



(51) International Patent Classification:

C07C 311/19 (2006.01) A61P 17/00 (2006.01)
A61K 31/196 (2006.01) A61P 35/00 (2006.01)

(21) International Application Number:

PCT/CA2015/000348

(22) International Filing Date:

29 May 2015 (29.05.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/005,308 30 May 2014 (30.05.2014) US

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, 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, 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

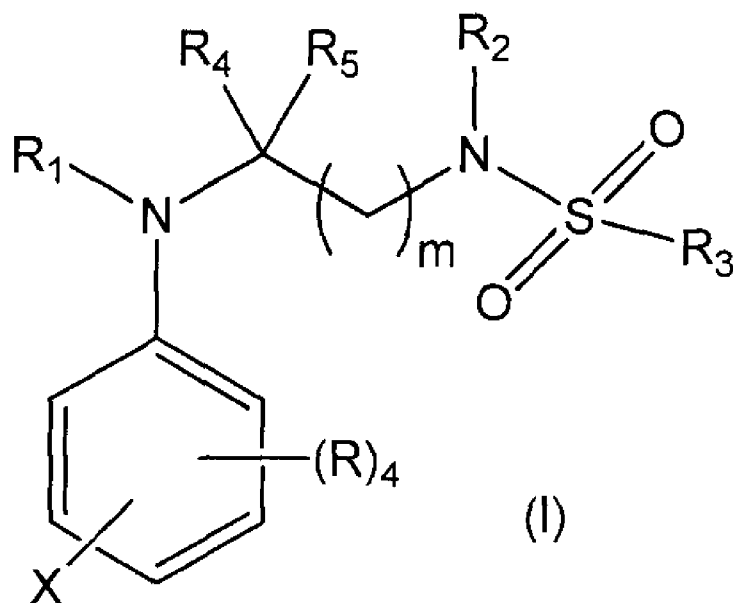
kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, 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))

[Continued on next page]

(54) Title: SULFONAMIDE COMPOUNDS AND THEIR USE AS STAT5 INHIBITORS



(57) Abstract: The present disclosure relates to compounds having the Formula (Formula (I)) which are inhibitors of STAT5.

— *with sequence listing part of description (Rule 5.2(a))*

SULFONAMIDE COMPOUNDS AND THEIR USE AS STAT5 INHIBITORS**FIELD**

[0001] The present disclosure relates to compounds which are inhibitors of the STAT5 protein, including compounds of the Formula (I).

INTRODUCTION

[0002] Numerous inhibitors have been developed to target the JAK-STAT signaling pathway, a major driving force in hematopoietic malignancies. While emphasis has focused on identifying effective upstream kinase inhibitors for suppressing STAT activity, inhibitors have suffered from poor kinase selectivity^[1], cardiovascular toxicity^[2,3], and in some clinical cases, acquired resistance.^[4] Multiple kinase inhibitors have been used in combination to try to combat resistance.^[5,6] An alternative strategy to reduce off-target toxicity, is to target proteins immediately downstream of the kinases, such as the Signal Transducer and Activator of Transcription (STAT) 5 protein.

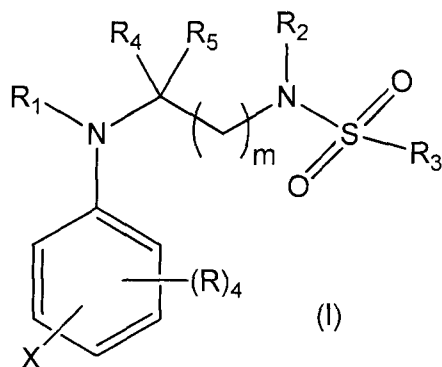
[0003] In normal cells, the activation of STAT5 proteins are tightly regulated by cytokines (IL-2, IL-5, IL-7, GM-CSF, erythropoietin (EPO), thrombopoietin, and prolactin) and growth factors.^[7] Binding of these extracellular ligands to their target receptors induces the activation of receptor-associated JAK kinases that phosphorylate key tyrosine residues within the receptor, providing docking sites for the SRC homology 2 (SH2) domains of the inactive cytoplasmic STAT5 monomers. STAT5 is then phosphorylated at specific tyrosine residues, either Y694 (STAT5A) or Y699 (STAT5B) of the C-terminus. Phosphorylated STAT5 monomers form either homo- or hetero-^[8,9] STAT5X-STATX dimers through reciprocal phosphotyrosine-SH2 interactions. Activated STAT5 dimers translocate to the nucleus where they bind to STAT5 DNA response elements inducing transcription of genes involved in proliferation (Bcl-xl, c-Myc, *pim-1*), cell differentiation (p21), cell survival (MCL-1) inflammation (Osm) and apoptosis (JAB).^[10] In contrast, mutations within cytosolic kinases (TEL-JAK2, Bcr-Abl, FLT-3) as well as overactive receptor associated tyrosine kinases (SRC, EGFR) induces constitutive phosphorylation of STAT5 proteins increasing the production of anti-apoptotic genes which can contribute to driving the cancer phenotype.^[11]

[0004] Approaches aimed at directly targeting STAT5 have been limited to a chromone-derived acyl hydrazine inhibitor, identified through a high-throughput fluorescence polarization (FP) screen. While this agent exhibited promising *in vitro*

disruption of the STAT5:EPOR phosphopeptide interaction, higher concentrations were required to inhibit STAT5 in cells.^[12]

SUMMARY

[0005] In one embodiment, the present disclosure relates to compounds of the Formula (I) which are inhibitors of the STAT5 protein. In one embodiment, the compound of the Formula (I) has the following structure



wherein

R_1 is $-(CH_2)_n-(C_6-C_{10})$ -aryl or $-C(=O)-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

R_2 is $-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

R_3 is $-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

X is $-COOR''$, $-P(O)(OR'')_2$, tetrazole, $-C(=O)NR''-OH$, or $-CF_2OH$, wherein R'' is H or (C_1-C_4) -alkyl;

R₄ and R₅ are H, or taken together R₄ and R₅ are -C(=O);

R is H, OH, halo, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;

n is 0, 1, 2, 3, 4, 5, or 6; and

m is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, solvate, prodrug and/or stereoisomer thereof.

[0006] The present disclosure also includes pharmaceutical compositions comprising compounds of the disclosure and pharmaceutically acceptable excipients, carriers and/or additives.

[0007] In one embodiment, the compounds of the disclosure are inhibitors of the STAT5 protein. In an aspect of the disclosure, the compounds of the Formula (I) are useful for treating or preventing conditions of a condition or disease mediated by the STAT5 protein. In another embodiment, the condition or disease is hematopoietic malignancies, skin conditions, non-melanoma skin cancer, prostate cancer or inflammation.

[0008] Other features and advantages of the present application will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the application are given by way of illustration only, since various changes and modifications within the spirit and scope of the application will become apparent to those skilled in the art from this detailed description.

DRAWINGS

[0009] The disclosure will now be described in greater detail with reference to the following drawings in which:

[0010] Figure 1 is a Treemap dendrogram demonstrating that a compound of the disclosure does not inhibit the tested kinases (a hit is defined as >35% inhibition);

[0011] Figure 2 shows Surface Plasmon Resonance (SPR) curves displaying the binding affinities of compounds of the disclosure against the STAT3 and STAT5 proteins;

[0012] Figure 3 are calibration curves for wildtype STAT5b and STAT3 protein using fluoresceinated-phosphopeptides (5-FAM-pYLPQTC and 5-FAM-GpYLVLDKW for STAT3 and STAT5B, respectively);

[0013] Figure 4 are normalized Fluorescence Polarization (FP) curves displaying the competitive binding of control STAT5 inhibitors (pimozide and chromone) to wildtype STAT5B protein.

[0014] Figure 5 are normalized FP curves displaying the competitive binding of compounds 13a-d of the disclosure against wildtype STAT5B and STAT3 proteins.

[0015] Figure 6 are graphs showing the cytotoxic potential of compounds 13a-d of the disclosure in K562 cell viability assays;

[0016] Figure 7 are graphs showing the cytotoxic potential of compounds 13a-d of the disclosure in MV4-11 cell viability assays;

[0017] Figure 8 is a graph showing A) Inhibition of pSTAT5 with a compound of the disclosure in K562 cells; B) Initiation of apoptosis after 24 hrs and knockdown of MCL-1; C) the compound shows no effect on pSTAT3 in MDA-MB-231 cells up to 20 μ M; and D) knockdown of downstream target c-Myc after 5 hrs;

[0018] Figure 9 shows a series of LC-MS spectra showing the metabolic stability in mouse hepatocytes of a compound of the disclosure at various time points: A) 0 min; B) 120 min; and C) 240 min;

[0019] Figure 10 shows a tandem mass spectra of a first peak from the LC-MS spectra of Figure 9;

[0020] Figure 11 shows a tandem mass spectra of a second peak from the LC-MS spectra of Figure 9;

[0021] Figure 12 shows a tandem mass spectra of a third peak from the LC-MS spectra of Figure 9;

[0022] Figure 13 shows a tandem mass spectra of a fourth peak from the LC-MS spectra of Figure 9; and

[0023] Figure 14 shows the effects of a compound of the disclosure on CD34+ and MV4-11 AML cells.

[0024] Figure 15 shows A) a normalized FP curve displaying the competitive binding of a compound of the disclosure to wildtype STAT1 protein; B) Effect of a compound of the disclosure on the phosphorylation levels of STAT1 in K562 and MDA-MB-231 cells; C) Phosphorylation levels of STAT5 within MDA-MB-231 cells. D) Cell viability of a compound of the disclosure in MDA-MB-231 cells.

[0025] Figure 16 shows A) Inhibition of pSTAT5 with a compound of the disclosure (10 μ M, yellow arrows) in MV-4;11 cells at 5 and 24 h; B) After 24h, apoptosis was initiated by the detectable cleaved PARP-1; C) a compound of the disclosure induced complete knockdown of downstream target gene, MCL-1 at 10 μ M.

[0026] Figure 17 shows the metabolic stability of a compound of the disclosure in HLS9 and MMLS9 with NADPH at 60 min.

[0027] Figure 18 shows A) the metabolic stability of a compound of the disclosure and positive control (verapamil) in human and mouse hepatocytes at 120 min. B) Remaining percentages of the compound and positive control (verapamil) in boiled human and mouse hepatocytes at 120 min as the negative control.

[0028] Figure 19 shows a single phase decay fit for the analytical HPLC data points of a compound of the disclosure in the presence of excess glutathione tripeptide (10mM).

DESCRIPTION OF VARIOUS EMBODIMENTS

DEFINITIONS

[0029] The term "(C₁-C_p).alkyl" as used herein means straight and/or branched chain, saturated alkyl radicals containing from one to "p" carbon atoms and includes (depending on the identity of p) methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, 2,2-dimethylbutyl, n-pentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, n-hexyl and the like, where the variable p is an integer representing the largest number of carbon atoms in the alkyl radical.

[0030] The term "(C₁-C_p).alkoxy" means an alkyl group, as defined above, having an oxygen atom attached thereto. As used herein, the term means straight and/or branched chain, saturated alkyl radicals having an oxygen atom attached thereto and containing from one to "p" carbon atoms and includes (depending on the identity of p) methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, s- butoxy, isobutoxy, t- butoxy, 2,2-

dimethylbutoxy, n-pentoxy, 2-methylpentoxy, 3-methylpentoxy, 4-methylpentoxy, n-hexoxy and the like, where the variable p is an integer representing the largest number of carbon atoms in the alkoxy radical.

[0031] The term "halo-substituted-(C₁.C_p).alkyl" as used herein means straight and/or branched chain, saturated alkyl radicals containing from one to "p" carbon atoms, in which at least one, and up to and including all, of the hydrogen atoms have been replaced with halogen atoms and includes (depending on the identity of p) fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 1-fluoroethyl, 1,1-difluoroethyl and the like, where the variable p is an integer representing the largest number of carbon atoms in the alkyl radical.

[0032] The term "aryl" as used herein refers to cyclic groups that contain at least one aromatic ring, for example a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). In an embodiment of the present disclosure, the aryl group contains 6, 9 or 10 atoms such as phenyl, naphthyl, indanyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like.

[0033] The term "halo" as used herein refers to a halogen atom and includes fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

[0034] The term "pharmaceutically acceptable salt" refers, for example, to a salt that retains the desired biological activity of a compound of the present disclosure and does not impart undesired toxicological effects thereto; and may refer to an acid addition salt or a base addition salt.

[0035] The term "solvate" as used herein means a compound or its pharmaceutically acceptable salt, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a "hydrate". The formation of solvates will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions.

[0036] In embodiments of the present disclosure, the compounds may have an asymmetric center. These compounds exist as enantiomers. Where compounds possess more than one asymmetric center, they may exist as diastereomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present disclosure. It is to be further understood that while the stereochemistry of the compounds may be as shown in any given compound listed herein, such compounds may also contain certain amounts (e.g. less than 20%, suitably less than 10%, more suitably less than 5%) of compounds of the disclosure having alternate stereochemistry. For example, compounds of the disclosure that are shown without any stereochemical designations are understood to be racemic mixtures (i.e. contain an equal amount of each possible enantiomer or diastereomer). However, it is to be understood that all enantiomers and diastereomers are included within the scope of the present disclosure, including mixtures thereof in any proportion.

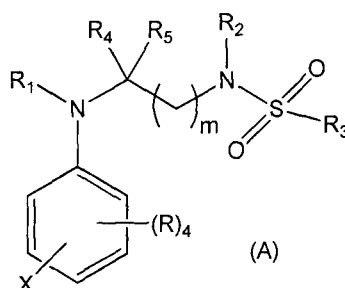
[0037] The term "effective amount" or "therapeutically effective amount" or "pharmaceutically effective amount" as used herein means an amount effective, at dosages and for periods of time necessary to achieve the desired result. For example in the context of treating a subject with a disease mediated by STAT5, an effective amount is an amount that, for example, inhibits the STAT5 protein in the subject. Effective amounts may vary according to factors such as the disease state, age, sex and/or weight of the subject. The amount of a given compound that will correspond to such an amount will vary depending upon various factors, such as the given drug or compound, the pharmaceutical formulation, the route of administration, the type of condition, disease or disorder, the identity of the subject being treated, and the like, but can nevertheless be routinely determined by one skilled in the art.

[0038] As used herein, the term "prodrug" refers to a substance that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of, for example, endogenous enzymes or other chemicals and/or conditions. Prodrug derivatives of the compounds of the disclosure or pharmaceutically acceptable salts or solvates thereof, can be prepared by methods known to those of ordinary skill in the art, and include esters of any free hydroxyl or carboxyl moieties of the compounds.

[0039] As used herein, a “subject” refers to all members of the animal kingdom including mammals, and suitably refers to humans. A member of the animal kingdom includes, without limitation, a mammal (such as a human, primate, swine, sheep, cow, equine, horse, camel, canine, dog, feline, cat, tiger, leopard, civet, mink, stone marten, ferret, house pet, livestock, rabbit, mouse, rat, guinea pig or other rodent, seal, whale and the like), fish, amphibian, reptile, and bird (such as water fowl, migratory bird, quail, duck, goose, poultry, or chicken). In an embodiment of the present disclosure, the subject is in need of a compound or composition of the disclosure.

COMPOUNDS OF THE DISCLOSURE

[0040] In one embodiment, the present disclosure relates to compounds of the Formula (A), which are STAT5 inhibitors. In one embodiment, the compound of the Formula (A) has the following structure



wherein

R_1 is $-(CH_2)_n-(C_6-C_{10})$ -aryl or $-C(=O)-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

R_2 is $-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

R_3 is $-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy,

halo-substituted-(C₁-C₄)-alkyl, -(cyclopropyl)-CF₃, -NO₂, CN, -SO₃R' and -COOR', wherein R' is H or (C₁-C₄)-alkyl;

X is -COOR'', -P(O)(OR'')₂, tetrazole, -C(=O)NR''-OH, or -CF₂OH, wherein R'' is H or (C₁-C₄)-alkyl or -(CH₂)-(C₆-C₁₀)-aryl;

R₄ and R₅ are independently or simultaneously H or CF₃ wherein at least one of R₄ or R₅ is H, or taken together R₄ and R₅ are -C(=O) or -C(=S);

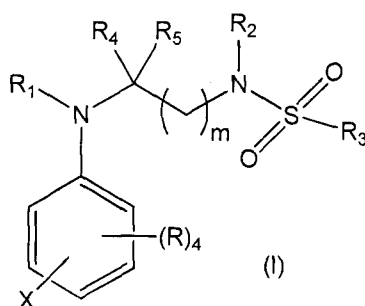
R is H, OH, halo, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;

each n is independently or simultaneously 0, 1, 2, 3, 4, 5, or 6; and

m is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, solvate, prodrug and/or stereoisomer thereof.

[0041] In one embodiment, the compound of the Formula (A) is a compound of the Formula (I) which are STAT5 inhibitors. In one embodiment, the compound of the Formula (I) has the following structure



wherein

R₁ is -(CH₂)_n-(C₆-C₁₀)-aryl or -C(=O)-(CH₂)_n-(C₆-C₁₀)-aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halo-substituted-(C₁-C₄)-alkyl, -(cyclopropyl)-CF₃, -NO₂, CN, -SO₃R' and -COOR', wherein R' is H or (C₁-C₄)-alkyl;

R₂ is -(CH₂)_n-(C₆-C₁₀)-aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy,

halo-substituted-(C₁-C₄)-alkyl, -(cyclopropyl)-CF₃, -NO₂, CN, -SO₃R' and -COOR', wherein R' is H or (C₁-C₄)-alkyl;

R₃ is -(CH₂)_n-(C₆-C₁₀)-aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halo-substituted-(C₁-C₄)-alkyl, -(cyclopropyl)-CF₃, -NO₂, CN, -SO₃R' and -COOR', wherein R' is H or (C₁-C₄)-alkyl;

X is -COOR'', -P(O)(OR'')₂, tetrazole, -C(=O)NR''-OH, or -CF₂OH, wherein R'' is H or (C₁-C₄)-alkyl;

R₄ and R₅ are H, or taken together R₄ and R₅ are -C(=O);

R is H, OH, halo, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;

each n is independently or simultaneously 0, 1, 2, 3, 4, 5, or 6; and

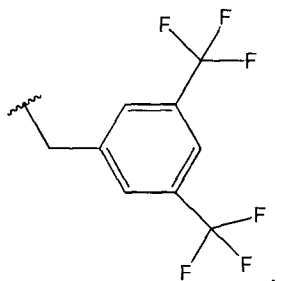
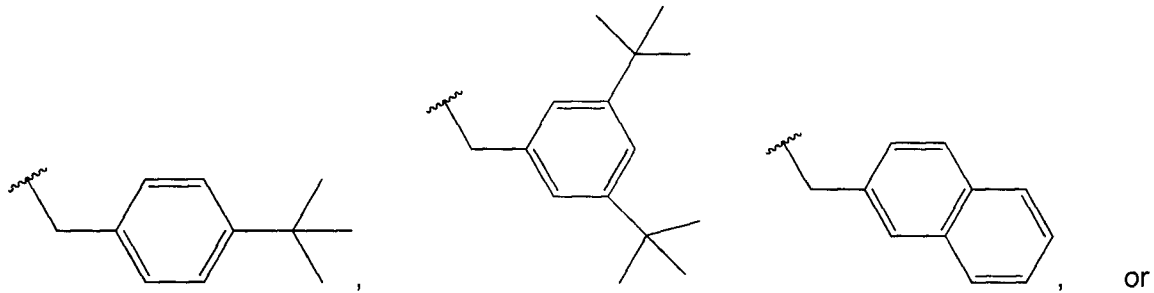
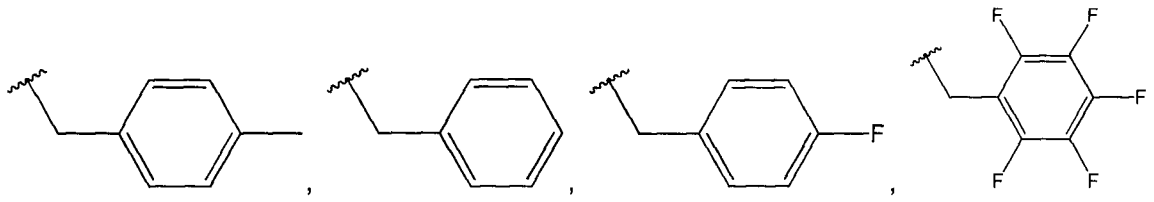
m is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, solvate, prodrug and/or stereoisomer thereof.

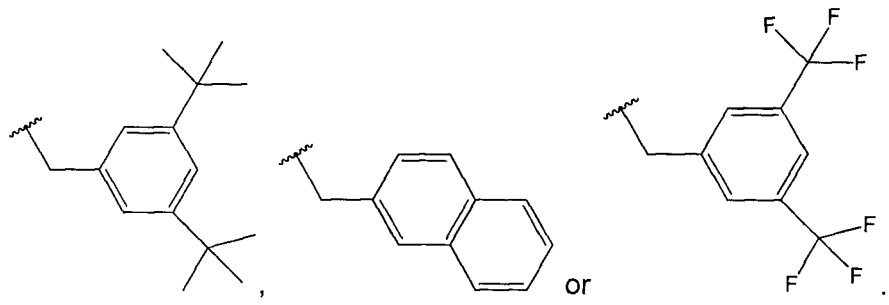
[0042] In one embodiment of the disclosure, R₁ is -(C₆-C₁₀)-aryl, -(CH₂)-(C₆-C₁₀)-aryl or -C(=O)-(C₆-C₁₀)-aryl. In another embodiment, R₁ is phenyl, naphthyl, -CH₂-phenyl, -CH₂-naphthyl, -C(=O)-phenyl or -C(=O)-naphthyl.

[0043] In another embodiment of the disclosure, the optional substituents on the aryl group of R₁ are selected from one to five of halo, CN, (C₁-C₆)-alkyl, halo-substituted-(C₁-C₄)-alkyl and (C₁-C₆)-alkoxy. In another embodiment of the disclosure, the optional substituents on the aryl group of R₁ are selected from one to five of halo, (C₁-C₆)-alkyl and (C₁-C₆)-alkoxy. In another embodiment, the optional substituents on the aryl group of R₁ are selected from one to five of fluoro, chloro, bromo, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy. In a further embodiment, the optional substituents on the aryl group of R₁ are selected from one to three substituents selected from fluoro, methyl and t-butyl. In one embodiment, the optional substituents on the aryl group of R₁ are selected from one to three substituents selected from CN, -CF₃, -CH₃, F, isopropyl and t-butyl.

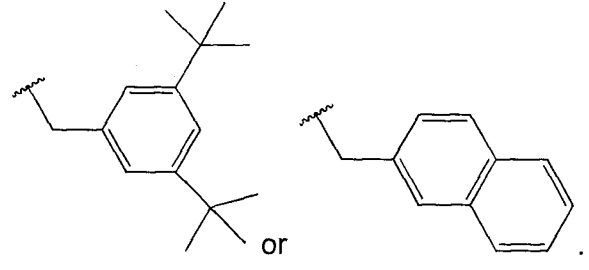
[0044] In one embodiment of the disclosure, the R₁ moiety is



[0045] In another embodiment, the R₁ moiety is



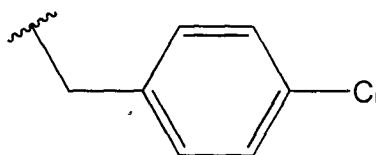
[0046] In another embodiment, the R₁ moiety is



[0047] In one embodiment of the disclosure, R_2 is $-(C_6-C_{10})$ -aryl or $-(CH_2)-(C_6-C_{10})$ -aryl. In another embodiment, R_2 is phenyl or $-CH_2$ -phenyl.

[0048] In another embodiment, the optional substituents on the aryl group of R_2 are selected from one to five of halo, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN , $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl. In another embodiment, the optional substituents on the aryl group of R_2 are selected from one to three of halo, halo-substituted- (C_1-C_4) -alkyl, and $-(cyclopropyl)-CF_3$. In another embodiment, the optional substituents on the aryl group of R_2 are one to three chloro groups, CF_3 , or $-(cyclopropyl)-CF_3$.

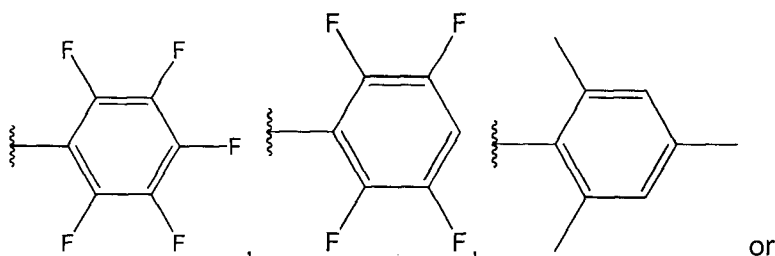
[0049] In another embodiment, the R_2 moiety is

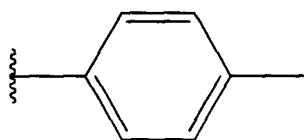


[0050] In another embodiment of the disclosure, R_3 is $-(C_6-C_{10})$ -aryl or $-(CH_2)-(C_6-C_{10})$ -aryl. In another embodiment, R_3 is phenyl or $-CH_2$ -phenyl.

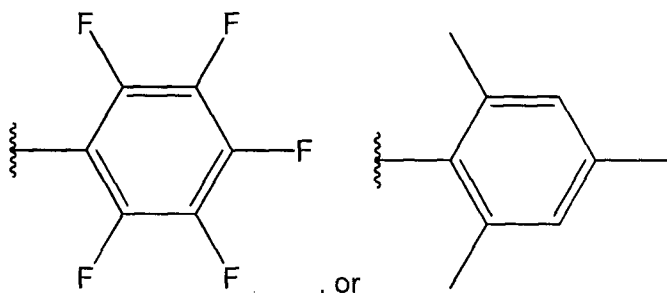
[0051] In one embodiment, the optional substituents on the aryl group of R_3 are selected from one to five of halo, OH, (C_1-C_6) -alkyl, and (C_1-C_6) -alkoxy. In another embodiment, the optional substituents on the aryl group of R_3 are selected from one to five of fluoro, chloro, bromo, OH, (C_1-C_3) -alkyl, and (C_1-C_3) -alkoxy. In another embodiment, the optional substituents on the aryl group of R_3 are selected from one to five of fluoro, chloro, bromo, and (C_1-C_3) -alkyl.

[0052] In one embodiment, the R_3 moiety is





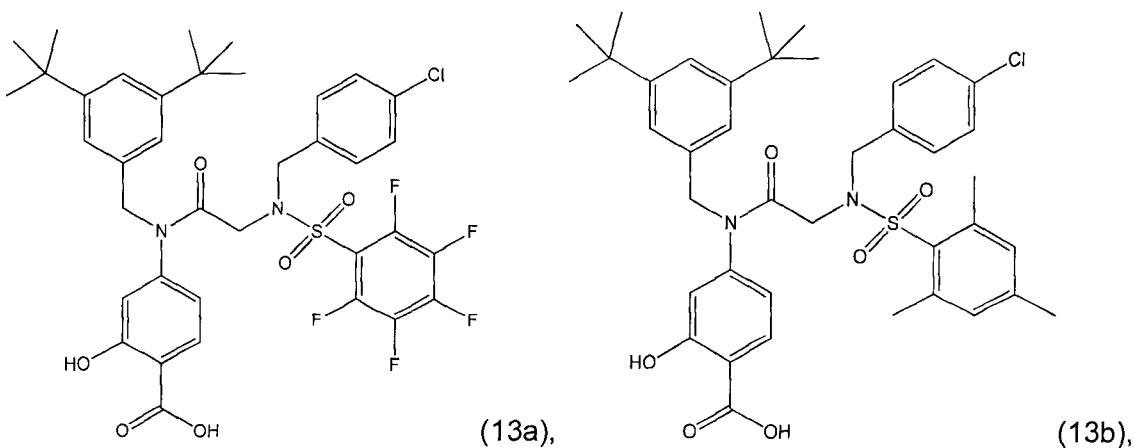
[0053] In another embodiment, the R₃ moiety is

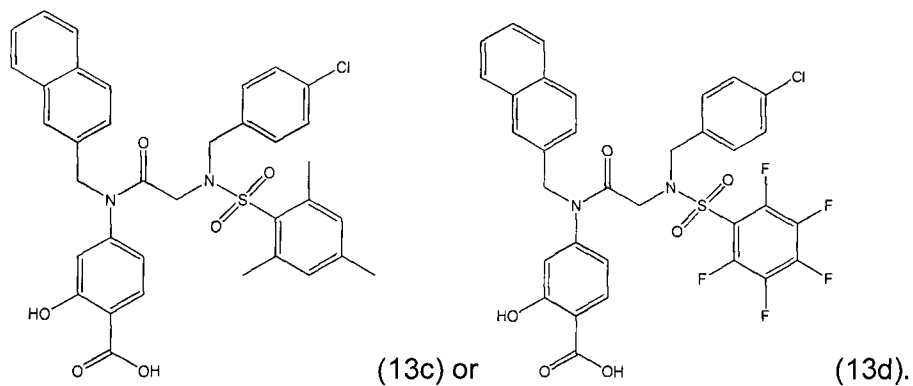


[0054] In a further embodiment of the disclosure, R is H, OH, fluoro, chloro, bromo, or (C₁-C₄)-alkyl. In another embodiment, H, F or OH.

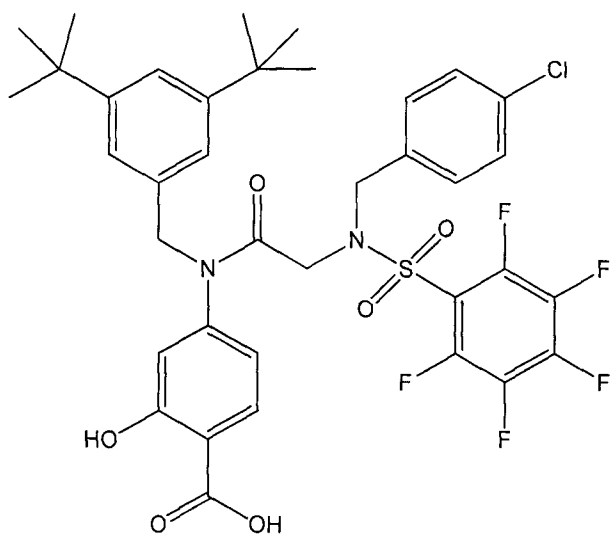
[0055] In another embodiment of the disclosure, X is COORⁿ, -P(O)(ORⁿ)₂ or tetrazole, wherein Rⁿ is H, or (C₁-C₄)-alkyl (such as t-butyl). In one embodiment, X is -COORⁿ, wherein Rⁿ is H or (C₁-C₄)-alkyl. In one embodiment, X is -COOH. In one embodiment, X is -COO-benzyl.

[0056] In another embodiment of the disclosure, the compound of the Formula (I) has the following structure

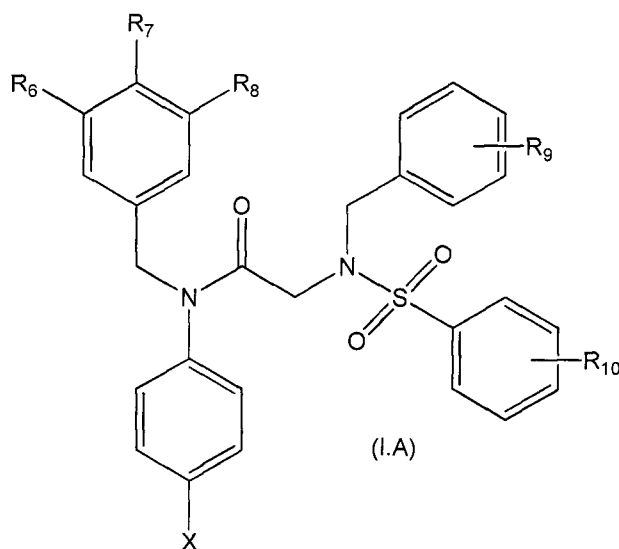




[0057] In a further embodiment, the compound of the Formula (I) has the following structure



[0058] In another embodiment of the disclosure, the compound of the Formula (I) is a compound of the Formula (I.A)



wherein

R_6 , R_7 and R_8 are independently or simultaneously selected from H, halo, OH, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halo-substituted-(C₁-C₄)-alkyl, -(cyclopropyl)-CF₃, -NO₂, CN, -SO₃R' and -COOR', wherein R' is H or (C₁-C₄)-alkyl;

R_9 and R_{10} are independently or simultaneously selected from one to five of halo, OH, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, halo-substituted-(C₁-C₄)-alkyl, -(cyclopropyl)-CF₃, -NO₂, CN, -SO₃R' and -COOR', wherein R' is H or (C₁-C₄)-alkyl;

X is -COOR'', -P(O)(OR'')₂, tetrazole, -C(=O)NR''-OH, or -CF₂OH, wherein R'' is H, (C₁-C₄)-alkyl, or -CH₂-(C₆-C₁₀)aryl;

or a pharmaceutically acceptable salt, solvate, prodrug and/or stereoisomer thereof.

[0059] In another embodiment of the disclosure, R_6 , R_7 and R_8 are independently or simultaneously selected from H, halo, CN, (C₁-C₆)-alkyl, halo-substituted-(C₁-C₄)-alkyl and (C₁-C₆)-alkoxy. In another embodiment of the disclosure, R_6 , R_7 and R_8 are independently or simultaneously selected from H, halo, CN, CF₃, (C₁-C₆)-alkyl and (C₁-C₆)-alkoxy. In another embodiment, R_6 , R_7 and R_8 are independently or simultaneously selected from H, fluoro, chloro, bromo, CN, CF₃, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy. In one embodiment, R_6 , R_7 and R_8 are independently or simultaneously selected from H, CN, -CF₃, -CH₃, F, isopropyl and t-butyl. In another embodiment, R_6 and R_8 are independently or simultaneously selected from H, CN, -CF₃,

(C₁-C₄)-alkyl (such as -CH₃, isopropyl or t-butyl). In one embodiment, R₆ and R₈ are t-butyl and R₇ is H.

[0060] In one embodiment, R₉ and R₁₀ are independently or simultaneously selected from one to five of halo, OH, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, or halo-substituted-(C₁-C₄)-alkyl. In one embodiment, R₉ and R₁₀ are independently or simultaneously selected from one to five of Cl, F, Br, OH, or (C₁-C₆)-alkyl. In one embodiment, R₉ is Cl in the *para*-position. In another embodiment, R₁₀ is five fluoro atoms. In another embodiment, R₁₀ is four fluoro atoms in the ortho- and meta-positions. In another embodiment, R₁₀ is three methyl groups in the ortho and para-positions.

[0061] In one embodiment, X is -COOR", wherein R" is H, (C₁-C₄)-alkyl, or -CH₂-(C₆-C₁₀)aryl. In one embodiment, X is -COOH, -COO(t-butyl) or -COO-benzyl. In another embodiment, X is -COOH.

COMPOSITIONS

[0062] The present disclosure also includes pharmaceutical compositions comprising a compound of the Formula (A), (I) and (I.A) as defined above (compounds of the disclosure), or pharmaceutically acceptable salts, solvates, and prodrugs thereof, and a pharmaceutically acceptable carrier or diluent. The compounds are suitably formulated into pharmaceutical compositions for administration to subjects, preferably humans in a biologically compatible form suitable for administration *in vivo*.

[0063] The compositions containing the compounds of disclosure can be prepared by known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (2003 - 20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999. On this basis, the compositions include, albeit not exclusively, solutions of the substances in association with one or more pharmaceutically acceptable vehicles or diluents, and contained in buffered solutions with a suitable pH and iso-osmotic with the physiological fluids.

[0064] The compounds of disclosure may be used pharmaceutically in the form of the free base, in the form of salts, solvates and as hydrates. All forms are within the

scope of the disclosure. Acid and basic addition salts may be formed with the compounds of the disclosure for use as sources of the free base form even if the particular salt per se is desired only as an intermediate product as, for example, when the salt is formed only for the purposes of purification and identification. All salts that can be formed with the compounds of the disclosure are therefore within the scope of the present disclosure.

METHODS OF MEDICAL TREATMENTS AND USES

[0065] The compounds of the disclosure, including compounds of the Formula (A), (I) and (I.A) are inhibitors of the STAT5 protein. In one embodiment, the compounds of the disclosure are STAT5 selective inhibitors in relation to their activity against STAT5 and STAT3. In one embodiment, the compounds of the disclosure have K_D values of less than 200nM, optionally less than 150nM, optionally less than 100nM, or optionally less than 50nM.

[0066] Accordingly, in one embodiment of the disclosure, there is included a method of treating or preventing a disease or condition mediated by signal transducer and activator of transcription 5 (STAT5) protein, comprising administering a pharmaceutically effective amount of a compound of the disclosure to a subject in need thereof. In one embodiment, the disease or condition mediated by STAT5 is a disease or condition in which inhibition of the STAT5 protein would be beneficial. In one embodiment, the disease or condition is a hematopoietic malignancy, skin condition, non-melanoma skin cancer, prostate cancer or inflammation, comprising administering a pharmaceutically effective amount of a compound of the disclosure to a subject in need thereof. In one embodiment, the hematopoietic malignancy is leukemia. In another embodiment, the leukemia is acute leukemia, chronic leukemia, lymphocytic leukemia or myelogenous leukemia. In another embodiment, the skin condition is psoriasis or dermatitis.

