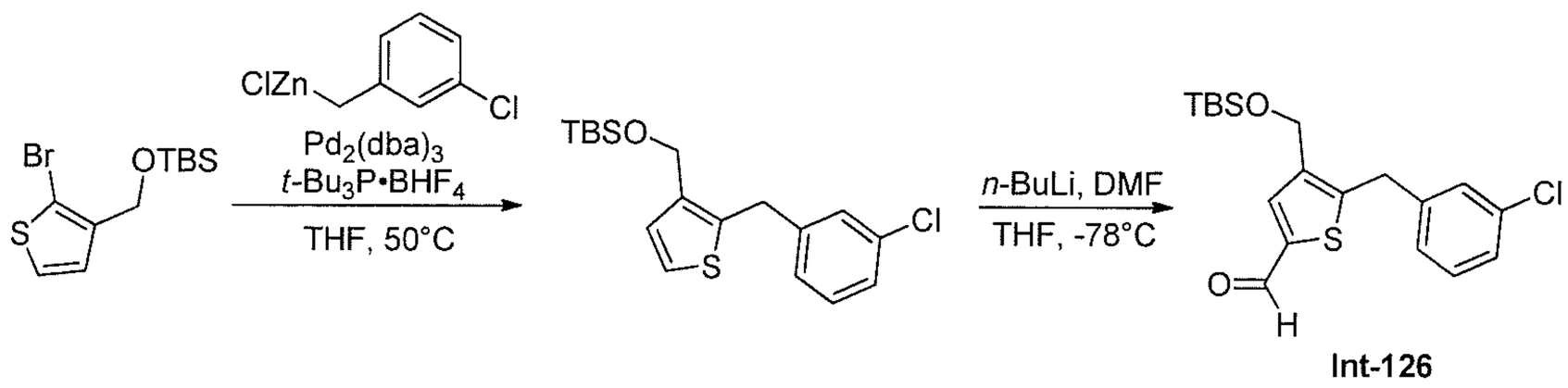
[00501] To a solution of rac-*tert*-butyl({5-chloro-4-[2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}methoxy)dimethylsilane (290 mg, 0.68 mmol) in THF (10 mL) was added a solution of TBAF monohydrate (283 mg, 1.01 mmol) in THF (3.0 mL) at rt, and the mixture was stirred for 1 hour. The reaction was quenched by addition of water (50 mL) and extracted with EtOAc (60 mLx3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (20% - 30% EtOAc in hexanes as eluent) to give 207mg (97%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 (t, *J* = 1.7 Hz, 1H), 7.38 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.28 – 7.24 (m, 1H), 6.92 (s, 1H), 4.76 – 4.65 (m, 4H), 3.53 (dt, *J* = 11.3, 7.8 Hz, 1H), 3.12 (dt, *J* = 11.3, 7.4 Hz, 1H), 1.86 (t, *J* = 6.0 Hz, 1H).

Step 5: rac-5-Chloro-4-[2-(3-chlorophenyl)oxetan-2-yl]thiophene-2-carbaldehyde.

[00502] To a solution of rac-{5-chloro-4-[2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}methanol (205 mg, 0.65 mmol) in DCM (20.0 mL) was added MnO_2 (565 mg, 6.50 mmol) at rt, and the mixture was stirred for 14 h. The reaction was filtered through a Celite pad and the residual filter cake was rinsed with DCM several times. The filtrate was concentrated in vacuo and the residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 188 mg

(92%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.76 (s, 1H), 7.74 (s, 1H), 7.51 (s, 1H), 7.37 – 7.27 (m, 3H), 4.70 (t, *J* = 7.7 Hz, 2H), 3.44 (dt, *J* = 11.4, 7.7 Hz, 1H), 3.20 (dt, *J* = 11.4, 7.6 Hz, 1H).

Example 76**: 4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-5-(3-chlorobenzyl)thiophene-2-carbaldehyde. Int-126**



Int-126

Step 1: *tert*-Butyl{[2-(3-chlorobenzyl)-3-thienyl]methoxy}dimethylsilane.

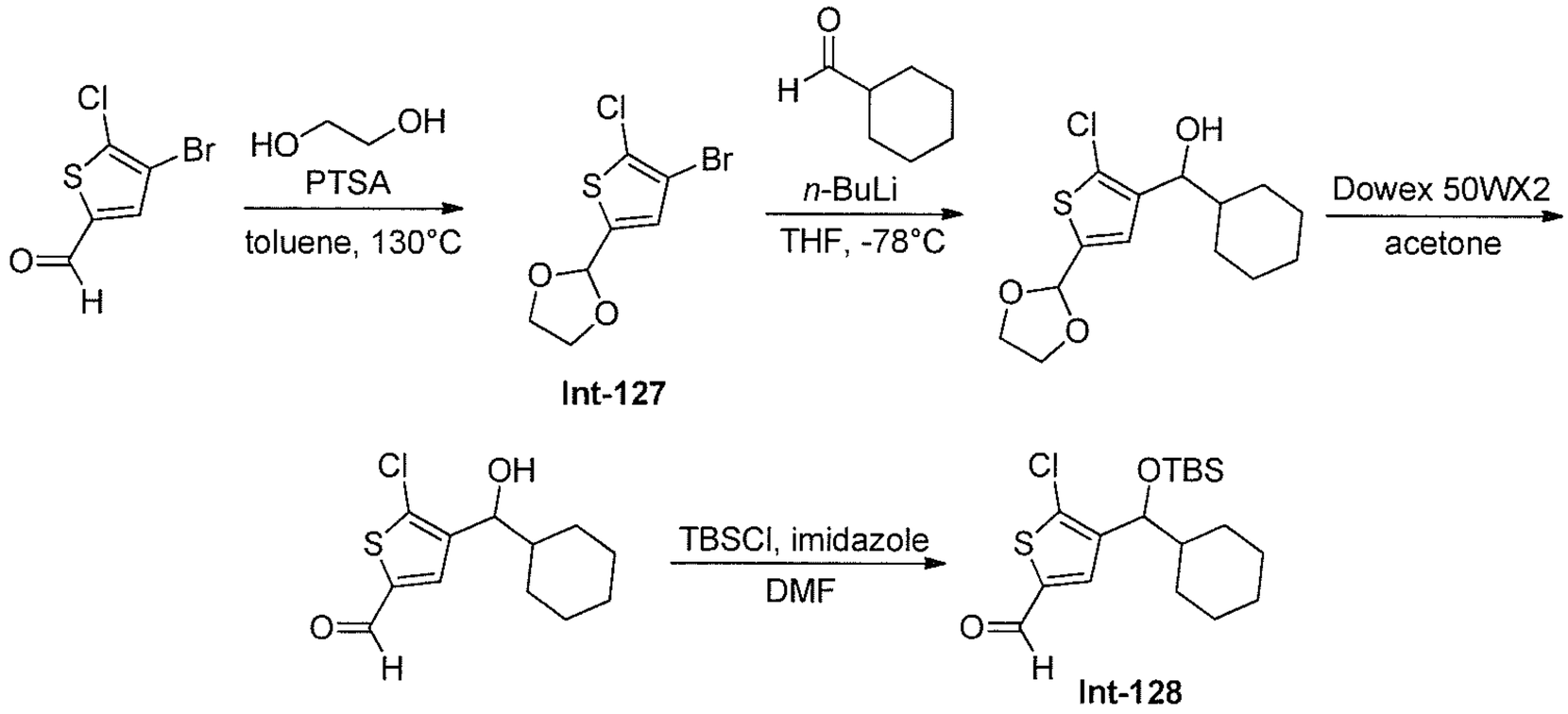
[00503] A 20mL of microwave reaction tube was charged with [(2-bromo-3-thienyl)methoxy](tert-butyl)dimethylsilane (1.63 g, 5.30 mmol), $Pd_2(dba)_3$ (194 mg, 0.21 mmol), and tri-*tert*-butylphosphonium tetrafluoroborate (123 mg, 0.42 mmol). After addition of THF (11.2 mL), the reaction vessel was purged with argon followed by sealing with a cap. After the mixture was stirred for 5 min at rt, 0.5 M of 3-chlorobenzylzinc chloride in THF (12.2 mL, 6.10 mmol) was added to the mixture. The reaction was stirred at rt for 2 h, and then the resulting mixture was heated at 50 °C for 1 hour. The mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with water (50mL) and brine. After drying over Na_2SO_4, the mixture was filtered through a glass frit funnel and the filtrate was concentrated in vacuo. The residue was purified by ISCO column chromatography (10 % EtOAc in hexanes as eluent) to give 1.4g (76%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.10 (m, 3H), 7.04 (m, 2H), 6.94 (d, *J* = 5.2 Hz, 1H), 4.57 (s, 2H), 4.05 (s, 2H), 0.85 (s, 9H), 0.00 (s, 6H).

Step 2: 4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-5-(3-chlorobenzyl)thiophene-2-carbaldehyde.

[00504] To a solution of *tert*-butyl{[2-(3-chlorobenzyl)-3-thienyl]methoxy}dimethylsilane (1.40 g, 3.97 mmol) in THF (30.0 mL) was added dropwise 2.5 M *n*-BuLi in hexane (2.1 mL, 5.16 mmol) at -78 °C and the mixture was stirred for 3 min. To the mixture was added DMF (0.49 mL, 6.34 mmol) at -78 °C and the reaction was allowed to stir for 10 min, and then warmed to rt for 10 min. The reaction mixture was added saturated NH_4Cl and extracted with EtOAc (x2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (15 % EtOAc in hexanes as eluent) to give 0.75g (50%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (s, 1H), 7.75 (s,

1H), 7.28 (t, J = 7.5 Hz, 3H), 7.16 (d, J = 6.3 Hz, 1H), 4.70 (s, 2H), 4.20 (s, 2H), 0.99 (s, 9H), 0.16 (s, 6H).

Example 77: **2-(4-Bromo-5-chloro-2-thienyl)-1,3-dioxolane Int-127 and rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(cyclohexyl)methyl]-5-chlorothiophene-2-carbaldehyde Int-128**



Step 1: 2-(4-Bromo-5-chloro-2-thienyl)-1,3-dioxolane.

[00505] To a solution of 4-bromo-5-chlorothiophene-2-carbaldehyde (4.1 g, 18 mmol) in toluene (60 mL) was added 1,2-ethanediol (5.07 mL, 90.9 mmol) and p-toluenesulfonic acid monohydrate (0.17 g, 0.91 mmol) and then the mixture was heated to reflux with a Dean-Stark apparatus for 3 h. After cooling to rt, the reaction mixture was quenched by addition of saturated $NaHCO_3$ (100 mL) and water (50 mL). The resulting mixture was extracted with hexane (150 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (10% EtOAc in hexanes as eluent) to give the title compound as colorless solid (yield = 4.75 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (s, 1H), 6.03 (s, 1H), 4.07 – 3.99 (m, 2H), 3.99 – 3.91 (m, 2H).

Step 2: rac-[2-Chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](cyclohexyl)methanol.

[00506] 2-(4-bromo-5-chloro-2-thienyl)-1,3-dioxolane (1.09 g, 4.04 mmol) was placed in a 50mL 2-neck round bottom flask under an atmosphere of argon. THF (6.50 mL) was added and the reaction was cooled at -78 °C. 2.50 M of *n*-BuLi in hexane (1.80 mL, 4.50 mmol) was added dropwise and the solution was stirred for 30 min. Concurrently, Cerium trichloride (1.00 g, 4.06 mmol) was placed in a two-neck round-bottom flask under an atmosphere of argon. THF (10.0 mL) was added and the slurry was cooled at -78 °C. 2-(4-bromo-5-chloro-2-thienyl)-1,3-dioxolane lithiated species was added dropwise quickly to the above solution and the solution was stirred for 1 hour at -78 °C. Cyclohexanecarboxaldehyde (0.60 mL, 4.80 mmol) in THF (2.0 mL) was added dropwise to the solution at -78 °C. The reaction was stirred for 30 min at -78 °C. The

reaction was quenched with saturated NH_4Cl and the mixture was extracted with EtOAc. An emulsion formed and was filtered through a pad of Celite. The filtrate layers were separated and the organic was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via ISCO column chromatography (10% -30% EtOAc in hexanes as eluent) to give an orange oil (yield = 622 mg). LCMS (FA): *m/z* = 303.1 (M+1)

Step 3: rac-5-Chloro-4-[cyclohexyl(hydroxy)methyl]thiophene-2-carbaldehyde.

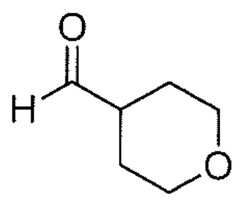
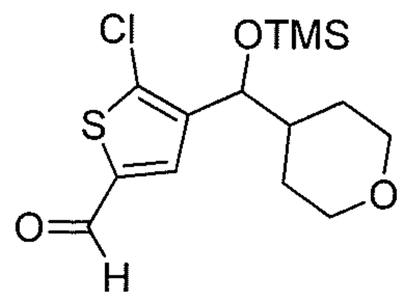
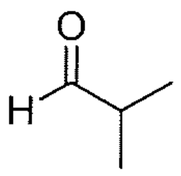
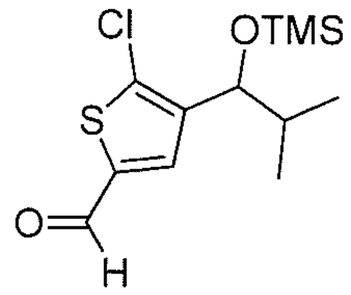
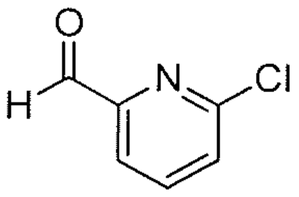
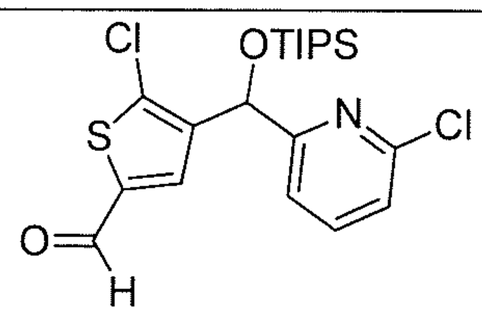
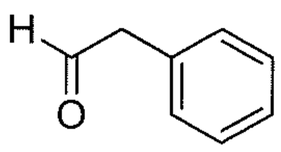
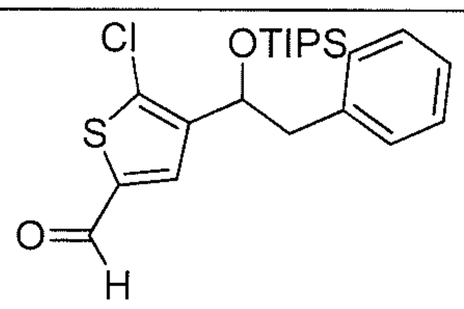
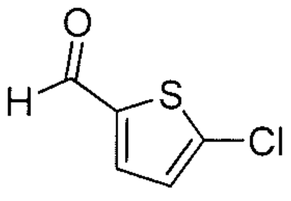
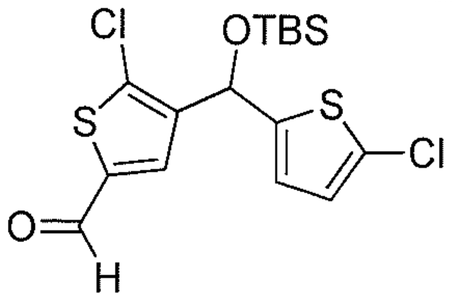
[00507] Dowex 50WX2-200 (H) (1 g) was added to a solution of rac-[2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](cyclohexyl)methanol (0.62 g, 2.04 mmol) in acetone (40 mL) at rt. The reaction was allowed to stir at rt for 17 h. The reaction was filtered to remove solid resin and the filtrate was concentrated. The crude material was purified on ISCO silica gel (100% hexanes then 20% EtOAc/hexanes as eluent) to give the title compound as yellow oil (yield = 338 mg). LCMS (FA): *m/z* = 259.1 (M+1)

Step 4: rac-4-[{[*tert*-Butyl(dimethyl)silyl]oxy}(cyclohexyl)methyl]-5-chlorothiophene-2-carbaldehyde.

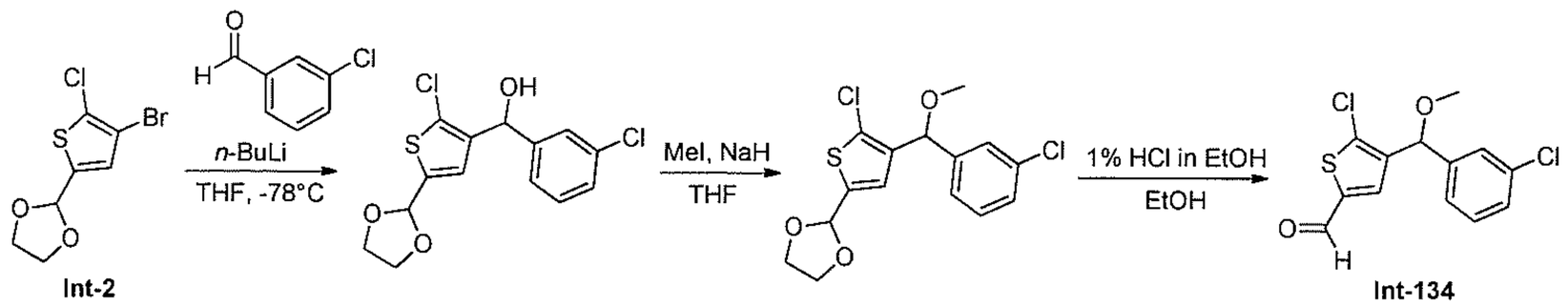
[00508] rac-5-Chloro-4-[cyclohexyl(hydroxy)methyl]thiophene-2-carbaldehyde (338 mg, 1.31 mmol), 1H-imidazole (267 mg, 3.92 mmol), N,N-dimethylaminopyridine (16.0 mg, 0.13 mmol), and DMF (10.0 mL) were combined in a 100 mL round bottom flask under an atmosphere of argon. The solution was cooled at 0 °C. TBSCl (225 mg, 1.49 mmol) was added and the reaction was warmed to rt. After 5 h, 1H-imidazole (88.9 mg, 1.31 mmol) and TBSCl (98.4 mg, 0.65 mmol) were added and the reaction was stirred overnight. The reaction was quenched with saturated NH_4Cl, diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted EtOAc. The combined organics were washed with 10% aqueous LiCl solution (x3), brine (x1), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via ISCO column chromatography (10% EtOAc in hexanes as eluent) to give colorless oil (yield = 386 mg). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (s, 1H), 7.61 (s, 1H), 4.50 (d, *J* = 7.1 Hz, 1H), 1.98 – 1.57 (m, 4H), 1.44 – 0.88 (m, 7H), 0.86 (s, 9H), 0.04 (s, 3H), -0.18 (s, 3H).

[00509] The compounds listed in the table below were prepared in an analogous fashion to that described above starting from the appropriate starting materials. The following alternative conditions could be employed in the described reaction steps. Step 4; Condition A: TMSCl/imidazole/DCM, B: TIPSCl/NaH/THF, C: TBSCl/imidazole/DMF.

Step 2 aldehyde	Step 4 Condition	Compound Name / No.	Characterization Data

	**A**	 **Int-129**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (s, 1H), 7.64 (s, 1H), 4.51 (d, *J* = 7.2 Hz, 1H), 4.01 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.94 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.40 – 3.23 (m, 2H), 1.79 (dtq, *J* = 15.3, 7.5, 3.7 Hz, 2H), 1.49 – 1.33 (m, 2H), 1.25 – 1.16 (m, 1H), 0.03 (s, 9H).^{1}H NMR
	**A**	 **Int-130**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (s, 1H), 7.64 (s, 1H), 4.46 (d, *J* = 7.0 Hz, 1H), 1.88 (dq, *J* = 13.5, 6.7 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.02 (s, 9H).^{1}H NMR
	**B**	 **Int-131**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.71 – 7.65 (m, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.22 – 7.17 (m, 1H), 6.03 (s, 1H), 1.20 – 1.08 (m, 3H), 1.02 – 0.96 (m, 18H).^{1}H NMR
	**B**	 **Int-132**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.62 (s, 1H), 7.41 (s, 1H), 7.15 – 7.07 (m, 3H), 6.94 – 6.87 (m, 2H), 5.07 (t, *J* = 6.1 Hz, 1H), 2.99 (dd, *J* = 13.2, 5.5 Hz, 1H), 2.89 (dd, *J* = 13.2, 6.8 Hz, 1H), 1.00 – 0.81 (m, 21H).^{1}H NMR
	**C**	 **Int-133**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.75 (s, 1H), 7.70 (s, 1H), 6.71 (d, *J* = 3.8 Hz, 1H), 6.57 (dd, *J* = 3.8, 1.1 Hz, 1H), 6.01 (d, *J* = 0.9 Hz, 1H), 0.91 (s, 9H), 0.11 – 0.00 (m, 6H).^{1}H NMR

Example 78: **rac-5-Chloro-4-[(3-chlorophenyl)(methoxy)methyl]thiophene-2-carbaldehyde Int-134**



Step 1: rac-2-Chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](3-chlorophenyl)methanol.

[00510] A 100 mL 2-neck round bottom flask was charged with THF (20 mL) then the flask was purged with argon, and was cooled at -78 °C. To the THF, 2.50 M of *n*-BuLi in hexane (1.86 mL,

4.64 mmol was added dropwise via syringe and the mixture was stirred for 10 min at -78 °C. **Int-2** (1.0 g, 3.7 mmol) was added dropwise at -78 °C. The solution was stirred for 30 min at -78 °C. 3-Chlorobenzaldehyde (422 uL, 3.71 mmol) was added to the solution at once at -78 °C and stirred for 15 min. The reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 494 mg (40%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 – 7.02 (m, 4H), 6.78 (s, 1H), 5.76 (s, 1H), 5.75 (s, 1H), 3.93 – 3.87 (m, 2H), 3.84 – 3.77 (m, 2H).

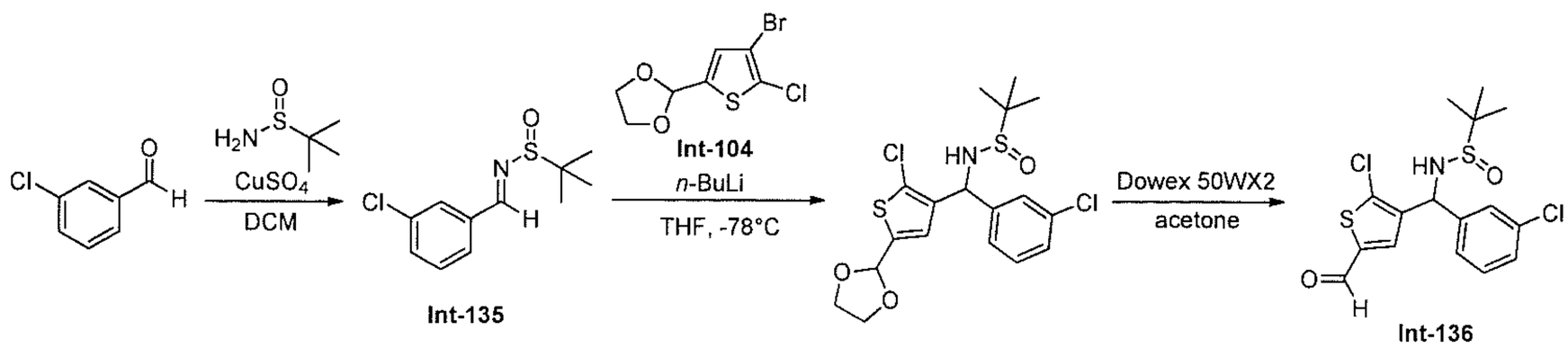
Step 2: rac-2-{5-Chloro-4-[(3-chlorophenyl)(methoxy)methyl]-2-thienyl}-1,3-dioxolane.

[00511] A 100 mL round bottom flask was charged with rac-[2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl] (3-chlorophenyl)methanol (490 mg, 1.48 mmol). To the mixture THF (14.5 mL), and 60% NaH in mineral oil (213 mg, 4.44 mmol) were added at rt and the reaction mixture was purged with argon followed by the addition of MeI (276 uL, 4.44 mmol) and heated at 50 °C for 2 h. The solution was quenched with saturated NH_4Cl solution and was extracted with DCM (30 mLx2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 35% EtOAc in hexanes as eluent) to give 404 mg (79%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 – 7.04 (m, 4H), 6.79 (s, 1H), 5.80 (s, 1H), 5.24 (s, 1H), 3.98 – 3.92 (m, 2H), 3.88 – 3.82 (m, 2H), 3.23 (s, 3H).

Step 3: rac-5-Chloro-4-[(3-chlorophenyl)(methoxy)methyl]thiophene-2-carbaldehyde.

[00512] rac-2-{5-Chloro-4-[(3-chlorophenyl)(methoxy)methyl]-2-thienyl}-1,3-dioxolane (1.0 g, 2.9 mmol) was dissolved in 1% HCl (20 mL) in EtOH. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with water, extracted with DCM (20 mLx2). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 0.8 g (90%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.61 (s, 1H), 7.44 (s, 1H), 7.19 – 7.05 (m, 4H), 5.26 (s, 1H), 3.26 (s, 3H).

Example 79: ***N*-[(*E*)-(3-Chlorophenyl)methylene]-2-methylpropane-2-sulfinamide Int-135 and rac-*N*-[(2-Chloro-5-formyl-3-thienyl)(3-chlorophenyl)methyl]-2-methylpropane-2-sulfinamide. Int-136**



Step 1: *N*-[(*E*)-(3-Chlorophenyl)methylene]-2-methylpropane-2-sulfinamide.

[00513] Copper(II) sulfate (2.9 g, 18.0 mmol) and 3-chlorobenzaldehyde (1.3 g, 9.1 mmol) were added to a solution of 2-methyl-2-propanesulfinamide (1.0 g, 8.2 mmol) in DCM (16 mL) at rt. The resulting suspension was allowed to stir for 15 h. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with DCM. The filtrate was concentrated and the crude mixture was purified on ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound (yield = 1.32 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.86 (t, *J* = 1.7 Hz, 1H), 7.69 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.49 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 1.27 (s, 9H). LCMS (FA): *m/z* = 244.3 (M+H).

Step 2: rac-*N*-{[2-Chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](3-chlorophenyl)methyl}-2-methylpropane-2-sulfinamide.

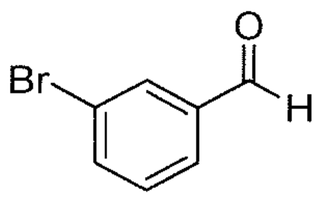
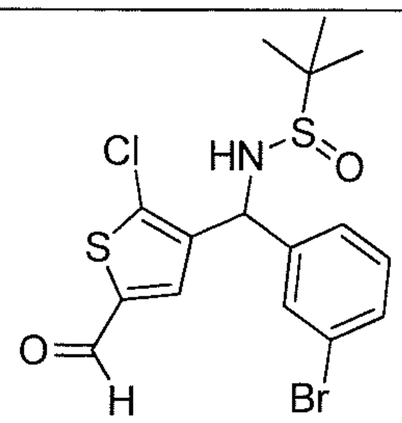
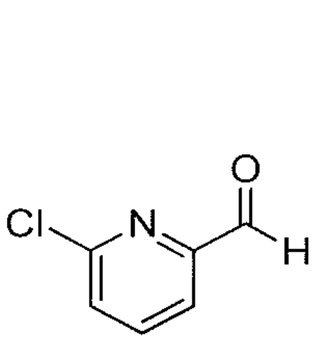
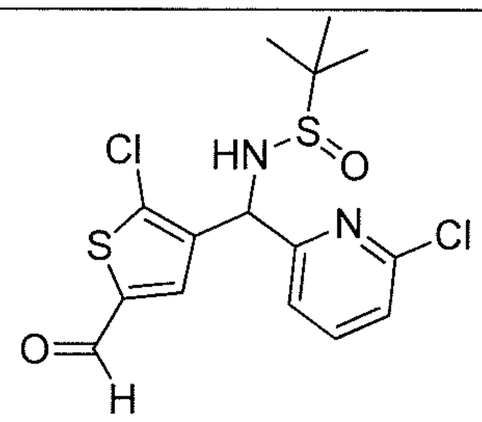
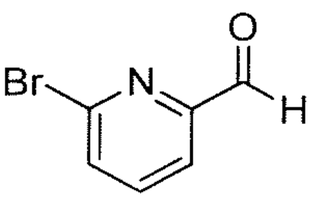
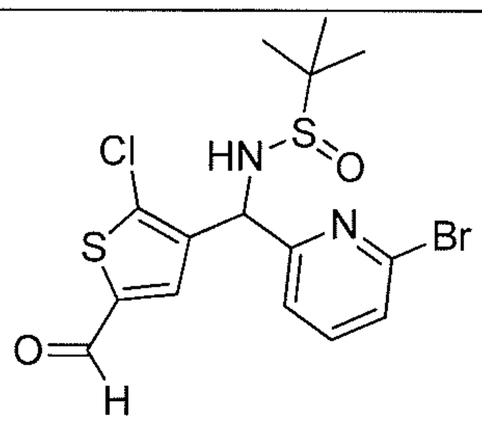
[00514] A solution of 2-(4-bromo-5-chloro-2-thienyl)-1,3-dioxolane (900 mg, 3.30 mmol) in THF (30 mL) was cooled to -78 °C and 2.50 M of *n*-BuLi in hexane (1.66 mL, 4.15 mmol) was added dropwise. Immediately after a solution of N-[(E)-(3-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide (0.97 g, 3.97 mmol) in THF (4 mL) was added quickly to the reaction mixture. The resulting solution was allowed to stir for 15 min at that temperature. After warming to ~ 0 °C, the reaction was quenched by addition of water. The mixture was extracted with EtOAc (3x) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified on ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound (yield = 1.2 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 17.9 Hz, 1H), 7.36 – 7.24 (m, 3H), 6.98 (d, *J* = 10.3 Hz, 1H), 5.97 (d, *J* = 6.8 Hz, 1H), 5.76 (dd, *J* = 7.5, 2.6 Hz, 1H), 4.15 – 4.07 (m, 2H), 4.06 – 3.96 (m, 2H), 3.69 – 3.61 (m, 1H), 1.33 – 1.22 (m, 9H).

Step 3: rac-*N*-[(2-Chloro-5-formyl-3-thienyl)(3-chlorophenyl)methyl]-2-methylpropane-2-sulfinamide.

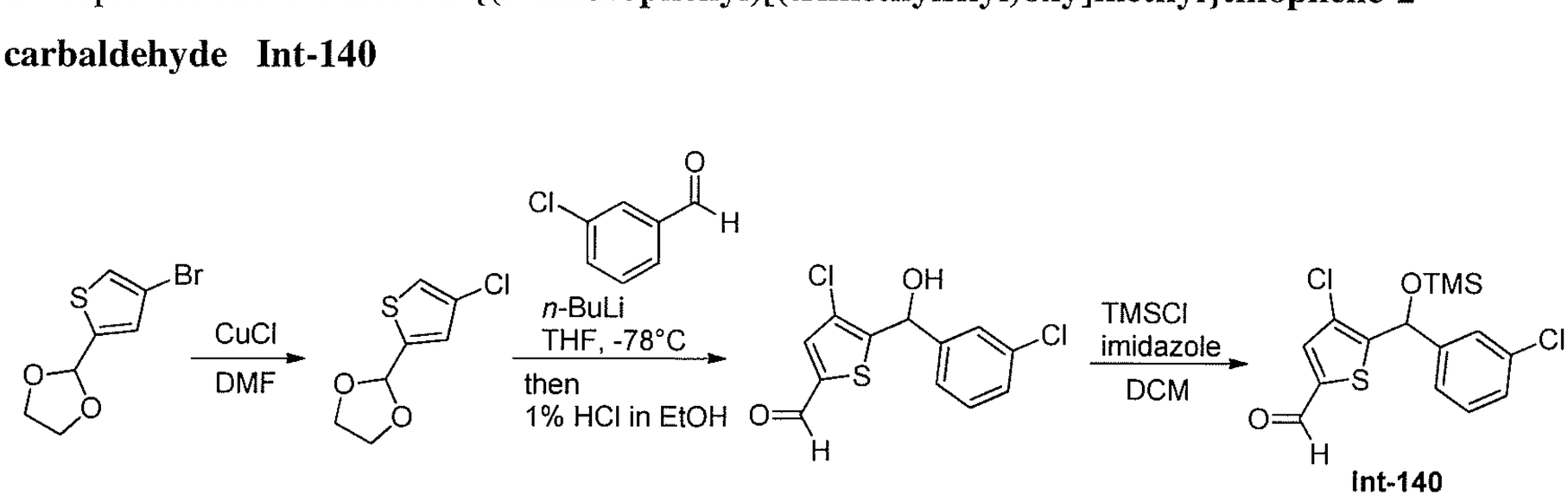
[00515] Dowex 50WX2-200 (H) (1 g) was added to a solution of N-{[2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](3-chlorophenyl)methyl}-2-methylpropane-2-sulfinamide (0.90 g, 2.10 mmol) in acetone (20 mL) at rt. The reaction was allowed to stir for 1 hour. The reaction was filtered to remove solid resin and the crude material was purified on ISCO chromatography eluting with a hexane/EtOAc gradient to afford the title compound (yield = 750 mg). ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 9.75 (d, *J* = 4.0 Hz, 1H), 7.63 (d, *J* = 16.4 Hz, 1H), 7.38 (d, *J* = 12.8 Hz, 1H), 7.34 – 7.27 (m, 3H), 5.78 (dd, *J* = 15.0, 3.1 Hz, 1H), 3.80 – 3.70 (m, 1H), 1.27 (s, 9H).

[00516] The compounds listed in the table below were prepared in a similar fashion to that described above starting from the listed starting materials:

Starting material	Compound Name / No.	Characterization Data
	 **Int-137**	LCMS (FA): *m/z* = 436.1 (M+H).
	 **Int-138**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.73 (s, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.59 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 5.83 (d, *J* = 2.9 Hz, 1H), 5.38 (s, 1H), 1.27 (s, 9H).^{1}H NMR
	 **Int-139**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.74 (s, 1H), 7.57 (s, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 5.82 (d, *J* = 3.6 Hz, 1H), 5.40 (d, *J* = 3.4 Hz, 1H), 1.27 (s, 9H).^{1}H NMR

Example 80**: rac-4-Chloro-5-{(3-chlorophenyl)[(trimethylsilyl)oxy]methyl}thiophene-2-carbaldehyde Int-140**



Int-140

Step 1: 2-(4-Chloro-2-thienyl)-1,3-dioxolane.

[00517] 2-(4-Bromothiophen-2-yl)-1,3-dioxolane (2.81 g, 12.0 mmol) was dissoloved into DMF (3.0 mL) in a microwave tube, and then CuCl (1.66 g, 16.7 mmol) was added to this solution. The reaction was heated at 180 °C with stirring for 90 min. The solid was filtered, and the residual solid was washed with DCM. The filtrate was poured into 50ml water, and the mixture was extracted with DCM (40 mL x2). The combined organic layers were concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 1.40g (61%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (s, 1H), 7.07 (s, 1H), 6.07 (s, 1H), 4.16 – 4.09 (m, 2H), 4.07 – 4.00 (m, 2H).

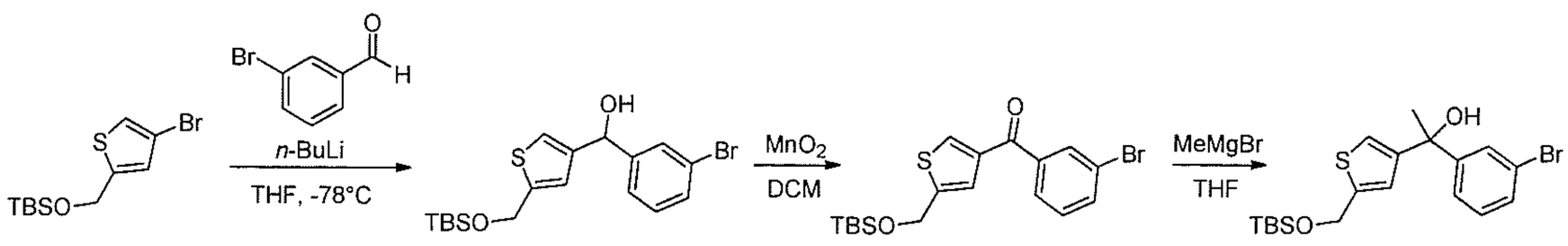
Step 2: rac-4-Chloro-5-[(3-chlorophenyl)(hydroxy)methyl]thiophene-2-carbaldehyde.

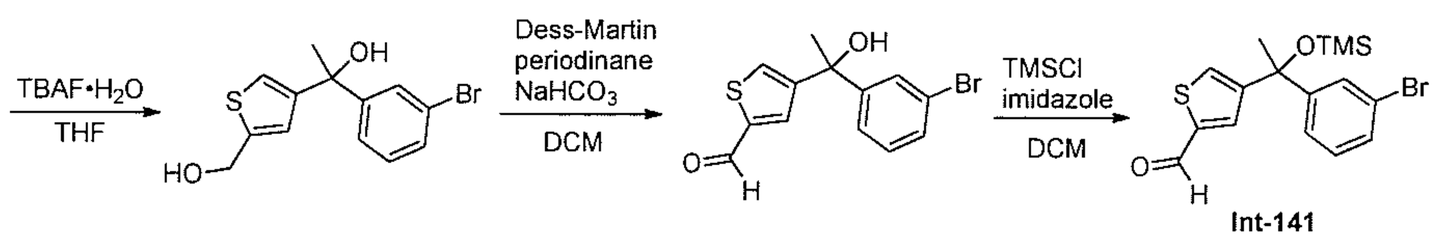
[00518] 2.50 M of *n*-BuLi in hexane (1.44 mL, 3.59 mmol) was added dropwise via syringe into THF (40 mL), and then cooled down at -78 °C. 2-(4-Chloro-2-thienyl)-1,3-dioxolane (489 mg, 2.57 mmol) was added to this solution at -78 °C, then 3-chlorobenzaldehyde (433 mg, 3.08 mmol) was added to the solution at once at -78 °C. The reaction was stirred at -78 °C for 15 min. The solution was poured into 60ml saturated NH_4Cl solution and the mixture was extracted with EtOAc (50 ml x2). The combined the organic layers were concentrated in vacuo and the residues were dissolved into 30ml 1% HCl in MeOH with 5ml water. The mixture was stirred at rt for 30 min. The reaction mixture was poured into 30 ml saturated $NaHCO_3$ solution, and extracted with DCM (30 ml x3). The combined the organic layers were concentrated in vacuo and the residue was purified by ISCO column (0% - 40% EtOAc in hexanes as eluent) to give 402 mg (55%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.75 (s, 1H), 7.53 (s, 1H), 7.49 – 7.40 (m, 1H), 7.40 – 7.25 (m, 3H), 6.12 (s, 1H), 3.81 – 3.23 (br s, 1H).

Step 3: rac-4-Chloro-5-{(3-chlorophenyl)[(trimethylsilyl)oxy]methyl}thiophene-2-carbaldehyde.

[00519] To a solution of rac-4-chloro-5-[(3-chlorophenyl)(hydroxy)methyl]thiophene-2-carbaldehyde (0.42 g, 1.47 mmol) in DCM (25.0 mL) was added TMSCl (0.24 mL, 1.91 mmol) followed by 1H-imidazole (0.20 g, 2.94 mmol), and the reaction was stirred at for 1 hour. The reaction mixture was poured into saturated aqueous NH_4Cl (50 mL) at rt and the mixture was extracted with DCM (x3). The combined organic layers were washed with water, brine, dried using $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 20% EtOAc in hexanes as eluent) to give 296 mg (56%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.68 (s, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.06 (m, 2H), 5.89 (s, 1H), -0.01 (s, 9H).

Example 81**: rac-4-{1-(3-Bromophenyl)-1-[(trimethylsilyl)oxy]ethyl}thiophene-2-carbaldehyde. Int-141**





Step 1: rac-(3-Bromophenyl)[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]methanol.

[00520] Magnesium turnings (370 mg, 15.2 mmol) were weighed into a 100mL round bottom flask and the reaction vessel was purged with argon followed by addition of THF (8.0 mL). A separate bottom flask was charged with [((4-bromothiophen-2-yl)methoxy)(*tert*-butyl)dimethylsilane (1.17 g, 3.81 mmol) and the substrate was dissolved in THF (8.0 mL). An aliquot of this solution (0.1mL) was added into the magnesium suspension and the mixture was heated with a heat gun. The remainder of the solution was added dropwise into the magnesium suspension and the mixture was stirred for 2 h. This resulting mixture was cooled to at 0 °C with ice-bath. To the Grignard reagent solution was added dropwise a solution of 3-bromobenzaldehyde (704 mg, 3.81 mmol) in THF (40.0 mL) at 0 °C, and the mixture was stirred for 30 min at rt. The reaction was quenched by addition of saturated NH_4Cl (50mL) and the mixture was extracted with EtOAc (x3). The combined orgnaic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% EtOAc in hexanes as eluent) to give 1.28 g (82%) of the title compound as a light yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 6.77 (s, 1H), 5.78 (d, *J* = 3.7 Hz, 1H), 4.80 (s, 2H), 2.18 (d, *J* = 3.8 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 6H).

Step 2: (3-Bromophenyl)[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]methanone.

[00521] To a solution of rac-(3-bromophenyl)[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]methanol (934 mg, 2.26 mmol) in DCM (20.0 mL) was added MnO_2 (1.96 g, 22.6 mmol). The mixture was stirred for 19 h at rt. The reaction was then filtered through a Celite pad and the residual solid was washed with DCM several times. The filtrate was concentrated in vacuo to obtain 881 mg (95%) of the title compound as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (s, 1H), 7.82 (d, *J* = 1.3 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.73 – 7.66 (m, 1H), 7.40 – 7.32 (m, 2H), 4.92 – 4.86 (m, 2H), 0.94 (s, 9H), 0.13 (s, 6H).

Step 3: rac-1-(3-Bromophenyl)-1-[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]ethanol.

[00522] A round-bottom flask was charged with 3-bromophenyl)[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]methanone (125 mg, 0.30 mmol) and the content was dissolved in THF (2.8 mL). The solution was cooled to 0 °C and 3.0 M of methylmagnesium bromide in Et_2O (0.20 mL, 0.61 mmol) was added dropwise over 10 min. The reaction was then stirred at 0 °C for 1 hour. To the mixture was added 3.0 M of methylmagnesium bromide in Et_2O (1.5 mL, 4.58 mmol) and the resulting mixture was stirred for 1 hour. The reaction was quench reaction with saturated NH_4Cl and the mixture was extracted with EtOAc (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. No further purification was done (100% yield assumed). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 1.7 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 1.5 Hz, 1H), 6.75 (s, 1H), 4.81 – 4.77 (m, 2H), 1.88 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Step 4: rac-1-(3-Bromophenyl)-1-[5-(hydroxymethyl)-3-thienyl]ethanol.

[00523] To a solution of rac-1-(3-bromophenyl)-1-[5-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-thienyl]ethanol (0.92 g, 2.14 mmol) in THF (30.0 mL) was added TBAF hydrate (1.20 g, 4.28 mmol) was then added and the reaction was stirred at rt for 3 h. The reaction was quenched by addition of saturated $NaHCO_3$ and the mixture was extracted with EtOAc (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 100% EtOAc in hexanes as eluent) to give 676 mg (100%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.16 – 7.12 (m, 1H), 6.86 (s, 1H), 4.75 (s, 2H), 1.90 (s, 3H), 1.87 – 1.67 (br s, 2H).

Step 5: rac-4-[1-(3-Bromophenyl)-1-hydroxyethyl]thiophene-2-carbaldehyde.

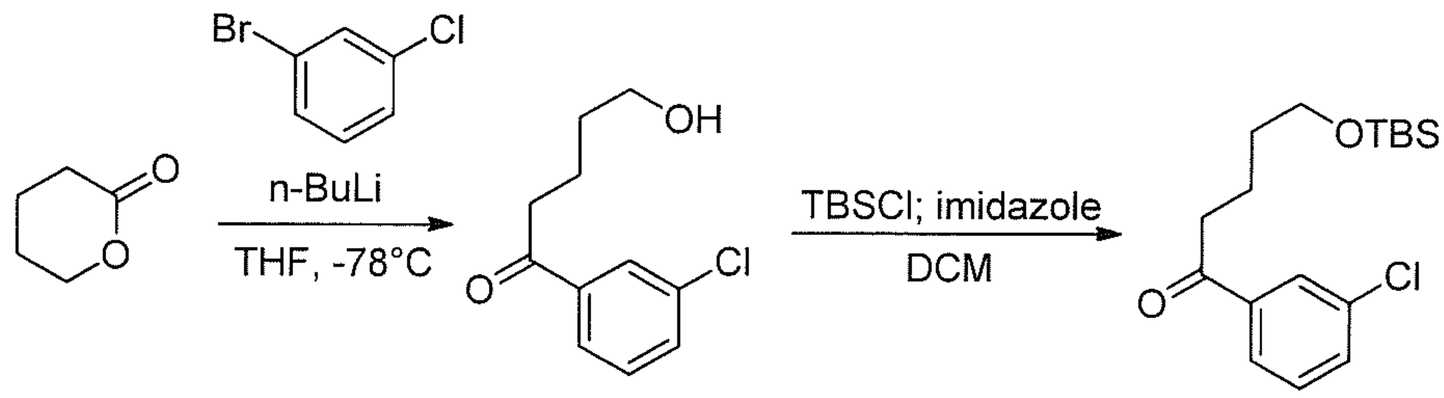
[00524] A round bottom flask was charged with rac-1-(3-bromophenyl)-1-[5-(hydroxymethyl)-3-thienyl]ethanol (676 mg, 2.16 mmol) and the content was dissolved in DCM (20.0 mL). To the solution was added $NaHCO_3$ (544 mg, 6.48 mmol) followed by Dess-Martin periodinane (1.10 g, 2.59 mmol) and the reaction was stirred at rt for 1 hour. The reaction was then quenched by the addition of saturated $Na_2S_2O_3$, extracted with DCM (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 396 mg (59%) of the title compound. LCMS (FA): *m/z* = 313.1 (M+1).

Step 6: rac-4-{1-(3-Bromophenyl)-1-[(trimethylsilyl)oxy]ethyl}thiophene-2-carbaldehyde.

