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- (73) Patenthaver: **The United States of America, as represented by The Secretary, Department of Health and Human Services, Office of Technology Transfer , National Institutes of Health , 6011 Executive Boulevard, Suite 325 , MSC 7660, Bethesda, MD 20892-7660, USA**
The Trustees of The University of Pennsylvania, Penn center for Innovation , 3160 Chestnut Street, Suite 200, Philadelphia, PA 19104, USA
The UAB Research Foundation, 701 20th Street South , 770 Administration Building, Birmingham, AL 35294-0107, USA
Vanderbilt University, 305 Kirkland Hall, 2201 West End Avenue, Nashville, TN 37240, USA
- (72) Opfinder: **MALONEY, David J., 1721 Canal Clipper Court, Point of Rocks, Maryland 21777, USA**
JADHAV, Ajit, 27358 Bridle Place, Chantilly, Virginia 20152, USA
BANTUKALLU, Ganesha Rai, 1021 Arlington Bouleavrd 1009, Arlington, Virginia 22209, USA
BRIMACOMBE, Kyle Ryan, 4890 Battery Lane Apt. 411, Bethesda, Maryland 20814, USA
MOTT, Bryan T., 4906 Edgewood Road, College Park, Maryland 20740, USA
YANG, Shyh Ming, 4895 Redfield Road, Doylestown, Pennsylvania 18902, USA
URBAN, Daniel Jason, 9800 Medical Center Drive, Building B, Room 1034A, Rockville, Maryland 20850, USA
HU, Xin, 4112 Brushfield Drive, Frederick, Maryland 21704, USA
SIMEONOV, Anton, 7805 Green Twig Road, Bethesda, Maryland 20817, USA
KOUZNETSOVA, Jennifer L., 1309 Cresthaven Drive, Silver Spring, Maryland 20903, USA
WATERSON, Alex Gregory, 2201 West End Avenue, Nashville, Tennessee 37235, USA
SULIKOWSKI, Gary Allen, 2201 West End Avenue, Nashville, Tennessee 37235, USA
KIM, Kwangho, 2201 West End Avenue, Nashville, Tennessee 37235, USA
CHRISTOV, Plamen, 2201 West End Avenue, Nashville, Tennessee 37235, USA
JANA, Somnath, 2201 West End Avenue, Nashville, Tennessee 37235, USA
DARLEY-USMAR, Victor M., 2514 River Trace Circle, Birmingham, AL 35243, USA
NECKERS, Leonard M., 5121 Wissioming Road, Bethesda, MD 20816, USA
MOORE, William J., 10927 Sassan Lane, Hagerstown, MD 21742, USA

Fortsættes ...

DANG, Chi V., 1475 Flat Road, Penn Valley, PA 19072, USA

- (74) Fuldmægtig i Danmark: **Novagraaf Brevets, Bâtiment O2, 2 rue Sarah Bernhardt CS90017, F-92665 Asnières-sur-Seine cedex, Frankrig**
- (54) Benævnelse: **SMÅMOLEKYLEDE HÆMMERE AF LAKTASEDEHYDROGENASE OG FREMGANGSMÅDER TIL BRUG DERAFT**
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None

Description

BACKGROUND

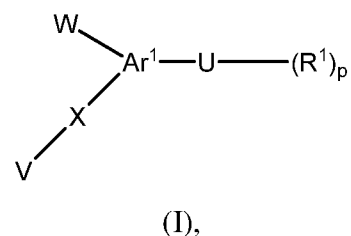
[0001] Agents that target enzymes involved in cancer cell metabolism offer an attractive therapeutic route in view of the potential to preferentially target cancer tissue over normal tissue. While normal tissue typically uses glycolysis only when the oxygen supply is low, cancer tissue relies heavily on aerobic glycolysis regardless of the oxygen supply level. This property is known as the Warburg effect (Vander Heiden et al., Science, 2009, 324(5930): 1029-1033). Lactate dehydrogenase (LDH) is involved in the final step of glycolysis, in which pyruvate is converted to lactate. The decrease in the rate of pyruvate entering the TCA (tricarboxylic acid) cycle and the concurrent increase in lactate production is vital for the growth and survival of tumors. There are two different subunits of LDH, LDHA and LDHB, but both subunits have the same active site and catalyze the conversion of pyruvate to lactate. In cancer patients, serum total lactate dehydrogenase (LDH5, a tetramer of LDHA sub-units; the major LDH isoenzyme involved in glycolysis) levels are often increased, and the gene for LDHA, is up-regulated. Tumor cells can then metabolize lactate as an energy source. Inhibition of LDH results in the stimulation of mitochondrial respiration as a compensatory mechanism. LDH inhibition is expected to reduce the ability of the cell to effectively metabolize glucose and reduce tumor cell proliferation and tumor growth. Thus, compounds that inhibit LDH activity have potential for the development of anti-cancer therapeutics.

[0002] LDHA inhibitors have been known previously. For example, gossypol is a nonselective inhibitor of LDH that blocks the binding of NADH, with a K_i for LDHA and lactate dehydrogenase B (LDHB) of 1.9 and 1.4 μM , respectively (Doherty et al., J. Clin. Invest., 2013, 123(9): 3685-3692). Billiard et al. (Cancer and Metabolism, 2013, 1(19): 1-17) reports that certain derivatives of 3-((3-carbamoyl-7-(3,5-dimethylisoxazol-4-yl)-6-methoxyquinolin-4-yl) amino) benzoic acid are potent inhibitors of LDH and were 10- to 80-fold more selective for LDHA inhibition than LDHB inhibition. However, the *in vivo* bioavailability of the inhibitors was found to be poor. Note that WO2013092753A1 discloses indole derivative inhibitors of lactate dehydrogenase (LDH).

[0003] In view of the foregoing, there remains a need to provide novel LDH inhibitors with improved potency, selectivity, and/or bioavailability for the treatment of cancer.

SUMMARY

[0004] The present disclosure relates to compounds of formula (I)



in which Ar^1 , R^1 , U, V, W, X, and p are as described herein. It has been discovered that a compound defined by formula (I) is effective in inhibiting lactate dehydrogenase A (LDHA) and/ or lactate dehydrogenase B (LDHB) activity, thereby making the compound effective in treating cancer. It has also been discovered that inhibitors of LDHA and/ or LDHB are useful for treating fibrosis, including idiopathic pulmonary fibrosis. It is envisioned that a compound of formula (I) is desirable for treating cancer because the compound tends to be selective for LDHA and/ or LDHB relative to other dehydrogenases (e.g., GAPDH and PHGDH) and/or have a desired solubility, permeability, and/or pharmacokinetics profile (e.g., ADME) for an anti-cancer agent.

[0005] Thus, the disclosure further describes a method of treating cancer in a patient comprising administering to the patient an effective amount of the compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

[0006] The disclosure also describes a method of treating fibrosis, including idiopathic pulmonary fibrosis, in a patient comprising administering to the patient an effective amount of the compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

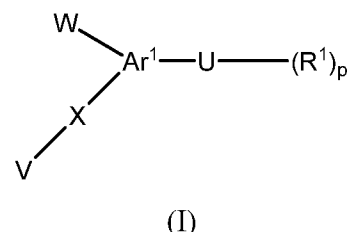
[0007] Also described is a method of treating a patient with cancer cells resistant to an anti-cancer agent, comprising administering to the patient an effective amount of the compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof, and the anti-cancer agent, whereby the compound, prodrug, or pharmaceutically acceptable salt thereof re-sensitizes the cancer cells to the anti-cancer agent.

[0008] Also described is a method of inhibiting lactate dehydrogenase A (LDHA) and/ or lactate dehydrogenase B activity in a cell comprising administering a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt

thereof to a cell. However, the claimed invention is set out in the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[0009] The present disclosure relates to compounds of formula (I)



wherein

Ar¹ is an optionally substituted moiety comprising at least one 5- or 6-membered monocyclic heteroaryl that contains one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur;

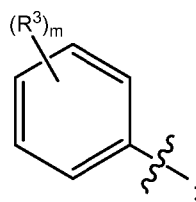
U is aryl, -C(O)aryl, Het, or -C(O)Het, each of which is optionally substituted, wherein Het is a monocyclic or bicyclic moiety comprising a heterocycloalkyl that contains at least two double bonds and one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur;

R¹ is independently chosen from halo, -CO₂R⁴, -C(O)NR⁵R⁶, -(C₁-C₈hydrocarbyl), -C(O)NHOH, -(C₀-C₄hydrocarbyl)(mono- or bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)O-(C₀-C₄hydrocarbyl)(mono- or bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -P(O)(OH)₂, -SO₂(OH), -B(OR¹³)(OR¹⁴), -C(O)NHS(O)₂Me and -SO₂NR⁵R⁶, each of which R¹ except halo is substituted or unsubstituted;

R² is independently chosen from hydroxyl, halo, -CN, -NO₂, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -P(O)(OH)₂, -B(OR¹³)(OR¹⁴), -SO₂(OH), -C(O)NHS(O)₂Me and -SO₂NR⁵R⁶, each of which R¹ except halo is substituted or unsubstituted;

V is aryl, heteroaryl, or heterocycloalkyl, each of which is substituted with -(R²)_n, wherein the heteroaryl or heterocycloalkyl is a 5- or 6-membered monocyclic moiety that contains one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur;

W is -(R³)_m or



R² is independently chosen from hydroxyl, halo, -CN, -NO₂, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, each of which C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic

heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted; R^3 is independently chosen from hydroxyl, halo, -CN, -NO₂, -SF₅, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, each of which C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted; or

when W is phenyl, then two R³ moieties and the phenyl group to which they are attached form a naphthyl group that is optionally substituted with at least one additional R³ moiety;

each R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂aryl, heteroaryl, or heterocycloalkyl;

each R¹³ and R¹⁴ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂aryl, wherein R¹³ and R¹⁴ are optionally connected to each other to form a ring;

X is a bond, -CR⁸R⁹-, -NR⁵-, -CR⁸NR⁵-, -NR⁵CR⁸-, -NR⁵C(O)-, -O-, -SO-, -SO₂-, or -S-;

m, n, and q are the same or different and each is 0 or an integer from 1-5; and

p is 0, 1, or 2;

provided

when Ar¹ is quinoliny, then U is not pyrimidinyl;

when Ar¹-U is 2-(1H-indol-1-yl)thiazolyl, then X at the 3-position on the indolyl group is not a bond or -CH₂-, or W at the 3-position on the indolyl group is not phenyl, or R³ at the 3-position on the indolyl group is not benzyl; and

when Ar¹-U is 2-(1H-pyrazol-1-yl)thiazolyl, then W at the 3-position on the pyrazolyl group is not 4-trifluoromethylphenyl or 4-nitrophenyl, or X at the 4-position on the pyrazolyl group is not a bond,

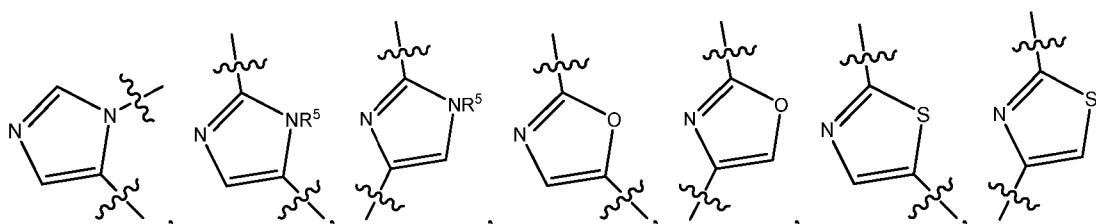
or a prodrug or pharmaceutically acceptable salt thereof.

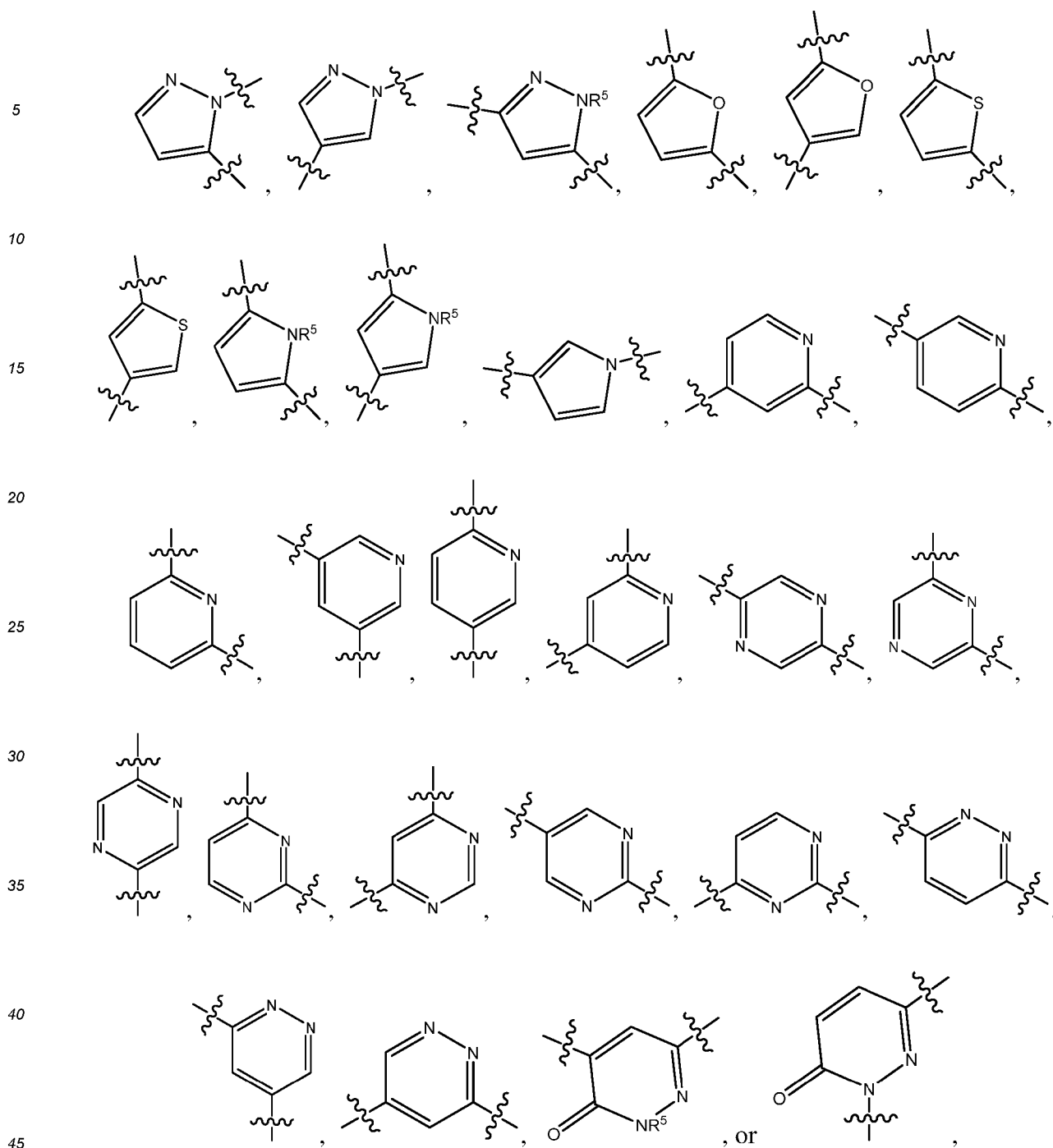
[0010] In an aspect of the disclosure, Ar¹ is indolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-b]pyridinyl, quinoliny, indazolyl, imidazolyl, oxazolyl, thiazolyl, furanyl, thiofuranyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, or pyrimidinyl, each of which is optionally substituted. When Ar¹ is substituted, there can be 1 to 3 substituents (e.g., 1, 2, or 3 substituents) that are the same or different. Suitable substituents include, e.g., C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylalkyl, hydroxyl, C₁-C₈alkoxy, C₃-C₆cycloalkyloxy, C₁-C₈haloalkoxy, C₁-C₈haloalkyl, halo, -CN, cyanoalkyl, -NO₂, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵(SO₂)R⁴, -NR⁵C(O)R⁴, -NR⁷C(O)NR⁵R⁶, -NR⁵R⁶, -SO₂NR⁵R⁶, -SO₂R⁴, aryl, heteroaryl, and/or heterocycloalkyl.

[0011] In certain compounds, Ar¹ is pyrazolyl, indolyl, or pyrrolo[2,3-b]pyridinyl, each of which is optionally substituted. For example, Ar¹ can be pyrazolyl or indolyl substituted with a substituent, such as, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₃-C₆cycloalkyl, C₃-C₆cycloalkylalkyl, hydroxyl, C₁-C₈alkoxy, C₃-C₆cycloalkyloxy, C₁-C₈haloalkoxy, C₁-C₈haloalkyl, halo, -CN, cyanoalkyl, -NO₂, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵(SO₂)R⁴, -NR⁵C(O)R⁴, -NR⁷C(O)NR⁵R⁶, -NR⁵R⁶, -SO₂NR⁵R⁶, -SO₂R⁴, aryl, alkylalkyl, heteroaryl, heteroarylalkyl, or heterocycloalkyl. The pyrazolyl can be substituted with C₁-C₈alkyl, cyclopropyl, -CH₂-cyclopropyl, -CH=CH₂, -C=C-cyclopropyl, -OH, -CO₂H, C₁-C₈alkoxy, CF₃, Cl, F, I, -CN, -CH₂CN, NH₂, -C(O)NH₂, -NH-pyridinyl, -CH₂-tetrazolyl, phenyl, benzyl, or -SO₂Me.

[0012] In any of the foregoing aspects, U is phenyl, -C(O)phenyl, indolyl, imidazolyl, oxazolyl, thiazolyl, furanyl, thiofuranyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, or 6-oxo-1,6-dihydropyridazin-3-yl, each of which is optionally substituted.

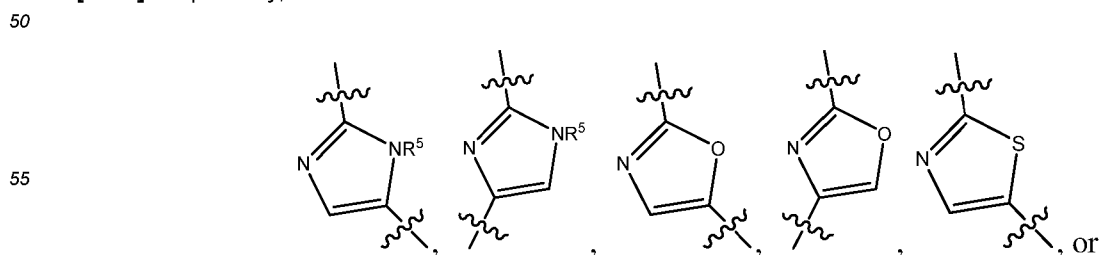
[0013] In other aspects, U is Het or -C(O)Het, and Het is

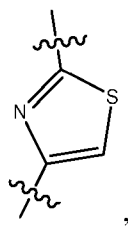




wherein R^5 is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, aryl, heteroaryl, or heterocycloalkyl, each of these Het moieties is optionally substituted, and each point of attachment can be either Ar^1 or R^1 .

[0014] Optionally, U is

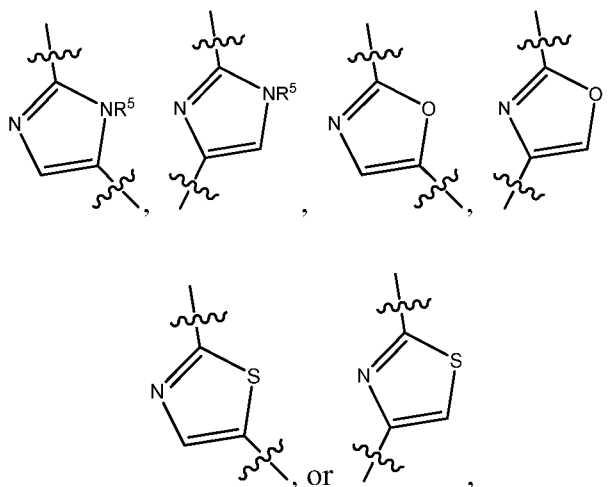




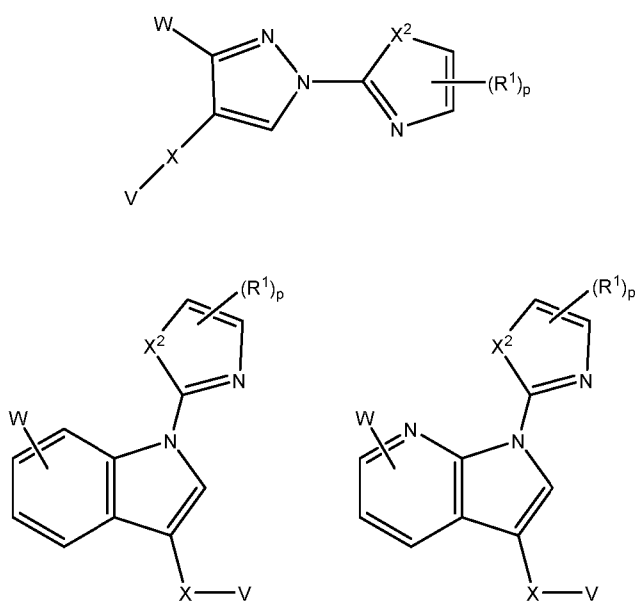
each of which is optionally substituted, and wherein each point of attachment can be either Ar¹ or R¹.

[0015] When U is substituted, there can be 1 or 2 substituents that are the same or different. Suitable substituents include, e.g., C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyl, C₁-C₈ alkoxy, C₃-C₆ cycloalkyloxy, C₁-C₈ haloalkoxy, C₁-C₈ haloalkyl, halo, -CN, cyanoalkyl, -NO₂, CO₂R⁴, C(O)NR⁵R⁶, NR⁵(SO₂)R⁴, NR⁵C(O)R⁴, NR⁷C(O)NR⁵R⁶, -NR⁵R⁶, -SO₂NR⁵R⁶, -SO₂R⁴, aryl, arylalkyl, heteroaryl, and/or heterocycloalkyl.

[0016] Optionally, Ar¹ is pyrazolyl, indolyl, or pyrrolo[2,3-b]pyridinyl, each of which is optionally substituted, and U is



each of which is optionally substituted. In this aspect, the following core structures of formula (I) can be formed:



in which X² is -NR⁵-, -O-, or -S-; p is 0; 1 or 2; and R¹ is halo, -CO₂R⁴, -C(O)NR⁵R⁶, -CH₂OH, -CHCF₃OH, -C(CF₃)₂OH, -C(O)NHOH-C(O)OCR⁵R⁶OC(O)OR⁴, -C(O)O-2,3-dihydro-1*H*-indenyl, -C(O)O-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl,

1,3,4-oxadiazol-2(3H)-one, isoxazol-3(2H)-one, $-P(O)(OH)_2$, $-B(OR^{13})(OR^{14})$, $-SO_2(OH)$, $-SO_2NR^5R^6$, or tetrazolyl.

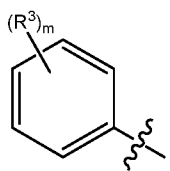
[0017] Optionally, R^1 is $-CO_2H$ or $-CO_2(C_1-C_8 \text{ alkyl})$, wherein the C_1-C_8 alkyl is substituted or unsubstituted, or a prodrug or a pharmaceutically acceptable salt thereof.

[0018] Optionally, V is phenyl, piperazinyl, pyrrolinyl, pyranyl, piperidyl, tetrahydrofuranyl, tetrahydrothiophenyl, morpholinyl, pyridinyl, pyridazinyl, pyrimidyl, or pyrazinyl, each of which is substituted with $-(R^2)_n$. In some aspects, V is phenyl substituted with $-(R^2)_n$.

[0019] Optionally, R^2 is $-SO_2NR^5R^6$; and R^5 and R^6 are the same or different and each is H or C_1-C_8 alkyl (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *sec*-butyl, or *tert*-butyl). In some aspects, R^2 is $-SO_2NH_2$.

[0020] Optionally, n is 1, so that V is monosubstituted.

[0021] Optionally, W is

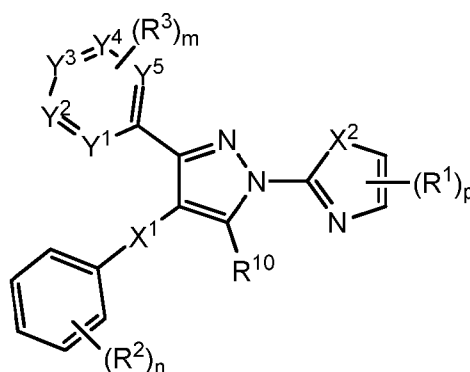


[0022] Optionally, R^3 is independently halo, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, substituted or unsubstituted C_1-C_4 alkyl, or substituted or unsubstituted phenyl.

[0023] Optionally, m is 1 or 2.

[0024] Optionally, X is $-CR^8R^9-$ (e.g., $-CH_2-$), $-O-$, or $-NH-$, in which R^8 and R^9 are the same or different and each is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or aryl.

[0025] However, the claimed invention provides a compound of formula (Ia), or a pharmaceutically acceptable salt thereof:



(Ia)

wherein

Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each independently CH or N;

R^1 is independently chosen from halo, $-C(O)R^4$, $-CH_2OH$, $-C(O)NHCN$, $-C(O)NHSO_2H$, $-C(S)R^4$, $-CO_2R^4$, $-C(O)NR^5R^6$, $-(C_1-C_8 \text{ hydrocarbyl})$, $-C(O)NHOH$, $-C(O)OCR^5R^6OC(O)OR^4$, $-(C_0-C_4 \text{ hydrocarbyl})$ (mono- or bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), $-C(O)O-(C_0-C_4 \text{ hydrocarbyl})$ (mono- or bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), $-P(O)(OH)_2$, $-B(OR^{13})(OR^{14})$, $-SO_2(OH)$, $-C(O)NHS(O)_2Me$ and $-SO_2NR^5R^6$, each of which R^1 except halo is substituted or unsubstituted;

R^2 is independently chosen from hydroxyl, halo, $-CN$, $-NO_2$, C_1-C_8 hydrocarbyl, $-O(C_1-C_8 \text{ hydrocarbyl})$, $-(C_0-C_4 \text{ hydrocarbyl})C_3-C_8$ cycloalkyl, $-O(C_0-C_4 \text{ hydrocarbyl})C_3-C_8$ cycloalkyl, $-(C_0-C_4 \text{ hydrocarbyl})C_3-C_8$ cycloalkenyl, $-O(C_0-C_4 \text{ hydrocarbyl})C_3-C_8$ cycloalkenyl, $-O(C_0-C_4 \text{ hydrocarbyl})C_6-C_{12}$ aryl, $-(C_0-C_4 \text{ hydrocarbyl})C_6-C_{12}$ aryl, $-O(C_0-C_4 \text{ hydrocarbyl})$ (mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), $-(C_0-C_4 \text{ hydrocarbyl})$ (mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^5R^6$, $-NR^5C(O)R^4$, $-(CH_2)_qNR^5(SO_2)R^4$, $-(CH_2)_qNR^5C(O)R^4$, $-(CH_2)_qNR^7C(O)NR^5R^6$, $-(CH_2)_qNR^5R^6$, $-(CH_2)_qSO_2NR^5R^6$, $-(CH_2)_qSO_2R^4$, each of which C_1-C_8 hydrocarbyl, $-O(C_1-C_8 \text{ hydrocarbyl})$,

-(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted;

R³ is independently chosen from hydroxyl, halo, -CN, -NO₂, -SF₅, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, each of which C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted; or two R³ moieties and the phenyl group to which they are attached form a naphthyl group or its heterocyclic analog that is optionally substituted;

each R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, aryl, heteroaryl, or heterocycloalkyl;

R¹⁰ is hydrogen, halo, -CN, -NO₂, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵(SO₂)R⁴, -NR⁵C(O)R⁴, -NR⁷C(O)NR⁵R⁶, -NR⁵R⁶, -SO₂NR⁵R⁶, -SO₂R⁴, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), each of which R¹⁰ except hydrogen, halo, -CN, and -NO₂ is substituted or unsubstituted;

each R¹³ and R¹⁴ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, wherein R¹³ and R¹⁴ are optionally connected to each other to form a ring;

X¹ is a bond, -CR⁸R⁹-, -NR⁵-, -CR⁸NR⁵-, -NR⁵CR⁸-, -NR⁵C(O)-, -O-, or -S-;

X² is -NR⁵-, -O-, -CO-, -SO₂-, or -S-;

m, n, and q are the same or different and each is 0 or an integer from 1-5; and

p is 1 or 2, wherein "substituted" means that any one or more hydrogens on the designated atom or group is replaced with one selected from a halogen, a cyano group, a hydroxyl group, a nitro group, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 8 carbon atoms, a (cycloalkyl)alkyl group having 4 to 8 carbon atoms, an alkenyl having one or more unsaturated linkages and 2 to 8 carbon atoms, an alkynyl group having one or more unsaturated linkages and from 2 to 8 carbon atoms, an alkoxy group having one or more oxygen linkages and 1 to 8 carbon atoms, an aryloxy group, and an alkylthio group having one or more thioether linkages and 1 to 8 carbon atoms.

[0026] In an embodiment of formula (Ia),

R¹ is independently chosen from halo, -CO₂R⁴, -CONH₂, -C(O)NHOH, -P(O)(OH)₂, -B(OR¹³)(OR¹⁴), -SO₂(OH), -SO₂NR⁵R⁶, -(C₁-C₈alkylene)OH, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, heteroaryl, and -C(O)O-heteroaryl, each of which R¹ except hydrogen, halo, -P(O)(OH)₂, -CONH₂, and -SO₂(OH), is substituted or unsubstituted; each R⁴, R⁵, and R⁶ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, heteroaryl, or heterocycloalkyl, each of which R⁴, R⁵, and R⁶ except H is substituted or unsubstituted;

R² is independently chosen from hydroxyl, halo, -CN, -NO₂, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₁-C₈ alkoxy, -O-C₃-C₆cycloalkyl, C₆-C₁₂ aryl, -O-C₆-C₁₂ aryloxy, -(CH₂)_qaryl, -(CH₂)_qheteroaryl, -(CH₂)_qheterocycloalkyl, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, and -(CH₂)_qSO₂R⁴, each of which R² except hydrogen, hydroxyl, halo, -CN, -NO₂, SF₅, is substituted or unsubstituted;

R³ is independently chosen from hydroxyl, halo, -CN, -NO₂, SF₅, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ alkenynyl, C₁-C₈alkoxy, -(CH₂)_qC₃-C₈cycloalkyl, -O(CH₂)_qC₃-C₈cycloalkyl, -(CH₂)_qC₃-C₈cycloalkenyl, -(C₂-C₄alkynyl)(C₃-C₆cycloalkenyl), -(CH₂)_qC₆-C₁₂aryl, -O(CH₂)_qC₆-C₁₂aryl, -(CH₂)_qheteroaryl, -O(CH₂)_qheteroaryl, -(C₂-C₄alkenyl)heteroaryl, -(C₂-C₄alkynyl)heteroaryl, -(CH₂)_qheterocycloalkenyl, -O(CH₂)_q(heterocycloalkenyl), -(C₂-C₄alkenyl)heterocycloalkenyl, -(C₂-C₄alkynyl)heterocycloalkenyl, -(CH₂)_qheterocycloalkyl, -O(CH₂)_qheterocycloalkyl, -(C₂-C₄alkenyl)heterocycloalkyl, and -(C₂-C₄alkynyl)heterocycloalkyl, each of which R³ except hydrogen, hy-

droxyl, halo, -CN, -NO₂, and SF₅ is substituted or unsubstituted;

R¹⁰ is hydrogen, -CN, halo, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₆alkoxy, - (C₀-C₂alkyl)NR⁵R⁶, - (C₀-C₂alkyl)C₃-C₆cycloalkyl, -C≡C(C₃-C₆cycloalkyl), - (C₀-C₂alkyl)heterocycloalkyl, or - (C₀-C₂alkyl)heteroaryl, each of which R¹⁰ except hydrogen and halo is substituted or unsubstituted; and

each R¹³ and R¹⁴ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, wherein R¹³ and R¹⁴ are optionally connected to each other to form a ring.

[0027] In another embodiment of formula (Ia),

R¹ is independently chosen from halo, hydroxyl, -CONH₂, C₁-C₄alkyl, C₁-C₄alkoxy, -CO₂R⁴, -CH₂OH, -CHCF₃OH, -C(CF₃)₂OH, -C(O)NHOH, -P(O)(OH)₂, -B(OR¹³)(OR¹⁴), -SO₂(OH), -SO₂NR⁵R⁶, -C(O)O-2,3-dihydro-1*H*-indenyl, -C(O)O-(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, 1,3,4-oxadiazol-2(3*H*)-one, isoxazol-3(2*H*)-one, and tetrazolyl, each of which R¹ except hydrogen, halo is substituted or unsubstituted;

R² is independently chosen from halo and -(CH₂)_qSO₂NR⁵R⁶, where one of R² is -(CH₂)_qSO₂NR⁵R⁶;

R³ is independently chosen from hydroxyl, halo, -CN, -NO₂, SF₅, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ alkenynyl, C₁-C₈alkoxy,

-(CH₂)_qC₃-C₈cycloalkyl, -O(CH₂)_qC₃-C₆cycloalkyl, -(CH₂)_qC₃-C₆cycloalkenyl, -(C₂-C₄alkynyl)(C₃-C₆cycloalkenyl),

-(CH₂)_qC₆-C₁₂phenyl, -O(CH₂)_qC₆-C₁₂phenyl,

-(CH₂)_qheteroaryl, -O(CH₂)_qheteroaryl, -(C₂-C₄alkenyl)heteroaryl, and -(C₂-C₄alkynyl)heteroaryl, where the heteroaryl group is a oxazolyl, thienyl, thiazolyl, furanyl, pyrazolyl, and imidazolyl group;

-(CH₂)_qheterocycloalkenyl, -O(CH₂)_q(heterocycloalkenyl), -(C₂-C₄alkenyl)heterocycloalkenyl, -(C₂-C₄alkynyl)heterocycloalkenyl, where the heterocycloalkenyl is dihydropyranyl, dihydrofuranyl, dihydrothiopyranyl, and dihydropyridinyl,

-(CH₂)_qheterocycloalkyl, -O(CH₂)_qheterocycloalkyl, -(C₂-C₄alkenyl)heterocycloalkyl, -(C₂-C₄alkynyl)heterocycloalkyl, where the heterocycloalkyl is tetrahydropyranyl, tetrahydrofuranyl, piperazinyl, piperidinyl, and pyrrolidinyl, each of which

R³ except hydrogen, hydroxyl, halo, -CN, -NO₂, and SF₅ is substituted or unsubstituted;

each R⁴, R⁵, and R⁶ is the same or different and each is H or C₁-C₈ alkyl, wherein C₁-C₈ alkyl is substituted or unsubstituted;

R¹⁰ is hydrogen, halo, -CH₂OH, -CN, -CH₂CN, -NH₂, C₁-C₄alkyl, C₂-C₄alkenyl, C₁-C₄alkoxy, C₁-C₂haloalkyl, C₁-C₂haloalkoxy, -(C₀-C₃ alkyl)-cyclopropyl, -(C₀-C₃ alkyl)-cyclobutyl, -C≡C-cyclopropyl, -C≡C-cyclobutyl, or -CH₂-tetrazolyl, each of which cyclopropyl, -(C₁-C₃ alkyl)-cyclopropyl, -CH=CH₂ or -C≡C-cyclopropyl is substituted or unsubstituted; and

each R¹³ and R¹⁴ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, wherein R¹³ and R¹⁴ are optionally connected to each other to form a ring.