[0067] In another embodiment, the compounds of the disclosure are useful for inhibiting the signal transducer and activator of transcription 5 (STAT5) protein. In another embodiment, the compounds of the disclosure are useful for the preparation of a medicament for inhibiting the signal transducer and activator of transcription 5 (STAT5) protein. In one aspect of the disclosure, the compounds of the disclosure are useful for the treatment or prevention of hematopoietic malignancies, skin conditions,

non-melanoma skin cancer, prostate cancer or inflammation. In one embodiment, the hematopoietic malignancy is leukemia. In another embodiment, the leukemia is acute leukemia, chronic leukemia, lymphocytic leukemia or myelogenous leukemia. In another embodiment, the skin condition is psoriasis or dermatitis.

[0068] In another embodiment, the compounds of the disclosure are useful as probes for investigating the function of STAT5 in various diseased cells. In one embodiment, the compounds of the disclosure specifically inhibit STAT5, and therefore, the compounds are used as probes in determining whether STAT5 is involved in a disease or condition.

[0069] Although the disclosure has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present disclosure.

[0070] The operation of the disclosure is illustrated by the following representative examples. As is apparent to those skilled in the art, many of the details of the examples may be changed while still practicing the disclosure described herein.

EXAMPLES

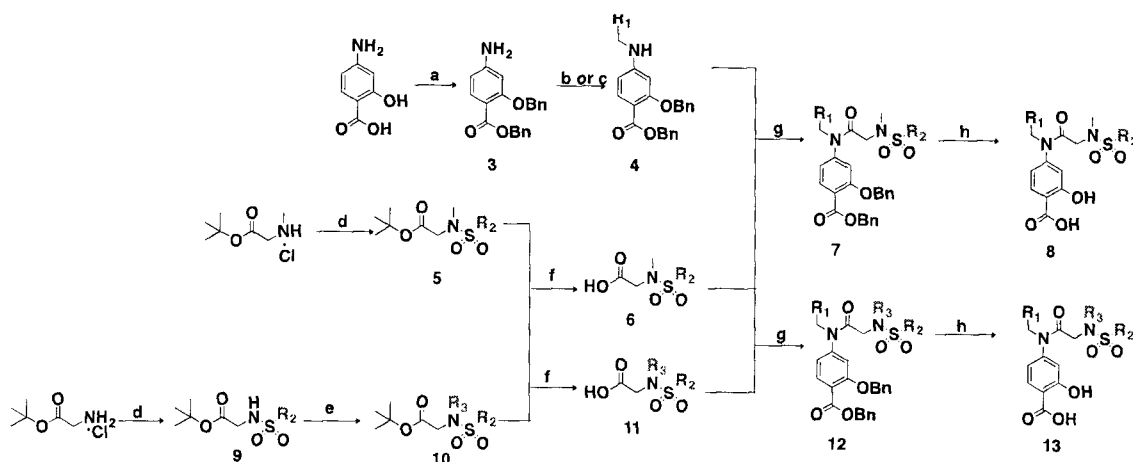
[0071] *Experimental Protocols*

[0072] *Example 1. Chemistry Methods*

[0073] Anhydrous solvents methanol, DMSO, CH₂Cl₂, THF and DMF were purchased from Sigma Aldrich and used directly from Sure-Seal bottles. Molecular sieves were activated by heating to 300 °C under vacuum overnight. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware and were monitored for completeness by thin-layer chromatography (TLC) using silica gel (visualized by UV light, or developed by treatment with KMnO₄ stain). NMR spectra were recorded in Bruker Avance III spectrometer at 23°C, operating at 400 MHz for ¹H NMR and 100 MHz ¹³C NMR spectroscopy either in CDCl₃, CD₃OD or d₆-DMSO. Chemical shifts (δ) are reported in parts per million (ppm) after calibration to residual isotopic

solvent. Coupling constants (J) are reported in Hz. Mass spectrometry was performed with an AB/Sciex QStar mass spectrometer with an ESI source, MS/MS and accurate mass capabilities, associated with an Agilent 1100 capillary LC system. Before biological testing, inhibitor purity was evaluated by reversed-phase HPLC (rpHPLC). Analysis by rpHPLC was performed using a Phenomenex Luna 5u C18 150 mm x 4.6 mm column run at 1.2 mL/min, and using gradient mixtures. The linear gradient consisted of a changing solvent composition of either (I) 15 % MeCN and 85 % H₂O with 0.1 % TFA (v/v) to 100 % MeCN over 30 minutes and (II) 15 % MeCN and 85 % H₂O with 0.1 % TFA (v/v) to 100 % MeCN over 60 minutes, UV detection at 250 nm. For reporting HPLC data, percentage purity is given in parentheses after the retention time for each condition. All biologically evaluated compounds are >95 % chemical purity as measured by HPLC. The HPLC traces for all tested compounds are provided in supporting information.

[0074] Compounds of the disclosure were synthesized in the following general manner as shown in Scheme 1.



Scheme 1: a) i) K^tOBu, BnBr, DMF, 0°C → RT., 1h; then K^tOBu, BnBr, DMF, 0°C → RT, 16h, 47%; b) 1) Aldehyde, AcOH, 3Å Mol. sieves, CH₃OH, 45°C, 2h; 2) NaCNBH₃, 45°C, 16h, 36-96 %; c) Aldehyde, 3Å Mol. sieves, CH₂Cl₂, NaOAc, Na(OAc)₃BH, RT, 16h, 88%; d) (CH₃)₃CSO₂Cl or C₅F₅SO₂Cl, K₂CO₃, CH₃CN, 16h, 0°C → RT, 60-77%; e) 1) p-Cl(C₆H₄)BnBr, Cs₂CO₃, DMF, R.T., N₂, 2h, 70%; f) CH₂Cl₂:TFA 1:1, RT, 1h, 90%; g) PPh₃Cl₂, CHCl₃, 30 min, 100°C microwave assisted heating, 20-98%; h) H₂, Pd/C, 1:1

THF/CH₃OH, 3-10h, RT, 35-95%. DMF = *N,N*-dimethylformamide, TFA = Trifluoroacetic acid

[0075] **General Procedure a (dibenzylation of salicylic acid).** To a stirred solution of 4-aminosalicylic acid (1.0 eq) in DMF (0.1 M) at 0 °C was added KO^tBu (1.2 eq). After 15 min, benzyl bromide (1.2 eq) was added drop-wise. The suspension was allowed to stir at room temperature for a further 4 h before the reaction vessel was again cooled to 0 °C. Once again, KO^tBu (1.2 eq) was added prior to the dropwise addition of benzyl bromide (1.2 eq). The reaction was left to stir overnight before quenching with H₂O. The solution was then repeatedly extracted with ethyl acetate and the organic phases combined. The organics were then washed with H₂O and brine then concentrated, dried over Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified using the Biotage Isolera automated column chromatographer with a 4:1 Hexanes/EtOAc gradient under reduced pressure.

[0076] **General Procedure b (reductive amination using sodium cyanoborohydride).** To a solution of benzyl protected 4-amino salicylic acid **5** (1.0 eq) and acetic acid (1.5 eq) stirred in anhydrous CH₃OH (0.1 M) with 3 Å mol. sieves was added the aldehyde (1.0 eq). The solution was heated to 45 °C for 3 hr and then allowed to cool to rt. Next, NaCNBH₃ (1.3 equiv) was added portion-wise and the reaction was allowed to stir at rt overnight. The reaction was diluted with CH₂Cl₂, filtered and concentrated *in vacuo*. The concentrate was purified using the Biotage Isolera automated column chromatographer using a gradient of Hexanes/EtOAc.

[0077] **General Procedure c (reductive amination using sodium triacetoxyborohydride).** To a solution of benzyl protected 4-amino salicylic acid **5** (1.2 eq) and acetic acid (1.2 eq) stirred in anhydrous dichloroethane (0.1 M) with 3 Å mol. sieves was added the aldehyde (1.0 eq). The solution was then stirred at rt for 5 min after which Na(OAc)₃BH (1.5 eq) was added and left to stir at rt overnight. The reaction was diluted with CH₂Cl₂, filtered and concentrated *in vacuo*. The concentrate was purified using the Biotage Isolera automated column chromatographer using a gradient of Hexanes/EtOAc.

[0078] **General Procedure d (sulfonylation of glycine and sarcosine *t*-butyl ester).** A solution of amino acid *t*-butyl ester (1 eq) and K₂CO₃ (1.1 eq) were dissolved in anhydrous acetonitrile and cooled to 0 °C before sulfonyl chloride (1 eq) was added.

The resultant solution was allowed to stir overnight at rt. The reaction was concentrated *in vacuo* and residue was dissolved in CH₂Cl₂. The organics were combined and then washed sequentially with 0.1 M HCl, saturated NaHCO₃ and brine. The organics were then dried over Na₂SO₄ and concentrated *in vacuo* to furnish derivatives **7** & **8** with no further purification.

[0079] **General Procedure e (alkylation of sulfonamide).** A solution of **8** (1 eq) and Cs₂CO₃ (1.3 eq) were dissolved in anhydrous DMF followed by the addition of p-ClBnBr (1 eq). The resultant solution was allowed to stir for 2h at r.t. The reaction was quenched with H₂O and then repeatedly extracted with ethyl acetate. The organic phases were combined and washed with H₂O, brine, dried over Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified using the Biotage Isolera automated column chromatographer with a 2:1 Hexanes/EtOAc gradient under reduced pressure.

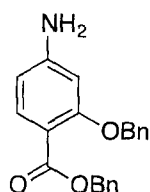
[0080] **General Procedure f (t-butyl ester deprotection).** A solution of amino acid t-butyl ester (1 eq) was dissolved in TFA and immediately diluted with CH₂Cl₂ in a 1:1 mixture (0.1 M) solution. The resultant solution was allowed to stir for 1h and then co-evaporated with CH₃OH (3x) and CHCl₃ (3x). The resultant residue was carried forward with no purification.

[0081] **General Procedure g (PPh₃Cl₂ peptide coupling).** To a stirred solution of carboxylic acid **10** (1.1 eq) in CHCl₃ (0.1 M) was added PPh₃Cl₂ (2.5 eq). The reaction was allowed to stir 5 min at rt or until complete dissolution, followed by the drop-wise addition of the secondary aniline **6** (1.0 eq). The reaction mixture was then heated in a microwave at 100 °C for 30 min. The reaction mixture was allowed to cool to rt followed by sequential washing with saturated NaHCO₃ and brine. The organic layers were then dried over Na₂SO₄ and concentrated *in vacuo*. The concentrate was absorbed directly onto silica for column chromatography purification using a gradient of hexanes and EtOAc.

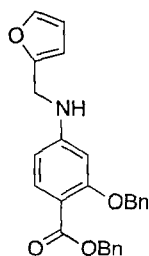
[0082] **General Procedure h (hydrogenolysis of the benzyl ester and benzyl ether).** The benzyl protected salicylic acid, **11** (1 eq) was dissolved in a stirred solution of CH₃OH/THF (1:2, 0.1 M). The solution was thoroughly degassed before the careful addition of 10 % Pd/C (10 mg/mmol). H₂ gas was bubbled through the solvent for 5 min before the solution was put under an atmosphere of H₂ gas and stirred continuously for

2-5h, monitoring completion of reaction via TLC. The H₂ gas was evacuated and the reaction filtered through celite to remove Pd catalyst and concentrated *in vacuo*. The resulting residue was adsorbed onto silica and columned using a Biotage Isolera in a gradient of CH₂Cl₂, CH₃OH and 1% acetic acid.

[0083] *Intermediate characterization data*

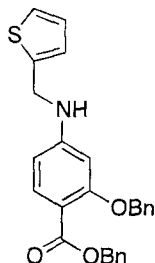


[0084] **Benzyl 4-amino-2-(benzyloxy)benzoate (3).** Compound **3** was synthesized according to general procedure **a**, yielding the final product as an orange solid (47%): δ_{H} (400 MHz, *d*-CDCl₃) 5.07 (s, 2H, CH₂), 5.21 (s, 2H, CH₂), 5.99 (br s, 2H, NH₂), 6.18 (dd, *J* = 8.6 and 1.8 Hz, 1H, CH), 6.32 (d, *J* = 1.7 Hz, 1H, CH), 7.28-7.38 (8H, m, CH), 7.47 (d, *J* = 7.2 Hz, 2H, CH), 7.60 (d, *J* = 8.6 Hz, 1H, CH); δ_{C} (400 MHz, CDCl₃) 65.8, 70.2, 99.1, 106.7, 109.0, 126.8, 127.5, 127.7, 127.9, 128.3, 128.4, 134.3, 136.6, 136.7, 152.2, 160.7, 165.7; LRMS (ES⁺) calculated for [C₂₁H₁₉NO₃ + H] 333.18, found 334.2.



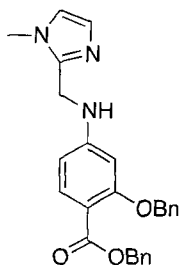
[0085] **Benzyl 2-(benzyloxy)-4-((furan-2-ylmethyl)amino)benzoate.** Derivative **4** synthesized *via* furan-2-carbaldehyde on a 1.5 mmol scale using general procedure **b** (74%): δ_{H} (400 MHz, *d*-CDCl₃) 4.36 (d, *J* = 5.4 Hz, 2H, CH₂), 4.54 (br s, 1H, NH), 5.12 (s, 2H, CH₂), 5.31 (s, 2H, CH₂), 6.19 (d, *J* = 3.4 Hz, 1H, CH), 6.21 (d, *J* = 2.0 Hz, 1H, CH), 6.24 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH), 6.31 (q, *J* = 3.0, 1.8, and 4.6 Hz, 1H, CH) 7.26 - 7.50 (m, 11H, 11 CH), 7.84 (d, *J* = 8.6 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 40.6,

65.7, 70.4, 97.5, 104.9, 107.2, 108.9, 110.3, 126.8, 127.5, 127.6, 127.9, 128.2, 128.4, 134.2, 136.6, 136.7, 142.0, 151.4, 152.2, 160.7, 165.5 LRMS (ES+) Calculated for $[C_{26}H_{23}NO_4 + H]$ 413.16 found 414.2.



[0086] **Benzyl 2-(benzyloxy)-4-((thiophen-2-ylmethyl)amino)benzoate.**

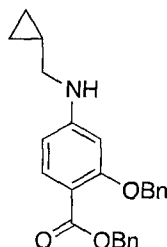
Derivative **4** synthesized *via* thiophene-2-carbaldehyde on a 1.5 mmol scale using General Procedure **b** (73%): δ_H (400 MHz, *d*-CDCl₃) 4.50 (s, 2H, CH₂), 4.54 (br s, 1H, NH), 5.10 (s, 2H, CH₂), 5.31 (s, 2H, CH₂), 6.20 (d, *J* = 2.0 Hz, 1H, CH), 6.25 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH), 6.97 (br, 2H, CH), 7.23 (dd, *J* = 1.3, 4.8 Hz, 1H, CH), 7.27 - 7.58 (m, 10H, 10 CH), 7.84 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 51.6, 65.4, 70.6, 96.5, 104.9, 109.5, 125.6, 126.2, 127.0, 127.1, 127.6, 128.8, 136.5, 140.3, 152.5, 161.3, 168.8 LRMS (ES+) Calculated for $[C_{26}H_{23}NO_3S + H]$ 429.14 found 430.2.



[0087] **Benzyl-2-(benzyloxy)-4-((1-methyl-1H-imidazol-2-yl)methyl)amino)benzoate.**

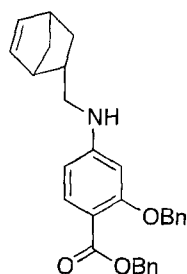
Derivative **4** synthesized *via* 1-methyl-1H imidazole-2-carbaldehyde on a 1.5 mmol scale using general procedure **b** (43%): δ_H (400 MHz, *d*-CDCl₃) 3.53 (s, 3H, CH₃), 4.27 (d, *J* = 5.4 Hz, 2H, CH₂), 5.08 (s, 2H, CH₂), 5.21 (br, 1H, NH), 5.31 (s, 2H, CH₂), 6.24 (dd, *J* = 8.6, 2.0 Hz, 1H, CH), 6.30 (d, *J* = 2.0 Hz, 1H, CH), 6.81 (s, 1H, CH), 6.96 (s, 1H, CH), 7.23 - 7.51 (m, 10H, 10 CH), 7.84 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 14.1, 20.9, 29.6, 32.4, 40.1, 60.2, 65.7, 70.3, 97.6, 104.7,

108.6, 121.6, 126.9, 127.1, 127.5, 127.9, 128.2, 134.2, 136.7, 144.0, 152.5, 160.7, 165.7
LRMS (ES+) Calculated for [C₂₆H₂₅N₃O₃ + H] 427.19 found 428.21.



[0088] **Benzyl 2-(benzyloxy)-4-((cyclopropylmethyl)amino)benzoate.**

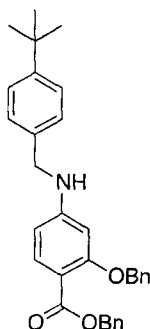
Derivative **4** synthesized *via* cyclopropanecarbaldehyde on a 1.5 mmol scale using general procedure **b** (66%): δ_{H} (400 MHz, *d*-CDCl₃) 0.25 (dd, *J* = 5.3 and 10.0 Hz, 2H, CH₂), 0.56 (dd, *J* = 5.7, 13.0 Hz, 2H, CH₂), 1.05 (br, 1H, CH), 2.97 (s, 2H, CH₂), 4.40 (br, 1H, NH), 5.13 (s, 2H, CH₂), 5.33 (s, 2H, CH₂), 6.15 (d, *J* = 2.0 Hz, 1H, CH), 6.19 (dd, *J* = 8.6, 2.0 Hz, 1H, CH), 7.27 - 7.58 (m, 10H, 10 CH), 7.84 (d, *J* = 8.6 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 3.4, 10.4, 14.1, 48.2, 60.3, 65.7, 70.3, 96.9, 104.6, 107.9, 126.8, 127.4, 127.6, 127.9, 128.2, 128.3, 134.3, 136.7, 136.8, 153.1, 160.9, 165.7 LRMS (ES+) Calculated for [C₂₅H₂₅NO₃+ H] 387.18 found 388.20.



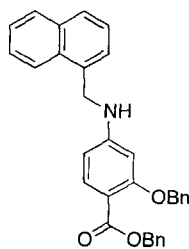
[0089] **Benzyl-2-(benzyloxy)-4-((bicyclo[2.2.1]hept-5-en-2-**

ylmethyl)amino)benzoate. Derivative **4** synthesized *via* bicycle [2.2.1] hept-5-ene-2-carbaldehyde on a 1.5 mmol scale *via* general procedure **b** (36%): δ_{H} (400 MHz, *d*-CDCl₃) 0.58-0.73 (m, 1H, CH₂), 1.25-1.46 (m, 2H, CH₂), 1.47-1.60 (m, 1H, CH₂), 1.85-2.03 (m, 1H, CH), 2.31 (br, 1H, CH), 2.79 (br, 1H, CH), 2.84-2.98 (m, 2H, CH₂), 4.38 (br, 1H, NH), 5.14 (s, 2H, CH₂), 5.35 (s, 2H, CH₂), 5.94-6.00 (m, 1H, CH), 6.20-6.27 (m, 1H, CH), 6.15 (d, *J* = 2.0 Hz, 1H, CH), 6.19 (dd, *J* = 8.6, 2.0 Hz, 1H, CH), 7.27 - 7.50 (m,

10H, 10 CH), 7.84 (d, $J = 8.6$ Hz, 1H, CH); δ_C (100 MHz, $d\text{-CDCl}_3$) 30.2, 38.4, 42.3, 44.2, 47.4, 49.5, 65.7, 70.3, 96.9, 104.6, 107.6, 126.9, 127.5, 127.6, 127.9, 128.3, 128.4, 131.8, 134.2, 136.1, 136.7, 136.8, 137.8, 153.2, 160.9, 165.8 LRMS (ES+) Calculated for $[\text{C}_{29}\text{H}_{29}\text{NO}_3 + \text{H}]$ 439.21 found 440.21.

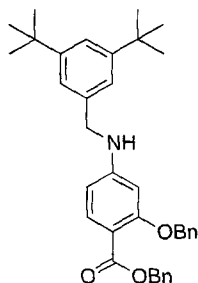


[0090] **Benzyl 2-(benzyloxy)-4-(4-tert-butylbenzyl)amino)benzoate.** Derivative **4** synthesized *via* 4-tert-butylbenzaldehyde on a 0.9 mmol scale using general procedure **b** (96%): δ_H (400 MHz, $d\text{-CDCl}_3$) 1.19 (s, 9H, 3 CH_3), 4.13 (s, 2H, CH_2), 4.40 (br s, 1H, NH), 4.92 (s, 2H, CH_2), 5.17 (s, 2H, CH_2), 6.02 (d, $J = 2.0$ Hz, 1H, CH), 6.06 (dd, $J = 8.6, 2.0$ Hz, 1H, CH), 7.08 - 7.32 (m, 14H, 14 CH), 7.71 (d, $J = 8.6$ Hz, 1H, CH); δ_C (100 MHz, $d\text{-CDCl}_3$) 31.0, 34.2, 47.0, 65.5, 70.1, 96.9, 104.6, 107.9, 125.3, 126.7, 126.9, 127.3, 127.4, 127.7, 128.1, 128.2, 134.1, 134.9, 136.5, 136.6, 150.2, 152.8, 160.6, 165.5; LRMS (ES+) Calculated for $[\text{C}_{32}\text{H}_{33}\text{NO}_3 + \text{H}]$ 480.25 found 481.26.



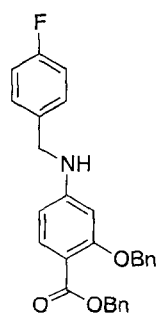
[0091] **Benzyl 2-(benzyloxy)-4-(naphthalen-2-ylmethylamino)benzoate.** Derivative **4** synthesized *via* 2-naphthaldehyde on a 0.9 mmol scale using general procedure **c** (88 %): δ_H (400 MHz, $d\text{-CDCl}_3$) 4.35 (s, 2H, NH_2CH_2), 4.52 (br s, 1H, NH), 4.92 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 6.70 (d, $J = 2.0$ Hz, 1H, CH), 6.12 (dd, $J = 8.6, 2.0$ Hz, 1H, CH), 7.11 - 7.22 (m, 6H, CH), 7.25 - 7.30 (m, 4H, 4 CH), 7.34 - 7.39 (m, 2H, 2 CH), 7.61 - 7.75 (m, 5H, 5 CH); δ_C (100 MHz, $d\text{-CDCl}_3$) 47.1, 65.2, 69.7, 96.7, 104.4, 107.9, 124.7, 125.2, 125.3, 125.7, 126.2, 126.9, 127.0, 127.1, 127.3, 127.7, 127.8, 127.9, 132.1, 132.7,

133.7, 135.1, 136.1, 152.3, 160.3, 165.1; LRMS (ES+) Calculated for $[C_{32}H_{27}NO_3 + H]$ 474.21, found 475.21.



[0092] **Benzyl 2-(benzyloxy)-4-(3,5-di-tert-butylbenzyl)amino)benzoate.**

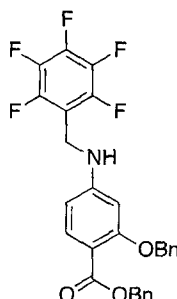
Derivative **4** synthesized *via* 3,5-di-*tert*-butylbenzaldehyde on a 0.9 mmol scale using general procedure **b** (60%): δ_H (400 MHz, *d*-CDCl₃) 1.34 (s, 18H, 6 CH₃), 4.30 (s, 2H, CH₂), 4.40 (br s, 1H, NH), 5.11 (s, 2H, CH₂), 5.32 (s, 2H, CH₂), 6.22 (d, *J* = 2.0 Hz, 1H, CH), 6.26 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH), 7.15 - 7.53 (m, 13H, 13 CH), 7.87 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 31.0, 34.2, 47.0, 65.5, 70.1, 96.9, 104.6, 107.9, 121.8, 122.4, 125.3, 126.7, 126.9, 127.3, 127.4, 127.7, 128.1, 128.2, 134.1, 134.9, 136.5, 136.6, 150.2, 152.8, 160.6, 165.5; LRMS (ES+) Calculated for $[C_{36}H_{41}NO_3 + H]$ 535.31 found 536.30.



[0093] **Benzyl 2-(benzyloxy)-4-((4-fluorobenzyl)amino)benzoate.** Derivative **4**

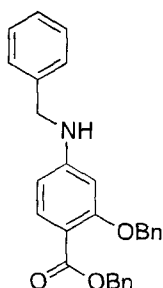
synthesized *via* 4-fluorobenzaldehyde on a 0.4 mmol scale using general procedure **b** (45%): δ_H (400 MHz, *d*-CDCl₃) 4.30 (s, 2H, CH₂), 4.50 (br s, 1H, NH), 5.07 (s, 2H, CH₂), 5.30 (s, 2H, CH₂), 6.14 (d, *J* = 2.0 Hz, 1H, CH), 6.20 (dd, *J* = 8.6 and 2.0 Hz, 1H, CH), 6.96-7.08 (m, 2H, CH), 7.22 - 7.40 (m, 10H, 10 CH), 7.40-7.45 (m, 2H, CH), 7.87 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 46.9, 65.7, 70.3, 97.3, 104.8, 115.3, 115.6,

126.7, 127.5, 127.6, 127.8, 128.2, 128.3, 128.7, 128.8, 133.7, 134.2, 136.6, 152.4, 160.7, 160.8, 165.5; LRMS (ES+) Calculated for $[C_{28}H_{24}FNO_3 + H]$ 441.17 found 442.20.

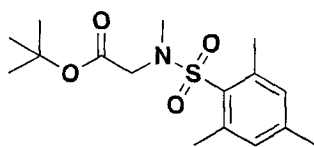


[0094] **Benzyl 2-(benzyloxy)-4-(((perfluorophenyl)methyl)amino)benzoate.**

Derivative **4** synthesized *via* 2,3,4,5,6-pentafluorobenzaldehyde on a 0.4 mmol scale using general procedure **b** (36%): δ_H (400 MHz, *d*-CDCl₃) 4.45 (s, 2H, CH₂), 4.75 (br s, 1H, NH), 5.09 (s, 2H, CH₂), 5.27 (s, 2H, CH₂), 6.21 (d, *J* = 2.0 Hz, 1H, CH), 6.22 (dd, *J* = 8.6, 2.0 Hz, 1H, CH), 7.21-7.50 (m, 10H, 10 CH), 7.80 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 13.9, 20.8, 35.0, 60.2, 65.8, 70.1, 97.0, 104.7, 109.4, 126.7, 127.5, 127.6, 127.8, 128.2, 128.3, 134.3, 136.4, 136.5, 151.3, 160.7, 165.4, 171.0; LRMS (ES+) Calculated for $[C_{28}H_{20}F_5NO_3 + H]$ 513.14 found 514.20.

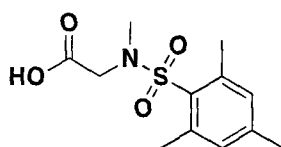


[0095] **Benzyl 4-(benzylamino)-2-(benzyloxy)benzoate.** Derivative **4** synthesized *via* benzaldehyde on a 1.2 mmol scale *via* General Procedure A (210 mg, 40%): δ_H (400 MHz, *d*-CDCl₃) 4.21 (s, 2H, CH₂), 4.95 (s, 2H, CH₂), 5.20 (s, 2H, CH₂), 6.03 (d, *J* = 2.0 Hz, 1H, CH), 6.09 (dd, *J* = 8.6, 2.1 Hz, 1H, CH), 7.15 - 7.34 (m, 15H, CH), 7.73 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 47.5, 66.7, 70.3, 97.2, 104.8, 108.3, 126.8, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.3, 128.6, 134.2, 136.6, 136.7, 138.1, 152.8, 160.8, 165.6; LRMS (ES+) Calculated for $[C_{28}H_{25}NO_3 + H]$ 424.19 found 425.22.

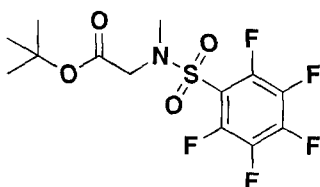


[0096] **Tert-butyl 2-(N, 2, 4, 6-tetramethylphenylsulfonamido)acetate.**

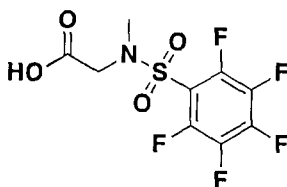
Derivative **5** synthesized using general procedure **d** (77 %): δ_{H} (400 MHz, CDCl_3) 1.37 (s, 9H, CH_3) 2.30 (s, 3H, CH_3), 2.61 (s, 6H, CH_3) 2.82 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 6.95 (s, 2H, CH); δ_{C} (400 MHz, CDCl_3) 21.0, 22.9, 27.5, 35.1, 51.6, 130.6, 137.4, 141.3, 145.5, 170.2; LRMS (ES+) calculated for $[\text{C}_{16}\text{H}_{25}\text{NO}_4\text{S} + \text{H}]$ 285.10, found 286.22.



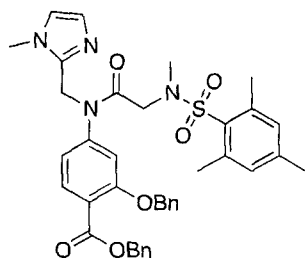
[0097] **2-(N,2,4,6-tetramethylphenylsulfonamido)acetic acid.** Derivative **6** was synthesized via general procedure **f** (95%): δ_{H} (400 MHz, CDCl_3) 2.32 (s, 3H, CH_3), 2.61 (s, 6H, CH_3), 2.82 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 6.95 (s, 2H, CH); δ_{C} (400 MHz, CDCl_3) 21.0, 22.9, 35.1, 51.6, 130.6, 137.4, 141.3, 145.5, 170.2; LRMS (ES+) calculated for $[\text{C}_{12}\text{H}_{17}\text{NO}_4\text{S} + \text{H}]$ 271.09, found 272.28.



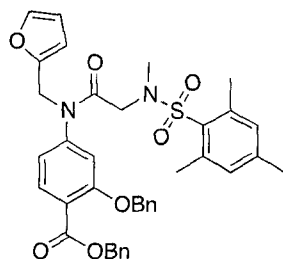
[0098] **Tert-butyl 2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetate.** Derivative **5** was synthesized using general procedure **d** (90%): δ_{H} (400 MHz, CDCl_3) 1.37 (s, 9H, CH_3) 3.03 (s, 3H, CH_3), 4.10 (s, 2H, CH_2); δ_{C} (400 MHz, CDCl_3) 27.5, 35.1, 51.6, 82.8, 115.6, 136.5, 144.8, 145.9, 167.0; LRMS (ES+) calculated for $[\text{C}_{13}\text{H}_{14}\text{F}_5\text{NO}_4\text{S} + \text{H}]$ 376.06, found 377.09.



[0099] **2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetic acid.** Derivative **6** was synthesized using general procedure **f** (97%): δ_{H} (400 MHz, CDCl_3) 2.86 (s, 3H, CH_3), 4.10 (s, 2H, CH_2); δ_{C} (400 MHz, CDCl_3) 35.5, 51.6, 115.6, 136.5, 144.8, 145.9, 167.0; LRMS (ES+) calculated for $[\text{C}_9\text{H}_6\text{F}_5\text{NO}_4\text{S} + \text{H}]$ 320.00, found 321.05.

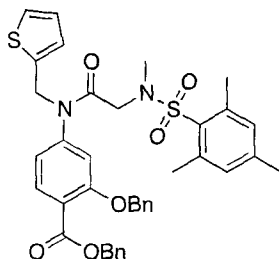


[00100] **Benzyl-2-(benzyloxy)-4-(N-((1-methyl-1H-imidazol-2-yl)methyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative of **6** on a 0.16 mmol scale *via* general procedure **g** (60%): δ_{H} (400 MHz, *d*- CDCl_3) 2.32 (s, 3H, CH_3), 2.62, (s, 6H, 2 CH_3), 2.90 (s, 3H, CH_3), 3.39 (d, $J = 3.1$ Hz, 3H, CH_3) 3.44- 3.59 (m, 2H, CH_2), 3.92, (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 5.33 (s, 2H, CH_2), 6.93 (dd, $J = 8.6$ and 2.1 Hz, 1H, CH), 7.00 (s, 2H, CH), 7.27 - 7.55 (m, 11H, CH), 7.68 (d, $J = 2.0$ Hz, 1H, CH), 7.89 (d, $J = 8.6$ Hz, 1H, CH); δ_{C} (100 MHz, *d*- CDCl_3) 21.6, 22.5, 33.4, 35.6, 48.1, 49.3, 65.6, 70.7, 104.5, 113.8, 116.2, 120.2, 126.8, 127.1, 127.6, 128.8, 130.4, 131.1, 136.3, 136.7, 137.2, 141.3, 145.2, 147.0, 152.3, 161.3, 166.5, 168.3; LRMS (ES+) Calcd for $[\text{C}_{38}\text{H}_{40}\text{N}_4\text{O}_6\text{S} + \text{H}]$ 680.27 found 681.28.

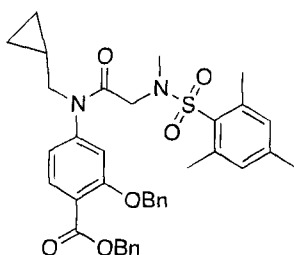


[00101] **Benzyl-2-(benzyloxy)-4-(N-(furan-2-ylmethyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 1.0 mmol scale *via* general procedure **g** (30%): δ_{H} (400 MHz, *d*- CDCl_3) 2.27 (s, 3H, CH_3), 2.54, (s, 6H, 2 CH_3), 2.77 (s, 3H, CH_3), 3.67 (s,

2H,CH₂), 4.77 (s, 2H, CH₂), 5.06 (s, 2H, CH₂), 5.36 (s, 2H, CH₂), 6.08 (d, *J* = 2.0 Hz, 1H, CH), 6.25 (dd, *J* = 8.6 and 2.1 Hz, 1H, CH), 6.60 (m, 2H, CH), 6.92 (s, 2H, CH), 7.27 - 7.49 (m, 11H, CH), 7.84 (d, *J* = 8.6 Hz, 1H, CH); δ_c (100 MHz, *d*-CDCl₃) 20.8, 22.7, 34.6, 66.9, 70.7, 109.4, 110.4, 113.6, 119.8, 126.9, 128.0, 128.1, 128.1, 128.4, 128.5, 131.7, 133.1, 135.6, 135.7, 140.4, 142.1, 142.4, 149.7, 158.8, 165.2, 166.7; LRMS (ES+) Calculated for [C₃₈H₃₈N₂O₇S + H] 666.24, found 667.24.

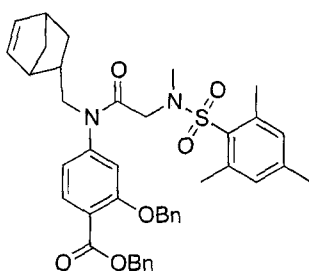


[00102] **Benzyl 2-(benzyloxy)-4-(2-(N-(2,4,6-tetramethylphenyl)sulfonamido)-N-(thiophen-2-ylmethyl)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.9 mmol scale *via* general procedure **g** (24%): δ_H (400 MHz, *d*-CDCl₃) 2.28 (s, 3H, CH₃), 2.56 (s, 6H, 2CH₃), 2.78 (s, 3H, CH₃), 3.67 (s, 2H, CH₂), 4.90 (s, 2H, CH₂), 5.03 (s, 2H, CH₂), 5.36 (s, 2H, CH₂), 6.50-6.63 (m, 2H, 2CH), 6.72 (d, *J* = 3.1 Hz, 1H, CH), 6.86 (m, 1H, CH), 6.91 (s, 2H, CH), 7.21(d, 1H, CH), 7.29 - 7.43 (m, 10H, CH), 7.84 (d, *J* = 8.6 Hz, 1H, CH); δ_c (100 MHz, *d*-CDCl₃) 20.8, 22.7, 29.6, 34.6, 47.5, 49.4, 66.9, 70.7, 113.7, 119.8, 121.0, 125.0, 126.4, 126.9, 127.7, 128.1, 128.4, 128.6, 131.8, 133.2, 135.6, 138.6, 140.5, 142.4, 144.5, 158.8, 165.2, 166.6; LRMS (ES+) Calculated for {C₃₈H₃₈N₂O₆S₂ + H} 682.22, found 683.18.

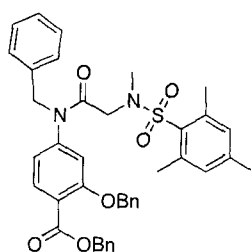


[00103] **Benzyl-2-(benzyloxy)-4-(N-(cyclopropylmethyl)-2-(N-2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.8 mmol scale *via* general procedure **g** (34%): δ_H (400 MHz, *d*-CDCl₃): 0.035 (dd, *J* = 5.1 and 10.0 Hz, 2H, CH₂), 0.33 (dd, *J* = 5.3 and

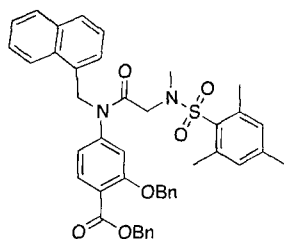
12.9 Hz, 2H, CH₂), 1.05 (br, 1H, CH), (2.27 (s, 1H, CH₃), 2.56 (s, 6H, CH₃), 2.77 (s, 3H, CH₃), 3.47 (d, *J* = 8.3 Hz, 2H, CH₂), 3.67 (s, 2H, CH₂), 5.18 (s, 2H, CH₂), 5.38 (s, 2H, CH₂), 6.77 (dd, *J* = 1.6 and 8.0 Hz, 1H, CH), 6.81 (d, *J* = 1.6 Hz, 1H, CH), 6.92 (s, 2H, CH), 7.25 - 7.46 (m, 10H), 7.89 (d, *J* = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 3.6, 9.6, 14.1, 22.7, 34.6, 53.5, 60.2, 66.9, 70.7, 114.1, 120.1, 120.7, 126.9, 127.9, 128.1, 128.1, 128.4, 128.5, 131.7, 133.1, 135.7, 140.5, 142.2, 145.4, 158.8, 165.2, 166.4 LRMS (ES+) Calculated for [C₃₇H₄₀N₂O₆S] 640.26, found 641.24.