[00525] To a solution of rac-4-[1-(3-bromophenyl)-1-hydroxyethyl]thiophene-2-carbaldehyde (396 mg, 1.27 mmol) in DMF (5.0 mL) was added 1H-imidazole (260 mg, 3.82 mmol) followed by TMSCl (0.24 mL, 1.91 mmol) at rt and the reaction was then stirred for 3 h. The reaction mixture

was poured into saturated aqueous $NaHCO_3$ (50 mL) at rt and extracted with EtOAc (x3). The combined organic layers were washed with water, brine, dried using Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 10% EtOAc in hexanes as eluent) to give 334 mg (68%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.82 (d, *J* = 1.1 Hz, 1H), 7.60 (s, 1H), 7.55 (s, 1H), 7.52 (d, *J* = 1.4 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 1.94 (s, 3H), 0.03 (s, 9H).

Example 82: **5-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(3-chlorophenyl)pentan-1-one. Int-142**



Int-142

Step 1: 1-(3-Chlorophenyl)-5-hydroxypentan-1-one.

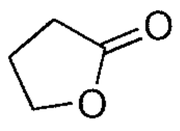
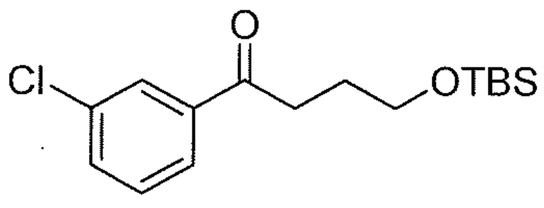
[00526] A 100mL 2-neck round bottom flask was charged with 3-chlorobromobenzene (3 mL, 20 mmol) then the flask was purged with argon. The content was dissolved in THF (50 mL), and the solution was cooled at -78 °C. To the solution was added dropwise 2.50 M of *n*-BuLi in hexane (12.3 mL, 30.7 mmol) at -78 °C and the mixture was stirred for 30 min at same temperature. To the mixture was added dropwise a solution of δ-valerolactone (2.37 mL, 25.5 mmol) in THF (2.0 mL) at -78 °C, and the reaction was stirred for 15 min followed by stirring at rt for 30 min. The reaction was quenched by addition of saturated NH_4Cl (15 mL) and extracted with EtOAc (50 mL x3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 5.0 g (90%) of the title compound as light yellow oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.92 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 1.85 – 1.80 (m, 2H), 1.67 – 1.62 (m, 2H).

Step 2: 5-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(3-chlorophenyl)pentan-1-one.

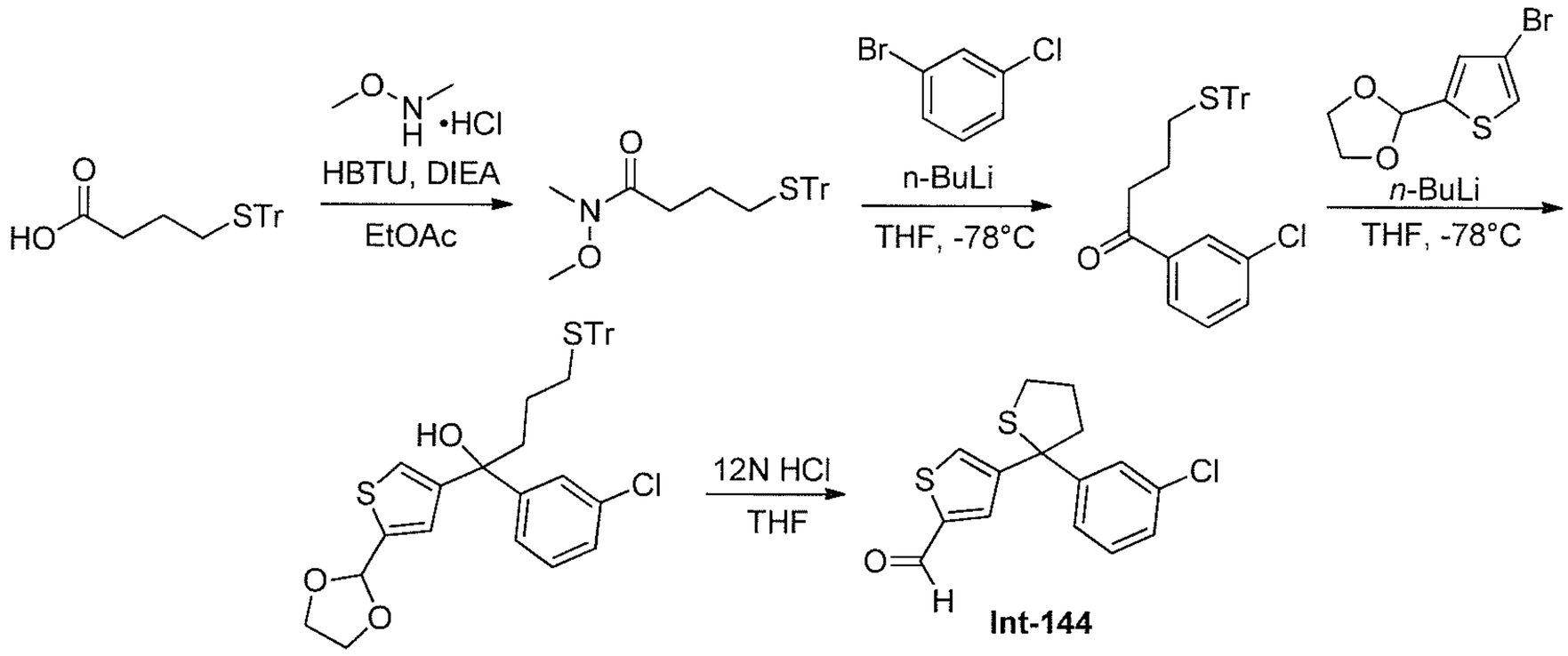
[00527] A 250 mL round bottom flask was charged with1-(3-chlorophenyl)-5-hydroxypentan-1-one (5.0 g, 22 mmol), then the flask was purged with argon. The content was dissolved into DCM (100 mL), then 1H-imidazole (2.45 g, 36.0 mmol) was added followed by the addition of TBSCl (4.70 g, 31.2 mmol) at rt for 1 hour. The reaction was quenched by addition of water (15 mL) and extracted with DCM (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% -

30% EtOAc in hexanes as eluent) to give 7.0 g (90%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.92 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.65 – 1.53 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

[00528] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Starting material	Compound Name / No.	Characterization Data
	 **Int-143**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (t, *J* = 1.7 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 3.70 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 1.94 (p, *J* = 6.4 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H).^{1}H NMR

Example 83**: rac-2-(3-Chlorophenyl)-2,3,4,5-tetrahydro-2,3'-bithiophene-5'-carbaldehyde. Int-144**



Step 1: *N*-Methoxy-N-methyl-4-(tritylsulfanyl)butanamide.

[00529] To a solution of 4-(tritylsulfanyl)butanoic acid (5.91 g, 16.3 mmol) and N,O-dimethylhydroxylamine hydrochloride (2.06 g, 21.1 mmol) in DMF (96.4 mL) was added N,N-diisopropylethylamine (11.4 mL, 65.2 mmol) and O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (6.76 g, 17.8 mmol). The reaction was stirred at rt overnight. The reaction was partitioned between 50mL water/50mL brine and 250 mL EtOAc. The organic layer was separated and washed with saturated $NaHCO_3$ (3x110mL), brine (100mL), dried over Na_2SO_4, filtered, and concentrated to give 7.43 g of the title compound as yellow oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.43 (d, J = 7.5 Hz, 5H), 7.36 – 7.18 (m, 10H), 3.65 (s, 3H),

3.15 (s, 3H), 2.40 (m, 2H), 2.25 (t, J = 7.1 Hz, 2H), 1.74 (p, J = 7.2 Hz, 2H); LCMS (FA): *m/z*=428.1 (M+H+Na)

Step 2: 1-(3-Chlorophenyl)-4-(tritylsulfanyl)butan-1-one.

[00530] To a solution of N-methoxy-N-methyl-4-(tritylsulfanyl)butanamide (6.93 g, 13.9 mmol) in THF (36.2 mL) at 0 °C under argon was added 0.5 M of 3-chlorophenylmagnesium bromide in THF (33.4 mL, 16.7 mmol). The resulting reaction mixture was stirred at 0 °C for 15 min. Then the cold bath was removed and the reaction was stirred at rt for 60 min. The reaction was quenched with addition of saturated NH_4Cl. The mixture was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by ISCO column chromatography (0% - 6% EtOAc in hexane as eluent) to give 5.03 g (80%) of the title compound as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (t, *J* = 1.8 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.54 – 7.50 (m, 1H), 7.44 – 7.36 (m, 7H), 7.30 – 7.23 (m, 10H, overlaps with CDCl3), 7.23 – 7.17 (m, 3H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.30 (t, *J* = 7.0 Hz, 2H), 1.80 (p, *J* = 7.0 Hz, 2H); LCMS (FA): *m/z*=479.1 (M+1+Na)

Step 3: rac-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-4-(tritylsulfanyl)butan-1-ol.

[00531] An oven-dried 500mL 3-neck flask equipped with septam, stir bar and 3-way stop cock with argon balloon was purged with argon. THF (55.6 mL) was added into the flask and cooled at -78 °C with dry-ice/acetone bath. 2.50 M of *n*-BuLi in hexane (5.34 mL, 13.3 mmol) was added, and the mixture was stirred 3 min. To the mixture was added by quick steady stream a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (3.14 g, 13.3 mmol) in THF (22.5 mL) and stirred for 3 min at -78 °C. To the orange mixture was added dropwise a solution of 1-(3-chlorophenyl)-4-(tritylsulfanyl)butan-1-one (5.08 g, 11.1 mmol) in THF (15.0 mL) at -78 °C, and the resulting orange solution was stirred for 10 min. The reaction was quenched by addition of water (30mL) and extracted with EtOAc (100 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The oil was purified by silica gel column chromatography (0 - 30% EtOAc in hexanes as eluent) to afford 4.01 g of the title compound as yellow foam (15% other isomer present, overall 50% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.33 (m, 6H), 7.29 – 7.22 (m, 13H, overlaps with CDCl3), 7.22 – 7.16 (m, 5H), 7.11 (d, *J* = 1.5 Hz, 1H), 6.95 (d, *J* = 1.1 Hz, 1H), 5.97 (s, 1H), 4.16 – 4.05 (m, 2H), 4.03 – 3.94 (m, 2H), 2.20 – 2.13 (m, 2H), 2.11 – 2.05 (m, 2H), 1.48 – 1.35 (m, 1H), 1.20 (m, 1H).

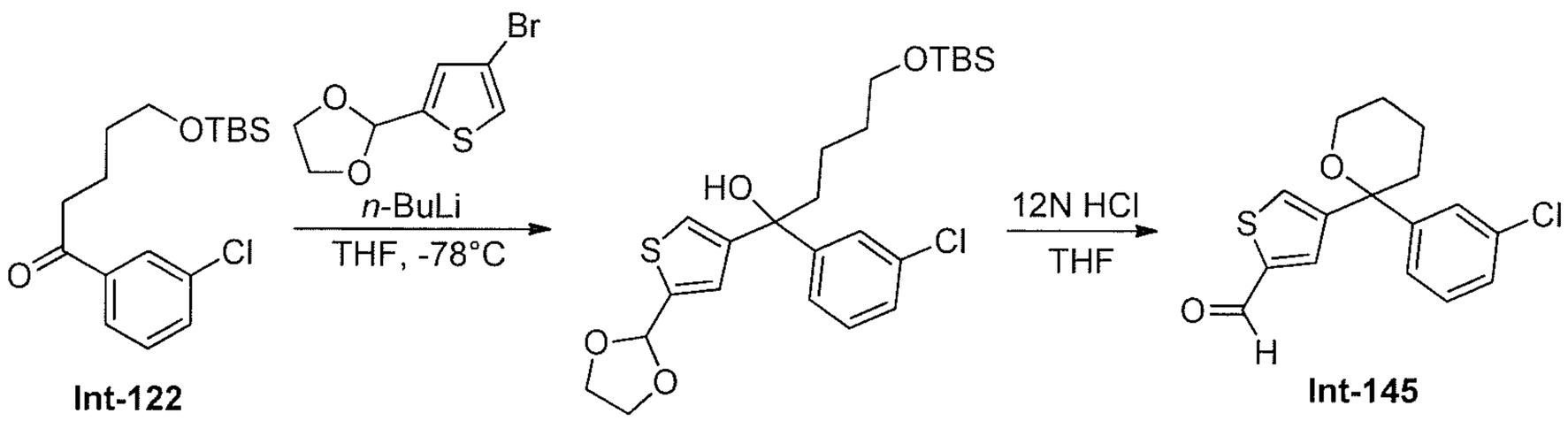
Step 4: rac-2-(3-Chlorophenyl)-2,3,4,5-tetrahydro-2,3'-bithiophene-5'-carbaldehyde.

[00532] To rac-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-4-(tritylsulfanyl)butan-1-ol (4.01 g, 6.54 mmol) was added slowly TFA (9.57 mL, 124 mmol), and the resulting orange-red

solution was stirred at rt for 30 min. The reaction was quenched with 50 mL saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ (2x50mL). The aqueous phase was backwashed with EtOAc (50 mL). The combined organics were washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The crude red granular oil was purified by ISCO column chromatography (0 - 15% EtOAc in hexanes as eluent) to give 1.61 g (73%) of the title compound as an orange oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.82 (d, J = 1.1 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.32 – 7.28 (m, 1H), 7.25 – 7.22 (m, 2H), 3.15 (t, J = 6.9 Hz, 2H), 2.66 – 2.58 (m, 2H), 2.14 – 2.04 (m, 2H). LCMS (FA): *m/z*=309.0 (M+H).

Example 84**: rac-4-[2-(3-Chlorophenyl)tetrahydro-2*H*-pyran-2-yl]thiophene-2-carbaldehyde.**

Int-145



Int-122 Int-145

Step 1: rac-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]pentan-1-ol.

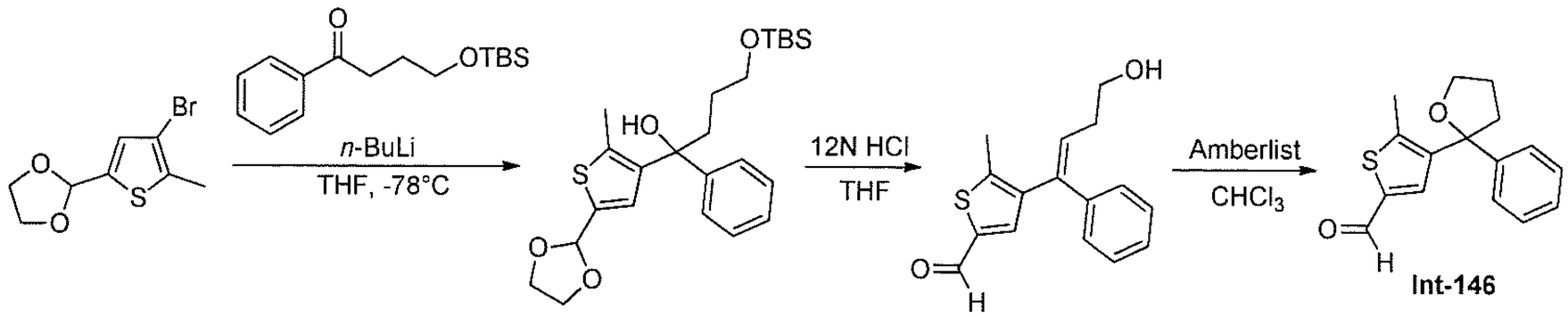
[00533] A 250mL 2-neck round bottom flask was charged with THF (125 mL) then the flask was purged with argon, and was cooled at -78 °C. To the THF, 2.50 M of *n*-BuLi in hexane (4.68 mL, 11.7 mmol) was added dropwise via syringe and the mixture was stirred for 10 min at -78 °C. 2-(4-Bromothiophen-2-yl)-1,3-dioxolane (2.38 g, 10.1 mmol) was added dropwise at -78 °C. The solution was stirred for 30 min at -78 °C. Int-142 (2.55 g, 7.80 mmol) was added to the solution at once at -78 °C and stirred for 30 min. The reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with EtOAc (75 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 40% EtOAc in hexanes as eluent) to give 3.1g (82%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 (s, 1H), 7.24 – 7.15 (m, 4H), 7.03 (s, 1H), 5.99 (s, 1H), 4.13 – 4.08 (m, 3H), 4.02 – 3.94 (m, 2H), 3.58 (t, *J* = 6.2 Hz, 2H), 2.20 (t, *J* = 8.0 Hz, 2H), 1.57 – 1.46 (m, 2H), 1.45 – 1.32 (m, 1H), 0.85 (s, 9H), 0.01 (s, 6H).

Step 2: rac-4-[2-(3-Chlorophenyl)tetrahydro-2*H*-pyran-2-yl]thiophene-2-carbaldehyde.

[00534] To a solution of rac-5-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]pentan-1-ol (533 mg, 1.10 mmol) in THF (4.0 mL) was added 12 M of

HCl (12.0 mL) was added and the reaction mixture was heated at 68 °C. After 2 h, the reaction mixture was allowed to rt, and poured into a solution of Na_2CO_4 (9.75 g) in 100mL of water. The aqueous layer was extracted with EtOAc (15 mLx2). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by ISCO column chromatography (0% - 100% EtOAc in hexanes as eluent) to give 233 mg (69%) of the title compound as an oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.84 (s, 1H), 7.64 (s, 1H), 7.54 (s, 1H), 7.42 (s, 1H), 7.27 – 7.18 (m, 3H), 3.80 – 3.63 (m, 2H), 2.24 (t, *J* = 6.0 Hz, 2H), 1.79 – 1.69 (m, 2H), 1.68 – 1.59 (m, 2H).

Example 85**: rac-5-Methyl-4-(2-phenyltetrahydrofuran-2-yl)thiophene-2-carbaldehyde. Int-146**



Step 1: rac-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]-1-phenylbutan-1-ol.

[00535] To a round bottom flask was added THF (12.0 mL) and 2.50 M of *n*-BuLi in hexane (1.87 mL, 4.67 mmol). The solution was cooled at -78 °C and 2-(4-bromo-5-methyl-2-thienyl)-1,3-dioxolane (1.07 g, 4.31 mmol) in THF (5.0 mL) was added and the mixture was stirred for 10 minute. 4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-phenylbutan-1-one (1.00 g, 3.59 mmol) in THF (5.0 mL) was then added quickly via syringe and the mixture was stirred at -78 °C for 1 hour. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3X). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 1.27 g (79%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.33 (m, 2H), 7.30 – 7.24 (m, 2H), 7.22 – 7.16 (m, 1H), 7.14 (s, 1H), 5.99 (s, 1H), 4.17 – 4.08 (m, 2H), 4.05 – 3.96 (m, 2H), 3.67 – 3.59 (m, 2H), 3.42 (s, 1H), 2.43 – 2.32 (m, 1H), 2.32 – 2.20 (m, 1H), 2.17 (s, 3H), 1.65 – 1.52 (m, 2H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

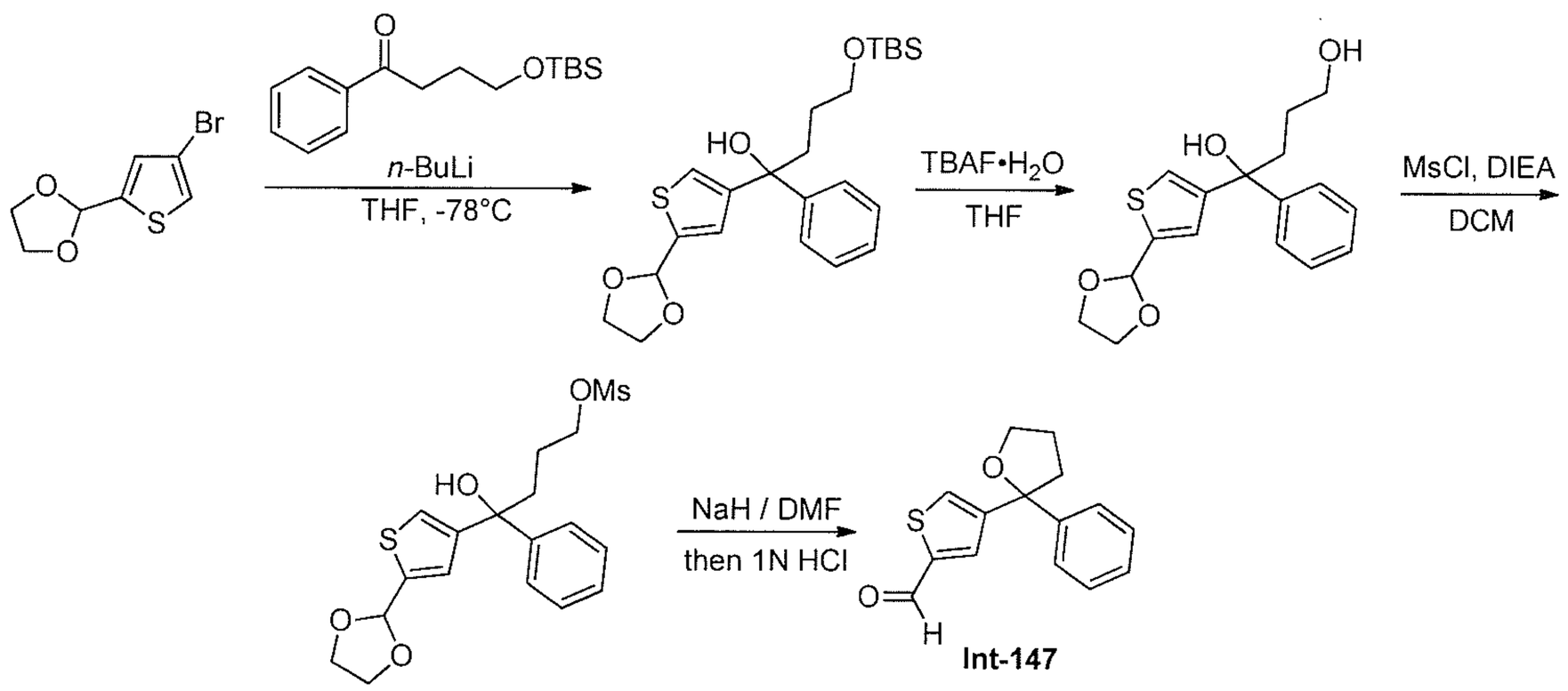
Step 2: rac-4-[(1Z)-4-Hydroxy-1-phenylbut-1-en-1-yl]-5-methylthiophene-2-carbaldehyde.

[00536] To a round bottom flask was added rac-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]-1-phenylbutan-1-ol (1.27 g, 2.84 mmol) in THF (5.0 mL). 12 M of HCl in water (2.0 mL, 24 mmol) was added and the solution was heated to reflux for 1 hour. The reaction was then cooled to rt and quenched with saturated $NaHCO_3$ and extracted with EtOAc (3X). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. No purification was done to give crude title compound. LCMS (FA): *m/z* = 273.3 (M+H)

Step 3: rac-5-Methyl-4-(2-phenyltetrahydrofuran-2-yl)thiophene-2-carbaldehyde.

[00537] rac-4-[(1Z)-4-Hydroxy-1-phenylbut-1-en-1-yl]-5-methylthiophene-2-carbaldehyde (773 mg, 2.84 mmol) was dissolved in chloroform (20.0 mL) and Amberlyst 15 ion-exchange resin (2 g) was added and the mixture was heated to 50 °C for 7 h. The reaction was then filtered to remove resin, rinsed with DCM and concentrated to dryness. The reaction was stopped before complete consumption of starting material to avoid decomposition of product. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 261 mg (34%, over 2 steps) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.78 (s, 1H), 7.74 (s, 1H), 7.36 – 7.27 (m, 4H), 7.26 – 7.19 (m, 1H), 4.14 – 4.06 (m, 1H), 4.03 – 3.95 (m, 1H), 2.61 – 2.44 (m, 2H), 2.35 (s, 3H), 2.06 – 1.94 (m, 2H).

Example 86**: rac-4-(2-Phenyltetrahydrofuran-2-yl)thiophene-2-carbaldehyde. Int-147**



Step 1: rac-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-1-phenylbutan-1-ol.

[00538] To a round bottom flask was added THF (20.0 mL) and 2.50 M of *n*-BuLi in hexane (3.57 mL, 8.92 mmol). The mixture was cooled at -78 °C and 2-(4-bromothiophen-2-yl)-1,3-dioxolane (1.94 g, 8.23 mmol) in THF (10.0 mL) was added and the mixture was stirred for 10 min. 4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-phenylbutan-1-one (1.91 g, 6.86 mmol) in THF (10.0 mL) was then added quickly via syringe and the mixture was stirred at -78 °C for 1 hour. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 2.57 g (86%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.41 (m, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.18 (m, 1H), 7.17 (d, *J* = 1.4 Hz, 1H), 7.07 (d, *J* = 1.1 Hz, 1H), 6.00

(s, 1H), 4.16 – 4.06 (m, 2H), 4.03 – 3.94 (m, 2H), 3.92 (s, 1H), 3.67 – 3.61 (m, 2H), 2.43 – 2.28 (m, 2H), 1.62 – 1.52 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H).

Step 2: rac-1-[5-(1,3-Dioxolan-2-yl)-3-thienyl]-1-phenylbutane-1,4-diol.

[00539] rac-4-{[tert-butyl(dimethyl)silyl]oxy}-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-1-phenylbutan-1-ol (2.56 g, 5.89 mmol) in THF (50.0 mL) was added TBAF hydrate (1.98 g, 7.07 mmol) at rt and the reaction was stirred overnight. To the reaction was added water and the mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 100% EtOAc in hexanes as eluent) to give 1.68 g (89%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.39 (m, 2H), 7.35 – 7.28 (m, 2H), 7.26 – 7.20 (m, 1H), 7.18 (s, 1H), 7.06 (s, 1H), 5.99 (s, 1H), 4.15 – 4.06 (m, 2H), 4.03 – 3.94 (m, 2H), 3.69 – 3.62 (m, 2H), 3.13 (s, 1H), 2.43 – 2.30 (m, 2H), 1.71 (s, 1H), 1.66 – 1.49 (m, 2H).

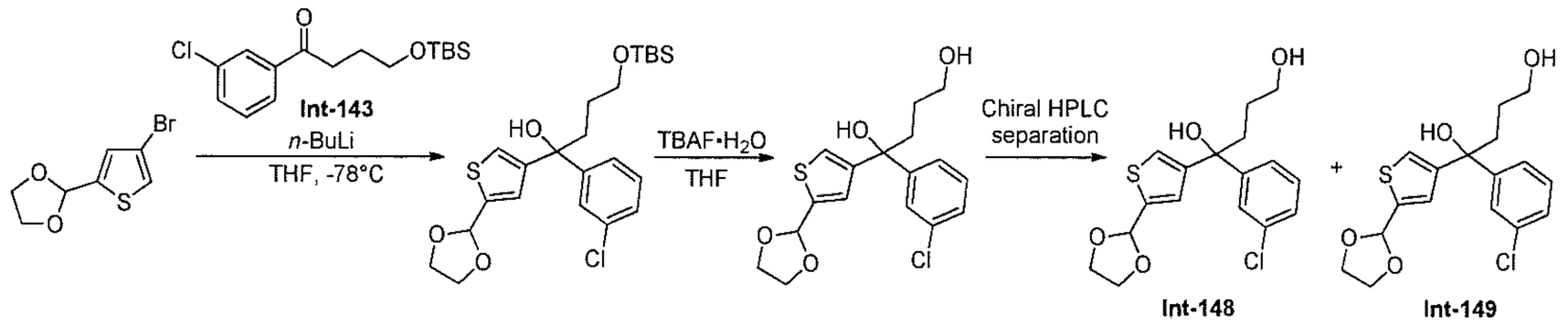
Step 3: rac-4-[5-(1,3-Dioxolan-2-yl)-3-thienyl]-4-hydroxy-4-phenylbutyl methanesulfonate.

[00540] To a solution of rac-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-1-phenylbutane-1,4-diol (0.69 g, 2.14 mmol) in DCM (20 mL) cooled to 0 °C was added N,N-diisopropylethylamine (0.56 mL, 3.21 mmol) followed by methanesulfonyl chloride (182 uL, 2.36 mmol) and the reaction was stirred for 1 hour. The reaction was quenched by addition of water and extracted with DCM (3X). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. No further purification was done to give crude title compound. LCMS (FA): *m/z* = 399.2 (M+H)

Step 4: rac-4-(2-Phenyltetrahydrofuran-2-yl)thiophene-2-carbaldehyde.

[00541] To a solution of rac-4-[5-(1,3-dioxolan-2-yl)-3-thienyl]-4-hydroxy-4-phenylbutyl methanesulfonate (853 mg, 2.14 mmol) in THF (15.0 mL) and DMF (5.0 mL) was added 60% NaH in mineral oil (128 mg, 3.21 mmol) and the reaction was stirred for 2 h. The reaction was quenched by addition of water and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then dissolved in acetone (15.0 mL) and to the solution was added water (7.0 mL) followed by 1.0 M of HCl (0.6 mL, 0.6 mmol) at rt. The resulting solution was then stirred for 30 min. The reaction was quenched by addition of saturated $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 30% EtOAc in hexanes as eluent) to give 414 mg (75%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (d, *J* = 1.2 Hz, 1H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.45 – 7.41 (m, 2H), 7.37 – 7.31 (m, 2H), 7.28 – 7.23 (m, 1H), 4.12 – 4.01 (m, 2H), 2.56 – 2.49 (m, 2H), 2.09 – 1.94 (m, 2H).

Example 87: **(1*S*)-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol or 1*R*)-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol (Peak 1) Int-148, and (1*S*)-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol or (1*R*)-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol (Peak 2) Int-149**



Step 1: rac-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butan-1-ol.

[00542] THF (20.0 mL) was added into a 250mL 2-neck flask under atmosphere of argon and cooled at -78 °C. 2.50 M of *n*-BuLi in hexane (1.92 mL, 4.79 mmol) was added into the THF. To the mixture was added quick dropwise a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (1.13 g, 4.79 mmol) in THF (8.0 mL) and the mixture was stirred for 3 min at -78 °C. To the mixture was added dropwise a solution of Int-143 (1.25 g, 3.99 mmol) in THF (5 mL, 60 mmol) at -78 °C, and the reaction was stirred for 10 min. The reaction was quenched by addition of water (100 mL) and extracted with EtOAc (100 mL x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (10% - 30% EtOAc in hexanes as eluent) to give 1.44 g of the title compound (71%) colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 – 7.42 (m, 1H), 7.36 (d, J = 1.4 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 7.08 (d, J = 1.3 Hz, 1H), 5.92 (s, 1H), 5.73 (s, 1H), 4.02 – 3.93 (m, 2H), 3.93 – 3.84 (m, 2H), 3.52 (tt, J = 10.0, 5.1 Hz, 2H), 2.22 – 2.08 (m, 2H), 1.53 – 1.38 (m, 1H), 1.32 – 1.19 (m, 1H), 0.83 (s, 9H), -0.02 (s, 3H), -0.03 (s, 3H).

Step 2: rac-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol.

[00543] To a solution of rac-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butan-1-ol (1.43 g, 2.80 mmol) in THF (40.0 mL) was added TBAF monohydrate (941 mg, 3.37 mmol) at rt, and the reaction was stirred for 15 min. The reaction was concentrated in vacuo. To the residue was added water and then the mixture was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (20% EtOAc in DCM as eluent) to give 935mg (89%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.44 (m, 1H), 7.38 (d, J = 1.4 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.24 (dt, J = 6.7, 2.1 Hz, 1H), 7.09 (d, J = 1.3 Hz, 1H), 5.92 (s, 1H), 5.74 (s, 1H), 4.40 (t, J = 5.2 Hz, 1H),

4.01 – 3.94 (m, 2H), 3.94 – 3.83 (m, 2H), 3.41 – 3.30 (m, 2H), 2.14 (tq, *J* = 13.9, 6.9, 5.4 Hz, 2H), 1.48 – 1.35 (m, 1H), 1.28 – 1.14 (m, 1H).

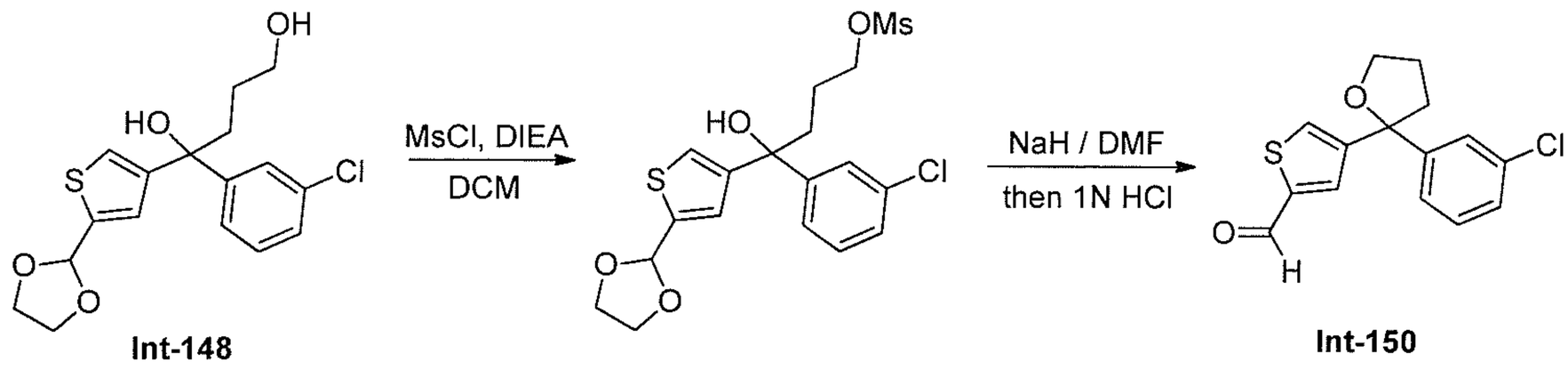
Step 3: (1*S*)-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol and (1*R*)-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol.

[00544] rac-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol was separated to enantiomers by chiral HPLC (chiral column IB 4.6X50 mm, 70/10/20/0.1 Hexane/IPA/EtOH/DEA 1.3 mL/min) to yield Peak 1: 381 mg (41%) >98%ee and Peak 2: 398 mg (43%) >98%ee.

[00545] Peak 1: (1*S*)-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol or (1*R*)-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.44 (m, 1H), 7.37 (d, *J* = 1.4 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.24 (dt, *J* = 6.8, 2.1 Hz, 1H), 7.09 (d, *J* = 1.3 Hz, 1H), 5.93 (s, 1H), 5.73 (s, 1H), 4.39 (t, *J* = 5.2 Hz, 1H), 4.03 – 3.94 (m, 2H), 3.94 – 3.84 (m, 2H), 3.40 – 3.32 (m, 2H), 2.14 (tq, *J* = 13.8, 6.8, 5.4 Hz, 2H), 1.49 – 1.35 (m, 1H), 1.29 – 1.16 (m, 1H).

[00546] Peak 2: (1*S*)-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol or (1*R*)-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.43 (m, 1H), 7.37 (d, *J* = 1.3 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.24 (dt, *J* = 6.8, 2.1 Hz, 1H), 7.09 (d, *J* = 1.2 Hz, 1H), 5.93 (s, 1H), 5.73 (s, 1H), 4.39 (t, *J* = 5.2 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.94 – 3.84 (m, 2H), 3.40 – 3.32 (m, 2H), 2.14 (tq, *J* = 13.7, 6.8, 5.3 Hz, 2H), 1.49 – 1.35 (m, 1H), 1.29 – 1.15 (m, 1H).

Example 88**: 4-[(2*S*)-2-(3-Chlorophenyl)tetrahydrofuran-2-yl]thiophene-2-carbaldehyde or 4-[(2*R*)-2-(3-Chlorophenyl)tetrahydrofuran-2-yl]thiophene-2-carbaldehyde. Int-150**



Int-148 Int-150

Step 1: (4*S*)-4-(3-Chlorophenyl)-4-[5-(1,3-dioxolan-2-yl)-3-thienyl]-4-hydroxybutyl methanesulfonate or (4*R*)-4-(3-Chlorophenyl)-4-[5-(1,3-dioxolan-2-yl)-3-thienyl]-4-hydroxybutyl methanesulfonate (Peak 1) .

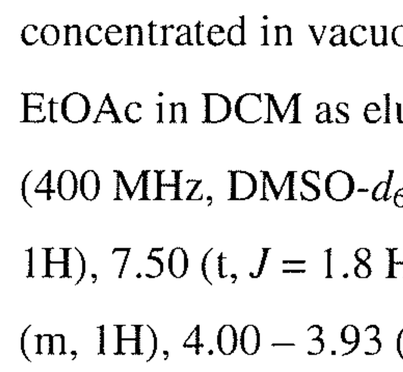
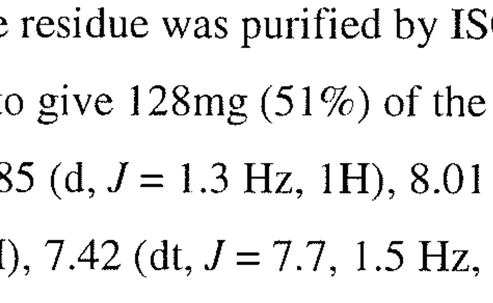
[00547] To a solution of (1*S* or 1*R*)-1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]butane-1,4-diol (Int-148, 375 mg, 1.06 mmol) (Peak 1) in DCM (10.0 mL) was added N,N-diisopropylethylamine (0.28 mL, 1.59 mmol) followed by methanesulfonyl chloride (0.09 mL,

1.16 mmol) at rt, and the reaction was stirred for 1 hour. The reaction was quenched by addition of water (50 mL) and extracted with DCM (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO silica gel column chromatography (24g, eluting with 5% EtOAc in DCM for 3min then gradient to 20% EtOAc in DCM over 15min, 40mL/min flow) to give 372mg (81%) of the title compound as a colorless oil. LCMS (AA): *m/z* = 433.0 (M+H).

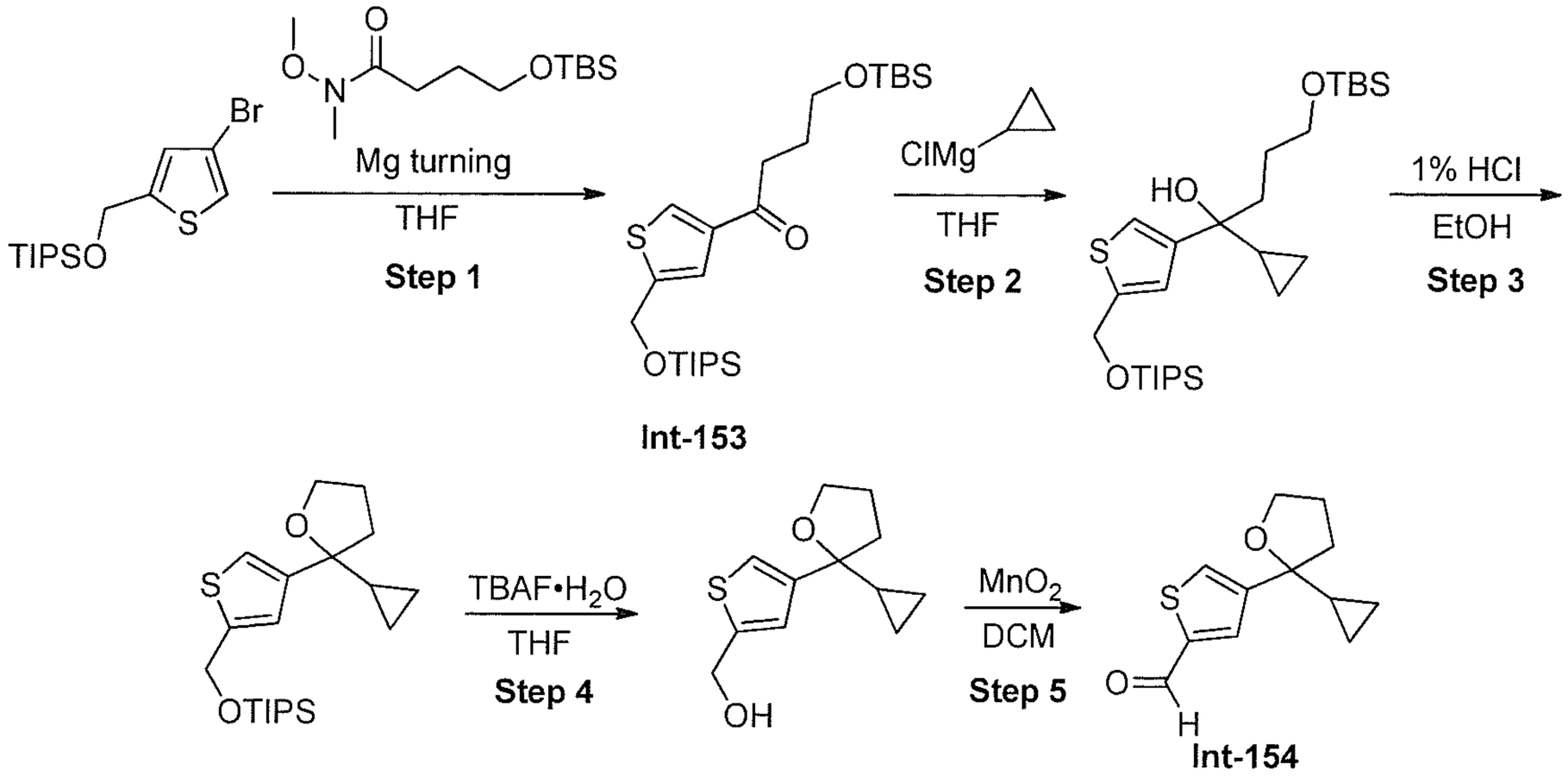
Step 2: 4-[(2*S*)-2-(3-Chlorophenyl)tetrahydrofuran-2-yl]thiophene-2-carbaldehyde or 4-[(2*R*)-2-(3-Chlorophenyl)tetrahydrofuran-2-yl]thiophene-2-carbaldehyde.

[00548] To a solution of (4*S* or 4*R*)-4-(3-chlorophenyl)-4-[5-(1,3-dioxolan-2-yl)-3-thienyl]-4-hydroxybutyl methanesulfonate (368 mg, 0.85 mmol) in DMF (5.5 mL) was added 60% NaH in mineral oil (51.0 mg, 1.28 mmol) and the reaction was stirred for 1 hour. The reaction was quenched by addition of water (50 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in acetone (6.0 mL, 81.7 mmol). To the solution was added water (3.0 mL) followed by 1.0 M of HCl in water (0.30 mL, 0.30 mmol) at rt, and the mixture was stirred for 1 hour. The reaction was quenched by addition of saturated $NaHCO_3$ (50 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 5% EtOAc in DCM as eluent) to give 128mg (51%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (d, *J* = 1.3 Hz, 1H), 8.01 (t, *J* = 1.4 Hz, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 7.50 (t, *J* = 1.8 Hz, 1H), 7.42 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.28 (m, 1H), 4.00 – 3.93 (m, 2H), 2.70 – 2.61 (m, 1H), 2.40 (dt, *J* = 12.6, 7.5 Hz, 1H), 1.98 – 1.82 (m, 2H).

[00549] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Starting material	Compound Name / No.	Characterization Data
 **Int-151**	 **Peak 2** **Int-152**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (d, *J* = 1.3 Hz, 1H), 8.01 (t, *J* = 1.4 Hz, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 7.50 (t, *J* = 1.8 Hz, 1H), 7.42 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.28 (m, 1H), 4.02 – 3.91 (m, 2H), 2.70 – 2.60 (m, 1H), 2.40 (dt, *J* = 12.6, 7.5 Hz, 1H), 1.97 – 1.82 (m, 2H). LCMS (AA): *m/z* = 293.0 (M+H).

Example 89: **4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-one Int-153, and rac-4-(2-Cyclopropyltetrahydrofuran-2-yl)thiophene-2-carbaldehyde Int-154**



Step 1: 4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-one.

[00550] A round bottom flask with condenser was charged with magnesium turnings (204 mg, 8.39 mmol) and purged with argon. To the reaction vessel was added THF (1.70 mL) followed by 1,2-dibromoethane (30.1 uL, 0.35 mmol) at rt, and the mixture was heated with a heat gun several times until tiny bubbles from Mg metal observed constantly. After tiny bubbles observation, [(4-bromo-2-thienyl)methoxy](triisopropyl)silane (2.44 g, 6.99 mmol) in THF (12.2 mL) was added to the magnesium suspension and the mixture was stirred for 4 h at 40 °C. This Grignard solution was cooled to rt and carried on to the next reaction.

[00551] To a solution of 4-{[*tert*-butyl(dimethyl)silyl]oxy}-*N*-methoxy-*N*-methylbutanamide (1.33 g, 5.08 mmol) in THF (30.0 mL) was added the above Grignard solution (13.0 mL, 6.10 mmol) at 0 °C, and the reaction was stirred for 30 min at rt. The reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 10% EtOAc in hexane) to give 1.79 g (75%) of the title compound as a light brown oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 1.2 Hz, 1H), 7.32 (s, 1H), 4.94 (s, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 2.93 (t, *J* = 7.3 Hz, 2H), 1.98 – 1.87 (m, 2H), 1.23 – 1.02 (m, 21H), 0.89 (s, 9H), 0.04 (s, 6H).

Step 2: rac-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-cyclopropyl-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-ol.

[00552] To a solution of 4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-one (202 mg, 0.43 mmol) in THF (1.8 mL) was added 0.5 M of cyclopropylmagnesium bromide in THF (2.41 mL, 1.21 mmol) at 0 °C, and then the reaction was allowed to warm to rt. After 1 h, the reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 5% EtOAc in hexane) to afford 186 mg (84%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (s, 1H), 6.80 (s, 1H), 4.88 (s, 2H), 3.64 – 3.49 (m, 2H), 2.79 (s, 1H), 2.04 – 1.91 (m, 1H), 1.91 – 1.78 (m, 1H), 1.59 – 1.51 (m, 2H), 1.18 – 0.97 (m, 22H), 0.85 (s, 9H), 0.43 – 0.33 (m, 2H), 0.34 – 0.24 (m, 2H), 0.04 (s, 6H).

Step 3: rac-{[4-(2-Cyclopropyltetrahydrofuran-2-yl)-2-thienyl]methoxy}(triisopropyl)silane.