[0028] In yet another embodiment of formula (Ia),

R¹ is independently chosen from hydroxyl, halo, -CO₂H, -SO₂NH₂, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₂haloalkyl optionally substituted with halo, C₁-C₂haloalkoxy, and -CO₂(C₁-C₆ alkyl),

R² is chosen from F and -SO₂NH₂, where one of R² is -SO₂NH₂;

R³ is independently chosen from

(a) halogen, hydroxyl, SF₅;

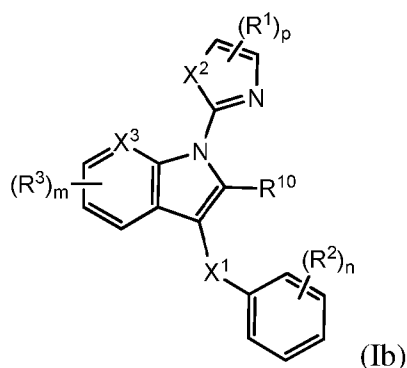
(b) C₁-C₆hydrocarbyl where any alkylene (CH₂) group in the hydrocarbyl chain is optionally replaced with NH, O, or S;

(c) -C₀-C₂hydrocarbyl (phenyl), -C₀-C₂hydrocarbyl (phenyl), -C₀-C₂hydrocarbyl (thiophenyl), -C₀-C₂hydrocarbyl (oxazolyl), -C₀-C₂hydrocarbyl (thiazolyl), -C₀-C₂hydrocarbyl (tetrahydrofuranlyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkenyl), -C₀-C₂hydrocarbyl (tetrahydropyrenyl), -C₀-C₂hydrocarbyl (imidazolyl), -C₀-C₂hydrocarbyl(thiophenyl), where any alkylene (CH₂) group in the C₀-C₂hydrocarbyl chain is optionally replaced with NH, O, or S;

where each of (b) is unsubstituted or substituted with 1 or more substituents independently chosen from halogen, hydroxyl, cyano, amino, C₁-C₂haloalkyl, and C₁-C₂haloalkoxy;

where each of (c) is unsubstituted or substituted with 1 or more substituents independently chosen from halogen, hydroxyl, cyano, amino, C₁-C₄alkyl, C₁-C₆cycloalkyl, mono- or di-C₁-C₄alkylamino, C₁-C₄alkoxy, C₁-C₂haloalkyl, and C₁-C₂haloalkoxy

[0029] The claimed invention also provides a compound of formula (Ib), or a pharmaceutically acceptable salt thereof:



wherein

R^1 is independently chosen from halo, $-\text{CO}_2R^4$, $-\text{C}(\text{O})\text{NR}^5R^6$, $-(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-\text{C}(\text{O})\text{NHOH}$, $-\text{C}(\text{O})\text{OCR}^5R^6\text{OC}(\text{O})\text{OR}^4$, $-\text{P}(\text{O})(\text{OH})_2$, $-\text{B}(\text{OR}^{13})(\text{OR}^{14})$, $-\text{SO}_2(\text{OH})$, $-\text{C}(\text{O})\text{NHS}(\text{O})_2\text{Me}$ and $-\text{SO}_2\text{NR}^5R^6$, each of which R^1 except halo is substituted or unsubstituted;

R^2 is independently chosen from hydroxyl, halo, $-\text{CN}$, $-\text{NO}_2$, $\text{C}_1\text{-C}_8\text{hydrocarbyl}$, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-\text{C}(\text{O})R^4$, $-\text{CO}_2R^4$, $-\text{C}(\text{O})\text{NR}^5R^6$, $-\text{NR}^5\text{C}(\text{O})R^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)R^4$, $-(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})R^4$, $-(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2R^4$, $-(\text{CH}_2)_q\text{aryl}$, $-(\text{CH}_2)_q\text{heteroaryl}$, or $-(\text{CH}_2)_q\text{heterocycloalkyl}$, each of which $\text{C}_1\text{-C}_8\text{hydrocarbyl}$, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$ is substituted or unsubstituted;

R^3 is independently chosen from hydroxyl, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{SF}_5$, $\text{C}_1\text{-C}_8\text{hydrocarbyl}$, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-\text{C}(\text{O})R^4$, $-\text{CO}_2R^4$, $-\text{C}(\text{O})\text{NR}^5R^6$, $-\text{NR}^5\text{C}(\text{O})R^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)R^4$, $-(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})R^4$, $-(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2R^4$, each of which $\text{C}_1\text{-C}_8\text{hydrocarbyl}$, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$ is substituted or unsubstituted; or

each R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is the same or different and each is hydrogen, $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{C}_2\text{-C}_8\text{alkenyl}$, $\text{C}_3\text{-C}_6\text{cycloalkyl}$, aryl , heteroaryl , or heterocycloalkyl , each of which $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{C}_2\text{-C}_8\text{alkenyl}$, $\text{C}_3\text{-C}_6\text{cycloalkyl}$, aryl , heteroaryl , or heterocycloalkyl is substituted or unsubstituted;

R^{10} is hydrogen, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2R^4$, $-\text{C}(\text{O})\text{NR}^5R^6$, $-\text{NR}^5(\text{SO}_2)R^4$, $-\text{NR}^5\text{C}(\text{O})R^4$, $-\text{NR}^7\text{C}(\text{O})\text{NR}^5R^6$, $-\text{NR}^5R^6$, $-\text{SO}_2\text{NR}^5R^6$, $-\text{SO}_2R^4$, $\text{C}_1\text{-C}_8\text{hydrocarbyl}$, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8\text{cycloalkenyl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, each of which R^{10} except hydrogen, halo, $-\text{CN}$, and $-\text{NO}_2$ is substituted or unsubstituted;

each R^{13} and R^{14} is the same or different and each is hydrogen, $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{C}_2\text{-C}_8\text{alkenyl}$, $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $\text{C}_6\text{-C}_{12}\text{aryl}$, wherein R^{13} and R^{14} are optionally connected to each other to form a ring;

X^1 is a bond, $-\text{CR}^8R^9$, $-\text{NR}^5$, $-\text{CR}^8\text{NR}^5$, $-\text{NR}^5\text{CR}^8$, $-\text{NR}^5\text{C}(\text{O})$, $-\text{O}$, $-\text{CO}$, $-\text{SO}_2$, or $-\text{S}$;

X^2 is $-\text{NR}^5$, $-\text{O}$, $-\text{SO}$, or $-\text{SO}_2$, or $-\text{S}$;

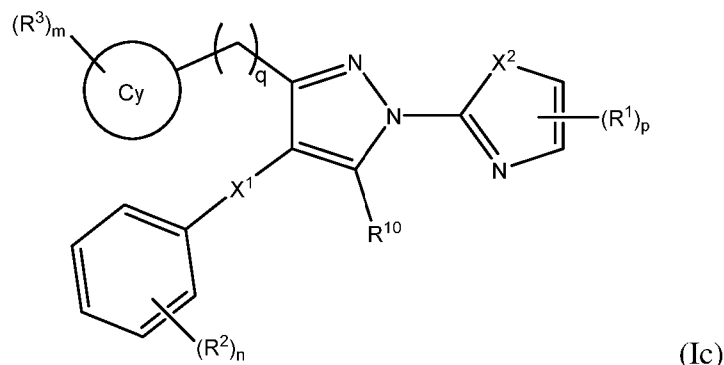
X^3 is CH or N ;

m and q are the same or different and each is 0 or an integer from 1-5;

n is an integer from 1-5; and

p is 1 or 2, wherein "substituted" means that any one or more hydrogens on the designated atom or group is replaced with one selected from a halogen, a cyano group, a hydroxyl group, a nitro group, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 8 carbon atoms, a (cycloalkyl)alkyl group having 4 to 8 carbon atoms, an alkenyl having one or more unsaturated linkages and 2 to 8 carbon atoms, an alkynyl group having one or more unsaturated linkages and from 2 to 8 carbon atoms, an alkoxy group having one or more oxygen linkages and 1 to 8 carbon atoms, an aryloxy group, and an alkylthio group having one or more thioether linkages and 1 to 8 carbon atoms.

[0030] Described is a compound of formula (I) that is a compound, prodrug, or pharmaceutically acceptable salt of formula (Ic)



wherein

R¹ is independently chosen from halo, -CO₂R⁴, -C(O)NR⁵R⁶, -(C₁-C₈hydrocarbyl), -C(O)NHOH, -P(O)(OH)₂, -B(OR¹³)(OR¹⁴), -SO₂(OH), -C(O)NHS(O)₂Me and -SO₂NR⁵R⁶, each of which R¹ except halo is substituted or unsubstituted;

R² is independently chosen from hydroxyl, halo, -CN, -NO₂, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, each of which C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted;

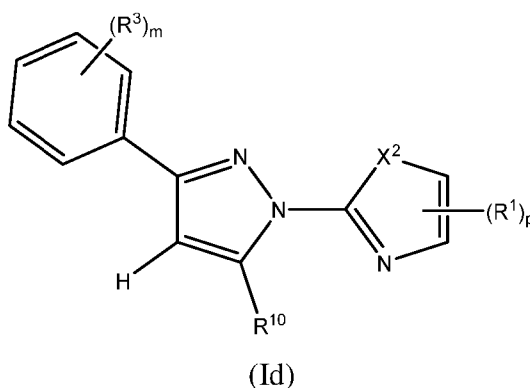
R³ is independently chosen from hydroxyl, halo, -CN, -NO₂, -SF₅, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, each of which C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted;

each R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ is the same or different and each is hydrogen, C₁-C₈alkyl, C₂-C₈alkenyl, C₃-C₆cycloalkyl, aryl, heteroaryl, or heterocycloalkyl;

R¹⁰ is hydrogen, halo, -CN, -NO₂, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵(SO₂)R⁴, -NR⁵C(O)R⁴, -NR⁷C(O)NR⁵R⁶, -NR⁵R⁶,

-SO₂NR⁵R⁶, -SO₂R⁴, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), each of which R¹⁰ except hydrogen, halo, -CN, and -NO₂ is substituted or unsubstituted; each R¹³ and R¹⁴ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, wherein R¹³ and R¹⁴ are optionally connected to each other to form a ring; ring Cy is substituted or unsubstituted C₃-C₆ cycloalkyl, X¹ is a bond, -CR⁸R⁹-, -NR⁵-, -CR⁸NR⁵-, -NR⁵CR⁸-, -NR⁵C(O)-, -O-, -CO-, -SO-, -SO₂-, or -S-; X² is -NR⁵-, -O-, -SO₂-, or -S-; m, n, and q are the same or different and each is 0 or an integer from 1-5; and p is 1 or 2.

[0031] Described is a compound of formula (I) that is a compound, prodrug, or pharmaceutically acceptable salt of formula (Id)



wherein

R¹ is independently chosen from halo, -CO₂R⁴, -C(O)NR⁵R⁶, -(C₁-C₈hydrocarbyl), -C(O)NHOH, -(C₀-C₄hydrocarbyl)(mono- or bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)O-(C₀-C₄hydrocarbyl)(mono- or bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -P(O)(OH)₂, -B(OR¹³)(OR¹⁴), -SO₂(OH), -SO₂NR⁵R⁶, each of which R¹ except halo is substituted or unsubstituted; R³ is independently chosen from hydroxyl, halo, -CN, -NO₂, -SF₅, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, each of which C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted; or two R³ moieties and the phenyl group to which they are attached form a naphthyl group or its heterocyclic analog that is optionally substituted; each R⁴, R⁵, R⁶, and R⁷ is the same or different and each is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂aryl, C₁-C₁₂heteroaryl, or C₁-C₁₂heterocycloalkyl, each of which C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂aryl, C₁-C₁₂heteroaryl, or C₁-C₁₂heterocycloalkyl is substituted or unsubstituted; R¹⁰ is hydrogen, halo, -CN, -NO₂, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵(SO₂)R⁴, -NR⁵C(O)R⁴, -NR⁷C(O)NR⁵R⁶, -NR⁵R⁶, -SO₂NR⁵R⁶, -SO₂R⁴, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S), -(C₀-C₄hydrocarbyl)(mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S) is substituted or unsubstituted; or

cloalkenyl, $-(C_0-C_4\text{hydrocarbyl})C_6-C_{12}\text{aryl}$, $-(C_0-C_4\text{hydrocarbyl})C_6-C_{12}\text{aryl}$, $-(C_0-C_4\text{hydrocarbyl})(\text{mono- and bi-cyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, $-(C_0-C_4\text{hydrocarbyl})(\text{mono- and bicyclic heterocycle having 1 to 4 heteroatoms independently chosen from N, O, and S})$, each of which R^{10} except hydrogen, halo, $-\text{CN}$, and $-\text{NO}_2$ is substituted or unsubstituted;
 each R^{13} and R^{14} is the same or different and each is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_6 cycloalkyl, C_6-C_{12} aryl, wherein R^{13} and R^{14} are optionally connected to each other to form a ring;
 X^2 is $-\text{NR}^5$, $-\text{O}$, $-\text{SO}$, $-\text{SO}_2$, or $-\text{S}$;
 m and q are the same or different and each is 0 or an integer from 1-5; and
 p is 1 or 2.

[0032] Within the limitations set out above, R^{10} can be hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylalkyl, aryl, arylalkyl, hydroxyl, hydroxyalkyl, halo, C_1-C_8 haloalkyl, $-\text{CN}$, cyanoalkyl, $-\text{NR}^5R^6$, or heteroarylalkyl. Optionally, R^{10} is hydrogen, C_1-C_8 alkyl, $-\text{CH}=\text{CH}_2$, cyclopropyl, $-\text{C}\equiv\text{C}$ -cyclopropyl, $-\text{OH}$, $-\text{CH}_2\text{OH}$, $-\text{CF}_3$, $-\text{CF}_2\text{CF}_3$, $-\text{Cl}$, $-\text{F}$, $-\text{I}$, $-\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{NH}_2$, phenyl, benzyl, or $-\text{CH}_2$ -tetrazolyl.

[0033] Within the limitations set out above for formula (Ia)-(Id), R^1 can be $-\text{CO}_2\text{H}$ or substituted or unsubstituted $-\text{CO}_2(C_1-C_8\text{ alkyl})$ or a prodrug or a pharmaceutically acceptable salt thereof. Optionally, p is 1.

[0034] Within the limitations set out above for formula (Ia)-(Ic), R^2 can be $-\text{SO}_2\text{NR}^5R^6$; and R^5 and R^6 are the same or different and each is hydrogen or substituted or unsubstituted C_1-C_8 alkyl.

[0035] Within the limitations set out above for formula (Ia)-(Ic), n can be 1.

[0036] Within the limitations set out above for formula (Ia)-(Id), R^3 can be hydrogen, halo, substituted or unsubstituted C_1-C_8 haloalkyl, substituted or unsubstituted C_1-C_8 haloalkoxy, or substituted or unsubstituted aryl.

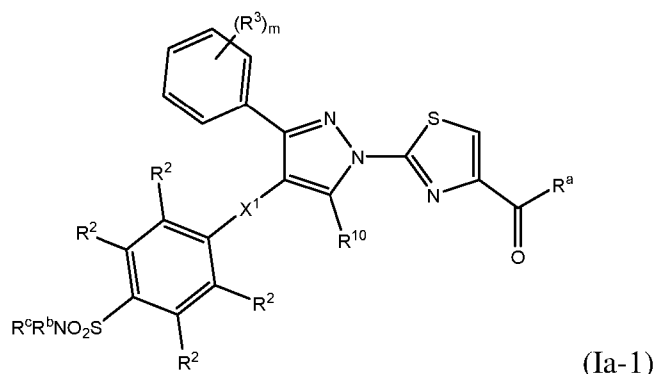
[0037] Within the limitations set out above for formula (Ia)-(Id), m can be 1 or 2.

[0038] Within the limitations set out above for formula (Ia)-(Ic), X^1 can be $-\text{CR}^8R^9$ -(e.g., $-\text{CH}_2$ -), $-\text{O}$ -, or $-\text{NH}$ -, in which R^8 and R^9 are the same or different and each is hydrogen, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_3-C_6 cycloalkyl, or substituted or unsubstituted aryl.

[0039] Within the limitations set out above for formula (Ia)-(Id), X^2 can be $-\text{S}$.

[0040] Within the limitations set out above for formula (Ib), X^3 can be $-\text{CH}$.

[0041] Optionally, the compound of formula (Ia) is a compound or pharmaceutically acceptable salt of formula (Ia-1):



wherein

R^a is $-\text{R}^4$, $-\text{OR}^4$, or $-\text{NR}^5R^6$, each of which is substituted or unsubstituted;

R^b and R^c are the same or different and each is H or substituted or unsubstituted C_1-C_8 alkyl;

each R^2 is the same or different and is independently chosen from hydroxyl, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_6 cycloalkyl, C_1-C_8 alkoxy, C_3-C_6 cycloalkyloxy, aryloxy, halo, C_1-C_8 haloalkoxy, C_1-C_8 haloalkyl, haloaryl, haloaryloxy, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{R}^4$, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5R^6$, $-\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^4$, $-(\text{CH}_2)_q\text{aryl}$, $-(\text{CH}_2)_q\text{heteroaryl}$, and $-(\text{CH}_2)_q\text{heterocycloalkyl}$, each of which R^2 except hydroxyl and halo is substituted or unsubstituted;

R^3 is independently chosen from hydroxyl, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, $-(C_1-C_4\text{hydrocarbyl})C_3-C_6$ cycloalkyl, C_1-C_8 alkoxy, $-(C_0-C_4\text{alkoxy})C_3-C_6$ cycloalkyl, $-(C_0-C_4\text{alkoxy})\text{aryl}$, halo, C_1-C_8 haloalkoxy, C_1-C_8 haloalkyl, haloaryl, haloaryloxy, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{R}^4$, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5R^6$, $-\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5R^6$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^4$, $-(C_0-C_4\text{hydrocarbyl})\text{aryl}$, $-(C_0-C_4\text{hydrocarbyl})\text{heteroaryl}$, $-(C_0-C_4\text{alkoxy})\text{heteroaryl}$, $-(C_0-C_4\text{alkoxy})\text{heterocycloalkyl}$, and $-(C_0-C_4\text{hydrocarbyl})\text{heterocycloalkyl}$, each of which R^3 except hydroxyl and

halo is substituted or unsubstituted; or

two R³ moieties and the phenyl group to which they are attached form a naphthyl group that is optionally substituted; each R⁴, R⁵, R⁶, and R⁷ is the same or different and each is hydrogen, C₁-C₈ alkyl, or C₃-C₆ cycloalkyl, each of which C₁-C₈ alkyl and C₃-C₆ cycloalkyl is substituted or unsubstituted;

R¹⁰ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyalkyl, C₁-C₈ alkoxy, halo, C₁-C₈ haloalkyl, -CN, -CO₂R⁴, -NR⁵R⁶, heteroarylalkyl, or -SO₂R⁴, each of which R¹⁰ except hydrogen and halo is substituted or unsubstituted;

X¹ is a bond, -CR⁸R⁹-, -NR⁵-, -O-, -S(O)-, or -S(O)₂-, or -S-;

n is an integer from 0 to 4; and

m and q are the same or different and each is 0 or an integer from 1-5.

[0042] In an embodiment, compound of formula (Ia-1) comprise R^a is hydroxyl or -O(C₁-C₈ alkyl); R^b and R^c are H; R² is hydrogen; R³ is halo, aryl, or haloaryl (e.g., halo or phenyl); or two R³ moieties and the phenyl group to which they are attached form a naphthyl group that is optionally substituted; R¹⁰ is hydrogen, C₁-C₈ alkyl, cyclopropyl, -CH₂-cyclopropyl, -CH₂CH₂cyclopropyl, cyclobutyl, -CH₂-cyclobutyl, -CH=CH₂, -C≡C-cyclopropyl, -I, -CF₃, -NH₂, or -CN; and X¹ is -CH₂- or -NH-; and m is 0, 1, or 2.

[0043] In an embodiment, the disclosure includes compounds and salts of formula (Ia-1), wherein

R^a is R⁴, -OR⁴, or -NR⁵R⁶;

R² is one or more substituents independently chosen from halo, hydroxyl, -CN, -NO₂, amino, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, C₁-C₂ alkyl, C₁-C₂ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

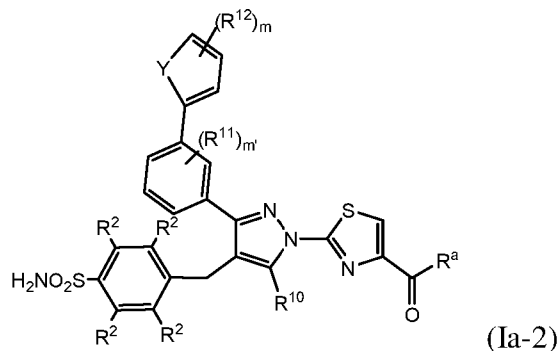
each R⁴, R⁵, and R⁶, is the same or different and each is hydrogen or C₁-C₂ alkyl; and

R¹⁰ is hydrogen, halo, -CN, C₁-C₄ alkyl, hydroxylC₁-C₄alkyl, C₁-C₄ alkoxy, C₂-C₄ alkenyl, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, C₁-C₂haloalkoxy, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴.

[0044] In an embodiment the disclosure also includes compounds and salts of formula (Ia-1) wherein:

one of R³ is selected from C₂-C₆alkynyl, -(C₀-C₂alkyl)C₃-C₆cycloalkyl, -(C₂-C₄alkenyl)C₃-C₆cycloalkyl, -(C₂-C₄alkynyl)C₃-C₆cycloalkyl, -(C₀-C₂alkoxy)C₃-C₆cycloalkyl, dihydropyranyl, -(C₀-C₄alkoxy)phenyl, -(C₀-C₄alkyl)phenyl, -(C₂-C₄alkenyl)phenyl, -(C₂-C₄alkynyl)phenyl, -(C₀-C₄alkoxy)heteroaryl, -(C₀-C₄alkyl)heteroaryl, -(C₂-C₄alkenyl)heteroaryl, and -(C₂-C₄alkynyl)heteroaryl, where heteroaryl is chosen from thienyl, furanyl, thiazolyl, pyrazolyl, imidazolyl; each of which one or more substituents selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkynyl, C₁-C₄ alkoxy, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy; and 0 or 1 or more R³ is selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy.

[0045] Optionally, a compound of formula (Ia-1) is a compound or pharmaceutically acceptable salt of formula (Ia-2):



Wherein

Y = -CH=CH-, O, S, NH;

R^a is -R⁴, -OR⁴, or -NR⁵R⁶, each of which R⁴, R⁵, and R⁶ is substituted or unsubstituted;

each R² is the same or different and each is hydrogen, hydroxyl, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₁-C₈ alkoxy, C₃-C₆ cycloalkyloxy, aryloxy, halo, C₁-C₈ haloalkoxy, C₁-C₈ haloalkyl, haloaryl, haloaryloxy, -CN, -NO₂, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, -(CH₂)_qaryl, -(CH₂)_qheteroaryl, or -(CH₂)_qheterocycloalkyl, each of which R² except hydrogen, hydroxyl and halo is substituted or unsubstituted;

Each R¹¹ and R¹² are independently selected from hydroxyl, halo, -CN, NO₂, C₁-C₈ alkyl, C₂-C₈ alkenylC₁-C₈ alkoxy, C₁-C₂ haloalkoxy, C₁-C₂ haloalkyl, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, and -(CH₂)_qSO₂R⁴, each of which

R¹¹ and R¹² other than hydroxyl, halo, -CN, NO₂, is substituted or unsubstituted;

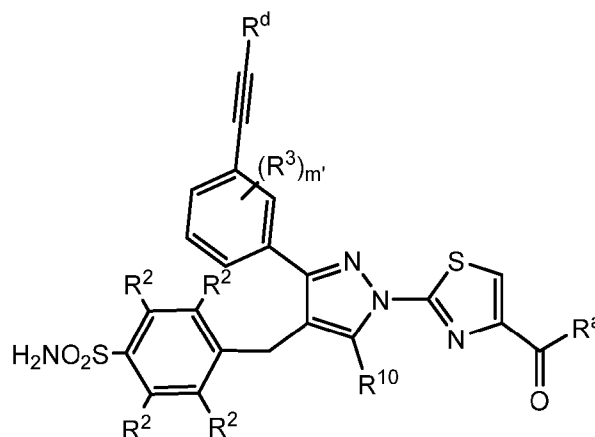
each R⁴, R⁵, R⁶, and R⁷ is the same or different and each is hydrogen, C₁-C₈ alkyl, or C₃-C₆ cycloalkyl, each of which C₁-C₈ alkyl and C₃-C₆ cycloalkyl is substituted or unsubstituted;

R¹⁰ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyalkyl, C₁-C₈ alkoxy, halo, C₁-C₈ haloalkyl, heteroarylalkyl, -CN, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴, each of which R¹⁰ except hydrogen and halo is substituted or unsubstituted;

m and q are the same or different and each; and

m' is 0 or an integer from 1-4.

[0046] Optionally, a compound of formula (Ia-1) is a compound or pharmaceutically acceptable salt of formula (Ia-3):



wherein

R^a is -R⁴, -OR⁴, or -NR⁵R⁶, each of which R⁴, R⁵, and R⁶ is substituted or unsubstituted;

each R² is the same or different and each is hydrogen, hydroxyl, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₁-C₈ alkoxy, C₃-C₆ cycloalkyloxy, aryloxy, halo, C₁-C₈ haloalkoxy, C₁-C₈ haloalkyl, haloaryl, haloaryloxy, -CN, -NO₂, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, -(CH₂)_qaryl, -(CH₂)_qheteroaryl, or -(CH₂)_qheterocycloalkyl, each of which R² except hydrogen, hydroxyl and halo is substituted or unsubstituted;

R³ is hydroxyl, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, C₁-C₈ alkoxy, C₃-C₆ cycloalkyloxy, aryloxy, halo, C₁-C₈ haloalkoxy, C₁-C₈ haloalkyl, haloaryl, haloaryloxy, -CN, -NO₂, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, -(CH₂)_qaryl, -(CH₂)_qheteroaryl, or -(CH₂)_qheterocycloalkyl, each of which R³ except hydroxyl and halo is substituted or unsubstituted;

each R⁴, R⁵, R⁶, and R⁷ is the same or different and each is hydrogen, C₁-C₈ alkyl, or C₃-C₆ cycloalkyl, each of which C₁-C₈ alkyl and C₃-C₆ cycloalkyl is substituted or unsubstituted;

R⁴ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyl, hydroxyalkyl, C₁-C₈ alkoxy, halo, C₁-C₈ haloalkyl, aryl, arylalkyl, heteroarylalkyl, -CN, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴; q are the same or different and each; and

m' is 0 or an integer from 1-4

R¹⁰ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyalkyl, C₁-C₈ alkoxy, halo, C₁-C₈ haloalkyl, heteroarylalkyl, -CN, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴, each of which R¹⁰ except hydrogen and halo is substituted or unsubstituted; and

R^d is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyl, hydroxyalkyl, C₁-C₈ alkoxy, halo, C₁-C₈ haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CN, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴; each of which R¹¹ other than hydrogen and -CN is optionally substituted.

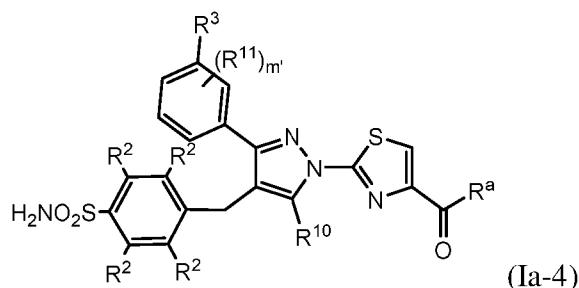
[0047] In certain embodiments R^d is phenyl, thienyl, thiazolyl, furanyl, oxazolyl, pyrazolyl, oxadiazolyl, or imidazolyl, each of which is substituted or unsubstituted. In certain embodiments R^d is phenyl, thienyl, thiazolyl, furanyl, oxazolyl, pyrazolyl, oxadiazolyl, or imidazolyl, each of which is unsubstituted or substituted with 1 or more substituents independently chosen from hydroxyl, cyano, amino, C₁-C₂alkyl, C₁-C₂alkoxy, mono- or di-C₁-C₂alkylamino, C₁-C₂haloalkyl, and C₁-C₂haloalkoxy. In certain embodiments R^d is thienyl substituted with methyl.

[0048] In certain embodiments, the disclosure includes compounds and salts of formula (Ia-3) wherein:

R^a is hydrogen, hydroxyl, amino, C₁-C₂alkyl, C₁-C₂alkoxy, and mono- or di-C₁-C₂alkylamino-;
 each R² is the same or different and is independently selected from hydrogen, halo, hydroxyl, -CN, -NO₂, amino,
 -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, C₁-C₂ alkyl, C₁-C₂ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;
 each R³ is independently chosen from hydroxyl, halo, -CN, NO₂, C₁-C₂ alkyl, C₁-C₂ alkoxy, C₁-C₂ haloalkoxy, and
 C₁-C₂ haloalkyl;
 each R⁴, R⁵, R⁶, and R⁷ is the same or different and each is hydrogen or C₁-C₂ alkyl;
 m' is 0 or an integer from 1-4; and
 R¹⁰ is hydrogen, halo, -CN, C₁-C₄ alkyl, hydroxylC₁-C₄alkyl, C₁-C₄ alkoxy, C₂-C₄ alkenyl, (C₃-C₆ cy-
 cloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, C₁-C₂haloalkoxy, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴.
 R^d in this embodiments can be thienyl substituted with methyl.

[0049] In an embodiment of the compound of formula (Ia-2): R^a is hydroxyl or substituted or unsubstituted -O(C₁-C₈
 alkyl); R² is hydrogen, substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted C₁-C₈ alkoxy, or halo; R¹¹
 and R¹² are each independently chosen from substituted or unsubstituted C₁-C₈ alkyl (e.g., C₁₋₄ alkyl, such methyl,
 ethyl, propyl, or butyl), substituted or unsubstituted C₁-C₈ alkoxy, or halo (e.g., -F, -I, -Cl, or -Br); R¹⁰ is hydrogen,
 substituted or unsubstituted C₁-C₈ alkyl, cyclopropyl, -CH₂-cyclopropyl, cyclobutyl, -CH₂-cyclobutyl, -CH=CH₂, -C≡C-
 cyclopropyl, -C≡C-cyclobutyl, -I, -CF₃, -NH₂, or -CN; m is 0, 1, or 2; and m' is 0.

[0050] Optionally, a compound of formula (Ia) is a compound or pharmaceutically acceptable salt of formula (Ia-4):



[0051] Within formula (Ia-4):

R^a is -R⁴, -OR⁴, or -NR⁵R⁶, each of which R⁴, R⁵, and R⁶ is substituted or unsubstituted;
 Each R² is the same or different and is hydrogen, hydroxyl, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆
 cycloalkylalkyl, C₁-C₈ alkoxy, C₃-C₆ cycloalkyloxy, aryloxy, halo, C₁-C₈ haloalkoxy, C₁-C₈ haloalkyl, haloaryl,
 haloaryloxy, -CN, -NO₂, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴,
 -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, -(CH₂)_qSO₂R⁴, -(CH₂)_qaryl, -(CH₂)_qheteroaryl, or
 -(CH₂)_qheterocycloalkyl, each of which R² except hydrogen, hydroxyl and halo is substituted or unsubstituted;
 R³ is selected from C₂-C₆alkynyl, -(C₀-C₂alkyl)C₃-C₆cycloalkyl, -(C₂-C₄alkenyl)C₃-C₆cycloalkyl,
 -(C₂-C₄alkynyl)C₃-C₆cycloalkyl, -(C₀-C₂alkoxy)C₃-C₆cycloalkyl, dihydropyranlyl, -(C₀-C₄alkoxy)phenyl,
 -(C₀-C₄alkyl)phenyl, -(C₂-C₄alkenyl)phenyl, -(C₂-C₄alkynyl)phenyl, -(C₀-C₄alkoxy)heteroaryl, -(C₀-C₄alkyl)hetero-
 oaryl, -(C₂-C₄alkenyl)heteroaryl, and -(C₂-C₄alkynyl)heteroaryl, where heteroaryl is a 5- or 6-membered heteroaryl
 having 1, 2, 3, or 4 heteroatoms independently chosen from N, O, and S, and where each R³ is unsubstituted or
 substituted with one or more substituents selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄
 alkynyl, C₁-C₄ alkoxy, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;
 each R¹¹ is independently selected from hydroxyl, halo, -CN, NO₂, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₂
 haloalkoxy, C₁-C₂ haloalkyl, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴,
 -(CH₂)_qNR⁷C(O)NR⁵R⁶, -(CH₂)_qNR⁵R⁶, -(CH₂)_qSO₂NR⁵R⁶, and -(CH₂)_qSO₂R⁴, each of which R¹¹ and R¹² other
 than hydroxyl, halo, -CN, NO₂, is substituted or unsubstituted;
 each R⁴, R⁵, R⁶, and R⁷ is the same or different and each is hydrogen, C₁-C₈ alkyl, or C₃-C₆ cycloalkyl, each of
 which C₁-C₈ alkyl and C₃-C₆ cycloalkyl is substituted or unsubstituted;
 R¹⁰ is hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylalkyl, hydroxyalkyl,
 C₁-C₈ alkoxy, halo, C₁-C₈ haloalkyl, -CN, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴, each of which R¹⁰ except hydrogen and halo
 is substituted or unsubstituted;
 m is 0 or 1, 2, 3, 4, or 5; and
 m' is 0 or an integer from 1-4.