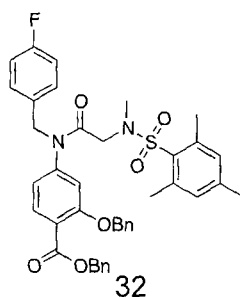
[00104] **Benzyl-2-(benzyloxy)-4-(*N*-(bicyclo[2.2.1]hept-5-en-2-ylmethyl)-2-(*N*,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline 4 was coupled to mesityl derivative 6 on a 0.4 mmol scale *via* general procedure g (25%): δ_H (400 MHz, *d*-CDCl₃) 0.40 (d, *J* = 2.7 Hz, 1H, CH), 0.78 - 0.94 (m, 1H, CH), 1.05 - 1.13 (m, 1H, CH₂), 1.22 - 1.44 (m, 4H, CH) 11.56 - 1.64 (m, 1H, CH), 2.05 - 2.13 (m, 1H, CH), 2.27 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.78 (s, 3H, CH₃), 3.68 (s, 2H, CH₂), 5.19 (d, *J* = 11.2 Hz, 2H, CH), 5.38 (d, *J* = 4.3 Hz, 2H, CH), 5.69 (dd, *J* = 2.5 and 5.4 Hz, 1H, CH), 6.07 (dd, *J* = 3.2, 5.7 Hz, 1H, CH), 6.68-6.78 (m, 2H, CH), 6.92 (s, 2H, CH), 7.25-7.45 (m, 10H, CH), 7.90 (d, *J* = 8.1 Hz, CH); δ_C (100 MHz, *d*-CDCl₃) 30.3, 31.0, 38.4, 38.7, 41.6, 42.3, 44.1, 44.3, 45.1, 47.4, 48.7, 49.5, 65.7, 70.3, 96.9, 104.6, 104.6, 107.6, 126.9, 127.5, 127.6, 127.9, 128.3, 128.4, 131.8, 134.2, 134.3, 136.2, 136.8, 136.9, 137.8, 153.3, 160.9, 165.8. LRMS (ES+) Calculated for [C₄₁H₄₄N₂O₆S] 692.29, found 693.30.



[00105] **Benzyl-4-(N-benzyl-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)-2-(benzyloxy)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.39 mmol scale *via* general procedure **g** (20%): δ_{H} (400 MHz, *d*-CDCl₃): 2.28 (s, 3H, CH₃), 2.55 (s, 6H, 2 CH₃), 2.79 (s, 3H, CH₃), 3.68 (s, 2H, CH₂), 4.79 (s, 2H, CH₂), 4.95 (s, 2H, CH₂), 5.34 (s, 2H, CH₂), 6.47 (s, 1H, CH), 6.51 (d, *J* = 8.0 Hz, 1H, CH), 6.92 (s, 2H, CH), 7.04 - 7.09 (m, 2H, CH), 7.23 - 7.27 (m, 4H, CH), 7.29 - 7.36 (m, 8H, CH), 7.37-7.42 (m, 2H, CH), 7.79 (d, *J* = 8.1 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 20.8, 22.7, 34.7, 49.5, 52.9, 66.9, 70.6, 126.9, 127.6, 127.9, 128.1, 128.1, 128.4, 128.5, 128.7, 131.8, 133.1, 135.6, 136.5, 140.5, 142.4, 158.7, 165.2, 166.8. LRMS (ES+) Calculated for [C₄₀H₄₀N₂O₆S] 676.26, found 677.28.

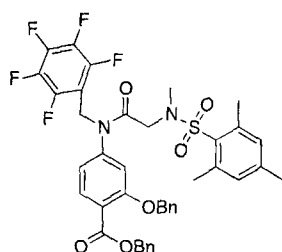


[00106] **Benzyl-2-(benzyloxy)-4-(N-(naphthalen-1-ylmethyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.39 mmol scale *via* general procedure **g** (20%): δ_{H} (400 MHz, *d*-CDCl₃): 2.28 (s, 3H, CH₃), 2.55 (s, 6H, 2 CH₃), 2.79 (s, 3H, CH₃), 3.68 (s, 2H, CH₂), 4.79 (s, 2H, CH₂), 4.95 (s, 2H, CH₂), 5.34 (s, 2H, CH₂), 6.47 (s, 1H, CH), 6.51 (d, *J* = 8.0 Hz, 1H, CH), 6.92 (s, 2H, CH), 7.04-7.09 (m, 2H, CH), 7.23 - 7.27 (m, 4H, CH), 7.29 - 7.36 (m, 8H, CH), 7.37 - 7.42 (m, 2H, CH), 7.79 (d, *J* = 8.1 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 20.8, 22.7, 34.7, 49.5, 52.9, 66.9, 70.6, 126.9, 127.6, 127.9, 128.1, 128.1, 128.4, 128.5, 128.7, 131.8, 133.1, 135.6, 136.5, 140.5, 142.4, 158.7, 165.2, 166.8. LRMS (ES+) Calculated for [C₄₀H₄₀N₂O₆S] 726.28, found 727.28.

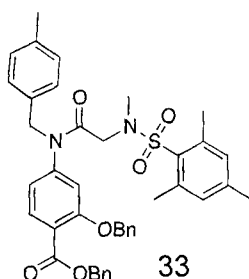


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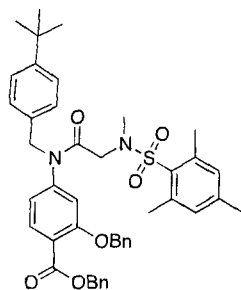
[00107] **Benzyl-2-(benzyloxy)-4-(N-(4-fluorobenzyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.39 mmol scale *via* general procedure **g** (39%): 2.27 (s, 1H, CH₃), 2.54 (s, 6H, CH₃), 2.77 (s, 3H, CH₃), 3.68 (s, 2H, CH₂), 3.73 (s, 2H, CH₂), 5.01 (s, 2H, CH₂), 5.35 (s, 2H, CH₂), 6.37 - 6.64 (m, 2H, CH), 6.87-6.99 (m, 4H, CH), 6.98-7.10 (m, 2H, CH), 7.27 - 7.46 (m, 10H, CH), 7.82 (d, *J* = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 20.8, 22.6, 34.7, 49.5, 52.1, 66.9, 70.6, 113.7, 115.1, 115.3, 119.8, 126.8, 127.9, 128.1, 128.4, 128.5, 130.5, 131.7, 132.3, 133.1, 135.5, 140.4, 142.4, 144.6, 158.7, 165.1, 166.8; LRMS (ES⁺) Calculated for [C₄₀H₃₉FN₂O₆S] 694.25, found 695.25.



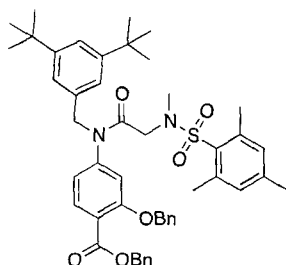
[00108] **Benzyl-2-(benzyloxy)-4-(N-((perfluorophenyl)methyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.27 mmol scale *via* general procedure **g** (58%): 2.28 (s, 1H, CH₃), 2.53 (s, 6H, CH₃), 2.77 (s, 3H, CH₃), 3.66 (s, 2H, CH₂), 4.97 (s, 2H, CH₂), 5.12 (s, 2H, CH₂), 5.36 (s, 2H, CH₂), 6.57 (dd, *J* = 8.6 and 2.1 Hz, 1H, CH), 6.67 (d, *J* = 2.0 Hz, 1H, CH), 6.92 (s, 2H, CH), 7.27-7.46 (m, 10H, CH), 7.83 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 14.0, 20.7, 22.6, 34.7, 39.9, 49.3, 67.0, 70.8, 113.3, 119.4, 121.4, 126.7, 128.0, 128.1, 128.4, 128.5, 131.7, 133.3, 135.4, 135.5, 140.4, 142.5, 143.5, 158.9, 164.9, 166.7; LRMS (ES⁺) Calculated for [C₄₀H₃₅F₅N₂O₆S] 766.21, found 767.25.



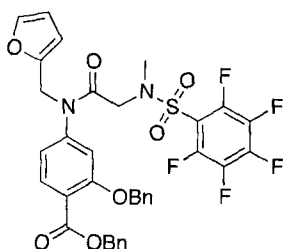
[00109] **Benzyl-2-(benzyloxy)-4-(N-(4-methylbenzyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.39 mmol scale *via* general procedure **g** (28%): δ_{H} (400 MHz, *d*-CDCl₃): 2.28 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 2.55 (s, 6H, 2 CH₃), 2.79 (s, 3H, CH₃), 3.66 (s, 2H, CH₂), 4.73 (s, 2H, CH₂), 4.96 (s, 2H, CH₂), 5.34 (s, 2H, CH₂), 6.38 - 6.57 (m, 2H, 2CH), 6.89 - 6.98 (m, 4H, CH), 7.04 (s, 2H, CH), 7.29 - 7.43 (m, 10H, 10 CH), 7.78 (d, *J* = 8.1 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 20.8, 20.9, 22.6, 34.6, 49.5, 52.5, 66.8, 70.6, 126.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.7, 129.0, 131.7, 133.0, 133.5, 135.6, 137.2, 140.4, 142.3, 158.6, 165.1, 166.6. LRMS (ES+) Calculated for [C₄₁H₄₂N₂O₆S] 690.28, found 691.28.



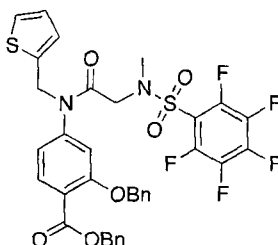
[00110] **Benzyl-2-(benzyloxy)-4-(N-(4-(tert-butyl)benzyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.39 mmol scale *via* general procedure **g** (37%): δ_{H} (400 MHz, *d*-CDCl₃): 1.28 (s, 9H, C(CH₃)), 2.28 (s, 3H, CH₃), 2.55 (s, 6H, 2 CH₃), 2.78 (s, 3H, CH₃), 3.67 (s, 2H, CH₂), 4.75 (s, 2H, CH₂), 4.91 (s, 2H, CH₂), 5.34 (s, 2H, CH₂), 6.44 (d, *J* = 2.0 Hz, 1H, CH), 6.55 (dd, *J* = 2.0 and 8.6 Hz, 1H, CH), 6.92 (s, 2H, CH), 7.01 (d, *J* = 8.4 Hz, 2H, CH), 7.27 (d, *J* = 8.3 Hz, 2H, CH), 7.29-7.48 (m, 10H, 10 CH), 7.80 (d, *J* = 8.3 Hz, 2H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 20.8, 22.6, 31.1, 34.3, 34.6, 49.5, 52.5, 66.8, 70.5, 125.2, 126.9, 127.9, 128.0, 128.1, 128.4, 128.5, 131.7, 133.0, 133.5, 135.6, 140.5, 142.3, 150.6, 158.6, 165.2, 166.6; LRMS (ES+) Calculated for [C₄₄H₄₈N₂O₆S] 732.32, found 733.36.



[00111] **Benzyl-2-(benzyloxy)-4-(N-(3,5-(di-tert-butyl)benzyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to mesityl derivative **6** on a 0.20 mmol scale *via* general procedure **g** (38%): δ_{H} (400 MHz, *d*-CDCl₃): 1.24 (s, 18H, 6CH₃), 2.04 (s, 3H, CH₃), 2.56 (s, 6H, 2 CH₃), 2.76 (s, 3H, CH₃), 3.70 (s, 2H, CH₂), 4.80 (s, 2H, CH₂), 4.85 (s, 2H CH₂), 5.34 (s, 2H, CH₂), 6.42 (d, *J* = 2.0 Hz, 1H, CH), 6.56 (dd, *J* = 2.0, 8.6 Hz, 1H, CH), 6.88 - 6.99 (m, 4H, CH) & 2CH), 7.27-7.44 (m, 11H, CH), 7.80 (d, *J* = 8.31 Hz, 2H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 20.7, 22.6, 31.2, 34.4, 34.6, 49.5, 53.3, 66.8, 70.5, 121.2, 123.0, 126.8, 127.9, 128.0, 128.3, 128.4, 131.7, 132.9, 135.5, 135.6, 140.5, 142.3, 150.9, 158.6, 165.1, 166.4; LRMS (ES⁺) Calculated for [C₄₈H₅₆N₂O₆S] 788.39, found 789.41.

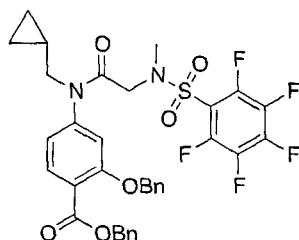


[00112] **Benzyl-2-(benzyloxy)-4-(N-(furan-2-ylmethyl)-2-(2,3,4,5,6-pentafluoro-N-methyl phenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to pentafluoro derivative **6** on a 0.4 mmol scale *via* general procedure **g** (31%): δ_{H} (400 MHz, *d*-CDCl₃) 3.05 (s, 3H, CH₃), 3.84 (s, 2H, CH₂), 4.68 (s, 2H, CH₂), 5.08 (s, 2H, CH₂), 5.36 (s, 2H, CH₂), 6.02 (d, *J* = 3.2 Hz, 1H, CH), 6.25 (m, 1H, CH), 6.58 (d, *J* = 2.0 Hz, 1H, CH), 6.67 (dd, *J* = 8.6, 2.1 Hz, 1H, CH), 7.26 - 7.53 (m, 11H, CH), 7.85 (d, *J* = 8.6 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 35.9, 51.6, 66.9, 70.6, 109.5, 110.3, 113.5, 119.6, 126.9, 128.0, 128.1, 128.4, 128.5, 133.2, 135.5, 142.4, 149.0, 158.7, 165.1; LRMS (ES⁺) Calculated for [C₃₅H₂₇F₅ N₂O₇S + H] 714.15, found 715.16.



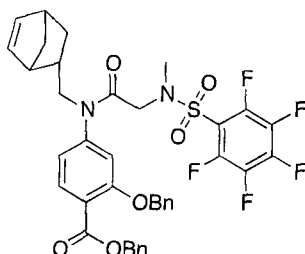
[00113] **Benzyl-2-(benzyloxy)-4-(2-(N-2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-N-(thiophen-2-ylmethyl)acetamido)benzoate.**

Secondary aniline **4** was coupled to pentafluoro derivative **6** on a 0.3 mmol scale *via* general procedure **g** (68%): δ_{H} (400 MHz, *d*-CDCl₃); 3.06 (s, 3H, CH₃), 3.87 (s, 2H, CH₂), 4.86 (s, 2H, CH₂), 5.07 (s, 2H, CH₂), 5.37 (s, 2H, CH₂), 6.60 (d, *J* = 2.0 Hz, 1H, CH), 6.68 (d, *J* = 2.1 Hz, 1H, CH), 6.70 (dd, *J* = 8.6, 2.1 Hz, 1H, CH), 6.88 (m, 1H, CH), 7.25 (d, *J* = 2.6 Hz, 1H, CH), 7.29 - 7.46 (m, 10H, CH), 7.88 (d, *J* = 8.6 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 14.0, 20.8, 24.5, 35.8, 36.4, 47.4, 51.6, 60.2, 66.9, 70.6, 113.6, 119.7, 121.3, 126.1, 126.4, 126.9, 127.7, 128.0, 128.1, 128.4, 128.5, 133.2, 135.5, 137.9, 143.7, 158.7, 165.1, 165.7; LRMS (ES⁺) Calculated for {C₃₅H₂₇F₅N₂O₆S + H} 730.12, found 731.12.



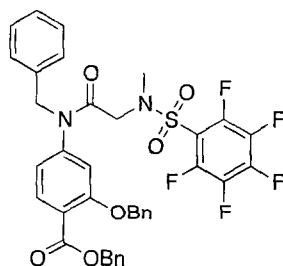
[00114] **Benzyl-2-(benzyloxy)-4-(N-(cyclopropylmethyl)-2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to pentafluoro derivative **6** on a 0.5 mmol scale *via* general procedure **g** (93%): δ_{H} (400 MHz, *d*-CDCl₃); 0.01 (dd, *J* = 5.1 and 10.0 Hz, 2H, CH₂), 0.36 (dd, *J* = 5.3 and 12.9 Hz, 2H, CH₂), 0.73 (br, 1H, CH), 3.04 (s, 3H, CH₃), 3.38 (d, *J* = 7.19 Hz, 2H, CH₂), 3.86 (s, 2H, CH₂), 5.22 (s, 2H, CH₂), 5.38 (s, 2H, CH₂), 6.84 (d, *J* = 1.6 Hz, 1H, CH), 6.85 (dd, *J* = 1.6 and 8.0 Hz, 1H, CH), 7.28 - 7.47 (m, 10H, CH), 7.91 (d, *J* = 8.0 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 3.4, 9.3, 14.0, 35.9, 51.7, 53.6, 66.9, 70.7,

113.9, 119.9, 126.9, 127.9, 128.1, 128.4, 128.5, 133.2, 135.5, 135.6, 144.7, 158.7, 165.1, 165.6; LRMS (ES+) Calculated for [C₃₄H₂₉F₅N₂O₆S] 688.17, found 689.19.



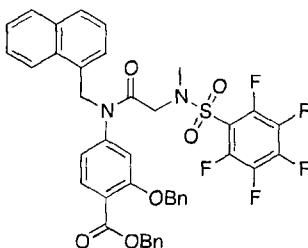
[00115] **Benzyl-2-(benzyloxy)-4-(N-(bicyclo[2.2.1]hept-5-en-2-ylmethyl)-2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetamido)benzoate.**

Secondary aniline 4 was coupled to pentafluoro derivative 6 on a 0.3 mmol scale *via* general procedure g (84%): δ_{H} (400 MHz, *d*-CDCl₃) 0.40 (d, *J* = 2.7 Hz, 1H, CH₂), 0.78 - 0.94 (m, 1H, CH), 1.05 - 1.13 (m, 1H, CH₂) 1.22 - 1.44 (m, 4H, CH) 11.56 - 1.64 (m, 1H, CH), 2.05 - 2.13 (m, 1H, CH), 2.78 (s, 3H, CH₃), 3.68 (s, 2H, CH₂), 5.19 (s, 2H, CH), 5.38 (s, 2H, CH), 5.69 (dd, *J* = 2.5 and 5.4 Hz, 1H, CH), 6.07 (*J* = 3.2, 5.7 Hz, 1H, CH), 6.68 - 6.78 (m, 2H, CH), 6.92 (s, 2H, CH), 7.25 - 7.45 (m, 10H, CH), 7.90 (d, *J* = 8.1 Hz, CH); δ_{C} (100 MHz, *d*-CDCl₃) 29.8, 35.9, 37.0, 41.7, 42.0, 44.2, 45.0, 49.3, 51.9, 53.4, 66.9, 70.7, 113.6, 119.4, 126.8, 126.9, 128.0, 128.1, 128.4, 128.6, 131.8, 133.2, 135.6, 137.4, 144.8, 158.7, 165.1, 165.6; LRMS (ES+) Calculated for [C₃₈H₃₃F₅N₂O₆S] 740.20, found 741.21.

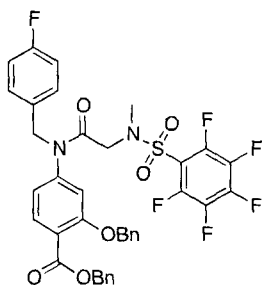


[00116] **Benzyl-4-(N-benzyl-2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetamido)-2-(benzyloxy)benzoate.** Secondary aniline 4 was coupled to pentafluoro derivative 6 on a 0.5 mmol scale *via* general procedure g (64%): δ_{H} (400 MHz, *d*-CDCl₃): 3.05 (s, 3H, CH₃), 3.87 (s, 2H, CH₂), 4.71 (s, 2H, CH₂), 4.99 (s, 2H, CH₂), 5.35 (s, 2H, CH₂), 6.49 (s, 1H, CH), 6.63 (d, *J* = 8.0 Hz, 1H, CH), 7.03 (m, 2H, CH), 7.19-7.44 (m, 12H, CH) 7.83(d, *J* = 8.1 Hz, 1H, CH); δ_{C} (100 MHz, *d*-

CDCl₃) 35.8, 51.8, 52.9, 66.9, 70.6, 113.8, 119.8, 121.2, 126.9, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 128.6, 133.2, 135.5, 135.9, 144.0, 158.6, 165.1, 165.8; LRMS (ES+) Calculated for [C₃₇H₂₉F₅N₂O₆S] 724.17, found 725.17.

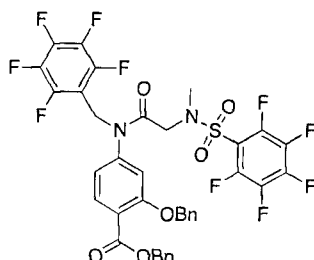


[00117] **Benzyloxy-2-(benzyloxy)-4-(N-(naphthalen-1-ylmethyl)-2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to pentafluoro derivative **6** on a 0.5 mmol scale *via* general procedure **g** (83 %): δ_H (400 MHz, *d*-CDCl₃): 3.06 (s, 3H, CH₃), 3.90 (s, 2H, CH₂), 4.87 (s, 2H, CH₂), 4.88(s, 2H CH₂), 5.33 (s, 2H, CH₂), 6.48 (s, 1H, CH), 6.63 (d, *J* = 8.0 Hz, 1H, CH), 7.14 - 7.53 (m, 14H, CH) 7.67 - 7.88 (m, 3H, CH) δ_C (100 MHz, *d*-CDCl₃) 35.8, 51.9, 53.0, 66.9, 70.6, 113.8, 119.8, 126.1, 126.2, 126.8, 127.5, 127.6, 127.8, 127.9, 128.1, 128.4, 132.7, 132.9, 133.2, 133.3, 135.4, 135.5, 158.7, 165.0, 166.0; LRMS (ES+) Calculated for [C₄₁H₃₁F₅N₂O₆S] 774.18, found 775.19



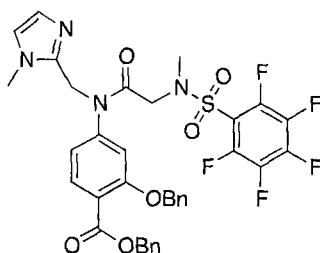
[00118] **Benzyloxy-2-(benzyloxy)-4-(N-(4-fluorobenzyl)-2-(2,3,4,5,6-pentafluoro-N-phenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to pentafluoro derivative **6** on a 0.2 mmol scale *via* general procedure **g** (73%): 3.05 (s, 3H, CH₃), 3.88 (s, 2H, CH₂), 4.67 (s, 2H, CH₂), 5.05(s, 2H, CH₂), 5.36 (s, 2H, CH₂), 6.53 (s, 2H, CH), 6.61 (dd, *J* = 2.05, 8.63Hz, 2H, CH), 6.87-7.04 (m, 4H, CH), 7.28 - 7.48 (m, 10H, CH), 7.84 (d, *J* = 8.0 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 35.8, 50.8, 51.8, 52.2,

67.0, 70.6, 113.7, 115.2, 115.4, 119.8, 121.3, 126.8, 128.0, 128.1, 128.4, 128.5, 130.3, 130.4, 131.7, 133.2, 135.4, 135.5, 143.8, 158.7, 161.0, 163.4, 165.0, 165.9; LRMS (ES+) Calculated for [C₃₇H₂₉F₆N₂O₆S] 742.16, found 743.16.



[00119] **Benzyl-2-(benzyloxy)-4-(2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-N-((perfluorophenyl)methyl)acetamido)benzoate.**

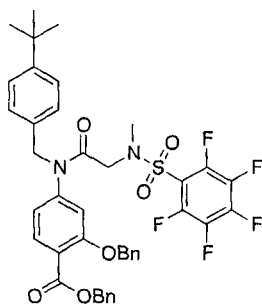
Secondary aniline 4 was coupled to pentafluoro derivative 6 on a 0.1 mmol scale *via* general procedure g (74 %): 3.04 (s, 3H, CH₃), 3.85 (s, 2H, CH₂), 4.88 (s, 2H, CH₂), 5.15 (s, 2H, CH₂), 5.36 (s, 2H, CH₂), 6.65 (d, *J* = 2.0 Hz, 1H, CH), 6.69 (dd, *J* = 8.6, 2.1 Hz, 1H, CH), 7.28-7.50 (m, 10H, CH), 7.87 (d, *J* = 8.6 Hz, 1H, CH); δ_C (100 MHz, *d*-CDCl₃) 35.3, 35.6, 48.3, 65.6, 70.9, 104.6, 112.2, 113.9, 115.4, 116.7, 127.1, 128.9, 131.3, 136.1, 136.2, 137.8, 141.4, 144.7, 147.3, 161.2, 166.8, 168.4; LRMS (ES+) Calculated for [C₃₇H₂₄F₁₀N₂O₆S] 814.12, found 815.14.



[00120] **Benzyl-2-(benzyloxy)-4-(N-((1-methyl-1H-imidazol-2-yl)methyl)-2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetamido)benzoate.**

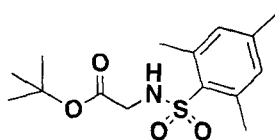
Secondary aniline 4 was coupled to pentafluoro derivative 6 on a 0.2 mmol scale *via* general procedure g (72%): δ_H (400 MHz, *d*-CDCl₃) 2.28 (s, 3H, CH₃), 3.80 (d, *J* = 3.1 Hz, 3H, CH₃), 3.20 (s, 2H, CH₂), 4.22 (s, 2H, CH₂), 4.51 (s, 2H, CH₂), 4.76 (s, 2H, CH₂),

6.26 (dd, $J = 8.6, 2.1$ Hz, 1H, CH), 6.29 (s, 2H, CH), 6.78 - 6.99 (m, 10H, CH), 6.35 (s, 1H, CH), 6.41 (s, 1H, CH), 7.68 (d, $J = 2.0$ Hz, 1H, CH), 7.44 (d, $J = 8.6$ Hz, 1H, CH); δ_C (100 MHz, d -CDCl₃) 33.4, 35.6, 48.1, 49.3, 65.6, 70.7, 104.5, 112.3, 113.8, 116.2, 120.2, 126.8, 127.1, 127.6, 128.8, 130.4, 131.1, 136.3, 136.7, 137.2, 144.9, 147.0, 152.3, 161.3, 166.5, 168.3; LRMS (ES+) Calcd for [C₃₅H₂₉F₅N₄O₆S + H] 728.17 found 729.18.



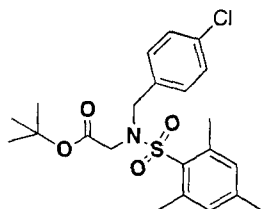
[00121] **Benzyl-2-(benzyloxy)-4-(N-(4-(tert-butyl)benzyl)-2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)acetamido)benzoate.** Secondary aniline **4** was coupled to pentafluoro derivative **6** on a 0.4 mmol scale *via* general procedure **g** (98%): δ_H (400 MHz, d -CDCl₃): 1.29 (s, 9H, C(CH₃)), 3.04 (s, 3H, CH₃), 3.85 (s, 2H, CH₂), 4.67 (s, 2H, CH₂), 4.94 (s, 2H, CH₂), 5.34 (s, 2H, CH₂), 6.46 (d, $J = 2.0$ Hz, 1H, CH), 6.65 (dd, $J = 2.0, 8.6$ Hz, 1H, CH), 6.96 (d, $J = 8.7$ Hz, 2H, CH), 7.27-7.42 (m, 12H, CH), 7.83 (d, $J = 8.3$ Hz, 2H, CH); δ_C (100 MHz, d -CDCl₃) 31.1, 34.3, 35.8, 51.8, 52.6, 66.9, 70.6, 113.8, 119.8, 125.3, 126.9, 128.0, 128.1, 128.4, 128.5, 132.9, 133.2, 135.4, 135.5, 150.8, 158.6, 165.1; LRMS (ES+) Calculated for [C₄₁H₃₇F₅N₂O₆S] 780.23, found 781.23.

[00122] *Synthesis of the tetrapodal Inhibitors (13a-d)*

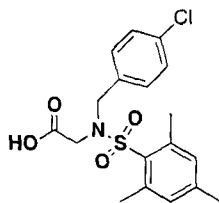


[00123] **tert-butyl (mesitylsulfonyl)glycinate.** Derivative **9** synthesized using general procedure **d** (71%): δ_H (400 MHz, CDCl₃) 1.36 (s, 9H, (CH₃)₃), 2.29 (s, 3H,

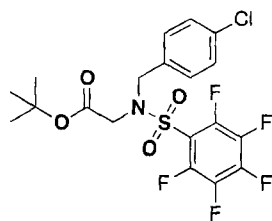
CH₃), 2.65 (s, 6H, CH₃), 3.60 (d, $J = 5.4$ Hz, 2H, CH₂), 5.08 (t, $J = 5.13$ Hz, 2H, CH); δ_C (400 MHz, CDCl₃) 20.8, 23.0, 27.7, 46.5, 81.9, 130.0, 137.4, 140.1, 145.0, 167.5; LRMS (ES+) calculated for [C₁₅H₂₃NO₄S + H] 313.13, found 314.11.



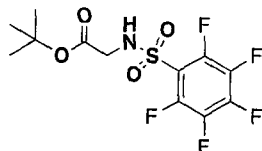
[00124] **tert-butyl N-(4-chlorobenzyl)-N-(mesitylsulfonyl)glycinate.** Derivative **10** synthesized using general procedure **e** (77%): δ_H (400 MHz, CDCl₃) 1.34 (s, 9H, (CH₃)₃), 2.29 (s, 3H, CH₃), 2.63 (s, 6H, CH₃), 3.70 (s, 2H, CH₂), 4.49 (s, 2H, CH₂) 6.95 (s, 2H, CH), 7.08 (d, $J = 8.1$ Hz, 2H, CH), 7.25 (d, $J = 8.1$ Hz, 2H, CH); δ_C (400 MHz, CDCl₃) 20.8, 23.0, 27.7, 46.5, 51.8, 81.9, 128.6, 130.0, 132.3, 134.6, 137.4, 140.1, 145.0, 167.5; LRMS (ES+) calculated for [C₂₂H₂₈ClNO₄S + H] 437.14, found 438.10.



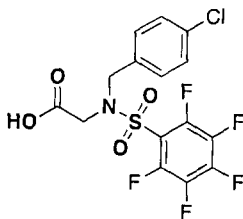
[00125] **N-(4-chlorobenzyl)-N-(mesitylsulfonyl)glycine.** Derivative **11** synthesized using general procedure **f** (90%): δ_H (400 MHz, CDCl₃) 2.29 (s, 3H, CH₃), 2.63 (s, 6H, CH₃), 3.70 (s, 2H, CH₂), 4.49 (s, 2H, CH₂) 6.95 (s, 2H, CH), 7.08 (d, $J = 8.0$ Hz, 2H, CH), 7.25 (d, $J = 8.0$ Hz, 2H, CH); δ_C (400 MHz, CDCl₃) 20.8, 23.0, 46.5, 51.8, 128.6, 130.0, 132.3, 134.6, 137.4, 140.1, 145.0, 167.5; LRMS (ES+) calculated for [C₁₈H₂₀ClNO₄S + H] 381.08, found 382.07.



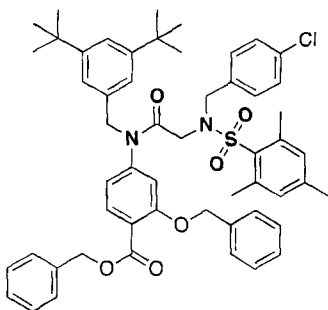
[00126] **tert-butyl ((perfluorophenyl)sulfonyl)glycinate.** Derivative **9** synthesized using general procedure **d** (71%): δ_{H} (400 MHz, CDCl_3) 1.40 (s, 9H, $\text{COO}(\text{CH}_3)_3$), 3.93 (s, 2H, CH_2), 5.54 (s, 1H, NH); δ_{C} (400 MHz, CDCl_3) 27.5, 45.1, 82.8, 115.6, 136.5, 144.8, 145.9, 167.0; LRMS (ES+) calculated for $[\text{C}_{12}\text{H}_{12}\text{F}_5\text{NO}_4\text{S} + \text{H}]$ 361.04, found 362.09.



[00127] **tert-butyl N-(4-chlorobenzyl)-N-((perfluorophenyl)sulfonyl)glycinate.** Derivative **10** synthesized using general procedure **e** (71%): δ_{H} (400 MHz, CDCl_3) 1.37 (s, 9H, $(\text{CH}_3)_3$), 3.93 (s, 2H, CH_2), 4.57 (s, 2H, CH_2), 7.24 (d, $J = 8.5$ Hz, 2H, CH), 7.33 (d, $J = 8.5$ Hz, 2H, CH); δ_{C} (400 MHz, CDCl_3) 27.5, 52.5, 53.0, 81.8, 112.6, 126.5, 130.1, 132.4, 134.3, 136.5, 144.8, 145.9, 167.0; LRMS (ES+) calculated for $[\text{C}_{19}\text{H}_{17}\text{F}_5\text{ClNO}_4\text{S} + \text{H}]$ 485.05, found 486.10.

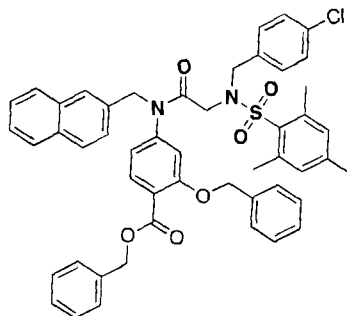


[00128] **N-(4-chlorobenzyl)-N-((perfluorophenyl)sulfonyl)glycine.** Derivative **11** synthesized using general procedure **f** (92%): δ_{H} (400 MHz, CDCl_3) 4.13 (s, 2H, CH_2), 4.58 (s, 2H, CH_2), 7.25 (d, $J = 8.2$ Hz, 2H, CH), 7.35 (d, $J = 8.2$ Hz, 2H, CH); δ_{C} (400 MHz, CDCl_3) 52.8, 54.2, 112.6, 126.5, 130.1, 132.4, 134.3, 136.5, 144.8, 145.9, 172.0; LRMS (ES+) calculated for $[\text{C}_{15}\text{H}_9\text{F}_5\text{ClNO}_4\text{S} + \text{H}]$ 428.99, found 429.99.



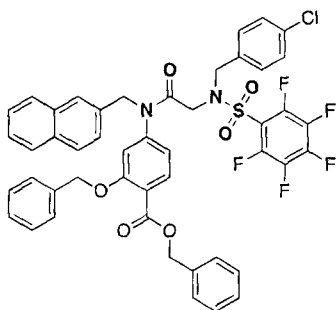
[00129] **Benzyl-2-(benzyloxy)-4-(2-((N-(4-chlorobenzyl)-2,4,6-trimethylphenylsulfonamido)-N-(3,5-di-tert-butylbenzyl)acetamido)benzoate.**

Derivative 12 synthesized using general procedure g (55%): δ_{H} (400 MHz, CDCl_3) 1.26 (s, 18H, $(\text{CH}_3)_3$), 2.31 (s, 3H, CH_3), 2.60 (s, 6H, CH_3), 3.58 (s, 2H, CH_2), 4.56 (s, 2H, CH_2), 4.75 (s, 4H, CH_2), 5.32 (s, 2H, CH_2), 6.24 (br s, 2H, CH), 6.93 (s, 2H, CH), 6.96 (s, 2H, CH), 7.03 (d, $J = 8.1$ Hz, 2H, CH), 7.14 (d, $J = 8.1$ Hz, 2H, CH), 6.93 (s, 2H, CH), 7.29-7.38 (m, 10H, CH), 7.70 (d, $J = 8.1$ Hz, 1H, CH); δ_{C} (400 MHz, CDCl_3) 20.8, 22.8, 31.4, 34.6, 45.7, 49.5, 53.3, 66.9, 70.5, 113.5, 120.0, 121.3, 123.4, 127.0, 127.9, 128.0, 128.3, 128.4, 128.5, 130.3, 131.9, 132.6, 133.7, 135.4, 135.5, 140.3, 142.5, 150.9, 158.5, 165.2, 166.2; LRMS (ES+) calculated for $[\text{C}_{54}\text{H}_{59}\text{ClN}_2\text{O}_6\text{S} + \text{H}]$ 898.38, found 899.39.



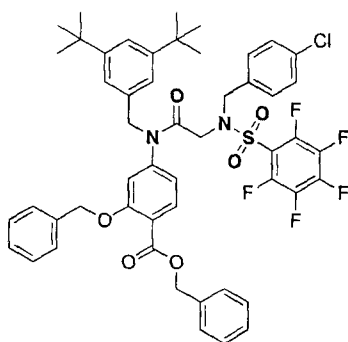
[00130] **Benzyl 2-(benzyloxy)-4-(2-((N-(4-chlorobenzyl)-2,4,6-trimethylphenylsulfonamido)-N-(naphthalen-2-ylmethyl)acetamido)benzoate.**

Derivative 12 synthesized using general procedure g (72%): δ_{H} (400 MHz, CDCl_3) 2.27 (s, 3H, CH_3), 2.59 (s, 6H, CH_3), 3.58 (s, 2H, CH_2), 4.62 (s, 2H, CH_2), 4.71 (s, 2H, CH_2), 4.86 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 6.21 (d, $J = 7.9$ Hz, 1H, CH), 6.27 (s, 1H, CH), 6.94 (s, 2H, CH), 7.07 (d, $J = 8.5$ Hz, 2H, CH), 7.16 (d, $J = 8.5$ Hz, 2H, CH), 7.19 (d, $J = 8.1$ Hz, 2H, CH), 7.22-7.27 (m, 2H, CH), 7.28-7.38 (m, 5H, CH), 7.42-7.53 (m, 4H, CH), 7.62-7.78 (m, 4H, CH), 7.82 (d, $J = 8.5$ Hz, 1H, CH); δ_{C} (400 MHz, CDCl_3) 20.8, 22.8, 45.6, 49.9, 52.9, 66.9, 70.5, 126.0, 126.2, 126.8, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 130.1, 131.8, 132.5, 132.6, 132.9, 133.6, 133.8, 135.3, 135.5, 140.3, 142.5, 158.6, 165.1, 166.6; LRMS (ES+) calculated for $[\text{C}_{50}\text{H}_{45}\text{ClN}_2\text{O}_6\text{S} + \text{H}]$ 836.27, found 837.28.