[00553] To a solution of rac-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-cyclopropyl-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-ol (186 mg, 0.36 mmol) in EtOH (3.1 mL) was added 1% HCl in EtOH (3.11 mL, 0.38 mmol) at rt and the reaction was stirred for 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and concentrated in vacuo to remove EtOH. To the residue was added water and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 5% EtOAc in hexane) to give 103 mg (75%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (s, 1H), 6.93 (s, 1H), 4.90 (s, 2H), 3.75 (t, J = 6.7 Hz, 2H), 2.18 – 2.04 (m, 1H), 2.01 – 1.83 (m, 2H), 1.81 – 1.66 (m, 1H), 1.30 – 0.95 (m, 22H), 0.43 – 0.22 (m, 4H).

Step 4: rac-[4-(2-Cyclopropyltetrahydrofuran-2-yl)-2-thienyl]methanol.

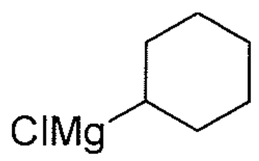
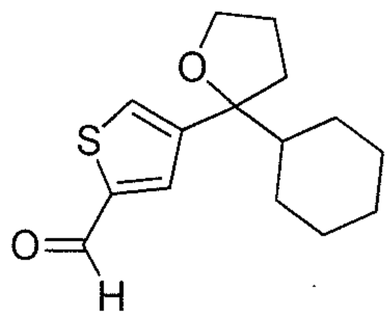
[00554] To a solution of rac-{[4-(2-cyclopropyltetrahydrofuran-2-yl)-2-thienyl]methoxy}(triisopropyl)silane (99.9 mg, 0.26 mmol) in THF (5.46 mL) was added TBAF hydrate (88.0 mg, 0.32 mmol) at rt and the reaction was stirred for 1 h. The reaction was concentrated in vacuo and the residue was purified by silica gel column chromatography (0 to 30% EtOAc in hexane) to give 54.5 mg (93%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (s, 1H), 6.97 (s, 1H), 4.81 (d, J = 6.0 Hz, 2H), 3.96 – 3.85 (m, 2H), 2.23 – 2.12 (m, 1H), 2.11 – 1.81 (m, 3H), 1.74 (t, J = 6.0 Hz, 1H), 1.27 – 1.19 (m, 1H), 0.50 – 0.35 (m, 4H).

Step 5: rac-4-(2-Cyclopropyltetrahydrofuran-2-yl)thiophene-2-carbaldehyde.

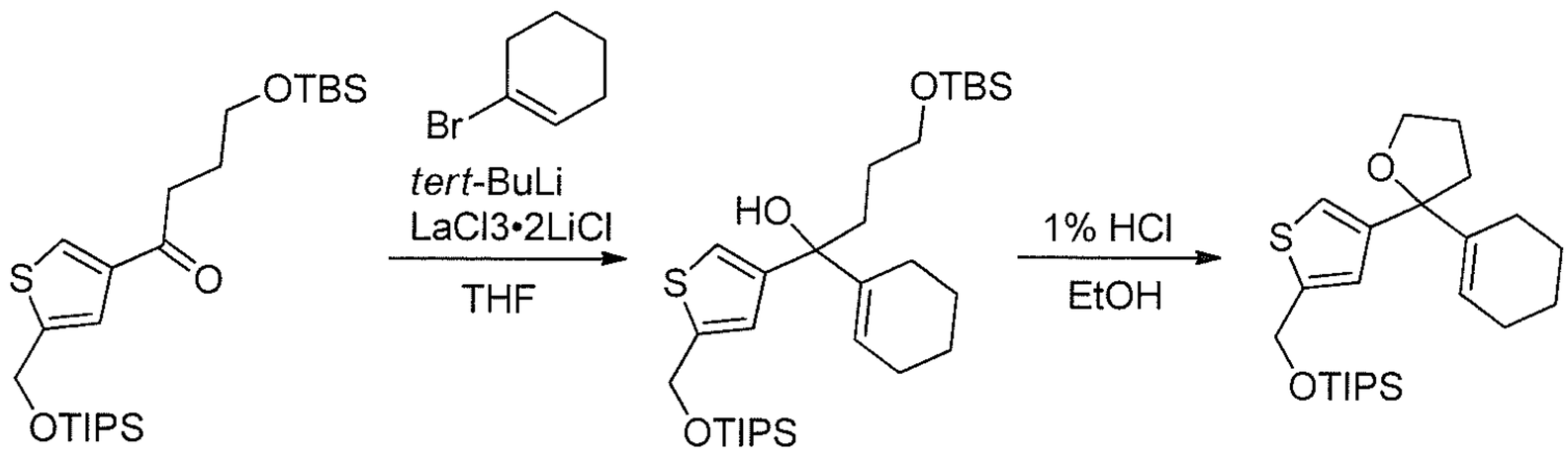
[00555] To a solution of rac-[4-(2-cyclopropyltetrahydrofuran-2-yl)-2-thienyl]methanol (54.5 mg, 0.24 mmol) in DCM (9.0 mL) was added Mn_2O (211 mg, 2.43 mmol) at rt, and the reaction was stirred overnight. The reaction was filtered through a Celite pad and the residual solid was rinsed

with DCM several times. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (0 to 20% EtOAc in hexane) to give 53.3 mg (98%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.91 (s, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 3.99 – 3.84 (m, 2H), 2.23 – 1.97 (m, 3H), 1.95 – 1.80 (m, 1H), 1.31 – 1.20 (m, 1H), 0.57 – 0.35 (m, 4H).

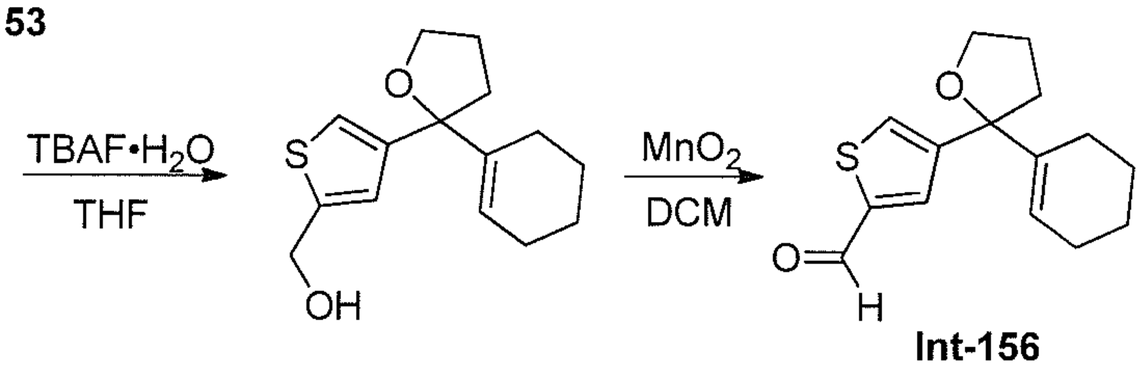
[00556] The compound listed in the table below was prepared using similar methods to that described above starting from the listed starting material.

Step 2 Grignard reagent	**Compound Name / No.**	**Characterization Data**
	 **Int-155**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.89 (d, *J* = 1.1 Hz, 1H), 7.65 (d, *J* = 1.3 Hz, 1H), 7.52 – 7.47 (m, 1H), 3.91 (q, *J* = 7.5, 7.1 Hz, 1H), 3.83 – 3.74 (m, 1H), 2.15 (ddd, *J* = 12.1, 8.0, 4.0 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.98 – 1.80 (m, 2H), 1.80 – 1.51 (m, 5H), 1.34 – 1.11 (m, 3H), 1.09 – 0.85 (m, 3H), 0.77 (qd, *J* = 12.7, 3.4 Hz, 1H).

Example 90: **rac-4-[2-(Cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]thiophene-2-carbaldehyde. Int-156**



Int-153



Int-156

Step 1: rac-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-(cyclohex-1-en-1-yl)-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-ol.

[00557] To a solution of 1-bromo-1-cyclohexene (880 uL, 7.85 mmol) in THF (15 mL) was added 1.70 M of *tert*-BuLi in pentane (9.24 mL, 15.7 mmol) at -78 °C, and the reaction was stirred for 1 hour at same temperature. To a separate flask, 4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-one (Int-xxx) (616 mg, 1.31 mmol) was added

followed by 0.6 M of lanthanum(III) chloride bis(lithium chloride) complex in THF (1.09 mL, 0.65 mmol) and the reaction mixture was stirred for 1 hour. The resulting lithiated cyclohexene solution was added to the ketone at 0 °C. After stirring for 30 min at rt, the reaction was quenched by adding saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 10% EtOAc in hexane) to give 662 mg (91%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 (s, 1H), 6.78 (s, 1H), 5.90 – 5.84 (m, 1H), 4.84 (s, 2H), 3.59 (t, *J* = 5.9 Hz, 2H), 2.80 (s, 1H), 2.07 – 1.98 (m, 4H), 1.99 – 1.88 (m, 2H), 1.87 – 1.79 (m, 2H), 1.55 – 1.44 (m, 4H), 1.17 – 0.93 (m, 21H), 0.84 (s, 9H), 0.05 (s, 6H).

Step 2: rac-({4-[2-(Cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}methoxy)(triisopropyl)silane.

[00558] To a solution of rac-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-(cyclohex-1-en-1-yl)-1-(5-{[(triisopropylsilyl)oxy]methyl}-3-thienyl)butan-1-ol (662 mg, 1.20 mmol) in EtOH (10.3 mL) was added 1% HCl in EtOH (10.3 mL, 1.24 mmol) at rt and the reaction was stirred for 30 min. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and concentrated in vacuo to remove EtOH. To the residue was added water and the mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 5% EtOAc in hexane) to afford 291 mg (58%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.96 (s, 1H), 6.74 (s, 1H), 5.76 – 5.70 (m, 1H), 4.88 (s, 2H), 3.88 (t, *J* = 7.1 Hz, 2H), 2.21 – 2.07 (m, 2H), 2.07 – 1.98 (m, 2H), 1.95 – 1.79 (m, 4H), 1.53 – 1.46 (m, 4H), 1.19 – 0.98 (m, 21H).

Step 3: rac-{4-[2-(Cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}methanol.

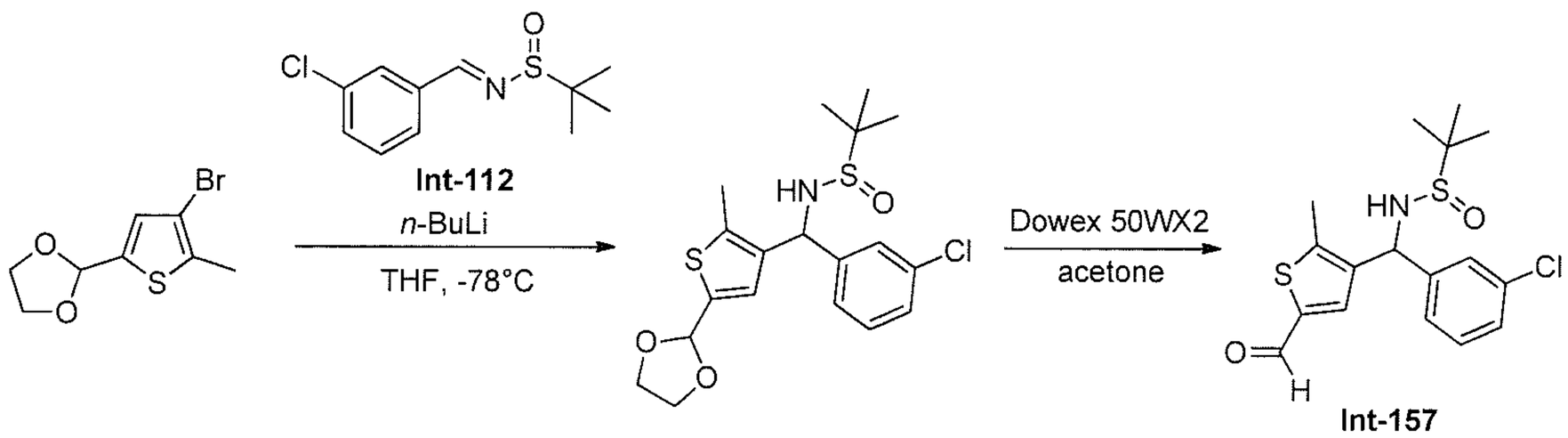
[00559] To a solution of rac-({4-[2-(cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}methoxy)(triisopropyl)silane (339 mg, 0.81 mmol) in THF (17 mL) was added TBAF hydrate (270 mg, 0.97 mmol) at rt. After 1 hour, the reaction was concentrated in vacuo and the residue was purified by silica gel column chromatography (0 to 30% EtOAc in hexane) to give 193 mg (91%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.07 (s, 1H), 6.90 (s, 1H), 5.84 – 5.76 (m, 1H), 4.79 (d, *J* = 5.7 Hz, 2H), 3.93 (t, *J* = 7.2 Hz, 2H), 2.27 – 2.11 (m, 2H), 2.11 – 2.04 (m, 2H), 2.02 – 1.84 (m, 4H), 1.76 (t, *J* = 6.0 Hz, 1H), 1.63 – 1.52 (m, 4H).

Step 4: rac-4-[2-(Cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]thiophene-2-carbaldehyde.

[00560] To a solution of rac-{4-[2-(cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}methanol (192 mg, 0.73 mmol) in DCM (26.9 mL) was added MnO_2 (634 mg, 7.29 mmol) at rt, and the reaction was stirred overnight. The reaction was filtered through a Celite pad and the residual solid was

rinsed with DCM several times. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (0 to 20% EtOAc in hexane) to give 176 mg (92%) of the title compound as colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.89 (s, 1H), 7.68 (s, 1H), 7.62 – 7.53 (m, 1H), 5.87 – 5.76 (m, 1H), 3.95 (t, *J* = 7.0 Hz, 2H), 2.37 - 2.27 (m, 1H), 2.19 – 2.06 (m, 3H), 2.06 – 1.83 (m, 4H), 1.64 – 1.52 (m, 4H).

Example 91: **rac-*N*-[(3-Chlorophenyl)(5-formyl-2-methyl-3-thienyl)methyl]-2-methylpropane-2-sulfinamide. Int-157**



Step 1: rac-*N*-{(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methyl}-2-methylpropane-2-sulfinamide.

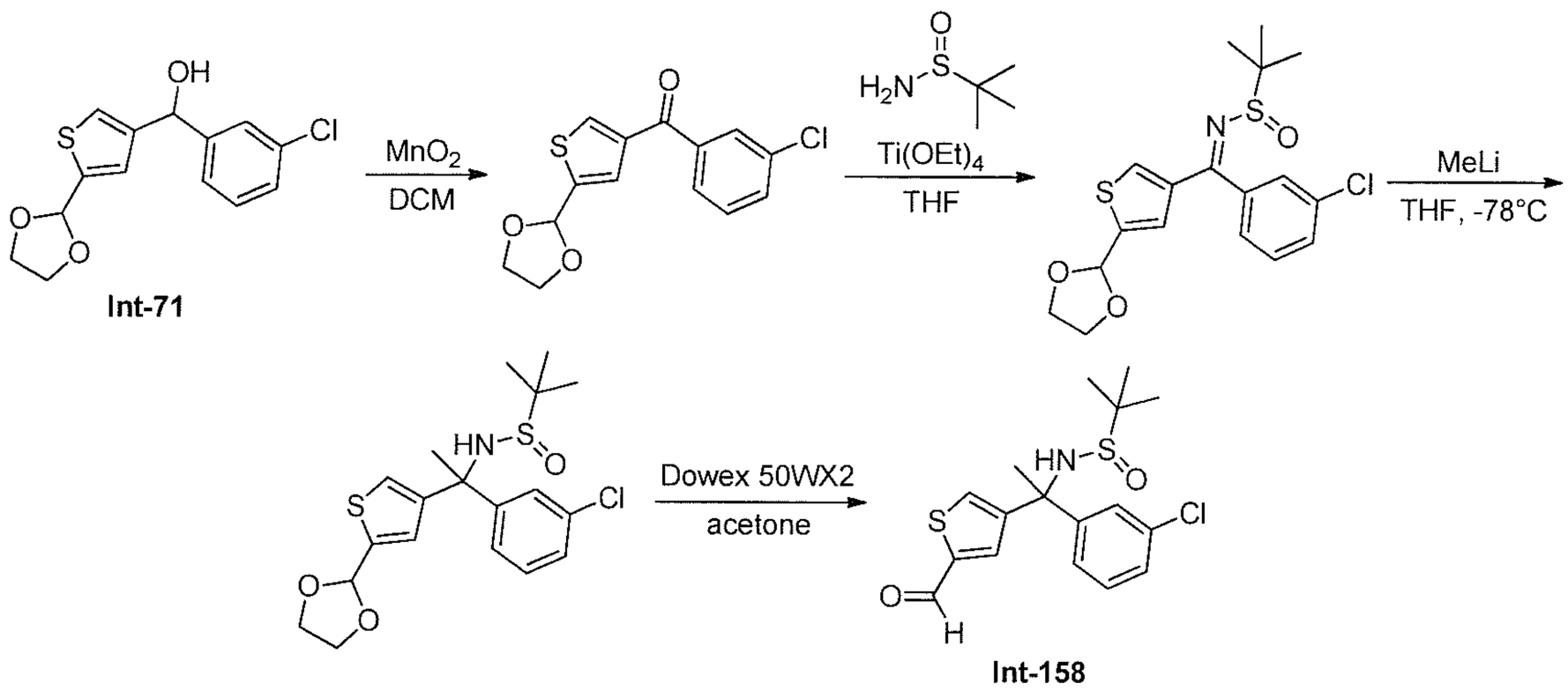
[00561] A solution of 2-(4-Bromo-5-methyl-2-thienyl)-1,3-dioxolane (3.1 g, 12.0 mmol) in THF (6 mL) was added dropwise to a solution of 2.50 M of *n*-BuLi in hexane (5.91 mL, 14.8 mmol) in THF (60 mL) at -78 °C. Immediately after addition was complete, N-[(E)-(3-chlorophenyl)methylene]-2-methylpropane-2-sulfinamide (3.0 g, 12.0 mmol) was added dropwise as a solution in THF (6 mL). The resulting mixture was allowed to stir 30 min at -78 °C and then allowed to warm to near rt. The reaction was quenched with water and the resulting mixture was extracted with EtOAc (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Residue was subjected to ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound (yield = 3.8 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 and 7.33 (each s, each 0.5H), 7.29 – 7.20 (m, 3H), 6.95 and 6.89 (each s, each 0.5H), 5.96 and 5.93 (each s, each 0.5H), 5.61 (d, *J* = 1.8 Hz, 0.5H), 5.60 (d, *J* = 2.7 Hz, 0.5H), 4.13 – 4.05 (m, 2H), 4.03 – 3.92 (m, 2H), 3.64 (d, *J* = 2.5 Hz, 0.5H), 3.49 (s, 0.5H), 2.49 and 2.47 (each s, each 1.5H), 1.25 and 1.24 (each s, each 4.5H).

Step 2: rac-*N*-[(3-Chlorophenyl)(5-formyl-2-methyl-3-thienyl)methyl]-2-methylpropane-2-sulfinamide.

[00562] Dowex 50WX2-200 (H) (3.80 g) was added to a solution of rac-*N*-{(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methyl}-2-methylpropane-2-sulfinamide (3.80 g, 9.20 mmol) in acetone (80 mL) at rt. The reaction was allowed to stir for 1 hour. The reaction was filtered to

remove solid resin and the crude material was purified on ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound (yield = 3.26 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.79 and 9.77 (each s, each 0.5H), 7.65 and 7.57 (each s, each 0.5H), 7.42 – 7.39 (m, 0.5H), 7.37 – 7.34 (m, 0.5H), 7.34 – 7.25 (m, 3H), 5.67 and 5.66 (each s, each 0.5H), 3.75 (d, *J* = 2.2 Hz, 0.5H), 3.58 (d, *J* = 2.5 Hz, 0.5H), 2.59 and 2.58 (each s, each 1.5H), 1.29 and 1.29 (each s, each 4.5H).

Example 92**: rac-*N*-[1-(3-Chlorophenyl)-1-(5-formyl-3-thienyl)ethyl]-2-methylpropane-2-sulfinamide. Int-158**



Step 1: (3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanone.

[00563] To a solution of Int-71 (1.8 g, 6.10 mmol) in DCM (54.5 mL) was added MnO_2 (5.80 g, 66.7 mmol). The mixture was stirred at rt for 14 h. The reaction was then filtered through a Celite pad and the residual solid was washed with DCM several times. The filtrate was concentrated in vacuo to yield 1.7 g of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 1.4 Hz, 1H), 7.80 (t, *J* = 1.8 Hz, 1H), 7.70 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.56 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 6.11 (s, 1H), 4.20 – 4.11 (m, 2H), 4.10 – 4.01 (m, 2H).

Step 2: *N*-{(*E*)-(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methylene}-2-methylpropane-2-sulfinamide.

[00564] (3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanone (1.70 g, 5.77 mmol) was added to a solution of $Ti(OEt)_4$ (5.30 g, 23.2 mmol) in THF (23 mL) under an atmosphere of argon. 2-methyl-2-propanesulfinamide (1.10 g, 9.08 mmol) was then added and the solution heated at 74 °C for 3 h. Additional 2-methyl-2-propanesulfinamide (0.46 g, 3.80 mmol) was added and the solution stirred at 80 °C for an additional 5 h. The reaction was allowed to cool to rt, and the mixture was poured into an equal volume of brine while rapidly stirring. The resulting suspension

was filtered through a medium frit filter, and the filter cake was washed with EtOAc. The filtrate was transferred to a separatory funnel where the organic layer was washed with brine. The combined aqueous layers were extracted with EtOAc (1x). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified on ISCO chromatography eluting with a hexane / EtOAc gradient to afford the title compound as a white solid (yield = 2.1 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (s, 1H), 7.55 – 7.28 (m, 5H), 6.09 (s, 1H), 4.20 – 4.09 (m, 2H), 4.09 – 4.00 (m, 2H), 1.28 (s, 9H).

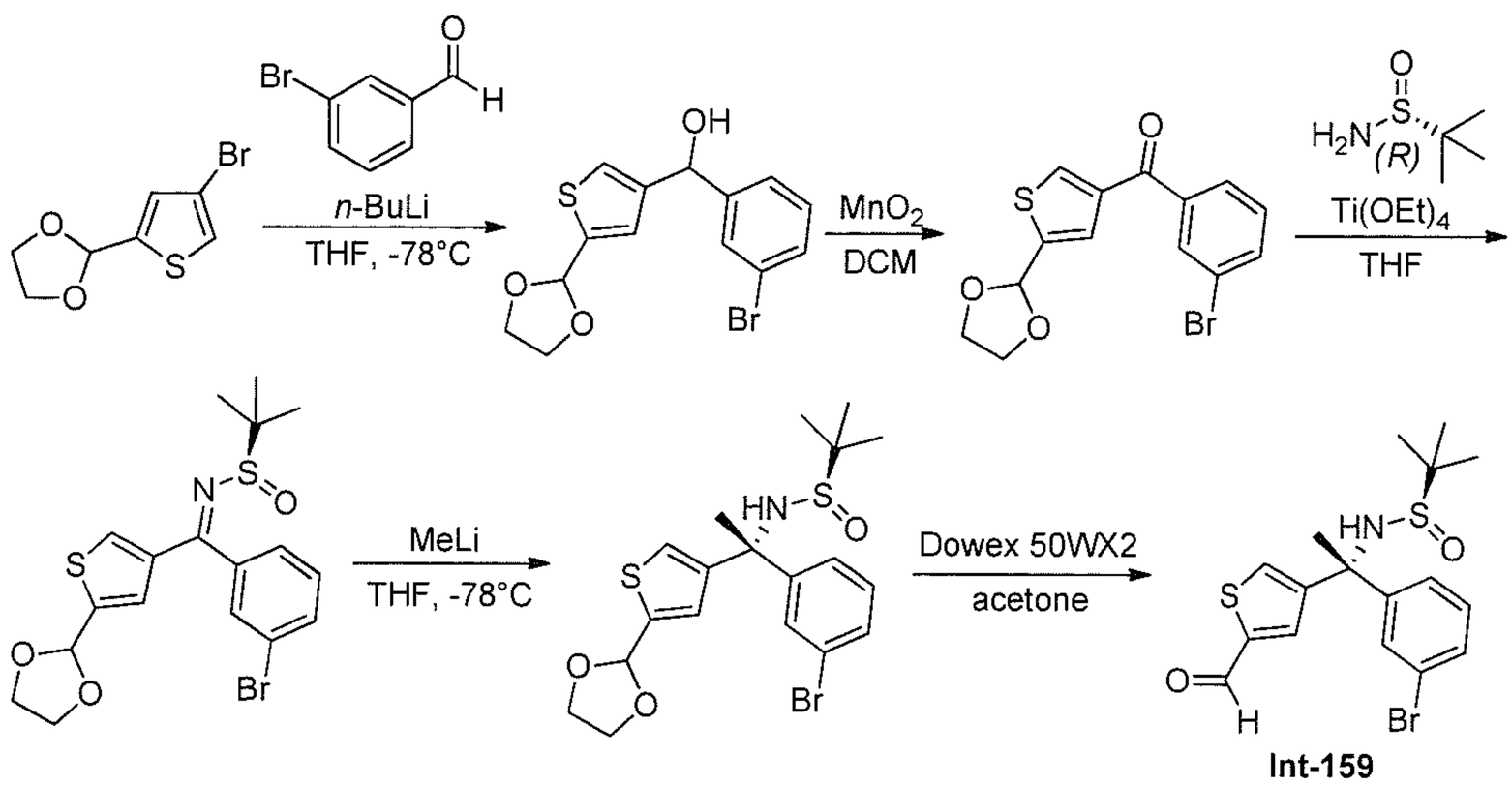
Step 3: rac-*N*-{1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]ethyl}-2-methylpropane-2-sulfinamide.

[00565] 1.6 M of MeLi in ether (4.12 mL, 6.60 mmol) was added dropwise to a solution of *N*-{(*E*)-(3-chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methylene}-2-methylpropane-2-sulfinamide (2.10 g, 5.28 mmol) in THF (20 mL) at -78 °C and the resulting solution allowed to stir for 40 min. After the reaction was warmed to 0 °C, the mixture was diluted with ether and quenched with water. The mixture was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 2.1 g of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.37 (m, 1H), 7.28 – 7.22 (m, 3H), 7.20 (d, *J* = 1.6 Hz, 1H), 6.95 (d, *J* = 1.2 Hz, 1H), 6.00 (s, 1H), 4.13 – 4.08 (m, 2H), 4.02 – 3.96 (m, 2H), 3.74 (s, 1H), 2.06 (s, 3H), 1.23 (s, 9H).

Step 4: rac-*N*-[1-(3-Chlorophenyl)-1-(5-formyl-3-thienyl)ethyl]-2-methylpropane-2-sulfinamide.

[00566] Dowex 50WX2-200 (H) (1.0 g) was added to a solution of rac-*N*-{1-(3-chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]ethyl}-2-methylpropane-2-sulfinamide (2.10 g, 5.07 mmol) in acetone (39 mL) at rt. The reaction was allowed to stir for 1 hour. The reaction was filtered to remove solid resin and the filtrate was concentrated in vacuo. The crude material was purified on silica gel (40g ISCO column; hex then 0-75% EtOAc/hex) to yield 1.8 g of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 1.2 Hz, 1H), 7.72 (t, *J* = 1.4 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.37 – 7.35 (m, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 3.81 (s, 1H), 2.10 (s, 3H), 1.28 (s, 9H).

Example 93**: [4-({(1*R*,3*R*,4*S*)-3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-[(triisopropylsilyl)oxy]cyclopentyl}amino)pyrimidin-5-yl]{5-chloro-4-[(*S*)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}methanone Int-159**



Step 1: rac-(3-Bromophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol.

[00567] An oven-dried 500mL two-neck round bottom flask under nitrogen was charged with THF (200 mL) and cooled to - 70 °C. A solution of 2.50 M of *n*-BuLi in hexane (21.3 mL, 53.2 mmol) was added. To the cooled solution was added 2-(4-bromothiophen-2-yl)-1,3-dioxolane (10.0 g, 42.5 mmol) in THF (10 mL) in small portions keeping the internal temperature less than -70 °C. The mixture was stirred for 5 min. Then a solution of 3-bromobenzaldehyde (4.96 mL, 42.5 mmol) in THF (10 mL) was added fast in a single portion. Internal temperature increased to -45 °C. The resulting mixture stirred for 5 min. Then saturated $NaHCO_3$ was added slowly to quench reaction. The solution was warmed to rt and extracted three times with EtOAc. The combined organic layers were then washed with brine, dried with $MgSO_4$, filtered, concentrated to dryness. The residue was purified by ISCO column chromatography (eluting with EtOAc/hexanes gradient) to give 9.27 g (64%) of the title compound. LCMS (FA): *m/z* = 343.2 (M+H).

Step 2: (3-Bromophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanone.

[00568] A 500mL round bottom flask was charged with rac-(3-bromophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol (9.00 g, 26.4 mmol) in DCM (200 mL). MnO_2 (22.9 g, 264 mmol) was added and the reaction was stirred at rt for 18 h. The reaction was then filtered through Celite pad, rinsed with DCM several times and the filtrate was concentrated to dryness. The residue was purified by ISCO column chromatography (eluting with EtOAc/hexanes gradient) to give 8.89 g (99%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.90 (m, 2H), 7.77 – 7.68 (m, 2H), 7.64 – 7.60 (m, 1H), 7.40 – 7.33 (m, 1H), 6.11 (s, 1H), 4.20 – 4.10 (m, 2H), 4.10 – 4.01 (m, 2H).

Step 3: *N*-{(*E*)-(3-Bromophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methylene}-2-methylpropane-2-sulfinamide.

[00569] A 500mL round bottom flask under nitrogen was charged with THF (30 mL) and $Ti(OEt)_4$ (6.7 g, 29 mmol) was added. To this solution was added a solution of (3-bromophenyl)[5-(1,3-

dioxolan-2-yl)-3-thienyl]methanone (2.50 g, 7.37 mmol) in a minimum amount of THF. Next was added (*R*)-(-)-2-methyl-2-propanesulfinamide (1.43 g, 11.8 mmol). The mixture was heated to reflux and stirred for 1 day. The reaction was cooled to rt and poured into 20 mL of brine with rapid stirring. The white precipitate was filtered off, and the filtrate was extracted with EtOAc (x2). The combined organic layers were then dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by ISCO column chromatography (eluting with 0% - 60% EtOAc/hexanes) to give 2.67 g (82%) of product. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.27 (m, 6H), 6.09 (s, 1H), 4.19 – 4.09 (m, 2H), 4.09 – 3.99 (m, 2H), 1.28 (s, 9H).

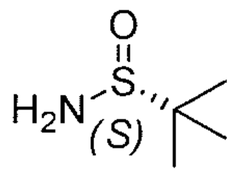
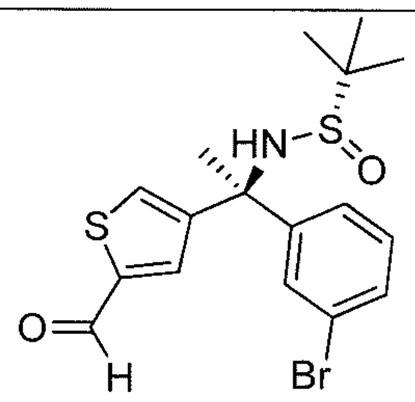
Step 4: *N*-{(1*R*)-1-(3-Bromophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]ethyl}-2-methylpropane-2-sulfinamide.

[00570] A 100mL round bottom flask under nitrogen was charged with *N*-{(*E*)-(3-bromophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methylene}-2-methylpropane-2-sulfinamide (2.67 g, 6.03 mmol) and THF (25.0 mL). The solution was cooled to -78 °C and a solution of 1.6 M of MeLi in Et_2O (5.65 mL, 9.04 mmol) was added dropwise over 20 min. The resulting solution was stirred for an additional 10 min with cooling. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (x3). The combined organic layers were then washed with water, brine, dried using Na_2SO_4, filtered and concentrated. The residue was purified by ISCO column chromatography (eluting with 0% - 50% EtOAc/hexanes) to give 1.30 g (47%) of the title compound (80% de). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.53 (m, 1H), 7.42 – 7.37 (m, 1H), 7.33 – 7.28 (m, 1H), 7.21 – 7.16 (m, 2H), 6.95 (d, *J* = 1.3 Hz, 1H), 6.00 (s, 1H), 4.16 – 4.06 (m, 2H), 4.04 – 3.96 (m, 2H), 3.74 (s, 1H), 2.06 (s, 3H), 1.23 (s, 9H).

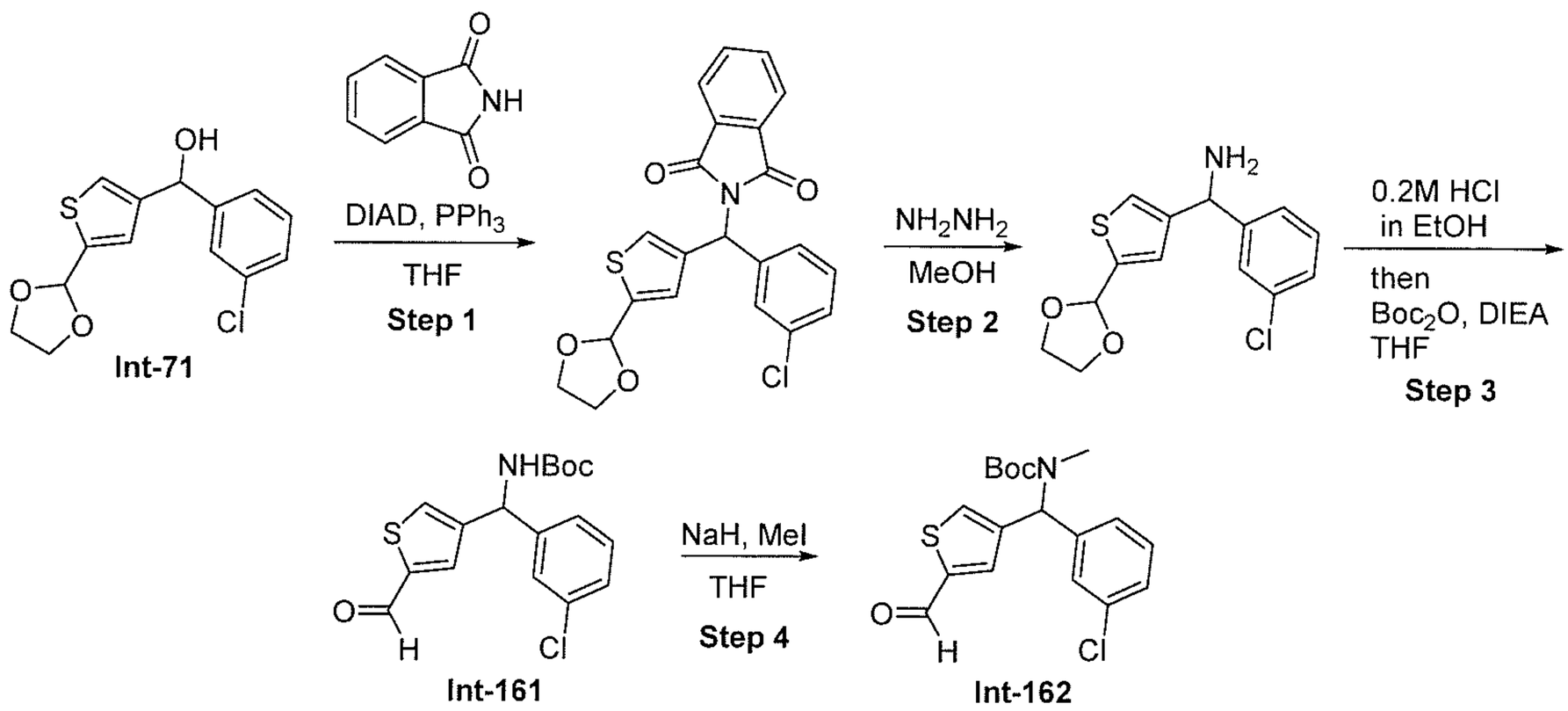
Step 5: *N*-[(1*R*)-1-(3-Bromophenyl)-1-(5-formyl-3-thienyl)ethyl]-2-methylpropane-2-sulfinamide.

[00571] Dowex 50WX2-200 (H) (1 g) was added to a solution of *N*-{(1*R*)-1-(3-bromophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]ethyl}-2-methylpropane-2-sulfinamide (993 mg, 2.17 mmol)(80% de) in acetone (20.0 mL) at rt. The reaction was allowed to stir for 1 hour. The reaction was then filtered to remove solid resin and the resin was washed with acetone, and the filtrate was concentrated to dryness. The crude material was then azetroped with toluene. The residue was purified by ISCO column chromatography (eluting with 0% - 80% EtOAc/hexanes) to give 0.865 g (96%) of the title compound (80% de). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (d, *J* = 1.1 Hz, 1H), 7.70 – 7.67 (m, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.46 – 7.42 (m, 1H), 7.30 – 7.19 (m, 2H), 3.78 (s, 1H), 2.08 (s, 3H), 1.25 (s, 9H).

[00572] The compound listed in the table below was prepared in an analogous fashion to that described above starting from the listed starting material:

Step 3 Reagent	Compound Name / No.	Characterization Data
	 **Int-160**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.85 (d, *J* = 1.2 Hz, 1H), 7.69 (t, *J* = 1.4 Hz, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.50 (t, *J* = 1.7 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.32 – 7.18 (m, 2H), 3.78 (s, 1H), 2.08 (s, 3H), 1.25 (s, 9H). LCMS (FA): *m/z* = 416.2 (M+H)

Example 94: **rac-*tert*-Butyl [(3-chlorophenyl)(5-formyl-3-thienyl)methyl]carbamate Int-161 and rac-*tert*-Butyl [(3-chlorophenyl){5-[(4-chloropyrimidin-5-yl)carbonyl]-3-thienyl}methyl]methylcarbamate. Int-162**



Step 1: rac-2-{(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methyl}-1*H*-isoindole-1,3(2*H*)-dione.

[00573] rac-(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methanol (827 mg, 2.79 mmol), phthalimide (656 mg, 4.46 mmol) and PPh_3 (1.32 g, 5.02 mmol) were dissoved into THF (40.0 mL), then diisopropyl azodicarboxylate (0.99 mL, 5.02 mmol) was added to this solution at rt. The reaction was heated at 70 °C for 5 h. The reaction mixture was concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 45% EtOAc in hexanes as eluent) to give 586 mg (49%) of the title compound as white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ

7.93 – 7.79 (m, 2H), 7.78 – 7.70 (m, 2H), 7.35 (m, 1H), 7.28 (d, *J* = 1.4 Hz, 1H), 7.26 (d, *J* = 1.1 Hz, 2H), 7.21 (m, 1H), 6.63 (s, 1H), 6.05 (s, 1H), 4.14 – 4.11 (m, 2H), 4.04 – 3.96 (m, 2H).

Step 2: rac-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]methanamine.

[00574] rac-2-{(3-Chlorophenyl)[5-(1,3-dioxolan-2-yl)-3-thienyl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (432 mg, 1.01 mmol) was dissolved into MeOH (15.0 mL), then hydrazine hydrate (508 mg, 10.1 mmol) was added to this solution. The reaction was stirred at rt overnight. The mixture was poured into 30 ml water, and extracted with DCM (20 ml x3). The combined the organic layers were concentrated and the residue was purified by ISCO column (0% - 15% MeOH in EtOAc as eluent) to give 95.3 mg (32%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 (s, 1H), 7.29 – 7.20 (m, 3H), 7.20 – 7.13 (d, 1H), 7.03 (d, 1H), 6.02 (s, 1H), 5.15 (s, 1H), 4.20 – 4.09 (m, 2H), 4.04 – 3.96 (m, 2H), 1.93 – 1.67 (broad, 2H)

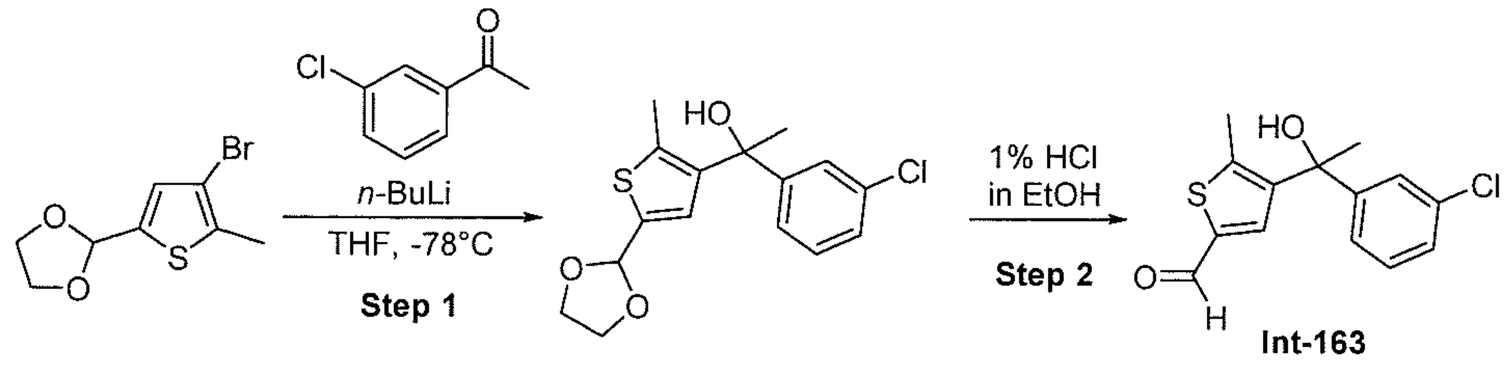
Step 3: rac-*tert*-Butyl [(3-chlorophenyl)(5-formyl-3-thienyl)methyl]carbamate.

[00575] rac-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-3-thienyl]methanamine (297 mg, 1.00 mmol) was dossolved into the solution of 0.2 M of HCl in EtOH (15.0 mL, 3.00 mmol) and water (0.20 mL, 11 mmol). The reaction was stirred at rt overnight and then was concentrated in vacuo. The residues were dissolved in THF (15.0 mL). To the solution was added N,N-diisopropylethylamine (0.70mL, 4.02 mmol) followed by di-tert-butyldicarbonate (658 mg, 3.02 mmol) and the mixture was heated at 45 °C for 2 h. The reaction mixture was concentrated in vacuo and the residue was purified by ISCO column chromatography (0% - 45% EtOAc in hexanes as eluent) to give 273 mg (77%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.84 (d, *J* = 1.3 Hz, 1H), 7.57 (d, *J* = 1.4 Hz, 1H), 7.46 (q, *J* = 1.3 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.29 – 7.26 (m, 1H), 7.18 – 7.14 (m, 1H), 5.96 (s, 1H), 5.24 (d, *J* = 8.0 Hz, 1H), 1.44 (s, 9H).

Step 4: rac-*tert*-Butyl [(3-chlorophenyl)(5-formyl-3-thienyl)methyl]methylcarbamate

[00576] To a solution of rac-*tert*-butyl [(3-chlorophenyl)(5-formyl-3-thienyl)methyl]carbamate (102 mg, 0.29 mmol) in THF (10.0 mL) was added 60% NaH in mineral oil (25.0 mg, 1.04 mmol) at rt and the mixture was stirred for 30 min. To the mixture was added methyl iodide (0.13 mL, 2.08 mmol) and the reaction was heated at 60 °C for 30 min. The reaction mixture was poured into 30 ml water, and extracted with DCM (30 ml x2). The combined organic layers were concentrated in vacuo and the residue was purified by ISCO column (0% - 50% EtOAc in hexanes as eluent) to give 50 mg of the title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.92 (s, 1H), 7.61 (s, 1H), 7.54 – 7.45 (m, 1H), 7.35 – 7.32 (m, 2H), 7.25 – 7.22 (m, 1H), 7.16 – 7.11 (m, 1H), 6.61 (s, 1H), 2.73 (s, 3H).

Example 95: **rac-4-[1-(3-Chlorophenyl)-1-hydroxyethyl]-5-methylthiophene-2-carbaldehyde. Int-163**



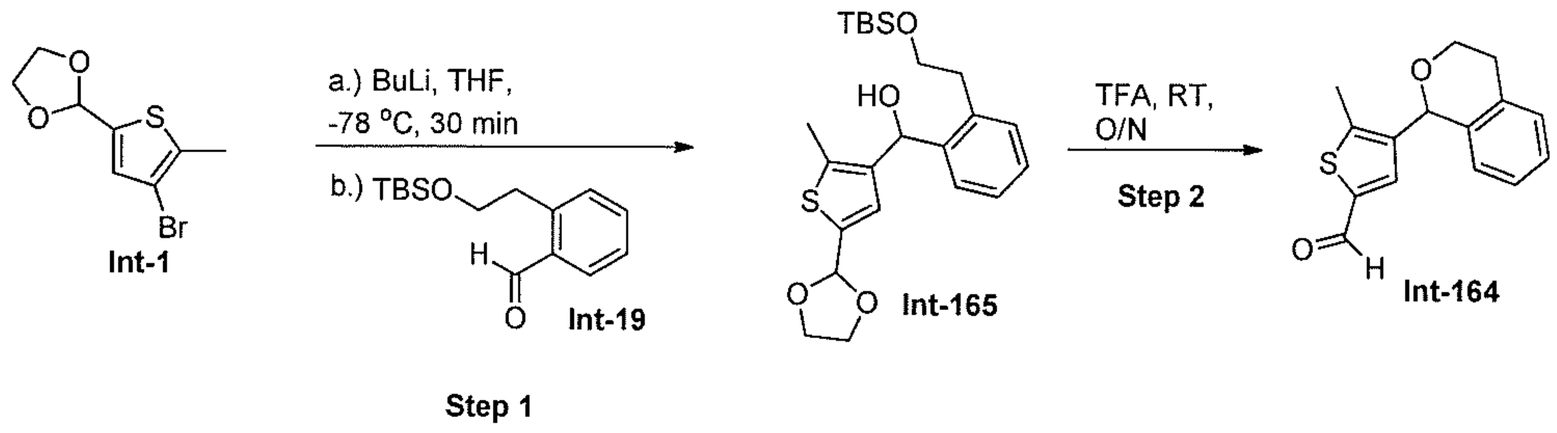
Step 1: rac-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]ethanol.