[0052] In an embodiment the disclosure includes a compound or salt of formula (Ia-4) wherein

R^a is hydrogen, hydroxyl, amino, C₁-C₂alkyl, C₁-C₂alkoxy, and mono- or di-C₁-C₂alkylamino;

each R² is the same or different and is independently selected from hydrogen, halo, hydroxyl, -CN, -NO₂, amino, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, C₁-C₂ alkyl, C₁-C₂ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

R³ is selected from C₂-C₆alkynyl, -(C₀-C₂alkyl)C₃-C₆cycloalkyl, -(C₂-C₄alkenyl)C₃-C₆cycloalkyl, -(C₂-C₄alkynyl)C₃-C₆cycloalkyl, -(C₀-C₂alkoxy)C₃-C₆cycloalkyl, dihydropyranyl, -(C₀-C₄alkoxy)phenyl, -(C₀-C₄alkyl)phenyl, -(C₂-C₄alkenyl)phenyl, -(C₂-C₄alkynyl)phenyl, -(C₀-C₄alkoxy)heteroaryl, -(C₀-C₄alkyl)heteroaryl, -(C₂-C₄alkenyl)heteroaryl, and -(C₂-C₄alkynyl)heteroaryl, where heteroaryl is chosen from thienyl, furanyl, thiazolyl, pyrazolyl, imidazolyl; each of which one or more substituents selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkynyl, C₁-C₄ alkoxy, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

Each R¹¹ is independently selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

Each R⁴, R⁵, and R⁶ is the same or different and each is hydrogen or C₁-C₂ alkyl;

m' is 0 or an integer from 1-4; and

R¹⁰ is hydrogen, halo, -CN, C₁-C₄ alkyl, hydroxylC₁-C₄alkyl, C₁-C₄ alkoxy, C₂-C₄ alkenyl, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, C₁-C₂haloalkoxy, -CO₂R⁴, -NR⁵R⁶, or -SO₂R⁴.

[0053] In certain embodiments, the disclosure includes a compound or salt of formula (Ia-4) in which:

R^a is hydrogen, hydroxyl, C₁-C₂alkyl, or C₁-C₂alkoxy;

each R² is the same or different and is independently selected from hydrogen, halo, hydroxyl, C₁-C₂ alkyl, C₁-C₂ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

R³ is selected from C₂-C₆alkynyl, -(C₀-C₂alkyl)C₃-C₆cycloalkyl, -(C₂-C₄alkenyl)C₃-C₆cycloalkyl, -(C₂-C₄alkynyl)C₃-C₆cycloalkyl, -(C₀-C₂alkoxy)C₃-C₆cycloalkyl, dihydropyranyl, -(C₀-C₄alkoxy)phenyl, -(C₀-C₄alkyl)phenyl, -(C₂-C₄alkenyl)phenyl, -(C₂-C₄alkynyl)phenyl, -(C₀-C₄alkoxy)heteroaryl, -(C₀-C₄alkyl)heteroaryl, -(C₂-C₄alkenyl)heteroaryl, and -(C₂-C₄alkynyl)heteroaryl, where heteroaryl is chosen from thienyl, furanyl, thiazolyl, pyrazolyl, imidazolyl; each of which one or more substituents selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkynyl, C₁-C₄ alkoxy, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

Each R¹¹ is independently selected from hydroxyl, halo, -CN, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₂ haloalkyl, and C₁-C₂haloalkoxy;

m' is 0 or an integer from 1-4; and

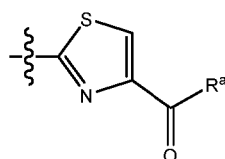
R¹⁰ is hydrogen, halo, -CN, C₁-C₄ alkyl, hydroxylC₁-C₄alkyl, C₁-C₄ alkoxy, C₂-C₄ alkenyl, (C₃-C₆ cycloalkyl)C₀-C₂alkyl, C₁-C₂ haloalkyl, or C₁-C₂haloalkoxy.

[0054] The disclosure further includes compounds and salts of formula (Ia-4) in which

R^a is hydroxyl; and

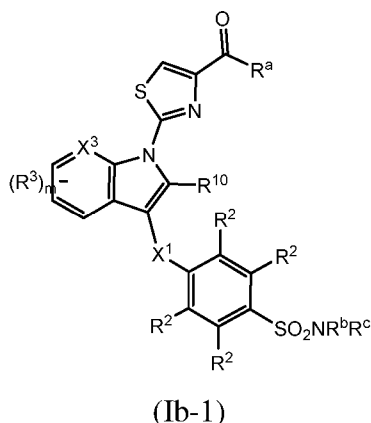
Each R² is independently chosen from hydrogen and halogen.

[0055] In any of embodiments of formula (Ia-1 to Ia-4) the group



can be a group in which R^a is hydroxyl, NHCN, or NHSO₂H, -NHSO₂alkyl, CH₂SO₂phenyl, -NHOH or -NHOalkyl, or can be a group in which -C(O)R^a is replaced by -CH₂OH, -P(O)(OH)₂, -P(O)(OH)alkyl, or -SO₂OH.

[0056] In some aspects, the compound of formula (Ib) is a compound or pharmaceutically acceptable salt of formula (Ib-1):



wherein

R^a is $-R^4$, $-OR^4$, or $-NR^5R^6$, each of which R^4 , R^5 , and R^6 is substituted or unsubstituted;

R^b and R^c are the same or different and each is H or substituted or unsubstituted C_1 - C_8 alkyl;

each R^2 is the same or different and each is hydrogen, hydroxyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_8 alkoxy, C_3 - C_6 cycloalkoxy, aryloxy, halo, C_1 - C_8 haloalkoxy, C_1 - C_8 haloalkyl, haloaryl, haloaryloxy, $-CN$, $-NO_2$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^5R^6$, $-NR^5C(O)R^4$, $-(CH_2)_qNR^5(SO_2)R^4$, $-(CH_2)_qNR^5C(O)R^4$, $-(CH_2)_qNR^5C(O)NR^5R^6$, $-(CH_2)_qNR^5R^6$, $-(CH_2)_qSO_2NR^5R^6$, $-(CH_2)_qSO_2R^4$, $-(CH_2)_q$ aryl, $-(CH_2)_q$ heteroaryl, or $-(CH_2)_q$ heterocycloalkyl, each of which R^2 except hydrogen, hydroxyl, halo, $-CN$, and $-NO_2$ is substituted or unsubstituted;

R^3 is halo, $-C(O)R^4$, C_2 - C_8 alkynyl, haloaryl, $-(CH_2)_q$ aryl, $-(CH_2)_q$ heteroaryl, or $-(CH_2)_q$ heterocycloalkyl, each of which R^3 is substituted or unsubstituted;

each R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is the same or different and each is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, aryl, heteroaryl, or heterocycloalkyl, each of which C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, aryl, heteroaryl, or heterocycloalkyl is substituted or unsubstituted;

R^{10} is hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, hydroxyl, hydroxyalkyl, C_1 - C_8 alkoxy, C_1 - C_8 haloalkyl, halo, aryl, arylalkyl, heteroarylalkyl, $-CN$, $-CO_2R^4$, $-NR^5R^6$, or $-SO_2R^4$, each of which R^{10} except hydrogen, hydroxyl, halo, and $-CN$ is substituted or unsubstituted;

X^1 is a bond, $-CR^8R^9$, $-NR^5$, $-O$, $-SO$, or $-SO_2$, or $-S$, each of which R^5 , R^8 , and

R^9 is substituted or unsubstituted;

X^3 is CH or N; and

m and q are the same or different and each is 0 or an integer from 1-5.

[0057] In an embodiment, the compound of formula (Ib-1) comprises R^a is hydroxyl or substituted or unsubstituted $-O(C_1$ - C_8 alkyl); R^b and R^c are each hydrogen; R^2 is hydrogen; R^3 is halo, substituted or unsubstituted $-C(O)$ morpholinyl, or substituted or unsubstituted 2-fluorophenyl; R^{10} is hydrogen, substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted $-CH=CH_2$, substituted or unsubstituted cyclopropyl, substituted or unsubstituted $-C=C$ -cyclopropyl, substituted or unsubstituted cyclobutyl, substituted or unsubstituted $-C=C$ -cyclobutyl, $-OH$, $-CH_2OH$, $-CF_3$, $-CF_2CF_3$, $-Cl$, $-F$, $-I$, $-CN$, $-CH_2CN$, $-NH_2$, substituted or unsubstituted phenyl, substituted or unsubstituted benzyl, or substituted or unsubstituted $-CH_2$ -tetrazolyl; X^1 is $-CH_2$ - or $-NH$ -; and m is 0, 1, or 2.

[0058] Compounds of formula (I), including compounds of formulas (Ia), (Ib), (Ic), and (Id), are set forth below in Table 6. Pharmaceutically acceptable salts of these compounds are also contemplated.

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[0059] The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the

specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or language denoting examples (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification

should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0060] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When the substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. When an oxo group substitutes a heteroaromatic moiety, the resulting molecule can sometimes adopt tautomeric forms. For example a pyridyl group substituted by oxo at the 2- or 4-position can sometimes be written as a pyridine or hydroxypyridine. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture and subsequent formulation into an effective therapeutic agent. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that aminoalkyl means the point of attachment of this substituent to the core structure is in the alkyl portion and alkylamino means the point of attachment is a bond to the nitrogen of the amino group.

[0061] Suitable groups that may be present on a "substituted" or "optionally substituted" position include, but are not limited to, halogen; cyano; -OH; nitro; alkyl groups (including cycloalkyl and (cycloalkyl)alkyl groups) having 1 to about 8 carbon atoms, or 1 to about 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 8, or 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 8, or from 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those having one or more thioether linkages and from 1 to about 8 carbon atoms, or from 1 to about 6 carbon atoms. For example, suitable groups that may be present on a "substituted" or "optionally substituted" position include hydroxyl, halogen, cyano, alkyl groups, and alkoxy groups.

[0062] In any of the embodiments above, the term "alkyl" implies a straight-chain or branched alkyl substituent containing from, for example, from about 1 to about 8 carbon atoms, e.g., from about 1 to about 6 carbon atoms. Examples of alkyl group include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, *n*-hexyl, and the like. This definition also applies wherever "alkyl" occurs as part of a group, such as, e.g., in C₃-C₆ cycloalkylalkyl, hydroxyalkyl, haloalkyl (e.g., monohaloalkyl, dihaloalkyl, and trihaloalkyl), cyanoalkyl, aminoalkyl, alkylamino, dialkylamino, arylalkyl, etc. The alkyl can be substituted or unsubstituted, as described herein. Even in instances in which the alkyl is an alkylene chain (e.g., -(CH₂)_n-), the alkyl group can be substituted or unsubstituted. An example of a substituted alkylene chain includes -CF₂-cyclopropyl.

[0063] In any of the embodiments above, the term "alkenyl," as used herein, means a linear alkenyl substituent containing from, for example, about 2 to about 8 carbon atoms (branched alkenyls are about 3 to about 8 carbons atoms), e.g., from about 3 to about 6 carbon atoms (branched alkenyls are about 3 to about 6 carbons atoms). In accordance with an embodiment, the alkenyl group is a C₂-C₄ alkenyl. Examples of alkenyl group include ethenyl, allyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, and the like. The alkenyl can be substituted or unsubstituted, as described herein.

[0064] In any of the embodiments above, the term "alkynyl," as used herein, means a linear alkynyl substituent containing at least one carbon-carbon triple bond and from, for example, about 2 to about 8 carbon atoms (branched alkynyls are about 4 to about 12 carbons atoms), e.g., from about 2 to about 6 carbon atoms (branched alkynyls can be from about 4 to about 8 carbon atoms), e.g., from about 2 to about 4 carbon atoms. Examples of such substituents include propynyl, propargyl, *n*-butynyl, pentynyl, isopentynyl, hexynyl, octynyl, and the like. The alkynyl can be substituted or unsubstituted, as described herein.

[0065] In any of the embodiments above, the term "cycloalkyl," as used herein, means a cyclic alkyl moiety containing from, for example, 3 to 6 carbon atoms or from 5 to 6 carbon atoms. Examples of such moieties include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. The cycloalkyl can be substituted or unsubstituted, as described herein. For example, a substituted cycloalkyl includes a halo- or haloalkyl-substituted cyclopropyl, such as 2-fluorocyclopropyl, 2,2-difluorocyclopropyl, 1-(trifluoromethyl)cyclopropyl, and 2-(trifluoromethyl)cyclopropyl.

[0066] In any of the embodiments above, the term "hydrocarbyl" means an aliphatic group having the specified number of carbon atoms and the appropriate valence in view of the number of substitutions shown in the structure. Hydrocarbyl groups contain at least carbon and hydrogen, and can contain single, double, and triple carbon-carbon bonds. In certain embodiments hydrocarbyl groups optionally contain 1 or more (e.g., 1-8) heteroatoms selected from N, O, S, Si, P, or a combination thereof. Hydrocarbyl groups can be unsubstituted or substituted with one or more substituent groups up to the valence allowed by the hydrocarbyl group. For example the hydrocarbyl group may be substituted with hydroxyl, cyano, amino, halogen, oxo, cycloalkyl, 5- to 7-membered heterocycloalkyl containing 1 to 3 heteroatoms selected from N, O, and S, 5- or 6-membered heteroaryl selected with 1 to 5 heteroatoms selected from N, O, and S, and phenyl.

[0067] In any of the embodiments above, the term "hydroxy" refers to the group -OH.

[0068] In any of the embodiments above, the terms "alkoxy" and "cycloalkyloxy" embrace linear or branched alkyl and cycloalkyl groups, respectively, that are attached to a divalent oxygen. The alkyl and cycloalkyl groups are the same as described herein. The term "aryloxy" refers to substituents that have an aryl group attached to divalent oxygen. The aryl group is the same as described herein.

[0069] In any of the embodiments above, the term "halo" refers to a halogen selected from fluorine, chlorine, bromine, and iodine.

[0070] In any of the embodiments above, the term "aryl" refers to a mono, bi, or tricyclic carbocyclic ring system having one, two, or three aromatic rings, for example, phenyl, naphthyl, anthracenyl, or biphenyl. The term "aryl" refers to an unsubstituted or substituted aromatic carbocyclic moiety, as commonly understood in the art, and includes monocyclic and polycyclic aromatics such as, for example, phenyl, biphenyl, naphthyl, anthracenyl, pyrenyl, and the like. An aryl moiety generally contains from, for example, 6 to 30 carbon atoms, from 6 to 18 carbon atoms, from 6 to 14 carbon atoms, or from 6 to 10 carbon atoms. It is understood that the term aryl includes carbocyclic moieties that are planar and comprise $4n+2\pi$ electrons, according to Hückel's Rule, wherein $n = 1, 2, \text{ or } 3$. This definition also applies wherever "aryl" occurs as part of a group, such as, e.g., in haloaryl (e.g., monohaloaryl, dihaloaryl, and trihaloaryl), arylalkyl, etc. The aryl can be substituted or unsubstituted, as described herein.

[0071] In any of the embodiments above, the term "heteroaryl" refers to aromatic 5 or 6 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S, or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. Illustrative examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidyl, pyrazinyl, benzimidazolyl, triazinyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, tetrazolyl, furyl, pyrrolyl, thienyl, isothiazolyl, thiazolyl, isoxazolyl, and oxadiazolyl. The heteroaryl can be substituted or unsubstituted, as described herein.

[0072] The term "Het" means a "heterocycloalkyl," which is a stable, monocyclic or bicyclic system containing at least two double bonds, 3 to 7 ring members of carbon atoms and one, two, or three heteroatoms selected from nitrogen, sulfur, and/or oxygen. In an aspect, "Het" is a 5, 6, or 7-membered monocyclic ring and contains one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur. In some instances, "Het" is a heteroaryl, as described herein.

[0073] The term "heterocycloalkyl" means a stable, saturated, or partially unsaturated monocyclic, bicyclic, and spiro ring system containing 3 to 7 ring members of carbon atoms and other atoms selected from nitrogen, sulfur, and/or oxygen. In an aspect, a heterocycloalkyl is a 5, 6, or 7-membered monocyclic ring and contains one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur. The heterocycloalkyl may be attached to the parent structure through a carbon atom or through any heteroatom of the heterocycloalkyl that results in a stable structure. Examples of such heterocycloalkyl rings are isoxazolyl, thiazolyl, imidazolidinyl, piperazinyl, homopiperazinyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyranyl, piperidyl, oxazolyl, and morpholinyl. The heterocycloalkyl can be substituted or unsubstituted, as described herein.

[0074] In any of the embodiments above, the alkyl, alkoxy, and alkylamino groups can be linear or branched.

[0075] In other aspects, any substituent that is not hydrogen (e.g., C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl) can be an optionally substituted moiety. The substituted moiety typically comprises at least one substituent (e.g., 1, 2, 3, 4, 5, 6, etc.) in any suitable position (e.g., 1-, 2-, 3-, 4-, 5-, or 6-position, etc.). When an aryl group is substituted with a substituent, e.g., halo, amino, alkyl, OH, alkoxy, and others, the aromatic ring hydrogen is replaced with the substituent and this can take place in any of the available hydrogens, e.g., 2, 3, 4, 5, and/or 6-position wherein the 1-position is the point of attachment of the aryl group in the compound of the present invention. Suitable substituents include, e.g., halo, alkyl, alkenyl, alkynyl, hydroxy, nitro, cyano, amino, alkylamino, alkoxy, aryloxy, aralkoxy, carboxyl, carboxyalkyl, carboxyalkyloxy, amido, alkylamido, haloalkylamido, aryl, heteroaryl, and heterocycloalkyl, each of which is described herein. In some instances, the substituent is at least one alkyl, halo, and/or haloalkyl (e.g., 1 or 2).

[0076] In any of the embodiments above, whenever a range of the number of atoms in a structure is indicated (e.g., a C_{1-12} , C_{1-8} , C_{1-6} , or C_{1-4} alkyl, cycloalkyl, etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-8 carbon atoms (e.g., C_1 - C_8), 1-6 carbon atoms (e.g., C_1 - C_6), 1-4 carbon atoms (e.g., C_1 - C_4), 1-3 carbon atoms (e.g., C_1 - C_3), or 2-8 carbon atoms (e.g., C_2 - C_8) as used with respect to any chemical group (e.g., alkyl, cycloalkyl, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, and/or 8 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon

atoms, 2-7 carbon atoms, 2-8 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, etc., as appropriate).

[0077] The subscripts "m" and "n" represent the number of substituents, e.g., R² or R³, in which each substituent, e.g., R² or R³, can be the same or different. The subscripts m and n can be the same or different and each is either 0 or an integer from 1-5 (i.e., 1, 2, 3, 4, or 5). When m or n is 0, then the corresponding substituent, i.e., R² or R³, is not present in the compound of formula (I). The subscripts "o" and "q" represent the number of methylene repeat units. The subscripts o and q are either 0 or an integer from 1-5 (i.e., 1, 2, 3, 4, or 5). When o or q is 0, then the respective moiety does not contain any methylene repeat units.

[0078] A compound can be provided as a prodrug, which is a drug derivative or drug precursor compound that typically is inactive or less than fully active until it is converted in the body through a normal metabolic process such as, for example, hydrolysis of an ester or amide form of the drug, to the active drug. A prodrug may be selected and used instead of the parent drug because, for example, in its prodrug form it is less toxic, and/or may have better absorption, distribution, metabolism and excretion (ADME) characteristics, and the like, than the parent drug. A prodrug might also be used to improve how selectively the drug interacts with cells or processes that are not its intended target. This approach may be employed particularly, for example, to prevent or decrease adverse effects, especially in cancer treatments, which may be especially prone to having severe unintended and undesirable side effects.

[0079] The term "prodrug" denotes a derivative of a compound, which derivative, when administered to warm-blooded animals, e.g., humans, is converted into the compound (drug). For example, the enzymatic and/or chemical hydrolytic cleavage of a derivative compound of the present invention occurs in such a manner that the proven drug form is released, and the moiety or moieties split off remain nontoxic or are metabolized so that nontoxic metabolites are produced. For example, a carboxylic acid group can be esterified, e.g., with a methyl group or ethyl group to yield an ester. When an ester is administered to a subject, the ester is cleaved, enzymatically or non-enzymatically, reductively, oxidatively, or hydrolytically, to reveal the anionic group. An anionic group can be esterified with moieties (e.g., acyloxymethyl esters) which are cleaved to reveal an intermediate compound which subsequently decomposes to yield the active compound.

[0080] The prodrug can be prepared *in situ* during the isolation and purification of the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or by separately reacting the purified compound with a suitable derivatizing agent. For example, hydroxy groups can be converted into esters via treatment with a carboxylic acid in the presence of a catalyst. Examples of cleavable alcohol prodrug moieties include substituted or unsubstituted, branched or unbranched alkyl ester moieties, e.g., ethyl esters, alkenyl esters, di-alkylamino alkyl esters, e.g., dimethylaminoethyl ester, acylamino alkyl esters, acyloxy alkyl esters (e.g., pivaloyloxymethyl ester), aryl esters, e.g., phenyl ester, aryl-alkyl esters, e.g., benzyl ester, optionally substituted, e.g., with methyl, halo, or methoxy substituents aryl and aryl-alkyl esters, amides, alkyl amides, di-alkyl amides, and hydroxy amides.

[0081] The effectiveness of a particular prodrug can be determined using one or more analytical methods (e.g. pharmacokinetics, bioassays, *in vivo* efficacy studies, and the like) that are well-known to those of ordinary skill in the art.

[0082] A prodrug of a compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), may be prepared using routine chemical procedures. For example, a hydroxyl substituent on a compound of formula (I) can be substituted with -CO-alkyl, -CO₂alkyl, -CONH-alkyl, -CO-alkenyl, -CO₂-alkenyl, -CONH-alkenyl, -CO-aryl, -CO₂-aryl, -CONH-aryl, -CO-heterocycle, -CO₂-heterocycle, -CONH-heterocycle, or -PO₃H₂. Specific modifying groups of hydroxyl include, for example, acetyl, propionyl, isobutyryl, pivaloyl, palmitoyl, benzoyl, 4-methylbenzoyl, dimethylcarbamoyl, dimethylaminomethylcarbonyl, sulfo, alanyl, and fumaryl group.

[0083] An amino group can be substituted with -CO-alkyl, -CO₂-alkyl, -CO-alkenyl, -CO₂-alkenyl, -CO₂-aryl, -CO-aryl, -CO-heterocycle, -CO₂-heterocycle, or -PO₃H₂. The alkyl, alkenyl, aryl, and heterocycle moieties are optionally substituted by halogen, alkyl, hydroxyl, alkoxy, carboxy, amino, an amino acid residue, -PO₃H₂, -SO₃H, -OPO₃H₂, and -OSO₃H. Specific modifying groups of amino include, for example, *tert*-butyl, docosanoyl, pivaloylmethoxy, alanyl, hexylcarbamoyl, pentylcarbamoyl, 3-methylthio-1-(acetylamino)propylcarbonyl, 1-sulfo-1-(3-ethoxy-4-hydroxyphenyl)methyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl, tetrahydrofuranyl, and pyrrolidylmethyl.

[0084] Suitable modifying groups of carboxyl include, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pivaloyloxymethyl, carboxymethyl, dimethylaminomethyl, 1-(acetyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl, 1-(isopropylloxycarbonyloxy)ethyl, 1-(cyclohexyloxycarbonyloxy)ethyl, carboxymethyl, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl, benzyl, phenyl, o-tolyl, morpholinoethyl, *N,N*-diethylcarbamoylmethyl, and phthalidyl.

[0085] In any of the embodiments above, the phrase "salt" or "pharmaceutically acceptable salt" is intended to include nontoxic salts synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. For example, an inorganic acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid, or hydrobromic acid), an organic acid (e.g., oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methylsulfonic acid, or benzylosulfonic acid), an inorganic base (e.g.,

sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, or ammonium hydroxide), an organic base (e.g., methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, guanidine, choline, or cinchonine), or an amino acid (e.g., lysine, arginine, or alanine) can be used. Generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are typical. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, and Journal of Pharmaceutical Science, 66, 2-19 (1977). For example, they can be a salt of an alkali metal (e.g., sodium or potassium), alkaline earth metal (e.g., calcium), or ammonium salt.

[0086] The methods described herein comprise administering a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof in the form of a pharmaceutical composition. In particular, a pharmaceutical composition will comprise at least one compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The pharmaceutically acceptable excipients described herein, for example, vehicles, adjuvants, carriers or diluents, are well-known to those who are skilled in the art and are readily available to the public. Typically, the pharmaceutically acceptable carrier is one that is chemically inert to the active compounds and one that has no detrimental side effects or toxicity under the conditions of use.

[0087] The pharmaceutical compositions can be administered as oral, sublingual, transdermal, subcutaneous, topical, absorption through epithelial or mucocutaneous linings, intravenous, intranasal, intraarterial, intramuscular, intratumoral, peritumoral, interperitoneal, intrathecal, rectal, vaginal, or aerosol formulations. The pharmaceutical composition can be administered orally or intravenously.

[0088] The compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof can be administered orally to a subject in need thereof. Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice and include an additive, such as cyclodextrin (e.g., α -, β -, or γ -cyclodextrin, hydroxypropyl cyclodextrin) or polyethylene glycol (e.g., PEG400); (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions and gels. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

[0089] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound of formula (I) or a salt thereof can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[0090] Oils, which can be used in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene-polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (3) mixtures thereof.

[0091] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the inhibitors in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation

at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multidose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0092] The inhibitors may be made into injectable formulations. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Co., Philadelphia, Pa., Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986).

[0093] Topically applied compositions are generally in the form of liquids (e.g., mouthwash), creams, pastes, lotions and gels. Topical administration includes application to the oral mucosa, which includes the oral cavity, oral epithelium, palate, gingival, and the nasal mucosa. In some embodiments, the composition contains at least one active component and a suitable vehicle or carrier. It may also contain other components, such as an anti-irritant. The carrier can be a liquid, solid or semi-solid. In embodiments, the composition is an aqueous solution, such as a mouthwash. Alternatively, the composition can be a dispersion, emulsion, gel, lotion or cream vehicle for the various components. In one embodiment, the primary vehicle is water or a biocompatible solvent that is substantially neutral or that has been rendered substantially neutral. The liquid vehicle can include other materials, such as buffers, alcohols, glycerin, and mineral oils with various emulsifiers or dispersing agents as known in the art to obtain the desired pH, consistency and viscosity. It is possible that the compositions can be produced as solids, such as powders or granules. The solids can be applied directly or dissolved in water or a biocompatible solvent prior to use to form a solution that is substantially neutral or that has been rendered substantially neutral and that can then be applied to the target site. In embodiments of the invention, the vehicle for topical application to the skin can include water, buffered solutions, various alcohols, glycols such as glycerin, lipid materials such as fatty acids, mineral oils, phosphoglycerides, collagen, gelatin and silicone based materials.

[0094] The compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

[0095] The dose administered to the mammal, particularly human and other mammals, in accordance with the present invention should be sufficient to affect the desired response. One skilled in the art will recognize that dosage will depend upon a variety of factors, including the age, condition or disease state, predisposition to disease, genetic defect or defects, and body weight of the mammal. The size of the dose will also be determined by the route, timing and frequency of administration as well as the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular inhibitor and the desired effect. It will be appreciated by one of skill in the art that various conditions or disease states may require prolonged treatment involving multiple administrations.

[0096] The described methods comprise administering an effective amount of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof. An "effective amount" means an amount sufficient to show a meaningful benefit in an individual, e.g., promoting at least one aspect of tumor cell cytotoxicity (e.g., inhibition of growth, inhibiting survival of a cancer cell, reducing proliferation, reducing size and/or mass of a tumor (e.g., solid tumor)), or treatment, healing, prevention, delay of onset, halting, or amelioration of other relevant medical condition(s) associated with a particular cancer. The meaningful benefit observed in the patient can be to any suitable degree (10, 20, 30, 40, 50, 60, 70, 80, 90% or more). Optionally, one or more symptoms of the cancer are prevented, reduced, halted, or eliminated subsequent to administration of a compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or a pharmaceutically acceptable salt thereof, thereby effectively treating the cancer to at least some degree.

[0097] Effective amounts may vary depending upon the biological effect desired in the individual, condition to be treated, and/or the specific characteristics of the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or a pharmaceutically acceptable salt thereof, and the individual. In this respect, any suitable dose of the compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof can be administered to the patient (e.g., human), according to the type of cancer to be treated. Various general considerations taken into account in determining the "effective amount" are known to those of skill in the art and are described, e.g., in Gilman et al., eds., *Goodman And Gilman's: The Pharmacological Bases of Therapeutics*, 8th ed., Pergamon Press, 1990; and Remington's *Pharmaceutical Sciences*, 17th Ed., Mack Publishing Co., Easton, Pa., 1990, each of which is herein incorporated by reference. The dose of the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or a pharmaceutically acceptable salt thereof desirably comprises about 0.1 mg per kilogram (kg) of the body weight of the mammal (mg/kg) to about 400 mg/kg (e.g., about 0.75 mg/kg, about 5 mg/kg, about 30 mg/kg, about 75 mg/kg, about

100 mg/kg, about 200 mg/kg, or about 300 mg/kg). In another embodiment, the dose of the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), comprises about 0.5 mg/kg to about 300 mg/kg (e.g., about 0.75 mg/kg, about 5 mg/kg, about 50 mg/kg, about 100 mg/kg, or about 200 mg/kg), about 10 mg/kg to about 200 mg/kg (e.g., about 25 mg/kg, about 75 mg/kg, or about 150 mg/kg), or about 50 mg/kg to about 100 mg/kg (e.g., about 60 mg/kg, about 70 mg/kg, or about 90 mg/kg).

[0098] In an aspect, a compound formula (I) inhibits LDHA and/ or LDHB. Optionally, a compound of formula (I) is selective for LDHA and/ or LDHB relative to other dehydrogenases (e.g., GAPDH and PHGDH). For example, the compound can be at least 2 times (e.g., at least 5 times, at least 10 times, at least 20 times, at least 50 times, or at least 100 times) more selective for LDHA and/ or LDHB compared to one or more other dehydrogenases.

[0099] While elevated levels of LDHA are a marker for many types of cancer, the majority of which are glycolytic and/or hypoxic, LDHB can be overexpressed in some cancers (e.g., lung adenocarcinoma, prostate cancer). See, e.g., McClelland et al., Clin Cancer Res, 2013; 19(4): 773-784 and Leiblich et al., Oncogene, 2006; 25(20): 2953-2960. Thus, optionally, it is envisioned to provide a compound that can selectively inhibit LDHB or inhibit both LDHA and LDHB. Optionally, a compound of formula (I) can effectively inhibit LDHB. Therein, the compound may or may not have selectivity for LDHA, such that the inhibition is more selective for LDHA compared to LDHB or the inhibition of LDHA is about equal to the inhibition of LDHB or the inhibition is more selective for LDHB relative to LDHA.

[0100] Inhibition of LDHA and/or LDHB has been described in the art as a viable treatment of cancer. See, e.g., Billiard et al. (Cancer and Metabolism, 2013, 1(19): 1-17). Thus, certain invention compounds of formula (I), which includes compounds of formulas (Ia), (Ib), (Ic), and (Id), or a prodrug or pharmaceutically acceptable salt thereof, can be administered to a patient in need thereof to treat cancer. While not wishing to be bound by any particular theory, it is believed that inhibition of LDH stimulates mitochondrial respiration and reduces cellular proliferative and tumorigenic potential. Anti-cancer activity can be measured by any suitable method, including the assays described herein. In general, activity will be measured as a function of lactate output, % ECAR (extracellular acidification rate), which quantifies glycolysis, and/or % OCR (oxygen consumption rate), which is a measure of mitochondrial respiration.

[0101] The type of cancer is not particularly limited, but optionally, the cancer is characterized as hypoxic and/or highly glycolytic relative to normal tissue of the same type. "Hypoxic" cells as used herein relates to one or more cells that are exposed, transiently or permanently, to an oxygen partial pressure (pO₂) that is lower than the typical pO₂ in cells in tissue that is considered as normal or healthy. Hypoxic cells can include, for example, cells with reduced or no access to vasculature, such as in a solid tumor.

[0102] Examples of cancer treatable with the described method include cancers of the head and neck, eye, skin, mouth, throat, esophagus, chest, bone, lung, colon, sigmoid, rectum, stomach, prostate, breast, ovaries, kidney, liver, pancreas, brain, intestine, heart, or adrenals. More particularly, cancers include solid tumor, sarcoma, carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endothelial sarcoma, lymphangiosarcoma, lymphangioendothelial sarcoma, synovial sarcoma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, Kaposi's sarcoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, a blood-borne tumor, acute lymphoblastic leukemia, acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute nonlymphocytic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, or multiple myeloma. See, e.g., Harrison's Principles of Internal Medicine, Eugene Braunwald et al., eds., pp. 491-762 (15th ed. 2001). Optionally, the cancer is a solid tumor. Optionally, the cancer is selected from leukemia, melanoma, liver cancer, pancreatic cancer, lung cancer, colon cancer, brain cancer, ovarian cancer, breast cancer, prostate cancer, and renal cancer. Optionally, the cancer is liver cancer, pancreatic cancer, non-small cell lung cancer, breast cancer, or renal cancer.

[0103] Described is a method of treating a patient with cancer cells resistant to an anti-cancer agent, comprising administering to the patient an effective amount of the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or a pharmaceutically acceptable salt thereof, and the anti-cancer agent, whereby the compound, prodrug, or pharmaceutically acceptable salt thereof re-sensitizes the cancer cells to the anti-cancer agent. The cancer cell is the same as described herein. Optionally, the cancer cells are selected from leukemia, melanoma, liver cancer, pancreatic cancer, lung cancer, colon cancer, brain cancer, ovarian cancer, breast cancer, prostate cancer, and renal cancer. Optionally, the cancer cells are liver cancer, pancreatic cancer, non-small cell lung cancer, breast cancer, or renal cancer.

[0104] Optionally, the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or

a pharmaceutically acceptable salt thereof can be co-administered with an anti-cancer agent (e.g., a chemotherapeutic agent) and/or radiation therapy. Optionally, the method comprises administering an amount of a compound, prodrug, or salt that is effective to sensitize the cancer cells to one or more therapeutic regimens (e.g., chemotherapy or radiation therapy). The terms "co-administered" or "coadministration" refer to simultaneous or sequential administration. A compound may be administered before, concurrently with, or after administration of another compound.