[00131] **Benzyl 2-(benzyloxy)-4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(naphthalen-2-ylmethyl)acetamido)benzoate.**

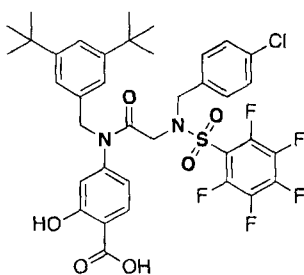
Derivative 12 synthesized using general procedure g (61%): δ_{H} (400 MHz, CDCl_3) 3.77 (s, 2H, CH_2), 4.67 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 4.83 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 6.31 (d, 1H, CH), 6.39 (d, $J = 8.3$ Hz, 1H, CH), 7.13-7.23 (m, 5H, CH), 7.23-7.29 (m, 5H, CH), 7.29-7.36 (m, 5H, CH), 7.41 (s, 1H, CH), 7.45-7.54 (m, 2H, CH), 7.64-7.75 (m, 2H, CH), 7.78 (d, $J = 8.4$ Hz, 1H, CH), 7.81-7.89 (m, 1H, CH); δ_{C} (400 MHz, CDCl_3) 47.5, 50.5, 53.0, 66.9, 70.6, 113.2, 119.5, 121.3, 126.1, 126.3, 126.9, 127.5, 127.9, 128.1, 128.3, 128.4, 128.9, 129.9, 132.7, 132.9, 133.1, 133.2, 134.3, 135.2, 135.4, 143.7, 158.7, 165.0, 165.8; LRMS (ES+) calculated for $[\text{C}_{47}\text{H}_{34}\text{ClF}_5\text{N}_2\text{O}_6\text{S} + \text{H}]$ 884.17, found 885.19.



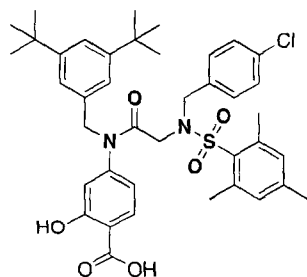
[00132] **Benzyl 2-(benzyloxy)-4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(3,5-di-tert-butylbenzyl)acetamido)benzoate.**

Derivative 12 synthesized using general procedure g (61%): δ_{H} (400 MHz, CDCl_3) 1.25 (s, 18H, $(\text{CH}_3)_3$), 3.75 (s, 2H, CH_2), 4.63 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 5.30 (s, 2H, CH_2), 6.25 (s, 1H, CH), 6.33 (d, $J = 8.1$ Hz, 1H, CH), 6.85 (s, 2H, CH),

7.17 (d, $J = 8.5$ Hz, 2H, CH), 7.25 (d, $J = 8.5$ Hz, 2H, CH), 7.28-7.37 (m, 12H, CH), 7.78 (d, $J = 8.1$ Hz, 1H, CH); δ_C (400 MHz, $CDCl_3$) 31.1, 34.5, 47.6, 50.3, 53.3, 111.3, 116.2, 117.2, 118.9, 121.6, 123.0, 128.9, 129.9, 132.0, 132.5, 134.3, 134.4, 136.4, 138.9, 143.5, 145.0, 145.9, 146.8, 151.0, 162.7, 165.3, 172.2; LRMS (ES+) calculated for $[C_{51}H_{48}ClF_5N_2O_6S + H]$ 946.28, found 947.30.

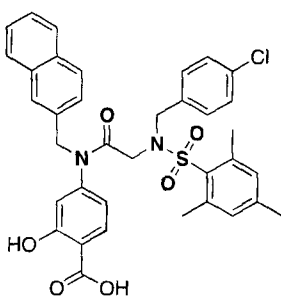


[00133] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(3,5-di-tert-butylbenzyl)acetamido)-2-hydroxybenzoic acid.** Derivative 13a synthesized using general procedure h (76%): δ_H (400 MHz, $CDCl_3$) 1.25 (s, 18H, $(CH_3)_3$), 3.80 (s, 2H, CH_2), 4.61 (s, 2H, CH_2), 4.73 (s, 2H, CH_2), 6.25 (s, 1H, CH), 6.36 (s, 1H, CH), 6.88 (s, 2H, CH), 7.15 (d, $J = 8.5$ Hz, 2H, CH), 7.24 (d, $J = 8.5$ Hz, 2H, CH), 7.31 (s, 1H, CH), 7.75 (d, $J = 8.5$ Hz, 1H, CH); δ_C (400 MHz, $CDCl_3$) 31.1, 34.5, 47.6, 50.3, 121.6, 128.7, 128.9, 129.9, 132.5, 134.4, 151.0, 162.7, 172.4; LRMS (ES+) calculated for $[C_{37}H_{36}ClF_5N_2O_6S + H]$ 766.19, found 765.18; HPLC (I), (II) $t_R = 48.22$ min (95.25%).

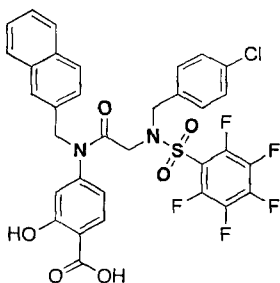


[00134] **4-(2-((N-(4-chlorobenzyl)-2,4,6-trimethylphenyl)sulfonamido)-N-(3,5-di-tert-butylbenzyl)acetamido)-2-hydroxybenzoic acid.** Derivative 13b synthesized using general procedure h (59%): δ_H (400 MHz, $CDCl_3$) 1.25 (s, 18H, $(CH_3)_3$), 2.29 (s, 3H, CH_3), 2.60 (s, 6H, CH_3), 3.59 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 6.11

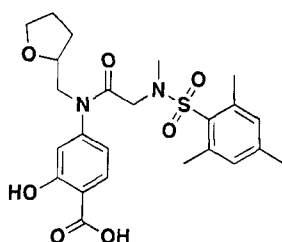
(s, 1H, CH), 6.25 (s, 1H, CH), 6.92 (s, 2H, CH), 6.96 (s, 2H, CH), 7.05 (d, $J = 8.3$ Hz, 2H, CH), 7.14 (d, $J = 8.3$ Hz, 2H, CH), 7.31 (s, 1H, CH), 7.73 (d, $J = 8.3$ Hz, 1H, CH); δ_C (400 MHz, $CDCl_3$) 20.6, 20.8, 22.7, 31.2, 34.5, 45.6, 49.6, 53.3, 117.1, 118.9, 121.4, 123.2, 128.6, 130.2, 131.9, 132.4, 133.6, 133.7, 134.8, 140.3, 142.6, 147.3, 150.8, 162.6, 166.1, 173.1, 177.4; LRMS (ES+) calculated for $[C_{40}H_{47}ClN_2O_6S + H]$ 718.28, found 717.3; HPLC (I) $tR = 32.08$ min (97.63%), (II) $tR = 49.69$ min (97.12%).



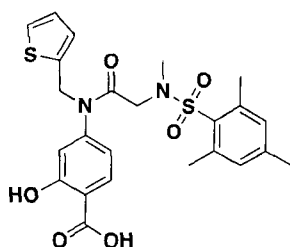
[00135] **4-(2-((N-(4-chlorobenzyl)-2,4,6-trimethylphenyl)sulfonamido)-N-(naphthalene-2-ylmethyl)acetamido)-2-hydroxybenzoic acid.** Derivative **13c** synthesized using general procedure **h** (72%): δ_H (400 MHz, $CDCl_3$) 2.34 (s, 3H, CH_3) 2.63 (s, 6H, CH_3) 3.88 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 6.31 (s, 1H, CH), 6.51 (s, 1H, CH), 7.03 (s, 2H, CH), 7.08 (d, $J = 8.3$ Hz, 2H, CH) 7.20 (d, $J = 8.3$ Hz, 2H, CH), 7.44-7.49 (m, 2H, CH), 7.67-7.93 (m, 5H, CH); δ_C (400 MHz, $CDCl_3$) 21.0, 23.0, 47.5, 50.5, 53.0, 107.0, 107.2, 110.7, 125.1, 126.0, 127.6, 1270, 127.3, 128.6, 130.1, 131.7, 132.5, 133.7, 134.2, 135.2, 137.7, 141.1, 143.8, 145.1, 148.3, 163.1, 166.9, 173.2 LRMS (ES+) calculated for $[C_{36}H_{33}ClN_2O_6S + H]$ 656.17, found 655.20; HPLC (I) $tR = \#$ min (#%), (II) $tR = \#$ min (#%). Fill in the blanks



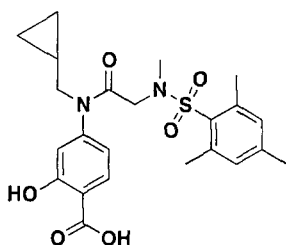
[00136] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(naphthalene-2-ylmethyl)acetamido)-2-hydroxybenzoic acid.** Derivative 13d synthesized using general procedure h (61%): δ_{H} (400 MHz, CDCl_3) 3.88 (s, 2H, CH_2), 4.66 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 6.31 (s, 1H, CH), 6.51 (s, 1H, CH), 7.15-7.36 (m, 4H, CH), 7.41-7.57 (m, 3H, CH), 7.67-7.93 (m, 5H, CH); δ_{C} (400 MHz, CDCl_3) 47.5, 50.5, 53.1, 66.9, 70.6, 113.2, 119.6, 121.2, 126.2, 126.3, 126.9, 127.5, 127.6, 127.8, 127.9, 128.1, 128.4, 128.6, 128.9, 129.9, 132.7, 132.9, 133.1, 133.2, 134.3, 135.2, 135.4, 143.7, 158.7, 165.0, 165.8; LRMS (ES+) calculated for $[\text{C}_{33}\text{H}_{22}\text{ClF}_5\text{N}_2\text{O}_6\text{S} + \text{H}]$ 704.08, found 703.09; HPLC (I) $t_R = 26.58$ min (94.41%), (II) $t_R = 41.17$ min (84.06%).



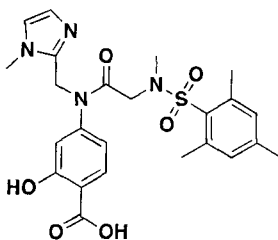
[00137] **2-(hydroxy)-4-(N-(tetrahydrofuran-2-yl)methyl)-2-(N,2,4,6-tetramethylphenylsulfonamido)acetamido)benzoic acid.** Derivative 8a hydrogenated on a 0.3 mmol scale via general procedure h (95%): δ_{H} (400 MHz, $d\text{-CDCl}_3$) 1.79-2.04 (m, 4H, 2CH_2), 2.29 (s, 3H, $\text{CH}_3(\text{Ph})$), 2.57 (s, 6H, $2\text{CH}_3(\text{Ph})$), 2.82 (s, 3H, CH_3NSO_2), 3.61-3.79 (m, 2H, COCH_2), 3.80-3.89 (m, 4H, NHCH_2 THF, O-CH_2), 4.02-4.17 (m, 1H, CH), 6.72 (d, $J = 8.3$ Hz, 1H, CH (Ph)), 6.79 (s, 1H, CH (Ph)), 6.93 (s, 2H, CH), 7.83 (d, $J = 8.3$ Hz, 1H, CH); δ_{C} (100 MHz, $d\text{-CDCl}_3$) 21.1, 22.9, 25.4, 29.3, 29.8, 34.9, 49.9, 53.3, 68.1, 117.1, 119.1, 131.7, 132.1, 132.3, 140.8, 142.9, 148.0, 163.1; HRMS (ES+) Calculated for $[\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_7\text{S} + \text{H}]$ 490.18, found 491.20; HPLC (I) $t_R = 16.45$ min (96.95%), (II) $t_R = 24.99$ min (96.49%).



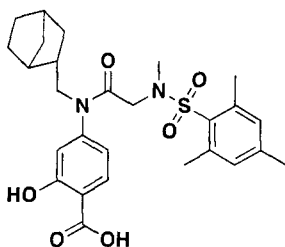
[00138] **2-(hydroxy)-4-(2-((N, 2,4,6 tetramethylphenylsulfonamido)-N-(thiophen-2-ylmethyl)acetamido)benzoic acid.** Derivative **8b** hydrogenated on a 0.2 mmol scale via general procedure **h** (82%); δ_{H} (400 MHz, *d*-CDCl₃) 2.28 (s, 3H, CH₃(Ph)), 2.57 (s, 6H, 2CH₃), 2.85 (s, 3H, CH₃NSO₂), 3.79 (s, 2H, COCH₂), 4.94 (s, 2H, CH₂Ar), 6.48 (d, 1H, *J* = 8.3 Hz, CH), 6.58 (s, 1H, CH), 6.77 (d, 1H, *J* = 3.1 Hz, CH), 6.85-6.87 (m, 1H, CH), 6.93 (s, 2H, CH), 7.21 (d, 1H, *J* = 5.3 Hz, CH), 7.88 (d, 1H, *J* = 8.4 Hz, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.8, 22.6, 29.5, 34.6, 47.6, 49.5, 118.8, 125.9, 126.4, 127.5, 131.4, 131.8, 132.4, 138.3, 140.6, 142.6, 165.2; HRMS (ES⁺) Calculated for [C₂₄H₂₆N₂O₆S₂ + H] 502.12, found 503.1; HPLC (I) *t*R = 18.77 min (87.95%), (II) *t*R = 29.19 min (87.95%).



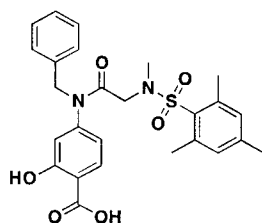
[00139] **4-(N-(cyclopropylmethyl)-2-((N,2,4,6 tetramethylphenyl)sulfonamido)-acetamido)-2-benzoic acid.** Derivative **8d** hydrogenated on a 0.3 mmol scale via general procedure **h** (90%); δ_{H} (400 MHz, *d*-CDCl₃) 0.05-0.18 (m, 2H, CH₂), 0.37-0.49 (m, 2H, CH₂), 0.77-0.97 (m, 1H, CH), 2.28 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.83 (s, 3H, CH₃), 3.53 (d, *J* = 71.2 Hz, 2H), 3.79 (s, 2H, CH₂), 6.71 (d, *J* = 8.4 Hz, 1H CH), 6.77 (d, *J* = 1.4 Hz, 1H, CH), 6.94 (s, 2H, CH), 7.94 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 3.6, 9.6, 20.6, 20.8, 22.6, 29.5, 34.7, 49.5, 53.6, 111.9, 117.2, 119.2, 131.5, 131.8, 132.3, 140.6, 142.6, 147.9, 162.9, 166.7, 172.7, 177.3; HRMS (ES⁺) Calculated for [C₂₃H₂₆N₂O₆S + H] 460.17, found 461.2; HPLC (I) *t*R = 18.10 min (93.12%), (II) *t*R = 27.83 min (93.25%).



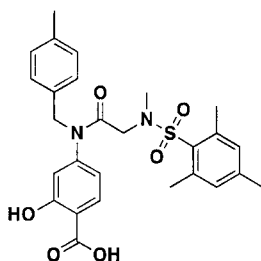
[00140] **2-hydroxy-4-(N-((1-methyl-1H-imidazol-2-yl)methyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)benzoic acid.** Derivative **8c** hydrogenated on a 0.15 mmol scale via general procedure **h** (40%); δ_{H} (400 MHz, *d*-CDCl₃) 2.28 (s, 3H, CH₃), 2.50 (s, 6H, CH₃), 2.81 (s, 3H, CH₃), 3.78 (s, 2H, CH₂), 4.06 (s, 2H, CH₂), 6.40 (d, *J* = 8.4 Hz, 1H, CH), 6.46 (s, 1H, CH), 6.91 (s, 2H, CH), 7.00 (s, 1H, CH), 7.25 (s, 1H, CH), 7.65 (d, *J* = 8.2 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.8, 22.6, 33.1, 34.6, 47.8, 49.5, 106.0, 113.2, 120.5, 127.1, 131.4, 131.9, 138.2, 140.6, 142.9, 147.3, 152.4, 164.8, 166.9, 171.8; HRMS (ES+) Calculated for [C₂₄H₂₈N₄O₆S + H] 500.17, found 501.20; HPLC (I) *t*R = 10.65 min (98.04%), (II) *t*R = 15.79 min (83.06%).



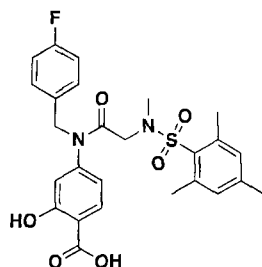
[00141] **4-(N-(bicyclo[2.2.1]heptan-2-ylmethyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)-2-hydroxybenzoic acid.** Derivative **8e** hydrogenated on a 0.14 mmol scale via general procedure **h** (35%); δ_{H} (400 MHz, *d*-CDCl₃) 0.78-1.06 (m, 2H, CH₂), 1.07-1.22 (m, 2H, CH₂), 1.29-1.60 (m, 3H, CH₂, CH), 1.82-2.04 (m, 2H, CH), 2.22 (s, 3H, CH₃), 2.47 (s, 6H, CH₃), 2.70 (s, 3H, CH₃), 3.45 (s, 2H, CH₂), 3.63 (s, 2H, CH₂), 3.81 (s, 2H, CH₂), 6.51 (d, *J* = 8.0 Hz, 1H, CH), 6.64 (s, 1H, CH), 6.86 (s, 2H, CH), 7.85 (d, *J* = 8.0 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.8, 22.5, 22.6, 29.7, 34.3, 34.4, 36.7, 38.7, 39.6, 51.3, 131.5, 131.8, 137.2, 140.4, 142.5, 148.3, 164.4, 166.2, 171.3; HRMS (ES+) Calculated for [C₂₇H₃₄N₂O₆S + H] 514.21, found 515.20; HPLC (I) *t*R = 22.48 min (99.40%), (II) *t*R = 35.27 min (96.56%).



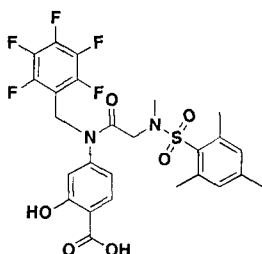
[00142] **4-(N-benzyl-2-((N,2,4,6 tetramethylphenyl)sulfonamido)-acetamido)-2-hydroxybenzoic acid.** Derivative **8g** hydrogenated on a 0.07 mmol scale via general procedure **h** (75%); δ_{H} (400 MHz, *d*-CDCl₃) 2.29 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.87 (s, 3H, CH₃), 3.81 (s, 2H, CH₂), 4.82 (s, 2H, CH₂), 6.41 (d, *J* = 8.1 Hz, 1H, CH), 6.54 (s, 1H, CH), 6.94 (s, 2H, CH), 7.06-7.16 (m, 2H, CH), 7.18-7.25 (m, 3H, CH), 7.84 (d, *J* = 8.5 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.8, 22.6, 34.6, 49.6, 52.9, 118.8, 127.6, 128.4, 131.6, 131.8, 136.2, 140.5, 142.5, 166.8; HRMS (ES⁺) Calculated for [C₂₆H₂₈N₂O₆S + H] 496.17, found 497.17; HPLC (I) *t*R = 19.17 min (98.29%), (II) *t*R = 29.81 min (97.35%).



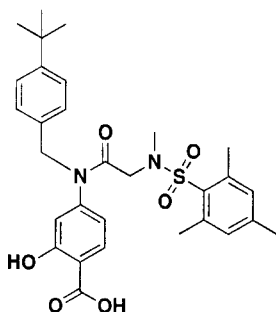
[00143] **2-hydroxy-4-(N-(4-methylbenzyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)benzoic acid.** Derivative **8f** hydrogenated on a 0.04 mmol scale via general procedure **h** (85%); δ_{H} (400 MHz, *d*-CDCl₃) 2.30 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.87 (s, 3H, CH₃), 3.79 (s, 2H, CH₂), 4.77 (s, 2H, CH₂), 6.41 (d, *J* = 8.5 Hz, 1H, CH), 6.52 (s, 1H, CH), 6.93 (s, 2H, CH), 6.98 (d, *J* = 8.3, 2H, CH), 7.04 (d, *J* = 8.3 Hz, 2H, CH), 7.82 (d, *J* = 8.3 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.8, 20.9, 22.6, 31.7, 34.6, 36.8, 49.5, 52.6, 116.7, 118.7, 128.3, 129.0, 131.5, 131.7, 132.0, 133.2, 137.2, 140.5, 142.5, 147.1, 162.7, 163.3, 166.7, 171.8; HRMS (ES⁺) Calculated for [C₂₆H₂₈N₂O₆S + H] 510.18, found 511.20; HPLC (I) *t*R = 20.32 min (95.53%), (II) *t*R = 31.81 min (93.81%).



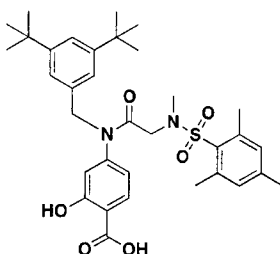
[00144] **4-(N-(4-fluorobenzyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)-2-hydroxybenzoic acid.** Derivative **8h** hydrogenated on a 0.1 mmol scale via general procedure **h** (89%); δ_{H} (400 MHz, *d*-CDCl₃): 2.29 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.86 (s, 3H, CH₃), 3.82 (s, 2H, CH₂), 4.79 (s, 2H, CH₂), 6.43 (d, *J* = 8.3 Hz, 1H, CH), 6.55 (s, 1H, CH), 6.84-7.01 (m, 4H, CH), 7.02-7.17 (m, 2H, CH), 7.85 (d, *J* = 8.3 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.8, 22.6, 29.5, 34.8, 49.6, 52.2, 111.7, 115.2, 115.4, 116.9, 118.9, 130.2, 130.3, 131.4, 131.8, 132.0, 132.3, 140.5, 142.6, 147.2, 160.9, 162.8, 163.4, 166.8, 171.8; HRMS (ES⁺) Calculated for [C₂₆H₂₇FN₂O₆S + H] 514.16, found 515.20; HPLC (I) *t*R = 19.48 min (96.92%), (II) *t*R = 30.84 min (92.79%).



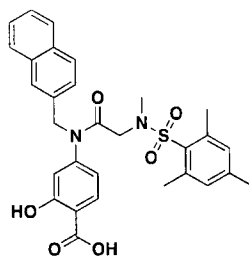
[00145] **2-hydroxy-4-(N-((perfluorophenyl)methyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)benzoic acid.** Derivative **8i** hydrogenated on a 0.16 mmol scale via general procedure **h** (90%); δ_{H} (400 MHz, *d*-DMSO): 2.24 (s, 3H, CH₃), 2.40 (s, 6H, CH₃), 2.73 (s, 3H, CH₃), 3.71 (s, 2H, CH₂), 4.93 (s, 2H, CH₂), 6.60 (d, *J* = 8.5 Hz, 1H, CH), 6.79 (s, 1H, CH), 6.97 (s, 2H, CH), 7.76 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-DMSO): 20.8, 22.6, 34.6, 36.8, 49.5, 115.4, 131.6, 136.4, 141.3, 145.3, 162.9, 166.7, 172.7; HRMS (ES⁺) Calculated for [C₂₆H₂₃F₅N₂O₆S + H] 586.12, found 587.10; HPLC (I) *t*R = 20.63 min (99.83%), (II) *t*R = 32.50 min (98.56%).



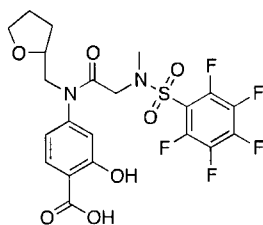
[00146] **4-(N-(4-(tert-butyl)benzyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)-2-hydroxybenzoic acid.** Derivative **8k** hydrogenated on a 0.08 mmol scale via general procedure **h** (40%); δ_{H} (400 MHz, *d*-CDCl₃): 1.29 (s, 9H, CH₃), 2.29 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.86 (s, 3H, CH₃), 3.81 (s, 2H, CH₂), 4.79 (s, 2H, CH₂), 6.47 (d, *J* = 8.5 Hz, 1H, CH), 6.57 (s, 1H, CH), 6.94 (s, 2H, CH), 7.03 (d, *J* = 8.2 Hz, 2H, CH), 7.27 (d, *J* = 8.2 Hz, 2H, CH), 7.84 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.5, 20.8, 22.6, 31.1, 34.3, 34.6, 49.5, 52.7, 116.8, 118.9, 125.3, 127.9, 131.5, 131.7, 132.2, 133.1, 140.5, 142.5, 150.5, 162.7, 166.7, 173.0, 177.0; HRMS (ES⁺) Calculated for [C₃₀H₃₆F₅N₂O₆S + H] 552.23, found 553.20; HPLC (I) *t*R = 23.33 min (98.57%), (II) *t*R = 37.15 min (98.89%).



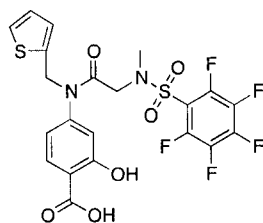
[00147] **4-(N-(3,5-di-tert-butylbenzyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)-acetamido)-2-hydroxybenzoic acid.** Derivative **8l** hydrogenated on a 0.07 mmol scale via general procedure **h** (65%); δ_{H} (400 MHz, *d*-CDCl₃): 1.24 (s, 18H, CH₃), 2.28 (s, 3H, CH₃), 2.58 (s, 6H, CH₃), 2.81 (s, 3H, CH₃), 3.83 (s, 2H, CH₂), 4.83 (s, 2H, CH₂), 6.46 (d, *J* = 8.4 Hz, 1H, CH), 6.55 (s, 1H, CH), 6.93 (s, 2H, CH), 6.95 (s, 2H, CH), 7.28 (s, 1H, CH), 7.83 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.5, 20.8, 22.6, 31.2, 34.4, 34.5, 49.5, 53.4, 121.3, 122.9, 131.4, 131.7, 132.0, 135.0, 140.5, 142.5, 150.8, 162.7, 177.1; HRMS (ES⁺) Calculated for [C₃₄H₄₄N₂O₆S + H] 608.29, found 609.30; HPLC (I) *t*R = 26.49 min (99.72%), (II) *t*R = 42.87 min (98.62%).



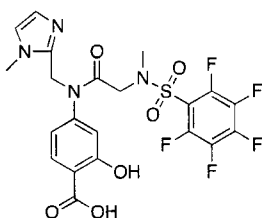
[00148] **2-hydroxy-4-(N-(naphthalen-2-ylmethyl)-2-((N,2,4,6-tetramethylphenyl)sulfonamido)acetamido)benzoic acid.** Derivative **8j** hydrogenated on a 0.09 mmol scale via general procedure **h** (40%); δ_{H} (400 MHz, *d*-CDCl₃): 2.24 (s, 3H, CH₃), 2.57 (s, 6H, CH₃), 2.89 (s, 3H, CH₃), 3.84 (s, 2H, CH₂), 4.99 (s, 2H, CH₂), 6.42 (d, *J* = 8.2 Hz, 1H, CH), 6.58 (s, 1H, CH), 6.91 (s, 2H, CH), 7.27 (s, 1H, CH), 7.38-7.50 (m, 2H, CH), 7.54 (s, 1H, CH), 7.68-7.88 (m, 4H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.5, 20.7, 22.6, 34.7, 49.6, 53.1, 111.8, 116.8, 118.9, 125.9, 126.1, 127.5, 127.6, 128.3, 131.4, 131.8, 132.2, 132.6, 133.0, 133.6, 140.5, 142.5, 147.4, 162.8, 167.0, 172.5, 177.0; HRMS (ES⁺) Calculated for [C₃₀H₃₀N₂O₆S + H] 546.18, found 547.20; HPLC (I) *t*R = 21.21 min (97.90%), (II) *t*R = 33.46 min (95.26%).



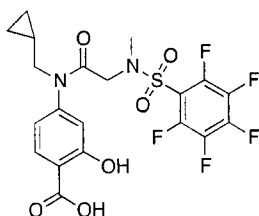
[00149] **2-hydroxy-4-(2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)-N-((tetrahydrofuran-2-yl)methyl)acetamido)benzoic acid.** Derivative **8m** hydrogenated on a 0.1 mmol scale via general procedure **h** (70%); δ_{H} (400 MHz, *d*-CDCl₃): 1.41-1.60 (m, 1H, CH), 1.79-2.01 (m, 3H, CH₂, CH), 3.07 (s, 3H, CH₃), 3.67 (d, *J* = 6.5 Hz, 2H, CH₂), 3.71-3.89 (m, 2H, CH₂), 3.93-4.21 (m, 2H, CH₂), 6.80 (d, *J* = 8.2 Hz, 1H, CH), 6.89 (s, 1H, CH), 7.95 (d, *J* = 8.3 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.5, 25.2, 28.8, 31.7, 35.7, 36.8, 52.0, 52.9, 67.7, 116.7, 118.6, 132.3, 146.9, 162.9, 163.3, 171.9, 176.1; HRMS (ES⁺) Calculated for [C₂₁H₁₉F₅N₂O₇S + H] 538.08, found 539.10; HPLC (I) *t*R = 24.63 min (97.67%), (II) *t*R = 26.45 min (95.84%).



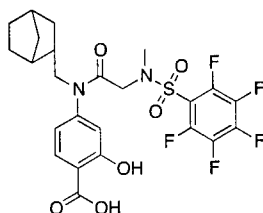
[00150] **2-hydroxy-4-(2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamide)-N-(thiophen-2-ylmethyl)acetamido)benzoic acid.** Derivative **8n** hydrogenated on a 0.1 mmol scale via general procedure **h** (95%): δ_{H} (400 MHz, *d*-CDCl₃) 3.03 (s, 3H, CH₃), 3.97 (s, 2H, CH₂), 4.83 (s, 2H, CH₂), 6.52 (d, *J* = 8.3 Hz, 1H, CH), 6.65 (s, 1H, CH), 6.68 (s, 1H, CH), 6.78-6.85 (m, 1H, CH), 7.17 (d, *J* = 5.4 Hz, 1H, CH), 7.87 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃) 20.5, 22.6, 29.3, 29.6, 31.6, 32.3, 34.2, 35.9, 47.8, 52.0, 52.2, 112.1, 117.1, 119.0, 126.3, 126.6, 127.6, 132.7, 137.8, 146.8, 147.1, 163.1, 163.2, 165.7, 172.5, 176.5; HRMS (ES⁺) Calculated for [C₂₁H₁₅F₅N₂O₆S₂ + H] 550.03, found 551.0.; HPLC (I) *t*R = 26.91 min (64.94%), (II) *t*R = 30.17 min (92.72%).



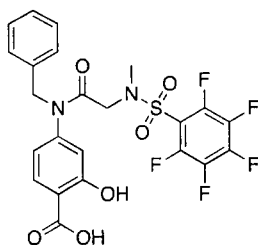
[00151] **2-hydroxy-4-(N-((1-methyl-1H-imidazol-2-yl)methyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)benzoic acid.** Derivative **8o** hydrogenated on a 0.16 mmol scale via general procedure **h** (54%): δ_{H} (400 MHz, *d*-DMSO) 2.94 (s, 3H, CH₃), 3.60 (s, 3H, CH₃), 3.61 (s, 2H, CH₂), 4.99 (s, 2H, CH₂), 6.64 (s, 1H, CH), 6.78 (s, 1H, CH), 7.18 (s, 1H, CH), 7.37 (s, 1H, CH), 7.72 (s, 1H, CH); δ_{C} (100 MHz, *d*-DMSO); 33.1, 34.6, 47.8, 49.5, 106.0, 113.2, 120.5, 127.1, 131.4, 131.9, 138.2, 140.6, 142.9, 147.3, 152.4, 164.8, 166.9, 171.8; HRMS (ES⁺) Calculated for [C₂₁H₁₇F₅N₄O₆S₂ + H] 548.08, found 549.10; HPLC (I) *t*R = 17.52 min (74.54%), (II) *t*R = 15.87 min (79.92%).



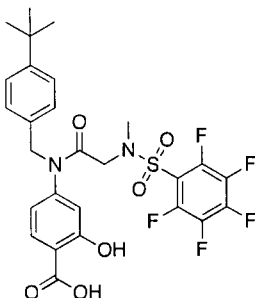
[00152] **4-(N-(cyclopropylmethyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)-2-hydroxybenzoic acid.** Derivative **8p** hydrogenated on a 0.4 mmol scale via general procedure **h** (87%): δ_{H} (400 MHz, *d*-CDCl₃) 0.04-0.18 (m, 2H, CH₂), 0.40-0.59 (m, 2H, CH₂), 0.78-1.00 (m, 1H, CH), 3.07 (s, 3H, CH₃), 3.49 (d, *J* = 7.2 Hz, 2H, CH₂), 4.04 (s, 2H, CH₂), 6.83 (s, 1H, CH), 6.90 (s, 1H, CH), 8.00 (d, *J* = 8.3 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 3.5, 9.4, 20.5, 35.8, 52.0, 53.8, 111.9, 117.2, 119.1, 132.6, 147.4, 163.0, 165.7, 172.9; HRMS (ES+) calculated for [C₂₀H₁₇F₅N₂O₆S₂ + H] 508.07, found 509.10; HPLC (I) *t*R = 26.33 min (97.61%), (II) *t*R = 29.31 min (96.90%).



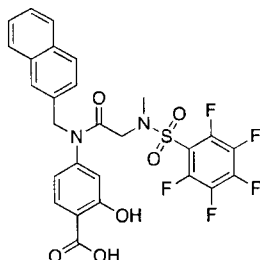
[00153] **4-(N-(bicyclo[2.2.1]heptan-2-ylmethyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)-2-hydroxybenzoic acid.** Derivative **8q** hydrogenated on a 0.3 mmol scale via general procedure **h** (66%): δ_{H} (400 MHz, *d*-CDCl₃) 0.40-0.61(m, 1H, CH), 0.85-1.07 (m, 2H, CH₂), 1.08-1.27 (m, 3H, CH₂, CH), 1.28-1.45 (m, 2H, CH₂), 1.72-1.90 (m, 1H, CH), 1.99 (s, 1H, CH₂), 2.07 (s, 1H, CH₂), 2.94 (s, 3H, CH₃), 3.48-3.70 (m, 2H, CH₂), 4.00 (s, 2H, CH₂), 6.83 (d, *J* = 8.4 Hz, 1H, CH), 6.91 (s, 1H, CH), 7.86 (d, *J* = 8.2 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 28.2, 29.4, 34.3, 34.4, 37.7, 38.7, 39.6, 42.6, 48.9, 113.2, 131.5, 131.8, 137.2, 140.4, 142.5, 148.3, 164.4, 166.2, 171.3; HRMS (ES+) calculated for [C₂₄H₂₃F₅N₂O₆S + H] 562.12, found 563.10; HPLC (I) *t*R = 30.77 min (98.73%), (II) *t*R = 36.21 min (99.12%).



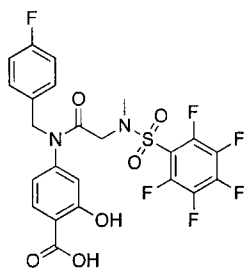
[00154] **4-(N-(benzyl-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)-2-hydroxybenzoic acid.** Derivative **8s** hydrogenated on a 0.3 mmol scale via general procedure **h** (87%): δ_{H} (400 MHz, *d*-CDCl₃) 3.10 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 4.78 (s, 2H, CH₂), 6.55 (d, *J* = 8.6 Hz, 1H, CH), 6.69 (s, 1H, CH), 7.04-7.16 (m, 2H, CH), 7.26-7.32 (m, 3H, CH), 7.89 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 29.6, 30.3, 35.9, 50.8, 52.2, 53.2, 111.9, 115.8, 117.1, 119.1, 128.0, 128.4, 128.6, 132.2, 132.6, 135.7, 139.1, 143.5, 146.1, 147.1, 163.1, 166.0, 172.3; HRMS (ES+) calculated for [C₂₃H₁₇F₅N₂O₆S + H] 544.07, found 545.10; HPLC (I) *t*R = 19.74 min (97.50%), (II) *t*R = 30.90 min (96.37%).



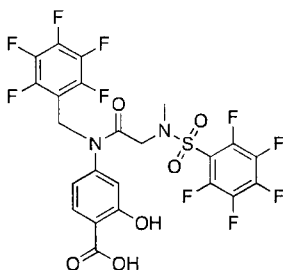
[00155] **4-(N-(4-tert-butyl)benzyl-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamido)acetamido)-2-hydroxybenzoic acid.** Derivative **8w** hydrogenated on a 0.4 mmol scale via general procedure **h** (92%): δ_{H} (400 MHz, *d*-CDCl₃) 1.29 (s, 9H, CH₃), 3.10 (s, 3H, CH₃), 4.08 (s, 2H, CH₂), 4.76 (s, 2H, CH₂), 6.59 (d, *J* = 8.4 Hz, 1H, CH), 6.72 (s, 1H, CH), 7.01 (d, *J* = 8.1 Hz, 2H, CH), 7.29 (d, *J* = 8.15 Hz, 2H, CH), 7.90 (d, *J* = 8.4 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 31.1, 32.0, 34.3, 35.8, 37.1, 52.1, 52.9, 116.9, 118.8, 125.4, 127.9, 132.50, 150.8, 162.92, 165.9, 172.4; HRMS (ES+) calculated for [C₂₇H₂₅F₅N₂O₆S + H] 600.14, found 601.10; HPLC (I) *t*R = 23.68 min (98.12%), (II) *t*R = 37.81 min (98.08%).