[00577] A 100mL 2-neck round bottom flask was charged with THF (30 mL) then the flask was purged with argon, and was cooled at -78 °C. To the THF, 2.50 M of *n*-BuLi in hexane (2.61 mL, 6.52 mmol) was added dropwise via syringe and the mixture was stirred for 10 min at -78 °C. 2-(4-Bromo-5-methyl-2-thienyl)-1,3-dioxolane (1.3 g, 5.2 mmol) was added dropwise at -78 °C. The solution was stirred for 30 min at -78 °C. 3'-chloroacetophenone (807 mg, 5.22 mmol)) was added to the solution at once at -78 °C and stirred for 15 min. The reaction was quenched by addition of saturated NH_4Cl (50 mL) and extracted with EtOAc (50 mLx3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 1.3g (77%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 (s, 1H), 7.22 – 7.19 (m, 3H), 7.15 (s, 1H), 5.99 (s, 1H), 4.18 – 4.09 (m, 2H), 4.03 – 3.95 (m, 2H), 2.13 (s, 3H), 1.86 (s, 3H).

Step 2: rac-4-[1-(3-Chlorophenyl)-1-hydroxyethyl]-5-methylthiophene-2-carbaldehyde.

[00578] rac-1-(3-Chlorophenyl)-1-[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]ethanol (1.1 g, 3.4 mmol) was dissolved in 1% HCl in EtOH (20 mL) and the reaction was stirred at rt for 2 h. The reaction mixture was diluted with water, extracted with DCM (20 mLx2). The combined organic layers were dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was purified by ISCO column chromatography (0% - 50% EtOAc in hexanes as eluent) to give 580 mg (61%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.77 (s, 1H), 7.75 (s, 1H), 7.41 – 7.36 (m, 1H), 7.24 – 7.24 (m, 1H), 7.23 (t, J = 1.1 Hz, 1H), 7.20 – 7.14 (m, 1H), 2.22 (s, 3H), 1.92 (s, 3H).

Example 96: 4-(3,4-Dihydro-1H-isochromen-1-yl)-5-methylthiophene-2-carbaldehyde Int-164



Step 1

Reaction conditions A (as depicted in Example 96): [2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)phenyl][5-(1,3-dioxolan-2-yl)- 2-methyl-3-thienyl]methanol Int-165

[00579] A solution of bromide **Int-1** (1.70 g, 6.82 mmol) in THF (26.6 mL, 328 mmol) was cooled to -78 °C, and then 2.50 M of *n*-BuLi in hexane (2.940 mL, 7.349 mmol) was added and the mixture was stirred for 10 min at -78 °C. A solution of aldehyde **Int-19** (1.39 g, 5.25 mmol) in THF (13.3 mL, 164 mmol) was then added, and the reaction was stirred for 10 min at -78 °C. The reaction was quenched by adding brine and then warmed to rt. The aqueous mixture was extracted 2 x EtOAc. The combined organic solvents were washed with brine, dried and concentrated in vacuo. The residue was purified by ISCO (80 g column, 0 to 20% EtOAc in hexanes as eluent) to afford the title compound as a pale yellow oil (yield = 1.96 g) that solidified upon standing in the refrigerator over the weekend. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.26 (m, 2H), 7.26 – 7.21 (m, 2H), 7.07 (s, 1H), 6.09 (d, J = 2.7 Hz, 1H), 6.03 (s, 1H), 4.19 – 4.13 (m, 2H), 4.06 – 4.00 (m, 2H), 3.96 – 3.89 (m, 1H), 3.87 – 3.77 (m, 1H), 3.52 (d, J = 2.9 Hz, 1H), 3.06 (ddd, J = 14.3, 8.4, 6.2 Hz, 1H), 2.87 (dt, J = 13.9, 5.2 Hz, 1H), 2.37 (s, 3H), 0.86 (s, 9H), -0.00 (s, 3H), -0.01 (s, 3H).

Step 2: 4-(3,4-Dihydro-1H-isochromen-1-yl)-5-methylthiophene-2-carbaldehyde

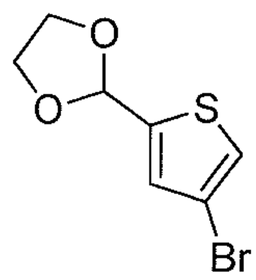
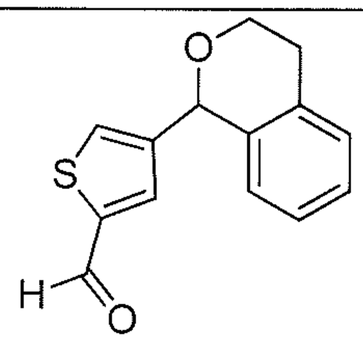
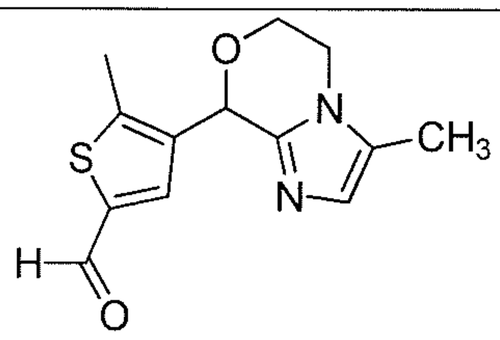
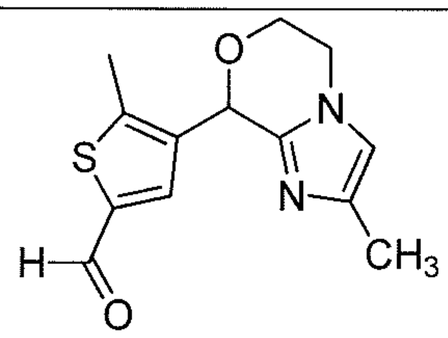
[00580] A 100mL round bottom flask was charged with [2-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)phenyl][5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]methanol (1.96 g, 4.51 mmol) and TFA (6.60 mL, 85.7 mmol) at rt. The resulting purple solution was stirred at rt overnight. The reaction mixture was carefully poured into saturated aqueous $NaHCO_3$ (~50 mL). The layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, then dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by ISCO (40 g column, 0 to 10% EtOAc in hexane as eluene) to afford the title compound as a pale brown oil (yield = 1.03 g). ^{1}H NMR (400 MHz, Chloroform-d) δ 9.73 (s, 1H), 7.41 (s, 1H), 7.27 – 7.19 (m, 2H), 7.18 – 7.12 (m, 1H), 6.75 (d, J = 7.7 Hz, 1H), 5.86 (s, 1H), 4.21 (ddd, J = 11.3, 5.5, 3.7 Hz, 1H), 3.97 (ddd, J = 11.4, 9.7, 4.0 Hz, 1H), 3.16 (ddd, J = 15.9, 9.4, 5.4 Hz, 1H), 2.85 (dt, J = 16.6, 3.6 Hz, 1H), 2.59 (s, 3H).

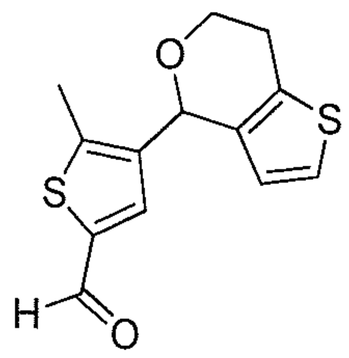
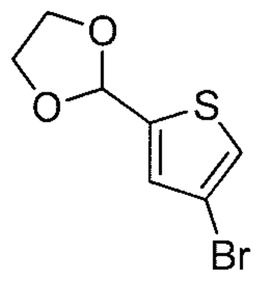
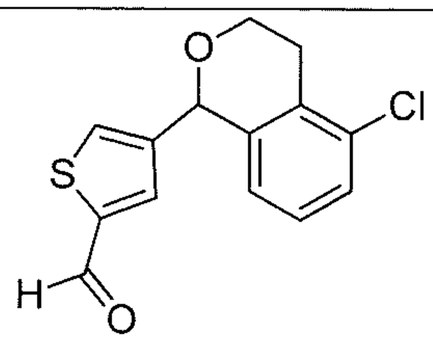
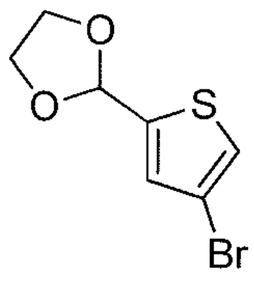
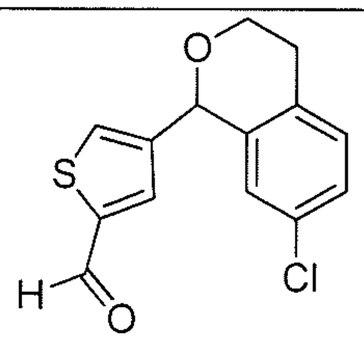
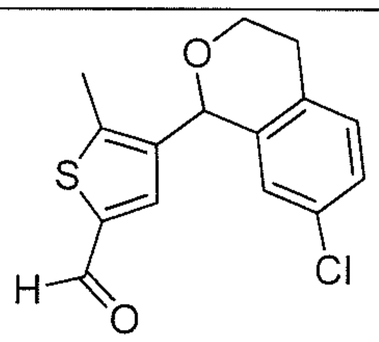
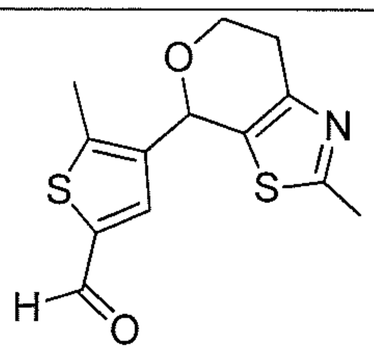
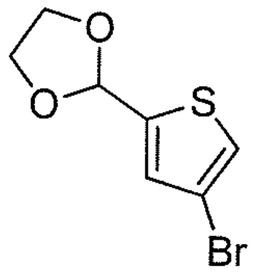
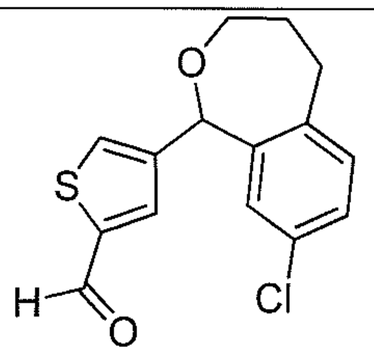
Alternative conditions for Step 1. Reaction conditions B (e.g., Entry 1, below): [2-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)phenyl][5-(1,3-dioxolan-2-yl)- 3-thienyl]methanol

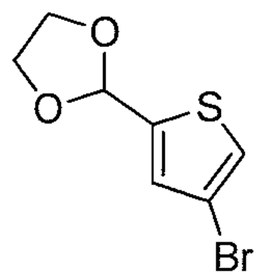
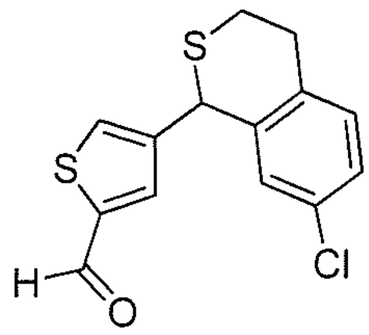
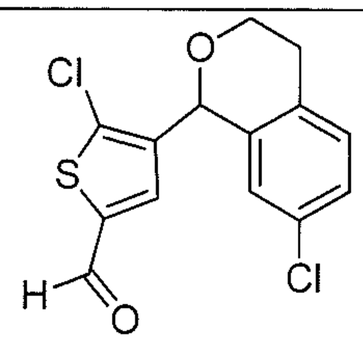
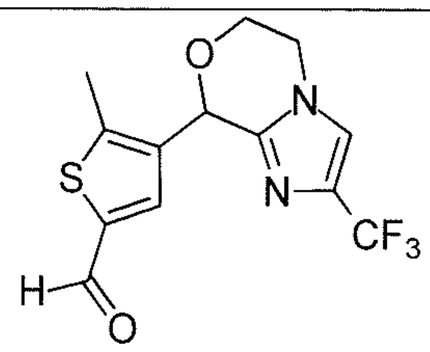
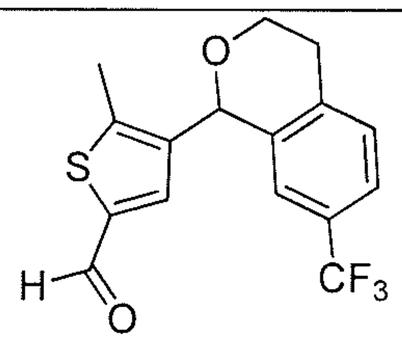
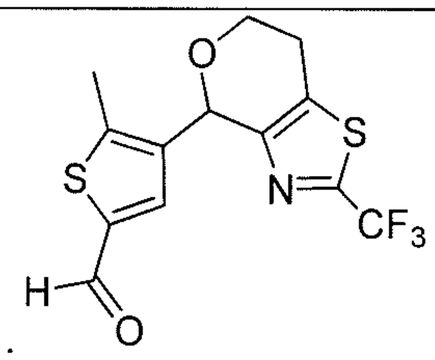
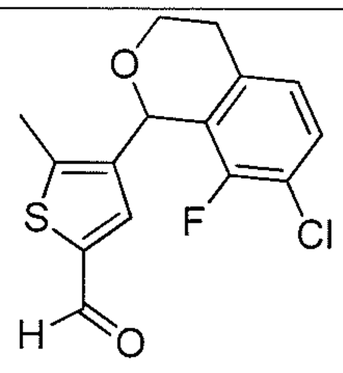
[00581] An oven-dried 250mL 2-neck flask under nitrogen was charged with THF (100 mL) and cooled in an ice bath to -76 °C. To this was added 2.50 M *n*-BuLi in hexane (8.365 mL, 20.91 mmol) followed by a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (4.565 g, 19.42 mmol) in THF in small portions keeping the internal temperature less than -70 °C. Next, a solution of

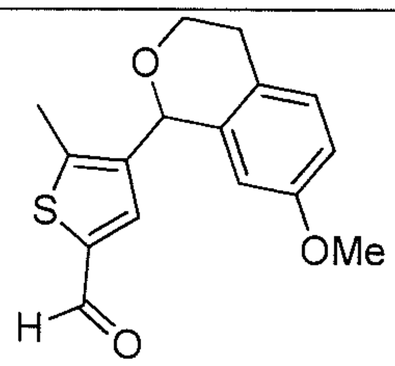
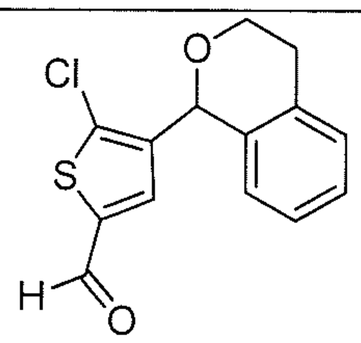
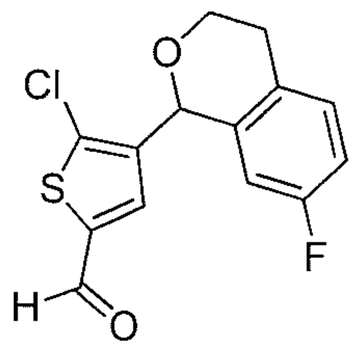
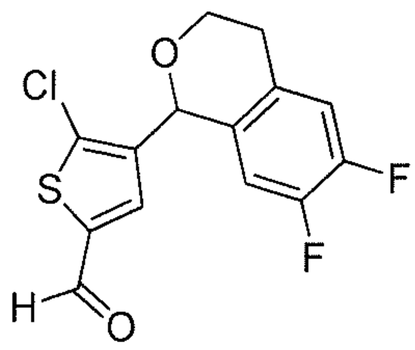
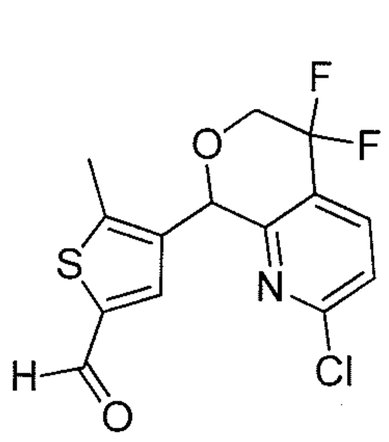
aldehyde **Int-19** (3.95 g, 14.9 mmol) in THF (5 mL, 60 mmol) was added in a single portion quickly, during which the temperature increased to -45 °C. Reaction was immediately quenched by slowly adding saturated ammonium chloride solution, and then was warmed to rt. The layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic portions were washed with brine; dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Crude residue was purified by column chromatography with a hexane / EtOAc gradient as eluent to provide the title compound as a yellow oil (yield = 4.20g). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 – 7.21 (m, 5H), 7.09 – 7.03 (m, 1H), 6.11 – 6.06 (m, 1H), 6.06 – 6.02 (m, 1H), 4.24 – 4.14 (m, 3H), 4.08 – 4.02 (m, 2H), 3.96 – 3.93 (m, 1H), 3.05 – 2.89 (m, 2H), 0.93 – 0.77 (m, 9H), 0.00 (s, 6H).

[00582] The compounds listed in the table below were prepared in an analogous fashion to that described in **Example 96** starting from the appropriate starting materials:

Entry	Bromide, aldehyde (starting materials)	Reaction conditions for Step 1	Product (Int #)	Characterization data
1	 **Int-19**	B	 **Int-166**	LCMS (FA): *m/z* = 245.1 (M+H)
2	**Int-1**, **Int-29**	A	 **Int-167**	LCMS (FA): *m/z* = 263.1 (M+H)
3	**Int-1**, **Int-28**	A	 **Int-168**	LCMS (FA): *m/z* = 263.1 (M+H)

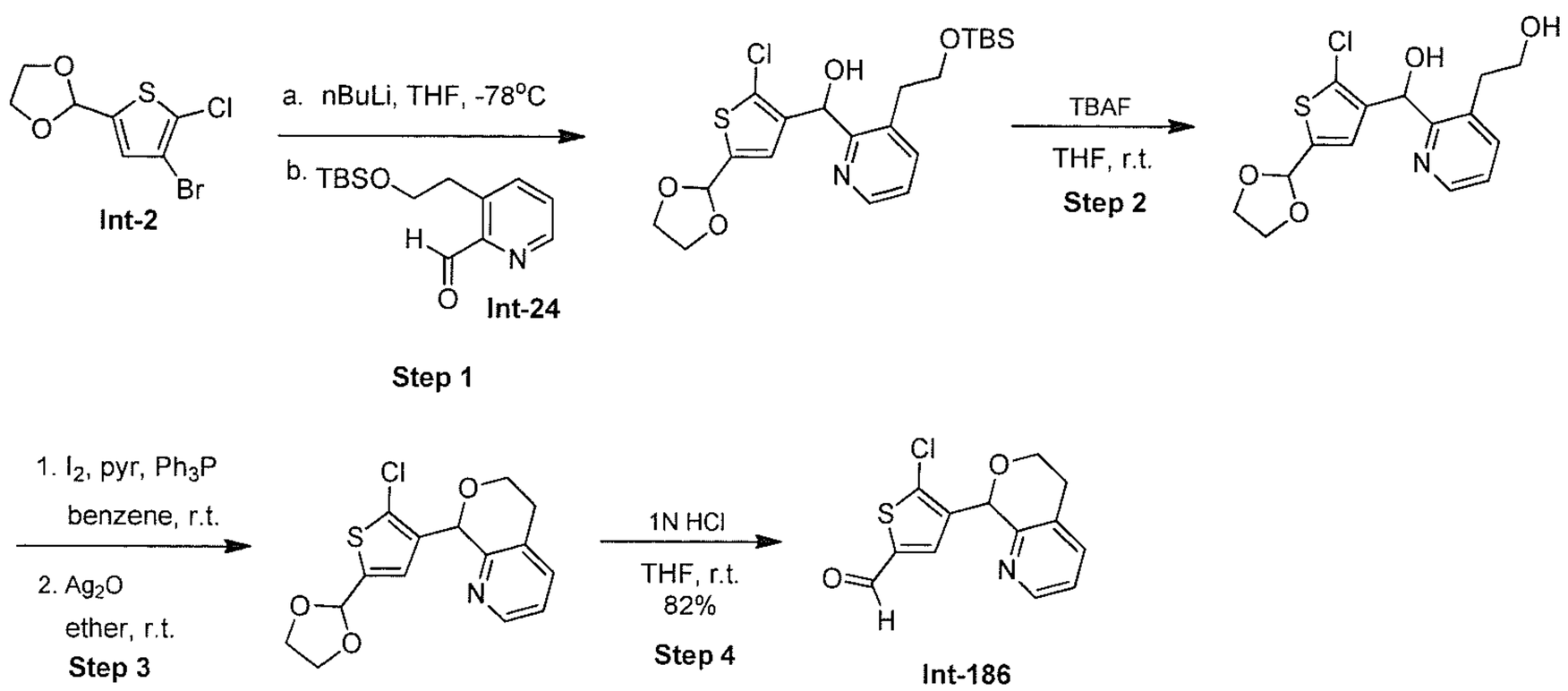
4	**Int-1**, **Int-27**	**A**	 **Int-169**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.66 (s, 1H), 7.49 (s, 1H), 7.13 (d, J = 5.2 Hz, 1H), 6.49 (d, J = 5.2 Hz, 1H), 5.97 – 5.78 (m, 1H), 4.27 – 4.20 (m, 1H), 3.99 (ddd, J = 11.4, 8.6, 4.2 Hz, 1H), 3.16 – 3.06 (m, 1H), 2.97 – 2.88 (m, 1H), 2.58 (s, 3H).
5	 **Int-17**	**B**	 **Int-170**	LCMS (FA): *m/z* = 279.1, 281.1 (M+H)
6	 **Int-15**	**B**	 **Int-171**	LCMS (FA): *m/z* = 279.3, 281.3 (M+H)
7	**Int-1**, **Int-15**	**A**	 **Int-172**	LCMS (FA): *m/z* = 293.4, 295.5 (M+H)
8	**Int-1**, **Int-20**	**A**	 **Int-173**	LCMS (FA): *m/z* = 280.2 (M+H)
9	 **Int-25**	**B**	 **Int-174**	LCMS (FA): *m/z* = 292.8, 295.0 (M+H)

10	 **Int-32**	**B**	 **Int-175**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.88 (s, 1H), 7.71 (s, 1H), 7.26 (s, 1H), 7.22 (dd, J = 8.2, 2.1 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 5.11 (s, 1H), 3.09 – 3.01 (m, 2H), 2.93 – 2.75 (m, 2H).
11	**Int-2**, **Int-15**	**A**	 **Int-176**	LCMS (FA): *m/z* = 313.0, 315.0, 317.1 (M+H)
12	**Int-1**, **Int-30**	**A**	 **Int-177**	LCMS (FA): *m/z* = 317.0 (M+H)
13	**Int-1**, **Int-16**	**A**	 **Int-178**	LCMS (FA): *m/z* = 327.0 (M+H)
14	**Int-1**, **Int-33**	**A**	 **Int-179**	LCMS (FA): *m/z* = 334.0 (M+H)
15	**Int-9**, **Int-36**	**A**	 **Int-180**	^{1}H NMR (400 MHz, DMSO-d6) δ 9.71 (s, 1H), 7.53 – 7.42 (m, 2H), 7.18 (d, J = 8.3 Hz, 1H), 6.09 (s, 1H), 3.91 – 3.72 (m, 2H), 2.98 – 2.81 (m, 2H), 2.58 (s, 3H).

16	**Int-38, Int-36**	**A**	 **Int-181**	LCMS (FA): *m/z* = 289.0 (M+H)
17	**Int-2, Int-19**	**A**	 **Int-182**	LCMS (FA): *m/z* = 279.0 (M+H)
18	**Int-2, Int-21**	**A**	 **Int-183**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.70 (s, 1H), 7.35 (s, 1H), 7.20-7.10 (m, 1H), 7.00– 6.90 (m, 1H), 6.55 – 6.45 (m, 1H), 5.85 – 5.80 (m, 1H), 4.30 – 4.20 (m, 1H), 4.00 – 3.85 (m, 1H), 3.20 – 3.05 (m, 1H), 2.80 – 2.70 (m, 1H)
19	**Int-2, Int-22**	**A**	 **Int-184**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.70 (s, 1H), 7.40 (s, 1H), 7.05-7.00 (m, 1H), 6.70 – 6.65 (m, 1H), 5.75 (s, 1H), 4.25 – 4.20 (m, 1H), 3.95 – 3.80 (m, 1H), 3.20 – 3.00 (m, 1H), 2.75 – 2.70 (m, 1H)
20	**Int-49, Int-36**	Performed in analogous fashion to **Example 11,** step 2, Reaction Conditions B	 **Int-185**	LCMS (FA): *m/z* = 330.0, 332.0 (M+H)

Example 97: 5-Chloro-4-(5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl)thiophene-2-carbaldehyde

Int-186



Step 1: [3-(2-{[tert-Butyl(dimethyl)silyl]oxy}ethyl)pyridin-2-yl][2-chloro-5-(1, 3-dioxolan-2-yl)-3-thienyl]methanol

[00583] To a -78°C cooled solution of 2.50 M of *n*-BuLi in hexane(2.727 mL, 6.818 mmol) in THF (25.0 mL, 308 mmol) was added a solution of bromide **Int-2** (1.648 g, 6.112 mmol) in THF (10.0 mL, 123 mmol), dropwise, via syringe. After 20 min, a solution of aldehyde **Int-24** (1.248 g, 4.702 mmol) in THF (10.0 mL, 123 mmol) was added dropwise via syringe. The reaction mixture was stirred at -78°C for 20 min then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted 3 x EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and then concentrated to give 2.689 g of crude product. The crude material was purified by silica gel chromatography to give 1.775 g (83% yield) of the title compound as a light brown oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.61 (d, J = 4.8, 1.4 Hz, 1H), 7.72 (d, J = 7.0 Hz, 1H), 7.37 – 7.34 (m, 1H), 6.70 (s, 1H), 6.11 (s, 1H), 5.96 (s, 1H), 4.20 – 4.09 (m, 2H), 4.09 – 3.99 (m, 2H), 3.84 – 3.77 (m, 1H), 3.62 – 3.54 (m, 1H), 2.93 – 2.83 (m, 1H), 2.72 (dt, J = 14.3, 5.7 Hz, 1H), 0.93 (s, 9H), 0.01 (d, J = 5.0 Hz, 6H); LCMS (FA) M+1 456.1

Step 2: 2-(2-{[2-Chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](hydroxy)methyl}pyridin- 3-yl)ethanol

[00584] To a solution of [3-(2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)pyridin-2-yl][2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl]methanol (1.035 g, 2.269 mmol) in THF (29.2 mL, 3.60E2 mmol) was added TBAF hydrate (0.9514 g, 3.404 mmol) The reaction mixture was stirred at rt overnight and then concentrated in vacuo. The crude residue was purified by silica gel chromatography to give 0.746 g (96% yield) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.56 – 8.50 (m, 1H), 7.64 (d, J = 6.3 Hz, 1H), 7.36 – 7.30 (m, 1H), 6.15 (s, 1H), 5.97 (s, 1H), 5.32 (s, 1H), 4.11 – 4.00 (m, 2H), 4.00 – 3.92 (m, 1H), 3.83 – 3.75 (m, 1H), 3.66 – 3.57 (m, 1H), 3.54 – 3.43 (m, 1H),

2.82 – 2.72 (m, 1H), 2.71 – 2.61 (m, 1H).

Step 3a: [2-Chloro-5-(1,3-dioxolan-2-yl)-3-thienyl][3-(2-iodoethyl)pyridin-2-yl]methanol

[00585] To a solution of 2-(2-{[2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl](hydroxy)methyl}pyridin-3-yl)ethanol (2.004 g, 5.863 mmol) in benzene (59.3 mL, 663 mmol) was added pyridine (1.43 mL, 17.7 mmol), triphenylphosphine (2.33 g, 8.88 mmol), and iodine (1.637 g, 6.449 mmol). The reaction mixture was stirred at 38 °C for 2 h, then filtered and the filter cake was washed with ether (50 mL). The filtrate was diluted with water (30 mL), the layers were separated, and the aqueous layer was extracted with ether (1x 30 mL). Combined organic layers were washed with water (20 mL) and brine (2x 20 mL), dried over magnesium sulfate, filtered, and then concentrated in vacuo. The crude residue was purified by silica gel chromatography to give 1.690 g (64% yield) of the title compound as a clear oil. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.59 – 8.55 (m, 1H), 7.57 (d, J = 7.7, 1.5 Hz, 1H), 7.35 – 7.29 (m, 1H), 6.59 (s, 1H), 5.97 (s, 1H), 5.87 (s, 1H), 4.10 – 4.00 (m, 2H), 4.00 – 3.90 (m, 2H), 3.17 – 3.05 (m, 2H), 3.05 – 2.91 (m, 2H); LCMS (FA) M+1 452.0.

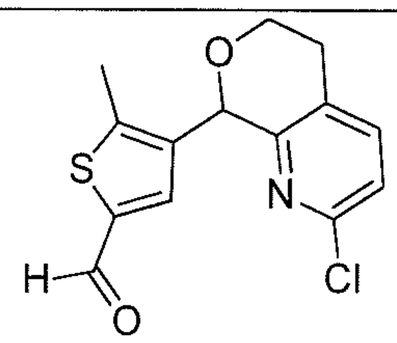
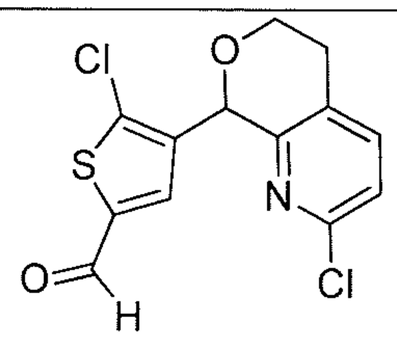
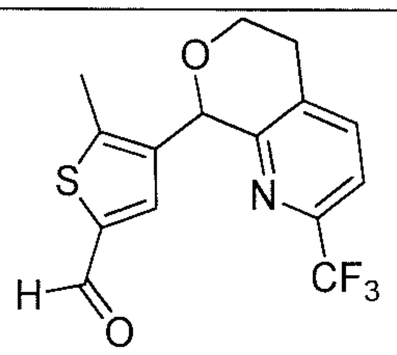
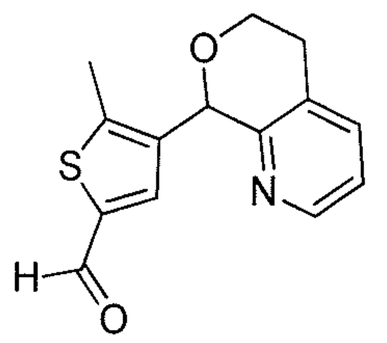
Step 3b: 8-[2-Chloro-5-(1,3-dioxolan-2-yl)-3-thienyl]-5,8-dihydro-6H-pyrano[3,4- b]pyridine

[00586] A solution of [2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl][3-(2-iodoethyl)pyridin-2-yl]methanol (1.690 g, 3.741 mmol) and silver(I) oxide (6.07 g, 26.2 mmol) in ether (50.0 mL, 476 mmol) was stirred at rt overnight, then at 40°C for an additional 45 min. The reaction mixture was filtered over a pad of Celite and the filter cake was washed with methanol. The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography to provide 0.331 g (66% yield) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.43 (d, J = 4.7, 1.6 Hz, 1H), 7.51 (d, J = 7.7 Hz, 1H), 7.19 – 7.14 (m, 1H), 6.57 (s, 1H), 5.94 (s, 1H), 5.94 (s, 1H), 4.19 – 4.13 (m, 1H), 4.11 – 4.02 (m, 3H), 4.01 – 3.91 (m, 4H); LCMS (FA) M+1 324.1

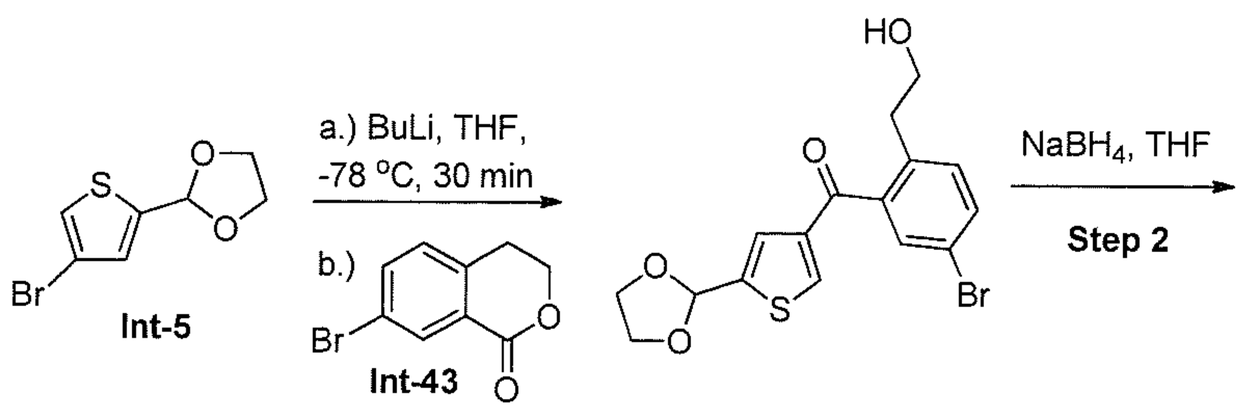
Step 4: 5-Chloro-4-(5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl)thiophene-2-carbaldehyde

[00587] To a solution of 8-[2-chloro-5-(1,3-dioxolan-2-yl)-3-thienyl]-5,8-dihydro-6H-pyrano[3,4-b]pyridine (799 mg, 2.47 mmol) in THF (24.2 mL, 298 mmol) was added a 1.0 M solution of HCl in water(12.0 mL, 12.0 mmol). The reaction mixture was stirred at rt overnight. Reaction was quenched with saturated aqueous $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and then concentrated in vacuo. The crude residue was purified by silica gel chromatography to give 0.567 g (82% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.69 (s, 1H), 8.45 (d, J = 3.6 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.25 – 7.17 (m, 1H), 5.98 (s, 1H), 4.25 – 4.16 (m, 1H), 4.07 – 3.97 (m, 1H), 3.22 – 3.11 (m, 1H), 2.96 – 2.84 (m, 1H); LCMS (FA) M+1 280.0

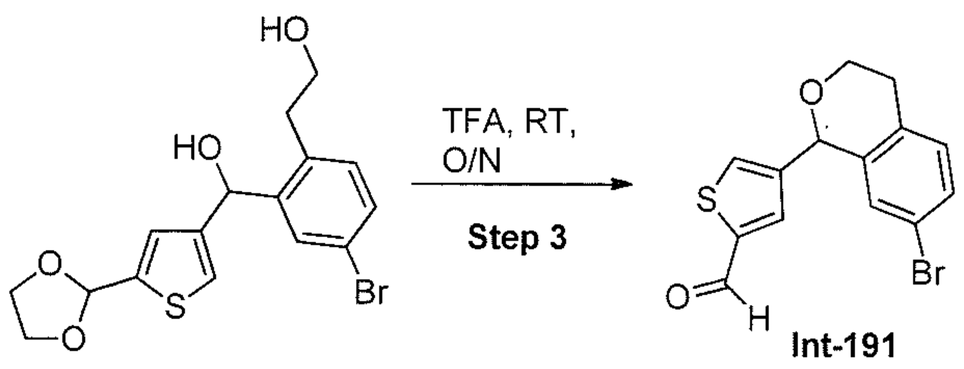
[00588] The compounds listed in the table below were prepared in an analogous fashion to that described in **Example 97** starting from the appropriate starting materials:

Entry	Bromide, aldehyde (starting materials)	Product (Int #)	LC/MS data
1	**Int-1**, **Int-23**	 **Int-187**	LCMS (FA): 294.1 (M + 1)
2	**Int-2**, **Int-23**	 **Int-188**	LCMS (FA) M+1 314.0
3	**Int-1**, **Int-26**	 **Int-189**	LCMS (FA): 328.0 (M + 1)
4	**Int-1**, **Int-24**	 **Int-190**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.66 (s, 1H), 8.43 – 8.37 (m, 1H), 7.55 – 7.48 (m, 1H), 7.24 (s, 1H), 7.16 (ddd, J = 7.7, 4.7, 0.6 Hz, 1H), 5.86 (s, 1H), 4.12 (dt, J = 11.6, 5.0 Hz, 1H), 3.92 (ddd, J = 11.6, 8.4, 4.2 Hz, 1H), 3.16 – 3.04 (m, 1H), 2.88 (dt, J = 16.5, 4.3 Hz, 1H), 2.61 – 2.55 (m, 3H).

Example 98: 4-(3,4-Dihydro-1H-isochromen-1-yl)-5-methylthiophene-2-carbaldehyde Int-191



Step 1



Step 1: [5-Bromo-2-(2-hydroxyethyl)phenyl][5-(1,3-dioxolan-2-yl)-3-thienyl]methanone

[00589] To a two-neck 100 mL round-bottom flask was cooled at -78 °C was added 2.50 M of *n*-BuLi in hexane(1.00 mL, 2.50 mmol). The solution was stirred for 10 min under an atmosphere of argon at -78 °C. A solution of **Int-5** (0.473 g, 2.01 mmol) in THF (4.00 mL, 49.3 mmol) was added dropwise quickly and a light yellow precipitate formed. The mixture was stirred at -78 °C for 10 min. A solution of **Int-43** (461 mg, 2.03 mmol) in THF (4.00 mL, 49.3 mmol) was added quickly and the reaction turned to a dark yellow/orange solution. The solution was allowed to stir for 10 min. The reaction was removed from the dry ice bath and quenched with saturated NH_4Cl. After warming to rt, the reaction was diluted with EtOAc and saturated NH_4Cl. The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (80g gold ISCO, 30% EtOAc in hexanes 5min to 70% EtOAc in hexanes over 30min). The appropriate fractions were concentrated to afford the title compound as a clear colorless oil (489 mg, 63%). LCMS: (FA) 385.0 (M + 1).

Step 2: 2-(4-Bromo-2-{[5-(1,3-dioxolan-2-yl)-3-thienyl](hydroxy)methyl}phenyl)ethanol

[00590] To a solution of [5-bromo-2-(2-hydroxyethyl)phenyl][5-(1,3-dioxolan-2-yl)-3-thienyl]methanone (0.489 g, 1.28 mmol) in methanol (7.85 mL, 194 mmol) was added sodium tetrahydroborate (57.9 mg, 1.53 mmol) at rt. When no further gas evolution was observed, the reaction was concentrated in vacuo to remove the methanol. The residue was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification was accomplished via column chromatography (80g Gold ISCO column, 50% EtOAc in hexanes to 100% EtOAc in hexanes over 30 min (50mL/min) to give the title compound as a clear colorless oil (438 mg, 89%). LCMS: (FA) 369.0 (M – OH)

Step 3: 4-(7-Bromo-3,4-dihydro-1H-isochromen-1-yl)thiophene-2-carbaldehyde

[00591] A 100 mL round bottom flask was charged with 2-(4-bromo-2-{[5-(1,3-dioxolan-2-yl)-3-thienyl](hydroxy)methyl}phenyl)ethanol (438 mg, 1.14 mmol) and TFA (3.00 mL, 38.9 mmol), and the mixture was stirred at rt for 1h. The reaction was carefully poured into saturated $NaHCO_3$, extracted 2x with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified via column chromatography (20% EtOAc in hexanes isocratic) to give the material as clear colorless oil (348 mg, 79%). LCMS: (FA) 325.0 (M + 1)

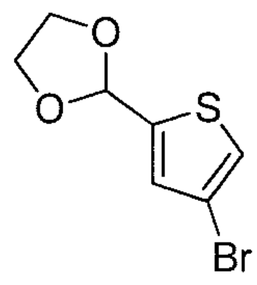
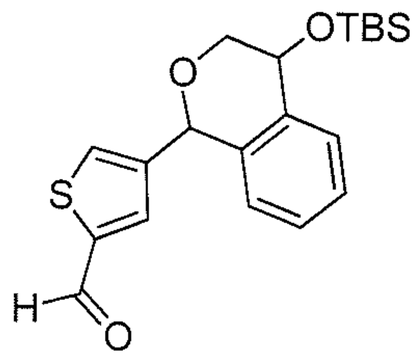
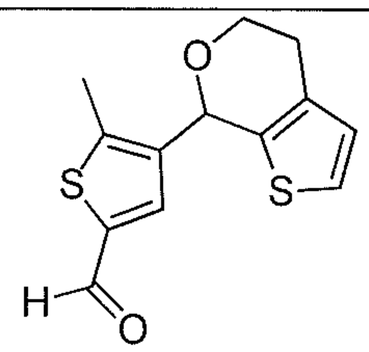
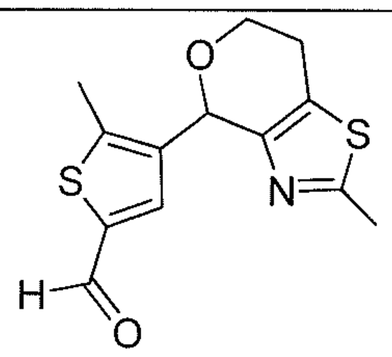
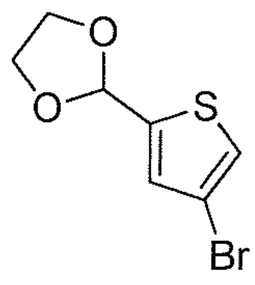
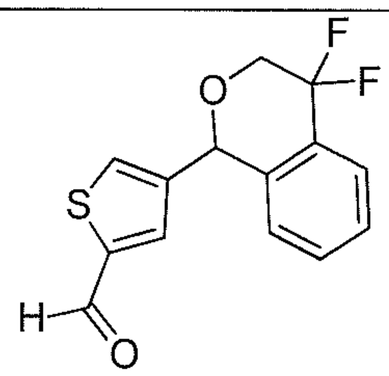
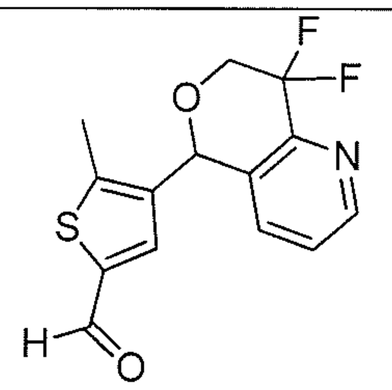
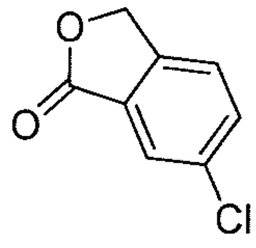
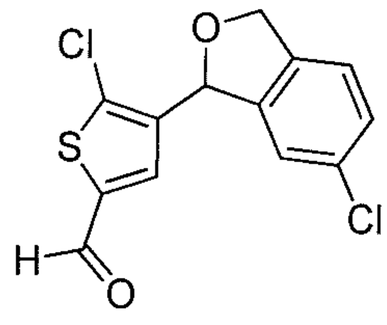
Alternative conditions for Step 3. Reaction conditions B (e.g., Entry 1, below): 4-(4-{[tert-Butyl(dimethyl)silyl]oxy}-3,4-dihydro-1H-isochromen-1-yl)thiophene- 2-carbaldehyde

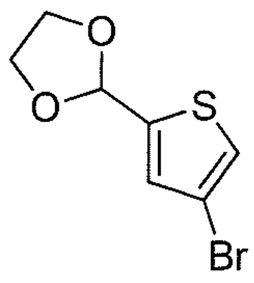
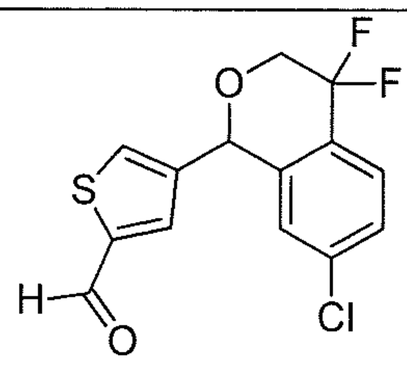
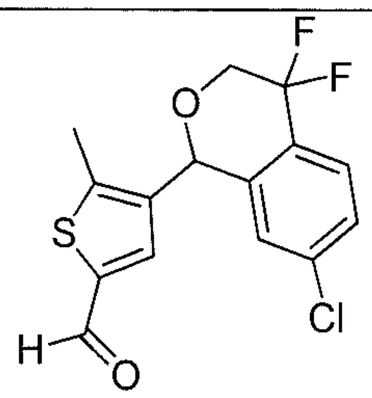
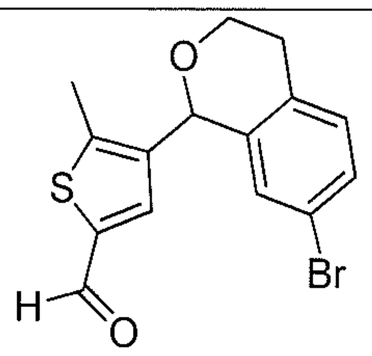
[00592] This step was accomplished by first generating the requisite isochroman ring system in an analogous fashion to that described in **Example 97**, Step 3. The resulting acetal was then converted to the title aldehyde as follows:

[00593] To a solution of tert-butyl({1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-3,4-dihydro-1H-isochromen-4-yl}oxy)dimethylsilane (1.021 g, 2.439 mmol) in acetone (15 mL, 2.0E2 mmol) was added Dowex 50WX2-200 (H) (1500 mg) at rt. The reaction was allowed to stir at rt and monitored by LCMS. TLC and LCMS show the reaction 50% conversion in 15 min. The reaction was done after 90 min at rt by LCMS monitor. The reaction solution was filtered to remove solid resin. The crude product was purified on silica gel (40g ISCO column; hexanes then 0-30% EtOAc/hexanes) to give the title compound 712.3 mg (78%). ^{1}H NMR (400 MHz, Chloroform-d) δ 9.72 (s, 1H), 7.60 (d, J = 1.4 Hz, 1H), 7.39 (q, J = 1.3 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.10 – 7.06 (m, 1H), 6.77 (d, J = 7.5 Hz, 1H), 5.69 (s, 1H), 4.69 (dd, J = 6.7, 4.6 Hz, 1H), 3.73 (dd, J = 11.4, 4.5 Hz, 1H), 3.57 (dd, 1H), 0.79 (s, 9H), 0.05 (s, 3H), -0.00 (s, 3H). LCMS (AA) M+1 375.