[0105] One or more than one, e.g., two, three, or more anti-cancer agents can be administered. In this regard, we describe a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a combination of the compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or a pharmaceutically acceptable salt thereof and at least one anti-cancer agent (e.g., chemotherapeutic agent).

[0106] Examples of anti-cancer agents include platinum compounds (e.g., cisplatin, carboplatin, oxaliplatin), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, nitrogen mustard, thiotepa, melphalan, busulfan, procarbazine, streptozocin, temozolomide, dacarbazine, bendamustine), antitumor antibiotics (e.g., daunorubicin, doxorubicin, idarubicin, epirubicin, mitoxantrone, bleomycin, mytomicin C, plicamycin, dactinomycin), taxanes (e.g., paclitaxel and docetaxel), antimetabolites (e.g., 5-fluorouracil, cytarabine, premetrexed, thioguanine, floxuridine, capecitabine, and methotrexate), nucleoside analogues (e.g., fludarabine, clofarabine, cladribine, pentostatin, nelarabine), topoisomerase inhibitors (e.g., topotecan and irinotecan), hypomethylating agents (e.g., azacitidine and decitabine), proteasome inhibitors (e.g., bortezomib), epipodophyllotoxins (e.g., etoposide and teniposide), DNA synthesis inhibitors (e.g., hydroxyurea), vinca alkaloids (e.g., vincristine, vindesine, vinorelbine, and vinblastine), tyrosine kinase inhibitors (e.g., imatinib, dasatinib, nilotinib, sorafenib, sunitinib), monoclonal antibodies (e.g., rituximab, cetuximab, panetumumab, tositumomab, trastuzumab, alemtuzumab, gemtuzumab, ozogamicin, bevacizumab), nitrosoureas (e.g., carmustine, fotemustine, and lomustine), enzymes (e.g., L-Asparaginase), biological agents (e.g., interferons and interleukins), hexamethylmelamine, mitotane, angiogenesis inhibitors (e.g., thalidomide, lenalidomide), steroids (e.g., prednisone, dexamethasone, and prednisolone), hormonal agents (e.g., tamoxifen, raloxifene, leuprolide, bicalutamide, goserelin, flutamide), aromatase inhibitors (e.g., letrozole and anastrozole), arsenic trioxide, tretinoin, nonselective cyclooxygenase inhibitors (e.g., non-steroidal anti-inflammatory agents, salicylates, aspirin, piroxicam, ibuprofen, indomethacin, naprosyn, diclofenac, tolmetin, ketoprofen, nabumetone, oxaprozin), selective cyclooxygenase-2 (COX-2) inhibitors, or any combination thereof.

[0107] For purposes of the present disclosure, the term "patient" typically is directed to a mammal. For example, the subject can be any patient with a disease that requires chemotherapy and/or radiation therapy. Mammals include, but are not limited to, the order Rodentia, such as mice, and the order Logomorpha, such as rabbits. Optionally, the mammals are from the order Carnivora, including Felines (cats) and Canines (dogs), Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). Optionally, the mammals are of the order Primates, Ceboidea, or Simioida (monkeys) or of the order Anthropoidea (humans and apes). Optionally, the patient is a human.

[0108] Further described is a method of inhibiting lactate dehydrogenase A (LDHA) and/or lactate dehydrogenase B (LDHB) activity in a cell comprising administering a compound of formula (I), including a compound of formula (Ia), (Ib), (Ic), or (Id), or a prodrug or a pharmaceutically acceptable salt thereof to a cell, whereby activity of LDHA and/or LDHB is inhibited. LDHA and LDHB activity can be measured by any method known in the art for measuring enzyme inhibitions, including by the assays described herein. Typically, inhibition of LDHA and LDHB activity will be demonstrated by a decrease in lactate accumulation and/or an increase in pyruvate relative to a control sample.

[0109] The following examples are provided for further illustration, and should not be construed as limiting in any way. Note that compounds 1-18, 21-22, 25, 34-35, 49, 62-64, 66, 71, 74-75, 84-85, 90-112, 114-116, 121-122, 126, 128-130, 138, 140, 143-145, 149-150, 152, 155, 161, 179, 185, 190-191, 210-211, 275, 297-302, 399, 424-427, 441, 474, and 544 do not fall within the scope of the appended claims (and are therefore references examples only).

EXAMPLES

Example 1

[0110] This example describes a human LDHA primary biochemical assay employed in the characterization of test compounds.

[0111] Test compounds were placed in a Greiner Bio-One (Monroe, NC) 1536-well black solid bottom assay plate. 200 millimolar (mM) Tris HCl, pH 7.4, 100 micromolar (μ M) EDTA and 0.01% TWEEN-20™, final concentration, was used as the assay buffer. The LDHA reagent was 2 nanomolar (nM) Human LDHA (Meridian Life Science, Inc., Memphis, TN), final concentration, in assay buffer. The substrate reagent was 0.06 mM NADH and 0.2 mM sodium pyruvate, final concentration, in assay buffer. The resazurin/diaphorase coupling reagent was 0.037 mM resazurin and 0.133 milligrams per milliliter (mg/mL) diaphorase, final concentration, in assay buffer. The sequence of steps, amount and types of reagents, and time required for each step are set forth in Table 1. The inhibition of LDHA activity was measured by fluorescence emission.

Table 1

Sequence	Parameter	Value	Notes
1	Reagent	3 μ L	LDHA reagent
2	Compound	23 nL	Compound of formula (I)
3	Time	15 min	RT incubation
4	Reagent	1 μ L	Substrate reagent
5	Time	7 min	RT incubation
6	Reagent	1 μ L	Resazurin/diaphorase coupling reagent
7	Detector	Fluorescence (ex 525 nm/ em 598 nm)	VIEWLUX™ in end-point mode: 2 sec exp., 5000 excitation energy

Example 2

[0112] This example describes a human LDHB counterscreen biochemical assay employed in the characterization of test compounds.

[0113] Test compounds were placed in a Greiner Bio-One (Monroe, NC) 1536-well black solid bottom assay plate. 200 mM Tris HCl, pH 7.4, 100 μ M EDTA and 0.01% TWEEN-20™, final concentration, was used as the assay buffer. The LDHB reagent was 2 nM Human LDHB (Meridian Life Science, Inc., Memphis, TN), final concentration, in assay buffer. The substrate reagent was 0.13 mM NADH and 0.16 mM sodium pyruvate, final concentration, in assay buffer. The resazurin/diaphorase coupling reagent was 0.037 mM resazurin and 0.133 mg/mL diaphorase, final concentration, in assay buffer. The sequence of steps, amount and types of reagents, and time required for each step are set forth in Table 2. The inhibition of LDHB activity was measured by fluorescence emission.

Table 2

Sequence	Parameter	Value	Notes
1	Reagent	3 μ L	LDHB reagent
2	Compound	23 nL	Compound of formula (I)
3	Time	15 min	RT incubation
4	Reagent	1 μ L	Substrate reagent
5	Time	7 min	RT incubation
6	Reagent	1 μ L	Resazurin/diaphorase coupling reagent
7	Detector	Fluorescence (ex 525 nm/ em 598 nm)	VIEWLUX™ in end-point mode: 2 sec exp., 5000 excitation energy

Example 3

[0114] This example describes a human PHGDH counterscreen biochemical assay employed in the characterization of test compounds.

[0115] Test compounds were placed in a Greiner Bio-One (Monroe, NC) 1536-well black solid bottom assay plate. 50 mM TEA, pH 8.0, 10 mM MgCl₂, 0.05% BSA, and 0.01% TWEEN-20™, final concentration, was used as the assay buffer. The substrate reagent was 10 μ M EDTA, 0.625 mM glutamate, 500 nM human PSAT1, 500 nM human PSPH, 0.05 mM 3-phosphoglycerate, 0.1 mM resazurin, and 0.1 mg/mL diaphorase, final concentration, in assay buffer. The PHGDH reagent was 0.15 mM NAD⁺ and 10 nM human PHGDH, final concentration, in assay buffer. The sequence of steps, amount and types of reagents, and time required for each step are set forth in Table 3. The inhibition of PHGDH activity was measured by fluorescence emission.

Table 3

Sequence	Parameter	Value	Notes
1	Reagent	3 μ L	Substrate reagent
2	Compound	23 nL	Compound of formula (I)
3	Reagent	1 μ L	PHGDH reagent
4	Detector	Fluorescence (ex 525 nm/ em 598 nm)	VIEWLUX™ in end-point mode: 2 sec exp., 5000 excitation energy, use Δ between 0 and 30 min

Example 4

[0116] This example describes a human GAPDH counterscreen biochemical assay employed in the characterization of test compounds.

[0117] Test compounds were placed in a Greiner Bio-One (Monroe, NC) 1536-well black solid bottom assay plate. 105 mM Tris HCl, pH 7.4, 10 μ M EDTA, 1.27 mM KH_2PO_4 , 0.875 mM MgCl_2 , 0.0875% BSA, 0.01 mM DTT, and 0.01% TWEEN-20™, final concentration, was used as the assay buffer. The substrate reagent was 0.48 mM glyceraldehyde 3-phosphate, 0.06 mM resazurin, and 0.21 mg/mL diaphorase, final concentration, in assay buffer. The GAPDH reagent was 0.007 mM NAD^+ and 2.5 nM human GAPDH, final concentration, in assay buffer. The sequence of steps, amount and types of reagents, and time required for each step are set forth in Table 4. The inhibition of GAPDH activity was measured by fluorescence emission.

Table 4

Sequence	Parameter	Value	Notes
1	Reagent	3 μ L	Substrate reagent
2	Compound	23 nL	Compound of formula (I)
3	Reagent	1 μ L	GAPDH reagent
4	Detector	Fluorescence (ex 525 nm/ em 598 nm)	VIEWLUX™ in kinetic mode: 1 sec exp., 5000 excitation energy, use Δ between 0 and 20 min

Example 5

[0118] This example describes cell-based metabolite assay by mass spectrometry (MS) employed in the characterization of test compounds.

[0119] The sequence of steps, amount and types of reagents, and time required for each step are set forth in Table 5.

Table 5

Sequence	Parameter	Value	Notes
1	Reagent	Snu398 cells	100k/well in 100 μ L RPMI 10% FBS - phenol red
2	Time	24 h	37 °C, 5% CO_2 incubation
3	Reagent	Wash	Aspirate media and replace with fresh
4	Reagent	Compound	Dose LDHA inhibitors/controls in media
5	Time	48 h	37 °C, 5% CO_2 incubation
6	Reagent	Media	Aspirate 75 μ L of media and collect in separate plate. Snap freeze and store at -80 °C. Pyruvate/lactate/NADH ion counts collected by Quintara Discovery, Inc. using MS-MS.

Example 6

[0120] This example describes a cell-based metabolite assay by colorimetric/fluorometric detection employed in the characterization of test compounds.

[0121] Cell-based HT Lactate assay is a miniaturized Biovision Lactate Colorimetric/Fluorometric Assay Kit (Cat# K607-100). The assay is roughly a 3.5 hour assay run in a 1536 plate format. Cell number optimization should be run for each cell line to achieve an optimal number in which lactate production equals roughly 90% of the standard curve range. Cell number per well optimization has been performed with the following cell lines: MiaPaCa2 - 500 cells/well, SNU398 - 500 cells / well, and P493 - 500 cells/well. The sequence of steps, amount and types of reagents, and time required for each step are set forth in Table 6.

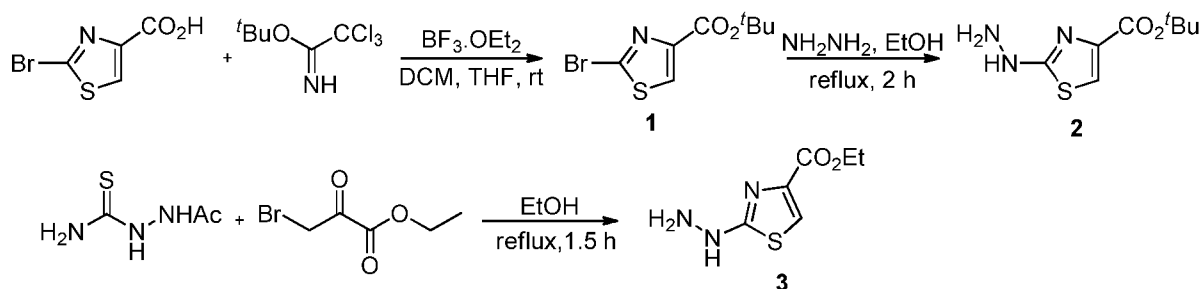
Table 6

Sequence	Parameter	Value	Notes
1	Reagent	MiaPaCa2 cells	500/well in 4 μ L in DMEM 4.5 g/L Glucose, - Glutamate, - FBS, - Phenol Red
2	Reagent	Compound	Dose LDHA inhibitors with pin tool
3	Time	2.5 hr	37 $^{\circ}$ C, 5% CO ₂ incubation
4	Reagent	Compound	2 μ L / well
5	Time	48 h	RT
6	Read	Media	Absorbance (570 nm) and Fluorescence (Ex/Em = 535/590 nm)

Example 7

[0122] This example describes the preparation of *tert*-butyl 2-bromothiazole-4-carboxylate **1**.

SCHEME 1



[0123] *Tert*-butyl 2,2,2-trichloroacetimidate (17.20 ml, 96 mmol, 2 eq) was added to a stirred suspension of 2-bromothiazole-4-carboxylic acid (10 g, 48.1 mmol, 1 eq) in dichloromethane (DCM) (100 mL) and tetrahydrofuran (THF) (50 mL), followed by dropwise addition of $\text{BF}_3 \cdot \text{OEt}_2$ (0.938 ml, 7.40 mmol, 10 mol%). The mixture was stirred at room temperature for 16 h, concentrated, quenched slowly with a saturated bicarbonate solution, and extracted with ethyl acetate. The organic layer was washed with saturated bicarbonate and brine, then dried, and the crude product was purified in a Biotage (Charlotte, NC) flash system eluting with 5-30% ethyl acetate in hexanes over 12 column volumes. The product fraction was concentrated to provide *tert*-butyl 2-bromothiazole-4-carboxylate **1** as a white solid (10.4 g, 82%).

Example 8

[0124] This example describes the preparation of *tert*-butyl 2-hydrazinylthiazole-4-carboxylate **2**. See Scheme 1.

[0125] A solution of *tert*-butyl 2-bromothiazole-4-carboxylate **1** (10.96 g, 41.5 mmol, 1 eq) from Example 1 and hydrazine hydrate (13 ml, 415 mmol, 10 eq) in EtOH (80 mL) was refluxed for 2 hr. After completion of the reaction, the solvent was removed and ice water was added. The precipitate formed was collected by filtration, washed with cold water, and dried under air. The crude product (*tert*-butyl 2-hydrazinylthiazole-4-carboxylate **2**) was pure enough to be used for the following reaction.

Example 9

[0126] This example describes the preparation of ethyl 2-hydrazinylthiazole-4-carboxylate **3**. See Scheme 1.

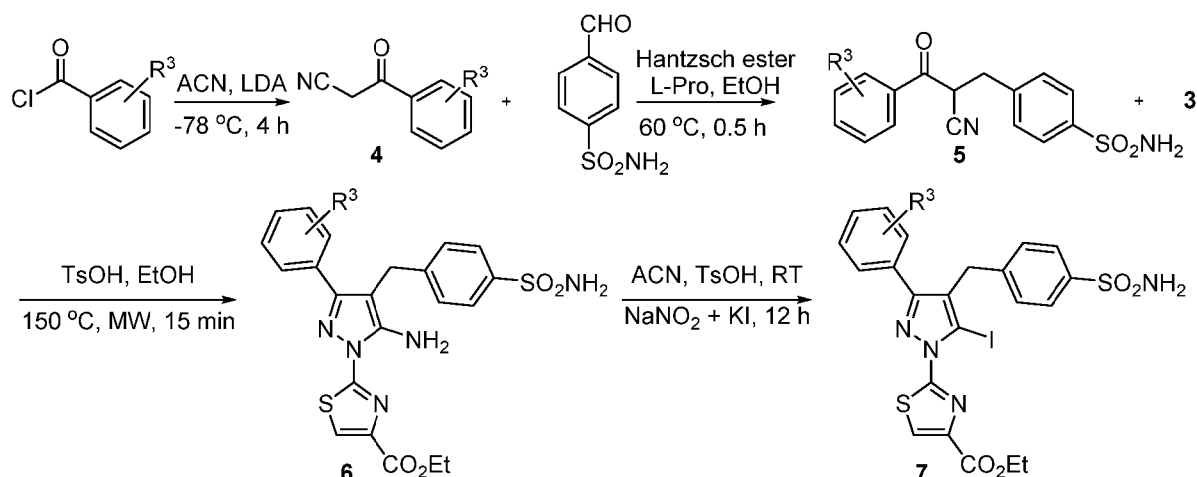
[0127] Ethyl bromopyruvate (15.71 ml, 113 mmol) was added to a suspension of 2-acetylhydrazinecarbothioamide

(15 g, 113 mmol) in ethanol (200 mL) and stirred at room temperature for 30 minutes until the solution became clear, then refluxed for 1.5 h. The solution was then concentrated and agitated with 20 mL of MeOH and 300 mL of ether. The yellow precipitate was collected by filtration, washed with ether, and dried to obtain a yellow solid (ethyl 2-hydrazinylthiazole-4-carboxylate **3**) as HBr salt.

Example 10

[0128] This example describes a general procedure for the synthesis of substituted benzoyl acetonitriles **4**.

SCHEME 2



[0129] Acetonitrile (ACN) (5.33 mL, 102 mmol, 2 eq) was added dropwise to a cooled solution of 1 molar lithium diisopropylamide (LDA) (102 mL, 102 mmol, 2 eq) in THF (40 mL) at -78 °C. The reaction mixture was stirred for 30 minutes, and then a solution of an acid chloride (51.0 mmol, 1 eq) in 20 mL of THF was added dropwise over 15 minutes. The reaction was allowed to come to room temperature over 4 h and then quenched with 1 M (molar) HCl. The product was extracted with ethyl acetate. The organic layer was subsequently washed with water and brine and dried over MgSO₄. The crude product was purified on Biotage (Charlotte, NC) flash system eluting with 5-75% ethyl acetate in hexanes over 12 column volumes to obtain a substituted benzoyl acetonitrile **4** as a yellow solid.

Example 11

[0130] This example describes a general procedure for the synthesis of 4-(2-cyano-3-oxo-3-arylpropyl)benzenesulfonamide **5**. See Scheme 2.

[0131] 2,6-Dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (Hantzsch ester) (12.21 g, 48.2 mmol, 1.4 eq) and L-proline (0.793 g, 6.89 mmol, 20 mol%) were added to a solution of 3-oxo-3-phenyl-propanenitrile **4** (34.4 mmol, 1 eq) and 4-formylbenzenesulfonamide (7.02 g, 37.9 mmol, 1.1 eq) in ethanol (150 mL). The mixture was stirred at 60 °C for 30 minutes. The mixture was then cooled, mixed with silica gel, concentrated, and purified on a Biotage (Charlotte, NC) flash system with 20-100% ethyl acetate in hexanes over 6 column volumes then with 100% ethyl acetate over 8 column volumes to obtain 4-(2-cyano-3-oxo-3-arylpropyl)benzenesulfonamide **5** as a white solid.

Example 12

[0132] This example describes a general procedure for the synthesis of 2-(5-amino-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **6**. See Scheme 2.

[0133] A mixture of ethyl 2-hydrazinylthiazole-4-carboxylate hydrogen bromide salt (**3**, 1.5 g, 5.59 mmol, 1 eq), 4-(2-cyano-3-oxo-3-arylpropyl)benzenesulfonamide (5.59 mmol, 1 eq) and tosylic acid (2.128 g, 11.19 mmol, 2 eq) in ethanol (15 mL) was heated in a microwave for 15 minutes. The precipitate formed was collected by filtration and washed with cold ethanol to obtain pure product (ethyl 2-(5-amino-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **6**) as a yellow solid.

Example 13

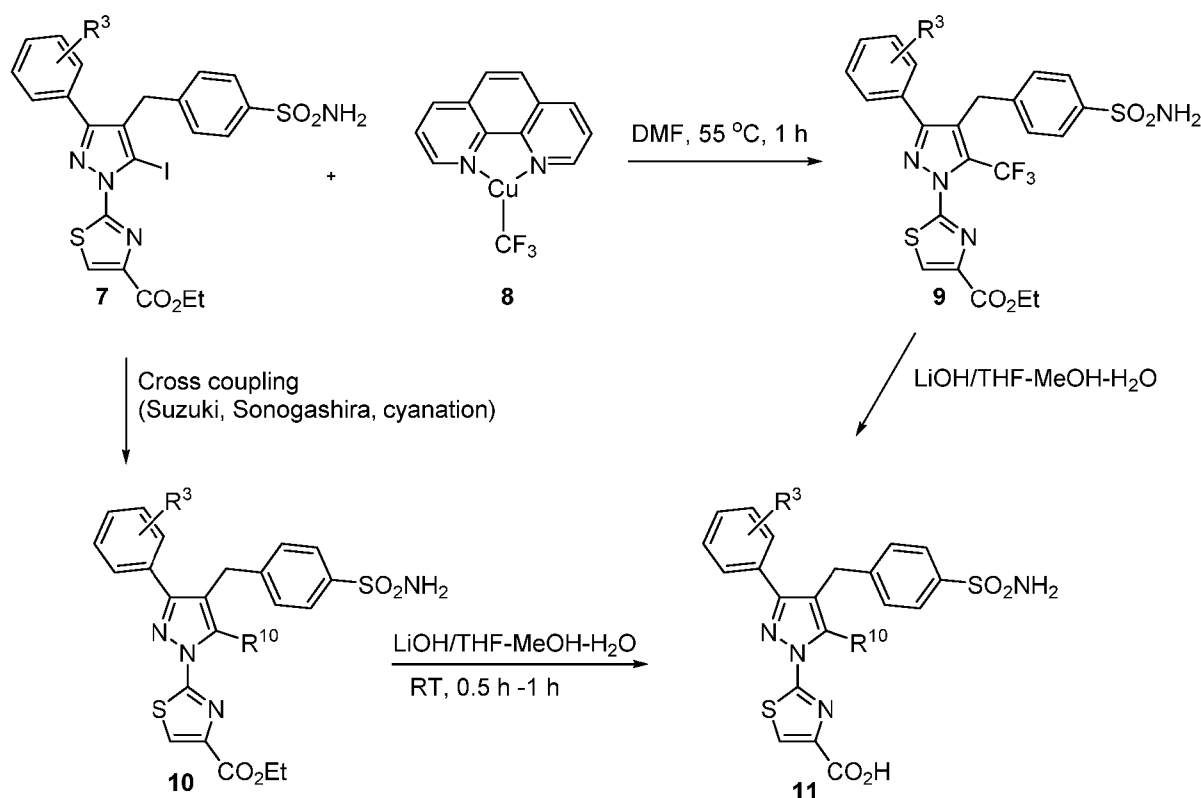
[0134] This example describes a general procedure for the synthesis of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **7**. See Scheme 2.

[0135] Tosic acid (5.37 g, 28.2 mmol, 3.5 eq) was added to a suspension of ethyl 2-(5-amino-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **6** (8.07 mmol, 1 eq) in ACN (100 mL) and stirred for 10 minutes. During this period, the solution became clear, then a premixed solution of NaNO₂ (1.113 g, 16.13 mmol, 2 eq) and KI (4.02 g, 24.20 mmol, 3 eq) in 10 mL water was added dropwise over a period of 10-15 minutes at room temperature. The reaction mixture was allowed to stir at room temperature overnight. After completion of the reaction, the excess solvent was removed under reduce pressure, and the crude product was extracted with ethyl acetate. The organic layer was subsequently washed with saturated sodium thiosulfate solution, water, and brine. The crude product was purified on a Biotage (Charlotte, NC) flash system using a high performance column eluting with either 1-15% acetone in dichloromethane or 1-100% ethyl acetate in hexanes over 20 column volumes to obtain pure products.

Example 14

[0136] This example describes a general procedure for the trifluoromethylation of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates.

SCHEME 3



[0137] A mixture of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **7** (0.4 g, 0.673 mmol) **7** and 1,10-phenanthroline(trifluoromethyl)copper(I) **8** (0.316 g, 1.009 mmol, 1.5 eq) was degassed with argon, then DMF (2 mL) was added and stirred at 55 °C for 1 h. The reaction mixture was diluted with ethyl acetate and washed with 1 molar HCl, water, and brine. The organic layer was dried with MgSO₄, concentrated, and purified on a Biotage (Charlotte, NC) flash system eluting with 20-100% ethyl acetate in hexanes over 12 column volumes to obtain an ethyl 2-(5-trifluoromethyl-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **9** as a white solid.

Example 15

[0138] This example describes a general procedure for the Suzuki coupling of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates.

benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates. See Scheme 3.

[0139] In a sealed microwave vial, 2 molar Na_2CO_3 (0.17 mL, 0.336 mmol, 2 eq) was added to a mixture of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **7** (0.168 mmol, 1 eq), SILIACAT™ DPP-Pd (0.1 g), boronic acid (0.336 mmol, 2 eq) in dimethyl ether (DME) (2 mL), then heated in a microwave for 30 minutes at 130 °C. The reaction mixture was concentrated by blowing forced air. The residue was taken up in DMF (2 mL) and stirred with a silica-bound DMT, followed by filtering through a thiol resin cartridge to remove any leached palladium. Finally the compounds were purified on a preparative HPLC to obtain pure coupling products **10**.

Example 16

[0140] This example describes a general procedure for the Sonogashira coupling of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates (**7**). See Scheme 3.

[0141] A mixture of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **7** (0.202 mmol, 1 eq), bis(triphenylphosphine)palladium(II) chloride (0.014 g, 0.020 mmol, 10 mol%), and CuI (3.84 mg, 0.020 mmol, 10 mol%) in THF (1 mL) was added triethylamine (TEA) (0.169 mL, 1.211 mmol, 6 eq) followed by the alkyne (0.404 mmol, 2 eq) under a nitrogen atmosphere. The vial was sealed and stirred at 80 °C for 4 h. After completion of the reaction, the product was extracted with ethyl acetate and the organic layer was washed with 1 molar HCl and brine. The crude product was purified on a Biotage (Charlotte, NC) flash system eluting with 20-100% ethyl acetate or in preparative HPLC to obtain pure coupling products **10**.

Example 17

[0142] This example describes a general procedure for the cyanation of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates. See Scheme 3.

[0143] A mixture of ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **7** (0.168 mmol, 1 eq) and CuCN (0.023 g, 0.252 mmol, 1.5 eq) in dimethylsulfoxide (DMSO) (0.5 mL) was heated in a microwave for 0.5 h at 160 °C. The product was extracted with ethyl acetate. The organic layer was washed with a saturated bicarbonate solution, water, and brine. The crude product was purified on a Biotage (Charlotte, NC) flash system eluting with 30-100% ethyl acetate in hexanes over 15 column volumes to obtain pure products **10**.

Example 18

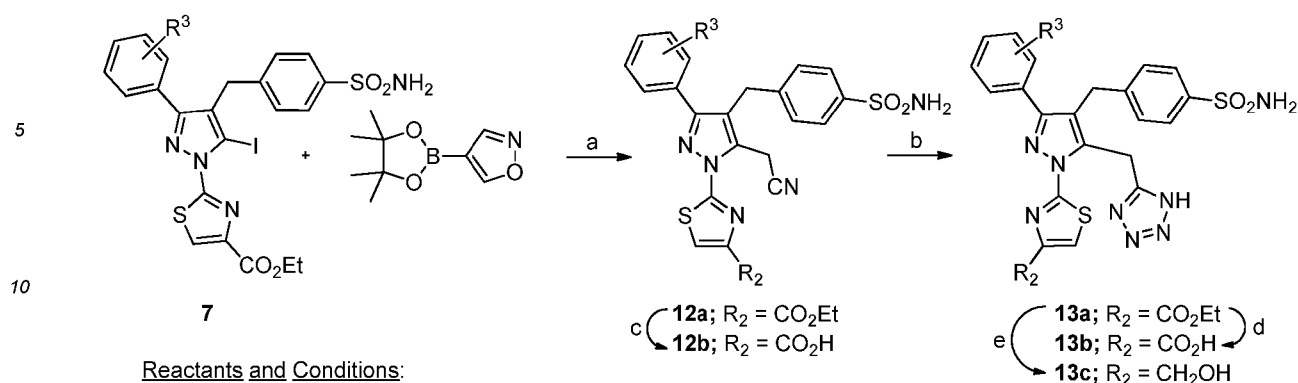
[0144] This example describes a general procedure for the hydrolysis of the ethyl and methyl esters **10**. See Scheme 3.

[0145] A 1.5 molar solution of LiOH in water was added to a solution of ethyl 2-(3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **10** (0.252 mmol, 1 eq) in THF/MeOH (3 mL/1.5 mL) and stirred at room temperature for 0.5 - 1 h. After completion of the reaction, the solvent was evaporated under reduced pressure, and the residue was taken up in DMSO. Finally the compounds **11** were purified on preparative HPLC.

Example 19

[0146] This example describes a general procedure for the ethyl 2-(5-(cyanomethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **12a** (Scheme 4, Step a).

SCHEME 4



[0147] DMSO (2.5 mL) was added to a solution of KF (0.147 g, 2.52 mmol, 3 eq) in 0.9 mL water, followed by ethyl 2-(5-iodo-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **7** (0.841 mmol, 1 eq), $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (0.137 g, 0.168 mmol, 20 mol%), and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (0.246 g, 1.262 mmol, 1.5 eq). The mixture was bubbled with argon for 2 minutes. Next, the vial was sealed and stirred on a preheated heating block at 130 °C for 3 h, then another portion of 0.9 mL of water was added, and the mixture was stirred at 130 °C for another 21 h. After completion of the reaction, a silica-bound metal scavenger was added and stirred for 30 minutes. The reaction mixture was diluted with ethyl acetate and filtered through a silica plug. The filtrate was washed with water, saturated ammonium chloride, and brine. The crude product was purified on a Biotage (Charlotte, NC) flash system eluting with 20-100% ethyl acetate in hexanes to obtain pure product ethyl 2-(5-(cyanomethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **12a** as a white solid.

Example 20

[0148] This example describes a general procedure for the 2-(5-(cyanomethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **12b**. See Scheme 4, Step c.

[0149] A mixture of ethyl 2-(5-(cyanomethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **12a** (0.049 mmol) and hydroxytrimethylstannane (0.018 g, 0.099 mmol, 2 eq) in dichloroethane (DCE) was stirred at 80 °C for 24 h. The solvent was removed by forced air. The residue was taken up in DMSO and passed through a sulfonic acid cartridge to remove the trimethyl tin hydroxide. The crude product 2-(5-(cyanomethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **12b** was purified on HPLC.

Example 21

[0150] This example describes a general procedure for the synthesis of tetrazoles **13a**. See Scheme 4, Step b.

[0151] A mixture of ethyl 2-(5-(cyanomethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **12a** (0.414 mmol, 1 eq), NH_4Cl (0.066 g, 1.241 mmol, 3 eq), and NaN_3 (0.081 g, 1.241 mmol, 3 eq) in DMF (2 mL) was heated in a microwave for 2 h at 125 °C. The product was purified on a reverse phase flash system to obtain pure products **13a**.

Example 22

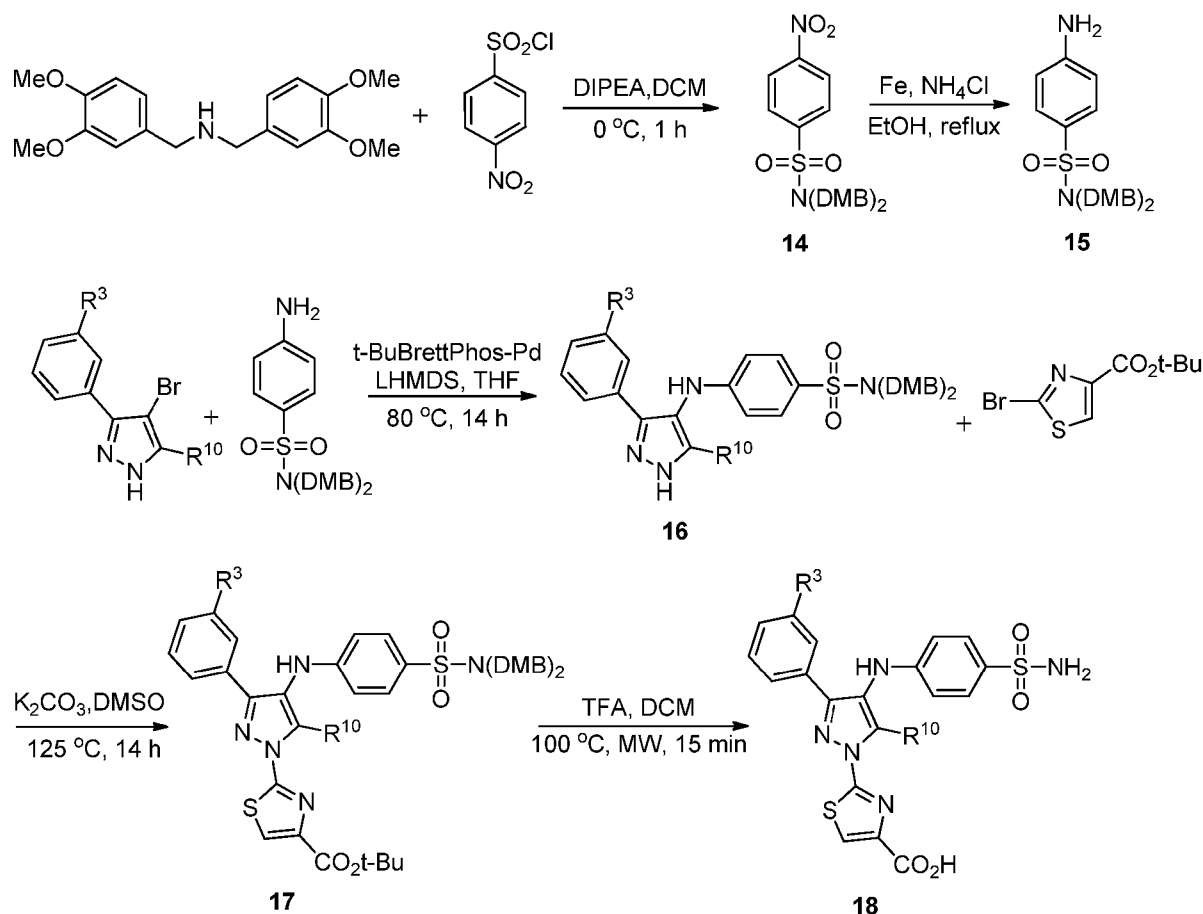
[0152] This example describes a general procedure for the synthesis of tetrazole derivatives **13c**. See Scheme 4, Step e.