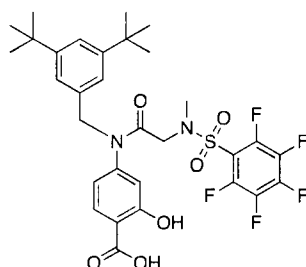
[00156] **2-hydroxy-4-(N-(naphthalene-2-ylmethyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamide)acetamido)benzoic acid**. Derivative **8v** hydrogenated on a 0.4 mmol scale via general procedure **h** (73%): δ_{H} (400 MHz, *d*-CDCl₃) 3.10 (s, 3H, CH₃), 4.09 (s, 2H, CH₂), 4.95 (s, 2H, CH₂), 6.54 (d, *J* = 8.4 Hz, 1H, CH), 6.72 (s, 1H, CH), 7.23 (s, 1H, CH), 7.40-7.56 (m, 3H, CH), 7.67-7.94 (m, 4H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.6, 35.7, 52.1, 53.1, 118.9, 125.8, 126.0, 126.1, 127.5, 127.6, 128.5, 132.5, 132.7, 133.0, 133.1, 162.8, 166.1, 177.5; HRMS (ES⁺) calculated for [C₂₇H₁₉F₅N₂O₆S + H] 594.09, found 595.10; HPLC (I) *t*R = 21.64 min (90.45%), (II) *t*R = 34.27 min (88.02%).



[00157] **4-(N-(4-fluorobenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamide)acetamido)-2-hydroxybenzoic acid**. Derivative **8t** hydrogenated on a 0.15 mmol scale via general procedure **h** (63%): δ_{H} (400 MHz, *d*-CDCl₃) 3.09 (s, 3H, CH₃), 4.05 (s, 2H, CH₂), 4.75 (s, 2H, CH₂), 6.54 (d, *J* = 8.53 Hz, 1H, CH), 6.68 (s, 1H, CH), 6.90-7.03 (m, 2H, CH), 7.03-7.12 (m, 2H, CH), 7.92 (d, *J* = 8.50 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 20.5, 29.6, 35.9, 52.0, 52.2, 52.4, 112.1, 115.5, 115.7, 117.1, 117.6, 119.1, 120.4, 129.6, 130.3, 130.4, 131.7, 132.7, 146.9, 147.0, 161.2, 163.1, 163.6, 165.9, 172.7, 176.5; HRMS (ES⁺) calculated for [C₂₃H₁₆F₆N₂O₆S + H] 562.06, found 563.10; HPLC (I) *t*R = 19.99 min (98.87%), (II) *t*R = 31.40 min (97.59%).

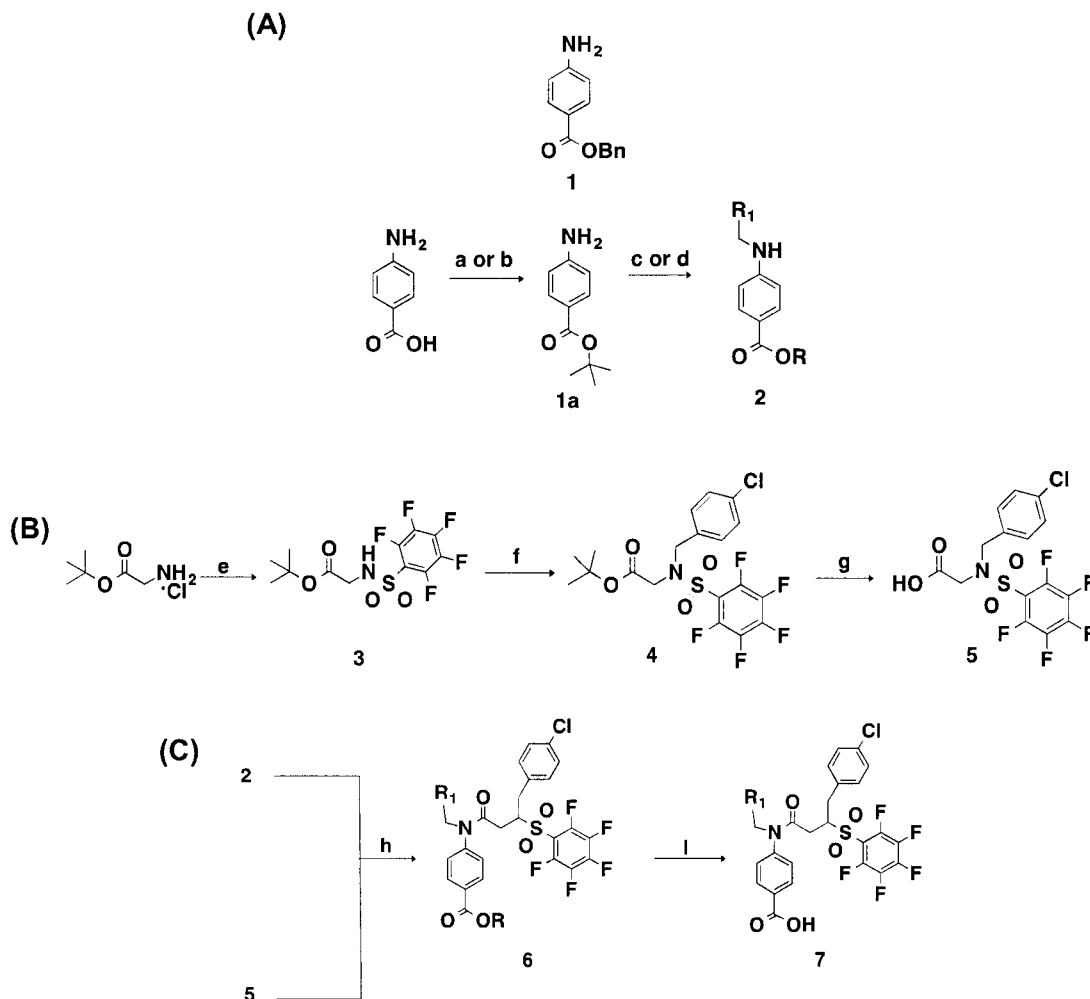


[00158] **2-hydroxy-4-(2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamide)-N-((perfluorophenyl)methyl)acetamido)benzoic acid**. Derivative **8u** hydrogenated on a 0.07 mmol scale via general procedure **h** (89%): δ_{H} (400 MHz, *d*-CDCl₃) 3.06 (s, 3H, CH₃), 4.01 (s, 2H, CH₂), 4.94 (s, 2H, CH₂), 6.62 (d, *J* = 8.34 Hz, 1H, CH), 6.73 (s, 1H, CH), 7.95 (d, *J* = 8.52 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 29.6, 30.8, 31.3, 35.8, 40.0, 52.0, 58.3, 61.4, 109.0, 112.9, 115.6, 116.8, 118.4, 125.9, 133.0, 136.1, 136.3, 136.5, 138.5, 138.6, 138.9, 142.5, 143.5, 144.0, 145.0, 146.0, 146.5, 163.1, 165.9, 171.5, 173.4; HRMS (ES⁺) calculated for [C₂₃H₁₂F₁₀N₂O₆S + H] 634.03, found 635.0; HPLC (I) *t*R = 20.88 min (98.71%), (II) *t*R = 33.06 min (98.39%).



4-(N-(3,5-di-tert-butylbenzyl)-2-((2,3,4,5,6-pentafluoro-N-methylphenyl)sulfonamide)acetamido)-2-hydroxybenzoic acid. Derivative **8x** hydrogenated on a 0.07 mmol scale via general procedure **h** (89%): δ_{H} (400 MHz, *d*-CDCl₃) 3.06 (s, 3H, CH₃), 4.01 (s, 2H, CH₂), 4.94 (s, 2H, CH₂), 6.62 (d, *J* = 8.34 Hz, 1H, CH), 6.73 (s, 1H, CH), 7.95 (d, *J* = 8.52 Hz, 1H, CH); δ_{C} (100 MHz, *d*-CDCl₃): 29.6, 30.8, 31.3, 35.8, 40.0, 52.0, 58.3, 61.4, 109.0, 112.9, 115.6, 116.8, 118.4, 125.9, 133.0, 136.1, 136.3, 136.5, 138.5, 138.6, 138.9, 142.5, 143.5, 144.0, 145.0, 146.0, 146.5, 163.1, 165.9, 171.5, 173.4; HRMS (ES⁺) calculated for [C₂₃H₁₂F₁₀N₂O₆S + H] 634.03, found 635.0; HPLC (I) *t*R = 26.48 min (99.42%), (II) *t*R = 43.39 min (98.62%).

Other compounds of the disclosure were synthesized according to Scheme 2:



Scheme 2: (A) a) i) K^tOBu , BnBr , DMF , $0^\circ\text{C} \rightarrow \text{RT.}$, 1h; then K^tOBu , BnBr , DMF , $0^\circ\text{C} \rightarrow \text{RT.}$, 16h, 60%; b) SOCl_2 , *t*-butanol, DCM , $0^\circ\text{C} \rightarrow \text{RT.}$, 83%; c) 1) Aldehyde, AcOH , 3\AA Mol. sieves, CH_3OH , 45°C , 2h; 2) NaCNBH_3 , 45°C , 16h, 56-96 %; d) Aldehyde, 3\AA Mol. sieves, CH_2Cl_2 , NaOAc , $\text{Na}(\text{OAc})_3\text{BH}$, RT , 16h, 82%; (e) d) $\text{C}_5\text{F}_5\text{SO}_2\text{Cl}$, K_2CO_3 , CH_3CN , 16h, $0^\circ\text{C} \rightarrow \text{RT.}$, 60-77%; f) 1) *p*- $\text{Cl}(\text{C}_6\text{H}_4)\text{BnBr}$, Cs_2CO_3 , DMF , R.T. , N_2 , 2h, 70%; g) CH_2Cl_2 : TFA 1:1, RT , 1h, 90%; h) PPh_3Cl_2 , CHCl_3 , 30 min, 100°C microwave assisted heating, 20-98%; i) H_2 , Pd/C , 1:1 $\text{THF}/\text{CH}_3\text{OH}$, 3-10h, RT , 35-95%. ia) 1:1 TFA/DCM , 30 min, *r.t.* $\text{DMF} = N,N$ -dimethylformamide, $\text{TFA} = \text{trifluoroacetic acid}$.

[00159] **General Procedure a (dibenzylation of salicylic acid).** To a stirred solution of 4-aminosalicylic acid (1.0 eq) in DMF (0.1 M) at 0°C was added K^tOBu (1.2

eq). After 15 min, benzyl bromide (1.2 eq) was added drop-wise. The suspension was allowed to stir at room temperature for a further 4 h before the reaction vessel was again cooled to 0 °C. Once again, KO^tBu (1.2 eq) was added prior to the dropwise addition of benzyl bromide (1.2 eq). The reaction was left to stir overnight before quenching with H₂O. The solution was then repeatedly extracted with ethyl acetate and the organic phases combined. The organics were then washed with H₂O and brine then concentrated, dried over Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified using the Biotage Isolera automated column chromatographer with a 4:1 Hexanes/EtOAc gradient under reduced pressure.

[00160] **General Procedure b (t-butyl protection of salicylic acid).** 4-aminobenzoic acid was suspended in SOCl₂ (2.0 eq.) at 25 °C. The suspension was refluxed for 2h. SOCl₂ was removed under reduced pressure, the last traces by azeotrope with CHCl₃ (x3). The resulting acid chloride was dissolved in CH₂Cl₂ and a solution of *t*-butanol in CH₂Cl₂ was added to the stirred solution which was cooled to 0 °C. A solid white precipitate was formed – the hydrochloride salt was quenched with 1.0M KOH and extracted with EtOAc (x4).

[00161] **General Procedure c (reductive amination using sodium cyanoborohydride).** To a solution of protected 4-amino salicylic acid **1/1a** (1.0 eq) and acetic acid (1.5 eq) stirred in anhydrous CH₃OH (0.1 M) with 3 Å mol. sieves was added the aldehyde (1.0 eq). The solution was heated to 45 °C for 3 hr and then allowed to cool to rt. Next, NaCNBH₃ (1.3 equiv) was added portion-wise and the reaction was allowed to stir at rt overnight. The reaction was diluted with CH₂Cl₂, filtered and concentrated *in vacuo*. The concentrate was purified using the Biotage Isolera automated column chromatographer using a gradient of Hexanes/EtOAc to furnish secondary anilines **2**.

[00162] **General Procedure d (reductive amination using sodium triacetoxyborohydride).** To a solution of protected 4-amino salicylic acid **1/1a** (1.2 eq) and acetic acid (1.2 eq) stirred in anhydrous dichloroethane (0.1 M) with 3 Å mol. sieves was added the aldehyde (1.0 eq). The solution was then stirred at rt for 5 min after which Na(OAc)₃BH (1.5 eq) was added and left to stir at rt overnight. The reaction was diluted with CH₂Cl₂, filtered and concentrated *in vacuo*. The concentrate was purified

using the Biotage Isolera automated column chromatographer using a gradient of Hexanes/EtOAc to furnish secondary aniline derivatives **2**.

[00163] **General Procedure e (sulfonylation of glycine and sarcosine *t*-butyl ester).** A solution of amino acid *t*-butyl ester (1 eq) and K_2CO_3 (1.1 eq) were dissolved in anhydrous acetonitrile and cooled to 0 °C before sulfonyl chloride (1 eq) was added. The resultant solution was allowed to stir overnight at rt. The reaction was concentrated *in vacuo* and residue was dissolved in CH_2Cl_2 . The organics were combined and then washed sequentially with 0.1 M HCl, saturated $NaHCO_3$ and brine. The organics were then dried over Na_2SO_4 and concentrated *in vacuo* to furnish derivatives **3** with no further purification.

[00164] **General Procedure f (alkylation of sulfonamide).** A solution of **3** (1 eq) and Cs_2CO_3 (1.3 eq) were dissolved in anhydrous DMF followed by the addition of *p*-ClBnBr (1 eq). The resultant solution was allowed to stir for 2h at r.t. The reaction was quenched with H_2O and then repeatedly extracted with ethyl acetate. The organic phases were combined and washed with H_2O , brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified using the Biotage Isolera automated column chromatographer with a 2:1 Hexanes/EtOAc gradient under reduced pressure to provide compound **4**.

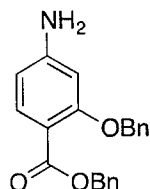
[00165] **General Procedure g (*t*-butyl ester deprotection).** A solution of amino acid *t*-butyl ester (1 eq) was dissolved in TFA and immediately diluted with CH_2Cl_2 in a 1:1 mixture (0.1 M) solution. The resultant solution was allowed to stir for 1h and then co-evaporated with CH_3OH (3x) and $CHCl_3$ (3x). The resultant residue was carried forward with no purification to yield compounds **5**.

[00166] **General Procedure h (PPh_3Cl_2 peptide coupling).** To a stirred solution of carboxylic acid (**5**) (1.1 eq) in $CHCl_3$ (0.1 M) was added PPh_3Cl_2 (2.5 eq). The reaction was allowed to stir 5 min at rt or until complete dissolution, followed by the drop-wise addition of the secondary aniline **2** (1.0 eq). The reaction mixture was then heated in a microwave at 100 °C for 30 min. The reaction mixture was allowed to cool to rt followed by sequential washing with saturated $NaHCO_3$ and brine. The organic layers were then dried over Na_2SO_4 and concentrated *in vacuo*. The concentrate was absorbed directly onto silica for column chromatography purification using a gradient of hexanes and EtOAc to furnish derivatives **6**.

[00167] **General Procedure i (hydrogenolysis of the benzyl ester and benzyl ether).** The benzyl protected salicylic acid, **6** (1 eq) were dissolved in a stirred solution of CH₃OH/THF (1:2, 0.1 M). The solution was thoroughly degassed before the careful addition of 10 % Pd/C (10 mg/mmol). H₂ gas was bubbled through the solvent for 5 min before the solution was put under an atmosphere of H₂ gas and stirred continuously for 2-5h, monitoring completion of reaction via TLC. The H₂ gas was evacuated and the reaction filtered through celite to remove Pd catalyst and concentrated *in vacuo*. The resulting residue was adsorbed onto silica and columned using a Biotage Isolera in a gradient of CH₂Cl₂, CH₃OH and 1% acetic acid to provide final molecule series **7**.

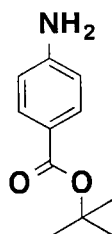
[00168] **General Procedure i (Acid deprotection of *t*-butyl functional groups).** The *t*-butyl protected salicylic acid, was dissolved with 1:1 ration of TFA/DCM and stirred for 30 min. The crude solution was concentrated down *in vacuo*. The resulting residue was adsorbed onto silica and columned using a Biotage Isolera in a gradient of CH₂Cl₂, CH₃OH and 1% acetic acid to provide final molecule series **7**.

[00169] **Intermediate characterization data**

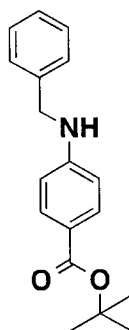


[00170] **Benzyl 4-amino-2-(benzyloxy)benzoate (Scheme 2 - 1).** Compound **1** was synthesized according to general procedure **a**, yielding the final product as an orange solid (47%): δ_{H} (400 MHz, *d*-CDCl₃) 5.07 (s, 2H, CH₂), 5.21 (s, 2H, CH₂), 5.99 (br s, 2H, NH₂), 6.18 (dd, *J* = 8.6 and 1.8 Hz, 1H, CH), 6.32 (d, *J* = 1.7 Hz, 1H, CH), 7.28-7.38 (8H, m, CH), 7.47 (d, *J* = 7.2 Hz, 2H, CH), 7.60 (d, *J* = 8.6 Hz, 1H, CH);; δ_{C} (400 MHz, CDCl₃) 65.8, 70.2, 99.1, 106.7, 109.0, 126.8, 127.5, 127.7, 127.9, 128.3, 128.4, 134.3, 136.6, 136.7, 152.2, 160.7, 165.7; LRMS (ESI+) calculated for C₂₁H₁₉NO₃ [M + H]⁺ 333.2, found 333.2.

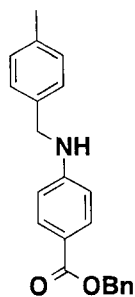
[00171]



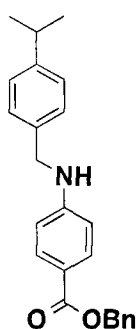
[00172] **Tert-butyl 4-aminobenzoate (1a)**. Derivative **1a** synthesized according to general procedure b on (83%): ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 1.06 – 1.19 (m, 7H), 1.39 (s, 1H), 1.46 (s, 16H), 1.52 (d, $J = 3.6$ Hz, 3H), 1.88 (s, 1H), 1.96 (s, 6H), 4.00 (q, $J = 7.1$ Hz, 4H), 5.82 (d, $J = 15.3$ Hz, 4H), 6.47 – 6.55 (m, 4H), 7.50 – 7.59 (m, 4H), 7.79 – 7.98 (m, 2H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 28.16, 28.30, 79.14, 112.80, 117.95, 119.36, 119.66, 129.89, 131.18, 153.37, 165.58. LRMS (ESI+) calculated for $\text{C}_{11}\text{H}_{16}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 194.11, found 194.15.



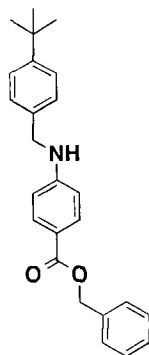
[00173] **Tert-butyl 4-(benzylamino)benzoate (2a)**. Derivative **2a** synthesized according to general procedure c on (67%): ^1H NMR (400 MHz, $\text{Chloroform-}d$) δ 1.62 (s, 9H), 4.37 (d, $J = 5.3$ Hz, 2H), 4.76 (t, $J = 5.7$ Hz, 1H), 6.54 – 6.63 (m, 2H), 7.26 – 7.41 (m, 5H), 7.84 – 7.94 (m, 2H). ^{13}C NMR (101 MHz, $\text{Chloroform-}d$) δ 28.27, 47.41, 79.74, 111.50, 120.25, 127.19, 127.26, 128.61, 131.25, 138.56, 151.50, 166.14. LRMS (ESI+) calculated for $\text{C}_{18}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 284.15, found 284.16.



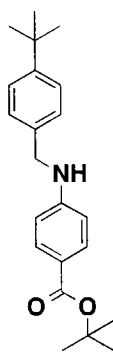
[00174] **Benzyl 4-((4-methylbenzyl)amino)benzoate (2b)**. Derivative **2b** synthesized according to general procedure c on (80%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.50 – 1.57 (m, 1H), 2.36 (s, 3H), 4.33 (d, J = 4.7 Hz, 2H), 4.57 (d, J = 5.4 Hz, 1H), 5.30 (d, J = 14.9 Hz, 6H), 6.55 – 6.63 (m, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 7.29 – 7.43 (m, 3H), 7.45 (dt, J = 6.1, 1.6 Hz, 2H), 7.88 – 7.97 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 20.97 , 47.24 , 53.36 , 65.83 , 111.51 , 118.22 , 127.26 , 127.84 , 128.37 , 129.31 , 131.58 , 135.17 , 136.58 , 137.06 , 151.83 , 166.50 . LRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 332.15, found 332.17.



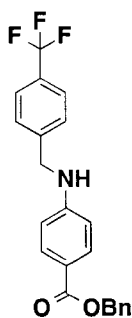
[00175] **Benzyl 4-((4-isopropylbenzyl)amino)benzoate (2c)**. Derivative **2c** synthesized according to general procedure c on (76%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.26 (d, J = 7.0 Hz, 6H), 2.91 (hept, J = 6.9 Hz, 1H), 4.34 (s, 2H), 4.53 (s, 1H), 5.32 (s, 2H), 6.59 (dd, J = 8.5, 1.2 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.24 – 7.40 (m, 4H), 7.44 (d, J = 7.9 Hz, 2H), 7.88 – 7.95 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 23.87, 33.68, 47.31, 65.82, 111.48, 118.30, 126.69, 127.39, 127.81, 127.84, 128.35, 131.59, 135.47, 136.56, 148.18, 151.76. LRMS (ESI+) calculated for $\text{C}_{24}\text{H}_{26}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 360.18, found 360.18.



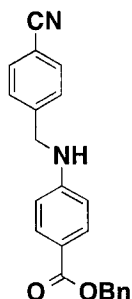
[00176] **Benzyl 4-((4-(*tert*-butyl)benzyl)amino)benzoate (2d)**. Derivative **2d** synthesized according to general procedure c: ^1H NMR (400 MHz, Chloroform-*d*) δ 1.34 (s, 9H), 4.35 (s, 2H), 5.33 (s, 2H), 6.56 – 6.63 (m, 2H), 7.23 – 7.48 (m, 9H), 7.89 – 7.96 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 31.23, 34.41, 47.21, 65.82, 111.49, 118.29, 125.56, 127.13, 127.82, 127.85, 128.36, 131.60, 135.13, 151.79, 166.46. LRMS (ESI+) calculated for $\text{C}_{25}\text{H}_{28}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 374.20, found 374.22.



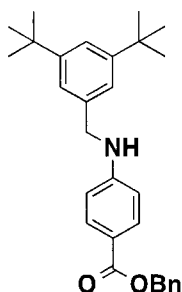
[00177] ***Tert*-butyl 4-((4-(*tert*-butyl)benzyl)amino)benzoate (2d)**. Derivative **2d** synthesized according to general procedure c on (71%): ^1H NMR (400 MHz, Methanol-*d*₄) δ 1.29 (s, 5H), 1.54 (s, 5H), 4.32 (s, 1H), 6.56 (d, $J = 8.7$ Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 7.62 – 7.70 (m, 1H). LRMS (ESI+) calculated for $\text{C}_{25}\text{H}_{28}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 331.22, found 331.24.



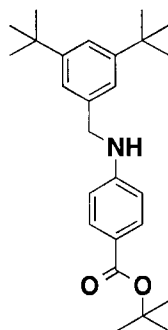
[00178] **Benzyl 4-((4-(trifluoromethyl)benzyl)amino)benzoate (2e)**. Derivative **2e** synthesized according to general procedure c on (71%): LRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{19}\text{F}_3\text{NO}_2$ $[\text{M} + \text{H}]^+$ 386.13, found 386.15.



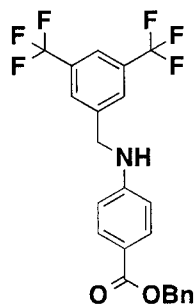
[00179] **Benzyl 4-((4-cyanobenzyl)amino)benzoate (2f).** Derivative **2f** synthesized according to general procedure d on (60%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.24 (t, $J = 7.2$ Hz, 1H), 2.02 (s, 1H), 4.10 (q, $J = 7.1$ Hz, 1H), 4.41 (d, $J = 4.4$ Hz, 2H), 4.72 (s, 1H), 5.12 (t, $J = 6.0$ Hz, 1H), 5.27 (s, 2H), 6.52 (d, $J = 8.4$ Hz, 2H), 7.23 – 7.46 (m, 8H), 7.54 (dd, $J = 8.1, 5.6$ Hz, 3H), 7.85 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 14.07, 46.77, 63.75, 65.90, 110.75, 111.65, 118.61 (d, $J = 19.5$ Hz), 126.87, 127.50, 127.85 (d, $J = 15.2$ Hz), 128.41, 131.58, 132.02, 132.33, 136.38, 144.38, 151.46, 166.51. LRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 343.13, found 343.14.



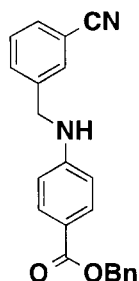
[00180] **Benzyl 4-((3,5-di-*tert*-butylbenzyl)amino)benzoate (2g).** Derivative **2g** synthesized according to general procedure d on (60%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.26 (d, $J = 7.0$ Hz, 6H), 2.91 (hept, $J = 6.9$ Hz, 1H), 4.34 (s, 2H), 5.32 (s, 2H), 6.59 (dd, $J = 8.5, 1.2$ Hz, 2H), 7.22 (d, $J = 7.9$ Hz, 2H), 7.24 – 7.40 (m, 4H), 7.44 (d, $J = 7.9$ Hz, 2H), 7.88 – 7.95 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 23.87, 33.68, 47.31, 65.82, 111.48, 118.30, 126.69, 127.39, 127.81, 127.84, 128.35, 131.59, 135.47, 136.56, 148.18, 151.76. LRMS (ESI+) calculated for $\text{C}_{29}\text{H}_{36}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$ 430.26, found 430.28.



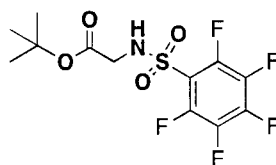
[00181] **Tert-butyl 4-((3,5-di-tert-butylbenzyl)amino)benzoate (2g).** Derivative **2g** synthesized according to general procedure d on (85%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.47 (s, 18H), 1.68 (s, 9H), 4.43 (d, $J = 5.1$ Hz, 2H), 4.67 (t, $J = 5.3$ Hz, 1H), 6.66 – 6.73 (m, 2H), 7.32 (d, $J = 1.8$ Hz, 2H), 7.50 (t, $J = 1.8$ Hz, 1H), 7.93 – 8.00 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 28.34, 31.49, 34.82, 48.43, 79.64, 111.45, 120.27, 121.47, 121.90, 131.32, 137.58, 151.18, 151.74, 166.15. LRMS (ESI+) calculated for $\text{C}_{26}\text{H}_{38}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 396.28, found 396.30.



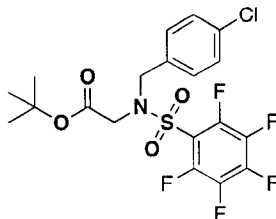
[00182] **Benzyl 4-((3,5-bis(trifluoromethyl)benzyl)amino)benzoate (2h).** Derivative **2h** synthesized according to general procedure c on (41%): ^1H NMR (400 MHz, Chloroform-*d*) δ 4.53 (d, $J = 5.8$ Hz, 2H), 4.71 (t, $J = 5.9$ Hz, 1H), 5.31 (s, 2H), 6.52 – 6.61 (m, 2H), 7.27 – 7.39 (m, 3H), 7.39 – 7.46 (m, 2H), 7.80 (s, 3H), 7.87 – 7.96 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 46.80, 65.99, 111.75, 119.52, 121.39, 127.01, 127.86, 127.89, 128.37, 131.66, 132.13, 136.35, 141.29, 150.87, 166.27. LRMS (ESI+) calculated for $\text{C}_{23}\text{H}_{18}\text{F}_6\text{NO}_2$ $[\text{M} + \text{H}]^+$ 454.12, found 454.15.



[00183] **Benzyl 4-((3-cyanobenzyl)amino)benzoate (2i).** Derivative **2i** synthesized according to general procedure d on (83%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.24 (q, $J = 7.6, 7.1$ Hz, 1H), 3.49 (d, $J = 7.9$ Hz, 1H), 4.38 (d, $J = 5.7$ Hz, 3H), 4.67 (d, $J = 2.9$ Hz, 3H), 5.14 (d, $J = 4.9$ Hz, 2H), 5.26 (s, 3H), 6.49 – 6.57 (m, 3H), 7.23 – 7.39 (m, 5H), 7.34 – 7.43 (m, 5H), 7.44 – 7.63 (m, 11H), 7.80 – 7.88 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 46.40, 63.43, 65.96, 111.68, 111.95, 112.33, 118.40, 127.78, 127.94, 128.42, 129.06, 129.42, 129.96, 130.36, 130.76, 130.89, 130.99, 131.49, 131.60, 136.33, 140.30, 142.65, 151.50, 166.67. LRMS (ESI+) calculated for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 343.13, found 343.16.

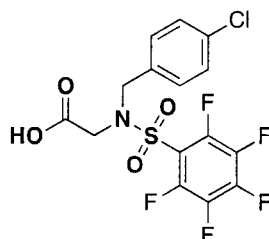


[00184] **tert-butyl ((perfluorophenyl)sulfonyl)glycinate (3).** Derivative **3** synthesized using general procedure e (71%): δ_{H} (400 MHz, CDCl_3) 1.40 (s, 9H, $\text{COO}(\text{CH}_3)_3$), 3.93 (s, 2H, CH_2), 5.54 (s, 1H, NH); δ_{C} (400 MHz, CDCl_3) 27.5, 45.1, 82.8, 115.6, 136.5, 144.8, 145.9, 167.0; LRMS (ESI+) calculated for $\text{C}_{12}\text{H}_{12}\text{F}_5\text{NO}_4\text{S}$ $[\text{M} + \text{H}]^+$ 361.0, found 362.1.

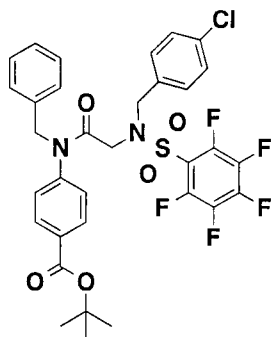


[00185] **tert-butyl N-(4-chlorobenzyl)-N-((perfluorophenyl)sulfonyl)glycinate (4).** Derivative **4** synthesized using general procedure f (71%): δ_{H} (400 MHz, CDCl_3)

1.37 (s, 9H, (CH₃)₃), 3.93 (s, 2H, CH₂), 4.57 (s, 2H, CH₂), 7.24 (d, *J* = 8.5 Hz, 2H, CH), 7.33 (d, *J* = 8.5 Hz, 2H, CH); δ_C (400 MHz, CDCl₃) 27.5, 52.5, 53.0, 81.8, 112.6, 126.5, 130.1, 132.4, 134.3, 136.5, 144.8, 145.9, 167.0; LRMS (ESI+) calculated for C₁₉H₁₇F₅ClNO₄S [M + H]⁺ 485.0, found 486.1.

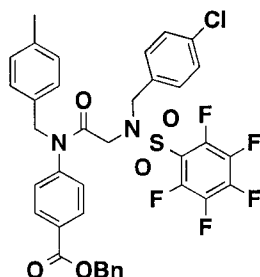


[00186] ***N*-(4-chlorobenzyl)-*N*-((perfluorophenyl)sulfonyl)glycine (5)**. Derivative **5** synthesized using general procedure **g** (92%): δ_H (400 MHz, CDCl₃) 4.13 (s, 2H, CH₂), 4.58 (s, 2H, CH₂), 7.25 (d, *J* = 8.2 Hz, 2H, CH), 7.35 (d, *J* = 8.2 Hz, 2H, CH); δ_C (400 MHz, CDCl₃) 52.8, 54.2, 112.6, 126.5, 130.1, 132.4, 134.3, 136.5, 144.8, 145.9, 172.0; LRMS (ESI+) calculated for C₁₅H₉F₅ClNO₄S [M + H]⁺ 428.9, found 429.9.



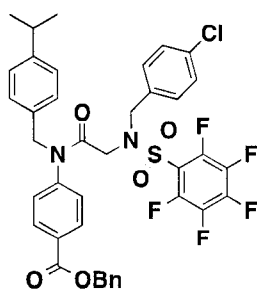
[00187] ***tert*-butyl 4-(*N*-benzyl-2-((*N*-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)acetamido)benzoate (6a)**. Derivative **6a** synthesized using general procedure **h** (61%): ¹H NMR (400 MHz, Chloroform-*d*) δ 1.25 (s, 3H), 1.56 (s, 27H), 2.04 (s, 1H), 3.72 (s, 3H), 4.65 (s, 4H), 4.72 (s, 6H), 6.79 (d, *J* = 8.0 Hz, 6H), 7.02 (dd, *J* = 6.5, 2.9 Hz, 6H), 7.18 (d, *J* = 8.4 Hz, 6H), 7.23 – 7.31 (m, 16H), 7.88 (d, *J* = 8.1 Hz, 6H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 27.93, 47.57, 50.51, 53.13, 81.66, 127.67, 127.85, 128.45, 128.57, 128.93, 129.89, 131.07, 132.72, 135.74, 143.14,

164.22 , 165.62 . LRMS (ESI+) calculated for $C_{33}H_{29}F_5ClN_2O_5S$ $[M + H]^+$ 695.14, found 695.16.



[00188] **Benzyl 4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-methylbenzyl)acetamido)benzoate (6b).**

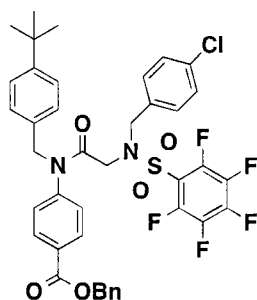
Derivative **6b** synthesized using general procedure **h** (68%): 1H NMR (400 MHz, Chloroform-*d*) δ 1.27 (t, $J = 7.1$ Hz, 2H), 2.05 (s, 1H), 2.33 (s, 5H), 3.73 (d, $J = 8.3$ Hz, 2H), 4.13 (q, $J = 7.1$ Hz, 1H), 4.68 (d, $J = 12.0$ Hz, 5H), 5.34 (s, 3H), 6.83 (d, $J = 8.1$ Hz, 3H), 6.91 (d, $J = 7.8$ Hz, 3H), 7.08 (d, $J = 7.8$ Hz, 3H), 7.16 – 7.23 (m, 3H), 7.23 – 7.47 (m, 11H), 7.98 (d, $J = 8.2$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 20.98, 47.62, 50.54, 52.87, 66.97, 127.97, 128.16, 128.31, 128.51, 128.55, 128.94, 129.14, 129.91, 130.46, 131.34, 132.66, 132.76, 134.25, 135.46, 137.66, 143.77, 164.96, 165.49. LRMS (ESI+) calculated for $C_{37}H_{29}ClF_5N_2O_5S$ $[M + H]^+$ 743.13, found 743.15.



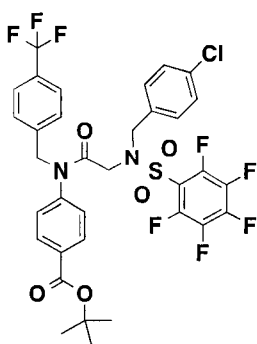
[00189] **Benzyl 4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-isopropylbenzyl)acetamido)benzoate (6c).**

Derivative **6c** synthesized using general procedure **h** (55%): 1H NMR (400 MHz, Chloroform-*d*) δ 0.88 (dt, $J = 11.6, 7.3$ Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 12H), 2.90 (p, $J = 6.9$ Hz, 2H), 3.73 (s, 2H), 4.68 (d, $J = 13.2$ Hz, 6H), 5.35 (s, 4H), 6.82 (d, $J = 8.1$ Hz,

3H), 6.95 (d, $J = 7.9$ Hz, 3H), 7.11 – 7.21 (m, 7H), 7.26 (d, $J = 3.1$ Hz, 4H), 7.29 – 7.47 (m, 9H), 7.98 (d, $J = 8.1$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 23.78 , 33.65 , 47.61 , 50.50 , 52.93 , 66.99 , 126.51 , 127.95 , 128.17 , 128.32 , 128.52 , 128.56 , 128.94 , 129.93 , 130.46 , 131.34 , 132.69 , 132.97 , 135.45 , 143.87 , 148.66 , 164.99 , 165.47 . LRMS (ESI+) calculated for $\text{C}_{39}\text{H}_{33}\text{ClF}_5\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 771.16, found 771.17.