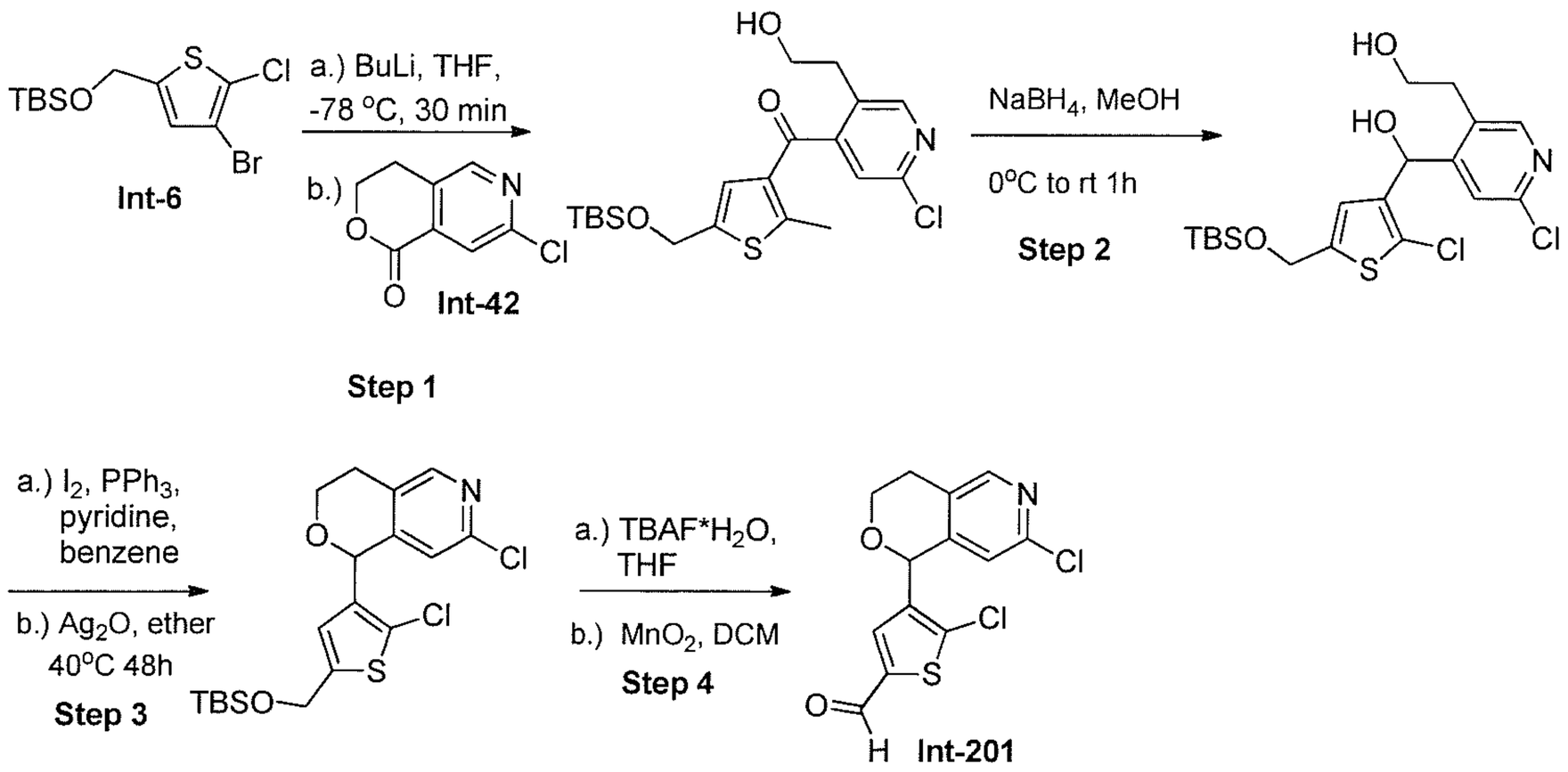
[00594] The compounds listed in the table below were prepared in an analogous fashion to that described in **Example 98** starting from the appropriate starting materials:

Entry	Bromide, lactone (starting materials)	Reaction conditions for Step 3	Product (Int #)	LC/MS data

1	 **Int-45**	**B**	 **Int-192**	FA: *m/z* = 375.2 (M+H)
2	**Int-1**, **Int-44**	**B**	 **Int-193**	FA: *m/z* = 265.1 (M+H)
3	**Int-1**, **Int-46**	**A**	 **Int-194**	FA: *m/z* = 280.1 (M+H)
4	 **Int-39**	**A**	 **Int-195**	FA: *m/z* = 281.0 (M+H)
5	**Int-1**, **Int-41**	**A**	 **Int-196**	FA: *m/z* = 296.2 (M+H)
6	**Int-2**, 	**A**	 **Int-197**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.72 (s, 1H), 7.43 (s, 1H), 7.35 (dd, J = 8.1, 1.5 Hz, 1H), 7.28 (d, J = 2.9 Hz, 1H), 7.13 (s, 1H), 6.37 (s, 1H), 5.32 (dd, J = 12.4, 2.5 Hz, 1H), 5.20 (dd, J = 12.4,

				1.4 Hz, 1H).
7	 Br , **Int-40**	**A**	 **Int-198**	LCMS: (FA) M+1 315.0
8	**Int-1**, **Int-40**	**A**	 **Int-199**	LCMS: (FA) M+1 329.2
9	**Int-1**, **Int-43**	**A**	 **Int-200**	LCMS: (FA) M+1 337.0

Example 99: 5-Chloro-4-(7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl)thiophene- 2-carbaldehyde Int-201



Steps 1 and 2: 2-(4-{[5-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl](hydroxy)methyl}-6-chloropyridin-3-yl)ethanol

[00595] Steps 1 and 2 were performed in an analogous fashion to that described in **Example 98**, Steps 1 and 2 starting from **Int-6** and **Int-42**. Step 3 was performed as follows.

Step 3a: [5-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl][2-chloro-5-(2-iodoethyl)pyridin-4-yl]methanol

[00596] To a solution of 2-(4-{[5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl](hydroxy)methyl}-6-chloropyridin-3-yl)ethanol (871.0 mg, 1.942 mmol) in benzene (22.8 mL) was added pyridine (475.6 uL, 5.881 mmol) and triphenylphosphine (771 mg, 2.94 mmol), followed by iodine (0.518 g, 2.04 mmol). The yellow mixture was stirred at rt under argon for 16 h. The reaction mixture was filtered through a pad of Celite, and the cake was washed with EtOAc. The filtrate was washed with water, and the aqueous layer was extracted with EtOAc twice. The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (0 to 30% EtOAc in hexane as eluent) to provide 1.003 g (92%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.64 (s, 1H), 6.61 – 6.58 (m, 1H), 6.39 (d, J = 4.5 Hz, 1H), 5.86 (d, J = 4.4 Hz, 1H), 4.72 (d, J = 0.9 Hz, 2H), 3.28 – 3.19 (m, 1H), 3.11 – 2.89 (m, 3H), 0.84 (s, 9H), 0.02 (s, 6H); LCMS (AA): (M+1) 558.0

Step 3b: 1-[5-({[tert-Butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl]-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridine

[00597] To a solution of [5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl][2-chloro-5-(2-iodoethyl)pyridin-4-yl]methanol (1.003 g, 1.796 mmol) in ether (27.8 mL) was added silver(I) oxide (2.08 g, 8.98 mmol), and the reaction was stirred at rt under argon for 15 h. The reaction mixture was then stirred at reflux at 40 °C for 36 h. The reaction was cooled to rt, filtered through a pad of Celite, and the cake was washed with EtOAc. The filtrate was concentrated and purified by silica gel column chromatography (0 to 30% EtOAc in hexane as eluent) to give 707 mg (91%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 6.75 (s, 1H), 6.64 – 6.59 (m, 1H), 5.85 – 5.80 (m, 1H), 4.78 – 4.69 (m, 2H), 4.16 – 4.08 (m, 1H), 3.92 – 3.83 (m, 1H), 3.02 – 2.91 (m, 1H), 2.86 – 2.77 (m, 1H), 0.85 (s, 9H), 0.03 (s, 6H); LCMS (AA): (M+1) 430.1

Step 4a: [5-Chloro-4-(7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl)-2-thienyl]methanol

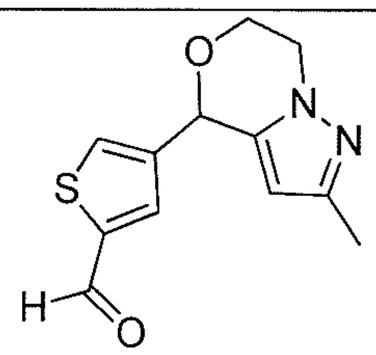
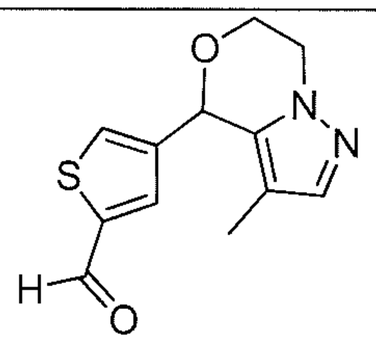
[00598] To a solution of 1-[5-({[tert-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-3-thienyl]-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridine (705 mg, 1.64 mmol) in THF (24.2 mL) under argon was added a solution of TBAF hydrate (686.6 mg, 2.457 mmol) in THF (7.3 mL), and the yellow solution was stirred at rt for 1 hour. The reaction was quenched by addition of water (20mL) and extracted with EtOAc (2x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (0 to 75% EtOAc in hexane as eluent) to afford 0.350 g (68%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 6.76 (s, 1H), 6.62 –

6.57 (m, 1H), 5.85 – 5.80 (m, 1H), 5.59 (t, J = 5.8 Hz, 1H), 4.51 (dd, J = 5.8, 0.8 Hz, 2H), 4.16 – 4.08 (m, 1H), 3.92 – 3.83 (m, 1H), 3.03 – 2.91 (m, 1H), 2.87 – 2.77 (m, 1H); LCMS (AA): (M+1) 316.0

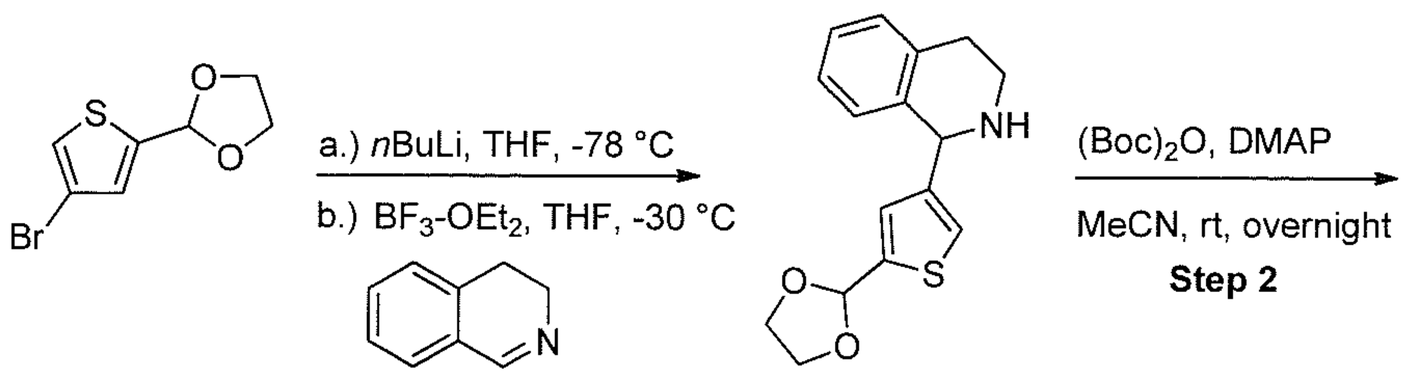
Step 4b: 5-Chloro-4-(7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl)thiophene- 2-carbaldehyde

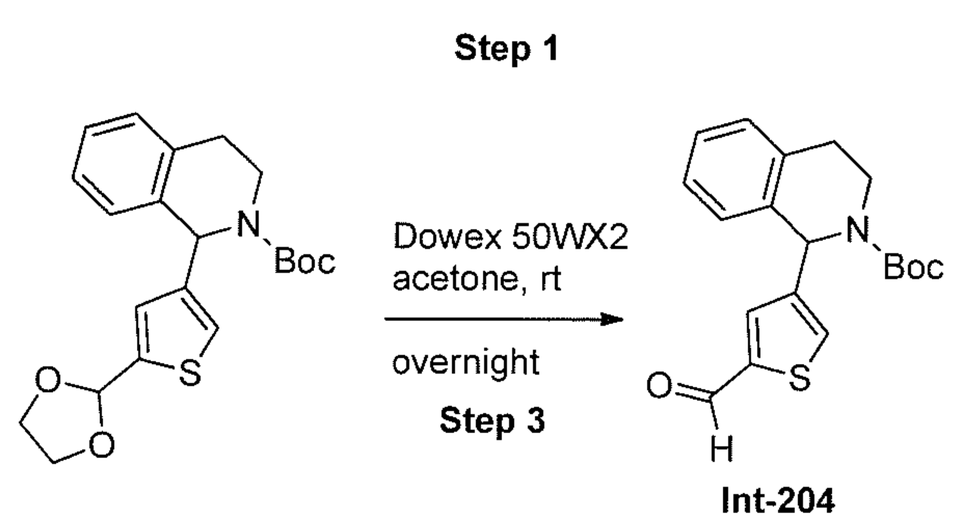
[00599] To a solution of [5-chloro-4-(7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl)-2-thienyl]methanol (348.0 mg, 1.100 mmol) in DCM (40. 6 mL) was added MnO_2 (0.9568 g, 11.00 mmol) at rt, and the reaction was stirred for 14 h under argon. The mixture was filtered through a pad of Celite, and the cake was washed with EtOAc. The filtrate was concentrated in vacuo and dried to afford 291 mg of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.76 (s, 1H), 8.36 (s, 1H), 7.75 (s, 1H), 6.94 (s, 1H), 5.96 (s, 1H), 4.15 – 4.07 (m, 1H), 3.95 – 3.86 (m, 1H), 3.05 – 2.94 (m, 1H), 2.90 – 2.81 (m, 1H); LCMS (AA): (M+1) 314.0.

[00600] The compounds listed in the table below were prepared in an analogous fashion to that described in **Example 99** starting from the appropriate starting materials:

Entry	Bromide, lactone (starting materials)	Product (Int #)	LC/MS data
1	**Int-4, Int-47**	 **Int-202**	LCMS: (FA) M+1 249.0
2	**Int-4, Int-48**	 **Int-203**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.81 (d, J = 1.0 Hz, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 7.17 (s, 1H), 5.80 (s, 1H), 4.20 – 4.09 (m, 2H), 4.07 – 3.89 (m, 2H), 1.63 (s, 3H).

Example 100: 4-(3,4-Dihydro-1H-isochromen-1-yl)-5-methylthiophene-2-carbaldehyde Int-204





Step 1:1-[5-(1,3-Dioxolan-2-yl)-3-thienyl]-1,2,3,4-tetrahydroisoquinoline

[00601] A solution of 3,4-dihydroisoquinoline (500 mg, 3.81 mmol) in THF (15.4 mL) was cooled at -30 °C. To this solution was added dropwise boron trifluoride etherate (0.53 mL, 4.19 mmol) at -30 °C, and the mixture was stirred for 20 min. Into a separate 50 mL 2-neck flask 2.50 M of n-BuLi in hexane (1.83 mL, 4.57 mmol) was added at -78 °C followed by a solution of 2-(4-bromothiophen-2-yl)-1,3-dioxolane (1.08 g, 4.57 mmol) in THF (10.0 mL). After 5 min, lithiated thiophene suspension was added to the above solution of dihydroisoquinoline BF3-OEt2 complex at -78 °C. The reaction was stirred for 20 min at -78 °C and then quenched by addition of water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 5% MeOH in DCM). All fractions with Rf ranging from 0.1 to 0.25 in TLC (5% MeOH in DCM, ninhydrin stain) were combined to give 513 mg of a mixture of the title compound and some impurities as a red amorphous solid. This mixture was used for the next step without further purification.

Step 2: tert-Butyl 1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-3,4- dihydroisoquinoline-2(1H)-carboxylate

[00602] The crude mixture from step 1was dissolved in MeCN (6.97 mL), to which was added $(Boc)_2O$ (1.25 g, 5.72 mmol) and N,N-dimethylaminopyridine (2.33 mg, 19.1 μmol) at rt. After stirring for 2 h, the reaction was quenched by adding water. The layers were separated and the aqueous layer was extracted with EtOAc 2x. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 20% EtOAc in hexane) to give 393 mg (27% for 2 steps) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 – 7.03 (m, 6H), 6.82 (s, 1H), 6.01 (s, 1H), 4.17 – 3.93 (m, 5H), 3.20 – 3.04 (m, 1H), 3.04 – 2.86 (m, 1H), 2.79 – 2.68 (m, 1H), 1.57 – 1.46

(m, 9H); LCMS (FA): m/z = 388.3 (M+H).

Step 3 (Reaction conditions A, as in Example 100): tert-Butyl 1-(5-formyl-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

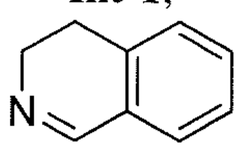
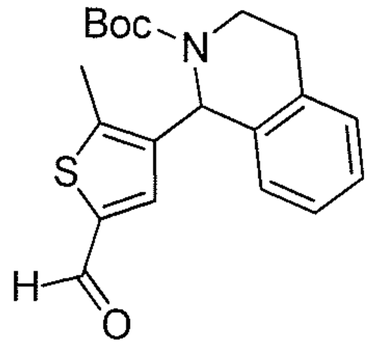
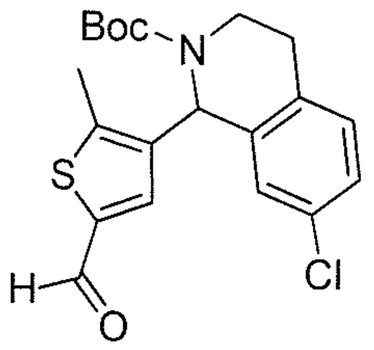
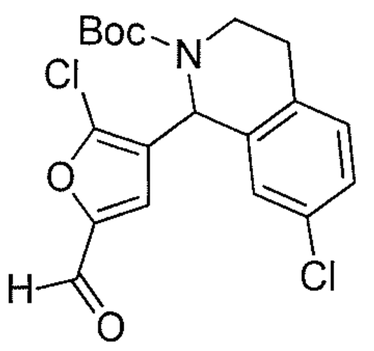
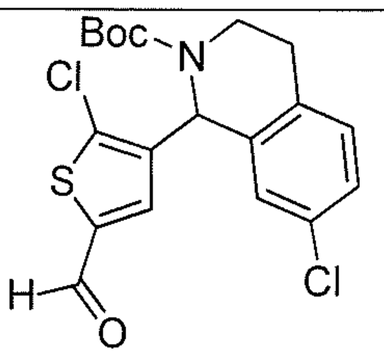
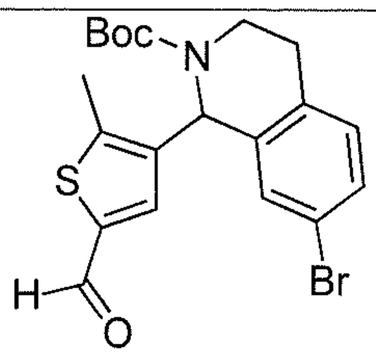
[00603] To a solution of tert-butyl 1-[5-(1,3-dioxolan-2-yl)-3-thienyl]-3,4-dihydroisoquinoline-2(1H)-carboxylate (393 mg, 1.01 mmol) in acetone (7.72 mL) was added 500 mg of Dowex 50WX-2-200 (H)(acid resin), and the mixture was shaken for 18 h at rt. The reaction was filtered through a glass frit funnel and the residual resin was rinsed with acetone several times. To the filtrate was added saturated aqueous $NaHCO_3$ (25.0 mL) and the mixture was concentrated to half volume in vacuo. The residue was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (0 to 15% EtOAc in hexane) to give 319 mg (91%) of the title compound as a colorless amorphous solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.84 (s, 1H), 7.64 (s, 1H), 7.30 – 7.07 (m, 5H), 6.48 – 6.23 (br s, 1H), 4.09 – 3.88 (m, 1H), 3.22 – 3.06 (m, 1H), 3.05 – 2.89 (m, 1H), 2.81 – 2.69 (m, 1H), 1.52 (s, 9H).

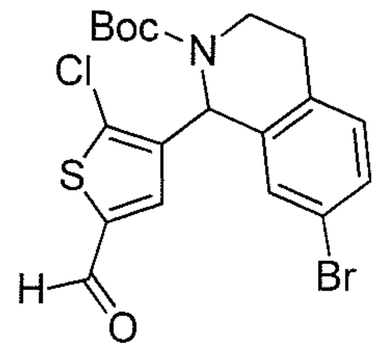
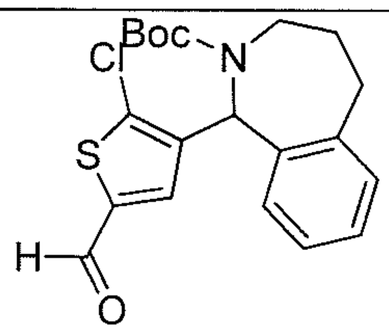
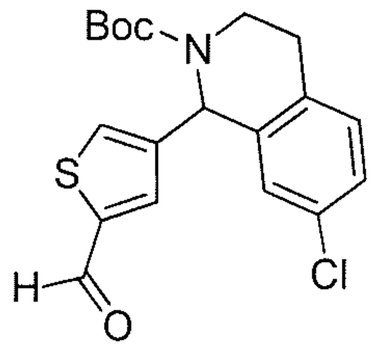
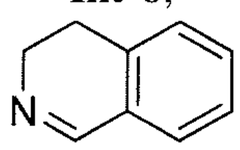
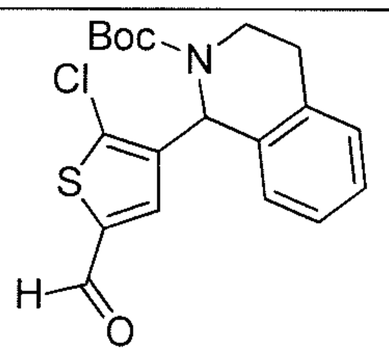
Alternative conditions for Step 3.

Reaction conditions B (e.g., Entry 2, below): tert-Butyl 7-chloro-1-(5-formyl-2-methyl-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[00604] To a solution of tert-butyl 7-chloro-1-[5-(1,3-dioxolan-2-yl)-2-methyl-3-thienyl]-3,4-dihydroisoquinoline-2(1H)-carboxylate (7.30 g, 16.7 mmol) in methanol (200 mL) and water (20 mL) was added a solution of HCl (4.00 mL, 130 mmol) in methanol (200 mL) and the reaction as stirred at rt for 1 hour. Reaction was quenched via addition of 50 mL of saturated $NaHCO_3$ with stirring for 5 min. MeOH was removed in vacuo, and the resulting aqueous mixture was diluted with EtOAc, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic portions were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified via silica gel chromatography eluting with a hexane / EtOAc gradient to afford the title compound (4.55g, 70%). ^{1}H NMR (400 MHz, Chloroform-d) δ 9.67 (s, 1H), 7.27 – 7.15 (m, 2H), 7.12 (s, 1H), 6.98 – 6.94 (m, 1H), 6.34 (m, 1H), 4.15 (s, 1H), 3.18 – 3.06 (m, 1H), 3.05 – 2.93 (m, 1H), 2.82 – 2.73 (m, 1H), 2.69 (s, 3H), 1.50 (s, 9H). LCMS: (AA) M+Na 414.2

[00605] The compounds listed in the table below were prepared in an analogous fashion to that described in **Example 100** starting from the appropriate starting materials:

Entry	Bromide, imine (starting materials)	Reaction conditions for Step 3	Product (Int #)	Characterization data
1	**Int-1**, 	A	 **Int-205**	LCMS: (FA) M+1 358.2
2	**Int-1**, **Int-50**	B	 **Int-206**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.67 (s, 1H), 7.27 – 7.15 (m, 2H), 7.12 (s, 1H), 6.98 – 6.94 (m, 1H), 6.34 (m, 1H), 4.15 (s, 1H), 3.18 – 3.06 (m, 1H), 3.05 – 2.93 (m, 1H), 2.82 – 2.73 (m, 1H), 2.69 (s, 3H), 1.50 (s, 9H). LCMS: (AA) M+Na 414.2
3	**Int-3**, **Int-50**	B	 **Int-207**	^{1}H NMR (400 MHz, Chloroform-d) δ 9.48 (s, 1H), 7.20 (dd, J = 8.2, 1.8 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.18 (br s, 1H), 4.17 (br s, 1H), 3.27 – 3.15 (m, 1H), 3.01 – 2.89 (m, 1H), 2.83 – 2.72 (m, 1H), 1.48 (s, 9H).
4	**Int-2**, **Int-50**	A	 **Int-208**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (s, 1H), 7.79 (s, 1H), 7.32 (d, *J* = 1.2 Hz, 2H), 7.14 (s, 1H), 6.24 (s, 1H), 3.97 (d, *J* = 13.3 Hz, 1H), 3.41 (s, 1H), 2.97 – 2.81 (m, 2H), 1.38 (s, 9H).
5	**Int-1**, **Int-51**	B		LCMS: (FA) M+1 438.3

			Int-209	
6	**Int-2**, **Int-51**	**A**	 **Int-210**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.60 (s, 1H), 7.28 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.22 (s, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.23 (s, 1H), 4.11 (s, 1H), 3.26 – 3.17 (m, 1H), 2.87 (ddd, *J* = 16.4, 10.8, 5.6 Hz, 1H), 2.73 (d, *J* = 16.4 Hz, 1H), 1.38 (s, 9H).
7	**Int-2**, **Int-52**	**A**	 **Int-211**	Rotameric mixture gave complex ^{1}H NMR spectra
8	**Int-5**, **Int-50**	Perfomed in analogous fashion to Example 99, step 4	 **Int-212**	^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.88 (d, *J* = 1.2 Hz, 1H), 7.65 (s, 1H), 7.38 (s, 1H), 7.25 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.13 (s, 1H), 6.37 (s, 1H), 4.15 (d, *J* = 7.3 Hz, 1H), 3.11 (s, 1H), 2.96 (s, 1H), 2.75 (d, *J* = 16.1 Hz, 1H), 1.54 (s, 9H).
9	**Int-6**, 	Perfomed in analogous fashion to Example 99, step 4	 **Int-213**	

Example 101: 5-Chloro-4-(6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl)thiophene-2-carbaldehyde Int-214

DEMANDE OU BREVET VOLUMINEUX

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

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 317

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 317

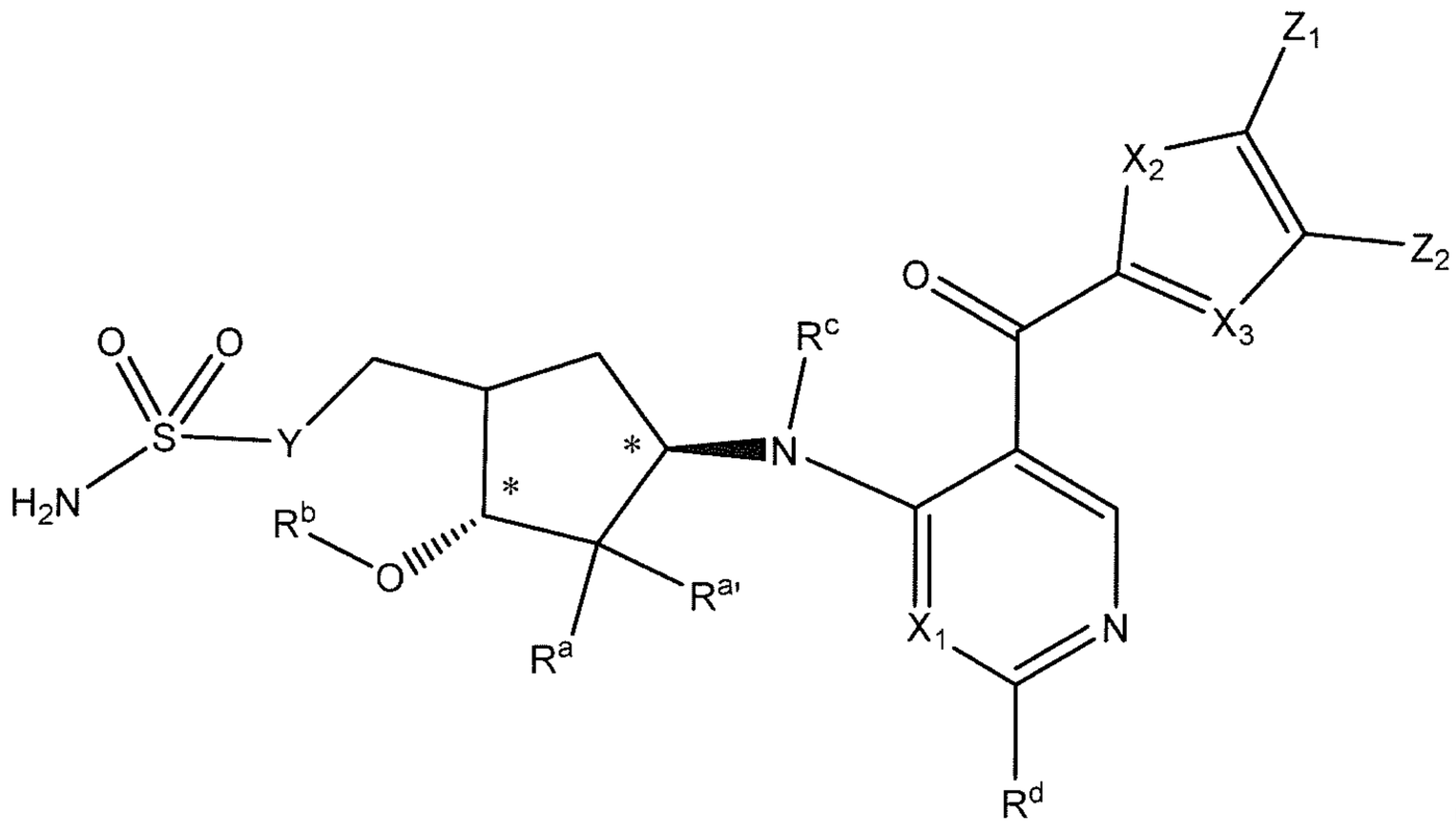
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED IS:

1. A chemical entity which is a compound or pharmaceutically acceptable salt of formula (I):



(I)

WHEREIN:

stereochemical configurations depicted at asterisked positions indicate absolute stereochemistry;

Y is -O-, $-CH_2-$, or -N(H)-;

R^a is hydrogen, fluoro, $-NH_2$, or hydroxyl;

$R^{a'}$ is hydrogen or fluoro, provided that when R^a is $-NH_2$ or hydroxyl, $R^{a'}$ is hydrogen;

R^b is hydrogen or, together with the oxygen to which it is attached, forms a prodrug;

R^c is hydrogen or C_{1-4} alkyl;

R^d is hydrogen, halogen, $-CF_3$, or C_{1-4} alkyl;

X_1 is C(H), C(F), or N;

X_2 is S or O;

X_3 is $C(R^{x3})$ or N;

R^{x3} is hydrogen, methyl, or halogen;

Z_1 is hydrogen, halogen, cyano, R^{z3}, $-S-R^{z3}$, $-S(O)-R^{z3}$, or $-S(O)_2-R^{z3}$;

R^{z3} is an optionally substituted phenyl, an optionally substituted 5- to 7-membered cycloaliphatic, an optionally substituted 5- to 7-membered heterocyclyl, or an optionally substituted C_{1-4} aliphatic;

wherein Z_1 is not hydrogen, halogen, methyl, or cyano if Z_2 is hydrogen or methyl; and

(a) Z_2 is a ring system having an optionally substituted 5- to 7-membered heterocyclyl with 1-2 heteroatoms or an optionally substituted 5- to 7-membered cycloaliphatic fused to

(i) an optionally substituted 5-membered heteroaryl or an optionally substituted 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) an optionally substituted 9-membered heteroaryl or an optionally substituted 10-membered aryl or heteroaryl to form a tricyclic group;

OR

(b) Z_2 is L-R^e wherein L is $–L_1$-, $-V_1-L_2$-, or $–L_1-V_1-L_2$-;

L_1 is a C_{1-3} alkylene chain wherein 1 or 2 saturated carbon atoms are optionally substituted by $(R^f)(R^{f'})$ and in which there are optionally one or two degrees of unsaturation;

each R^f is independently hydrogen; hydroxyl; $-N(R^h)(R^{h'})$; C_{1-4} aliphatic optionally substituted with hydroxyl, $-OCH_3$, or cyclopropyl; $-O-C_{1-4}$ aliphatic optionally substituted with hydroxyl, $-OCH_3$, or cyclopropyl; or, together with $R^{f'}$ and the carbon atom to which they are attached, form $C=CH_2$, or a 3- to 6-membered carbocycle or 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle;

each $R^{f'}$ is independently hydrogen; C_{1-4} aliphatic optionally substituted with hydroxyl, $-OCH_3$, or cyclopropyl; $-O-C_{1-4}$ aliphatic optionally substituted with hydroxyl, $-OCH_3$, or cyclopropyl; or, together with R^f and the carbon atom to which they are attached, form $C=CH_2$, or a 3- to 6-membered carbocycle or 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle; wherein if R^f is hydroxyl, $R^{f'}$ is not $-O-C_{1-4}$ aliphatic optionally substituted with hydroxyl, $-OCH_3$, or cyclopropyl;

R^h and $R^{h'}$ are each independently hydrogen or C_{1-4} alkyl;

V_1 is -S-, -O-, -S(O)-, $-S(O)_2$-, -C(O)- or $-N(R^g)$-;

L_2 is a C_{0-2} alkylene chain wherein one saturated carbon atom is optionally substituted by $(R^f)(R^{f'})$;

R^g is hydrogen or C_{1-4} alkyl; and

either (i) R^e is hydrogen, hydroxyl, halogen, $-CF_3$, or an optionally substituted C_{1-4} aliphatic,

with the proviso that R^e is not hydrogen if R^f and $R^{f'}$ are present and form a ring;

OR (ii) R^e is a ring chosen from optionally substituted 6-membered aryl, optionally substituted 5-to 6-membered heteroaryl, optionally substituted 3- to 7-membered

cycloaliphatic, or optionally substituted 4- to 7-membered heterocyclyl, which is optionally fused to a second optionally substituted 6-membered aryl, optionally substituted 5-to 6-membered heteroaryl, optionally substituted 3- to 7-membered cycloaliphatic, or optionally substituted 4- to 7-membered heterocyclyl;

OR

(c) Z_2 is hydrogen.

2. The chemical entity of claim 1, wherein:

(a) Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to

(i) a 5-membered heteroaryl or a 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) a 9-membered heteroaryl or a 10-membered aryl or heteroaryl to form a tricyclic group;

wherein the ring system is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and the ring system is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a spirocyclic 4- to 6-membered heterocycle;

each occurrence of R^{z7} is independently hydrogen or C_{1-4} alkyl;

each occurrence of R^{z8} is independently C_{1-4} alkyl;

T_2 is a C_{1-2} alkylene chain;

R^{z9} is cyano, $-N(R^{z7})_2$, $-OR^{z7}$, $-C(O)R^{z8}$, $-C(O)_2R^{z7}$,or $-C(O)N(R^{z7})_2$;

OR

(b) Z_2 is L-R^e wherein either:

(i) R^e is hydrogen, hydroxyl, halogen, $-CF_3$, or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, halogen, or C_{1-4} aliphatic,

with the proviso that R^e is not hydrogen if R^f and $R^{f'}$ are present and form a ring;

OR (ii) R^e is a ring chosen from 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, R^e being optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, $-N(R^{z7})_2$, $-C(O)R^{z8}$, $-S(O)R^{z8}$, $-S(O)_2R^{z8}$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, -

$OC(O)N(R^{z7})_2$, $-N(R^{z7})C(O)R^{z8}$, $-N(R^{z7})SO_2R^{z8}$, $-N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and which is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a spirocyclic 4- to 6-membered heterocycle;

each occurrence of R^{z7} is independently hydrogen or C_{1-4} alkyl;

each occurrence of R^{z8} is independently C_{1-4} alkyl;

T_2 is a C_1.C_2 alkylene chain; and

R^{z9} is cyano, $-NO_2$, $-N(R^{z7})_2$, $-OR^{z7}$, $-C(O)R^{z8}$, $-C(O)_2R^{z7}$, or $-C(O)N(R^{z7})_2$.

3. The chemical entity of claim 1 or claim 2, wherein L is $-C(R^f)(R^{f'})$-, -S-, -S(O)-, $-S(O)_2$-, -C(O)-, $-C(=CH_2)$-, $-C(R^f)(R^{f'})$-$C(=CH_2)$-, $-C(R^f)(R^{f'})$-C≡C-, $-C(R^f)(R^{f'})$-O-, $-C(R^f)(R^{f'})$-S-, $-C(R^f)(R^{f'})$-$N(R^g)$-, $-C(R^f)(R^{f'})$-$N(R^g)$-CH_2-, $-C(R^f)(R^{f'})$-CH_2-, $-C(R^f)(R^{f'})$-CH_2-CH_2-, or $-C(O)$-$C(R^f)(R^{f'})$-.

4. The chemical entity of any one of claims 1 to 3, wherein:

Z_1 is hydrogen, halogen, cyano, R^{z3}, -S-R^{z3}, -S(O)-R^{z3}, or $-S(O)_2$-R^{z3};

R^{z3} is a phenyl, 5- to 7-membered cycloaliphatic, 5- to 7-membered heterocyclyl, or C_{1-4} aliphatic, any of which may be substituted with one or more independently selected R^{z4};

R^{z4} is hydroxyl, halogen, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z5})_2$, $-C(O)R^{z6}$, $-C(O)_2R^{z5}$, 5- or 6-membered cycloaliphatic or heterocyclyl, or a phenyl optionally substituted with one or more independently selected halogens;

each occurrence of R^{z5} is independently hydrogen or C_{1-4} alkyl; and

each occurrence of R^{z6} is independently C_{1-4} alkyl.

5. The chemical entity of claim 4, wherein Z_1 is hydrogen; halogen; cyano; phenyl optionally substituted with one or more independently selected halogens; 5- to 7-membered cycloaliphatic or heterocyclyl optionally fused to a 6-membered aryl, wherein the 5- to 7-membered cycloaliphatic or heterocyclyl optionally fused to a 6-membered aryl is optionally substituted with one or more independently selected halogens; C_{1-4} fluoroaliphatic; or a C_{1-4} aliphatic group optionally substituted with one or more hydroxyl, C_{1-4} alkoxy, phenyl optionally substituted with one more independently selected halogens, 5- or 6-membered cycloaliphatic, 5- or 6-membered heterocyclyl, or $-N(R^{z5})_2$.

6. The chemical entity of any one of claims 2 to 5, wherein:

Z_2 is a ring system having a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to

(i) a 5-membered heteroaryl or 6-membered aryl or heteroaryl to form a bicyclic group; or

(ii) a 9-membered heteroaryl or 10-membered aryl or heteroaryl to form a tricyclic group;

wherein the ring system is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, -$N(R^{z7})_2$, -$C(O)R^{z8}$, -$S(O)R^{z8}$, -$S(O)_2R^{z8}$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -$OC(O)N(R^{z7})_2$, -$N(R^{z7})C(O)R^{z8}$, -$N(R^{z7})SO_2R^{z8}$, -$N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, 5- to 6-membered heteroaryl, 6-membered aryl, 3- to 6-membered cycloaliphatic or heterocyclyl; and the ring system is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a spirocyclic 4- to 6-membered heterocycle;

each occurrence of R^{z7} is independently hydrogen or C_{1-4} alkyl;

each occurrence of R^{z8} is independently C_{1-4} alkyl;

T_2 is a C_{1-2} alkylene chain; and

R^{z9} is cyano, -$N(R^{z7})_2$, -OR^{z7}, -$C(O)R^{z8}$, -$C(O)_2R^{z7}$, or -$C(O)N(R^{z7})_2$.

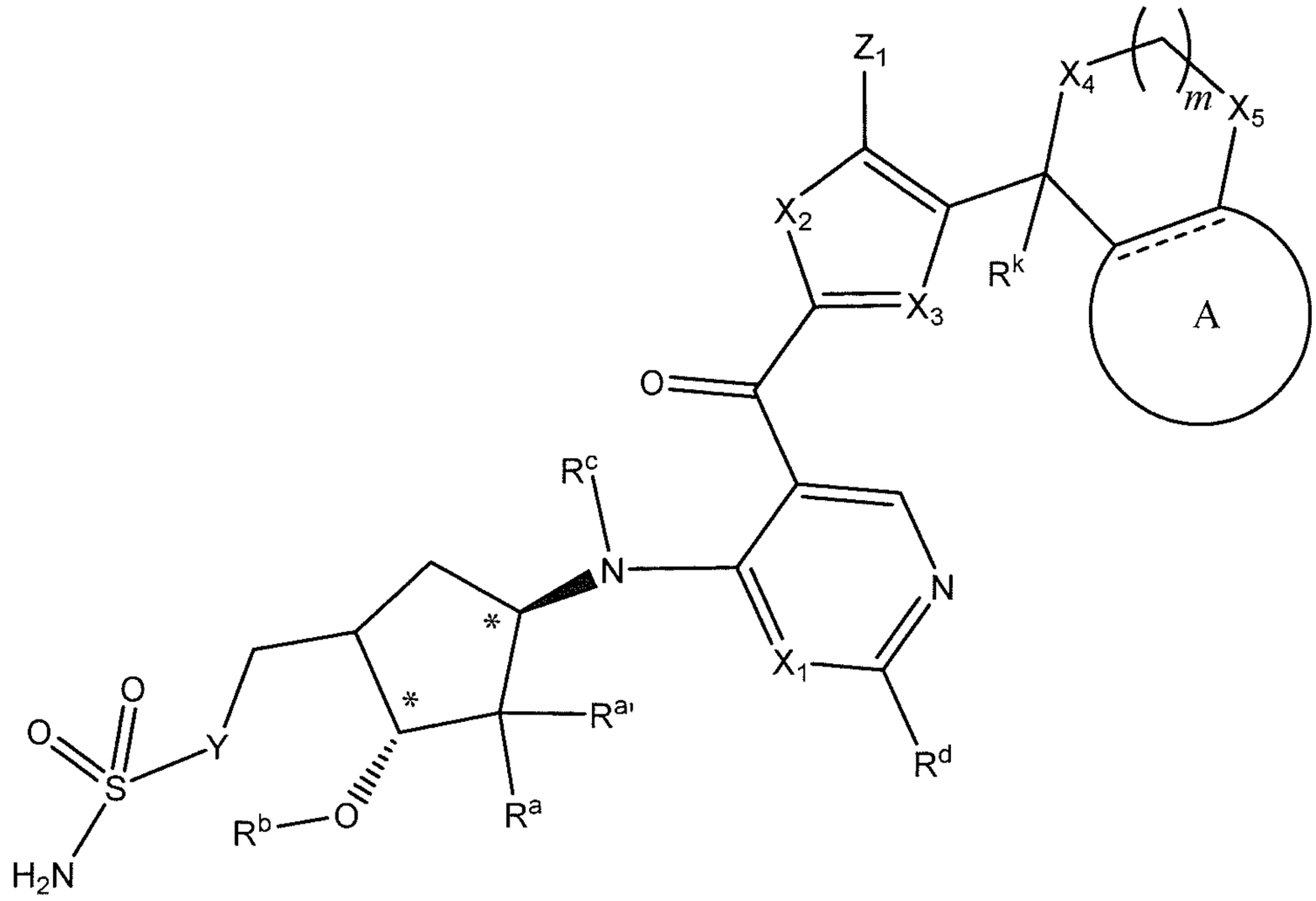
7. The chemical entity of claim 6, wherein:

Z_2 is a 5- to 7-membered heterocyclyl with 1-2 heteroatoms or a 5- to 7-membered cycloaliphatic fused to a 5-membered heteroaryl or 6-membered aryl or heteroaryl ring to form a bicyclic group, wherein the ring system is optionally substituted as defined in claim 6.

8. The chemical entity of claim 7, wherein:

Z_2 is a 6-membered heterocyclyl, the heterocyclyl containing 1 N or O atom, fused to a 6-membered aryl or heteroaryl ring to form a bicyclic group, wherein the ring system is optionally substituted as defined in claim 7.