[0153] A solution of ethyl 2-(5-(1H-tetrazol-5-ylmethyl)-3-aryl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **13a** (0.091 mmol, 1 eq) in THF (3 mL) was added to LiAlH_4 (0.363 mL, 0.363 mmol, 4 eq) upon cooling. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The residue was suspended in a DCM/MeOH mixture and filtered through a silica plug. The crude product **13c** obtained after evaporating the solvent was purified on a preparative HPLC.

Example 23

[0154] This example describes the preparation of *N,N*-bis(3,4-dimethoxybenzyl)-4-nitrobenzenesulfonamide **14**. See Scheme 5, first step.

SCHEME 5



[0155] 4-Nitrobenzene-1-sulfonyl chloride (1.746 g, 7.88 mmol, 1 eq) was added to a solution of bis(3,4-dimethoxybenzyl)amine (2.5 g, 7.88 mmol, 1 eq) and Hünig's base (2.75 ml, 15.75 mmol, 2 eq) in DCM (15 ml) upon cooling. The reaction mixture was stirred at room temperature for 1 h. The crude product obtained after evaporating the solvent was purified on a Biotage (Charlotte, NC) flash system eluting with 25-100% ethyl acetate in hexanes to obtain *N,N*-bis(3,4-dimethoxybenzyl)-4-nitrobenzenesulfonamide **14** as a yellow solid. Yield (2.85 g, 72%).

Example 24

[0156] This example describes the preparation of 4-amino-*N,N*-bis(3,4-dimethoxybenzyl)benzenesulfonamide **15**. See Scheme 5, second step.

[0157] A solution of ammonium chloride (0.8 g, 14.92 mmol) in 10 mL water and iron powder (1.389 g, 24.87 mmol) was added to a suspension of *N,N*-bis(3,4-dimethoxybenzyl)-4-nitrobenzenesulfonamide **14** (2.5 g, 4.97 mmol, 1 eq) in ethanol (50 mL). The reaction mixture was stirred overnight at 85 °C. The reaction mixture was diluted with methanol and filtered through a pad of CELITE™. The filtrate was concentrated, neutralized with bicarbonate, and extracted with DCM. The DCM layer was washed with bicarbonate and brine. The crude product was purified on a Biotage (Charlotte, NC) flash system eluting with 1-15% MeOH (ammoniated) in DCM to obtain 4-amino-*N,N*-bis(3,4-dimethoxybenzyl)benzenesulfonamide **15** as a white solid. Yield (2.2 g, 94%).

Example 25

[0158] This example describes a general preparation of *N,N*-bis(3,4-dimethoxybenzyl)-4-((3-aryl-1H-pyrazol-4-yl)amino)-benzenesulfonamide **16**. See Scheme 5, third step.

[0159] A mixture of 4-bromo-3-aryl-1H-pyrazole (1.569 mmol, 1 eq), 4-amino-*N,N*-bis(3,4-dimethoxybenzyl)benzenesulfonamide **15** (1.038 g, 2.197 mmol, 1.4 eq), *t*-butyl BrettPhos (CAS # 1160861-53-9) (Stem Chemicals, Newburyport, MA, Catalog # 15-1164) (0.038 g, 0.078 mmol, 5 mol%) and *t*-butyl BrettPhos Palladacycle (CAS # 1148148-01-9) (Stem Chemicals, Newburyport, MA, Catalog # 46-0325) (0.067 g, 0.078 mmol, 5 mol%) in a microwave (MW) vial was purged with argon, and then THF (4 ml) was added, followed by lithium hexamethyldisilazide (LHMDS) (2.62 ml, 3.92 mmol, 2.5 eq). The mixture was stirred in a preheated block at 80 °C for 14 h. The reaction mixture was poured into acidified water (1 molar HCl) and extracted with ethyl acetate. The organic layer was washed with water and brine. The crude product *N,N*-bis(3,4-dimethoxybenzyl)-4-((3-aryl-1H-pyrazol-4-yl)amino)-benzenesulfonamide **16** was purified on a Biotage (Charlotte, NC) flash system eluting with 30-100% ethyl acetate in hexanes.

Example 26

[0160] This example describes a general preparation of *tert*-butyl 2-(4-((4-(*N,N*-bis(3,4-dimethoxybenzyl)sulfamoyl)phenyl)-amino)-3-aryl-1H-pyrazol-1-yl)thiazole-4-carboxylate **17**. See Scheme 5, fourth step.

[0161] A mixture of *N,N*-bis(3,4-dimethoxybenzyl)-4-((3-aryl-1H-pyrazol-4-yl)amino)benzenesulfonamide **16** (0.732 mmol, 1 eq), K₂CO₃ (0.202 g, 1.464 mmol), and *tert*-butyl 2-bromothiazole-4-carboxylate (0.213 g, 0.805 mmol, 1.1 eq) in DMSO (1.5 mL) was stirred for 12 h at 125 °C. The reaction mixture was diluted with ethyl acetate and filtered through a pad of CELITE™. The filtrate was washed with saturated ammonium chloride and brine. The crude product *tert*-butyl 2-(4-((4-(*N,N*-bis(3,4-dimethoxybenzyl)sulfamoyl)phenyl)-amino)-3-aryl-1H-pyrazol-1-yl)thiazole-4-carboxylate **17** was purified on a Biotage (Charlotte, NC) flash system eluting with 40-100% ethyl acetate in hexanes.

Example 27

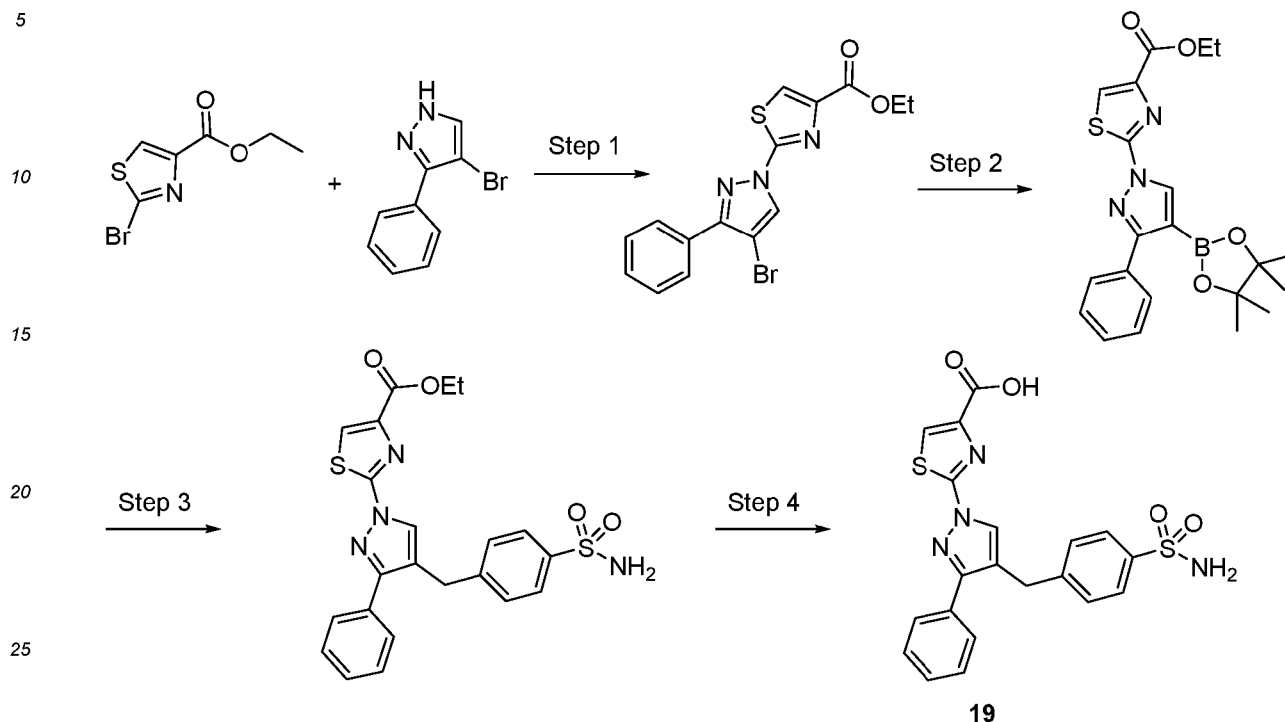
[0162] This example describes a general procedure for the deprotection of (*N,N*-bis(3,4-dimethoxybenzyl) and *t*-butyl groups and synthesis of compounds **18**. See Scheme 5, fifth step.

[0163] *Tert*-butyl 2-(4-((4-(*N,N*-bis(3,4-dimethoxybenzyl)sulfamoyl)-phenyl)amino)-3-aryl-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.251 mmol) **17** in a mixture of DCM (1.5 mL) and trifluoroacetic acid (TFA) (1.5 mL) was heated in microwave at 100 °C for 15 min at normal absorption. The solvent was removed by forced air, the crude product **18** was dissolved in DMSO, and then purified using preparative HPLC.

Example 28

[0164] This example describes the synthesis of 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **19** in an embodiment of the invention.

SCHEME 6



STEP 1: Synthesis of ethyl 2-(4-bromo-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0165] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (1058 mg, 4.48 mmol), 3-bromo-4-phenyl-1H-pyrazole (995 mg, 4.48 mmol), and K_2CO_3 (929 mg, 6.72 mmol). The tube was sealed and DMSO (4 ml) was added. The mixture was heated at 120 °C for 4 h. The mixture was poured into vigorously stirred H_2O (100 mL), and the solid was filtered, triturated with H_2O , and dried. The solid was re-dissolved in EtOAc and filtered. Some undissolved material was the hydrolyzed acid. The filtrate was concentrated and triturated with ca. 3% EtOAc/hexane to give ethyl 2-(4-bromo-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (1329 mg, 3.51 mmol, 78% yield).

STEP 2: Synthesis of ethyl 2-(3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0166] In a microwave tube was placed ethyl 2-(4-bromo-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (378 mg, 1 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (330 mg, 1.300 mmol), $PdCl_2(dppf)$ (73.2 mg, 0.100 mmol), and potassium acetate (294 mg, 3.00 mmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). Then, 1,4-dioxane (4 ml) was added and stirred at 95 °C (pre-heated) for overnight. The mixture was diluted with EtOAc and filtered through CELITE™ and eluted with EtOAc. After removal of the solvent, the product was purified by silica gel chromatography using 10-25% EtOAc/hexane as the eluent to give product, which was triturated with a small amount of hexane and then dried to give ethyl 2-(3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (540 mg, 0.762 mmol, 76% yield) as solid. The product contained about 40% of reduction (de-Br) product, which was used for the next step without further purification.

STEP 3: Synthesis of ethyl 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0167] In a microwave tube was placed ethyl 2-(3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (70.9 mg, 0.1 mmol), 4-(bromomethyl)benzenesulfonamide (25.01 mg, 0.100 mmol), and $Pd(Ph_3P)_4$ (11.56 mg, 10.00 μ mol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2N $Na_2CO_3(aq)$ (0.3 mL, 0.6 mmol, 6 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na_2SO_4) and filtered. After

removal of the solvent, the product was purified by silica gel chromatography using 30-60% EtOAc/hexane as the eluent to give ethyl 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (29 mg, 0.062 mmol, 61.9% yield) as a white solid.

STEP 4: Synthesis of 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (**19**)

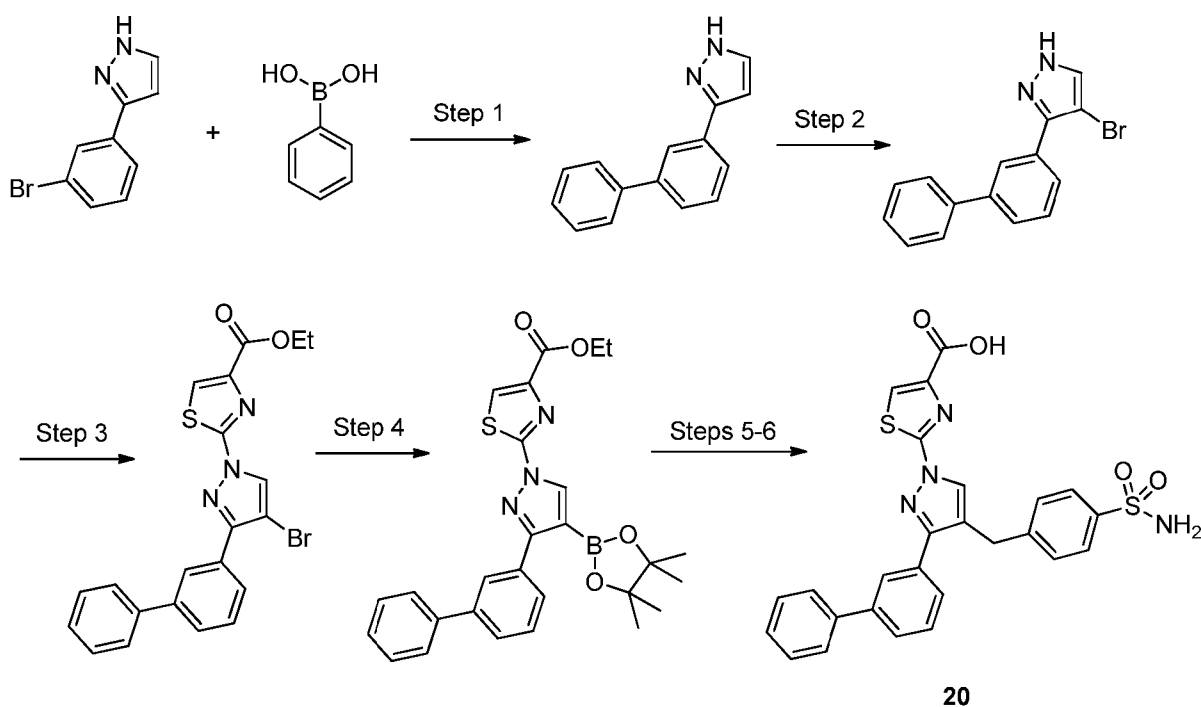
[0168] To a solution of ethyl 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (26 mg, 0.055 mmol) in THF (1 mL) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1N HCl_(aq) (ca. 0.6-0.65 mL) was added and until the pH of aqueous layer was around 4. Then, hexane (5 mL) was added and the resulting solid was filtered, triturated with H₂O (1 mL x 2), hexane (2 mL x 2), and dried to give 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **19** (21 mg, 0.048 mmol, 86% yield).

[0169] The compound was pure enough and was submitted (19 mg) to system directly. ¹H NMR (400 MHz, DMSO-d₆) δ 13.18 (s, 1H), 8.21 (s, 2H), 7.80 - 7.71 (m, 2H), 7.72 - 7.63 (m, 2H), 7.52 - 7.37 (m, 5H), 7.28 (s, 2H), 4.15 (s, 2H); MS (M+H)⁺ = 441.

Example 29

[0170] This example describes the synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **20** in an embodiment of the invention.

SCHEME 7



STEP 1: Synthesis of 3-([1,1'-biphenyl]-3-yl)-1H-pyrazole

[0171] In a 2-neck flask was placed 3-(3-bromophenyl)-1H-pyrazole (1115 mg, 5 mmol), phenylboronic acid (914 mg, 7.50 mmol), PdCl₂(dppf) (366 mg, 0.500 mmol), and K₂CO₃ (2073 mg, 15.00 mmol). The air was removed and re-filled with N₂ (2-3 times). Then a mixture of 1,4-dioxane (12 mL, ratio: 2.000) and water (6 mL, ratio: 1.000) was added and stirred at 95 °C (pre-heated) for 5 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 30-40-50% EtOAc/hexane as the eluent to give 3-([1,1'-biphenyl]-3-yl)-1H-pyrazole (1050 mg, 4.77 mmol, 95% yield).

STEP 2: Synthesis of 3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazole

[0172] To a solution of 3-([1,1'-biphenyl]-3-yl)-1H-pyrazole (1050 mg, 4.77 mmol) in DMF (7.5 ml) was added NBS (891 mg, 5.01 mmol). The mixture was stirred at room temperature for 1 h. The mixture was poured into EtOAc/H₂O/sat. Na₂CO_{3(aq)} (50 mL/30 mL/20 mL). The organic layer was washed with H₂O (50 mL), dried (Na₂SO₄), and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 20-30% EtOAc/hexane as the eluent to give 3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazole (1200 mg, 4.01 mmol, 84% yield).

STEP 3: Synthesis of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0173] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (472 mg, 2 mmol), 3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazole (596 mg, 2.000 mmol), and K₂CO₃ (415 mg, 3.00 mmol). The tube was sealed and DMSO (4 ml) was added. The mixture was heated at 130 °C for 4 h. The mixture was poured into H₂O (100 mL), and the solid was filtered, triturated with H₂O, and dried. The solid was dissolved in EtOAc and filtered. The undissolved material was the hydrolyzed acid (**21**, ca. 110 mg with a small amount of impurity). The filtrate was concentrated and triturated with ca. 5% EtOAc/hexane to give 420 mg of pure product. The solution was concentrated and combined with the extraction from the original aqueous layer and then purified by silica gel chromatography using 20-30% EtOAc/hexane as the eluent to give another 210 mg of product. Total 630 mg of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazol-1-yl)thiazole-4-carboxylate (630 mg, 1.387 mmol, 69.3% yield) was obtained.

STEP 4: Synthesis of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0174] In a microwave tube was placed ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazol-1-yl)thiazole-4-carboxylate (454 mg, 1 mmol), 4,4,4',4',5,5,5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (381 mg, 1.500 mmol), PdCl₂(dppf) (73.2 mg, 0.100 mmol), and potassium acetate (294 mg, 3.00 mmol). The tube was sealed and air was removed and re-filled with N₂ (2-3 times). Then, 1,4-dioxane (4 ml) was added and stirred at 95 °C (pre-heated) for overnight. The mixture was diluted with EtOAc and filtered through CELITE™ and eluted with EtOAc. After removal of the solvent, the product was purified by silica gel chromatography using 10-25% EtOAc/hexane as the eluent to give product, which was triturated with a small amount of hexane and then dried to give ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (450 mg, 0.494 mmol, 49.4% yield) as solid. The product contained about 45% of reduction (de-Br) product.

STEP 5: Synthesis of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0175] In a microwave tube was placed ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (91 mg, 0.1 mmol), 4-(bromomethyl)benzenesulfonamide (25.01 mg, 0.100 mmol), and Pd(Ph₃P)₄ (11.56 mg, 10.00 μmol). The tube was sealed and air was removed and re-filled with N₂ (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2N Na₂CO_{3(aq)} (0.3 mL, 0.6 mmol, 6 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 30-60% EtOAc/hexane as the eluent to give ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **20** (35 mg, 0.064 mmol, 64.3% yield) as a white solid. Some of the reduction product (ca. 30 mg) from either the reaction and/or from a previous step was collected and subjected to hydrolysis to give **22** (see Example 31, Scheme 7A).

STEP 6: Synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (**20**)

[0176] To a solution of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (35 mg, 0.064 mmol) in THF (1 ml) was added LiOH(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1N HCl(aq) (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added and the resulting solid was filtered, triturated with H₂O (1 mL x 2) and then hexane (2 mL x 2) and dried to give 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **20** (28 mg, 0.054 mmol, 84% yield).

[0177] The compound was pure enough and was submitted (24 mg) to system directly. ¹H NMR (400 MHz, DMSO-d₆) δ 13.20 (s, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.80 - 7.74 (m, 2H), 7.74 - 7.67 (m, 2H), 7.57 (d, J = 7.6 Hz, 3H), 7.50 - 7.42 (m, 4H), 7.37 (dd, J = 8.4, 6.3 Hz, 1H), 7.30 (s, 2H), 4.21 (s, 2H); MS (M+H)⁺ = 517.

Example 30

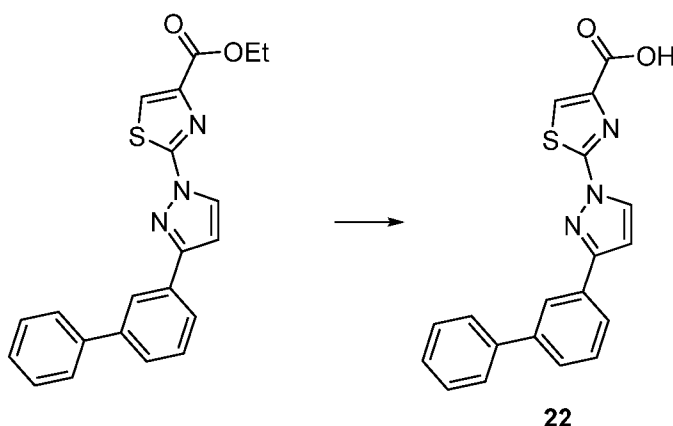
[0178] This example describes the synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **21**.

[0179] The side product of step 3 in Example 28 was re-purified by reverse phase chromatography to give 2-(3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **21**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.25 (s, 1H), 8.93 (s, 1H), 8.28 (s, 1H), 8.12 (d, $J = 1.8$ Hz, 1H), 7.85 (dd, $J = 7.7, 1.5$ Hz, 1H), 7.79 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.72 (dd, $J = 7.5, 1.7$ Hz, 2H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.40 (t, $J = 7.4$ Hz, 1H); MS ($\text{M}+\text{H}$) $^+ = 427$

Example 31

[0180] This example describes the synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **22**. See Scheme 7A.

SCHEME 7A

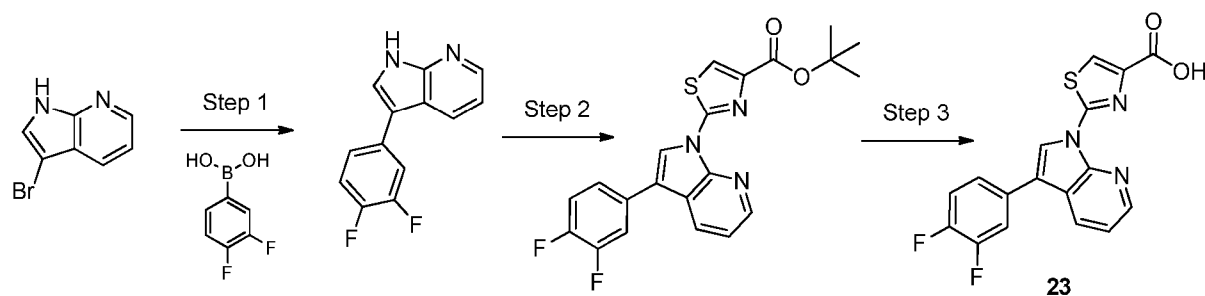


[0181] To a solution of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (30 mg, 0.080 mmol) in THF (1 mL) was added $\text{LiOH}_{(\text{aq})}$ (1.5 N in H_2O , 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1N $\text{HCl}_{(\text{aq})}$ (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added, and the resulting solid was filtered, triturated with H_2O (1 mL x 2) and then hexane (2 mL x 2), and dried. The product still contained a small amount of impurity, which was dissolved in DMF, filtered through a filter, and submitted for purification to give 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **22** (0.8 mg, 1.734 μmol , 2.170% yield). MS ($\text{M}+\text{H}$) $^+ = 348$.

Example 32

[0182] This example describes the synthesis of 2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA **23** in an embodiment of the invention.

SCHEME 8



STEP 1: Synthesis of 3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridine

[0183] In a 2-neck flask was placed 3-bromo-1H-pyrrolo[2,3-b]pyridine (788 mg, 4 mmol), (3,4-difluorophenyl)boronic acid (758 mg, 4.80 mmol), PdCl₂(dppf) (146 mg, 0.200 mmol), and K₂CO₃ (1658 mg, 12.00 mmol). The air was removed and re-filled with N₂ (2-3 times). Then a mixture of 1,4-dioxane (12 ml, ratio: 2.000) and water (6 ml, ratio: 1.000) was added and stirred at 95 °C (pre-heated) for 3 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL x 2). The combined organic was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 30-40% EtOAc/hexane as the eluent to give 3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridine (260 mg, 1.129 mmol, 28.2% yield).

STEP 2: Synthesis of *tert*-butyl 2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate

[0184] In a microwave tube was placed 3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridine (50.6 mg, 0.220 mmol), *tert*-butyl 2-bromothiazole-4-carboxylate (52.8 mg, 0.2 mmol), (1*S*,2*S*)-*N*¹,*N*²-dimethylcyclohexane-1,2-diamine (5.69 mg, 0.040 mmol), CuI (3.81 mg, 0.020 mmol), and K₃PO₄ (127 mg, 0.600 mmol). The air was removed and re-filled with N₂ (3 times). Then toluene (2 ml) was added and the mixture was stirred at 110 °C for overnight. After cooling to room temperature, the mixture was diluted with EtOAc (3 mL) and filtered through celite and eluted with EtOAc. The filtrate was concentrated and the mixture was purified by silica gel chromatography using 10-30% EtOAc/hexane as the eluent to give *tert*-butyl 2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (75 mg, 0.181 mmol, 91% yield). This material contained some Br-starting material and impurity was used for de-protection and purified in the next step.

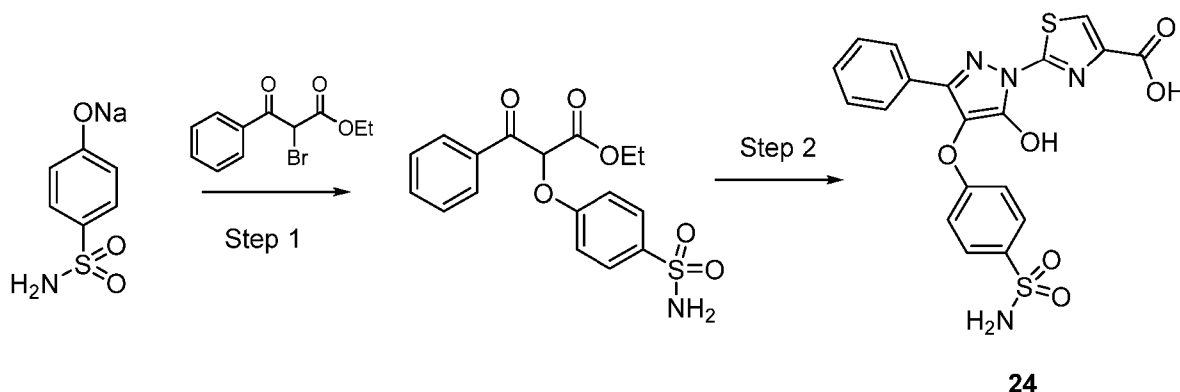
STEP 3: Synthesis of 2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA (23)

[0185] To a solution of *tert*-butyl 2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (75 mg, 0.181 mmol) in 1,4-dioxane (1 ml) was added HCl (4M in dioxane, 1 mL, 4 mmol). The mixture was stirred at room temperature for 2 h. The mixture was concentrated and the crude material was dissolved in DMF, filtered through a filter, and submitted for purification to give 2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA 23 (1.6 mg, 3.39 μmol, 1.871% yield). MS (M+H)⁺ = 358.

Example 33

[0186] This example describes the synthesis of 2-(5-hydroxy-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA 24 in an embodiment of the invention.

SCHEME 9

STEP 1: Synthesis of ethyl 3-oxo-3-phenyl-2-(4-sulfamoylphenoxy)propanoate

[0187] To a mixture of sodium 4-sulfamoylphenolate (195 mg, 1 mmol) and ethyl 2-bromo-3-oxo-3-phenylpropanoate (298 mg, 1.100 mmol) was added EtOH (1 ml). The mixture was stirred at room temperature for 30 min. The mixture was concentrated and purified by silica gel chromatography using 30-50% EtOAc/hexane as the eluent to give ethyl 3-oxo-3-phenyl-2-(4-sulfamoylphenoxy)propanoate (66 mg, 0.182 mmol, 18.16% yield).

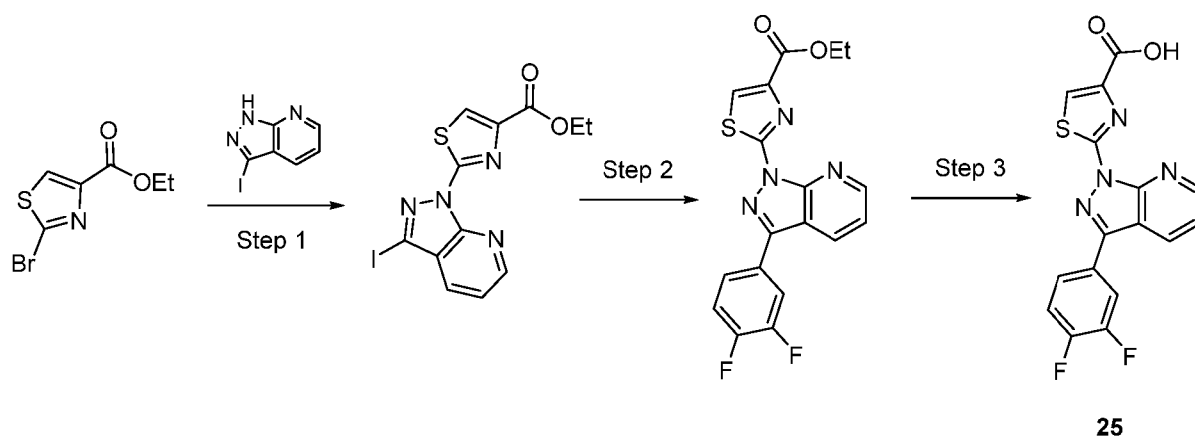
STEP 2: Synthesis of give 2-(5-hydroxy-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA (24**)**

[0188] In a microwave tube was placed ethyl 3-oxo-3-phenyl-2-(4-sulfamoylphenoxy)propanoate (66 mg, 0.182 mmol), ethyl 2-hydrazinylthiazole-4-carboxylate (34.0 mg, 0.182 mmol), and p-TsOH (34.5 mg, 0.182 mmol) and added EtOH (2 ml). The tube was sealed and heated at 150 °C for 20 min. The solvent was removed via air blow-down and then added THF (1 mL) and 1.5 N LiOH_(aq) (1 mL, 1.5 mmol). The mixture was stirred at room temperature for 1 h. Then 1 N HCl_(aq) (ca. 1.5-1.55 mL) was added (pH of aqueous layer is ca. 3), and the aqueous layer was extracted with EtOAc (3 mL x 4). The combined organic layer was dried (Na₂SO₄), filtered, and concentrated. The crude product was dissolved in DMF and submitted for purification to give 2-(5-hydroxy-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **24** (20.8 mg, 0.036 mmol, 20.00% yield). MS (M+H)⁺= 459

Example 34

[0189] This example describes the synthesis of 2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylic acid **25**.

SCHEME 10



STEP 1: Synthesis of ethyl 2-(3-iodo-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylate

[0190] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (472 mg, 2 mmol), 3-iodo-1H-pyrazolo[3,4-b]pyridine (515 mg, 2.100 mmol), and K₂CO₃ (304 mg, 2.200 mmol). The tube was sealed and DMSO (2 ml) was added. The mixture was heated at 140 °C for 2 h. The mixture was poured into EtOAc/H₂O (30 mL/30 mL). The organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 30-50-80% EtOAc/hexane as the eluent to give ethyl 2-(3-iodo-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylate (328 mg, 0.820 mmol, 41.0% yield).

STEP 2: Synthesis of ethyl 2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylate

[0191] In a 2-neck flask was placed ethyl 2-(3-iodo-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylate (40.0 mg, 0.1 mmol), (3,4-difluorophenyl)boronic acid (31.6 mg, 0.200 mmol), PdCl₂(dppf) (7.32 mg, 10.00 μmol), and K₂CO₃ (69.1 mg, 0.500 mmol). The air was removed and re-filled with N₂ (2-3 times). Then a mixture of 1,4-dioxane (1 mL, ratio: 2.000) and water (0.5 ml, ratio: 1.000) was added and stirred at 95 °C (pre-heated) for 3 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 40-70% EtOAc/hexane as the eluent to give ethyl 2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylate (11 mg, 0.028 mmol, 28.5% yield).

STEP 3: Synthesis of 2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylic acid (25**)**

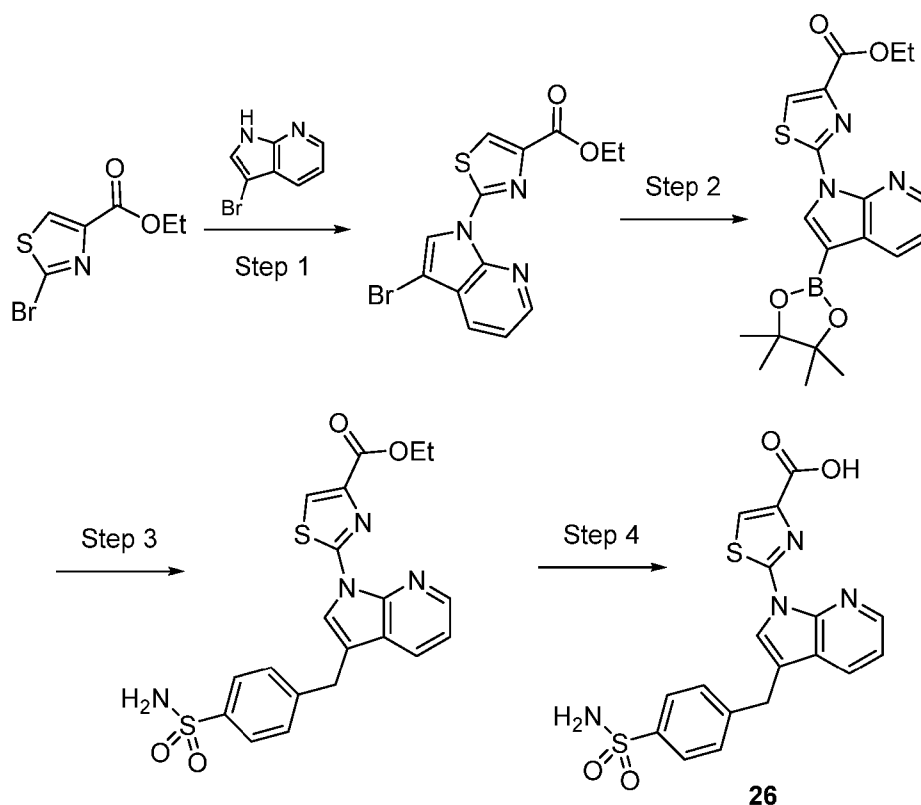
[0192] To a solution of ethyl 2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylate (10 mg, 0.026 mmol) in THF (1 ml) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room

temperature for 2 h. Then, 1 N HCl_(aq) (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added, and the resulting solid was filtered, triturated with hexane (2 mL x 2), and dried to give 2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylic acid **25** (6 mg, 0.017 mmol, 64.7% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.16 (s, 1H), 8.88 - 8.78 (m, 2H), 8.33 (s, 1H), 8.15 (ddd, *J* = 11.7, 7.7, 2.2 Hz, 1H), 8.05 - 7.97 (m, 1H), 7.68 (dt, *J* = 10.8, 8.5 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.6 Hz, 1H); MS (M+H)⁺ = 359.