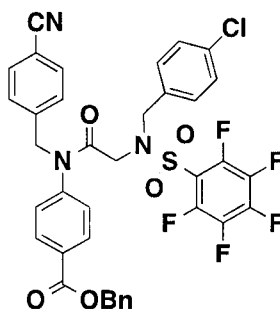


[00190] **Benzyl-4-(N-(4-(*tert*-butyl)benzyl)-2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)acetamido)benzoate (6d)**. Derivative **6d** synthesized using general procedure **h** (71%): ^1H NMR (400 MHz, Chloroform- d) δ 1.31 (d, $J = 1.3$ Hz, 10H), 3.72 (s, 1H), 4.67 (d, $J = 13.0$ Hz, 4H), 5.34 (s, 2H), 6.82 (d, $J = 8.0$ Hz, 2H), 6.95 (d, $J = 7.9$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz, 3H), 7.24 – 7.37 (m, 7H), 7.37 – 7.42 (m, 4H), 7.44 (d, $J = 1.9$ Hz, 1H), 7.98 (d, $J = 8.1$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform- d) δ 31.14, 34.41, 47.59, 50.48, 52.85, 67.00 , 125.35 , 127.93 , 128.17 , 128.24 , 128.33 , 128.52 , 128.94 , 129.93 , 131.35 , 132.57 , 132.66 , 134.27 , 135.42 , 143.90 , 165.00 , 165.45. LRMS (ESI+) calculated for $\text{C}_{40}\text{H}_{35}\text{ClF}_5\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 785.18 found 785.21.



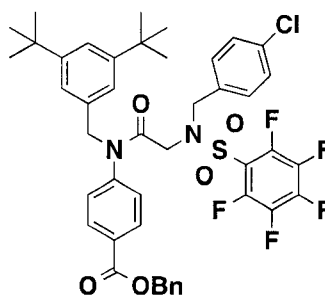
[00191] *tert*-butyl-4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-*N*-(4-(trifluoromethyl)benzyl)acetamido)benzoate (6e).

Derivative 6e synthesized using general procedure h (77%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.57 (s, 5H), 3.75 (s, 1H), 4.63 (s, 1H), 4.77 (s, 1H), 6.83 (d, $J = 8.1$ Hz, 1H), 7.18 (dd, $J = 8.2, 4.0$ Hz, 2H), 7.27 (d, $J = 9.0$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 27.92, 47.60, 50.51, 52.76, 77.06, 81.81, 125.44, 125.48, 127.50, 128.78, 128.97, 129.84, 131.31, 132.59, 132.68, 134.36, 139.71, 142.91, 166.03. LRMS (ESI+) calculated for $\text{C}_{34}\text{H}_{28}\text{ClF}_8\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 763.12 found 763.15.



[00192] **Benzyl-4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-cyanobenzyl)acetamido)benzoate (6f).**

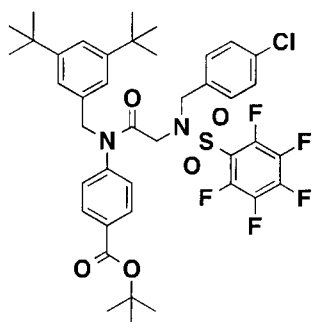
Derivative 6f synthesized using general procedure h (60%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.25 (t, $J = 7.1$ Hz, 1H), 2.04 (s, 1H), 3.77 (s, 1H), 4.62 (s, 2H), 4.78 (s, 2H), 5.34 (s, 2H), 6.86 (d, $J = 8.1$ Hz, 2H), 7.17 (dd, $J = 8.4, 2.6$ Hz, 4H), 7.24 – 7.30 (m, 2H), 7.30 – 7.45 (m, 5H), 7.55 – 7.62 (m, 2H), 7.97 – 8.05 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 47.67, 50.55, 52.85, 67.10, 127.65, 128.19, 128.37, 128.53, 128.99, 129.09, 129.82, 130.92, 131.67, 132.33, 132.51, 134.40, 135.32, 140.93, 143.34, 164.71, 166.16. LRMS (ESI+) calculated for $\text{C}_{37}\text{H}_{26}\text{ClF}_5\text{N}_3\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 754.11 found 754.15.



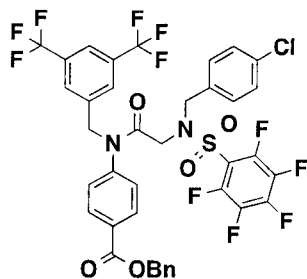
[00193] **Benzyl-4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(3,5-di-tert-butylbenzyl)acetamido)benzoate (6g).**

Derivative 6g synthesized using general procedure h (84%): ^1H NMR (400 MHz,

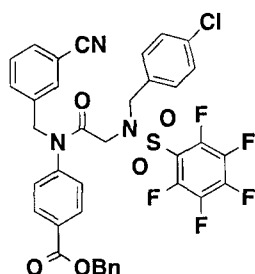
Chloroform-*d*) δ 0.82 – 0.93 (m, 1H), 1.24 – 1.37 (m, 25H), 3.71 (s, 2H), 4.62 (s, 2H), 4.74 (s, 3H), 5.35 (s, 3H), 6.75 (d, $J = 8.0$ Hz, 3H), 6.85 (s, 3H), 7.15 (d, $J = 8.1$ Hz, 3H), 7.24 (d, $J = 8.1$ Hz, 4H), 7.29 – 7.46 (m, 10H), 7.94 (d, $J = 8.0$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 31.18 , 34.56 , 47.70 , 50.27 , 53.34 , 66.94 , 121.51 , 123.13 , 128.05 , 128.09 , 128.28 , 128.51 , 128.92 , 129.97 , 131.11 , 132.59 , 134.31 , 134.47 , 135.47 , 150.98 , 165.27. LRMS (ESI+) calculated for $\text{C}_{44}\text{H}_{43}\text{ClF}_5\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 841.24 found 841.27.



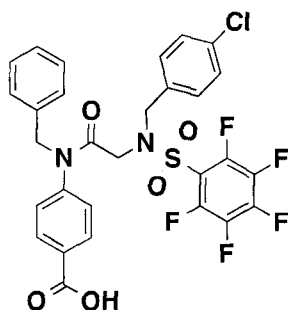
[00194] ***tert*-butyl** **4-(2-((*N*-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-*N*-(3,5-di-*tert*-butylbenzyl)acetamido)benzoate** (**6g**). ^1H NMR (400 MHz, Chloroform-*d*) δ 1.24 (s, 18H), 1.56 (s, 9H), 3.52 – 3.87 (m, 2H), 4.61 (s, 2H), 4.74 (d, $J = 12.3$ Hz, 2H), 6.71 (d, $J = 8.0$ Hz, 2H), 6.81 – 6.87 (m, 2H), 7.14 (d, $J = 8.5$ Hz, 2H), 7.20 – 7.34 (m, 3H), 7.84 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 27.94, 31.16, 34.55, 47.68, 50.26, 53.34, 81.60, 121.45, 123.10, 127.83, 128.91, 129.97, 130.81, 132.22, 132.62, 134.28, 134.55, 150.92, 164.26, 165.33. LRMS (ESI+) calculated for $\text{C}_{41}\text{H}_{45}\text{ClF}_5\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 807.26 found 807.29.



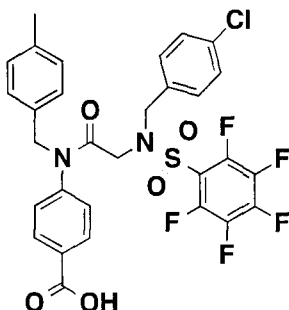
[00195] **Benzyl-4-(N-(3,5-bis(trifluoromethyl)benzyl)-2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)acetamido)benzoate (6h)**. Derivative 6h synthesized using general procedure h (89%): ^1H NMR (400 MHz, Chloroform-*d*) δ 0.81 – 0.94 (m, 1H), 1.21 – 1.32 (m, 3H), 2.04 (s, 1H), 3.46 (s, 1H), 3.79 (s, 3H), 4.13 (dt, $J = 14.3, 7.6$ Hz, 1H), 4.55 (d, $J = 17.3$ Hz, 2H), 4.62 (s, 4H), 4.87 (s, 5H), 5.32 (d, $J = 18.0$ Hz, 6H), 6.86 (d, $J = 8.1$ Hz, 5H), 7.17 (d, $J = 8.3$ Hz, 6H), 7.23 – 7.33 (m, 7H), 7.33 – 7.46 (m, 15H), 7.57 (s, 5H), 7.81 (d, $J = 9.5$ Hz, 4H), 7.90 (d, $J = 8.6$ Hz, 1H), 8.02 (d, $J = 8.2$ Hz, 5H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 46.75, 47.54, 50.35, 52.41, 65.94, 67.11, 111.72, 119.44, 121.50, 121.87, 124.21, 127.04, 127.51, 127.84, 128.14, 128.35, 128.39, 128.42, 128.52, 129.03, 129.82, 131.07, 131.45, 131.62, 131.79, 132.12, 132.40, 134.48, 135.32, 138.44, 143.28, 164.65, 166.42. LRMS (ESI+) calculated for $\text{C}_{38}\text{H}_{25}\text{ClF}_{11}\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 865.09 found 865.12.



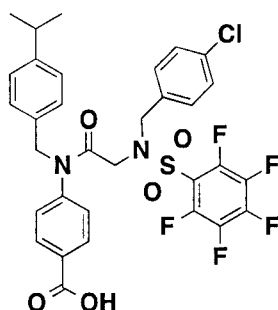
[00196] **Benzyl-4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(3-cyanobenzyl)acetamido)benzoate (6i)**. Derivative 6i synthesized using general procedure h (63%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.20 – 1.29 (m, 2H), 2.03 (s, 2H), 3.77 (s, 2H), 4.11 (q, $J = 7.1$ Hz, 1H), 4.62 (s, 2H), 4.76 (s, 3H), 5.34 (s, 3H), 6.85 (d, $J = 8.1$ Hz, 3H), 7.18 (d, $J = 8.2$ Hz, 3H), 7.28 (d, $J = 8.3$ Hz, 3H), 7.30 – 7.46 (m, 12H), 7.58 (dq, $J = 7.8, 1.2$ Hz, 2H), 8.00 (d, $J = 8.2$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 47.66, 50.48, 52.47, 67.08, 112.71, 127.66, 128.16, 128.34, 128.52, 129.00, 129.46, 129.83, 130.90, 131.62, 131.67, 131.83, 132.51, 132.81, 134.37, 135.35, 136.39, 137.35, 143.34, 164.71, 166.15. LRMS (ESI+) calculated for $\text{C}_{37}\text{H}_{26}\text{ClF}_5\text{N}_3\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 754.11 found 754.14.



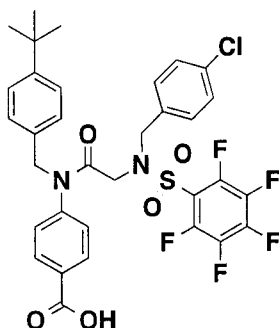
[00197] **4-(N-benzyl-2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)acetamido)benzoic acid (7a):** Derivative **7a** synthesized using general procedure i (45%): ^1H NMR (400 MHz, Chloroform-*d*) δ 3.75 (s, 2H), 4.65 (s, 2H), 4.74 (s, 2H), 6.68 – 6.90 (m, 2H), 6.90 – 7.14 (m, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 7.26 – 7.41 (m, 5H), 7.98 (d, $J = 8.1$ Hz, 2H), 11.25 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 20.66, 47.64, 50.50, 53.22, 127.86, 127.96, 128.04, 128.47, 128.52, 128.64, 128.80, 128.96, 129.93, 131.83, 131.99, 132.61, 134.33, 135.52, 143.38, 143.46, 144.33, 165.69, 170.43.



[00198] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-methylbenzyl)acetamido)benzoic acid (7b).** Derivative **7b** synthesized using general procedure i (53%): ^1H NMR (400 MHz, Chloroform-*d*) δ 2.11 (s, 6H), 2.33 (s, 3H), 3.74 (s, 1H), 4.70 (s, 4H), 6.77 (d, $J = 8.1$ Hz, 1H), 6.80 – 6.95 (m, 3H), 7.08 (d, $J = 7.7$ Hz, 2H), 7.16 – 7.35 (m, 5H), 7.96 (dd, $J = 22.4, 8.1$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 20.64, 20.97, 47.62, 50.51, 51.04, 52.87, 128.03, 128.34, 128.51, 128.67, 128.78, 128.95, 129.14, 129.92, 131.66, 131.79, 132.57, 133.98, 137.64, 144.46, 165.70, 170.35, 177.40. HRMS (ESI-) calculated for $[\text{C}_{30}\text{H}_{21}\text{ClF}_5\text{N}_2\text{O}_6\text{S}]^-$ 651.0785, found 651.0791;

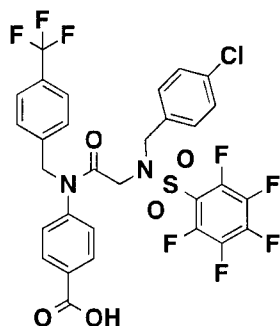


[00199] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-isopropylbenzyl)acetamido)benzoic acid (7c)**. Derivative **7c** synthesized using general procedure **i** (69%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.24 (dd, $J = 11.6, 7.0$ Hz, 7H), 2.06 (d, $J = 18.9$ Hz, 2H), 2.80 – 2.94 (m, 1H), 3.47 (s, 6H), 3.72 (s, 1H), 4.11 (q, $J = 7.1$ Hz, 1H), 4.63 (s, 2H), 4.68 (s, 2H), 6.81 (d, $J = 8.1$ Hz, 1H), 6.94 (dd, $J = 7.9, 4.0$ Hz, 2H), 7.15 (dd, $J = 19.3, 8.0$ Hz, 3H), 7.23 – 7.33 (m, 2H), 7.88 – 8.00 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 14.00, 20.59, 20.87, 23.74, 33.63, 47.62, 50.48, 50.50, 52.97, 53.26, 60.33, 77.08, 116.11, 116.26, 126.49, 127.93, 128.53, 128.66, 128.75, 128.93, 129.94, 130.22, 131.55, 131.67, 132.63, 132.88, 134.29, 136.40, 138.94, 142.39, 143.43, 144.13, 144.99, 146.04, 148.68, 165.54, 169.00, 171.22, 176.02. HRMS (ESI-) calculated for $[\text{C}_{32}\text{H}_{25}\text{ClF}_5\text{N}_2\text{O}_5\text{S}]^-$ 679.1098, found 679.1105.

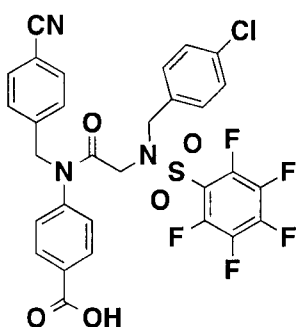


[00200] **4-(N-(4-(tert-butyl)benzyl)-2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)acetamido)benzoic acid (7d)**. Derivative **7d** synthesized using general procedure **i** (63%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.30 (s, 9H), 3.65 – 3.82 (s, 2H), 4.65 (s, 2H), 4.69 (s, 2H), 6.84 (d, $J = 7.1$ Hz, 2H), 6.95 (d, $J = 7.8$ Hz, 2H), 7.17 (s, 2H), 7.27 (dd, $J = 13.5, 7.9$ Hz, 5H), 7.97 (s, 1H), 10.22 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 31.12, 34.39, 47.63, 50.48, 52.95, 116.12, 125.35, 127.95, 128.22, 128.93, 129.96, 131.79, 132.49, 132.65, 134.27, 143.50,

144.24, 165.61. HRMS (ESI-) calculated for $[C_{33}H_{27}ClF_5N_2O_5S]^-$ 693.1255, found 693.1270.

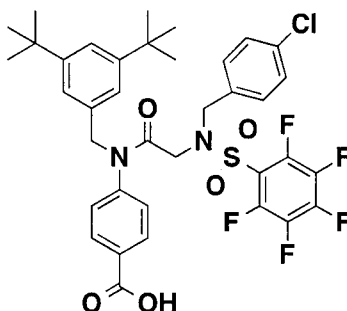


4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-(trifluoromethyl)benzyl)acetamido)benzoic acid (7e). Derivative 7e synthesized using general procedure i (95%): 1H NMR (400 MHz, Methanol- d_4) δ 3.87 (s, 2H), 4.61 (s, 2H), 4.86 (s, 2H) 7.02 (d, J = 8.0 Hz, 2H), 7.21 – 7.35 (m, 7H), 7.58 (d, J = 7.9 Hz, 2H), 7.95 (dd, J = 8.4, 1.5 Hz, 2H). ^{13}C NMR (101 MHz, MeOD) δ 47.91, 50.61, 52.16, 124.91, 124.95, 127.68, 128.45, 128.68, 129.83, 130.94, 131.03, 131.09, 131.18, 131.50, 133.29, 133.78, 140.61, 166.49, 166.83. HRMS (ESI-) calculated for $[C_{30}H_{18}ClF_8N_2O_5S]^-$ 705.0503, found 705.0513.

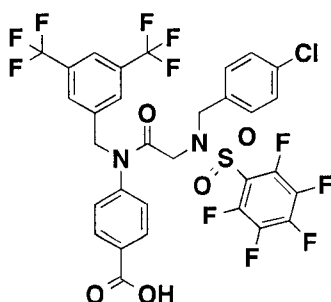


[00201] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(4-cyanobenzyl)acetamido)benzoic acid (7f).** Derivative 7f synthesized using general procedure i (54%): 1H NMR (400 MHz, Chloroform- d) δ 0.86 (t, J = 10.5 Hz, 4H), 1.25 (s, 10H), 1.42 (s, 2H), 2.10 (s, 7H), 3.78 (s, 3H), 4.59 – 4.67 (m, 4H), 4.78 (s, 4H), 6.80 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 7.9 Hz, 3H), 7.18 (dd, J = 8.4, 2.4 Hz, 7H), 7.29 (dd, J = 18.1, 10.1 Hz, 12H), 7.59 (d, J = 7.9 Hz, 6H), 7.77 (s, 1H), 7.99 (dd, J = 22.5, 7.9 Hz,

6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 20.72 , 22.53 , 29.54 , 47.66 , 50.54 , 51.04 , 52.90 , 77.07 , 112.00 , 116.09 , 118.14 , 127.68 , 128.48 , 128.61 , 128.83 , 129.00 , 129.05 , 129.85 , 131.97 , 132.10 , 132.33 , 132.36 , 132.45 , 133.78 , 134.46 , 136.37 , 138.95 , 140.85 , 140.97 , 143.44 , 143.83 , 145.95 , 166.22 , 166.32 , 169.86 , 177.13 . HRMS (ESI-) calculated for $[\text{C}_{30}\text{H}_{18}\text{ClF}_5\text{N}_3\text{O}_5\text{S}]$ 662.0581, found 662.0590.

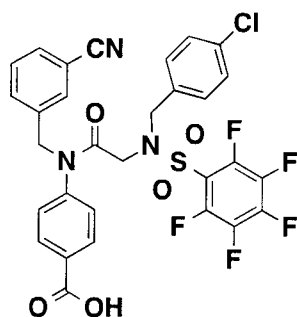


[00202] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(3,5-di-tert-butylbenzyl)acetamido)benzoic acid (7g)**. Derivative 7g synthesized using general procedure i (78%): ^1H NMR (400 MHz, Chloroform-*d*) δ 1.24 (d, J = 1.1 Hz, 10H), 4.62 (s, 1H), 4.75 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.18 – 7.28 (m, 2H), 7.28 – 7.34 (m, 1H), 7.96 (d, J = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 31.32 , 34.72 , 47.87 , 50.42 , 53.54 , 77.21 , 121.73 , 123.33 , 128.41 , 129.09 , 130.15 , 131.74 , 132.69 , 134.51 , 146.24 , 151.19 , 165.39 , 169.84 . HRMS (ESI-) calculated for $[\text{C}_{37}\text{H}_{35}\text{ClF}_5\text{N}_2\text{O}_5\text{S}]$ 749.1881, found 749.1902.



[00203] **4-(N-(3,5-bis(trifluoromethyl)benzyl)-2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)acetamido)benzoic acid (7h)**. Derivative 7h synthesized using general procedure i (86%): ^1H NMR (400 MHz, Chloroform-*d*) δ 2.12 (s, 6H), 3.81 (s, 4H), 4.64 (d, J = 10.9 Hz, 5H), 4.88 (d, J = 2.9 Hz, 6H), 6.78 (d, J = 8.1

Hz, 3H), 6.89 (d, $J = 8.1$ Hz, 3H), 7.14 – 7.25 (m, 6H), 7.25 – 7.35 (m, 8H), 7.56 (d, $J = 1.6$ Hz, 6H), 7.82 (d, $J = 6.8$ Hz, 4H), 8.01 (dd, $J = 26.3, 8.2$ Hz, 6H). ^{13}C NMR (101 MHz, Chloroform- d) δ 20.61, 47.54, 50.36, 50.88, 52.40, 52.46, 111.76, 121.48, 121.90, 124.19, 127.66, 128.43, 128.53, 128.61, 128.88, 129.04, 129.85, 130.07, 131.83, 132.12, 132.26, 132.33, 133.66, 138.28, 138.35, 143.90, 144.00, 166.47, 166.56, 170.12, 177.61. HRMS (ESI-) calculated for $[\text{C}_{31}\text{H}_{17}\text{ClF}_{11}\text{N}_2\text{O}_5\text{S}]^-$ 773.0377, found 773.0387.



[00204] **4-(2-((N-(4-chlorobenzyl)-2,3,4,5,6-pentafluorophenyl)sulfonamido)-N-(3-cyanobenzyl)acetamido)benzoic acid (7i)**. Derivative **7i** synthesized using general procedure i (67%): ^1H NMR (400 MHz, DMSO- d_6) δ 3.96 (s, 2H), 4.55 (s, 2H), 4.84 (s, 2H), 7.25 (t, $J = 7.6$ Hz, 4H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.39 – 7.51 (m, 2H), 7.58 (s, 1H), 7.69 (dt, $J = 7.4, 1.6$ Hz, 1H), 7.88 (d, $J = 8.1$ Hz, 2H), 13.10 (s, 1H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 28.27, 49.34, 51.31, 51.79, 111.72, 118.86, 128.32, 128.78, 128.29, 129.88, 130.35, 131.01, 131.08, 131.11, 131.09, 131.57, 132.90, 133.09, 134.44, 138.51, 166.58, 166.69. HRMS (ESI-) calculated for $[\text{C}_{30}\text{H}_{18}\text{ClF}_5\text{N}_3\text{O}_5\text{S}]^-$ 662.0581, found 662.0581.

[00205] *Example 2: DiscoverX Kinase Screen*

[00206] KINOMEscan kinase profiling was performed as previously described (Fabian et al., 2005; Karaman et al., 2008). For most assays, kinase-tagged T7 phage strains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis (90-150 minutes). The lysates were centrifuged (6,000 x g) and filtered (0.2 μm) to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently

tagged with DNA for qPCR detection as previously described (Wodicka et al., 2010). Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific phage binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20 % SeaBlock, 0.17x PBS, 0.05 % Tween 20, 6 mM DTT). **13a** was prepared as 40x stocks in 100% DMSO and directly diluted into the assay. All reactions were performed in polypropylene 384-well plates in a final volume of 0.04 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05 % Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05 % Tween 20, 0.5 μ M non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR and the data presented as %Ctrl (**Figure 1**). Data for **13a** is also depicted on a TreeSpot dendrogram for simplicity (**Figure 1**).

[00207] *Discussion*

[00208] To determine the selectivity of **13a** for STAT5, off-target kinase activity was screened as a possible alternative target for an effector of STAT5 phosphorylation. **13a** was assessed against 120 representative kinases covering the diversity of the kinase families (DiscoverX). Ultrasensitive quantitative PCR (qPCR) was used to measure levels of immobilized kinases after treatment with **13a** at 5 μ M. **13a** showed negligible effects against the bank of kinases and in particular, against upstream STAT5 activating kinases, JAK 1/2, ABL, and FLT-3. These data indicate that the inhibition of STAT5 phosphorylation is due to the interaction with STAT5's SH2 domain and not through inhibition of upstream kinases.

[00209] *Example 3: Surface Plasmon Resonance (SPR) Studies.*

[00210] Interactions of His-tagged STAT3 and STAT5 with small molecules were investigated using SPR spectroscopy. The binding experiments were carried on a ProteOn XPR36 (Bio-Rad) biosensor at 25°C using the HTE sensor chip (Bio-Rad, Ontario, Canada). The flow cells of the sensor chip were loaded with a nickel solution at

30 $\mu\text{L}/\text{min}$ for 120 s to saturate the Tris-NTA surface with Ni(II) ions. Purified His-tagged STAT3 and STAT5 (SignalChem, British Columbia, Canada) in PBST buffer (PBS with 0.005% (v/v) Tween-20 and 0.001% DMSO pH 7.4) was injected in the first and second channels of the chip respectively, in the vertical direction at a flow rate of 25 $\mu\text{g}/\mu\text{L}$ for 300 s, which attained, on average, ~ 8000 resonance unit (RU). After a wash with PBST buffer, compounds (**13a-d**) binding to the immobilized proteins was monitored by injecting a range of concentrations along with a blank at a flow rate of 100 $\mu\text{L}/\text{min}$ for 200 s for each of these compounds. When the injection of the compounds was completed, running buffer was allowed to flow over the immobilized substrates for the non-specifically bound inhibitors to dissociate for 600 s. Following dissociation of the compounds, the chip surface was regenerated with an injection of 1 M NaCl at a flow rate of 100 $\mu\text{L}/\text{min}$ for 18 s. Interspot channel reference was used for non-specific binding corrections and the blank channel used with each analyte injection served as a double reference to correct for possible baseline drift. Data were analysed using ProteOn Manager Software version 3.1. The Langmuir 1:1 binding model was used to determine the K_D values. Control experiments have already been reported that validates this protocol. Binding experiments were performed at multiple concentrations, **13b,d** (5, 1.67, 0.56, 0.19 μM , the top line being 5) and **13c** (10, 3.3, 1.1, 0.37 μM , the top line being 10) in figure 2.

[00211] *Discussion*

[00212] SPR binding experiments were conducted to measure the kinetic association and dissociation using a ProteOn XPR36 (Biorad) with full-length His-tagged, STAT5 and STAT3 (SignalChem) immobilized on a biosensor chip. Inhibitors exhibited nanomolar binding affinities for STAT5, and selectivity for the STAT5 instead of the STAT3 protein. Compound **13a** exhibited the most potent K_D ($k_{\text{off}}/k_{\text{on}}$) of 41.9 ± 4 nM with 7-fold selectivity for STAT5 vs. STAT3, $K_D = 287 \pm 29$ nM. ,

[00213] *Example 4: Fluorescence Polarization Assay*

[00214] Binding of compounds of the disclosure to the STAT5b SH2 domain was assessed using fluorescence polarization assays similar to those previously reported.¹⁵ Analogous assays were also performed with STAT3 protein to determine the specificity of the compounds (**13a-d**). Fluorescence assays were performed in flat black 384-well plates (Corning) and fluorescence polarization measurements were taken with the

Infinite M1000 machine (Tecan, Crailsheim, Germany). The buffer conditions for all assays were 20 mM HEPES, 50 mM NaCl, 1mM EDTA, 2mM dithiothreitol, pH 7.5 and the final DMSO concentration in the wells was kept constant at 10%.

[00215] Calibration curves for the wildtype STAT3 and STAT5b proteins were derived by incubating a 10 nM final concentration of fluoresceinated-phosphopeptide (5-FAM-pYLPQTC (SEQ ID NO:1) and 5-FAM-GpYLVLDKW (SEQ ID NO:2) for STAT3 and STAT5B, respectively), which are known to bind the SH2 domains, with increasing concentrations of protein (as shown in **Figure 3**). The point at which 80% of the fluoresceinated-phosphopeptide was bound was used as the optimal protein concentration required for the competitive fluorescent polarization assays.

[00216] For the STAT5b fluorescence polarization assays, the 5-FAM-GpYLVLDKW (SEQ ID NO:2) peptide and STAT5b protein were first incubated for 30 minutes at room temperature. Compounds were titrated at concentrations ranging from 1- >60,000 nM and incubated for a further 15 minutes at which point fluorescence polarization measurements were taken in triplicate. The final well concentrations of the fluoresceinated-phosphopeptide and STAT5B were 10 nM and 250 nM, respectively. The same protocol was used for the analogous STAT3 FP assays, except that the 5-FAM-pYLPQTC (SEQ ID NO:1) peptide was used as a probe and the final STAT3 concentration was 150 nM in each well.

[00217] The resulting fluorescence polarization measurements were normalized and plotted against compound concentration on a logarithmic scale. The raw data was fitted with a standard dose- normalized response inhibition curve using GraphPad Prism 6 software. The IC₅₀ values were converted to K_i values using **Equation 1**, which corrects for protein concentration and is a more accurate determination of inhibitory constants in a fluorescence polarization assay than the Cheng-Prusoff equation.¹⁵ All inhibitory constants and calculated K_i values are summarized in **Table 1**.

$$K_i = \frac{IC_{50}}{1 + \frac{[Peptide]}{K_d} + \frac{[Protein]}{K_d}}$$

[00218] **Equation 1:** Modified Cheng-Prusoff equation containing a correction factor for protein concentration. For STAT5b assays, [Peptide] = 10 nM, [Protein] = 250

nM, and $K_d = 170$ nM. For STAT3 assays, [Peptide] = 10 nM, [Protein] = 160 nM, and $K_d = 105$ nM.

[00219] As shown in Figures 4 and 5, compounds of the disclosure were evaluated using FP, in which **13a** was found to potently disrupt the phosphopeptide–STAT5B interactions, $K_i = 145$ nM. Moreover, **13a** was a 1000-fold more selective for STAT5B over STAT3, with a STAT3 $K_i = 143$ μ M.

[00220] *Example 5: Cell lines and culture techniques*

[00221] Human erythroleukemia K562 and MV-4-11 cells were cultured in Iscove's modified dulbecco's medium (Gibco) supplemented with 10% FBS (Sigma). Breast carcinoma lines MDA-MB-231 and MDA-MB-468 were grown in dulbecco's modified eagles medium (DMEM,) supplemented with 10% FBS (sigma). For downregulation of STAT5 activity, cells were treated with 5, 10, 15, 20 μ M of **13a-d** STAT5 compounds, for 3h and 5h time points. As a control, cells were treated with the DMSO alone.

[00222] As shown in Figures 6 and 7, **13a** was assessed for whole cell potency against STAT5 transformed CML and AML cell lines, K562 (Bcr-Abl) and MV-4;11 (FLT3-ITD), respectively. Cell viability was assessed following treatment at various concentrations of inhibitor (0.78-50 μ M) using a CellTiter-Blue cell viability assay (72 hours). As compared to the STAT5 inhibitors (**8j**, **8l**, **8v**, **8x**), IC_{50} values for **13a-d** were 2-3-fold higher in potency, with activities ranging from 3-20 μ M (supporting). **13a**, displayed the most potent activity in FLT3-ITD driven MV4;11 cells, $IC_{50} = 3.5$ μ M.

[00223] *Example 6: Western blotting*

[00224] 1×10^6 Cells were grown in a 25cm cell culture flasks (cellstar) and treated with **13a** inhibitor. Proteins were extracted using RIPA buffer with protease and phosphates inhibitors and a careful protein determination were preformed (BCA protein assay kit, Pierce). In each assay, 30 μ g of clarified whole cell extract were resolved on a 10% polyacrylamide–SDS gel and transferred to a nitrocellulose membrane (Bio-Rad). The membranes were blocked with 5 % nonfat milk for at least 1 h followed by an overnight incubation in primary antibody.

[00225] Immunodetection was performed using antibodies against the total STAT5 (Cell Signaling # 9363), phosphorylated STAT5(Tyr 694) (Cell Signaling, cat.# 9359), total STAT3 (Cell Signaling #4904) and phosphorylated STAT3 (Tyr 705) (Cell Signaling

#9661), Cleaved Caspase-3 (Asp175) (Cell Signaling #9661), Cleaved-Parp-1 (ab72805) Anti-Cyclin D1 (Abcam ab16663), Anti-Cyclin-D2 (Abcam ab94685), Anti-c-Myc (Abcam ab32072) and β -actin (Cell Signaling #3700) as a loading control, followed by fluorescent conjugated goat secondary antibodies Alexa Fluor 488 (Cell Signaling #4408) and Alexa Fluor 647.

[00226] As shown in Figure 8, **13a** mediated inhibition of STAT5 phosphorylation levels. K652 leukemia cells were treated with **13a** for 5 hrs, the cells were harvested, and the levels of phosphorylated STAT5 (Y694) were determined (A). **13a** decreased pSTAT5 in a dose dependant manner and ablated pSTAT5 above 10 μ M with no change in the total STAT5 concentration or cleavable PARP-1. However, K562 cells were found to undergo cell death (cleaved PARP-1, Caspase-3) at 24 hrs at 15 μ M, indicating that **13a** induces apoptosis as a result of STAT5 inactivation (B). To investigate selectivity, MDA-MB-231 breast cancer cells, which harbor high pSTAT3 and low pSTAT5 activity, were assessed for differential pSTAT inhibition by **13a**. pSTAT3 was not inhibited at doses corresponding to STAT5 inhibition within the leukemic cell line (C). Downstream of STAT5, modulation of the STAT5 transcriptional targets, MCL-1, CYCLIND1/D2 and MYC was assessed. It was reasoned that **13a** should decrease gene expression and induce apoptosis by 24 hrs. K562 cells were dosed with **13a** at the same concentrations observed for selective STAT5 inhibition. At 5hrs, dose-dependant decreases in MYC and complete knockdown of MCL-1 was observed at 24 hrs (D).

[00227] *Example 7 – ADME Properties*

[00228] The metabolic stability of compound 13a was assessed through an ADME profile screen in mouse hepatocytes, as shown in Figures 9-13. LC-MS and tandem MS/MS spectra were obtained, illustrating that the presence of metabolites of 13a is minimal and that the majority of intact 13a is recovered after 240 min.

[00229] As shown in Figure 9, compound 13a was assessed for its metabolic stability in mouse hepatocytes and LC-MS spectra were obtained at various time points. Peak 1: 13a conjugated to glutathione+dehydration (MW= 1054.2 g/mol). Peak 2: 13a conjugated to glutathione+acetylation+dehydration (MW=1096.3 g/mol). Peak 3: Oxidation of compound 13a (MW= 783.2 g/mol). Peak 4: Intact compound 13a (MW= 767). Relative peak areas for Peak 1: (<1%), Peak 2: (<1%), Peak 3 (1-10%), Peak 4: (>10%).

[00230] Figure 10 shows a tandem mass spectra (MS/MS) for Peak 1 illustrating fragmentation for the purpose of structure elucidation of compound 13a dehydrated and conjugated to glutathione. Figure 11 shows a tandem mass spectra (MS/MS) for Peak 2 illustrating fragmentation for the purpose of structure elucidation of compound 13a dehydrated, acetylated and conjugated to glutathione. Figure 12 shows a tandem mass spectra (MS/MS) for Peak 3 illustrating fragmentation for the purpose of structure elucidation of the oxidation of compound 13a. Figure 13 shows a tandem mass spectra (MS/MS) for Peak 4 illustrating fragmentation for the parent compound 13a.

[00231] *Example 8 – Effect on CD34+ Cells and MV4-11 AML Cells*

[00232] Compound **13a** was evaluated in healthy human CD34+ umbilical cord cells to determine off-target effects and the therapeutic window. There existed an approximate order of magnitude difference in sensitivity, with little reduction in cell viability at 10 μ M of **13a**, whilst MV-4;11 cells were abolished at the same concentrations.

[00233] As shown in Figure 14, compound 13a showed little effect on healthy human CD34+ cells umbilical cord cells at 10 μ M with limited effect on cell viability in comparison to MV4;11 cells.

[00234] *Example 9 – Effect on CML and AML Cells*

[00235] To investigate selectivity, MDA-MB-231 breast cancer cells, which harbor high pSTAT3 and negligible pSTAT5 activity, Figure 8c and Figure 15c, were assessed for differential pSTAT inhibition by **13a**. pSTAT3 was not inhibited at doses corresponding to pSTAT5 inhibition within the leukemic cell line and neither total STAT3 or STAT5 protein levels were affected. Furthermore, there were no detectable pSTAT1 levels in both K562 and MDA-MB-231 cells. Correspondingly, **13a** did not disrupt the phosphopeptide-STAT1 complex with IC₅₀ values of > 150 μ M, Figure 15a. It was also shown that **13a** was 3-fold less cytotoxic in MDA-MB-231 cells (IC₅₀ = 10 μ M) than in the high pSTAT5 leukemic cell line, Figure 15d.

[00236] Previous reports indicate that knockdown of pSTAT5 in leukemia cells abrogates downstream MCL-1 expression at both the mRNA and protein level and is sufficient to induce apoptosis. Furthermore, MCL-1 expression is highly dependent upon STAT5 signaling pathways, suggesting that STAT5 inhibitors might be important for

triggering apoptosis in leukemia cells. With selectivity established upstream of the transcription factor, as well as within the STAT family, the downstream effects of pSTAT5 knockdown were investigated, specifically the modulation of the STAT5 transcriptional targets. To confirm the inhibitory effects of **13a**, experiments were conducted to measure the changes in level of expression of known STAT5-regulated genes, MCL-1, CYCLIN D1/D2 and MYC in K562 cells.

[00237] K562 cells were dosed with **13a** at the same concentrations observed for selective pSTAT5 inhibition. After 5h, dose-dependent decreases in c-MYC expression were observed and complete knockdown of MCL-1 observed at 24 h at 15 μ M, which are both consistent with their respective cellular turnover rates, Figure 8d.