9. The chemical entity of claim 6, which is a compound or pharmaceutically acceptable salt of formula (V):



(V)

wherein:

m is 0, 1, or 2;

X_4 is S, O, or $N(R^{n4})$;

X_5 is O, C(O), or $C(R^{x5})(R^{x5'})$, wherein X_5 is not O if X_4 is $N(R^{n4})$ or S;

R^{n4} is hydrogen or C_{1-4} alkyl;

R^{x5} is hydrogen, fluoro, hydroxyl, or C_{1-4} alkyl;

$R^{x5'}$ is hydrogen, fluoro, or C_{1-4} alkyl, wherein $R^{x5'}$ is not fluoro if R^{x5} is hydroxyl;

or R^{x5} and $R^{x5'}$, taken together with the carbon atom to which they are attached, form a spirocyclic 3- to 6-membered carbocycle or a spirocyclic to 4- to 6-membered heterocycle comprising only one heteroatom, the heteroatom being chosen from O, N, or S;

dashed lines indicate single or double bonds;

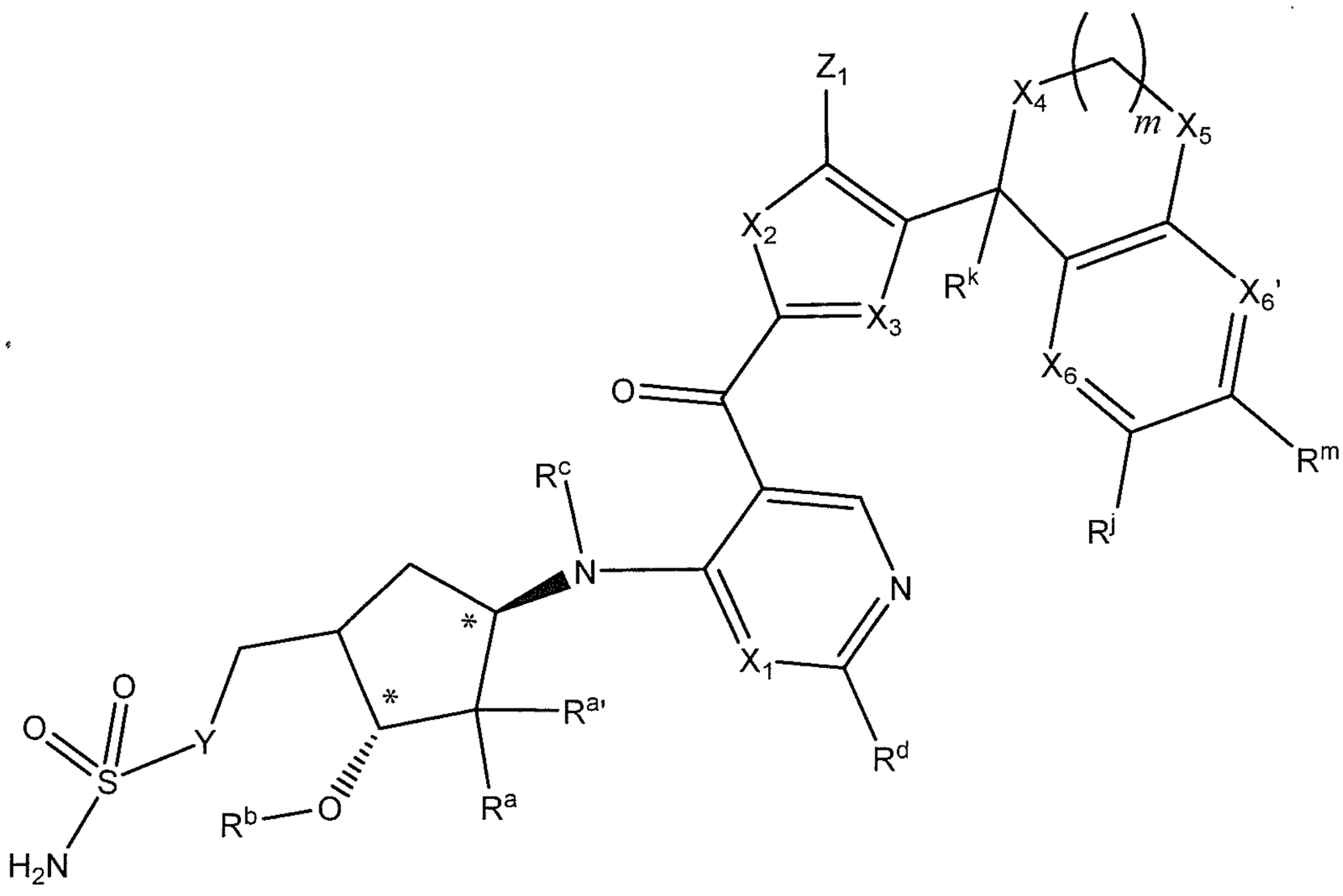
Ring A is a fused 5-membered heteroaryl or 6-membered aryl or heteroaryl optionally substituted with 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -S-C_{1-4} aliphatic, -S-C_{1-4} fluoroaliphatic, -$N(R^{z7})_2$, -$C(O)R^{z8}$, -$S(O)R^{z8}$, -$S(O)_2R^{z8}$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -$OC(O)N(R^{z7})_2$, -$N(R^{z7})C(O)R^{z8}$, -$N(R^{z7})SO_2R^{z8}$, -$N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl;

T_2 is a C_1-C_2 alkylene chain;

R^{z9} is cyano, -$N(R^{z7})_2$, -OR^{z7}, -$C(O)R^{z8}$, -$C(O)_2R^{z7}$,or -$C(O)N(R^{z7})_2$; and

R^k is hydrogen or methyl.

10. The chemical entity of claim 9, which is a compound or pharmaceutically acceptable salt of formula (VI):



(VI);

wherein:

m is 1 or 2;

X_6 is N or $C(R^{x6})$;

X_6' is N or $C(R^{x6'})$; and

each of R^{x6}, $R^{x6'}$, R^j and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl;

wherein at least one of R^{x6}, $R^{x6'}$, R^j and R^m is hydrogen.

11. The chemical entity of claim 10, wherein:

m is 1;

X_5 is CH_2;

R^{n4} is hydrogen or methyl; and

each of R^{x6}, $R^{x6'}$, R^j, and R^m is independently hydrogen, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$;

wherein at least one of R^{x6}, R^{x7}, R^j and R^m is hydrogen.

12. The chemical entity of claim 10 or 11, wherein:

X_4 is O or N(H);

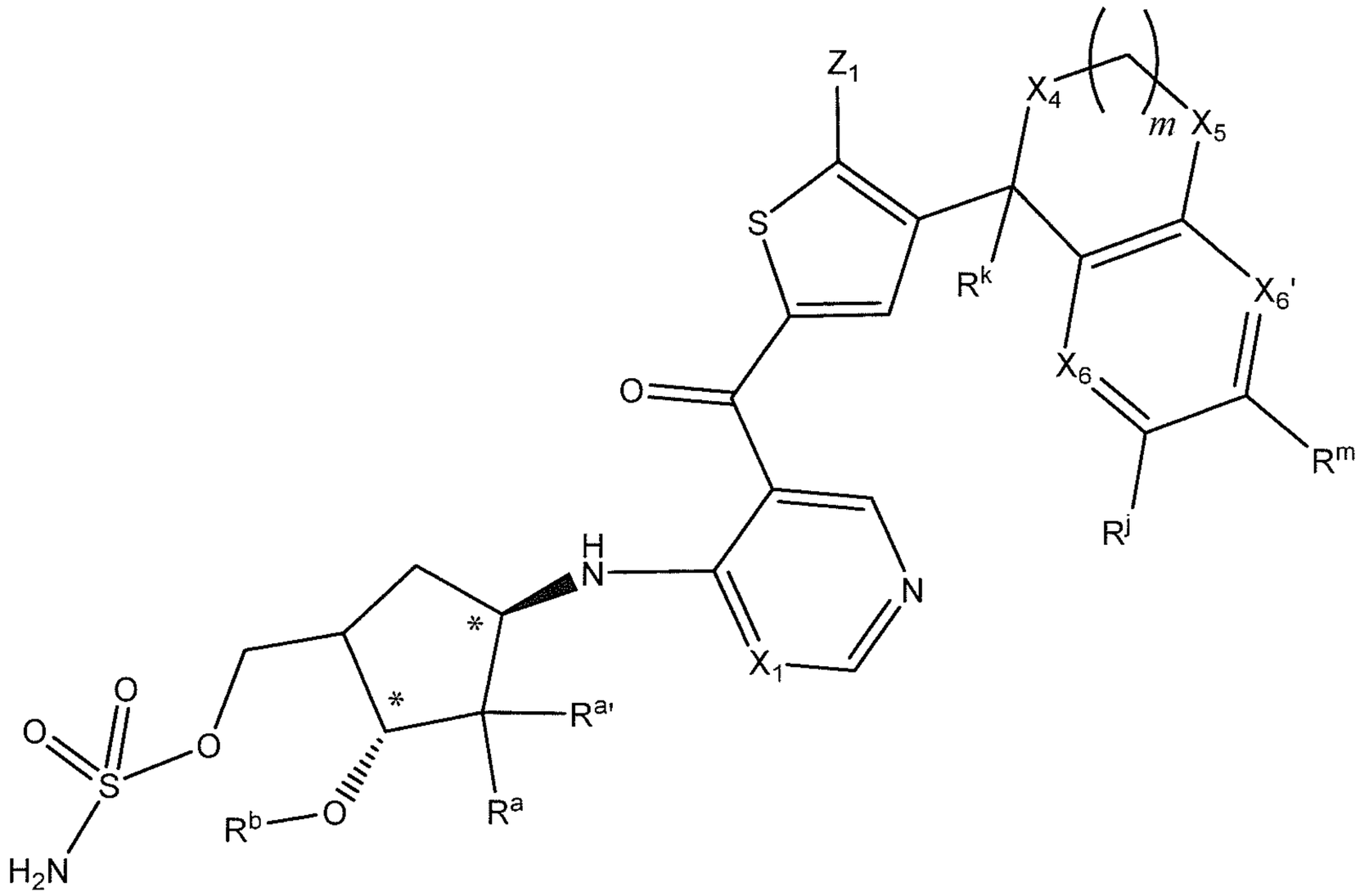
X_6 is N or C(H);

X_6' is C(H);

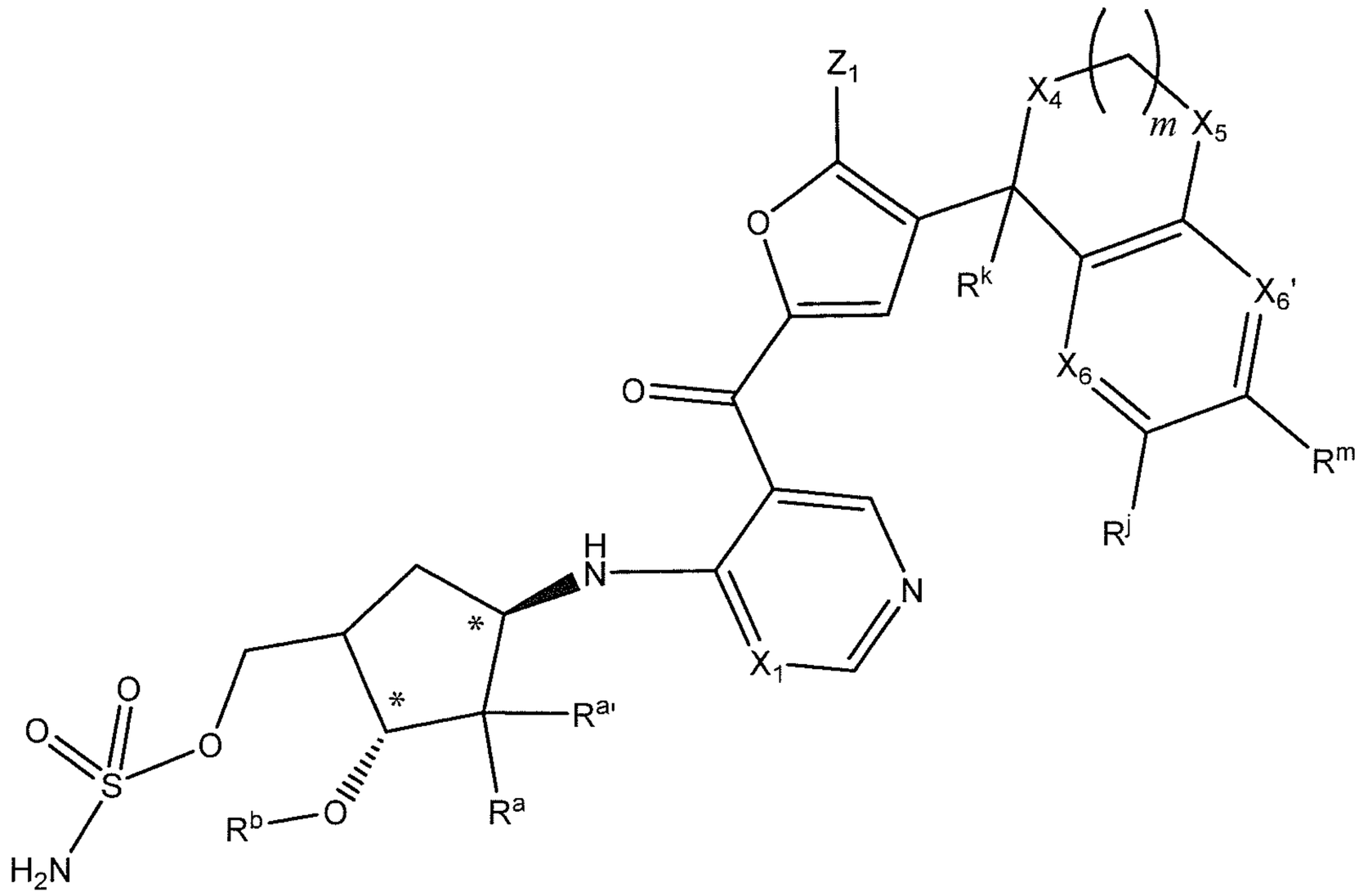
R^m is hydrogen, fluoro or chloro; and

R^j is methyl, ethyl, isopropyl, hydrogen, fluoro, chloro, bromo, cyclopropyl, -C≡CH or $-CF_3$.

13. The chemical entity of any one of claims 10 to 12, which is a compound or pharmaceutically acceptable salt of formula (VIa) or (VIb):

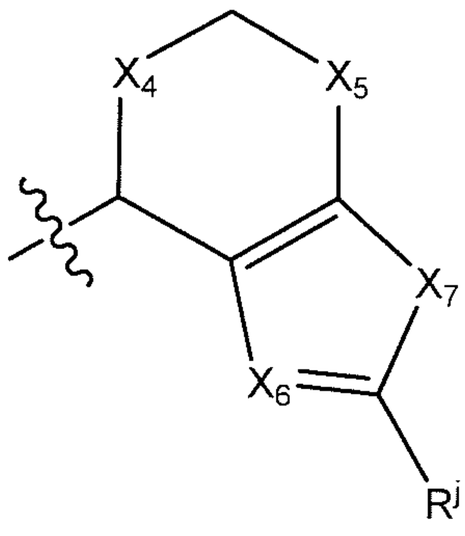
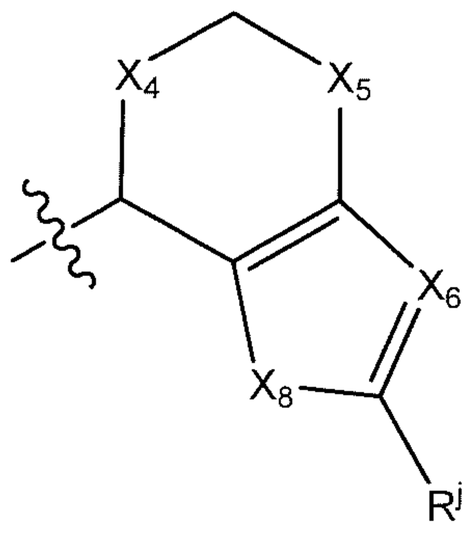


(VIa)



(VIb).

14. The chemical entity of claim 9, wherein Z_2 is

 or ; and wherein

X_4 is O or $N(R^{n4})$;

X_5 is $C(R^{x5})(R^{x5'})$;

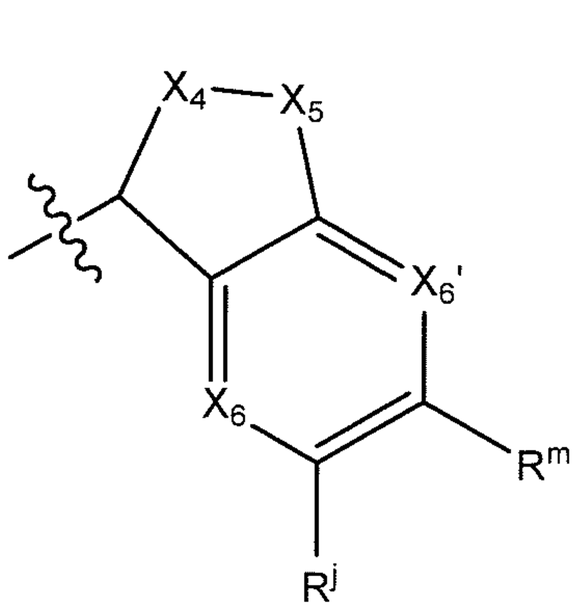
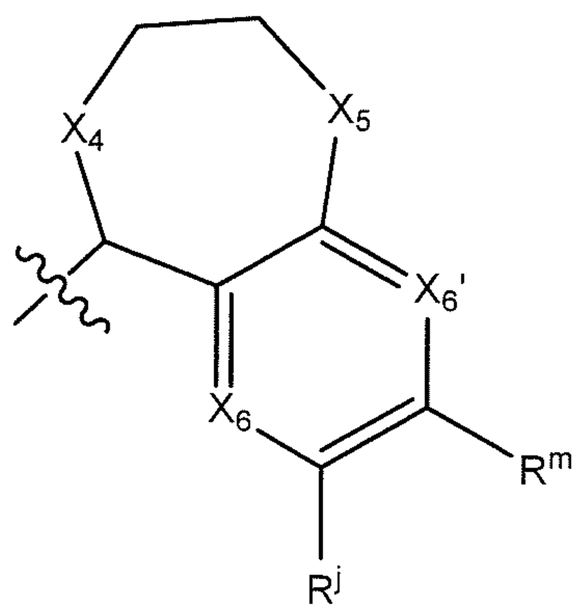
X_6 is N or $C(R^{x6})$;

X_7 is O or S;

X_8 is S or N(H); and

R^{x6} and R^j are each independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2N(R^{z7})_2$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl.

15. The chemical entity of claim 9, wherein Z_2 is

, or ; and wherein

X_4 is O or $N(R^{n4})$;

X_5 is $C(R^{x5})(R^{x5'})$;

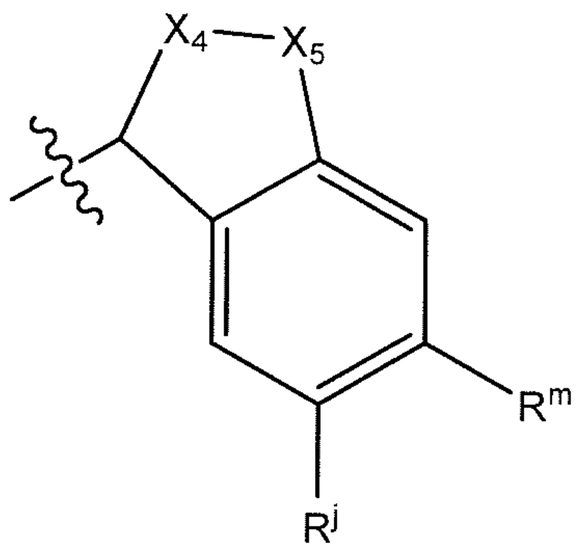
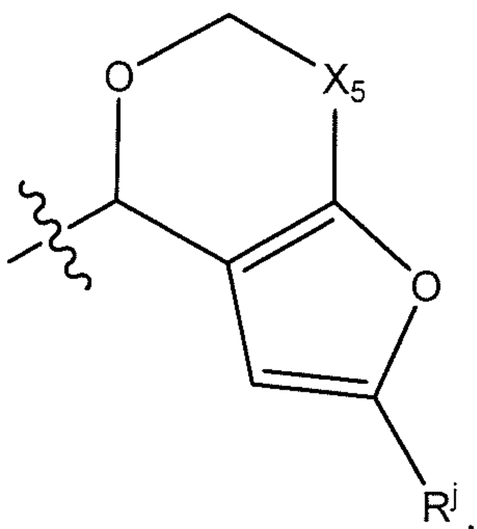
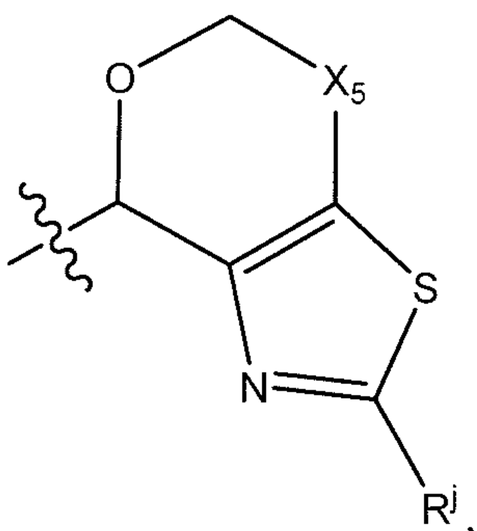
X_6 is N or $C(R^{x6})$;

X_6' is N or $C(R^{x6})$; and

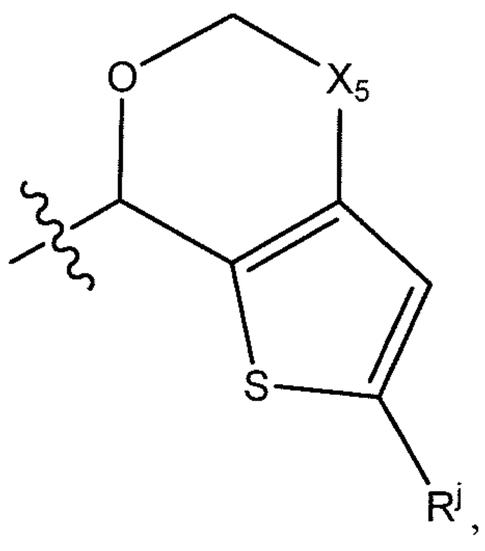
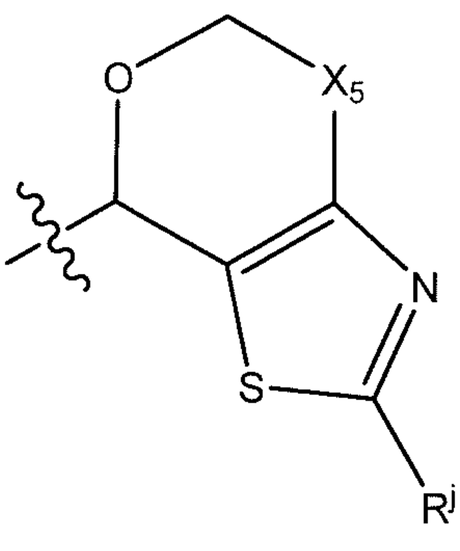
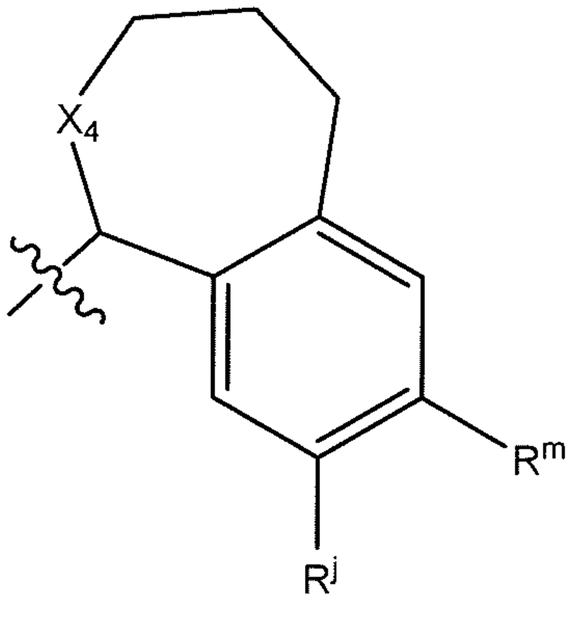
each R^{x6}, R^j, and R^m is independently hydrogen, halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2N(R^{z7})_2$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl,

wherein at least one R^{x6}, R^j, or R^m is hydrogen.

16. The chemical entity of claim 9, wherein Z_2 is

,

, or ;

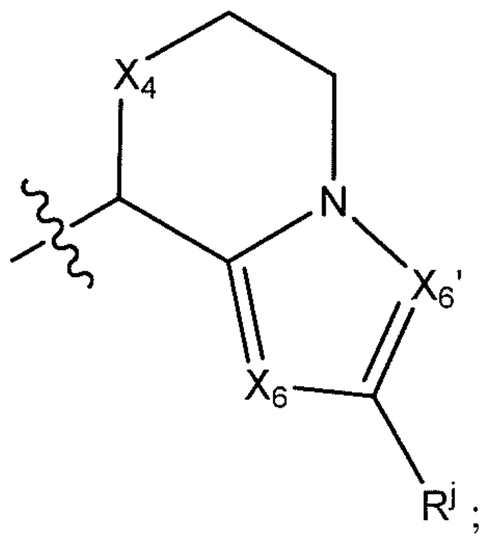
X_5 is $C(R^{x5})(R^{x5'})$;

R^{x5} and $R^{x5'}$ are independently hydrogen or fluoro; or, together with the carbon to which they are attached, form a cyclopropyl ring;

R^j is hydrogen, chloro, fluoro, bromo, methyl, ethyl, isopropyl, cyano, cyclopropyl, CF_3, $-OCH_3$, $-OCH_2CH_3$, or $-C\equiv CH$; and

R^m is hydrogen, fluoro, or chloro.

17. The chemical entity of claim 9, wherein Z_2 is



X_4 is O or $N(R^{n4})$;

X_6 is N or $C(R^{x6})$;

X_6' is N or $C(R^{x6})$;

R^{n4} is hydrogen or C_{1-4} alkyl; and

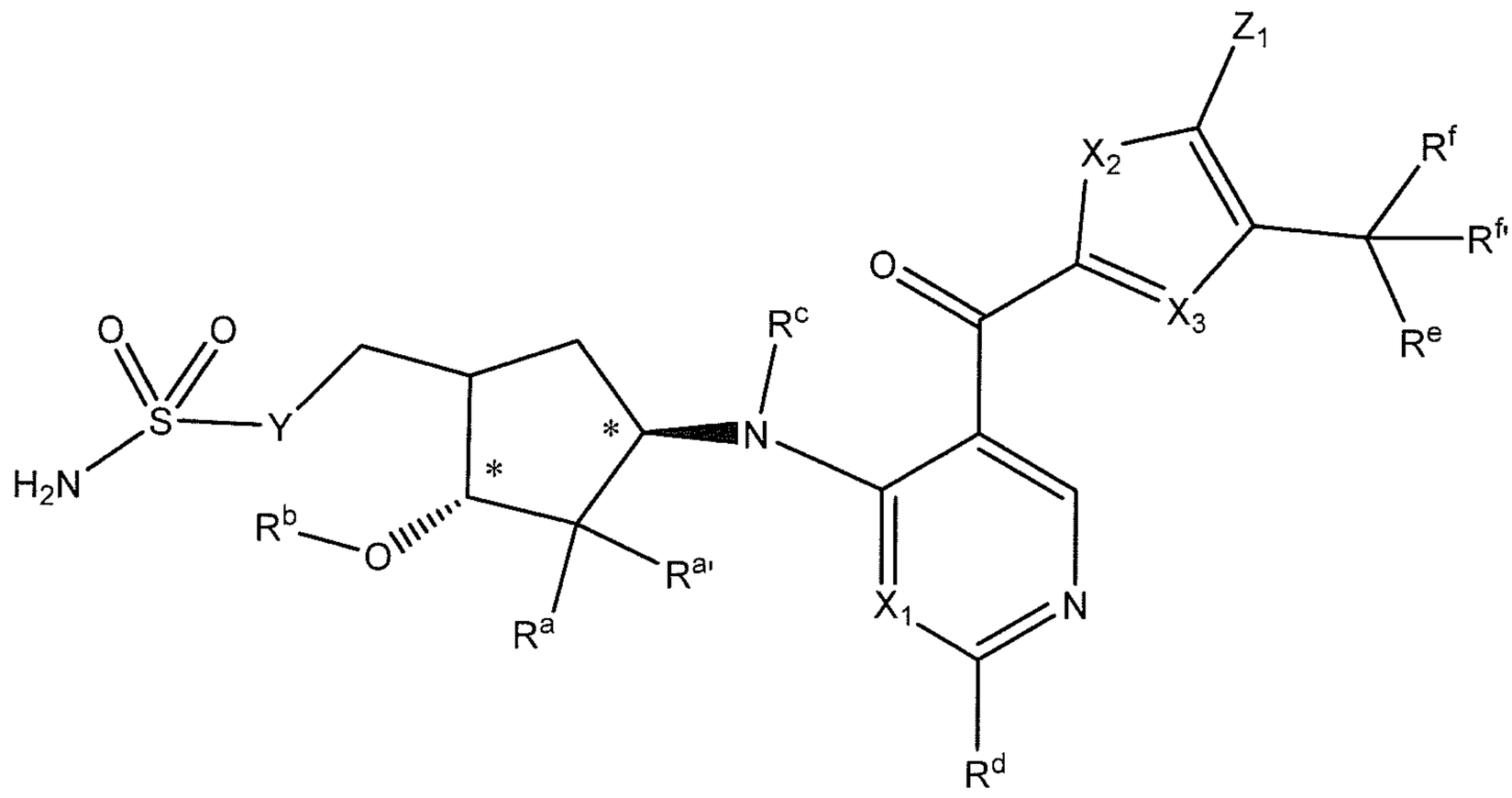
each of R^{x6}, R^j or R^m is independently halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, $-N(R^{z7})_2$, $-C(O)_2R^{z7}$, $-C(O)N(R^{z7})_2$, $-S(O)_2N(R^{z7})_2$, $-CH_2-OR^{z7}$, $-CH_2NR^{z7}$, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl.

18. The chemical entity of any one of claims 1 to 5, wherein Z_2 is $L-R^e$.

19. The chemical entity of claim 18, wherein:

L is $-C(R^f)(R^{f'})-$, $-S-$, $-C(=O)-$, $-C(R^f)(R^{f'})-O-$, $-C(R^f)(R^{f'})-S-$, $-C(R^f)(R^{f'})-N(R^g)-$, $-C(R^f)(R^{f'})-CH_2-$ or $-C(R^f)(R^{f'})-C\equiv C-$.

20. The chemical entity of claim 18 or 19, which is a compound or pharmaceutically acceptable salt of formula (VIII):



(VIII).

21. The chemical entity of any one of claims 18 to 20, wherein:

R^e is a ring chosen from 3- to 7-membered cycloaliphatic or 4- to 7-membered heterocyclyl, which is optionally fused to a second 6-membered aryl, 5- to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, which is optionally substituted by 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, S-C_{1-4} aliphatic, S-C_{1-4} fluoroaliphatic, -$N(R^{z7})_2$, -$C(O)R^{z8}$, -$S(O)R^{z8}$, -$S(O)_2R^{z8}$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -$OC(O)N(R^{z7})_2$, -$N(R^{z7})C(O)R^{z8}$, -$N(R^{z7})SO_2R^{z8}$, -$N(R^{z7})C(O)OR^{z8}$, T_2-R^{z9}, a 5- to 6-membered heteroaryl, a 6-membered aryl, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl; and which is optionally substituted at one saturated carbon with oxo, a spirocyclic 3- to 6-membered carbocycle, or a spirocyclic 4- to 6-membered heterocycle;

each occurrence of R^{z7} is independently hydrogen or C_{1-4} alkyl;

each occurrence of R^{z8} is independently C_{1-4} alkyl;

T_2 is a C_1-C_2 alkylene chain; and

R^{z9} is cyano, -$N(R^{z7})_2$, -OR^{z7}, -$C(O)R^{z8}$, -$C(O)_2R^{z7}$,or -$C(O)N(R^{z7})_2$.

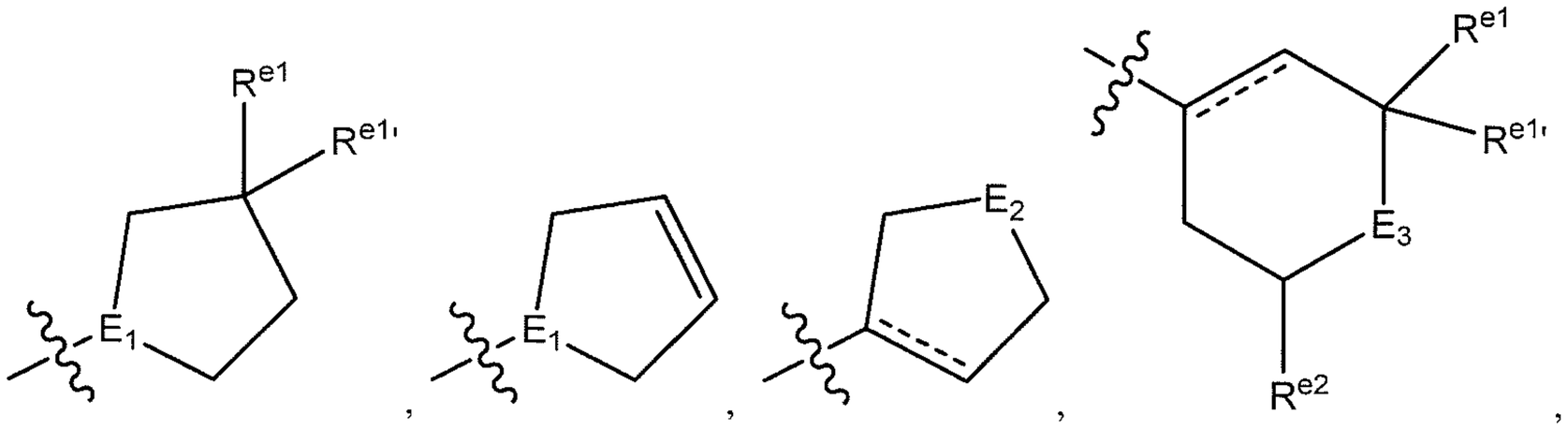
22. The chemical entity of any one of claims 18 to 21, wherein:

each R^f is independently hydrogen, hydroxyl, $N(R^h)(R^{h'})$, C_{1-4} alkoxy, cyclopropyl, or C_{1-4} alkyl optionally substituted with hydroxyl or -OCH_3;

each $R^{f'}$ is independently hydrogen, cyclopropyl, or C_{1-4} alkyl optionally substituted with hydroxyl or -OCH_3; and

R^e is a 5- to 7-membered cycloaliphatic ring or a 5- to 7-membered heterocyclyl having only one heteroatom, wherein the ring is optionally substituted as defined in any one of claims 18 to 21.

23. The chemical entity of any one of claims 18 to 22, wherein R^e is



and wherein

dashes indicate single or double bonds;

E_1 is N or C(H);

E_2 is O, S, or CH_2;

E_3 is O, S, $N(R^{e3})$, or $C(H)(R^{e3})$;

E_3' is O, $N(R^{e3})$ or $C(H)(R^{e3})$;

R^{e1} and $R^{e1'}$ are each independently hydrogen or fluoro;

R^{e2} is hydrogen or methyl; and

R^{e3} is hydrogen or methyl.

24. The chemical entity of claim 20, wherein:

R^f and $R^{f'}$ are each independently hydrogen, C_{1-4} alkyl, or cyclopropyl; or are taken together to form $=CH_2$; and

R^e is a ring chosen from 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, and is optionally substituted with 1-3 independent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4}

fluoroalkoxy, -$N(R^{z7})_2$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -CH_2-OR^{z7}, -CH_2NR^{z7} or a 3- to 6-membered cycloaliphatic or 4- to 6-membered heterocyclyl.

25. The chemical entity of claim 20, wherein:

R^f is hydrogen, hydroxyl, $N(R^h)(R^{h'})$, -OCH_3, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3;

$R^{f'}$ is hydrogen, cyclopropyl, or C_{1-4} aliphatic optionally substituted with hydroxyl or -OCH_3;

or, together with the carbon atom to which they are attached, R^f and $R^{f'}$ form a 4- to 6-membered heterocycle comprising a heteroatom chosen from N (which may be protonated or C_{1-4} alkylated), O, or S, the heteroatom optionally located immediately adjacent to the quaternary carbon of the heterocycle;

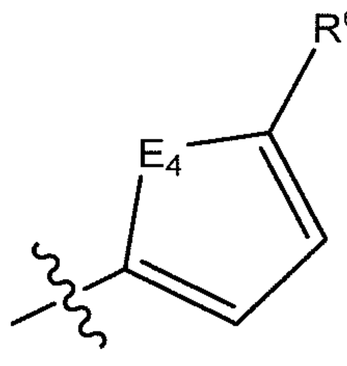
wherein at least one of R^f and $R^{f'}$ comprises at least one heteroatom; and

R^e is a ring chosen from 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally fused to a second 6-membered aryl, 5-to 6-membered heteroaryl, 3- to 7-membered cycloaliphatic, or 4- to 7-membered heterocyclyl, and is optionally substituted with one or more halogen, C_{1-4} aliphatic optionally substituted with 1-3 indpendent occurrences of halogen, hydroxyl, cyano, C_{1-4} aliphatic, C_{1-4} fluoroaliphatic, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, -$N(R^{z7})_2$, -$C(O)_2R^{z7}$, -$C(O)N(R^{z7})_2$, -$S(O)_2N(R^{z7})_2$, -CH_2-OR^{z7}, -CH_2NR^{z7}, a 3- to 6-membered cycloaliphatic, or a 4- to 6-membered heterocyclyl.

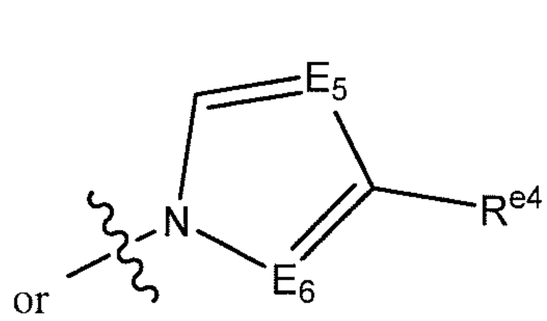
26. The chemical entity of any one of claims 18 to 20 or 24 to 25, wherein:

R^e is a ring chosen from 6-membered aryl or 5-to 6-membered heteroaryl, which is optionally substituted with 1-3 independent occurrences of chloro, fluoro, bromo, iodo, methyl, ethyl, cyano, cyclopropyl, CF_3, -OCH_3, -OCH_2CH_3, or -C≡CH.

27. The chemical entity of any one of claims 18 to 20 or 24 to 26, wherein R^e is:



or



;

E_4 is S or O;

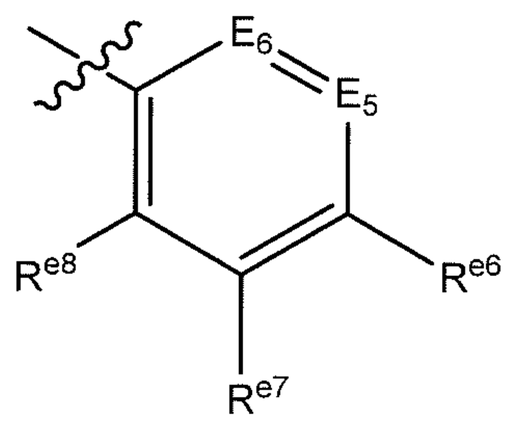
E_5 is N or $C(R^{e5})$;

E_6 is N or C(H);

R^{e4} is hydrogen, methyl, chloro, fluoro, bromo, iodo, cyano, or -CF_3; and

R^{e5} is hydrogen or halogen.

28. The chemical entity of any one of claims 18 to 20 or 24 to 26, wherein R^e is



;

E_5 is N or C(R^{e5});

E_6 is N or C(H);

each of R^{e5}, R^{e6}, R^{e7}, and R^{e8} is independently hydrogen, halogen, methyl, ethyl, isopropyl, -OCH_3, -CF_3, or -C≡CH;

and at least two of R^{e5}, R^{e6}, R^{e7}, and R^{e8} are hydrogen.

29. The chemical entity of any one of claims 18 to 20 or 24 to 26, wherein R^e is

;

E_5 is N or C(R^{e5});

E_6 is N or C(H);

R^{e5} is hydrogen, halogen, methyl, -OCH_3, -CF_3, or -C≡CH;

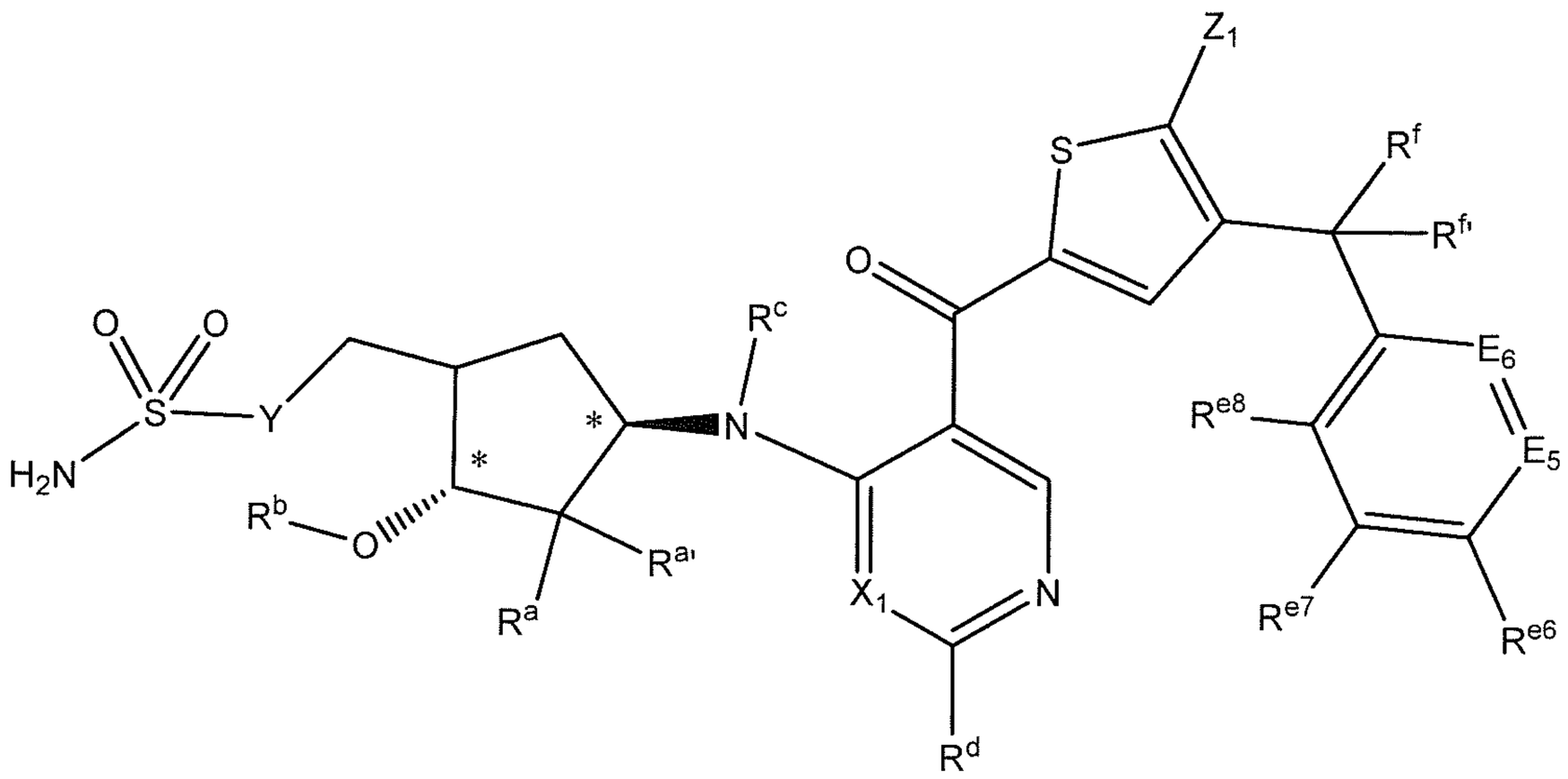
R^{e6} is hydrogen, fluoro, or chloro;

R^{e7} is hydrogen, fluoro, or chloro; and

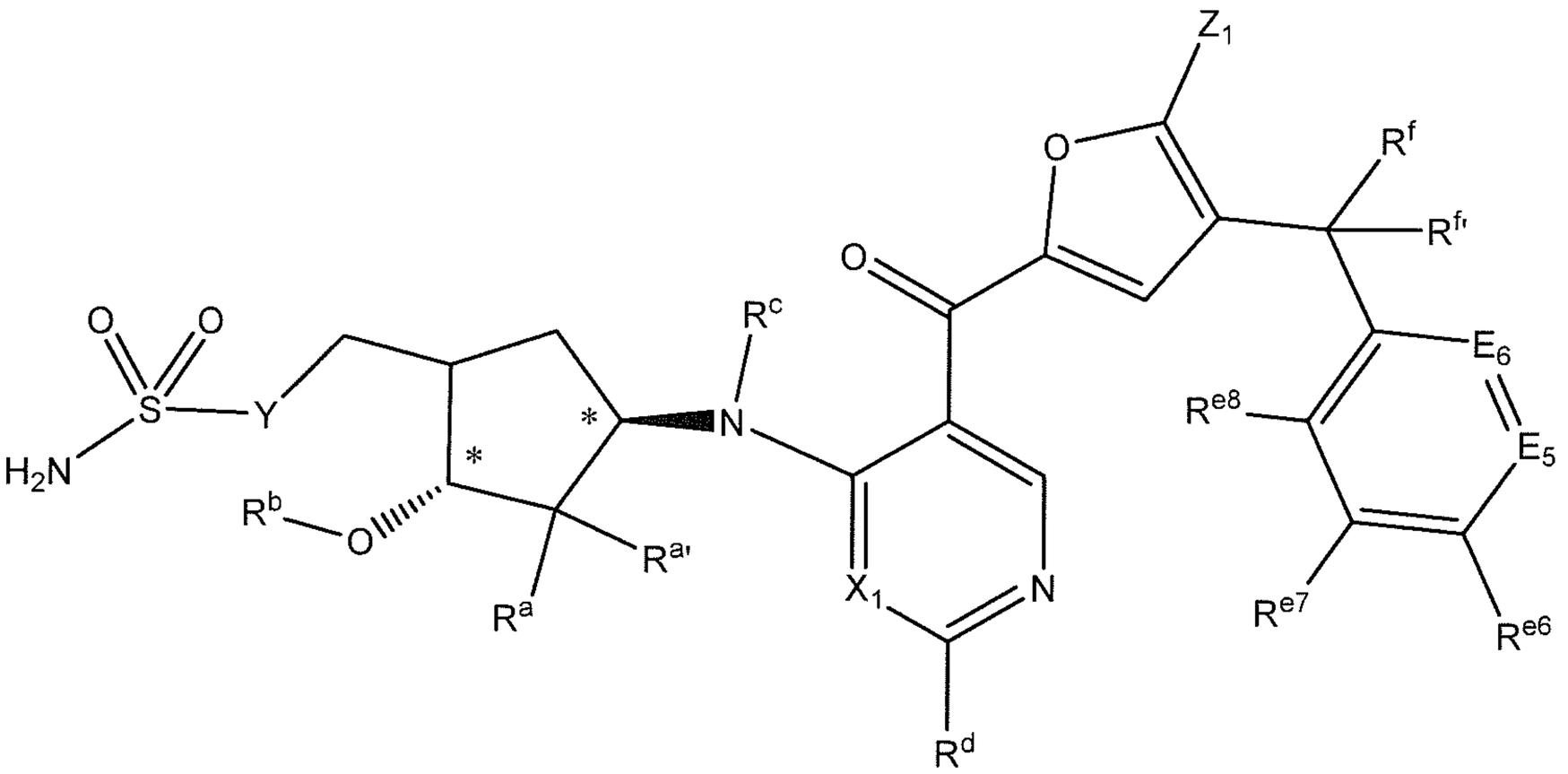
R^{e8} is hydrogen, halogen, methyl, -OCH_3, or cyano;

wherein at least one of R^{e6}, R^{e7}, and R^{e8} is hydrogen.