Example 35

[0193] This example describes the synthesis of 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid **26** in an embodiment of the invention.

SCHEME 11



STEP 1: Synthesis of ethyl 2-(3-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate

[0194] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (944 mg, 4 mmol), 3-bromo-1H-pyrrolo[2,3-b]pyridine (867 mg, 4.40 mmol), and K₂CO₃ (663 mg, 4.80 mmol). The tube was sealed and DMSO (7.5 ml) was added. The mixture was heated at 150 °C for 3 h. The mixture was poured into EtOAc/H₂O (30 mL/30 mL). The organic was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified (twice) by silica gel chromatography using 10-20% EtOAc/hexane as the eluent to give ethyl 2-(3-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (587 mg, 1.667 mmol, 41.7% yield).

STEP 2: Synthesis of ethyl 2-(3-(4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate

[0195] In a microwave tube was placed ethyl 2-(3-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (352 mg, 1 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (330 mg, 1.300 mmol), PdCl₂(dppf) (73.2 mg, 0.100 mmol), and AcOK (294 mg, 3.00 mmol). The tube was sealed and air was removed and re-filled with N₂ (2-3 times). Then, 1,4-dioxane (3 ml) was added and stirred at 95 °C (pre-heated) for overnight. The mixture was diluted with EtOAc and filtered through CELITE™ and eluted with EtOAc. After removal of the solvent, the product was purified by silica

gel chromatography using 10-25% EtOAc/hexane as the eluent to give product, which was triturated with a small amount of hexane to give ethyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (293 mg, 0.734 mmol, 73.4% yield) as solid.

STEP 3: Synthesis of ethyl 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate

[0196] In a microwave tube was placed ethyl 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (39.9 mg, 0.1 mmol), 4-(bromomethyl)benzenesulfonamide (25.01 mg, 0.100 mmol), and $\text{Pd}(\text{Ph}_3\text{P})_4$ (11.56 mg, 10.00 μmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2N $\text{Na}_2\text{CO}_3(\text{aq})$ (0.3 mL, 0.6 mmol, 6 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 30-80% EtOAc/hexane as the eluent to give ethyl 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (28 mg, 0.063 mmol, 63.3% yield) as a white solid.

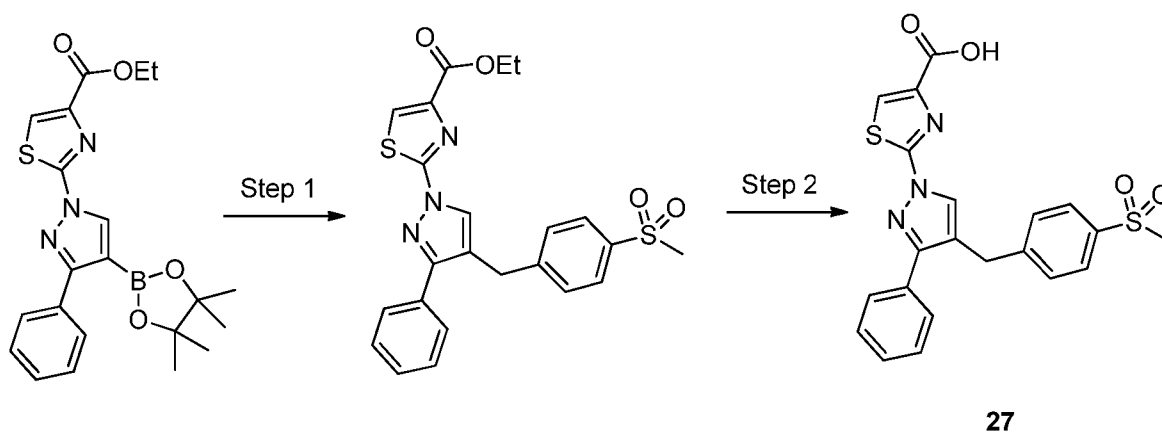
STEP 4: Synthesis of 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid (**26**)

[0197] To a solution of ethyl 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (28 mg, 0.063 mmol) in THF (1 ml) was added $\text{LiOH}(\text{aq})$ (1.5 N in H_2O , 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1N $\text{HCl}(\text{aq})$ (ca.0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added and the resulting solid was filtered, triturated with H_2O (1 mL x 2) and then hexane (2 mL x 2), and dried to give 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid **26** (21 mg, 0.051 mmol, 80% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.04 (s, 1H), 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 8.19 (s, 1H), 8.09 (dd, J = 7.8, 1.5 Hz, 1H), 8.07 (s, 1H), 7.80 - 7.72 (m, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.9, 4.8 Hz, 1H), 7.27 (s, 2H), 4.23 (s, 2H); MS (M+H) $^+$ = 415.

Example 36

[0198] This example describes the synthesis of 2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **27** in an embodiment of the invention.

SCHEME 12



STEP 1: Synthesis of ethyl 2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0199] In a microwave tube was placed ethyl 2-(3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (70.9 mg, 0.1 mmol), 1-(bromomethyl)-4-(methylsulfonyl)benzene (24.91 mg, 0.100 mmol), and $\text{Pd}(\text{Ph}_3\text{P})_4$ (11.56 mg, 10.00 μmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2N $\text{Na}_2\text{CO}_3(\text{aq})$ (0.3 mL, 0.6 mmol, 6 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 25-50% EtOAc/hexane as the

eluent to give ethyl 2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (35 mg, 0.075 mmol, 74.9% yield) as a white solid.

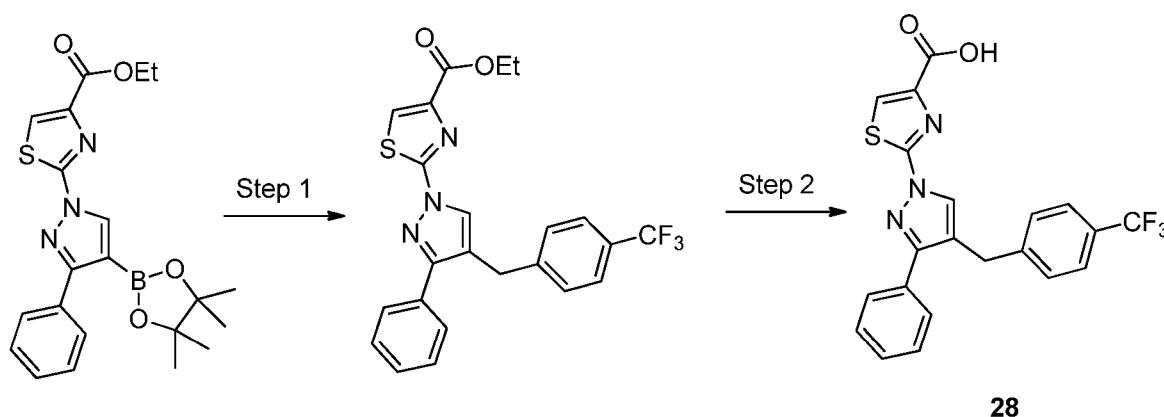
STEP 2: Synthesis of 2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (**27**)

[0200] To a solution of ethyl 2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (35 mg, 0.075 mmol) in THF (1 ml) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1 N HCl_(aq) (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added and the resulting solid was filtered, triturated with H₂O (1 ml x 2) and then hexane (2 mL x 2), and dried to give 2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **27** (30 mg, 0.068 mmol, 91% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.17 (s, 1H), 8.34 (s, 1H), 8.23 (d, *J* = 1.7 Hz, 1H), 7.86 - 7.79 (m, 2H), 7.70 - 7.62 (m, 2H), 7.53 - 7.37 (m, 5H), 4.19 (s, 2H), 3.17 (s, 3H); MS (M+H)⁺ = 440.

Example 37

[0201] This example describes the synthesis of 2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **28** in an embodiment of the invention.

SCHEME 13



STEP 1: Synthesis of ethyl 2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0202] In a microwave tube was placed ethyl 2-(3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (70.9 mg, 0.1 mmol), 1-(bromomethyl)-4-(trifluoromethyl)benzene (23.90 mg, 0.100 mmol), and Pd(Ph₃P)₄ (11.56 mg, 10.00 μmol). The tube was sealed and air was removed and re-filled with N₂ (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2 N Na₂CO_{3(aq)} (0.3 mL, 0.6 mmol, 6 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 10-25% EtOAc/hexane as the eluent to give ethyl 2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (58 mg, 0.070 mmol, 69.7% yield) as a white solid. This material was mixed with the reduction product and was used for hydrolysis directly and purified at the next step.

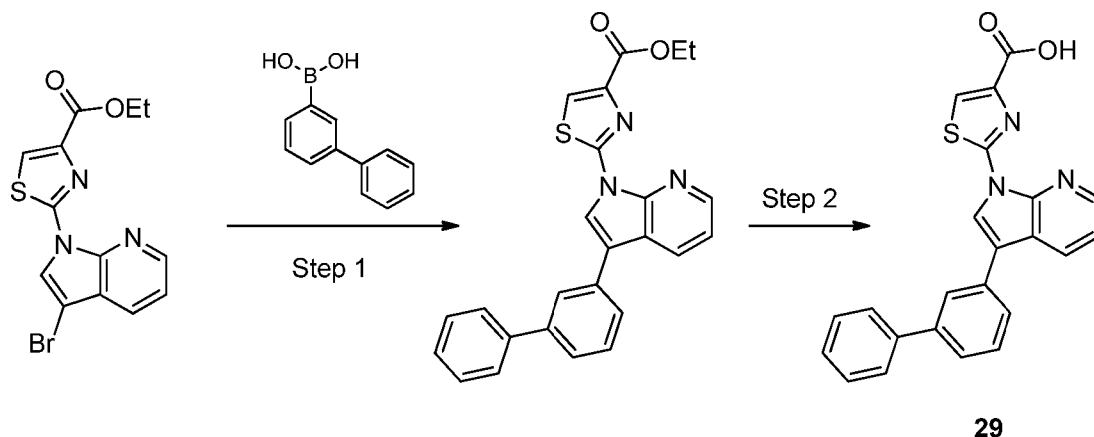
STEP 2: Synthesis of 2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA (**28**)

[0203] To a solution of ethyl 2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (58 mg, 0.070 mmol) in THF (1 ml) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1 N HCl_(aq) (ca. 0.6-0.65 mL) was added, and the pH of aqueous layer was around 4. Then, the mixture was concentrated and the residue was dissolved in DMF, filtered through a filter and submitted for purification to give 2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **28** (13 mg, 0.024 mmol, 34.3% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.17 (s, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 7.69 - 7.59 (m, 4H), 7.50 - 7.36 (m, 5H), 4.18 (s, 2H); MS (M+H)⁺ = 430.

Example 38

[0204] This example describes the synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA **29** in an embodiment of the invention.

SCHEME 14



STEP 1: Synthesis of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate

[0205] In a 2-neck flask was placed ethyl 2-(3-bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (35.2 mg, 0.1 mmol), [1,1'-biphenyl]-3-ylboronic acid (39.6 mg, 0.200 mmol), PdCl₂(dppf) (7.32 mg, 10.00 μmol), and K₂CO₃ (69.1 mg, 0.500 mmol). The air was removed and re-filled with N₂ (2-3 times). Then a mixture of 1,4-dioxane (1 mL, ratio: 2.000) and water (0.5 mL, ratio: 1.000) was added and stirred at 95 °C (pre-heated) for 3 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 40-70% EtOAc/hexane as the eluent to give ethyl 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (30 mg, 0.053 mmol, 52.9% yield). This product contained some impurity and was used for the next step without further purification.

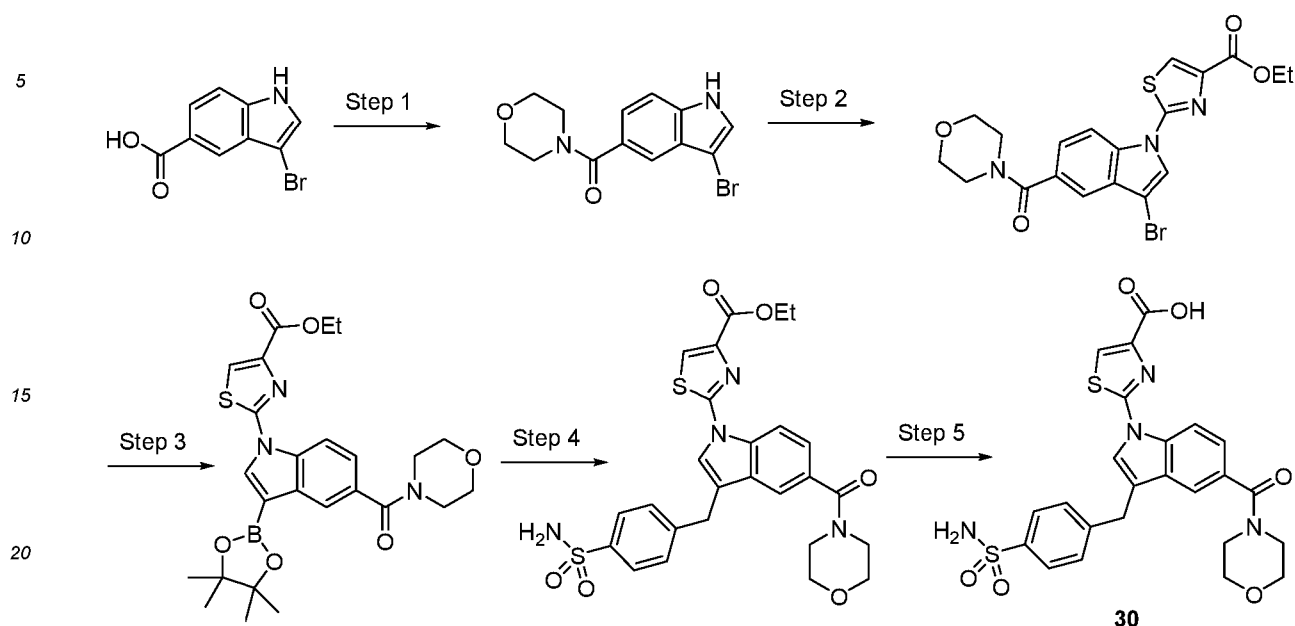
STEP 2: Synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA (**29**)

[0206] To a solution of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylate (30 mg, 0.071 mmol) in THF (1 mL) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 3 h. Then, 1 N HCl_(aq) (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. The mixture was concentrated and the residue was dissolved in DMF, filtered through a filter, and submitted for purification to give 2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA **29** (2.1 mg, 4.11 μmol, 5.82% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.08 (s, 1H), 8.68 (s, 1H), 8.57 (d, *J* = 4.7 Hz, 1H), 8.55 - 8.50 (m, 1H), 8.28 (s, 1H), 8.07 (d, *J* = 2.0 Hz, 1H), 7.83 (m, 3H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.54 - 7.44 (m, 3H), 7.43 - 7.35 (m, 1H); MS (M+H)⁺ = 398.

Example 39

[0207] This example describes the synthesis of 2-(5-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid **30** in an embodiment of the invention.

SCHEME 15

STEP 1: Synthesis of (3-bromo-1H-indol-5-yl)(morpholino)methanone

[0208] To a mixture of 3-bromo-1H-indole-5-carboxylic acid (960 mg, 4 mmol) and HATU (2281 mg, 6.00 mmol) was added DMF (5 ml) and then morpholine (697 mg, 8.00 mmol) and Hünig's base (1.048 ml, 6.00 mmol). The mixture was stirred at room temperature for 1.5 h. The mixture was poured into EtOAc/H₂O (60 mL/60 mL). The organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 50-100% EtOAc/hexane as the eluent to give (3-bromo-1H-indol-5-yl)(morpholino)methanone (1204 mg, 3.89 mmol, 97% yield).

STEP 2: Synthesis of ethyl 2-(3-bromo-5-(morpholine-4-carbonyl)-1H-indol-1-yl)thiazole-4-carboxylate

[0209] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (425 mg, 1.800 mmol), (3-bromo-1H-indol-5-yl)(morpholino)methanone (464 mg, 1.5 mmol), and K₂CO₃ (415 mg, 3.00 mmol). The tube was sealed and DMSO (3 ml) was added. The mixture was heated at 125 °C for overnight. The mixture was poured into vigorously stirred H₂O (100 mL) and the solid was filtered, triturated with H₂O, and dried. To the solid was added hexane (30 mL), and the mixture was sonicated and filtered. The solid was dried to give ethyl 2-(3-bromo-5-(morpholine-4-carbonyl)-1H-indol-1-yl)thiazole-4-carboxylate (485 mg, 1.045 mmol, 69.6% yield).

STEP 3: Synthesis of ethyl 2-(5-(morpholine-4-carbonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate

[0210] In a microwave tube was placed ethyl 2-(3-bromo-5-(morpholine-4-carbonyl)-1H-indol-1-yl)thiazole-4-carboxylate (464 mg, 1 mmol), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (381 mg, 1.500 mmol), PdCl₂(dppf) (73.2 mg, 0.100 mmol), and potassium acetate (294 mg, 3.00 mmol). The tube was sealed and air was removed and re-filled with N₂ (2-3 times). Then, 1,4-dioxane (3 ml) was added and stirred at 95 °C (pre-heated) for overnight. The mixture was diluted with EtOAc and filtered through CELITE™ and eluted with EtOAc. After removal of the solvent, the product was purified by silica gel chromatography using 40-100% EtOAc/hexane as the eluent to give product, which was triturated with a small amount of hexane to give ethyl 2-(5-(morpholine-4-carbonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate (360 mg, 0.669 mmol, 66.9% yield) as solid. This material contained a very small amount of reduction (de-Br) product, ~5%, and was used without further purification.

STEP 4: Synthesis of ethyl 2-(5-(morpholine-4-carbonyl)-3-(4-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate

[0211] In a microwave tube was placed ethyl 2-(5-(morpholine-4-carbonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate (77 mg, 0.15 mmol), 4-(bromomethyl)benzenesulfonamide (49.9 mg, 0.200

mmol), and $\text{Pd}(\text{Ph}_3\text{P})_4$ (17.33 mg, 0.015 mmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). A mixture of toluene (0.75 mL, ratio: 2.500)/EtOH (0.3 mL, ratio: 1.000) was added, and then 2 N $\text{Na}_2\text{CO}_{3(\text{aq})}$ (0.3 mL, 0.6 mmol, 4 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 90-100% EtOAc/hexane as the eluent to give ethyl 2-(5-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate (70 mg, 0.126 mmol, 84% yield) as a white solid.

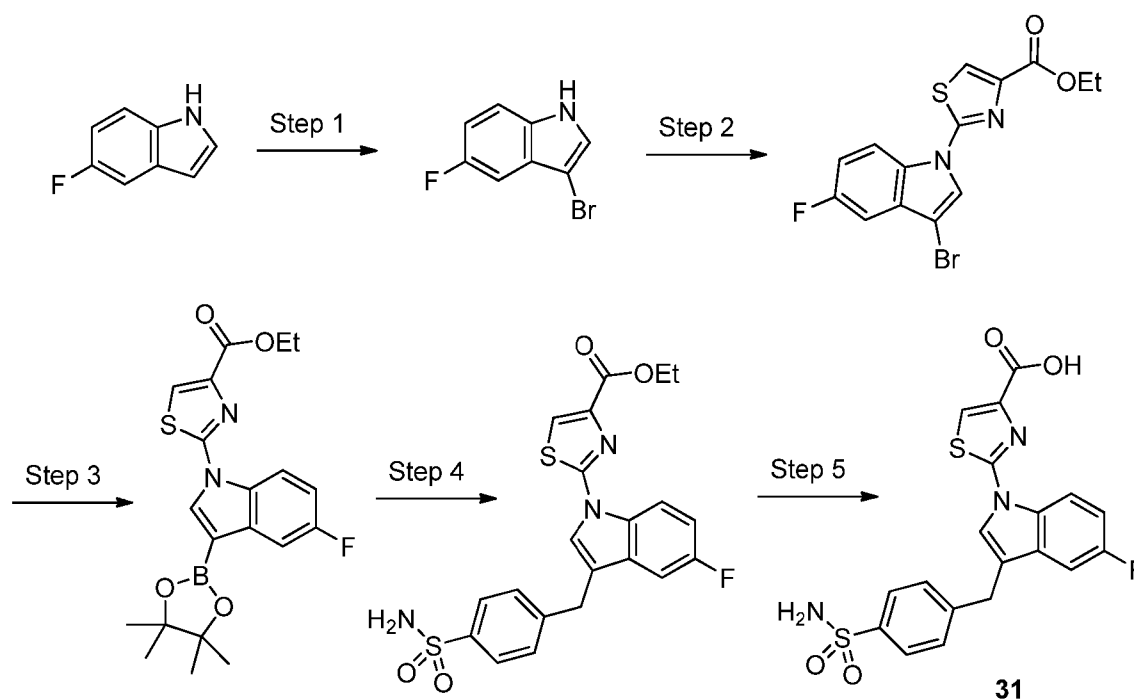
STEP 5: Synthesis of 2-(5-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid (**30**)

[0212] To a solution of ethyl 2-(5-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate (65 mg, 0.117 mmol) in THF (1 mL) was added $\text{LiOH}_{(\text{aq})}$ (1.5 N in H_2O , 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1 N $\text{HCl}_{(\text{aq})}$ (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added, and the resulting solid was filtered, triturated with H_2O (1 mL x 2) and then hexane (2 mL x 2), and dried. The solid was collected and 10% CH_2Cl_2 /hexane (15 mL) was added, and the mixture was sonicated and filtered. The solid was dried to give 2-(5-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid **30** (19 mg, 0.036 mmol, 30.8% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.20 (s, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.6 Hz, 1H), 7.25 (s, 2H), 4.21 (s, 2H), 3.76 - 3.34 (m, 8H); MS ($\text{M}+\text{H}$) $^+$ = 527.

Example 40

[0213] This example describes the synthesis of 2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid **31** in an embodiment of the invention.

SCHEME 16



STEP 1: Synthesis of 3-bromo-5-fluoro-1H-indole

[0214] To a solution of 5-fluoro-1H-indole (1351 mg, 10 mmol) in CHCl_3 (10 mL) and pyridine (1.779 mL, 22.00 mmol) at 0 °C was added NBS (1958 mg, 11.00 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was concentrated to remove most of the solvent. The residue was dissolved in EtOAc (50 mL) and the organic layer washed 0.5 N $\text{HCl}_{(\text{aq})}$ (50 mL), H_2O (50 mL), 2 N $\text{Na}_2\text{CO}_{3(\text{aq})}$ (50 mL), H_2O (50 mL), dried (Na_2SO_4), and filtered. The product was checked by LCMS and was dried to give 3-bromo-5-fluoro-1H-indole (1945 mg, 9.09 mmol, 91% yield). This material was used for the next step without further purification.

STEP 2: Synthesis of ethyl 2-(3-bromo-5-fluoro-1H-indol-1-yl)thiazole-4-carboxylate

[0215] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (708 mg, 3 mmol), 3-bromo-5-fluoro-1H-indole (642 mg, 3.00 mmol), and K_2CO_3 (829 mg, 6.00 mmol). The tube was sealed and DMSO (4 ml) was added. The mixture was heated at 125 °C for 5 h. The mixture was poured into vigorously stirred H_2O (100 mL) and the solid was filtered, triturated with H_2O and then hexane, and dried to give ethyl 2-(3-bromo-5-fluoro-1H-indol-1-yl)thiazole-4-carboxylate (800 mg, 2.167 mmol, 72.2% yield).

STEP 3: Synthesis of ethyl 2-(5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate

[0216] In a microwave tube was placed ethyl 2-(3-bromo-5-fluoro-1H-indol-1-yl)thiazole-4-carboxylate (554 mg, 1.5 mmol), 4,4,4',4',5,5,5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (571 mg, 2.250 mmol), $PdCl_2(dppf)$ (110 mg, 0.150 mmol), and potassium acetate (442 mg, 4.50 mmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). Then, 1,4-dioxane (4 ml) was added and stirred at 95 °C (pre-heated) for overnight. The mixture was diluted with EtOAc and filtered through CELITE™ and eluted with EtOAc. After removal of the solvent, the product was purified by silica gel chromatography using 5-20% EtOAc/hexane as the eluent to give product, which was triturated with a small amount of hexane to give ethyl 2-(5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate (730 mg, ca. 55% purity, 0.965 mmol, 64.3% yield) as solid. This material contained reduction (de-Br) product, -45%.

STEP 4: Synthesis of ethyl 2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate

[0217] In a microwave tube was placed ethyl 2-(5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate (114 mg, 0.15 mmol, -55% purity), 4-(bromomethyl)benzenesulfonamide (49.9 mg, 0.200 mmol), and $Pd(Ph_3P)_4$ (17.33 mg, 0.015 mmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2 N $Na_2CO_{3(aq)}$ (0.3 mL, 0.6 mmol, 4 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 20-50% EtOAc/hexane as the eluent to give ethyl 2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate (47 mg, 0.102 mmol, 68.2% yield) as a white solid.

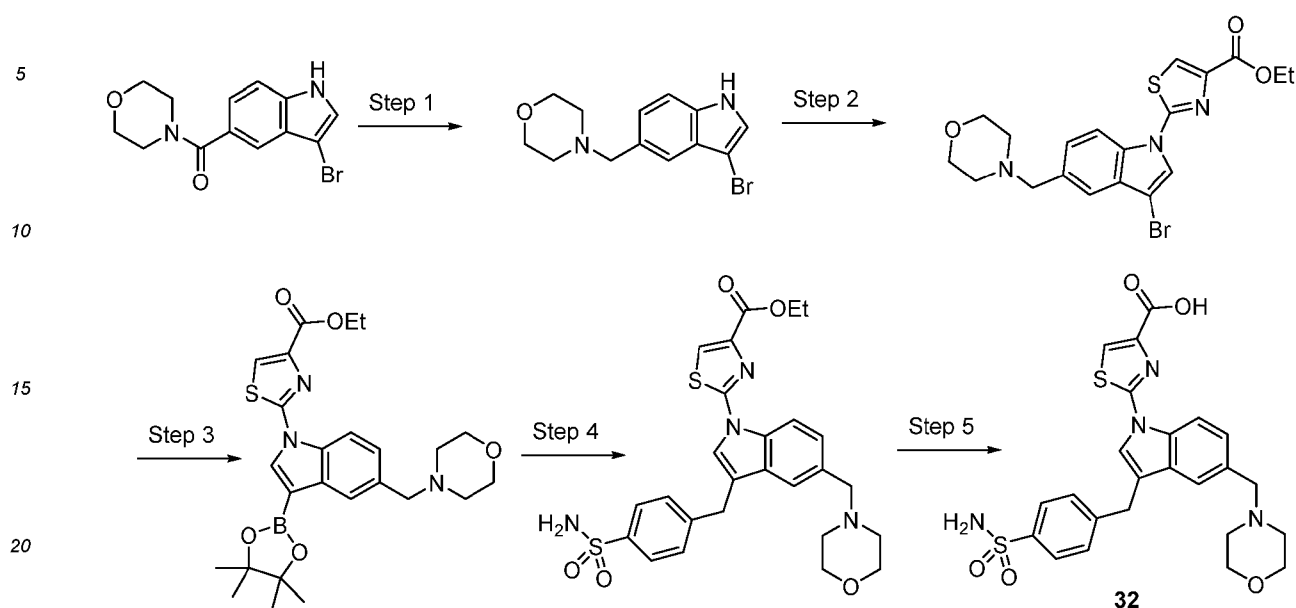
STEP 5: Synthesis of 2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid (31)

[0218] To a solution of ethyl 2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate (47 mg, 0.102 mmol) in THF (1 ml) was added $LiOH_{(aq)}$ (1.5 N in H_2O , 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1 N $HCl_{(aq)}$ (ca. 0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added and the resulting solid was filtered, triturated with H_2O (1 mL x 2) and then hexane (2 mL x 2) and dried to give 2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid **31** (37 mg, 0.086 mmol, 84% yield). ^1H NMR (400 MHz, $DMSO-d_6$) δ 13.17 (s, 1H), 8.40 (dd, $J = 9.2, 4.5$ Hz, 1H), 8.19 (d, $J = 1.0$ Hz, 1H), 7.93 (s, 1H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.37 (dd, $J = 9.2, 2.6$ Hz, 1H), 7.27 - 7.18 (m, 3H), 4.16 (s, 2H); MS ($M+H$) $^+ = 432$.

Example 41

[0219] This example describes the synthesis of 2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid **32** in an embodiment of the invention.

SCHEME 17



STEP 1: Synthesis of 4-((3-bromo-1H-indol-5-yl)methyl)morpholine

[0220] To a solution of (3-bromo-1H-indol-5-yl)morpholino-methanone (711 mg, 2.3 mmol) in CH_2Cl_2 (5 ml) under N_2 at 0 °C was added DIBAL-H (1636 mg, 11.50 mmol) (1 M in THF, 11.5 mL). After addition of DIBAL-H, the mixture was allowed to warm to room temperature for 2 h. The mixture was slowly poured into vigorously stirred sat. Rochelle salt solution (aq.) (15 mL) was added, and the mixture was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 50-100% EtOAc/hexane as the eluent to give 4-((3-bromo-1H-indol-5-yl)methyl)morpholine (477 mg, 1.616 mmol, 70.3% yield).

STEP 2: Synthesis of ethyl 2-(3-bromo-5-(morpholinomethyl)-1H-indol-1-yl)thiazole-4-carboxylate

[0221] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (443 mg, 1.875 mmol), 4-((3-bromo-1H-indol-5-yl)methyl)morpholine (443 mg, 1.5 mmol), and K_2CO_3 (311 mg, 2.250 mmol). The tube was sealed and DMSO (2 ml) was added. The mixture was heated at 125 °C for 3 h. The mixture was poured into EtOAc/ H_2O (50 mL/50 mL). The aqueous layer was extracted with EtOAc (50 mL x 2). The combined organic layer was dried (Na_2SO_4) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 40-100% EtOAc/hexane as the eluent to give ethyl 2-(3-bromo-5-(morpholinomethyl)-1H-indol-1-yl)thiazole-4-carboxylate (426 mg, 0.946 mmol, 63.1% yield).

STEP 3: Synthesis of ethyl 2-(5-(morpholinomethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate

[0222] In a microwave tube was placed ethyl 2-(3-bromo-5-(morpholinomethyl)-1H-indol-1-yl)thiazole-4-carboxylate (426 mg, 0.946 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (480 mg, 1.892 mmol), $\text{PdCl}_2(\text{dppf})$ (69.2 mg, 0.095 mmol), and potassium acetate (371 mg, 3.78 mmol). The tube was sealed and air was removed and re-filled with N_2 (2-3 times). Then, 1,4-dioxane (2 ml) was added and stirred at 95 °C (pre-heated) for 5 h. The mixture was diluted with EtOAc and filtered through celite and eluted with EtOAc. After removal of the solvent, the product was purified by silica gel chromatography using 50-100% EtOAc/hexane as the eluent to give ethyl 2-(5-(morpholinomethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate as solid.

STEP 4: Synthesis of ethyl 2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate

[0223] In a microwave tube was placed ethyl 2-(5-(morpholinomethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-1-yl)thiazole-4-carboxylate (99 mg, 0.2 mmol), 4-(bromomethyl)benzenesulfonamide (50.0 mg, 0.2 mmol), and

Pd(Ph₃P)₄ (23.11 mg, 0.020 mmol). The tube was sealed and air was removed and re-filled with N₂ (2-3 times). A mixture of toluene (0.75 ml, ratio: 2.500)/EtOH (0.3 ml, ratio: 1.000) was added, and then 2 N Na₂CO_{3(aq)} (0.3 mL, 0.6 mmol, 6 equiv) was added. The mixture was stirred at 80 °C (pre-heated) for 2 h. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 60-100% EtOAc/hexane as the eluent to give ethyl 2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate (37 mg, 0.068 mmol, 34.2% yield).

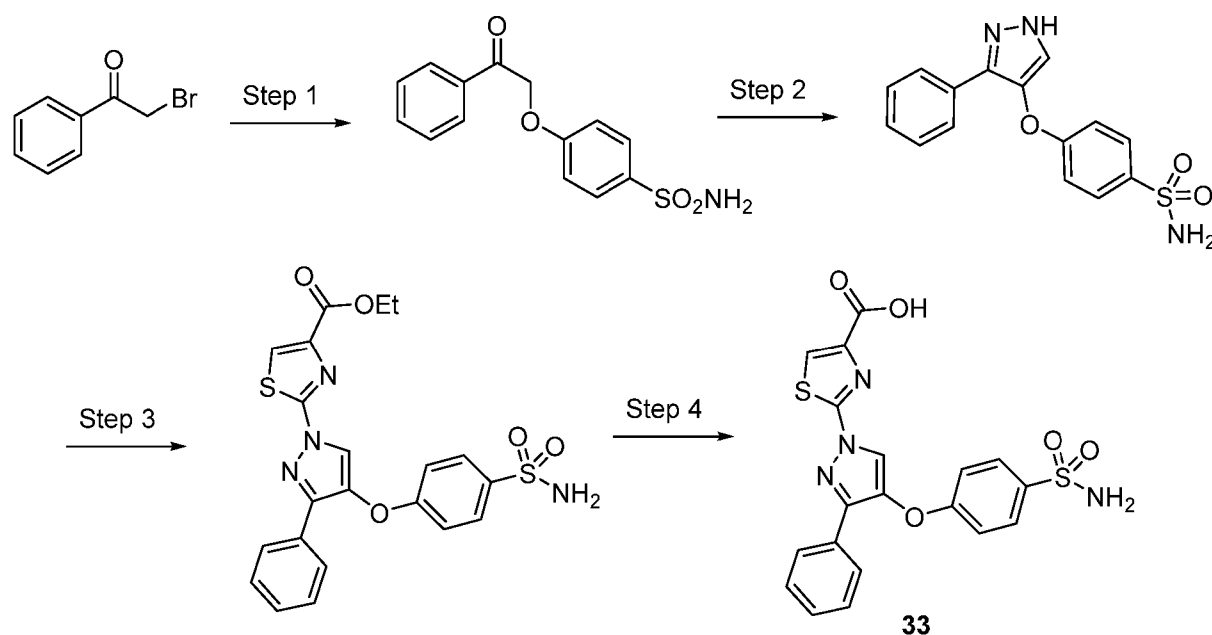
STEP 5: Synthesis of 2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid (**32**)

[0224] To a solution of ethyl 2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylate (37 mg, 0.068 mmol) in THF (1 ml) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1 N HCl_(aq) (ca.0.6 mL) was added and the pH of aqueous layer was around 6. Then, hexane (5 mL) was added and the solid was filtered, triturated with H₂O (1 ml x 2) and then hexane (2 mL x 2), and dried to give 2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid **32** (23 mg, 0.045 mmol, 65.6% yield). MS (M+H)⁺= 513.