[00238] Correspondingly, western blot analysis for protein levels of pSTAT5 and downstream target gene expression were also investigated within the AML cell line, MV-4;11. Consistent with the CML K562 cell line, **13a** at similar concentrations showed dose-dependent decrease of pSTAT5 at 5h with complete ablation of phosphorylation after 24 h at 10 μ M, Figure 16a. In addition, at 24h, the initiation of apoptosis was observed, Figure 16b, as well as complete knockdown of downstream target MCL-1 at 10 μ M, Figure 16c. Overall, **13a** had a more pronounced potency within AML than CML cells. These data, in conjunction with the Western blot analysis of pSTAT5, the potent *in vitro* disruption of STAT5/phosphopeptide complexation (Table 1), the SPR (Figure 2) and KINOME screen (Figure 1), and whole cell results (Figure 6 and 7), indicate that the STAT5 binding agents inhibit the transcriptional function of STAT5.

[00239] *Example 9 – Metabolic Studies*

[00240] Primary hepatocytes are popular for drug biotransformation due to their strong resemblance of the *in vivo* human liver. Intact hepatocytes contain phase I oxidative enzymes as well phase II enzymes like sulfo- and glucuronosyltransferases. Hepatocytes can be generated from various animal species, with the method requiring the whole liver, which may not be available in the case of the human liver. Rather, human liver is obtained from patients that undergo partial liver resection due to liver metastasis. Once isolated, hepatocytes are cryopreserved to maintain the catalytic activity of the metabolic enzymes. Therefore, to understand the physiochemical properties and metabolic profile of **13a**, absorption, distribution, metabolism and

excretion (ADME) screenings on both s9 fractions and intact hepatocytes were investigated.

[00241] The metabolic stability of **13a** was evaluated in both pooled human and mouse liver s9 fractions and human and mouse hepatocytes. The concentrations of the parent drug **13a** were evaluated by LC-MS/MS to estimate its stability in both reaction systems.

[00242] For the pooled s9 fractions, solution of the s9 fraction along with NADPH was added to each well. The negative control did not have NADPH, which was used to exclude the factor from the instability of the drug itself. The positive control used in the assay was Verapamil, a known drug to be metabolized by liver enzymes. The reaction was started by the addition of **13a** and performed in duplicate. Aliquots were taken from the reaction solution at 0 min and 60 min. The reaction was stopped by the addition of cold methanol. Samples were then analyzed through LC-MS/MS to determine the metabolic profile. As Figure 17 illustrates, after 60 min, **13a** was recovered at 59.82% in human liver s9 (HLS9) fractions with only 6.96% recovered in mouse liver s9 (MMLS9) fractions. The lower recovery of **13a** in MMLS9 vs. HLS9 is due to 1.5 times greater concentration of CPY450 and phase II conjugating enzymes.

[00243] **13a** was then evaluated within intact human and mouse hepatocytes. Like the s9 fractions, Verapamil was used as a positive control in the assay. Cryopreserved hepatocytes were thawed and plated to a working cell density of 0.5×10^6 viable cell/mL. A portion of the hepatocytes at 0.5×10^6 viable cell/mL were boiled for 5 min prior to adding to the plate as a negative control to eliminate the enzymatic activity so that little or no substrate turnover should be observed, and to exclude the possibility of instability from **13a** itself. Both **13a** and verapamil were added and the time points of 0 min and 120 min were taken by the addition of cold methanol to stop the reaction and the remaining percentages of **13a** was analyzed through LC-MS/MS. As Figure 18 shows, **13a** is recovered in a significant portion at 68.56% in human hepatocytes in comparison to 53.37% in mouse hepatocytes. As expected, the negative control had higher recoverable rates of **13a** at ~ 85% in both hepatic systems.

[00244] Overall, it is apparent that **13a** is stable amongst pooled mouse and human s9 fractions as well as hepatocytes. Within these studies, a series of phase I and phase II metabolites within mouse hepatocytes were identified. As Figure 9 illustrates,

13a is recoverable at >85% after 4h with three measurable phase I and phase II metabolites. Each peak from the initial mass spectrum is rerun through a tandem mass spec to identify the major peak along with the corresponding fractionation patterns of that metabolite. First, we analyzed the tandem mass spec of **peak 4**, which confirmed that the parent drug **13a** was recovered. Present between 1-10% after 4h, **peak 1** with a major m/z of 1054.2, corresponds to a phase II, glutathione conjugated metabolite of **13a**, Figure 10. **Peak 2** on the other hand is a combination of both phase I and phase II metabolism. With a major mass peak at m/z 1096.3, this corresponds to a glutathione-conjugated **13a** (m/z 1054.2), which has been further acetylated. Most likely, we deduced the acetylation is occurring at the acid position of the salicylic acid moiety, Figure 11.

[00245] As the major metabolite recovered between 10-20%, **peak 3** is a product of phase I metabolism in which **13a** (m/z 767.1) has been oxidized to produce the major peak with a m/z of 783.1. Based on the fragmentation pattern, the most likely site of oxidation could reside on the glycine core or the benzyl ring of the salicylic acid, Figure 12.

[00246] Two of the major peaks corresponded to a glutathione derivative of the parent drug **13a**, which collectively make up 10% of the metabolites recovered. The stability of **13a** under harsher conditions with an excess of the glutathione tripeptide was investigated. Considering the structure of **13a**, the pentafluorobenzene is the functional moiety that is likely most susceptible to nucleophilic attack from the GST enzyme. Specifically, the *para* position is highly electron withdrawn enabling for nucleophilic aromatic substitution to take place. HPLC experiments of **13a** with 1000x the concentration of the glutathione tripeptide (10 mM) relative to **13a** (100 μ M) were run in a phosphate (HEPES) buffer which was chosen based on the solubility of **13a** within this buffer system. Data points obtained with the analytical HPLC experiments were fit using ORIGIN software using an exponential decay equation. This equation models for chemical/biological processes whereby a rate in which something happens is proportional to the amount left. Each drug molecule has a certain probability of being metabolized in a small time interval. Thus, as a drug concentration goes down, the rate of its metabolism goes down as well. As Figure 19 illustrates, **13a** (decreasing line) was stable to glutathione conjugation (increasing line) over a time period of 20 h.

Table 1. Summary of the IC₅₀ values and inhibitory constants (K_i) derived from FP binding assays with compounds (13a-d), and the control STAT5 inhibitors (pimozide and chromone).

Compound	STAT5b		STAT3	
	IC ₅₀ (μM)	K _i (μM)	IC ₅₀ (μM)	K _i (μM)
13a	0.37	0.15	>150	>60
13b	6.53	2.57	>150	>60
13c	8.2	3.24	>150	>60
13d	3.95	1.56	>150	>60
Pimozide	75.11	29.64	n/a	n/a
Chromone	>150	>60	n/a	n/a

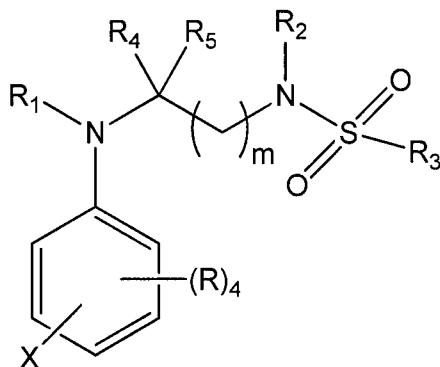
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CLAIMS:

1. A compound of the Formula



wherein

R_1 is $-(CH_2)_n-(C_6-C_{10})$ -aryl or $-C(=O)-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

R_2 is $-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

R_3 is $-(CH_2)_n-(C_6-C_{10})$ -aryl, wherein the aryl groups are optionally substituted with one to five substituents selected from halo, OH, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, halo-substituted- (C_1-C_4) -alkyl, $-(cyclopropyl)-CF_3$, $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1-C_4) -alkyl;

X is $-COOR''$, $-P(O)(OR'')_2$, tetrazole, $-C(=O)NR''-OH$, or $-CF_2OH$, wherein R'' is H or (C_1-C_4) -alkyl or $-CH_2-(C_6-C_{10})$ benzyl;

R_4 and R_5 are independently or simultaneously H or CF_3 , wherein one of R_4 or R_5 is H, or taken together R_4 and R_5 are $-C(=O)$ or $-C(=S)$;

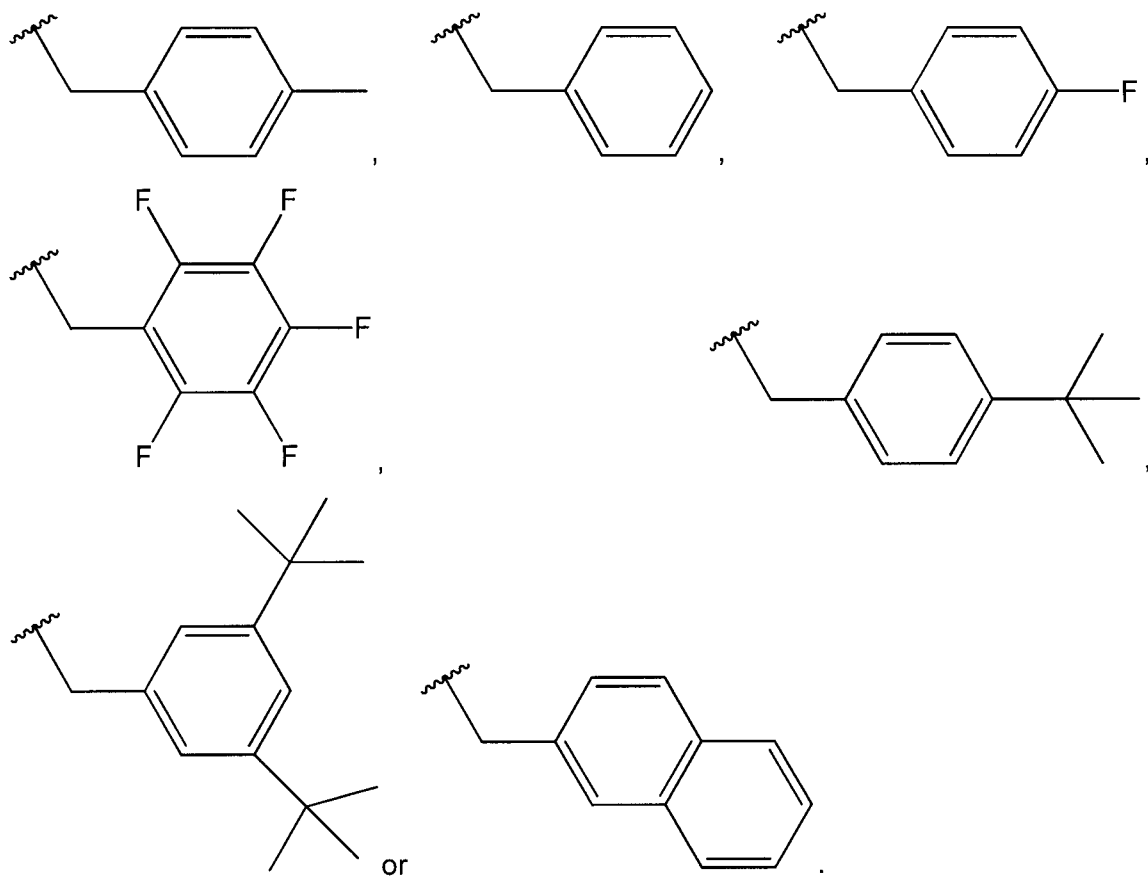
R is H, OH, halo, (C_1-C_6) -alkyl or (C_1-C_6) -alkoxy;

n is independently or simultaneously 0, 1, 2, 3, 4, 5, or 6; and

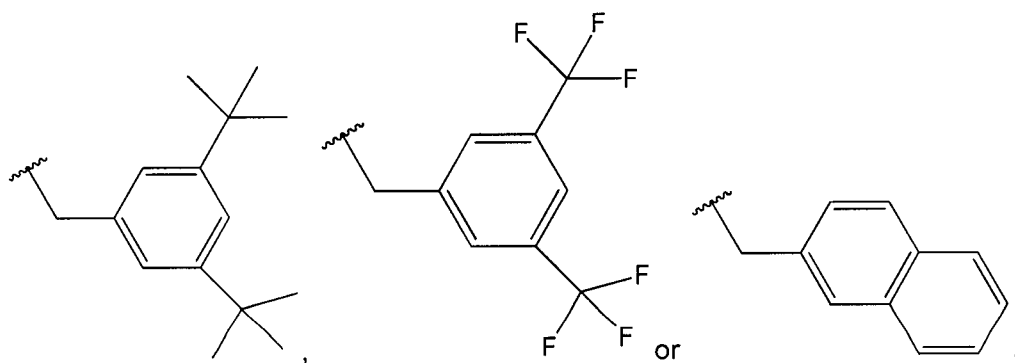
m is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, solvate, prodrug and/or stereoisomer thereof.

2. The compound according to claim 1, wherein R₁ is -(C₆-C₁₀)-aryl, -(CH₂)-(C₆-C₁₀)-aryl or -C(=O)-(C₆-C₁₀)-aryl.
3. The compound according to claim 2, wherein R₁ is phenyl, naphthyl, -CH₂-phenyl, -CH₂-naphthyl, -C(=O)-phenyl or -C(=O)-naphthyl.
4. The compound according to any one of claims 1 to 3, the optional substituents on the aryl group of R₁ are selected from one to five of halo, (C₁-C₆)-alkyl and (C₁-C₆)-alkoxy.
5. The compound according to 4, wherein the optional substituents on the aryl group of R₁ are selected from one to five of fluoro, chloro, bromo, (C₁-C₄)-alkyl or (C₁-C₄)-alkoxy.
6. The compound according to 5, the optional substituents on the aryl group of R₁ are selected from one to three substituents selected from fluoro, methyl or t-butyl.
7. The compound according to any one of claims 1 to 6, wherein R₁ is



8. The compound according to claim 7, wherein R_1 is



9. The compound according to any one of claims 1 to 8, wherein R_2 is $-(C_6-C_{10})$ -aryl or $-(CH_2)-(C_6-C_{10})$ -aryl.

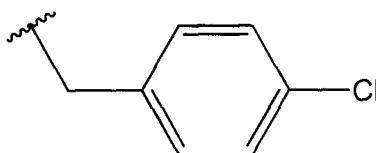
10. The compound according to claim 9, wherein R_2 is phenyl or $-CH_2$ -phenyl.

11. The compound according to claim 9 or 10, wherein the optional substituents on the aryl group of R_2 are selected from one to five of halo, halo-substituted-(C_1 - C_4)-alkyl, -(cyclopropyl)- CF_3 , $-NO_2$, CN, $-SO_3R'$ and $-COOR'$, wherein R' is H or (C_1 - C_4)-alkyl.

12. The compound according to claim 11, wherein the optional substituents on the aryl group of R_2 are selected from one to three of halo, halo-substituted-(C_1 - C_4)-alkyl, and -(cyclopropyl)- CF_3 .

13. The compound according to claim 12, wherein the optional substituents on the aryl group of R_2 are one to three chloro groups.

14. The compound according to claim 13, wherein R_2 is



15. The compound according to any one of claims 1 to 14, wherein R_3 is $-(C_6-C_{10})$ -aryl or $-(CH_2)-(C_6-C_{10})$ -aryl.

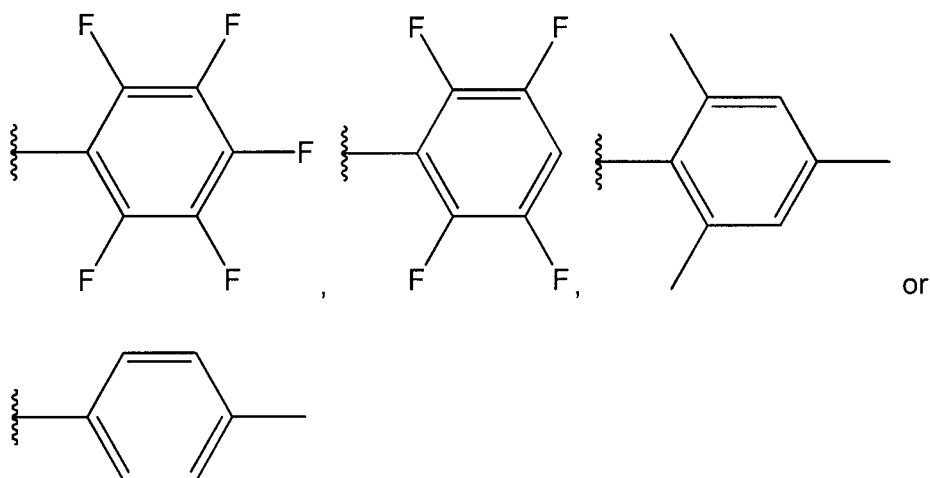
16. The compound according to claim 15, wherein R_3 is phenyl or $-CH_2$ -phenyl.

17. The compound according to claim 16, wherein the optional substituents on the aryl group of R_3 are selected from one to five of halo, OH, (C_1 - C_6)-alkyl, and (C_1 - C_6)-alkoxy.

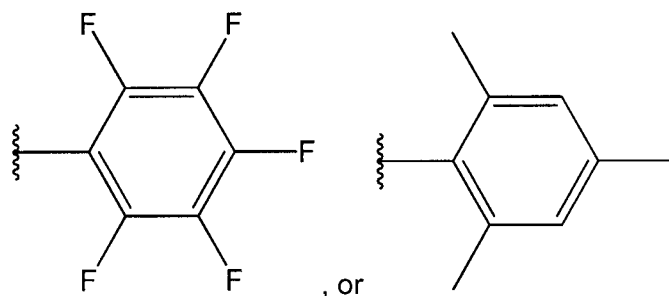
18. The compound according to claim 17, wherein the optional substituents on the aryl group of R_3 are selected from one to five of fluoro, chloro, bromo, OH, (C_1 - C_3)-alkyl, and (C_1 - C_3)-alkoxy.

19. The compound according to claim 18, wherein the optional substituents on the aryl group of R_3 are selected from one to five of fluoro, chloro, bromo, and (C_1 - C_3)-alkyl.

20. The compound according to claim 19, wherein R_3 is



21. The compound according to claim 20, wherein R₃ is



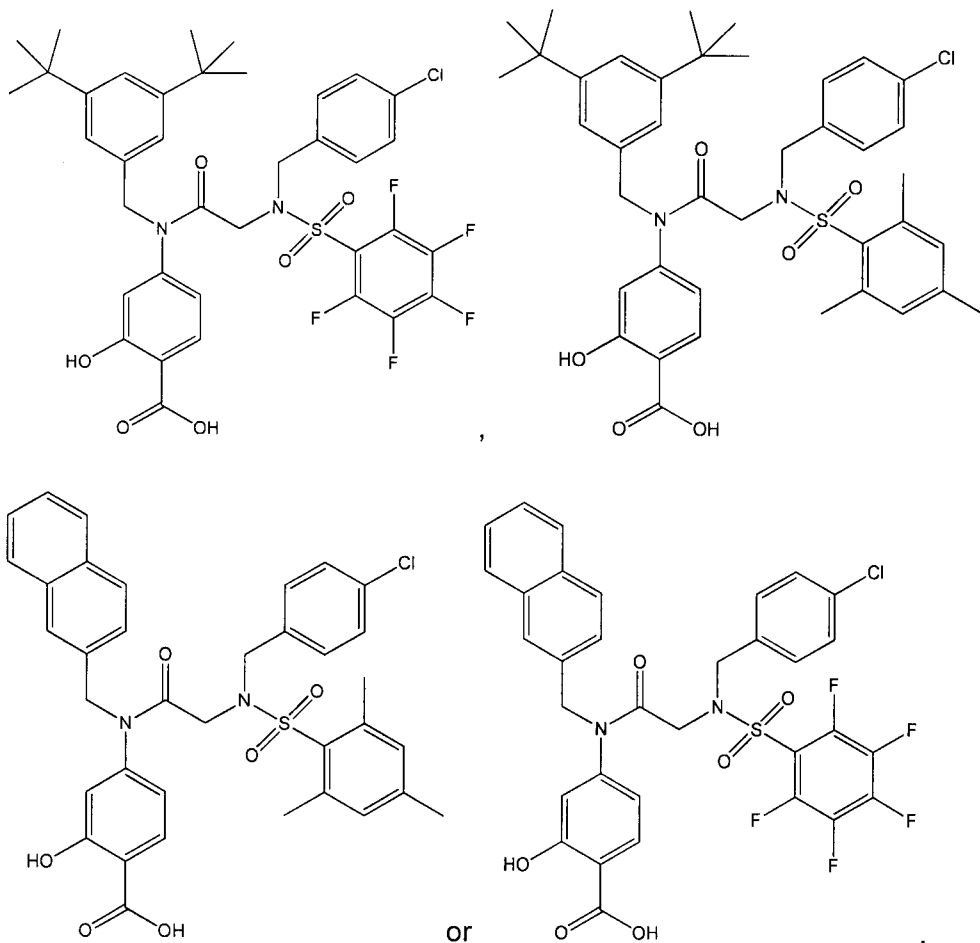
22. The compound according to any one of claims 1 to 21, wherein R is H, OH, fluoro, chloro, bromo, or (C₁-C₄)-alkyl.

23. The compound according to claim 22, wherein R is H, F or OH.

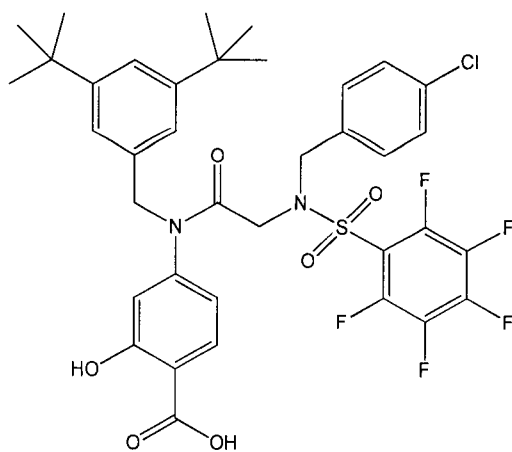
24. The compound according to any one of claims 1 to 23, wherein X is COOR", wherein R" is H or (C₁-C₄)-alkyl.

25. The compound according claim 24, wherein X is COOH.

26. The compound according to any one of claims 1 to 25, wherein the compound has the following structure



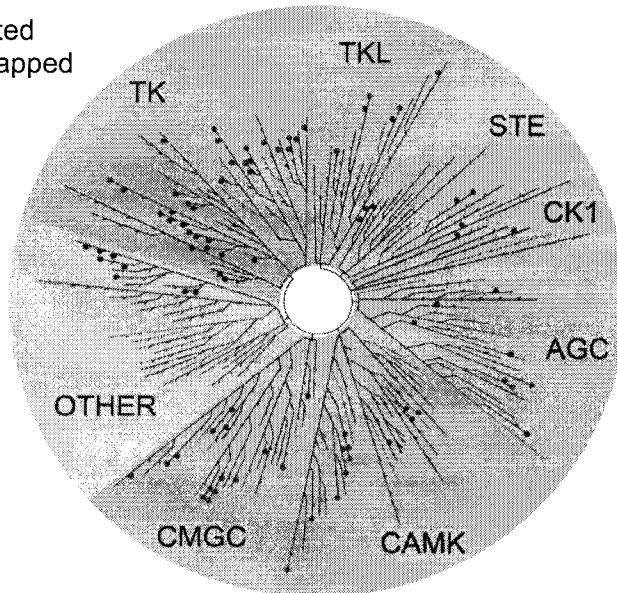
27. The compound according to claim 26, wherein the compound has the following structure



28. A use of a compound according to any one of claims 1 to 27, for inhibiting the signal transducer and activator of transcription 5 (STAT5) protein.
29. The use according to claim 28, for the treatment or prevention of hematopoietic malignancies, skin conditions, non-melanoma skin cancer, prostate cancer or inflammation.
30. The use according to claim 29, wherein the hematopoietic malignancies is leukemia.
31. The use according to claim 30, wherein the leukemia is acute leukemia, chronic leukemia, lymphocytic leukemia or myelogenous leukemia.
32. The use according to claim 29, wherein the skin condition is psoriasis or dermatitis.
33. A method for the treatment or prevention of a disease or condition mediated by signal transducer and activator of transcription 5 (STAT5) protein, comprising administering a pharmaceutically effective amount of a compound of any one of claims 1 to 27 to a subject in need thereof.
34. A method for the treatment or prevention of hematopoietic malignancies, skin conditions, non-melanoma skin cancer, prostate cancer or inflammation, the method comprising administering a pharmaceutically effective amount of a compound of any one of claims 1 to 27 to a subject in need thereof.
35. The method of claim 34, wherein the hematopoietic malignancies is leukemia.
36. The method of claim 35, wherein the leukemia is acute leukemia, chronic leukemia, lymphocytic leukemia or myelogenous leukemia.
37. The method of claim 34, wherein the skin condition is psoriasis or dermatitis.

Figure 1

13a (5000nM)
 120 Assays Tested
 0 Interactions Mapped
 S-Score(35) = 0



Percent Inhibition

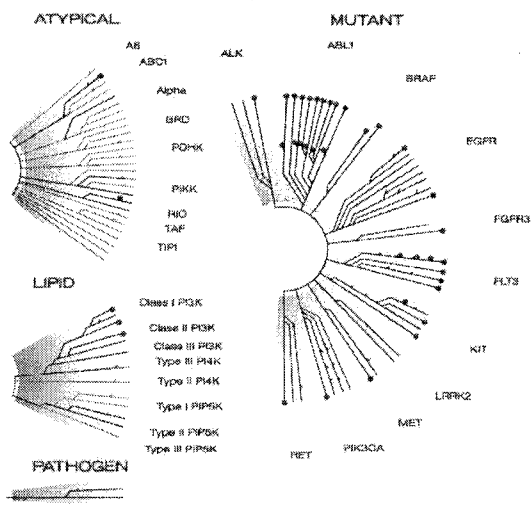
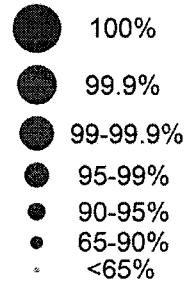
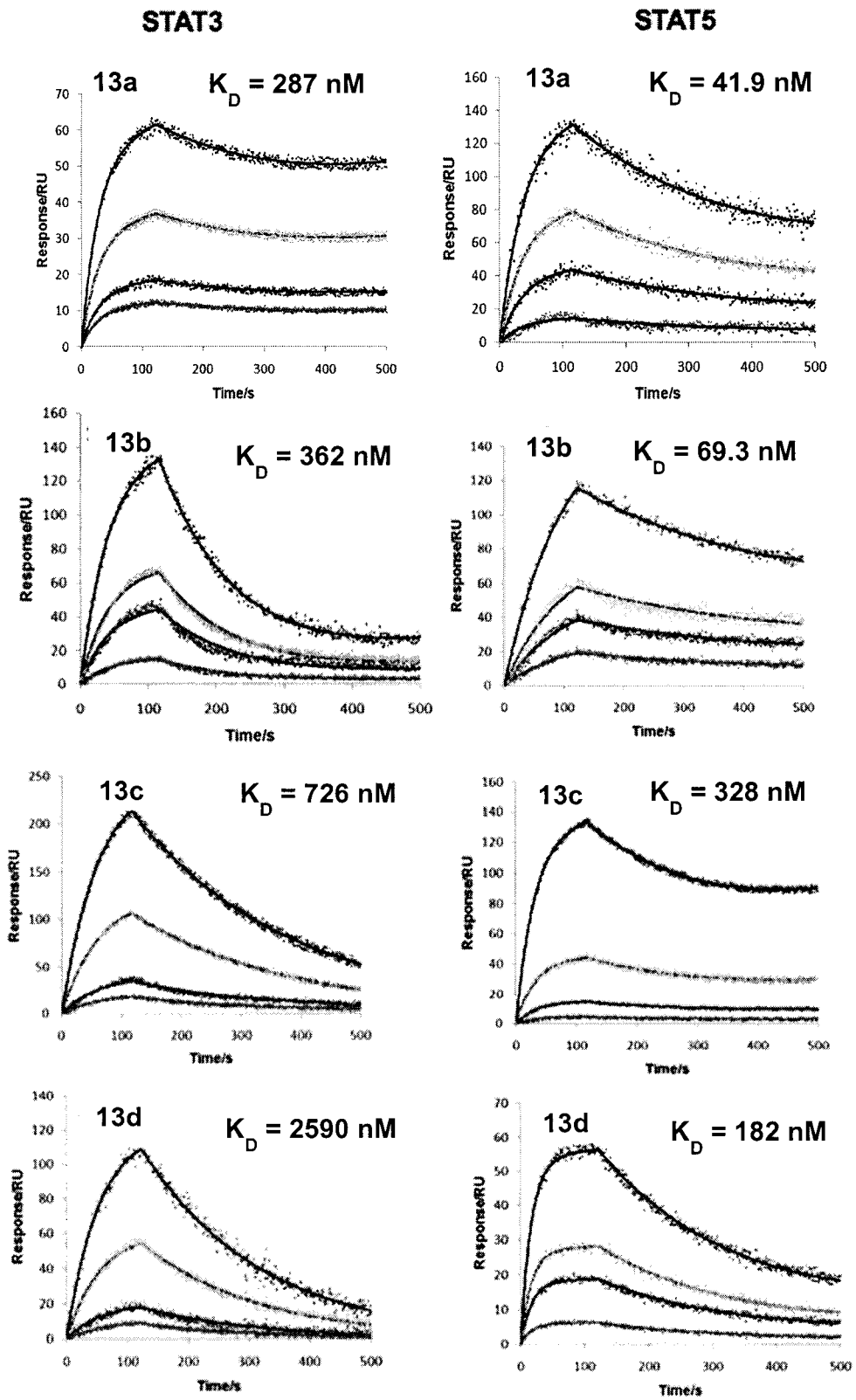
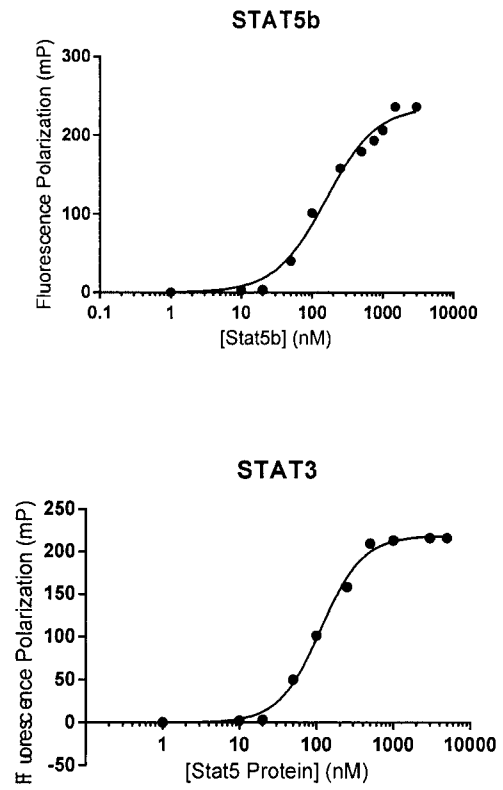


Figure 2



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Figure 3



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Figure 4

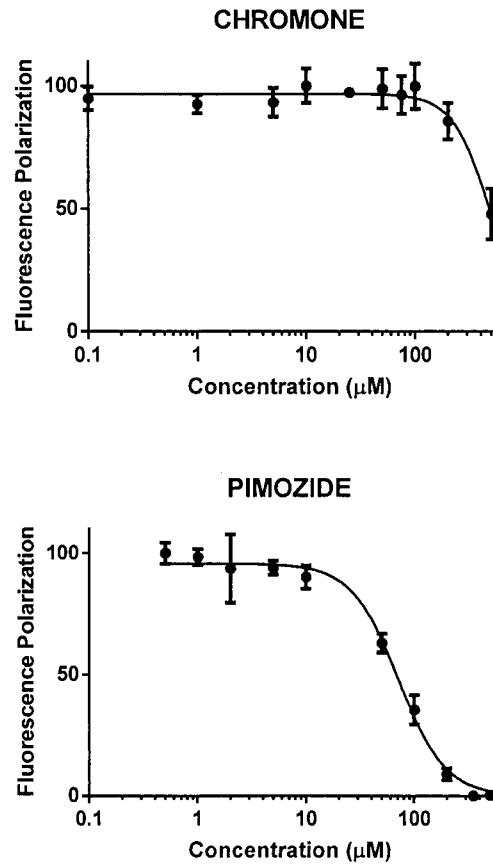
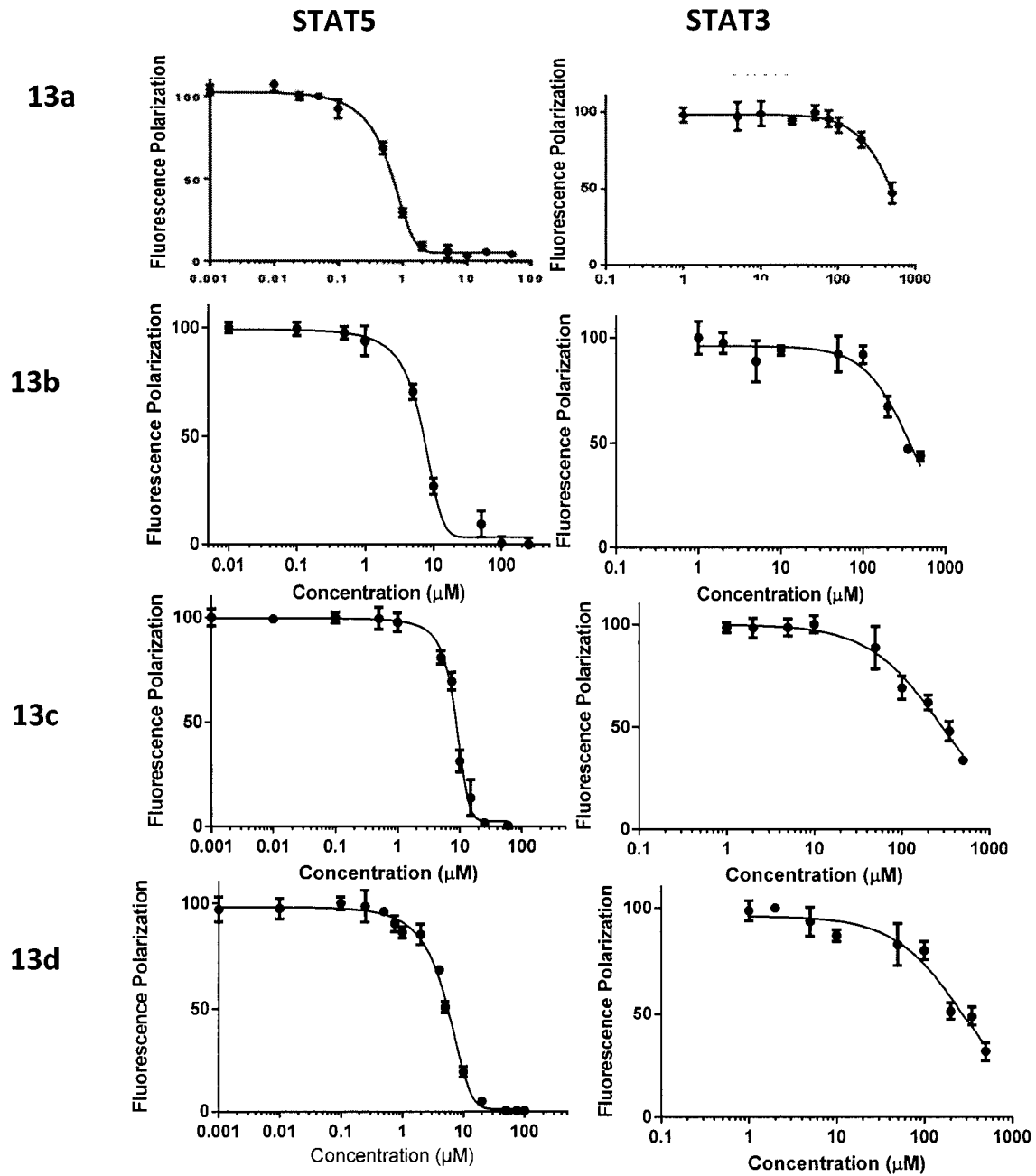