30. The chemical entity of claim 28 or 29, which is a compound or pharmaceutically acceptable salt of formula (VIIIa) or (VIIIb):



(VIIIa)



(VIIIb).

31. The chemical entity of any one of claims 18 to 20, wherein R^e is hydrogen, hydroxyl, halogen, $-CF_3$, or C_{1-4} alkyl optionally substituted with one or more hydroxyl, halogen, or C_{1-4} alkyl.

32. The chemical entity of any one of claims 1 to 31, wherein:

Z_1 is hydrogen, halogen, cyano, or C_{1-4} aliphatic optionally substituted with one or more hydroxyl, C_{1-4} alkoxy, $-N(R^{z5})_2$, or phenyl optionally substituted with one more independently selected halogens; and

each occurrence of R^{z5} is independently hydrogen or C_{1-4} alkyl.

33. The chemical entity of any one of claims 1 to 32, wherein Z_1 is hydrogen, chloro, or methyl.

34. The chemical entity of claim 5, wherein Z_2 is hydrogen.

35. The chemical entity of any one of claims 1 to 34, wherein R^b is hydrogen.

36. The chemical entity of any one of claims 1 to 34, wherein R^b is $-C(O)-R^{bx}$,

R^{bx} is C_{1-4} alkyl, $-CH(R^{by})-NH_2$, pyrrolidinyl, or $-L_b-OPO_3H_2$,

R^{by} is C_{1-4} alkyl optionally substituted with hydroxyl, phenyl, phenolyl, imidazolyl, carboxyl, amino, guanidino, $-SCH_3$, $-C(O)NH_2$, or indolyl,

L_b is a bivalent linker chosen from C_{1-4} alkylene, $-(CH_2)_{n1}$-phenylene-$(CH_2)_{n2}$- where n1 is 0 or 1 and n2 is 1 or 2.

37. The chemical entity of any one of claims 1 to 36, wherein at least one of the following is true:

Y is -O-;

R^a is hydrogen;

$R^{a'}$ is hydrogen;

R^c is hydrogen;

X_1 is N;

R^d is hydrogen; or

X_3 is C(H).

38. The chemical entity of claim 1, wherein the chemical entity is

[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-bromophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-

4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-(methoxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate
[(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate

[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-

thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(5-bromo-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(S)-(5-chloro-2-furyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(R)-(5-chloro-2-furyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-chloropyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2R,3S,4R)-4-[(5-{[4-(3-bromobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-1-amino-1-(3-bromophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-1-amino-1-(3-bromophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)sulfinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(S)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(R)-(6-chloropyridin-2-yl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
{(1R,2S,4R)-4-[(5-{4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2S)-2-phenyltetrahydrofuran-2-yl]-2-

thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2R)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[4-(3-chlorobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[4-(3-bromobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4-iodo-1H-pyrazol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)pyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4-bromo-1H-pyrazol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2S)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(2R)-tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
{(1R,2S,4R)-4-[(5-{4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-(methoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-methyl-4-(3-methylbenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(5-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(5-chloro-2-fluorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-(3-chlorophenyl)-1,3-dihydroxypropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-(3-chlorophenyl)-1,3-dihydroxypropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(cyclopropyl)hydroxymethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(cyclopropyl)hydroxymethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-bromopyridin-2-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(6-bromopyridin-2-yl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4-chloro-1H-pyrazol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-hydroxy(phenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-hydroxy(phenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[4-(3-methylbenzyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1S)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;
{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1R)-1-hydroxy-1-phenylethyl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-bromobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-methylbenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chloro-4-fluorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-iodobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(5-chloro-2-methoxyphenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(5-chloro-2-methoxyphenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3R,4R)-4-({5-[4-(3-bromobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3R,4R)-3-fluoro-2-hydroxy-4-({5-[5-methyl-4-(3-methylbenzyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(5-chloro-2-furyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(2R)-2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(2S)-2-(3-chlorophenyl)oxetan-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(R)-phenylsulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(S)-phenylsulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(5-methyl-4-{(R)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-({5-[(5-methyl-4-{(S)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-ethynylbenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-chloropyridin-2-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[5-chloro-4-(3-chlorobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4-methyl-1H-pyrazol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2R,3R,4R)-4-({5-[4-(3-chlorobenzyl)-5-methyl-2-furoyl]pyrimidin-4-yl}amino)-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2R,3S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-chloro-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-(3-chlorobenzyl)-5-[(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4-methyl-1H-pyrazol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[4-(3-chlorobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-methoxyphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[3-(methylsulfanyl)benzyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[5-(3-bromobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-chloro-2,3-dihydro-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chloro-2-fluorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-hydroxy(2-methoxyphenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-hydroxy(2-methoxyphenyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(2-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(2-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-(5-benzyl-2-furoyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-benzyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-fluoro-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(methoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(phenoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-pyrrolo[2,3-b]pyridin-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-({5-[5-(3-chlorobenzyl)-2-furoyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)sulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)sulfinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(methylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-benzyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-fluorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2-bromophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2R,3R,4R)-3-fluoro-2-hydroxy-4-[(5-{[4-(3-iodobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[1-(3-chlorophenyl)vinyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2R,3R,4R)-4-[(5-{[4-(3-bromobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-3-fluoro-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(5-chloro-2-thienyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(5-chloro-2-thienyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3,4-dichlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(3-methyl-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-chloro-4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(2-phenylethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-methyl-4-(1H-pyrazol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-(tetrahydro-2H-pyran-4-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-ethylbenzyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-chloro-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[3-(difluoromethoxy)benzyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-indol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2R,3S,4R)-4-({5-[(5-benzyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2R)-2-(cyclohex-1-en-1-yl)tetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-bromo-4-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[5-(trifluoromethyl)-2-furyl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(3-chlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(2S)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(2R)-2-phenyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(5-chloro-4-{(R)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-({5-[(5-chloro-4-{(S)-[3-(trifluoromethyl)phenyl]sulfinyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-methoxybenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2-cyanophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-chloro-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(6-methoxy-2,3-dihydro-1H-indol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-(5-benzyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-cyano-2,3-dihydro-1H-indol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2-chlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[4-(trifluoromethyl)-1H-pyrazol-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-methylphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(6-methyl-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-2,3-dihydroxy-4-{[5-(5-phenyl-2-furoyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-1-(3-chlorophenyl)ethyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxy-2-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxy-2-phenylethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-methyl-4-(phenylsulfanyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-{[(3-chlorophenyl)(methyl)amino]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-(4,5-dibenzyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(cyclohex-1-en-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxy-2-methylprop-2-en-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxy-2-methylprop-2-en-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-(3-chlorobenzyl)-4-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(3-chlorophenyl)sulfanyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4,5-dibenzyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-

hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(5-methyl-4-{[3-(trifluoromethyl)phenyl]sulfanyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[2-(3-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-{[(2-chlorophenyl)sulfanyl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4-bromo-2-cyano-1H-pyrrol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(2,5-dichlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(2,5-dichlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-3-cyclopropyl-1-hydroxyprop-2-yn-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-3-cyclopropyl-1-hydroxyprop-2-yn-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-[(1R)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-[(1S)-1-(3-chlorophenyl)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(dimethylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)tetrahydro-2H-pyran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)tetrahydro-2H-pyran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(2,3-dichlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2-ethoxyphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(4-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2R,3S,4R)-4-({5-[5-(2-chlorophenyl)-2-furoyl]pyrimidin-4-yl}amino)-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(5-chloro-2,3-dihydro-1H-indol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(3-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-iodophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2R,3R,4R)-4-({5-[(4-benzyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4-chlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[1-(3-bromophenyl)vinyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-

hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(2-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2S)-2-cyclohexyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2R)-2-cyclohexyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3,4-dihydroisoquinolin-2(1H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(6-cyano-1H-indol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(3-methyl-1H-pyrrol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-ylmethyl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-cyclohexyl(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-cyclohexyl(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3,6-dihydro-2H-thiopyran-4-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-hydroxy(tetrahydro-2H-pyran-4-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-hydroxy(tetrahydro-2H-pyran-4-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(3-chlorophenyl)sulfanyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[2-(trifluoromethoxy)phenoxy]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(phenylsulfanyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[2-(4-chlorophenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-cyano-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2,3-dichlorophenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(3-chlorophenyl)sulfonyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2-ethylphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[2-(2-methoxyphenyl)ethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[6-(trifluoromethyl)-1H-indol-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-cyanobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-pyrrolo[2,3-c]pyridin-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(1,3-dihydro-2H-isoindol-2-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[2-(trifluoromethyl)phenoxy]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(5-chloro-4-{[3-(trifluoromethyl)phenyl]sulfanyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-isopropylphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(1H-benzimidazol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(2,5-dihydrofuran-3-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(3-cyano-1H-pyrrol-1-yl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxy-2-methylpropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxy-2-methylpropyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3,6-dihydro-2H-pyran-4-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1S)-1-hydroxy-2-methylprop-2-en-1-yl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;
{(1R,2S,4R)-2-hydroxy-4-[(5-{4-[(1R)-1-hydroxy-2-methylprop-2-en-1-yl]-2-furoyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(cyclohexylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(phenylsulfonyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(2-isopropoxyphenoxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

{(1R,2R,3S,4R)-2,3-dihydroxy-4-[(5-{[5-(2-hydroxypropan-2-yl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(3-chlorophenyl)sulfonyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3,6-dihydropyridin-1(2H)-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2R,3R,4R)-4-[(5-{[5-(3-chlorobenzyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-3-fluoro-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[5-(hydroxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-chloro-4-(3-chlorobenzoyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-

hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-(4-benzoyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[(2S)-2-(3-chlorophenyl)-2,3,4,5-tetrahydro-2,3'-bithiophen-5'-yl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
{(1R,2S,4R)-4-[(5-{[(2R)-2-(3-chlorophenyl)-2,3,4,5-tetrahydro-2,3'-bithiophen-5'-yl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(5-chloropyridin-3-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-chloro-4-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[5-(methoxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-benzoyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[4-(hydroxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(methoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-chloro-4-(methoxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(2,5-dihydro-1H-pyrrol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[4-(2-hydroxypropan-2-yl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-({3-[(dimethylamino)methyl]-1H-indol-1-yl}methyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(benzylamino)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[4-(methoxymethyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(3,3-difluoropiperidin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[(3R)-3-methylpiperidin-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-({5-[(4-{[(3S)-3-methylpiperidin-1-yl]methyl}-2-thienyl)carbonyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1-hydroxyethyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2S)-2-(3-chlorophenyl)-1-methylpyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2R)-2-(3-chlorophenyl)-1-methylpyrrolidin-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-acetyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(hydroxymethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(1H-imidazol-1-ylmethyl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[5-(3-chlorobenzyl)-3-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-(4-acetyl-2-furoyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[5-(2-hydroxypropan-2-yl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2R,3S,4R)-4-{[2-chloro-5-(5-phenyl-2-furoyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(5-methyl-2-furyl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(2S)-2-cyclopropyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(2R)-2-cyclopropyltetrahydrofuran-2-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-({5-[5-(phenylsulfonyl)-2-furoyl]pyrimidin-4-yl}amino)cyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(2-hydroxypropan-2-yl)-2-thienyl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4-phenylpiperazin-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-acetyl-5-chloro-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4-bromo-1H-imidazol-1-yl)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,5-difluoro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(7S)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(7R)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
{(1R,2S,4R)-4-[(5-{4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2R,3R,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
{(1R,2S,4R)-4-[(5-{4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4S)-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(4R)-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4R)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(4S)-4H-1,3-benzodioxin-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'R)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1'S)-1'H-spiro[cyclopropane-1,4'-isochromen]-1'-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(8S)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(8R)-2-chloro-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6,7-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-methyl-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-4,4-difluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-fluoro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-2,3-dihydroxy-4-{[5-({4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-2,3-dihydroxy-4-{[5-({4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-3-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-3-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(trifluoromethyl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(4R)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(4S)-2-chloro-6,7-dihydro-4H-furo[3,2-c]pyran-4-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
{(1R,2S,4R)-4-[(5-{5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1S)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
[(1R,2R,3S,4R)-4-{[5-({5-chloro-4-[(1R)-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-8-fluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-8-fluoro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-methyl-6,7-dihydro-4H-pyrano[4,3-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-methyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyano-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyano-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4S)-2-(trifluoromethyl)-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(4R)-2-(trifluoromethyl)-6,7-dihydro-4H-pyrano[3,4-d][1,3]thiazol-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-2,3,4,5-tetrahydro-1H-2-benzazepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isothiochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-5-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-5-chloro-2-methyl-2,3-dihydro-1H-isoindol-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-pyrano[4,3-c]pyridin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-cyano-4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-cyano-4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-[(1R)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-[(1S)-5-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-6-chloro-3-oxo-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-6-chloro-3-oxo-1,3-dihydro-2-benzofuran-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-({5-[(4-{(1R)-7-[(dimethylamino)methyl]-3,4-dihydro-1H-isochromen-1-yl}-5-methyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-({5-[(4-{(1S)-7-[(dimethylamino)methyl]-3,4-dihydro-1H-isochromen-1-yl}-5-methyl-2-thienyl)carbonyl]pyrimidin-4-yl}amino)-2-hydroxycyclopentyl]methyl sulfamate;

(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl aminoacetate

[(1R,2S,4R)-4-{[5-({4-[(5R)-8,8-difluoro-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(5S)-8,8-difluoro-7,8-dihydro-5H-pyrano[4,3-b]pyridin-5-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4S)-2-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4R)-2-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4S)-3-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(4R)-3-methyl-6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-4-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

tert-butyl (1R)-7-chloro-1-(5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
tert-butyl (1S)-7-chloro-1-(5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

tert-butyl (1R)-7-chloro-1-(2-chloro-5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate
tert-butyl (1S)-7-chloro-1-(2-chloro-5-{[4-({(1R,3S,4R)-3-hydroxy-4-[(sulfamoyloxy)methyl]cyclopentyl}amino)pyrimidin-5-yl]carbonyl}-3-thienyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(trifluoromethyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(trifluoromethyl)-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl (2S)-2-amino-3-methylbutanoate

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8S)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(8R)-2-methoxy-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-7-methoxy-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-

2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-7-methoxy-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1R)-4-oxo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({4-[(1S)-4-oxo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({5-[(1R)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({5-[(1S)-8-chloro-1,3,4,5-tetrahydro-2-benzoxepin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazol-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazol-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl 3-[(phosphonooxy)methyl]benzoate

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-methyl-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8R)-2-(pyrrolidin-1-yl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(8S)-2-(pyrrolidin-1-yl)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-2,3-dihydro-1H-inden-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2R,3S,4R)-4-({5-[(5-benzyl-1,3-thiazol-2-yl)carbonyl]pyrimidin-4-yl}amino)-2,3-dihydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-2-hydroxy-4-[(5-{[4-(3-methylbenzyl)-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]cyclopentyl}methyl sulfamate;

{(1R,2R,3S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-methyl-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(3-chlorobenzyl)-5-methyl-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

{(1R,2R,3S,4R)-4-[(5-{[4-(3-bromobenzyl)-5-methyl-1,3-thiazol-2-yl]carbonyl}pyrimidin-4-yl)amino]-2,3-dihydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-5-methyl-1,3-thiazol-2-yl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

or a pharmaceutically acceptable salt thereof.

39. The chemical entity of claim 1, wherein the chemical entity is

[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(8R)-2,3-dimethyl-5,6-dihydro-8H-imidazo[2,1-c][1,4]oxazin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-6-chloro-1,3-dihydro-2-benzothiophen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

{(1R,2S,4R)-4-[(5-{[4-(7-chloro-3,4-dihydroisoquinolin-1-yl)-5-methyl-2-thienyl]carbonyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(difluoromethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(difluoromethyl)-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl (2S)-2-aminopropanoate;

(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl (2S,3S)-2-amino-3-methylpentanoate;

(1S,2R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-[(sulfamoyloxy)methyl]cyclopentyl [4-(phosphonooxy)phenyl]acetate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-8-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-8-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl](methyl)amino}-2-hydroxycyclopentyl]methyl sulfamate;
[(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-(hydroxymethyl)-2-thienyl}carbonyl)pyrimidin-4-yl](methyl)amino}-2-hydroxycyclopentyl]methyl sulfamate;

or a pharmaceutically acceptable salt thereof.

40. A pharmaceutical composition comprising the chemical entity of any one of claims 1 to 38 and a pharmaceutically acceptable carrier.

41. A method of treating cancer in a subject, comprising administering to a subject having cancer a therapeutically effective amount of the chemical entity of any one of claims 1 to 38.

42. The chemical entity of any one of claims 1 to 38, for use in treating cancer.

43. Use of the chemical entity of any of claims 1 to 38 for the treatment of cancer.

44. Use of the chemical entity of any of claims 1 to 38 in the manufacture of a medicament for the treatment of cancer.

45. A pharmaceutical composition for the treatment of cancer in a patient in need thereof, comprising the chemical entity of any of claims 1 to 38 and a pharmaceutically acceptable carrier.

46. A pharmaceutical composition comprising the chemical entity of claim 39 and a pharmaceutically acceptable carrier.

47. A method of treating cancer in a subject, comprising administering to a subject having cancer a therapeutically effective amount of the chemical entity of claim 39.

48. The chemical entity of claim 39, for use in treating cancer.

49. Use of the chemical entity of claim 39 for the treatment of cancer.

50. Use of the chemical entity of claim 39 in the manufacture of a medicament for the treatment of cancer.

51. A pharmaceutical composition for the treatment of cancer in a patient in need thereof, comprising the chemical entity of claim 39 and a pharmaceutically acceptable carrier.

52. A chemical entity which is

I-16a	[(1R,2S,4R)-4-{[5-({4-[(S)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(R)-(3-bromophenyl)(hydroxy)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-18b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(6-bromopyridin-2-yl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-22b	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-248a	[(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-24a	[(1R,2R,3S,4R)-4-{[5-({4-[(R)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(S)-amino(3-bromophenyl)methyl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
I-251a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-252b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-ethynyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-253a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-2-chloro-5,6,7,8-tetrahydro-1,7-naphthyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-254b	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-2-

	thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-255b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-256b	[(1R,2S,4R)-4-{[5-({4-[(1R)-3,4-Dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-257b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-Chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-258a	[(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1R)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate or [(1R,2S,4R)-2-hydroxy-4-{[5-({5-methyl-4-[(1S)-7-(trifluoromethyl)-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}cyclopentyl]methyl sulfamate;
I-259a	[(1R,2R,3S,4R)-4-{[5-({4-[(1R)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate or [(1R,2R,3S,4R)-4-{[5-({4-[(1S)-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-chloro-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2,3-dihydroxycyclopentyl]methyl sulfamate;
I-261b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-263a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-chloro-1,2,3,4-tetrahydroisoquinolin-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-264b	[(1R,2R,3R,4R)-4-{[5-({4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2R,3R,4R)-4-{[5-({4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;
I-266b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-268b	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-bromo-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-269a	[(1R,2S,4R)-4-{[5-({4-[(7S)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(7R)-4,7-dihydro-5H-thieno[2,3-c]pyran-7-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl

	sulfamate;
I-270b	{(1R,2S,4R)-4-[(5-{4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate or {(1R,2S,4R)-4-[(5-{4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-furoyl}pyrimidin-4-yl)amino]-2-hydroxycyclopentyl}methyl sulfamate;
I-271a	[(1R,2R,3R,4R)-4-{[5-({4-[(1R)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2R,3R,4R)-4-{[5-({4-[(1S)-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-3-fluoro-2-hydroxycyclopentyl]methyl sulfamate;
I-277a	[(1R,2S,4R)-4-{[5-({4-[(1R)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(1S)-7-cyclopropyl-3,4-dihydro-1H-isochromen-1-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-282b	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(1R)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(1S)-7-chloro-3,4-dihydro-1H-isochromen-1-yl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-285a	[(1R,2S,4R)-4-{[5-({4-[(8S)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(8R)-5,8-dihydro-6H-pyrano[3,4-b]pyridin-8-yl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-6a	[(1R,2S,4R)-4-{[5-({4-[(R)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({4-[(S)-amino(3-chlorophenyl)methyl]-5-methyl-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;
I-9a	[(1R,2S,4R)-4-{[5-({5-chloro-4-[(R)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate or [(1R,2S,4R)-4-{[5-({5-chloro-4-[(S)-(3-chlorophenyl)(hydroxy)methyl]-2-thienyl}carbonyl)pyrimidin-4-yl]amino}-2-hydroxycyclopentyl]methyl sulfamate;

or a pharmaceutically acceptable salt thereof.

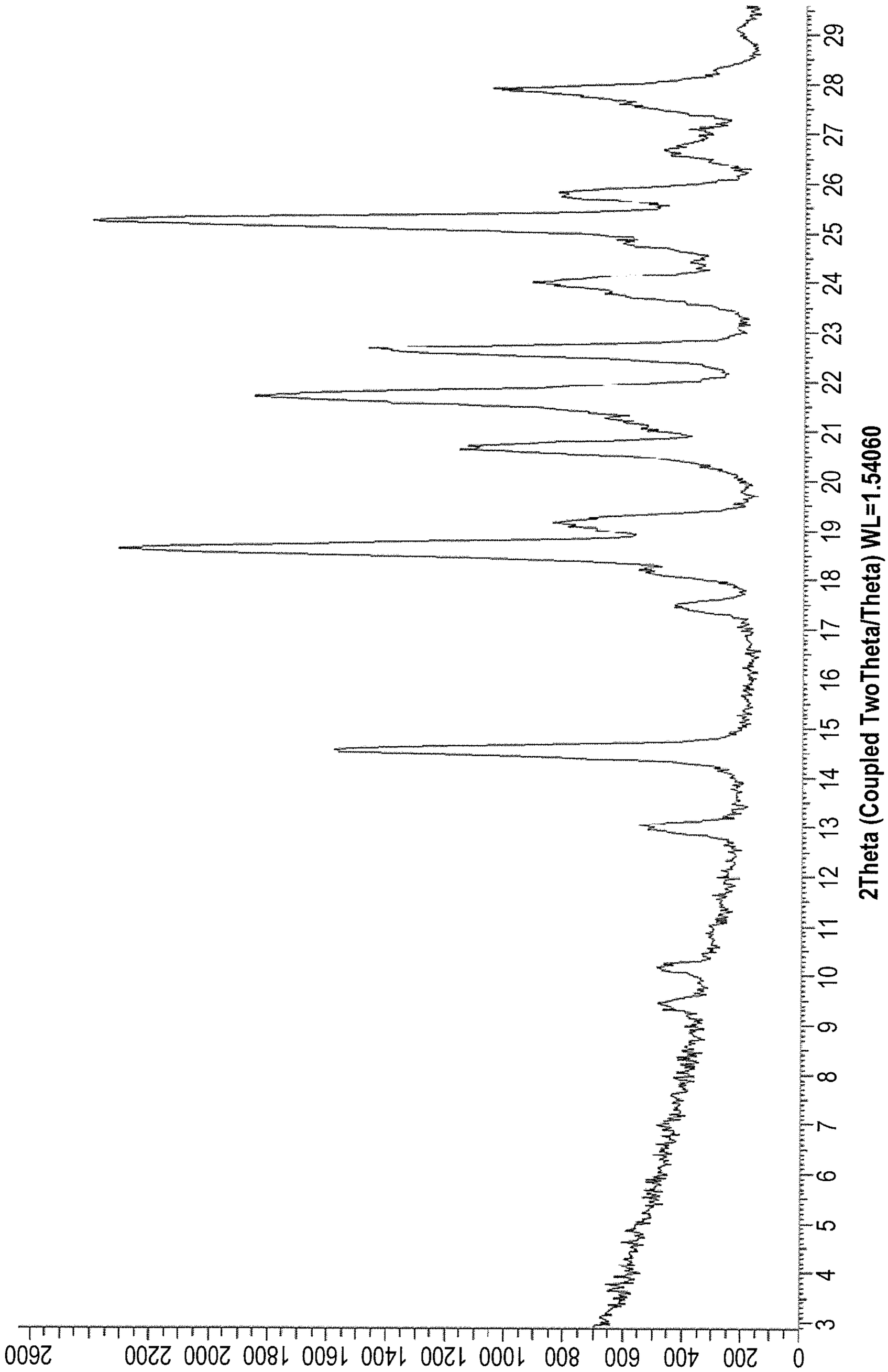

Counts
2600
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
2Theta (Coupled TwoTheta/Theta) WL=1.54060
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

FIG. 1

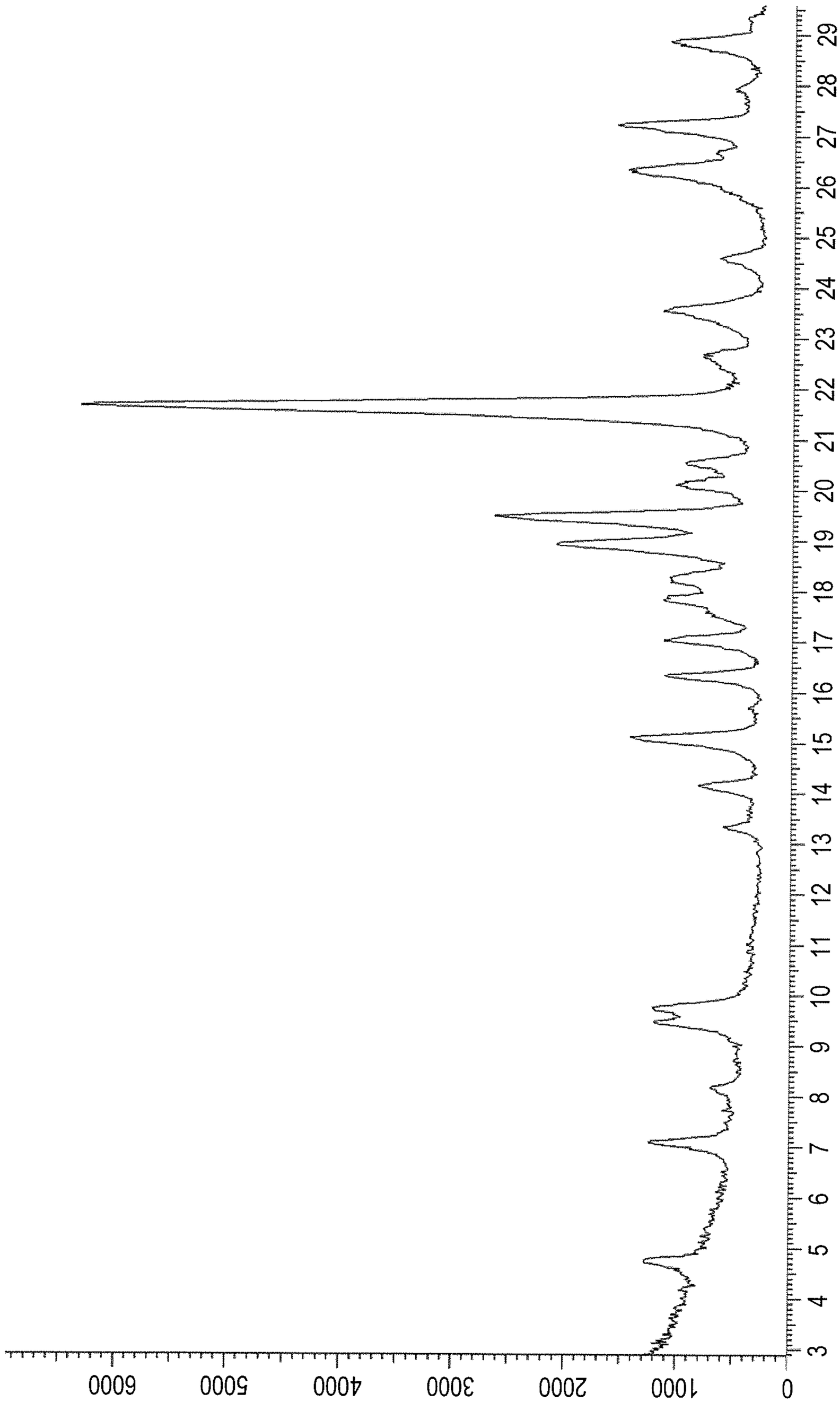

Counts
0
1000
2000
3000
4000
5000
6000
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
2Theta (Coupled TwoTheta/Theta) WL=1.54060

FIG. 2

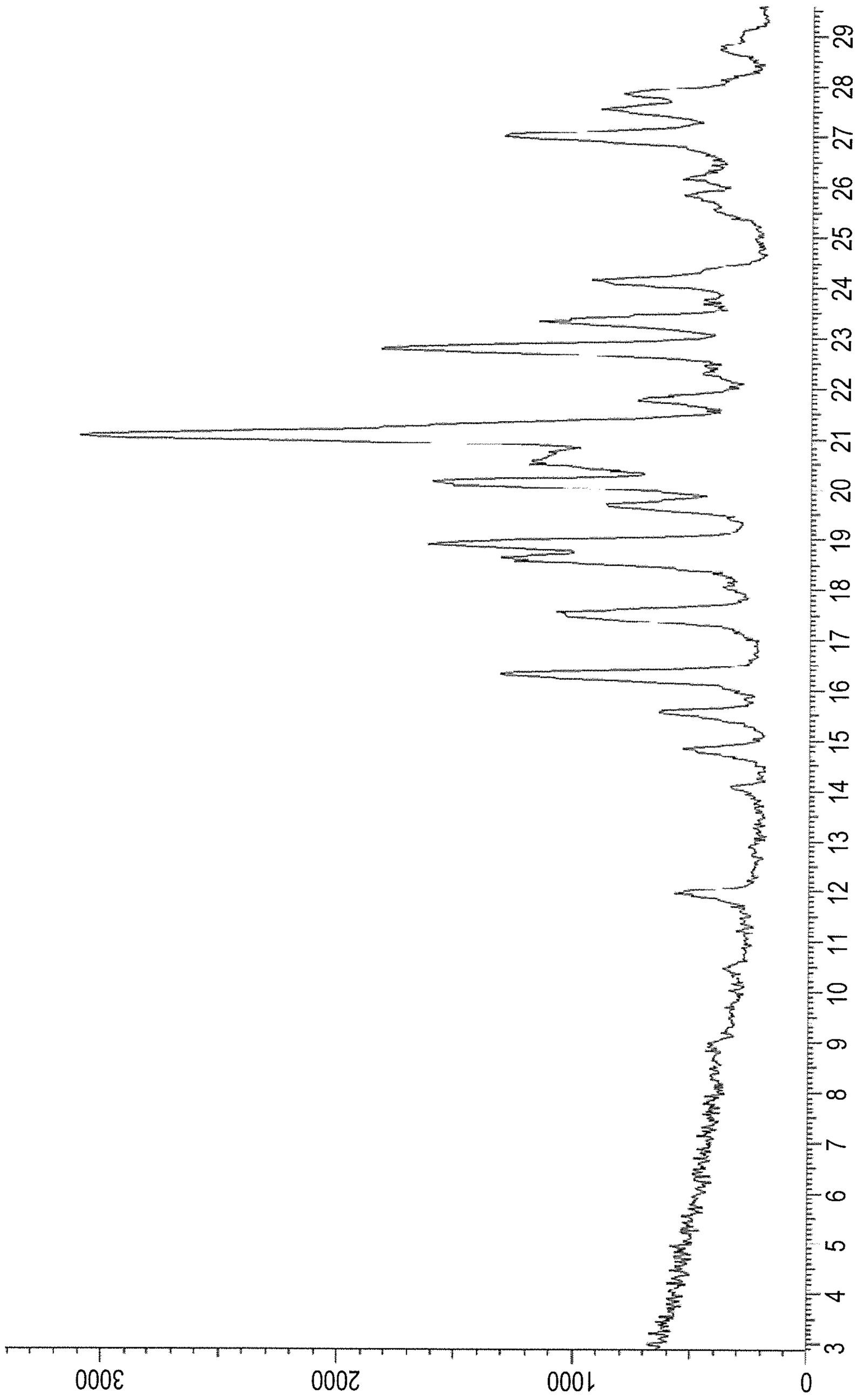

Counts
3000
2000
1000
0
2Theta (Coupled TwoTheta/Theta) WL=1.54060
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

FIG. 3

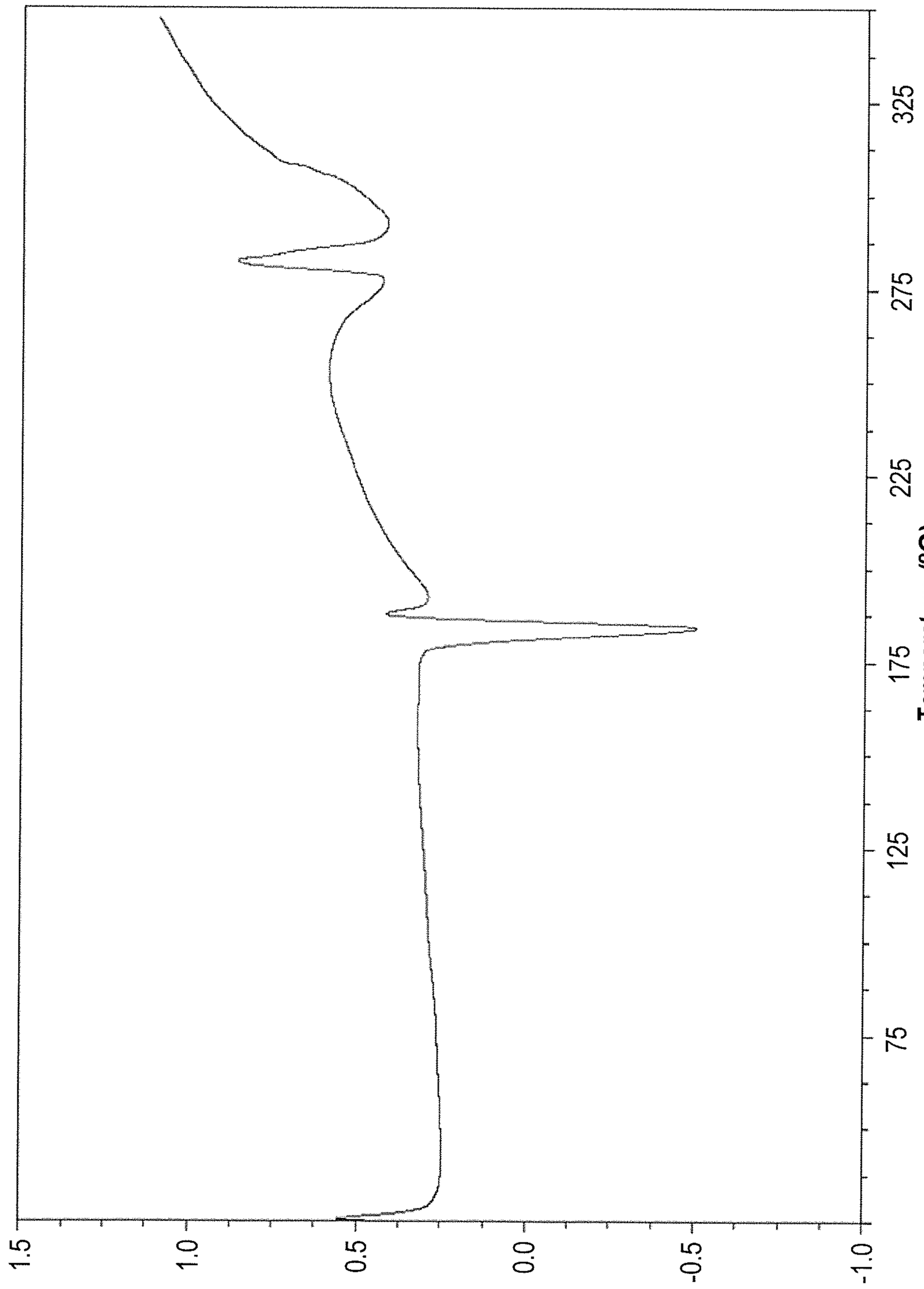

Heat Flow (W/g)
1.5
1.0
0.5
0.0
-0.5
-1.0
Temperature (°C)
75
125
175
225
275
325

FIG. 4

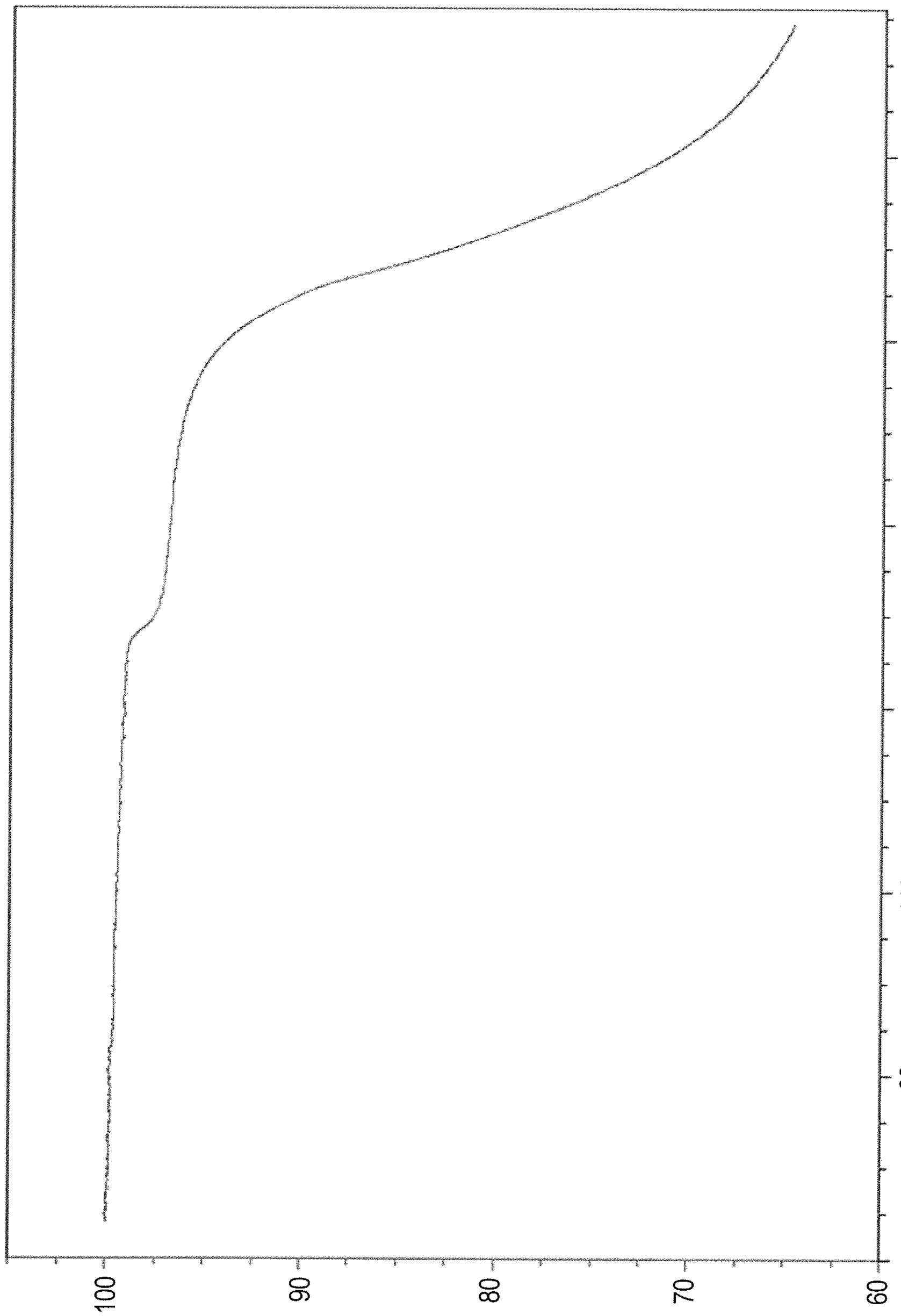


FIG. 5

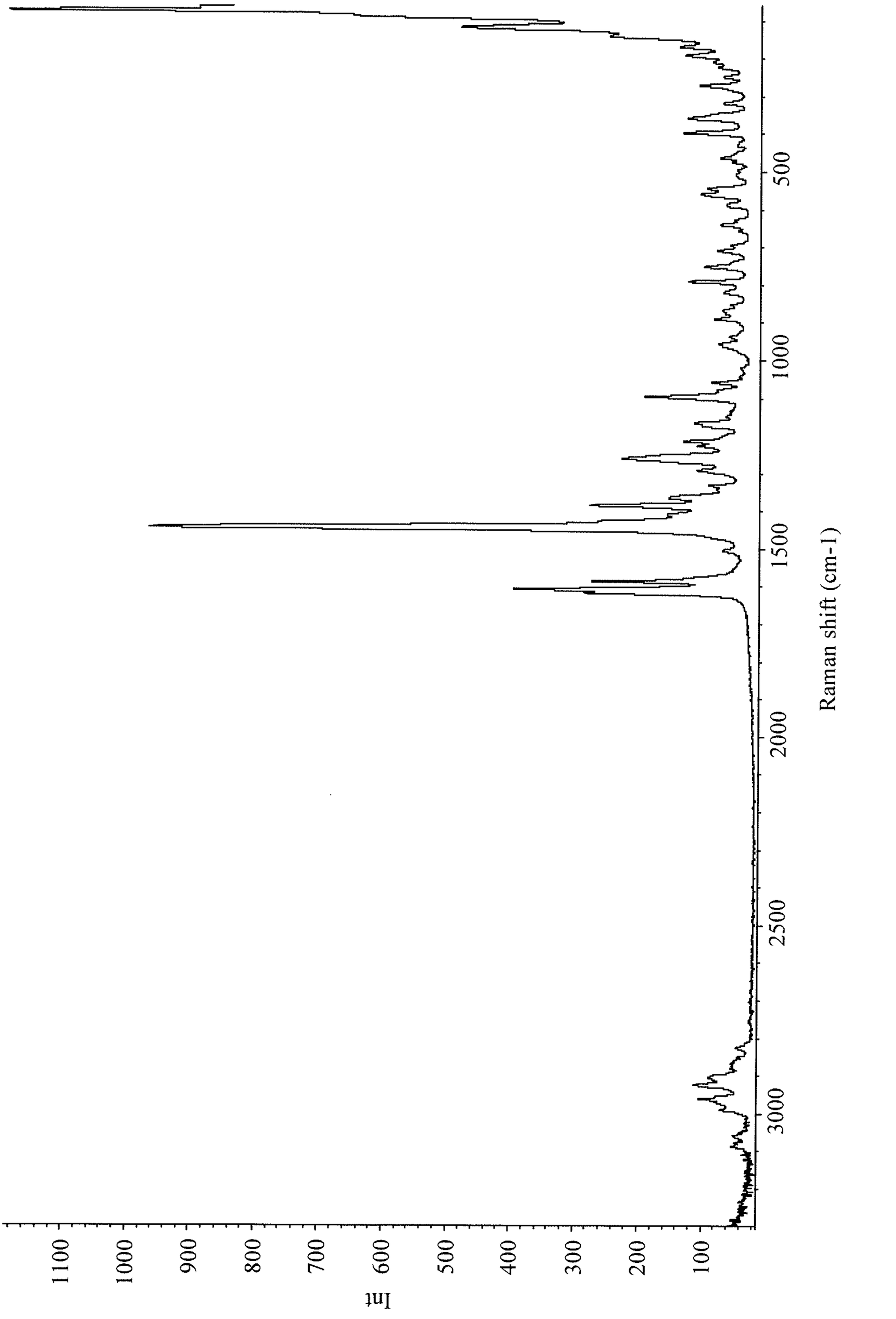

Raman shift (cm-1)
Int
500
1000
1500
2000
2500
3000
100
200
300
400
500
600
700
800
900
1000
1100

FIG. 6

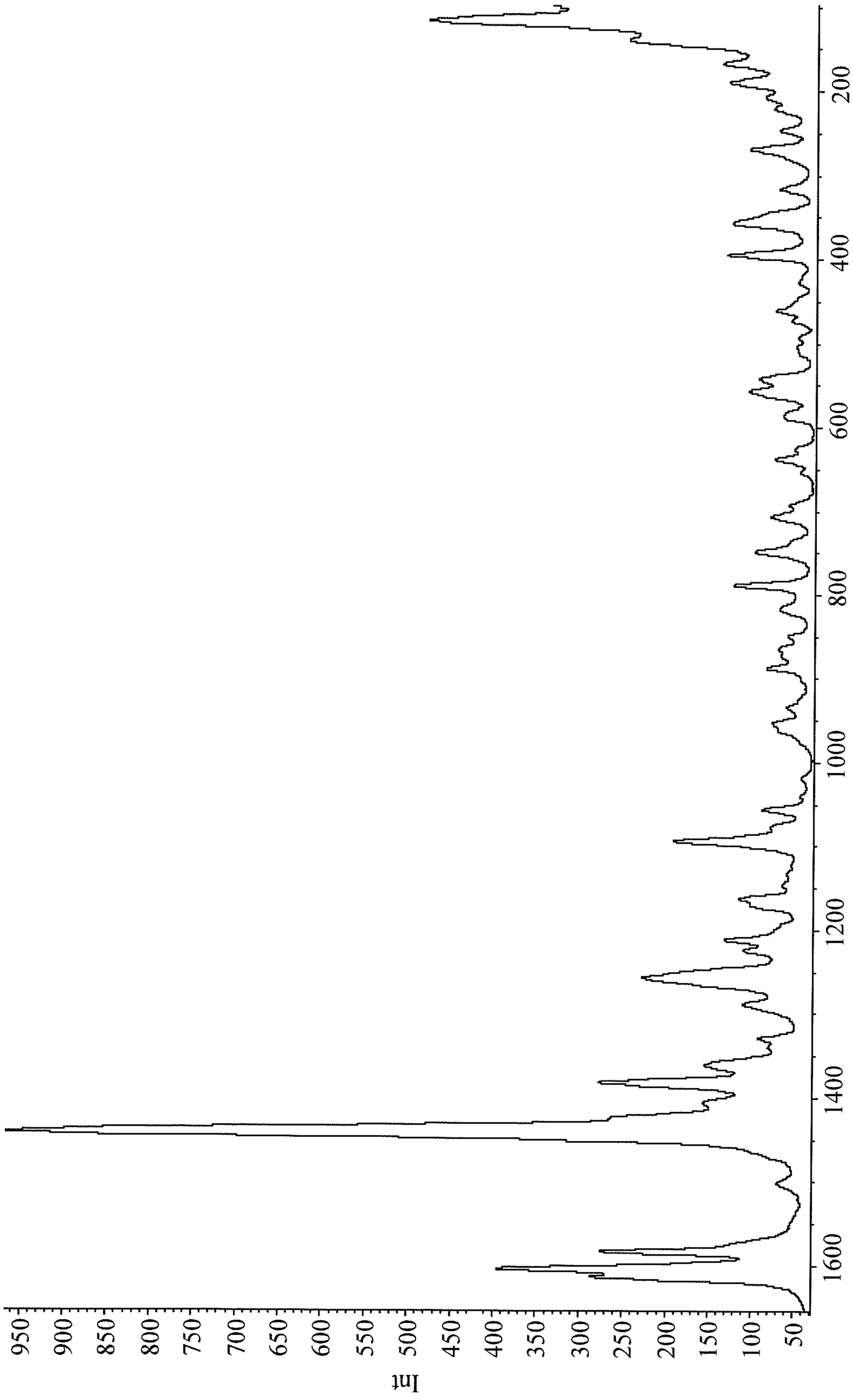

Int
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
1600
1400
1200
1000
800
600
400
200
Raman shift (cm-1)