Example 42

[0225] This example describes the synthesis of 2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **33** in an embodiment of the invention.

SCHEME 18



STEP 1: Synthesis of 4-(2-oxo-2-phenylethoxy)benzenesulfonamide

[0226] To a mixture of 4-hydroxybenzenesulfonamide (520 mg, 3.00 mmol) and K₂CO₃ (551 mg, 3.99 mmol) was added acetone (10 mL) and stirred at room temperature for 30 min. Then 2-bromo-1-phenylethanone (597 mg, 3 mmol) in acetone (5 mL) was added. The mixture was stirred at room temperature for 20 h. Then, H₂O (15 mL) and hexane (20 mL) were added to the reaction mixture. The solid was filtered and washed with H₂O (2 mL x 2) and then 5% EtOAc/hexane (5 mL x 3). The solid was dried to give 4-(2-oxo-2-phenylethoxy)benzenesulfonamide (804 mg, 2.76 mmol, 92% yield) as a white solid.

STEP 2: Synthesis of 4-((3-phenyl-1H-pyrazol-4-yl)oxy)benzenesulfonamide

[0227] In a microwave tube was placed 4-(2-oxo-2-phenylethoxy)benzenesulfonamide (291 mg, 1 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (1.5 ml, 11.29 mmol) (neat). The tube was sealed and heated at 90 °C for overnight.

The mixture was concentrated by blowing air and the residue was dried in vacuo for hours to give crude mixture of 4-((1-(dimethylamino)-3-oxo-3-phenylprop-1-en-2-yl)oxy)benzenesulfonamide (maybe some isomer or aldehyde). To the crude intermediate was added EtOH (4 mL) and N₂H₄ monohydrate (MW= 50, d= 1.032, 0.145 mL, 3 mmol). The mixture was sealed and heated at 60 °C for 4 h. After cooling to room temperature, the solvent was removed by blowing air, and the residue was purified by silica gel chromatography using 40-80% EtOAc/hexane as the eluent to give 4-((3-phenyl-1H-pyrazol-4-yl)oxy)benzenesulfonamide (85 mg, 0.270 mmol, 27.0% yield) (2 steps). This material contained some impurity and was used for the next step without further purification.

STEP 3: Synthesis of ethyl 2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0228] In a microwave tube was placed ethyl 2-bromothiazole-4-carboxylate (70.0 mg, 0.296 mmol), 4-((3-phenyl-1H-pyrazol-4-yl)oxy)benzenesulfonamide (85 mg, 0.270 mmol), and potassium carbonate (55.9 mg, 0.404 mmol). The tube was sealed and DMSO (1.5 ml) was added. The mixture was heated at 120 °C for 3 h. The mixture was poured into EtOAc/H₂O (30 mL/30 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of the solvent, the product was purified by silica gel chromatography using 30-50-60% EtOAc/hexane as the eluent to give ethyl 2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate (35 mg, 0.074 mmol, 27.6% yield).

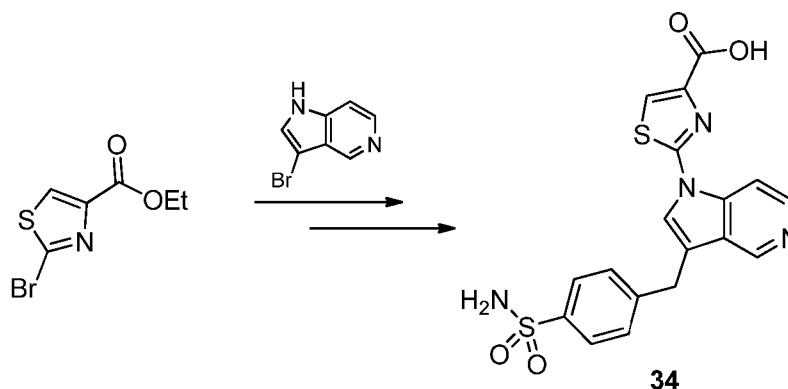
STEP 4: Synthesis of 2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (**33**)

[0229] To a solution of ethyl 2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate (32 mg, 0.068 mmol) in THF (1 ml) was added LiOH_(aq) (1.5 N in H₂O, 0.4 mL, 0.6 mmol). The mixture was stirred at room temperature for 2 h. Then, 1N HCl_(aq) (ca.0.6-0.65 mL) was added and the pH of aqueous layer was around 4. Then, hexane (5 mL) was added and the resulting solid was filtered, triturated with H₂O (1 ml x 2) and then hexane (2 mL x 2), and dried to give 2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **33** (21 mg, 0.047 mmol, 69.8% yield).

Example 43

[0230] This example describes the synthesis of 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)thiazole-4-carboxylic acid, NH₃ **34**.

SCHEME19

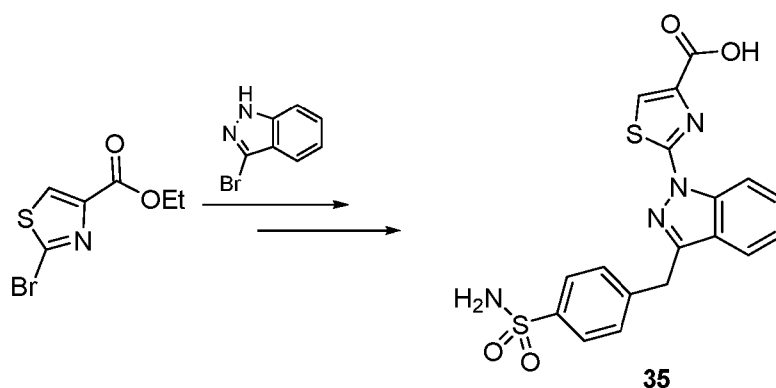


[0231] According to similar procedures described above for **26**, the title compound was prepared starting from 3-bromo-1H-pyrrolo[3,2-c]pyridine, and the final product was purified by reverse phase HPLC chromatography under basic conditions to give 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)thiazole-4-carboxylic acid, NH₃ **34** (NH₃ salt). MS (M+H)⁺= 415.

Example 44

[0232] This example describes the synthesis of 2-(3-(4-sulfamoylbenzyl)-1H-indazol-1-yl)thiazole-4-carboxylic acid (**35**).

SCHEME 20

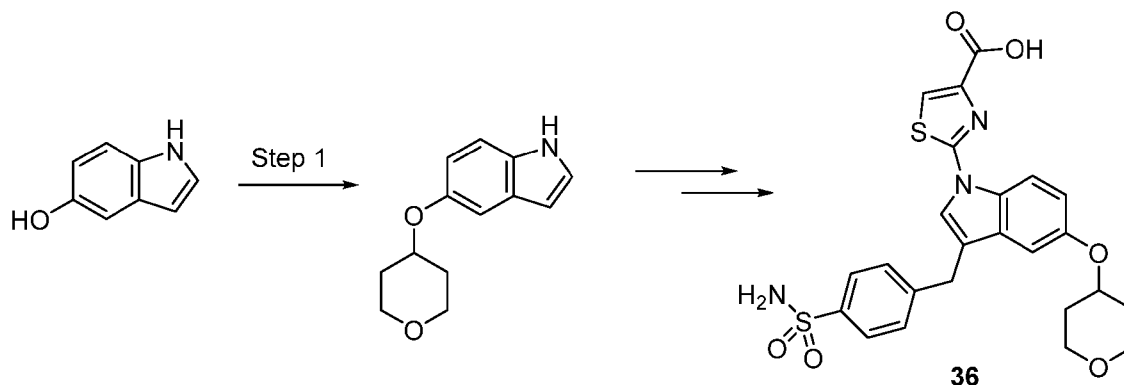


[0233] According to similar procedures described above for **26**, the title compound was prepared starting from 3-bromoindazole to give 2-(3-(4-sulfamoylbenzyl)-1H-indazol-1-yl)thiazole-4-carboxylic acid **35**. ^1H NMR (400 MHz, DM-SO-d_6) δ 13.15 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.18 (s, 1H), 7.80 (dd, J = 8.0, 1.0 Hz, 1H), 7.77 - 7.72 (m, 2H), 7.67 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.35 (ddd, J = 8.1, 7.0, 0.9 Hz, 1H), 7.27 (s, 2H), 4.49 (s, 2H); MS $(\text{M}+\text{H})^+ = 415$.

Example 45

[0234] This example describes the synthesis of 2-(3-(4-sulfamoylbenzyl)-5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH_3 **36** in an embodiment of the invention.

SCHEME 21



STEP 1: Synthesis of 5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indole

[0235] To a mixture of 1H-indol-5-ol (0.799 g, 6 mmol), tetrahydro-2H-pyran-4-ol (0.919 g, 9.00 mmol), and PPh_3 (2.361 g, 9.00 mmol) in THF (10 mL) under N_2 was added a solution of (E)-di-*tert*-butyl diazene-1,2-dicarboxylate (2.072 g, 9.00 mmol) in THF (6 mL). The mixture was then stirred at 50 °C for 3 h. Tetrahydropyran-4-ol (3 mmol) was added and then a solution of PPh_3 (3 mmol) and (E)-di-*tert*-butyl diazene-1,2-dicarboxylate (3 mmol) in THF (5 mL) was added. The mixture was stirred at 50 °C for another 3 h. The mixture was concentrated, and the residue was purified by silica gel chromatography using 20-40% EtOAc/hexane as the eluent to give 5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indole (1.18 g, 5.43 mmol, 91% yield).

STEP 2: Synthesis of 2-(3-(4-sulfamoylbenzyl)-5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH_3 (**36**)

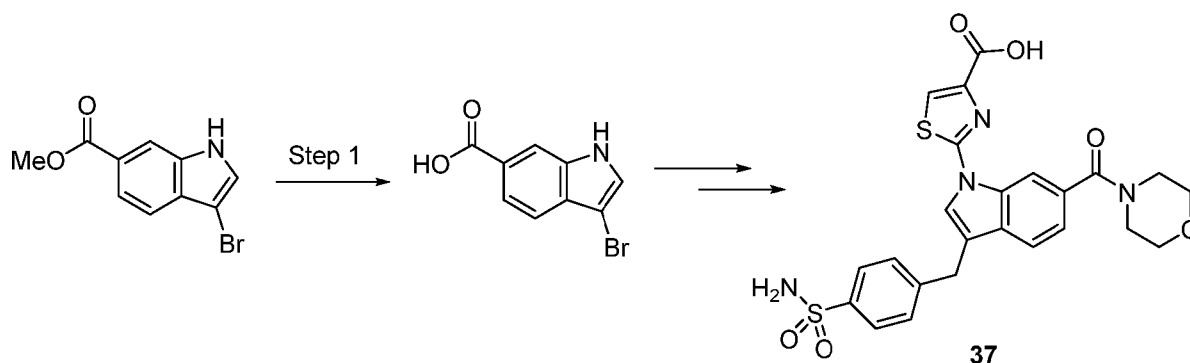
[0236] According to similar procedures described above for **31**, the title compound was prepared starting from 5-((tet-

rahydro-2H-pyran-4-yl)oxy)-1H-indole and the final product was purified by reverse phase HPLC chromatography under basic condition to give 2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)thiazole-4-carboxylic acid, NH_3 **36** (NH_3 salt). MS ($\text{M}+\text{H}$) $^+$ = 514.

Example 46

[0237] This example describes the synthesis of 2-(6-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH_3 **37** in an embodiment of the invention.

SCHEME 22



STEP 1: Synthesis of 3-bromo-1H-indole-6-carboxylic acid

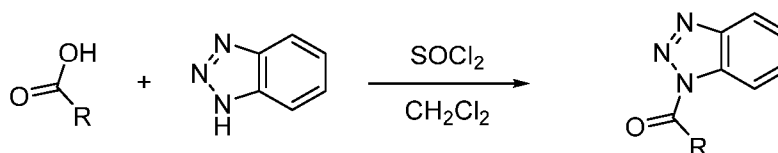
[0238] To a solution of methyl 3-bromo-1H-indole-6-carboxylate (1.270 g, 5 mmol) in THF (10 ml, ratio: 10.00) was added LiOH(aq) (1.5 N in H_2O , 12 mL, 18 mmol). The mixture was stirred at room temperature for 2 h. Then, 1N HCl(aq) was added and the pH of aqueous layer was around 4. Then, hexane (30 mL) was added and the resulting solid was filtered, triturated with H_2O (3 mL x 2) and then hexane (5 mL x 2), and dried to give 3-bromo-1H-indole-6-carboxylic acid (1.136 g, 4.73 mmol, 95% yield).

STEP 2: Synthesis of 2-(6-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH_3 **37**

[0239] According to similar procedures described above for **30**, the title compound was prepared starting from 3-bromo-1H-indole-6-carboxylic acid and the final product was purified by reverse phase HPLC chromatography under basic condition to give 2-(6-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH_3 **37** (NH_3 salt). MS ($\text{M}+\text{H}$) $^+$ = 527.

Example 47

[0240] This example describes the synthesis of 1-(1H-benzo[d][1,2,3]triazol-1-yl)-ketones.



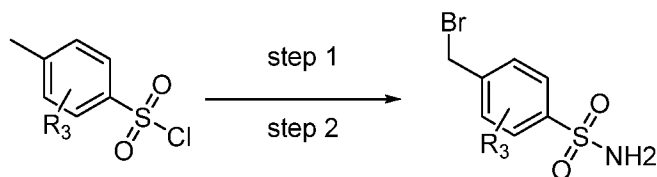
[0241] To a solution of 1H-benzo[d][1,2,3]triazole (4000 mmol) in CH_2Cl_2 was added thionyl chloride (SOCl_2 , 1000 mmol) and stirred at rt for 0.5 h. Alkyl carboxylic acid (1000 mmol) was then added and the reaction mixture was stirred for 2 h. Upon completion as detected by LCMS, the reaction mixture was filtered and the filter cake was washed with CH_2Cl_2 . The filtrate was neutralized with bicarbonate solution slowly and stirred for 30 minutes then transferred to a separatory funnel. The organic layer washed with bicarbonate solution then with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified directly on silica using organic gradient (0-20 % ethyl acetate in hexanes over 10 CV). The first peak was collected and dried to get an oil or solid.

Example 48

[0242] This example describes the synthesis of 4-(bromomethyl)benzenesulfonamides.

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STEP 1: Synthesis of 4-methylbenzenesulfonamide derivatives

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[0243] A stirring solution of 4-methylbenzene-1-sulfonyl chloride (95 g, 455 mmol) in CH_2Cl_2 was bubbled with ammonia for 45 minutes. The reaction mixture was then filtered. The filtrate was concentrated and dried under reduced pressure. The resulting off-white powder was taken to the next step without further purification or characterization; $(\text{M}+\text{H})^+ = 190$

STEP 2: Synthesis of 4-(bromomethyl)benzenesulfonamide derivatives

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[0244] A stirring solution of 4-methyl-2 or 3-fluorobenzenesulfonamide (7.3 mmol), N-bromosuccinimide (NBS 9.5 mmol) and AIBN (0.73 mmol) in CCl_4 (Volume: 20 mL) was refluxed for 24 h. The solvent was evaporated and the residue was suspended in ethyl acetate and filtered. The filtrate was washed with $\text{Na}_2\text{S}_2\text{O}_3$, NaHCO_3 and brine solutions, dried over Na_2SO_4 , and filtered. Silica gel was added and the solvent was removed under reduced pressure. The dry loaded product was purified on silica using gradient elution (5-100 % ethyl acetate in hexanes over 16 CV in a 120 g silica column). The pale colorless produced was used in the next step without further purification or characterization;

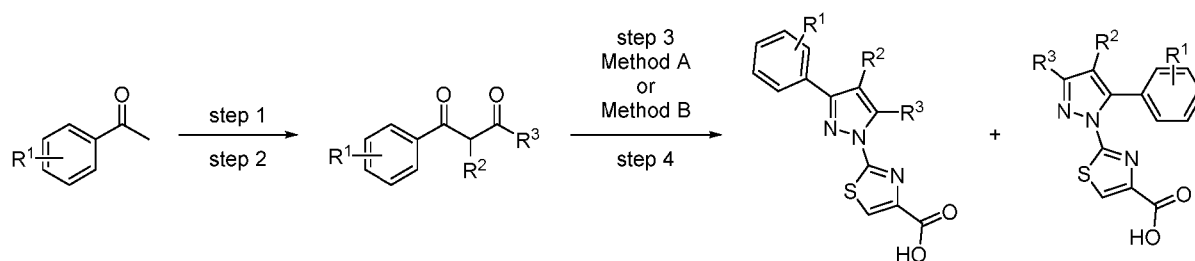
Example 49

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[0245] This example describes the synthesis of 2-(5-(alkyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids and 2-(3-(alkyl)-5-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids.

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STEP 1: Synthesis of 1-phenyl-3-alkyl-1,3-diones

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[0246] To a stirring solution of 1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-alkyl ketone (200 mmol) and magnesium bromide diethyl etherate (413 mmol) in CH_2Cl_2 was added 1-phenylethanone derivatives (165 mmol). Diisopropyl ethyl amine (500 mmol) was added dropwise over several minutes and the reaction mixture was stirred at rt for 2 h. Upon completion as detected by LCMS, the reaction was slowly quenched with 1.0 M HCl and washed with 1.0 M HCl and brine. The residue was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on silica using gradient elution (0-30 % ethyl acetate in hexanes over 20 CV). The resulting oils were used in the next step without further purification or characterization.

STEP 2: Synthesis of 4-(2-benzoyl-3-oxo)-3-alkyl-benzenesulfonamides

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[0247] 1-phenyl-3-alkyl-1,3-diones (150 mmol) and cesium carbonate (Cs_2CO_3 , 226 mmol) were dissolved in DMSO (50 ml). The reaction mixture was stirred at rt for 10 minutes at which time potassium iodide were added (KI, 150 mmol) and 4-(bromomethyl)-benzenesulfonamides (165 mmol). The resulting mixture was stirred at rt for 1 h. Upon completion as detected by LCMS, the reaction mixture was diluted with a large excess of ethyl acetate and filtered through celite. The filtrate was washed with 1 M HCl, sat aq NH_4Cl and brine, dried over Na_2SO_4 , filtered, and concentrated under

reduced pressure. The residue was purified directly on silica using gradient elution (20-40 % ethyl acetate in hexanes over 16 CV).

STEP 3: ethyl 2-(5-(alkyl)-3-phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates

[0248] Method A - A solution of 4-(2-benzoyl-3-oxo)-3-alkyl-benzenesulfonamide (6.7 mmol), ethyl 2-hydrazinylthiazole-4-carboxylate, 2 HBr (7.3 mmol) and *p*-toluene sulfonic acid (pTsOH, 20 mmol) in dioxane was heated in a sealed vessel in the microwave for 15 min at 160 °C. Upon completion as detected by LCMS, the reaction mixture was diluted with ethyl acetate and filtered through celite. The solvent was removed under reduced pressure and the crude product

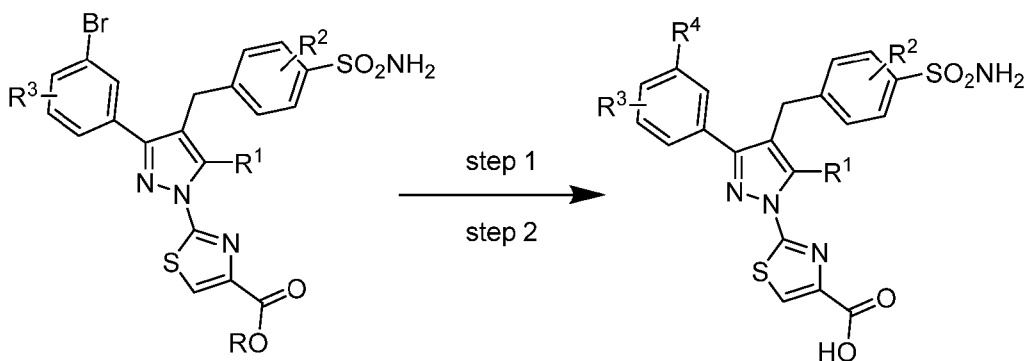
was purified directly on silica using gradient elution (0-100 % ethyl acetate in hexanes over 15 CV). **[0249]** Method B - A solution of 4-(2-(benzoyl)-3-oxo)-3-alkyl-benzenesulfonamide (113 mmol), *p*-toluene sulfonic acid (pTsOH, 57 mmol) and pyrrolidine (57 mmol) in ethanol was stirred at 100 °C for 1 h, after which time ethyl 2-hydrazinylthiazole-4-carboxylate, 2 HBr (136 mmol) was added. The resulting reaction mixture was refluxed overnight. Upon completion as detected by LCMS, the solvent was removed under reduced pressure and the residue was purified without work-up directly on silica using gradient elution (20-40 % ethyl acetate in hexanes over 20 CV). A mixture of regioisomers were collected as a single peak. After removing the solvent, the regioisomers were separated via reverse phase preparative column using gradient elution (50-100 % acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA over 25 CV). The second elution peak was pooled and concentrated, and the resulting solid was stirred with a clear solution of NaHCO₃. The precipitate was collected by filtration, washed with water and sequentially dried, first under air overnight then by high vacuum under P₂O₅, resulting in a colorless powder.

STEP 4: Synthesis of 2-(5-(alkyl)-3-phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids

[0250] To a solution of ethyl 2-(5-(alkyl)-3-phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.07 mmol) in THF/MeOH was added 1.5 M LiOH (0.27 mmol). The reaction mixture was stirred at rt for 1 h. Upon completion as detected by LCMS, the solvent was removed by forced air. The residue was taken into DMSO and purified directly via preparative reverse phase using gradient elution (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA). The product fractions were directly frozen and lyophilized overnight, yielding an off-white powder.

Example 50

[0251] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-3-(meta substituted-phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids.



STEP 1: Synthesis of ethyl 2-(5-(alkyl)-3-(3-(alk-1-yn-1-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylates

[0252] A solution of ethyl 2-(3-(3-bromophenyl)-5-(alkyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.161 mmol, prepared according to the procedure outlined in Example 49, Steps 1-3, using method B in Step 3), tri(tert-butylphosphonium)tetrafluoroborate (0.016 mmol), allylpalladium chloride dimer (0.008 mmol) and DABCO (0.323 mmol) in dioxane was bubbled with argon for 5 minutes. Alkylethyne was then added and the reaction mixture was stirred at rt overnight. Upon completion as detected by LCMS, the reaction mixture was diluted with ethyl acetate and palladium scavenging silica (DMT) was added. After stirring for 2 h at rt the slurry was filtered through a plug of silica. The filtrate was concentrated and the residue was purified directly on silica using gradient elution (20-40 % ethyl acetate in hexanes over 20 CV).

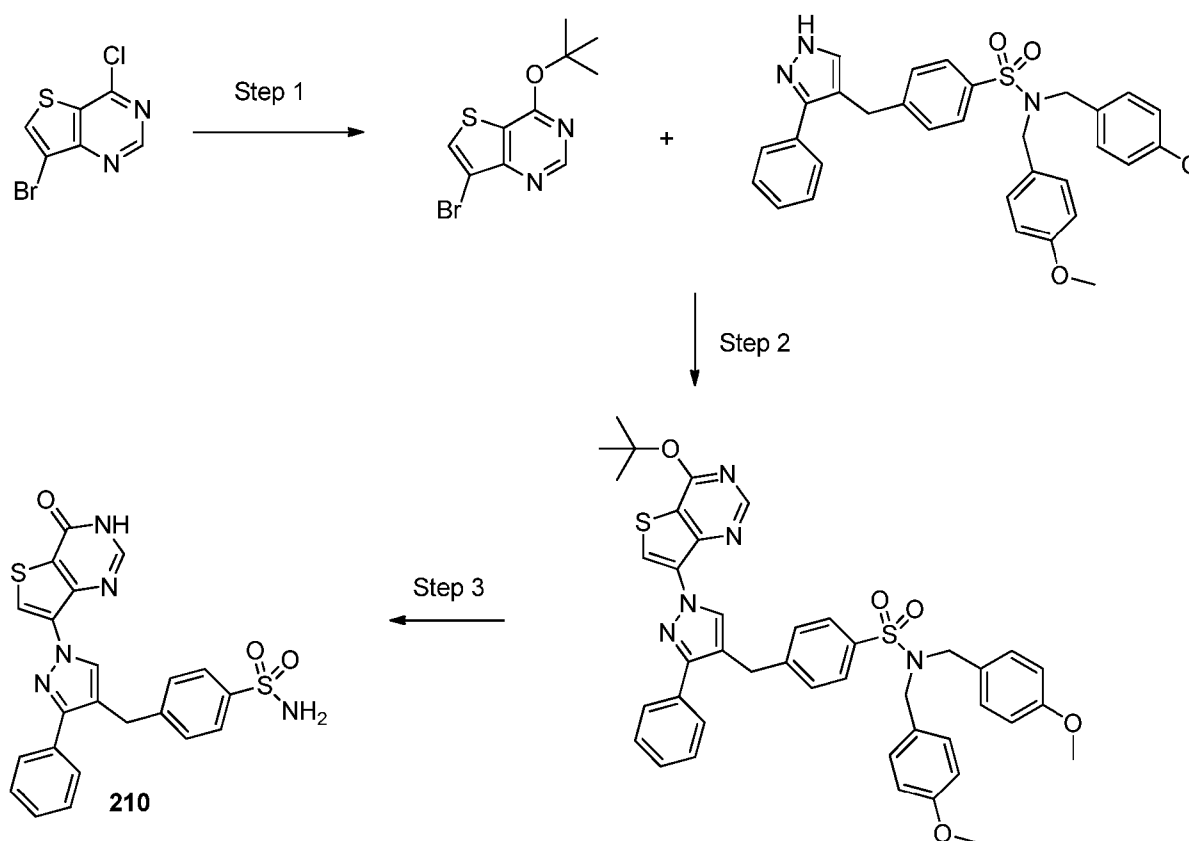
STEP 2: Synthesis of 2-(5-(alkyl)-3-(3-(alk-1-yn-1-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids

[0253] The desired compounds were synthesized according to the procedure outlined in Step 4 of Example 49 providing 2-(5-(alkyl)-3-(3-(alk-1-yn-1-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids as off-white solids.

Example 51

[0254] This example describes the synthesis of 4-((1-(4-oxo-3,4-dihydrothieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide **210**.

SCHEME 23



STEP 1: Synthesis of 7-bromo-4-(tert-butoxy)thieno[3,2-d]pyrimidine

[0255] To a partial suspension of 7-bromo-4-chlorothieno[3,2-d]pyrimidine (998 mg, 4 mmol) in THF (12 ml) at 0 °C was added KOtBu (4.40 ml, 4.40 mmol) (1M solution in THF). The mixture was stirred at 0 °C for 1.5 h. The mixture was poured into H₂O/NH₄Cl_(aq) (25 mL/25 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 5-10% EtOAc/hexane as the eluent to give 7-bromo-4-(tert-butoxy)thieno[3,2-d]pyrimidine (350 mg, 1.219 mmol, 30.5 % yield).

STEP 2: Synthesis of 4-((1-(4-(tert-butoxy)thieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)-N,N-bis(4-methoxybenzyl)benzenesulfonamide

[0256] In a microwave tube was placed N,N-bis(4-methoxybenzyl)-4-((3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (138 mg, 0.25 mmol), 7-bromo-4-(tert-butoxy)thieno[3,2-d]pyrimidine (71.8 mg, 0.250 mmol), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (7.11 mg, 0.050 mmol), CuI (4.76 mg, 0.025 mmol), and Phosphoric acid, potassium salt (159 mg, 0.750 mmol). The air was removed and re-filled with N₂ (3 times). Then Toluene (Volume: 2 ml) was added and the mixture was stirred at 110 °C for overnight. After cooling to rt, the mixture was dilute with EtOAc (3 mL) and

filtered through celite and eluted with EtOAc. The filtrate was concentrated and the mixture was purified by silica gel chromatography using 10-25% EtOAc/hexane as the eluent to give 4-((1-(4-(tert-butoxy)thieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)-N,N-bis(4-methoxybenzyl)benzenesulfonamide (64 mg, 0.084 mmol, 33.7 % yield). MS (M+H)⁺ = 760.

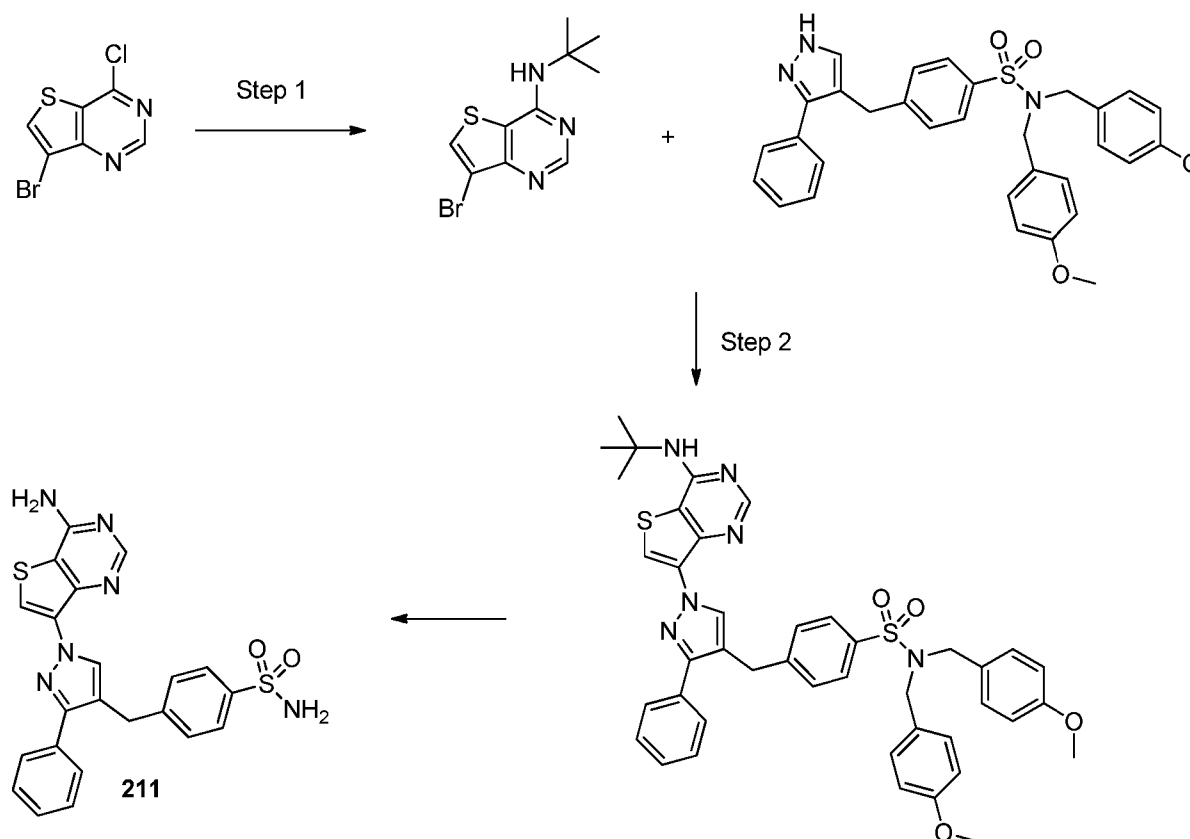
STEP 3: Synthesis of 4-((1-(4-oxo-3,4-dihydrothieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (**210**)

[0257] To a solution of 4-((1-(4-(tert-butoxy)thieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)-N,N-bis(4-methoxybenzyl)benzenesulfonamide (64 mg, 0.084 mmol) in 1,2-Dichloroethane (1 ml) was added TFA (1 ml, 12.98 mmol). The tube was sealed and heated at 100 °C for 30 min under microwave irradiation. The mixture was poured into EtOAc/H₂O (30 mL/30 mL) and Na₂CO_{3(aq)} was added until the pH of aqueous layer is ca. 7.5-8. The organic layer with some suspension was washed with H₂O (20 mL x 3) and then concentrated to remove all the solvent and trace of H₂O. The product was dried in vacuo for 10 min. Then, to the product was added EtOAc (5 mL) and then hexane (50 mL). The solid was filtered and washed with 5% EtOAc/hexane (3 mL x 3) and then dried to give 4-((1-(4-oxo-3,4-dihydrothieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide **210** (36.5 mg, 0.079 mmol, 93 % yield) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 12.79 (s, 1H), 8.71 (s, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 7.74 - 7.68 (m, 2H), 7.68 - 7.62 (m, 2H), 7.45 - 7.39 (m, 2H), 7.39 - 7.34 (m, 3H), 7.25 (s, 2H), 4.16 (s, 2H); MS (M+H)⁺ = 464.

Example 52

[0258] This example describes the synthesis of 4-((1-(4-aminothieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide, TFA 211.

SCHEME 24



STEP 1: Synthesis of 7-bromo-N-(tert-butyl)thieno[3,2-d]pyrimidin-4-amine

[0259] To a partial suspension of 7-bromo-4-chlorothieno[3,2-d]pyrimidine (0.998 g, 4 mmol) in EtOH (6 ml) at 80 °C was added 2-methylpropan-2-amine (0.585 g, 8.0 mmol) and then Hunig's Base (0.699 ml, 4.0 mmol). The mixture was

seared and stirred at 80 °C for overnight. The mixture was diluted with CH₂Cl₂ and concentrated to remove all the solvent. The product was dissolved in EtOAc (50 mL) and washed with H₂O (50 mL). The organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 2-5-10% EtOAc/CH₂Cl₂ as the eluent to give 7-bromo-*N*-(tert-butyl)thieno[3,2-*d*]pyrimidin-4-amine (1.09 g, 3.81 mmol, 95 % yield).