Figure 5



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Figure 6

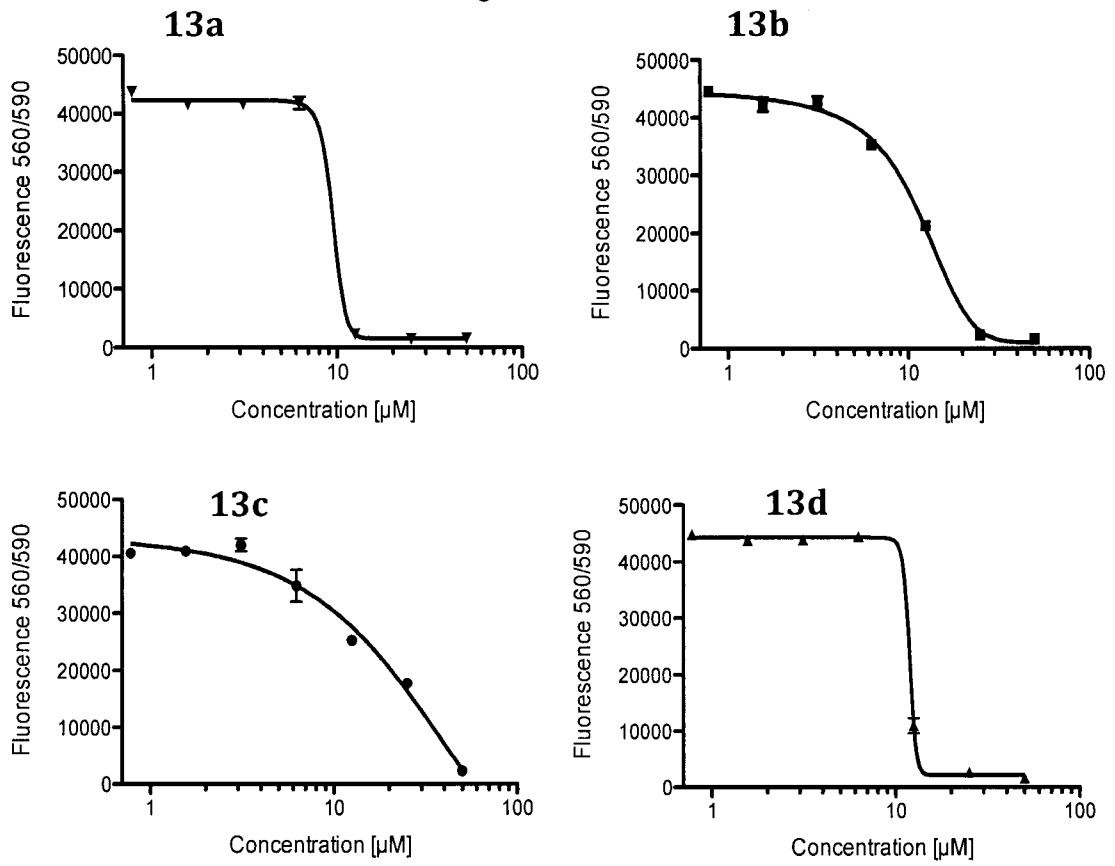
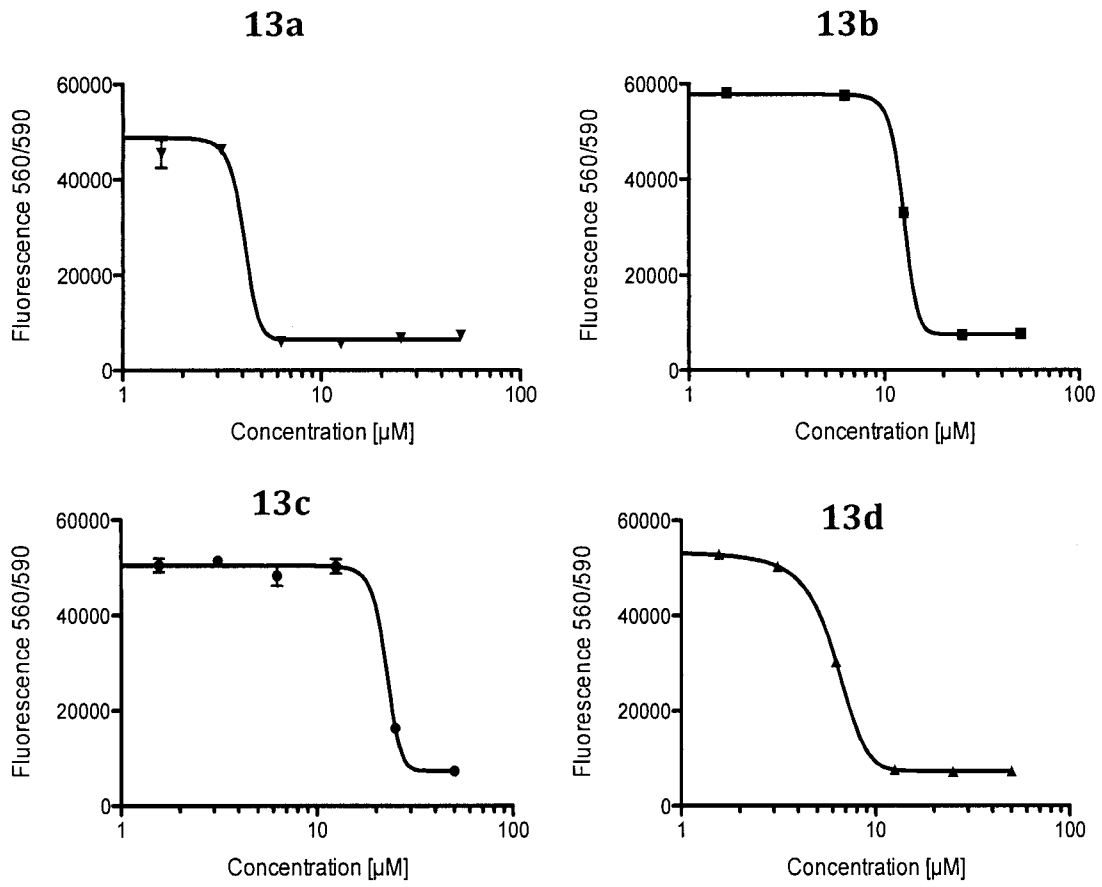
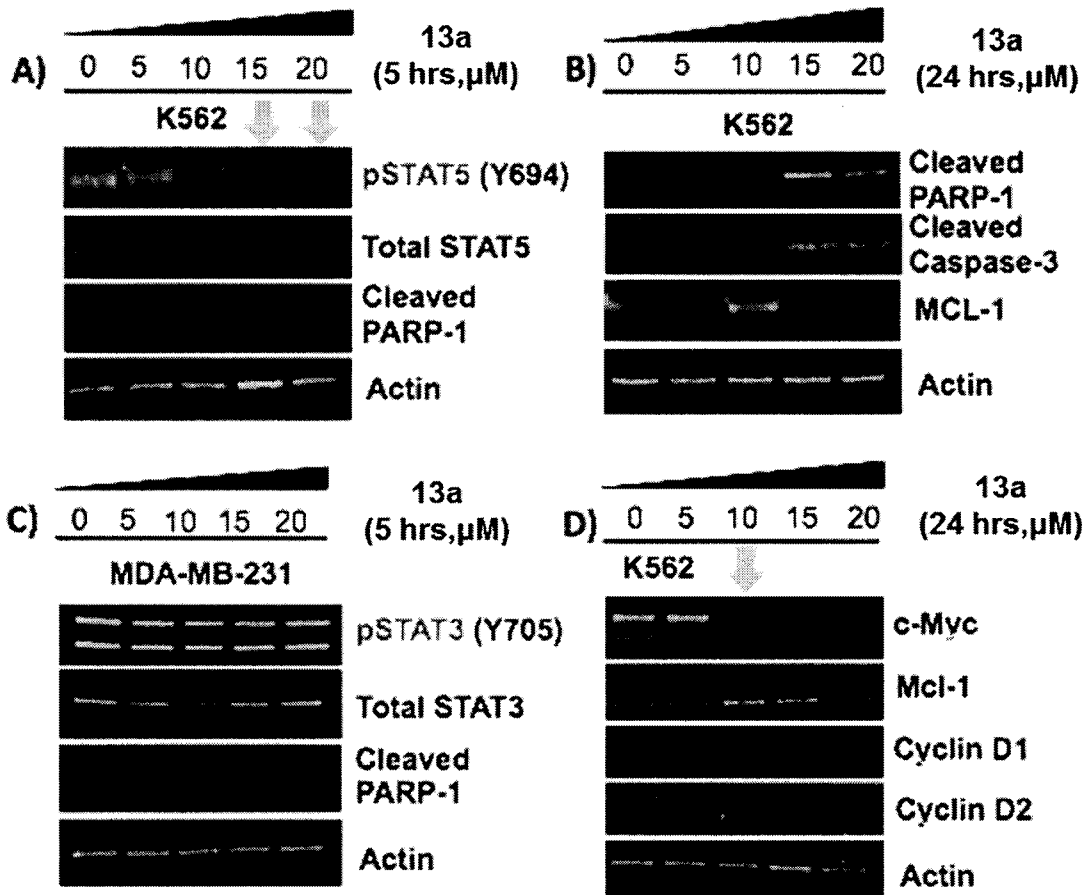


Figure 7



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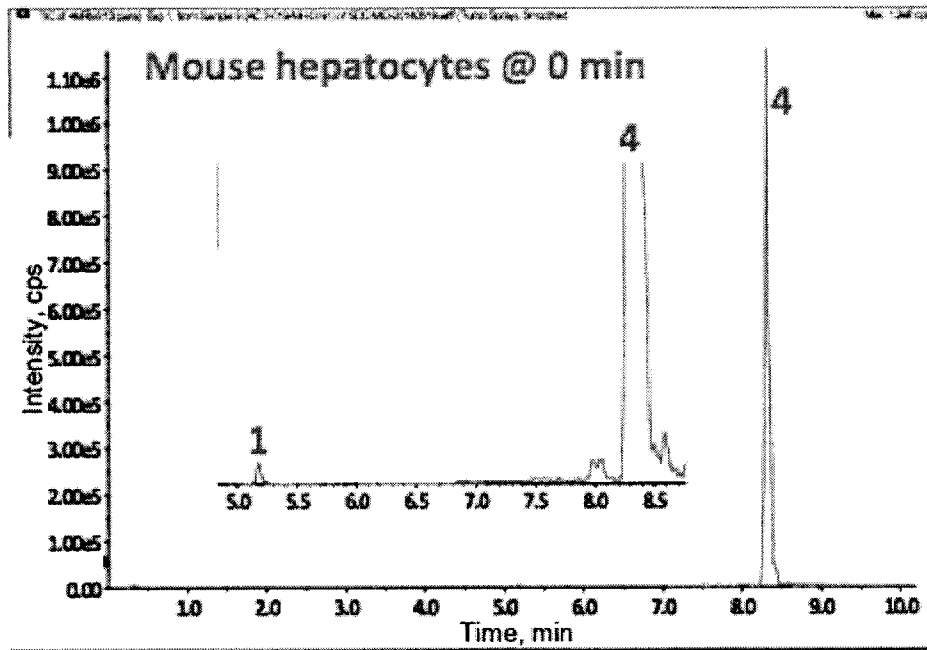
Figure 8



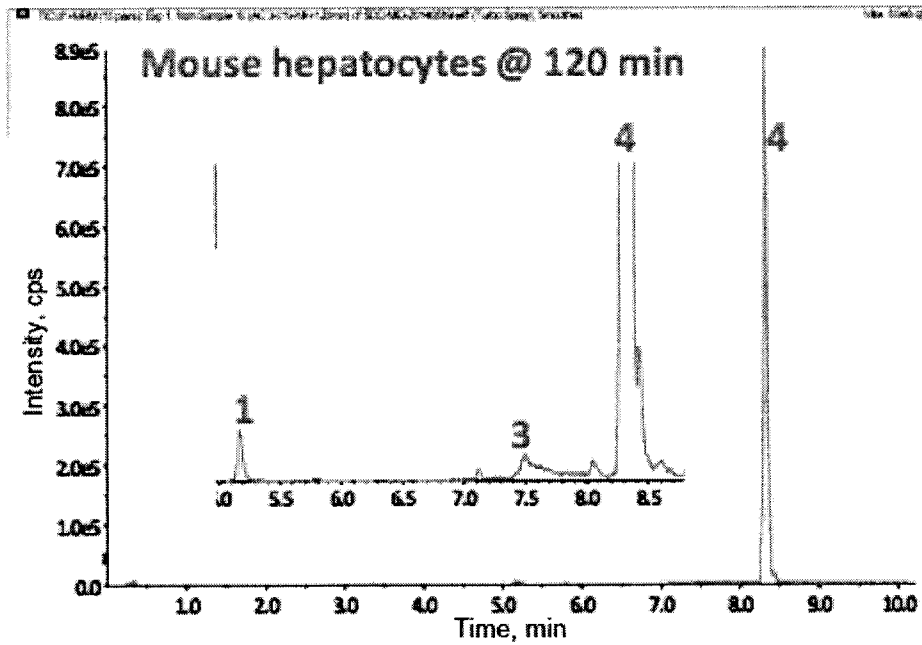
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Figure 9

A)



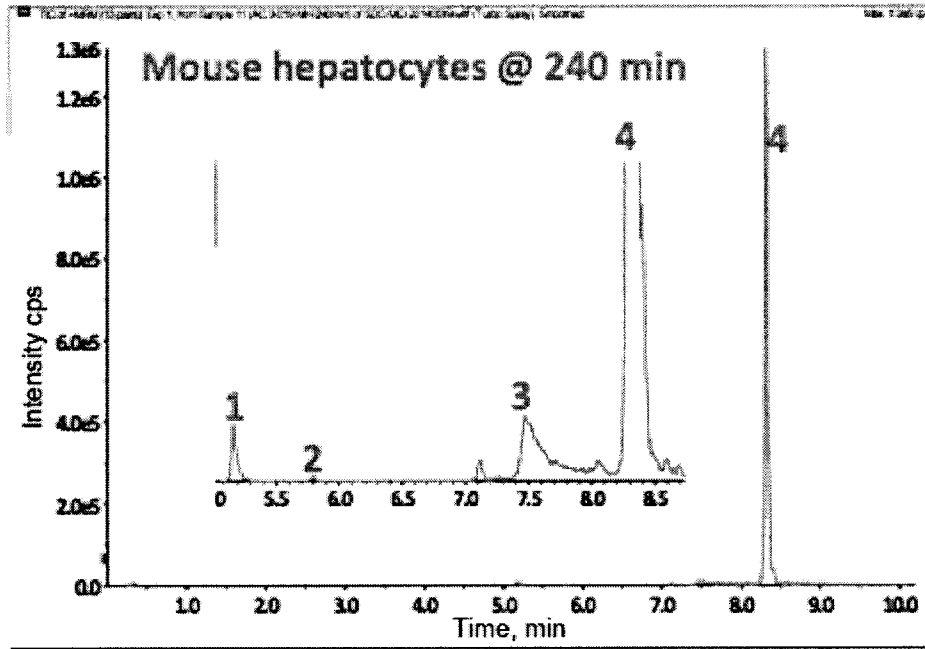
B)



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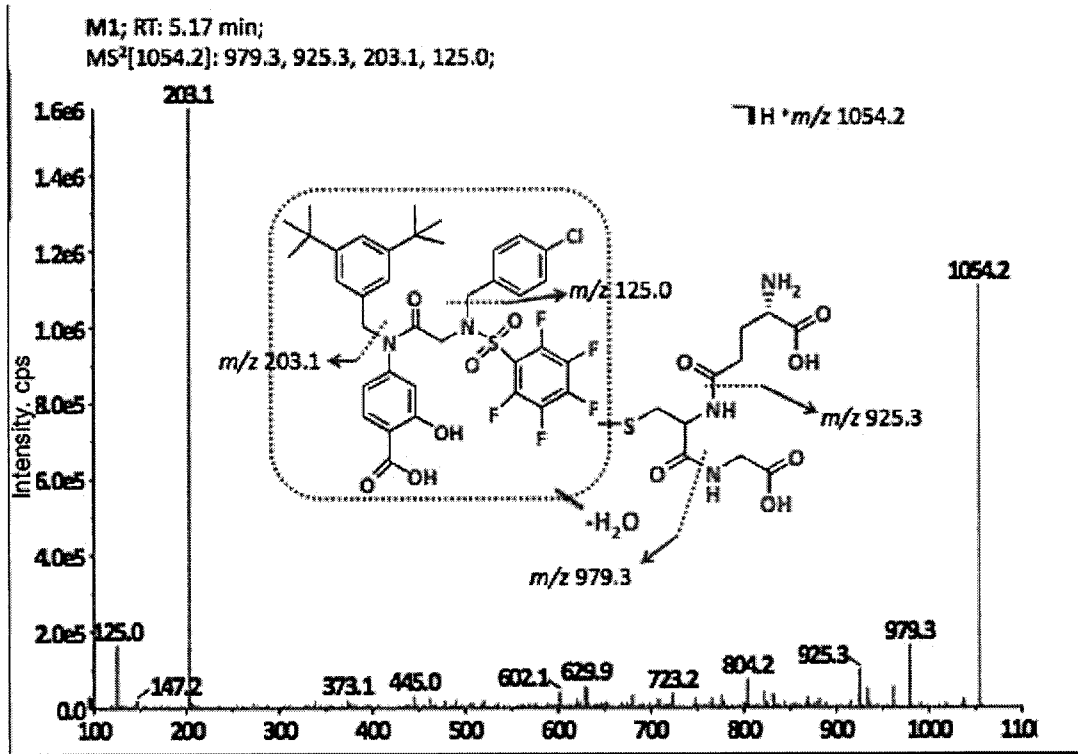
Figure 9 (Cont'd)

C)



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Figure 10



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Figure 11

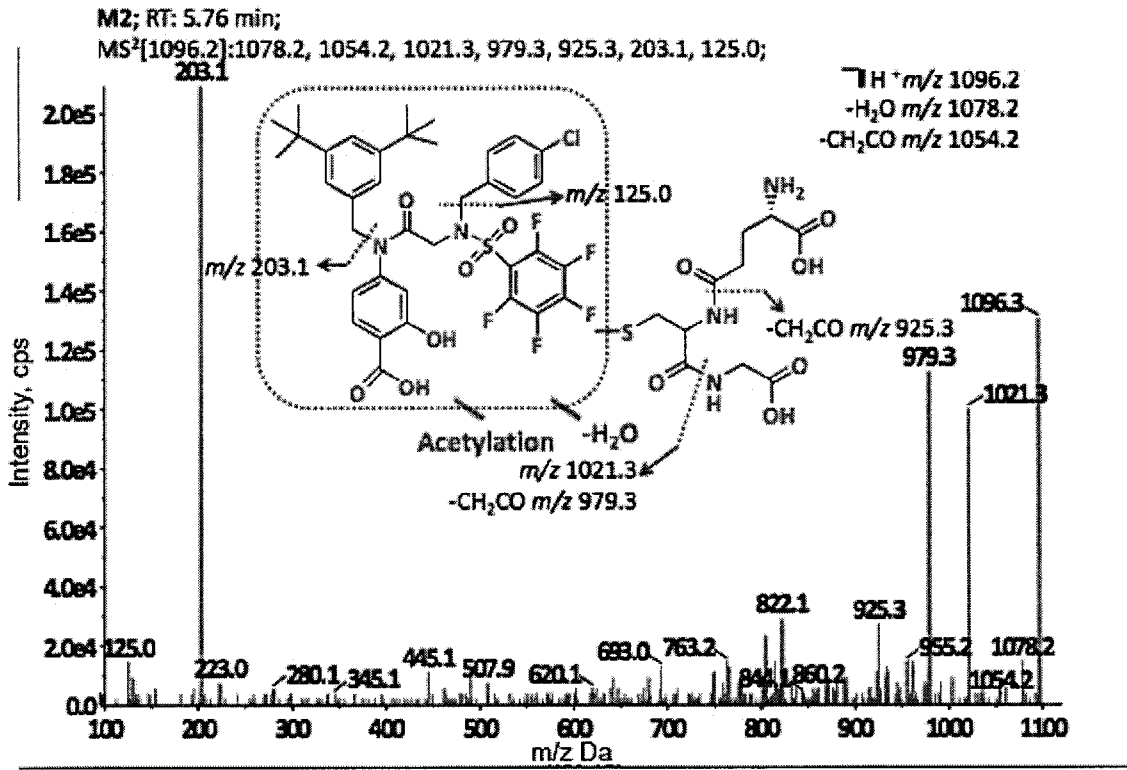
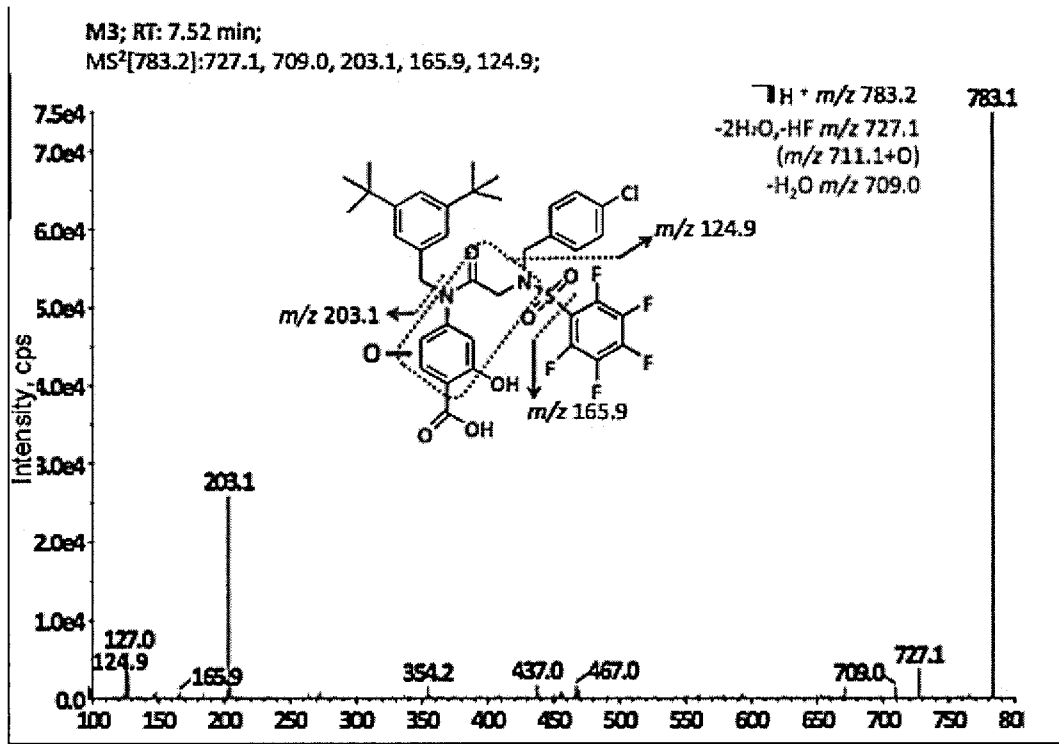
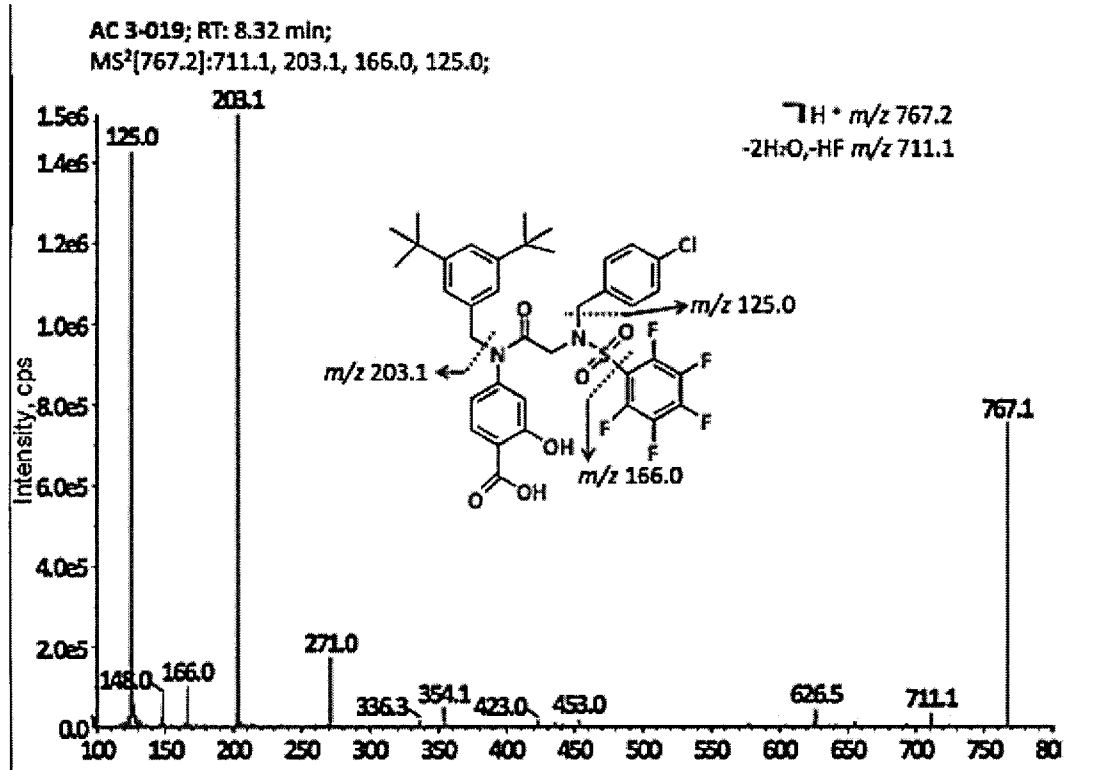


Figure 12



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Figure 13



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Figure 14

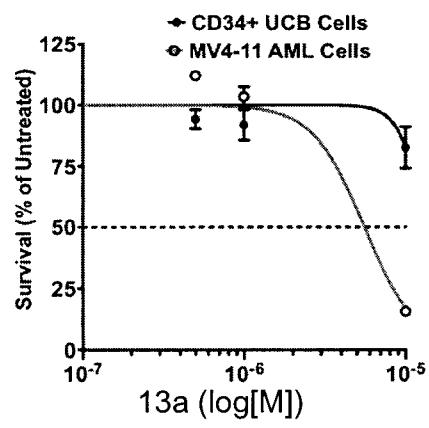
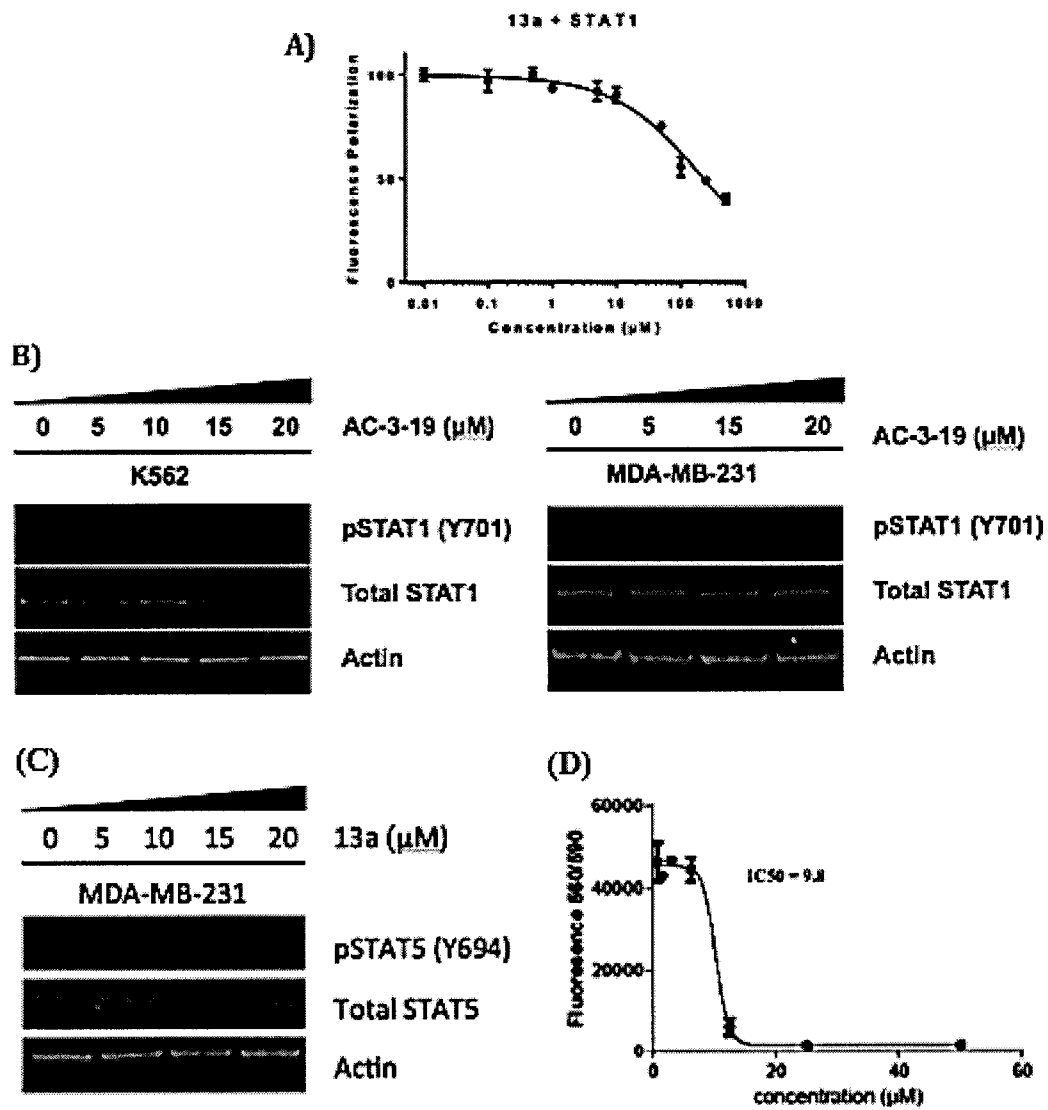


Figure 15



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Figure 16

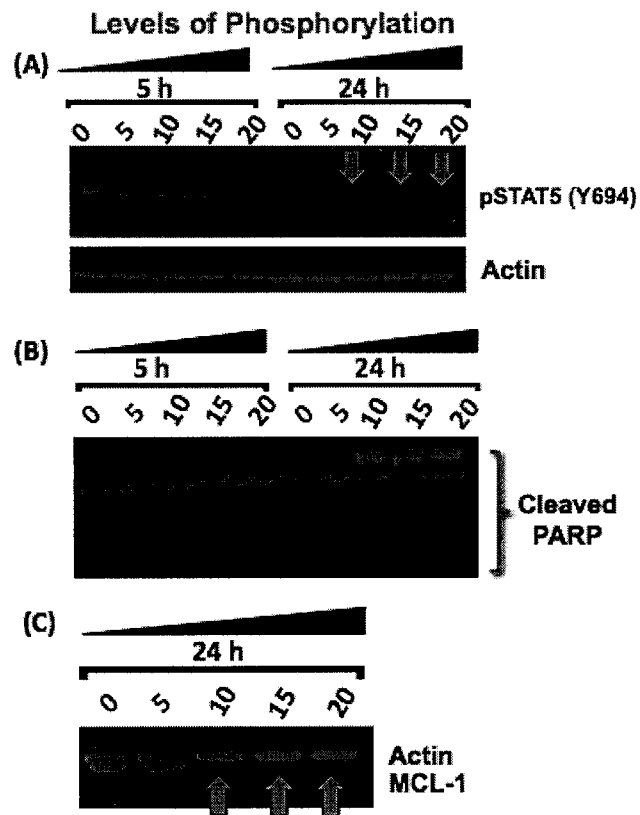
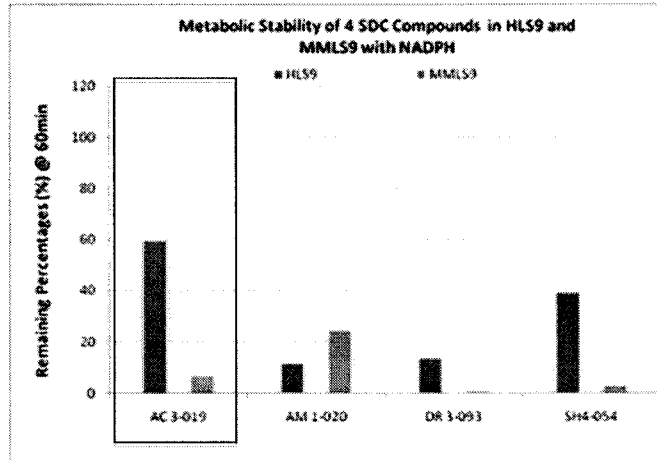


Figure 17



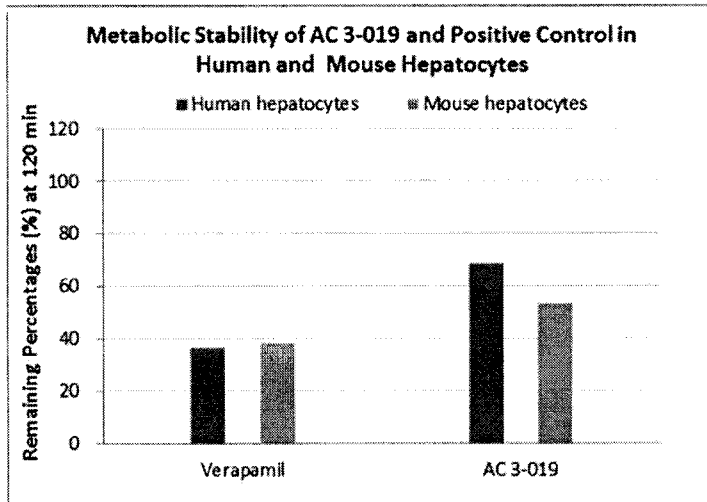
Compound	Remaining Percentages @ 60 minutes (%)	
	HLS9	MMLS9
Verapamil	16.92	15.86
AC 3-019	59.82	6.96
AM 1-020	11.76	24.69
DR 3-093	13.79	0.82
SH4-054	39.18	2.88

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Figure 18

A)

Compound ID	Remaining Percentage @ 120 min (%)	
	Human	Mouse
Verapamil	36.58	38.35
AC 3-019	68.56	53.37

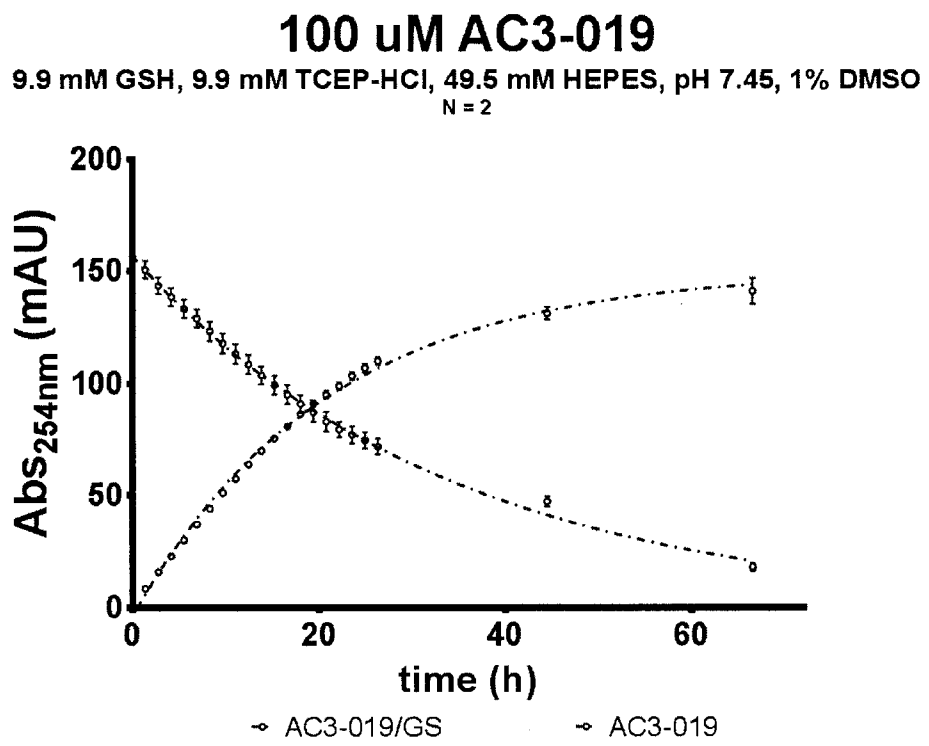


B)

Compound ID	Remaining Percentage @ 120 min (%)	
	Human	Mouse
Verapamil	92.52	93.19
AC 3-019	83.95	85.58

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Figure 19



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2015/000348

A. CLASSIFICATION OF SUBJECT MATTER
 IPC: **C07C 311/19** (2006.01), **A61K 31/196** (2006.01), **A61P 17/00** (2006.01), **A61P 35/00** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC: **C07C 311/19** (2006.01), **A61K 31/196** (2006.01), **A61P 17/00** (2006.01), **A61P 35/00** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
 Canadian Patent Database, STN (structure), Questel-Orbit

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/070859 A1 (SEBTI, S. M. <i>et al.</i>) 8 May 2014 (08-05-2014) See the compound of formula III, compounds 9a and 9c, the first compound of p. 43, the first compound of page 44 and claims 24 and 36 to 40	1 to 7, 9, 10, 15 to 20, 22 to 25 and 28 to 37
X	CA 2 874 057 A1 (FISHEL, M. L. <i>et al.</i>) 28 November 2013 (28-11-2013) See the compound of formula I as well as claims 1 and 7 to 19	1 to 3, 9 to 25 and 28 to 37
X	Urlam, M. K. <i>et al.</i> , "Development of new N-arylbenzamides as STAT3 dimerization inhibitors", Med. Chem. Commun., 2013, 4, 932-941 See compounds 11a and 11c as well as the abstract	1 to 5, 9, 10, 15 to 20, 22 to 25 and 28 to 37

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
31 July 2015 (31-07-2015)

Date of mailing of the international search report
26 August 2015 (26-08-2015)

Name and mailing address of the ISA/CA
 Canadian Intellectual Property Office
 Place du Portage I, C114 - 1st Floor, Box PCT
 50 Victoria Street
 Gatineau, Quebec K1A 0C9
 Facsimile No.: 001-819-953-2476

Authorized officer

Alain Paquin (819) 997-2068

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

a. forming part of the international application as filed:

in the form of an Annex C/ST.25 text file.

on paper or in the form of an image file.

b. furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. furnished subsequent to the international filing date for the purposes of international search only:

in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

While sequence listings were provided with the international application as filed, no search was carried out as the sequence listings do not form part of the inventive concept.

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.: 33 to 37
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 33 to 37 are directed to a method for treatment of the human or animal body by surgery or therapy, which the International Searching Authority is not required to search under Rule 39.1(iv) of the PCT. However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in said claims.
2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CA2015/000348

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2014070859A1	08 May 2014 (08-05-2014)	None	
CA2874057A1	28 November 2013 (28-11-2013)	CA2874057A1 EP2854819A2 US2015158894A1 WO2013177534A2 WO2013177534A3	28 November 2013 (28-11-2013) 08 April 2015 (08-04-2015) 11 June 2015 (11-06-2015) 28 November 2013 (28-11-2013) 28 May 2015 (28-05-2015)