FIG. 7

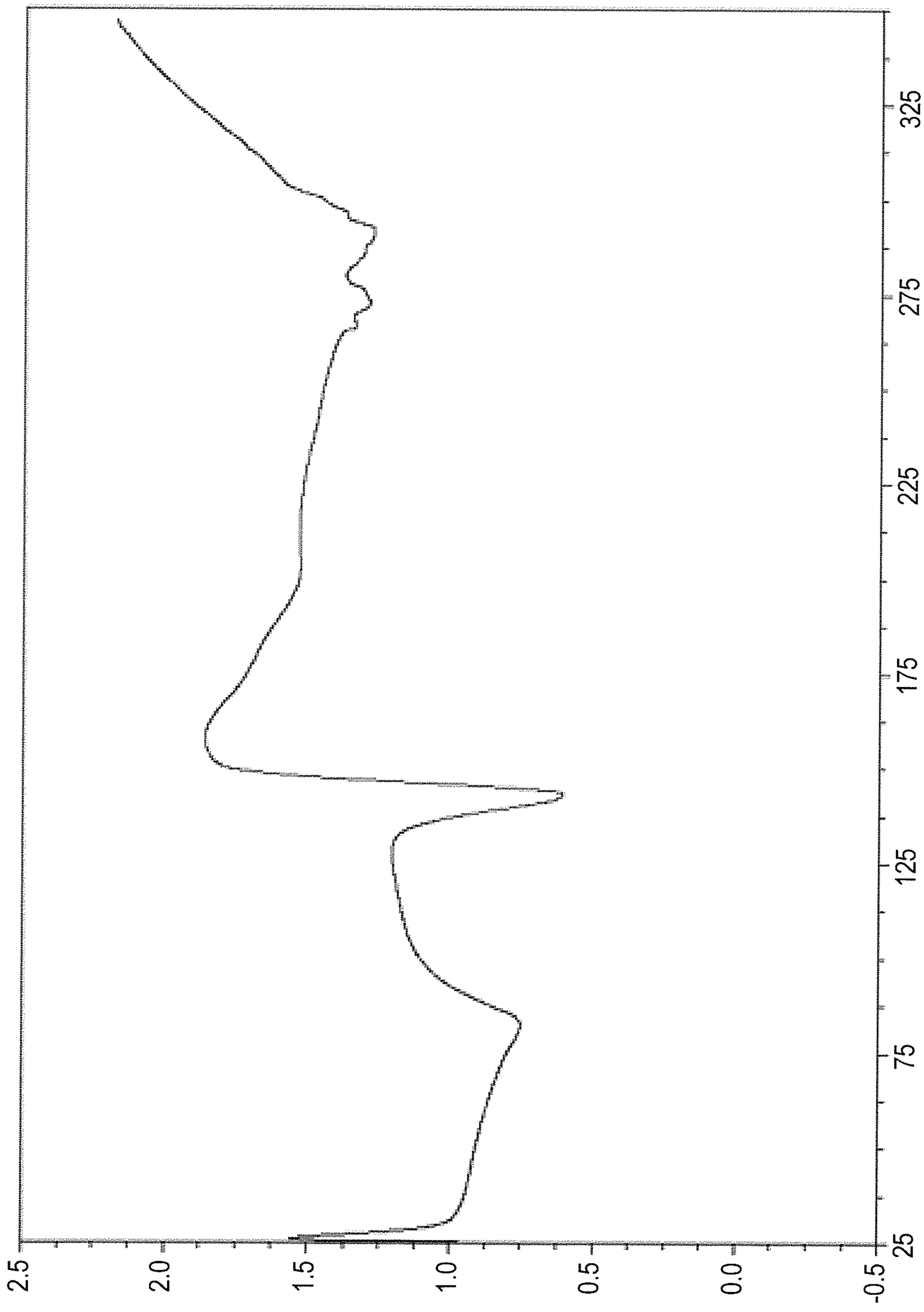

Heat Flow (W/g)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Temperature (°C)
25
75
125
175
225
275
325

FIG. 8

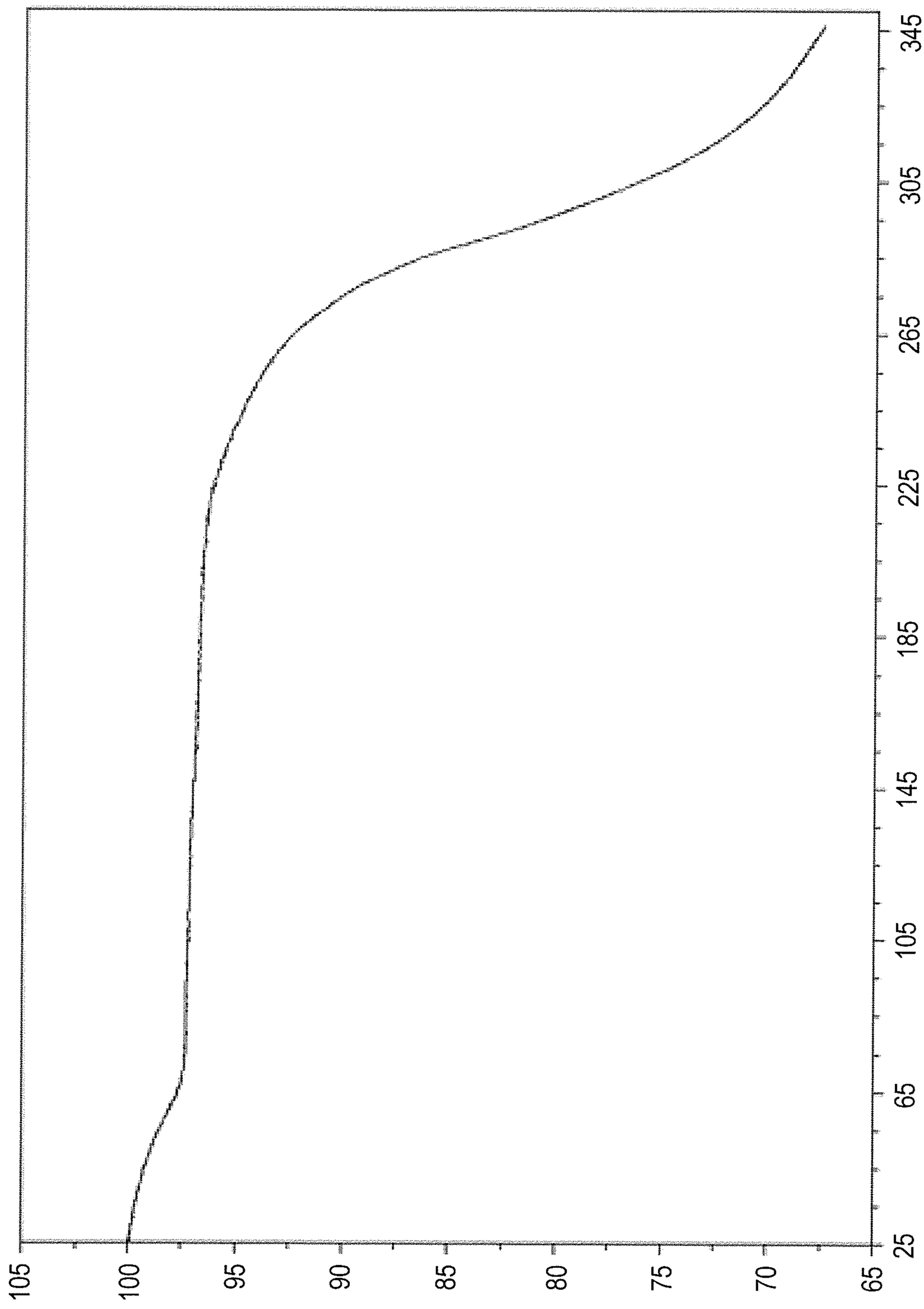

Weight (%)
105
100
95
90
85
80
75
70
65
Temperature (°C)
25
65
105
145
185
225
265
305
345

FIG. 9

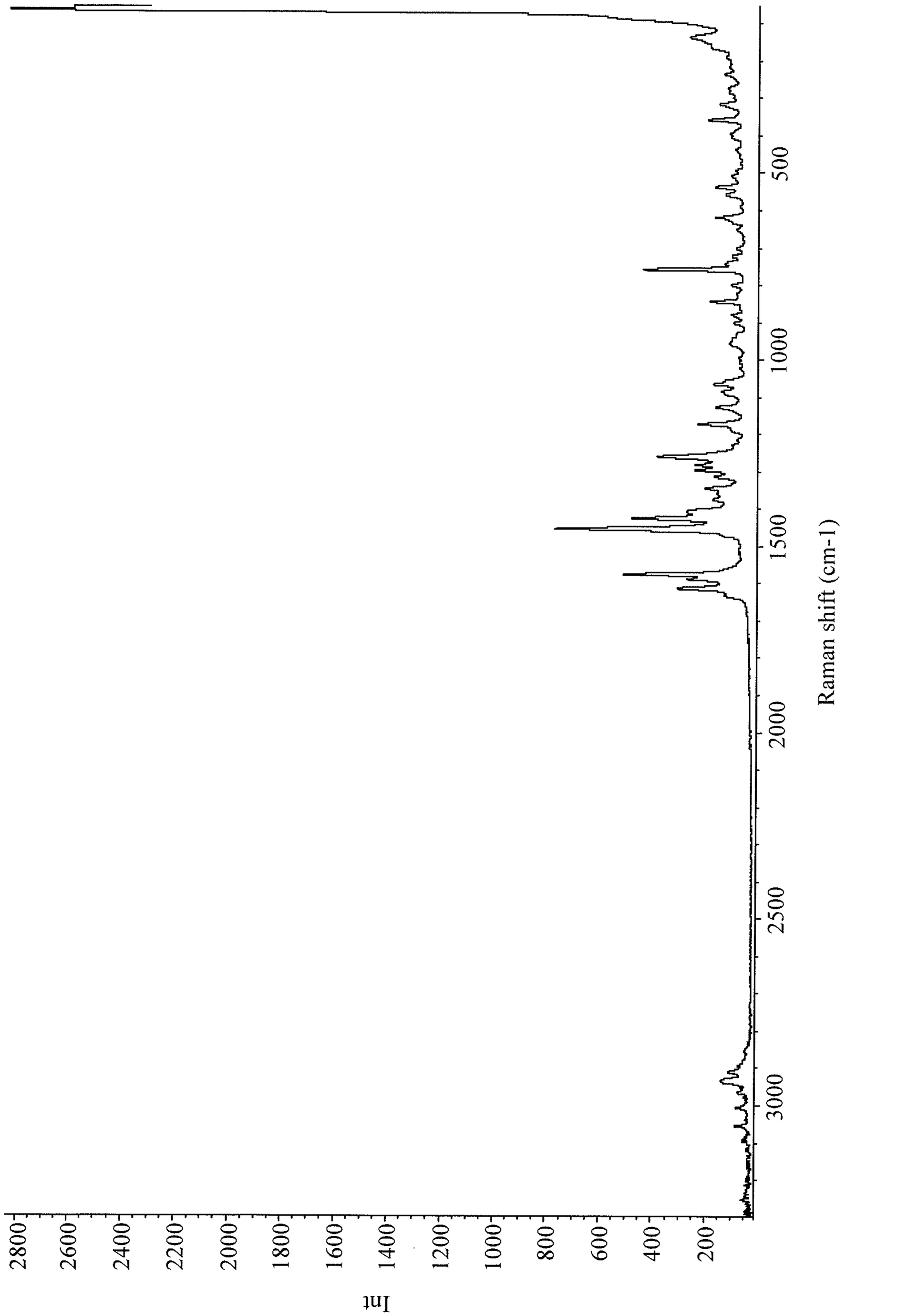

Int
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
Raman shift (cm-1)
3000
2500
2000
1500
1000
500

FIG. 10

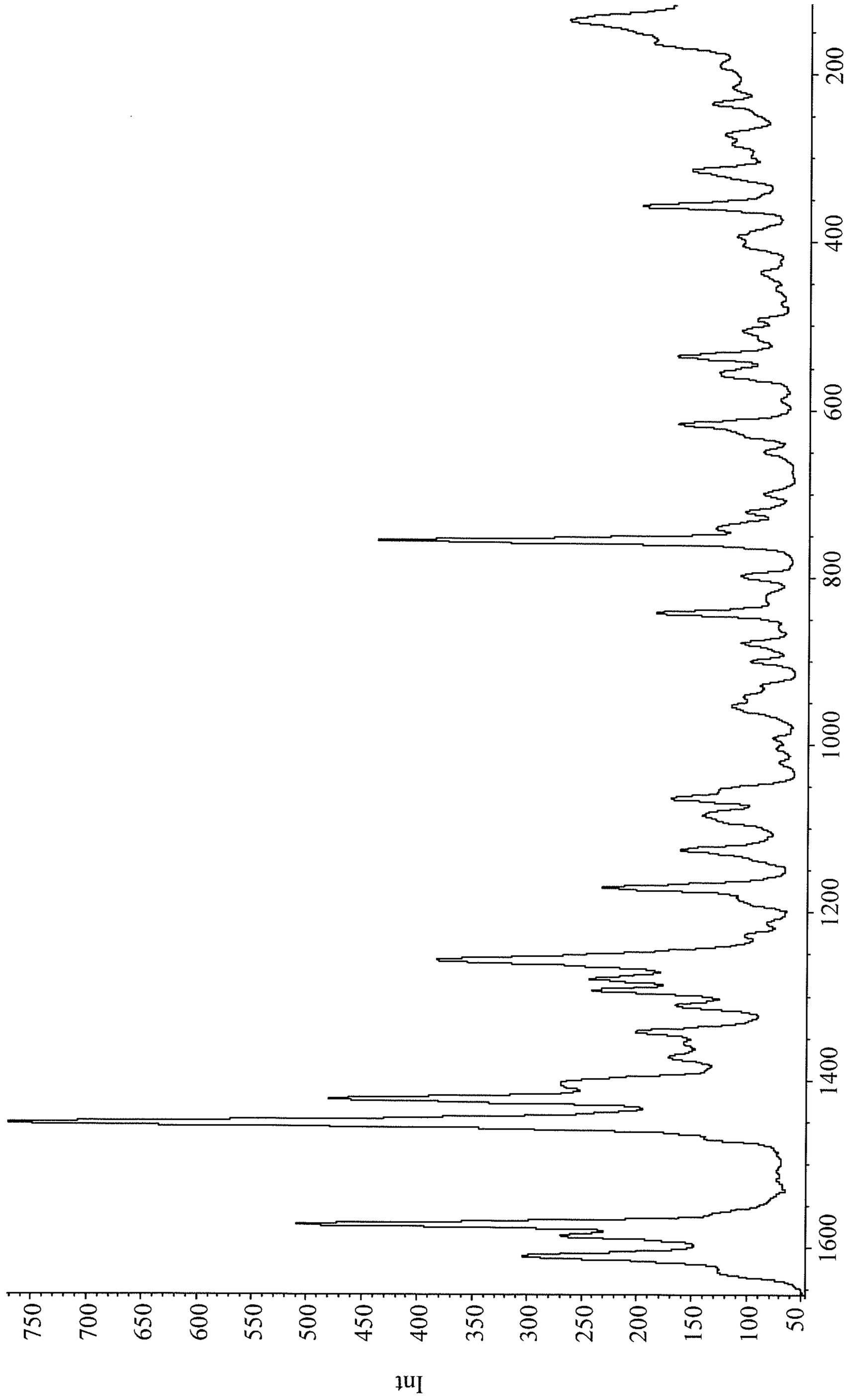

Raman shift (cm-1)
200
400
600
800
1000
1200
1400
1600
Int
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50

FIG. 11

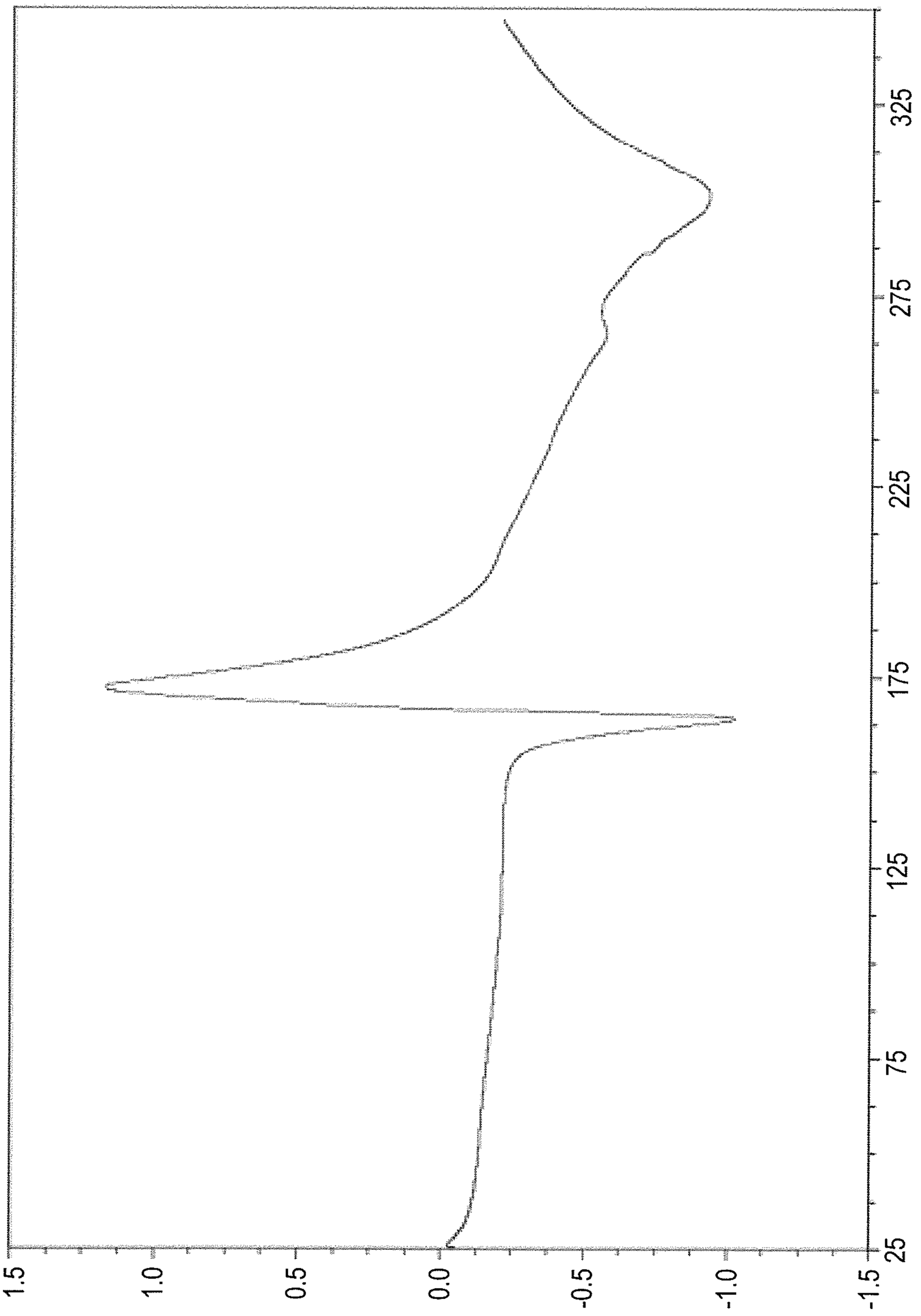

Heat Flow (W/g)
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
Temperature (°C)
25
75
125
175
225
275
325

FIG. 12

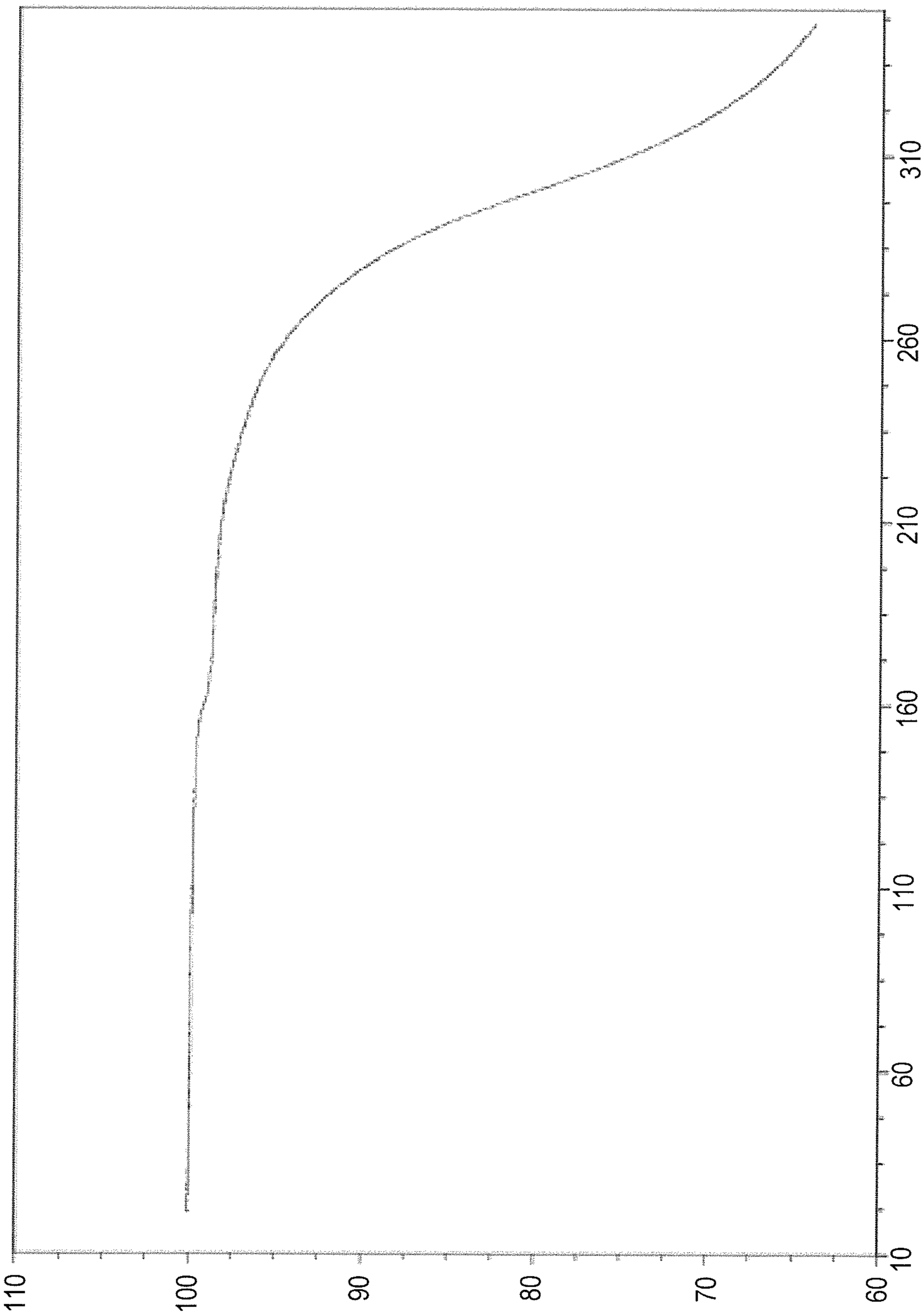

Weight (%)
110
100
90
80
70
60
Temperature (°C)
10
60
110
160
210
260
310

FIG. 13

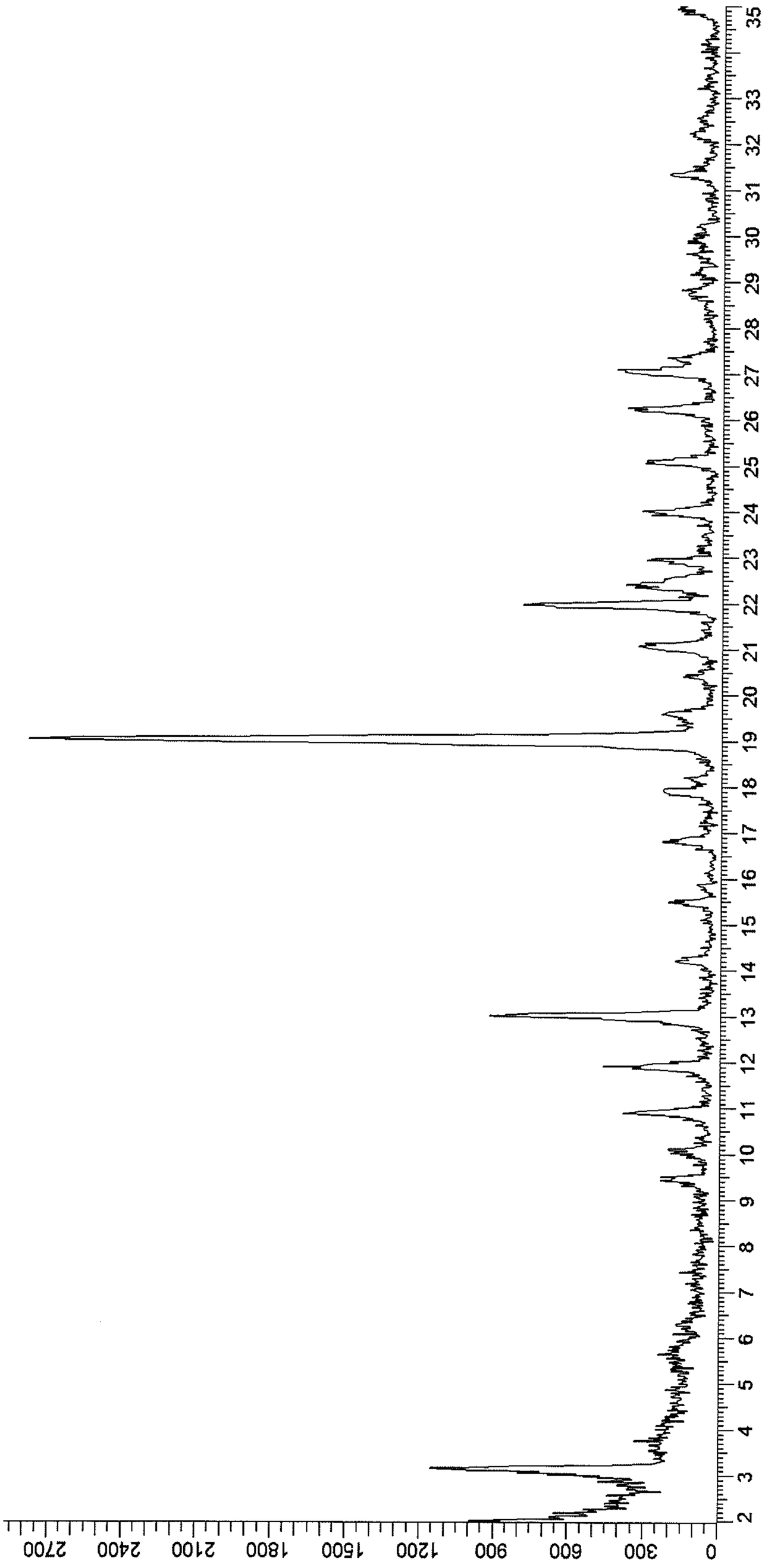


FIG. 14

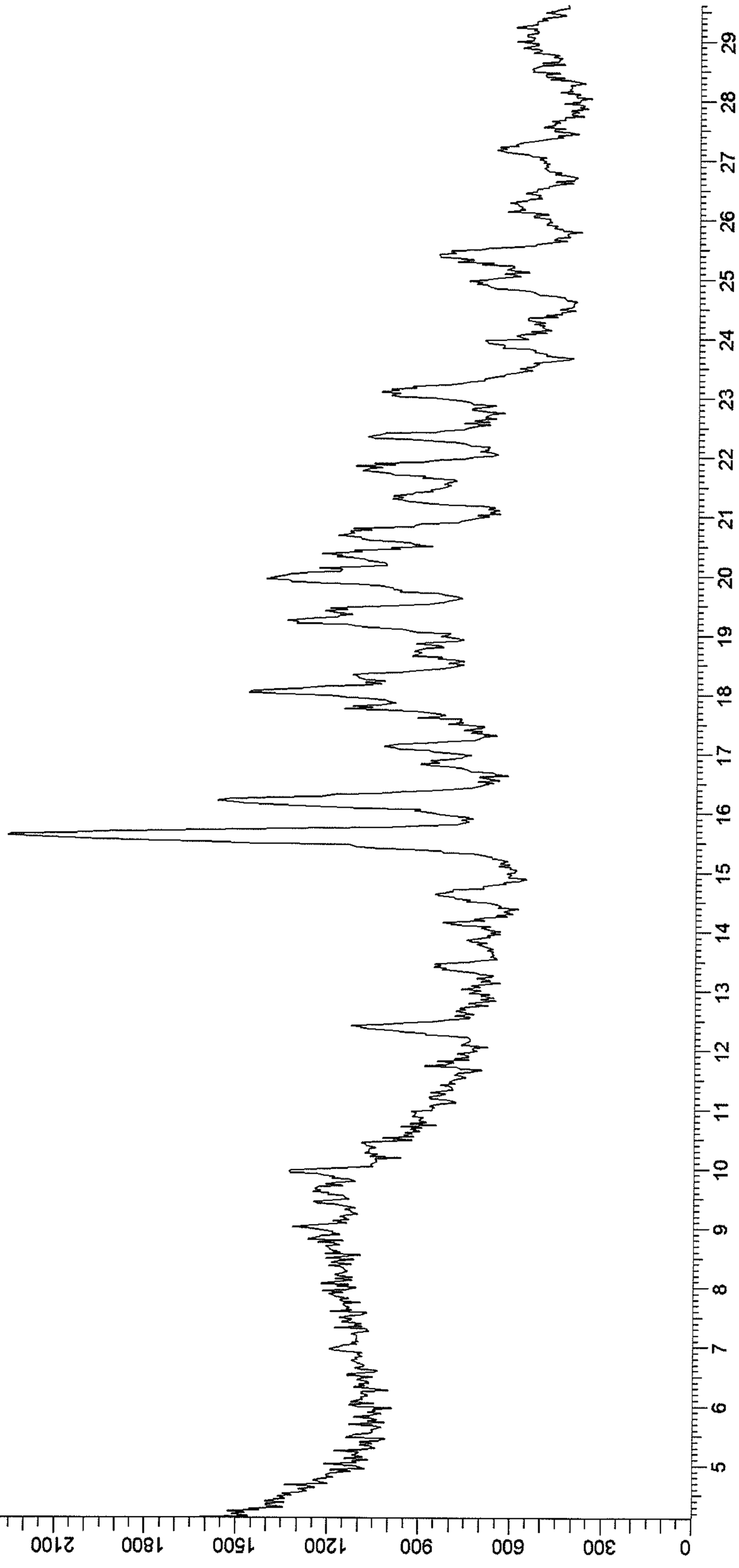

Counts
0
300
600
900
1200
1500
1800
2100
2Theta (Coupled TwoTheta/Theta) WL=1.54060
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29

FIG. 15

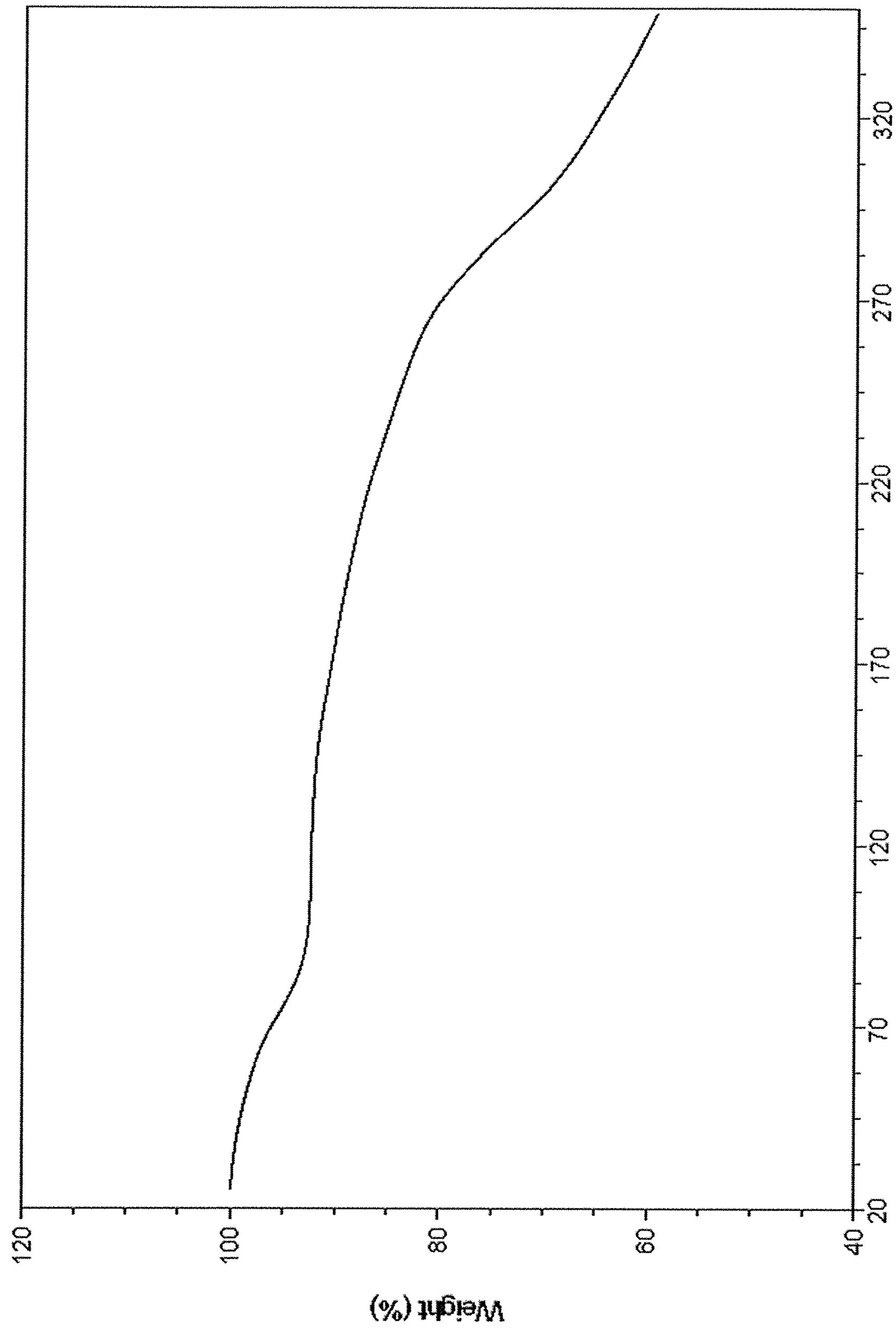


FIG. 16

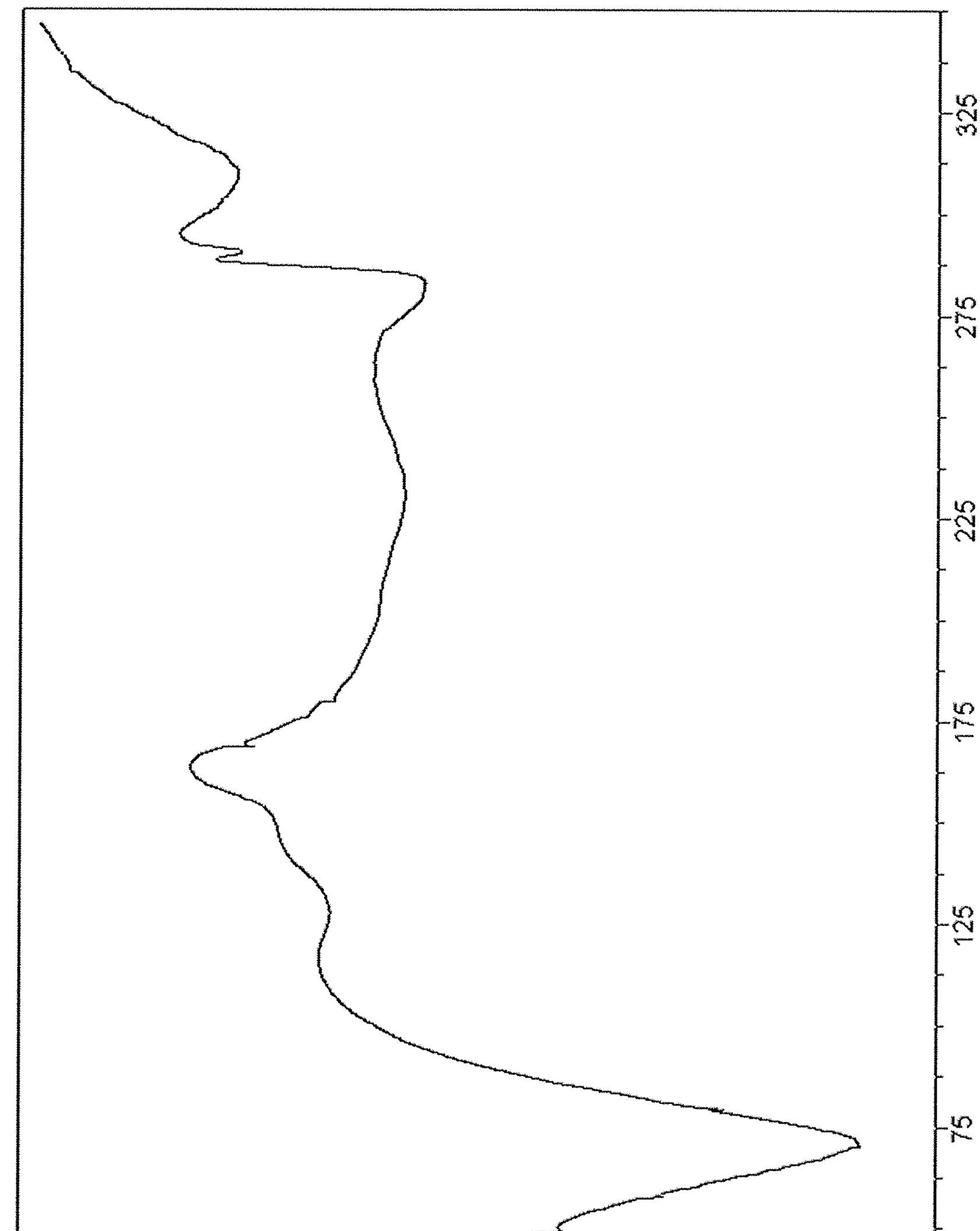
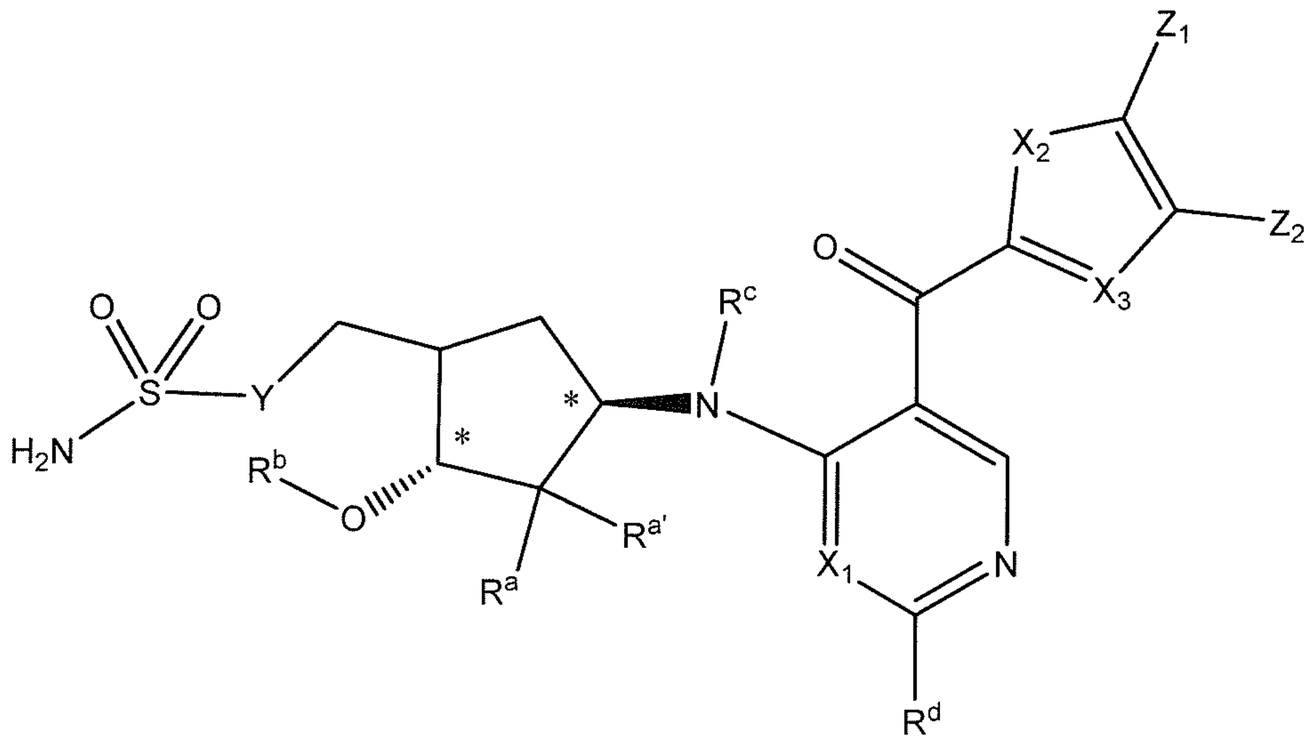

Heat Flow (W/g)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
Temperature (°C)
25
75
125
175
225
275
325

FIG. 17


Z1
X2
Z2
O
X3
Rc
O
O
S
Y
N
*
*
H2N
Rb
O
Ra'
Ra
X1
N
Rd

(*I*);

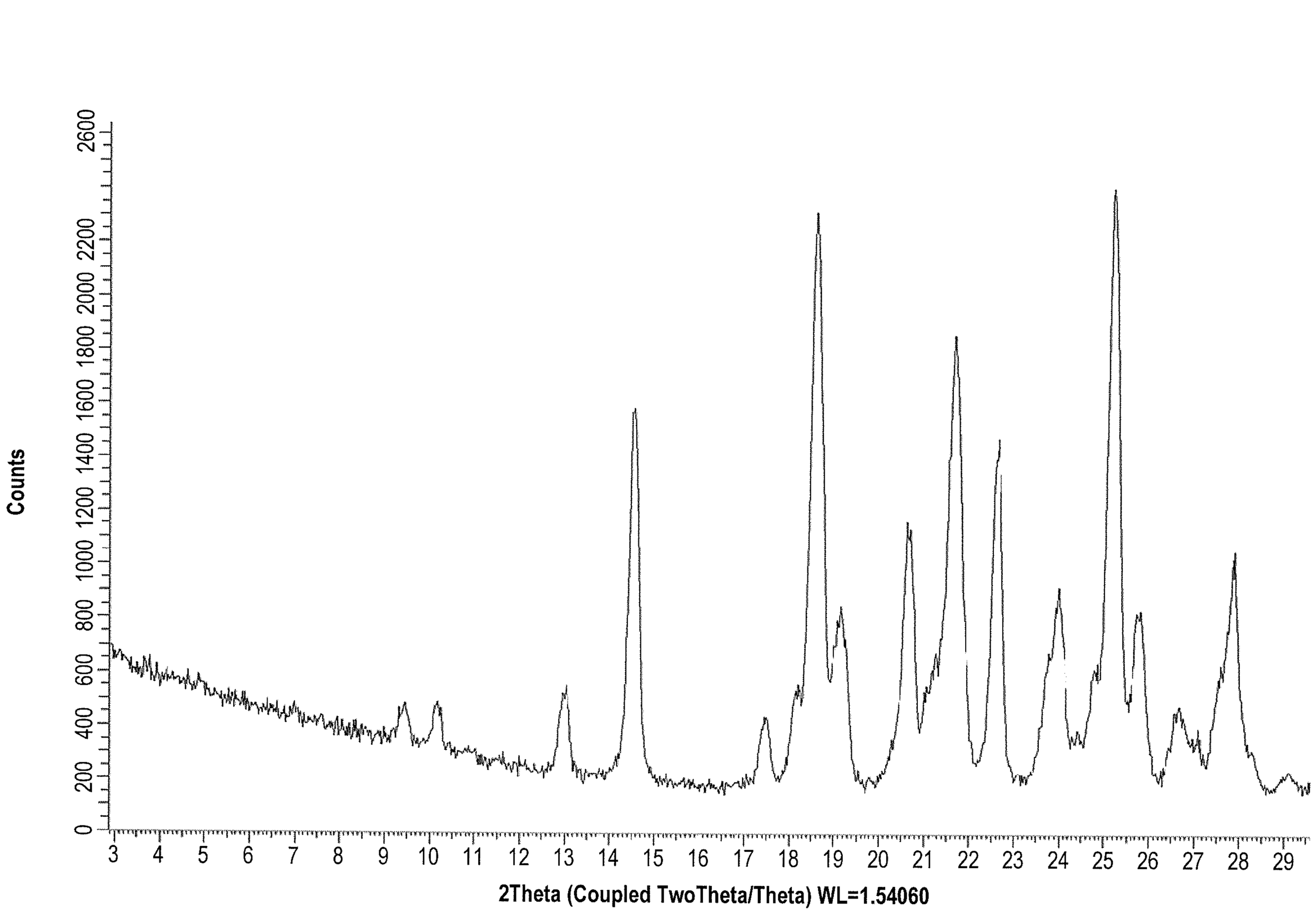

Counts
0
200
400
600
800
1000
1200
1400
1600
1800
2000
2200
2600
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
2Theta (Coupled TwoTheta/Theta) WL=1.54060

FIG. 1