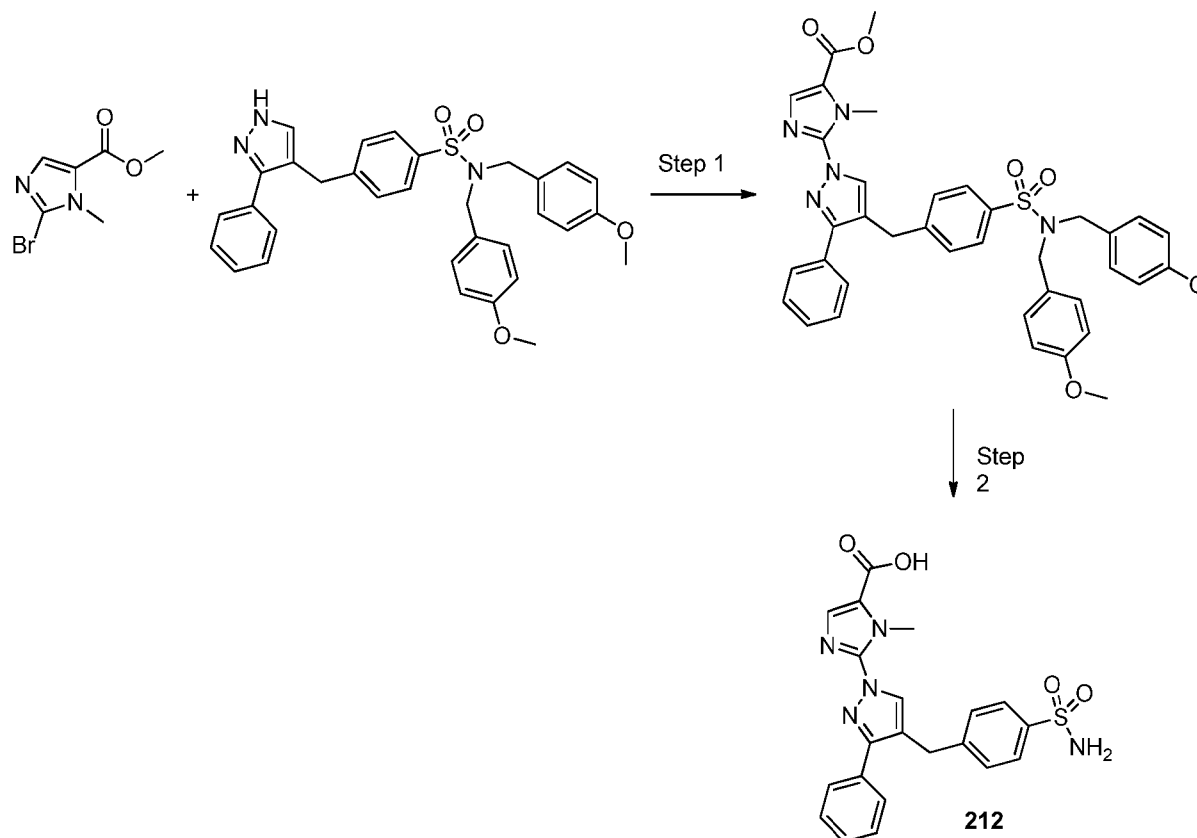
STEP 2: Synthesis of 4-((1-(4-aminothieno[3,2-*d*]pyrimidin-7-yl)-3-phenyl-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide, TFA (211**)**

[0260] In a microwave tube was placed *N,N*-bis(4-methoxybenzyl)-4-((3-phenyl-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide (138 mg, 0.25 mmol), 7-bromo-*N*-(tert-butyl)thieno[3,2-*d*]pyrimidin-4-amine (71.5 mg, 0.250 mmol), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (7.11 mg, 0.050 mmol), CuI (4.76 mg, 0.025 mmol), and Phosphoric acid, potassium salt (159 mg, 0.750 mmol). The air was removed and re-filled with N₂ (3 times). Then Toluene (2 ml) was added and the mixture was stirred at 110 °C for overnight. After cooling to rt, the mixture was dilute with EtOAc (3 mL) and filtered through celite and eluted with EtOAc. The filtrate was concentrated and the mixture was purified by silica gel chromatography using 10-25% EtOAc/hexane as the eluent to give 4-((1-(4-(tert-butylamino)thieno[3,2-*d*]pyrimidin-7-yl)-3-phenyl-1*H*-pyrazol-4-yl)methyl)-*N,N*-bis(4-methoxybenzyl)benzenesulfonamide. The product was contained some impurity and was subjected for removing the protection groups directly. The product was dissolved in TFA/dichloroethane (2 mL/1 mL) and was heated at 100 °C for 1 h under microwave irradiation. Then, the mixture heated at 120 °C for another 1.5 h under microwave irradiation. The mixture was concentrated and submit for purification to give 4-((1-(4-aminothieno[3,2-*d*]pyrimidin-7-yl)-3-phenyl-1*H*-pyrazol-4-yl)methyl)benzenesulfonamide, TFA **211** (5.7 mg, 9.89 μmol, 3.95 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 (d, *J* = 4.9 Hz, 1H), 8.47 (d, *J* = 1.6 Hz, 1H), 8.32 (d, *J* = 2.2 Hz, 1H), 7.87 (s, 2H), 7.69 (m, 4H), 7.49 - 7.30 (m, 5H), 7.26 (s, 2H), 4.17 (s, 2H); MS (M+H)⁺ = 463.

Example 53

[0261] This example describes the synthesis of 1-methyl-2-(3-phenyl-4-(4-sulfamoylbenzyl)-1*H*-pyrazol-1-yl)-1*H*-imidazole-5-carboxylic acid, TFA **212** in an embodiment of the invention.

SCHEME 25



STEP 1: Synthesis of methyl 2-(4-(4-(*N,N*-bis(4-methoxybenzyl)sulfamoyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)-1-methyl-1H-imidazole-5-carboxylate

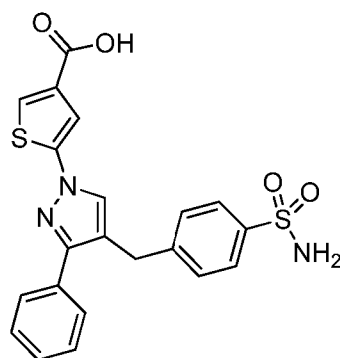
[0262] In a microwave tube was placed *N,N*-bis(4-methoxybenzyl)-4-((3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (138 mg, 0.25 mmol), methyl 2-bromo-1-methyl-1H-imidazole-5-carboxylate (54.8 mg, 0.25 mmol), (1*S*,2*S*)-*N*1,*N*2-dimethylcyclohexane-1,2-diamine (14.22 mg, 0.100 mmol), CuI (9.52 mg, 0.050 mmol), and Phosphoric acid, potassium salt (159 mg, 0.750 mmol). The air was removed and re-filled with N₂ (3 times). Then Toluene (2 ml) was added and the mixture was stirred at 110 °C for overnight. After cooling to rt, the mixture was dilute with EtOAc (3 mL) and filtered through celite and eluted with EtOAc. The filtrate was concentrated and the mixture was purified by silica gel chromatography using 10-25% EtOAc/hexane as the eluent to give methyl 2-(4-(4-(*N,N*-bis(4-methoxybenzyl)sulfamoyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)-1-methyl-1H-imidazole-5-carboxylate (57 mg, 0.082 mmol, 33.0 % yield). MS (M+H)⁺ = 692.

STEP 2: Synthesis of 1-methyl-2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-1H-imidazole-5-carboxylic acid, TFA **212**

[0263] To a solution of methyl 2-(4-(4-(*N,N*-bis(4-methoxybenzyl)sulfamoyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)-1-methyl-1H-imidazole-5-carboxylate (57 mg, 0.082 mmol) in THF (1 mL) was added LiOH(aq) (1.5 N, 0.4 mL, 0.6 mmol). The mixture was stirred at rt for 2 h. Then, 1 N HCl(aq) was added slowly until the pH of aqueous layer was about 4-5. The mixture was extracted with EtOAc (2 mL x 10) until no product was detected by UV from organic layer. The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was dried in vacuo to give crude acid intermediate. The intermediate was then dissolved in 1,2-dichloroethane/TFA (0.6 mL/0.6 mL) in a microwave tube. The tube was sealed and heat at 100 °C under microwave irradiation for 20 min. The mixture was concentrated and the residue was dissolved in DMF, filter, and submitted for purification to give 1-methyl-2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-1H-imidazole-5-carboxylic acid, TFA **212** (2 mg, 3.63 μmol, 4.40 % yield). MS (M+H)⁺ = 438.

Example 54

[0264] This example describes the synthesis of 5-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiophene-3-carboxylic acid, TFA **213** in an embodiment of the invention.

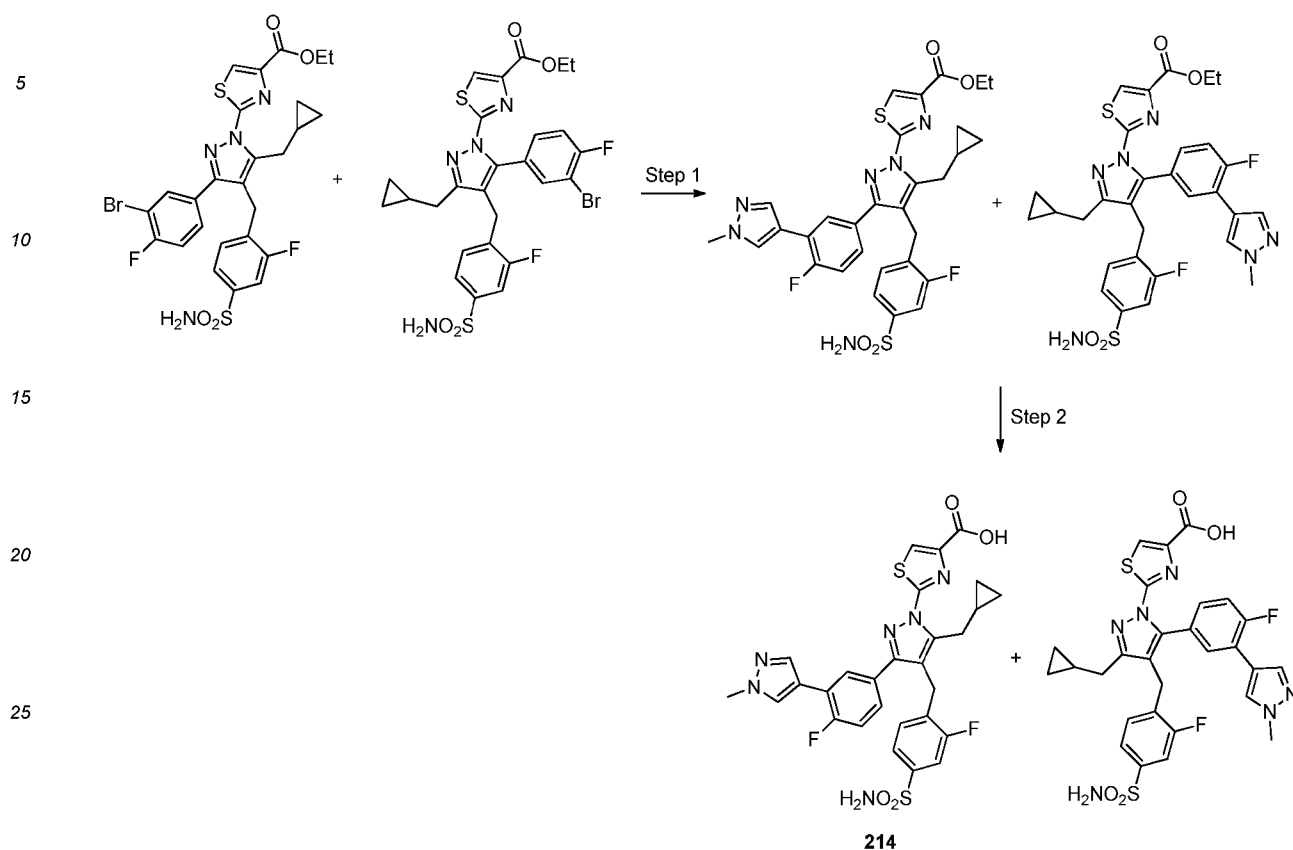
**213**

[0265] According to similar procedures described above for **212**, the title compound was prepared starting from *N,N*-bis(4-methoxybenzyl)-4-((3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide and ethyl 5-bromothiophene-3-carboxylate and then hydrolyzed. The final product was purified by reverse phase HPLC chromatography to give 5-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiophene-3-carboxylic acid, TFA **213**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.88 (s, 1H), 8.45 (s, 1H), 7.96 (d, *J* = 1.6 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.63 - 7.55 (m, 3H), 7.44 - 7.32 (m, 5H), 7.26 (s, 2H), 4.08 (s, 2H); MS (M+H)⁺ = 440.

Example 55

[0266] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **214** in an embodiment of the invention.

SCHEME 26



STEP 1: Synthesis of ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate and ethyl 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0267] In a microwave tube was placed ethyl 2-(3-(3-bromo-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (63.8 mg, 0.1 mmol) (2 regio-isomers), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (41.6 mg, 0.20 mmol), PdCl₂(dppf)-CH₂Cl₂ adduct (8.17 mg, 10.0 μmol), and K₂CO₃ (69.1 mg, 0.50 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, a mixture of 1,4-Dioxane (1.5 ml)/Water (0.5 ml) was added. The mixture was stirred at 95 °C (pre-heated) for 1.5 h. After cooling to rt, the mixture was extracted with EtOAc (2 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 40-70% EtOAc/hexane as the eluent to give ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (27 mg, 0.042 mmol, 42.3 % yield) and ethyl 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (27 mg, 0.042 mmol, 42.3 % yield), total 54 mg.

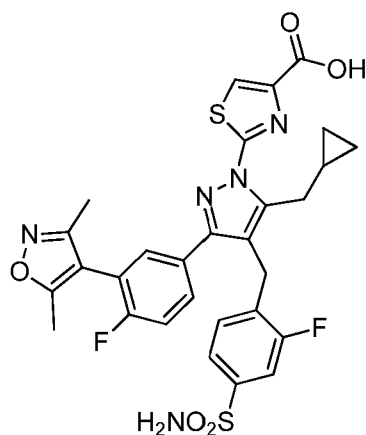
STEP 2: Synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA (214**)**

[0268] To a solution of ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (27 mg, 0.042 mmol) and ethyl 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (27 mg, 0.042 mmol) in THF (1 ml)/MeOH (0.3 ml) was added LiOH(aq) (1.5 N, 0.4 mL, 0.6 mmol). The mixture was stirred at 50 °C for 2 h. After cooling to rt, 1N HCl(aq) was added until the pH of aqueous layer is ca. 4. The mixture was concentrated and the residue was dissolved in DMF, filtered through a filter, and submitted for purification to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA (0.9 mg, 1.242 μmol, 2.94 % yield) **214** (powder weight: 0.9 mg, tR = 5.30 min, final QC) and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-

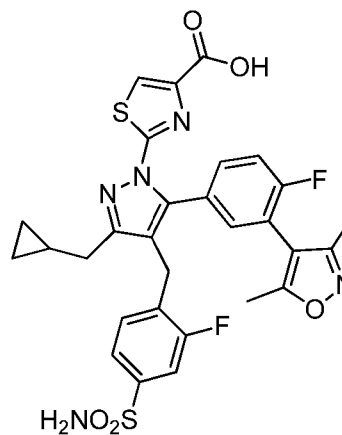
pyrazol-1-yl)thiazole-4-carboxylic acid, TFA (not collected) (for **214**) ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.15 (s, 1H), 8.29 (s, 1H), 8.01 (d, $J = 2.1$ Hz, 1H), 7.78 - 7.72 (m, 2H), 7.52 (dd, $J = 9.6, 1.8$ Hz, 1H), 7.46 (dd, $J = 8.0, 1.8$ Hz, 1H), 7.40 (s, 2H), 7.34 (ddd, $J = 8.5, 5.0, 2.2$ Hz, 1H), 7.26 (dd, $J = 11.0, 8.5$ Hz, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 4.10 (s, 2H), 3.85 (s, 3H), 3.15 (d, $J = 7.0$ Hz, 2H), 1.14 - 1.01 (m, 1H), 0.37 - 0.14 (m, 4H); MS ($\text{M}+\text{H}$) $^+$ = 611.

Example 56

[0269] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **215** and 2-(3-(cyclopropylmethyl)-5-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **216** in an embodiment of the invention.



215

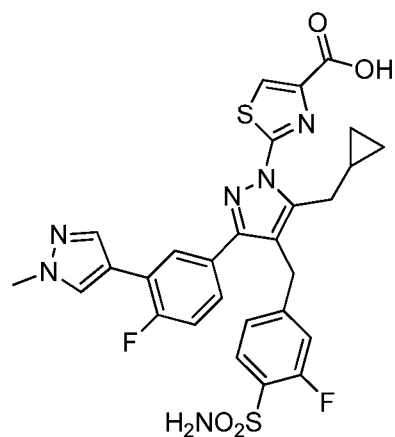
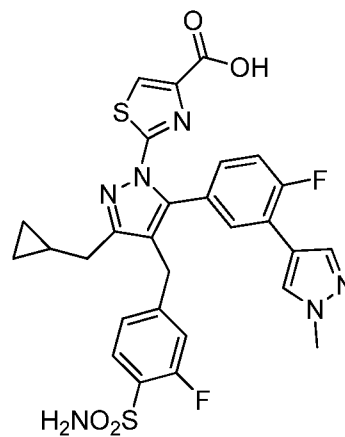


216

[0270] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **215** and 2-(3-(cyclopropylmethyl)-5-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **216**. MS ($\text{M}+\text{H}$) $^+$ = 626.

Example 57

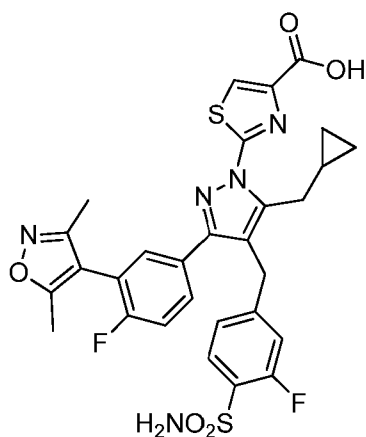
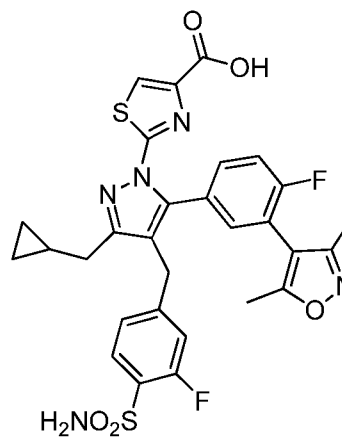
[0271] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **217** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **218** in an embodiment of the invention.

**217****218**

[0272] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **217** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **218**. MS (M+H)⁺ = 611.

Example 58

[0273] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **219** and 2-(3-(cyclopropylmethyl)-5-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **220** in an embodiment of the invention.

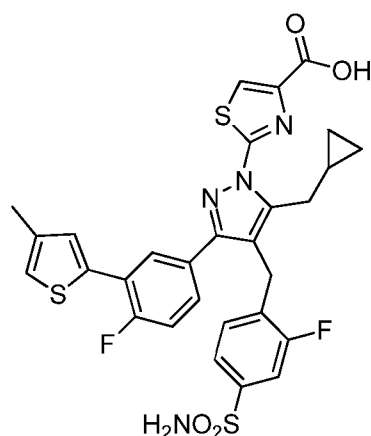
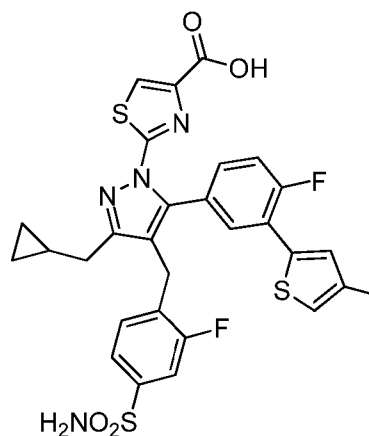
**219****220**

[0274] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **219** and 2-(3-(cyclopropylmethyl)-5-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **220**. MS (M+H)⁺ = 626.

Example 59

[0275] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **221** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **222** in an embodiment of the invention.

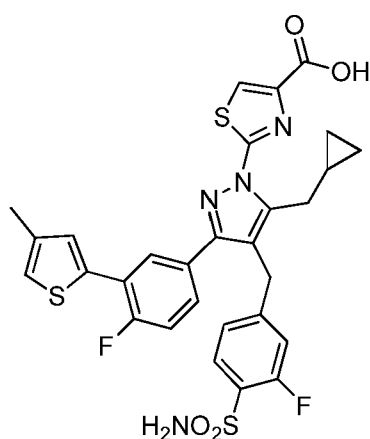
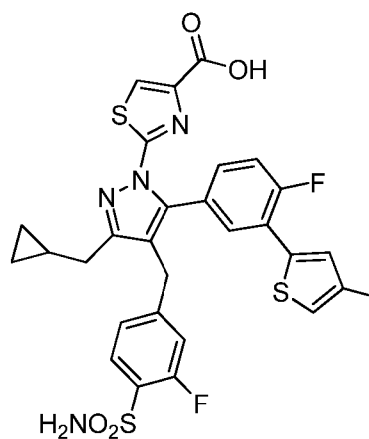
4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **221** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **222** in an embodiment of the invention.

**221****222**

[0276] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **221** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **222**. MS (M+H)⁺ = 627.

Example 60

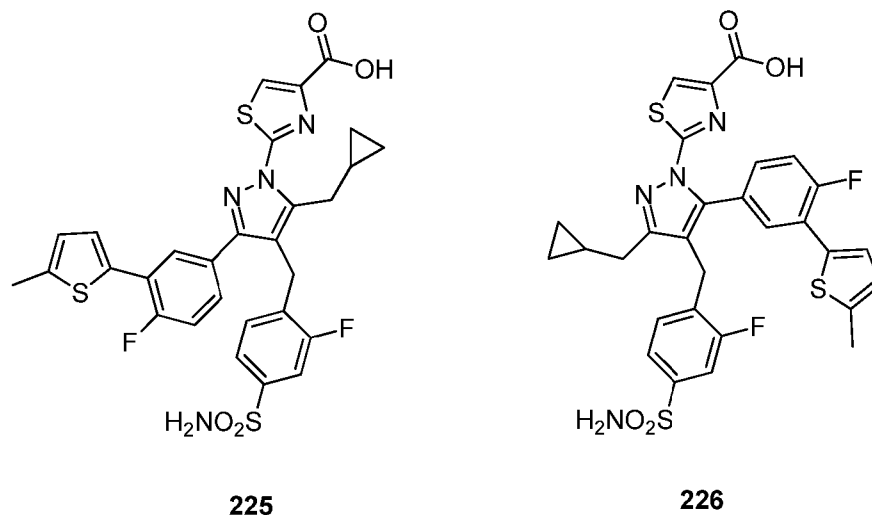
[0277] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **223** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **224** in an embodiment of the invention.

**223****224**

[0278] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **223** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **224**. MS (M+H)⁺ = 627.

Example 61

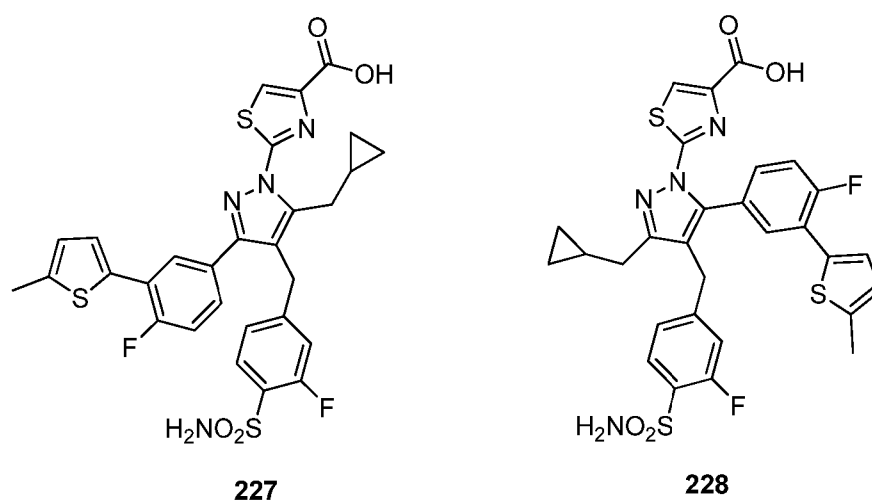
[0279] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **225** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **226** in an embodiment of the invention.



[0280] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **225** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **226**. MS (M+H)⁺= 627.

Example 62

[0281] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **227** and 2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **228** in an embodiment of the invention.

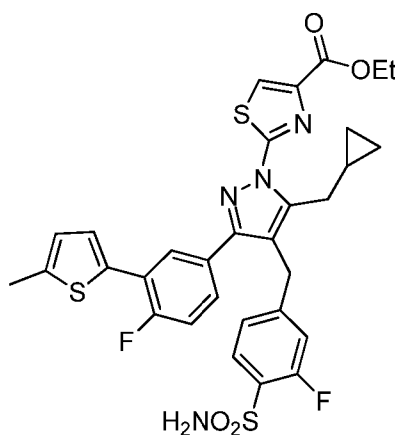


[0282] According to similar procedures described above for **212**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **227** and 2-(3-(cy-

clopropylmethyl)-5-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **228**. MS (M+H)⁺ = 627; (for **227**, HCl salt). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13 (s, 1H), 8.29 (s, 1H), 7.67 (t, *J* = 7.9 Hz, 1H), 7.62 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.58 (s, 2H), 7.50 (ddd, *J* = 8.5, 4.8, 2.2 Hz, 1H), 7.34 (dd, *J* = 11.3, 8.6 Hz, 1H), 7.19 (dd, *J* = 11.3, 1.6 Hz, 1H), 7.13 (dd, *J* = 3.6, 0.9 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.81 (dt, *J* = 3.6, 1.1 Hz, 1H), 4.14 (s, 2H), 3.15 (d, *J* = 6.9 Hz, 2H), 2.44 (d, *J* = 1.1 Hz, 3H), 1.19 - 1.03 (m, 1H), 0.39 - 0.28 (m, 2H), 0.24 - 0.14 (m, 2H).

Example 63

[0283] This example describes the synthesis of ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **229** in an embodiment of the invention.

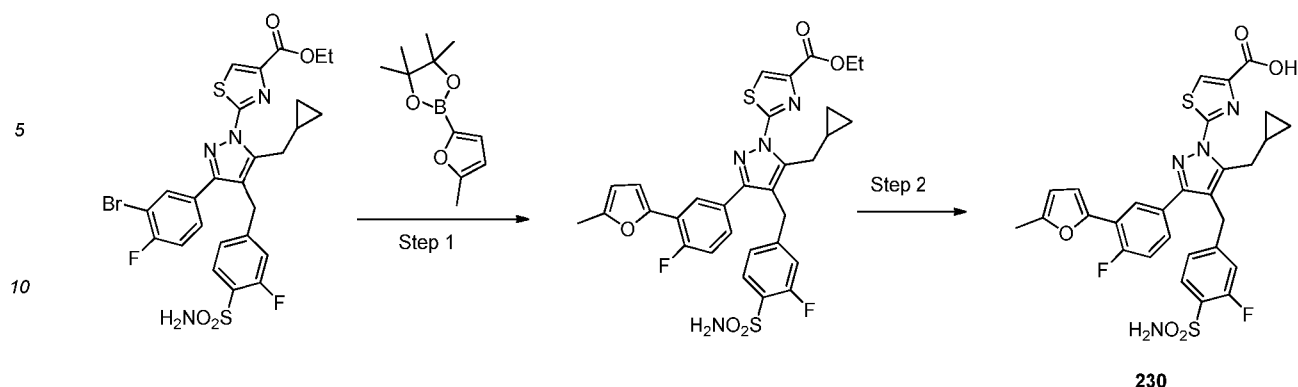


229

[0284] In a microwave tube was placed ethyl 2-(3-(3-bromo-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (287 mg, 0.45 mmol) (2 regio-isomers), PdCl₂(dppf)-CH₂Cl₂ adduct (55.1 mg, 0.068 mmol), and K₂CO₃ (466 mg, 3.38 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, a solution of 4,4,5,5-tetramethyl-2-(5-methylthiophen-2-yl)-1,3,2-dioxaborolane (252 mg, 1.125 mmol) in 1,4-Dioxane (4.5 ml) and Water (1.5 ml) was added. The mixture was stirred at 90 °C (pre-heated) for 1.5 h. After cooling to rt, the mixture was extracted with EtOAc (5 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 25-35% EtOAc/hexane as the eluent to give desired product. The product has light brown color and can be re-crystallized from CH₂Cl₂/hexane system. Dissolved the product in CH₂Cl₂ (5 mL) and then added hexane (ca. 10 mL). Then slowly removed solvent by air blow to ca. 1/4 amount of solvent and then added hexane (15 mL). The solid was filtered and triturated with hexane (3 mL x 3) and then dried to give ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate **229** (276 mg, 0.422 mmol, 94 % yield) as a off-white solid. 241 mg + 35 mg, total 276 mg (2 crops). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.37 (ddd, *J* = 8.5, 4.7, 2.2 Hz, 1H), 7.15 - 7.04 (m, 3H), 7.00 (dd, *J* = 11.1, 1.6 Hz, 1H), 6.73 (dt, *J* = 3.7, 1.0 Hz, 1H), 4.93 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.07 (s, 2H), 3.21 (d, *J* = 6.8 Hz, 2H), 2.49 (d, *J* = 1.1 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.19 - 1.06 (m, 1H), 0.49 - 0.38 (m, 2H), 0.28 (dt, *J* = 6.1, 4.7 Hz, 2H); MS (M+H)⁺ = 655.

Example 64

[0285] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **230** in an embodiment of the invention.



STEP 1: Synthesis of ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

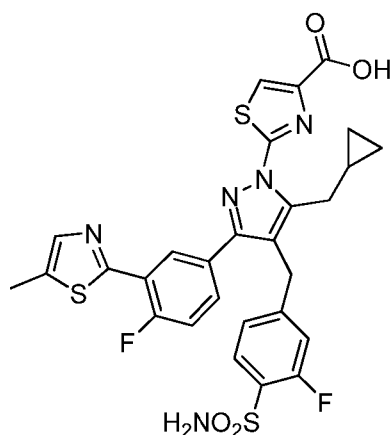
[0286] In a microwave tube was placed ethyl 2-(3-(3-bromo-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (31.9 mg, 0.05 mmol) (2 regio-isomers), PdCl₂(dppf)-CH₂Cl₂ adduct (8.17 mg, 10.0 μmol), and K₂CO₃ (51.8 mg, 0.375 mmol). The air was removed and re-filled with N₂ (repeat for 3 times). Then, a solution of 4,4,5,5-tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane (26.0 mg, 0.125 mmol) in 1,4-Dioxane (1 ml) and Water (0.5 ml) was added. The mixture was stirred at 90 °C (pre-heated) for 1.5 h. After cooling to rt, the mixture was extracted with EtOAc (3 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was purified by silica gel chromatography using 20-40% EtOAc/hexane as the eluent to give ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (30 mg, 0.047 mmol, 94 % yield). MS (M+H)⁺= 639.

STEP 2: Synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (230)

[0287] To a solution of ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (30 mg, 0.047 mmol) in THF (1 ml)/MeOH (0.3 ml) was added LiOH(aq) (1.5 N, 0.4 mL, 0.6 mmol). The mixture was stirred at 50 °C for 1 h. After cooling to rt, 1N HCl_(aq) was added until the pH of aqueous layer is ca. 3-4. The mixture was poured into EtOAc/H₂O (5 mL/5 mL). The aqueous layer was extracted with EtOAc (5 mL x 3). The combined organic layer was dried (Na₂SO₄) and filtered. After removal of solvent, the product was dissolved in CH₂Cl₂ (2 mL) and then added hexane (40 mL). The resulted solid was filtered and triturated with hexane (3 mL x 3) and then dried under house vacuum at 50 °C for overnight to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **230** (22 mg, 0.036 mmol, 77 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.10 (s, 1H), 8.29 (s, 1H), 7.76 (dd, *J* = 7.4, 2.3 Hz, 1H), 7.67 (t, *J* = 7.9 Hz, 1H), 7.57 (s, 2H), 7.54 (ddd, *J* = 8.6, 4.8, 2.3 Hz, 1H), 7.33 (dd, *J* = 11.2, 8.6 Hz, 1H), 7.20 (dd, *J* = 11.3, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.70 (t, *J* = 3.5 Hz, 1H), 6.22 (dt, *J* = 3.1, 1.0 Hz, 1H), 4.15 (s, 2H), 3.15 (d, *J* = 6.9 Hz, 2H), 2.27 (s, 3H), 1.17 - 1.06 (m, 1H), 0.38 - 0.28 (m, 2H), 0.24 - 0.14 (m, 2H); MS (M+H)⁺= 611.

Example 65

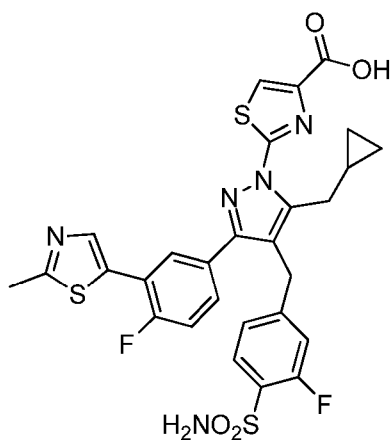
[0288] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiazol-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **231** in an embodiment of the invention.

**231**

[0289] According to similar procedures described above for **230**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiazol-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **231**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13 (s, 1H), 8.30 (dd, *J* = 7.2, 2.3 Hz, 1H), 8.28 (s, 1H), 7.70 - 7.59 (m, 3H), 7.54 (s, 2H), 7.43 (dd, *J* = 11.1, 8.7 Hz, 1H), 7.16 (dd, *J* = 11.4, 1.6 Hz, 1H), 7.05 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.14 (s, 2H), 3.19 - 3.14 (m, 2H), 2.49 (d, *J* = 1.2 Hz, 3H), 1.18 - 1.05 (m, 1H), 0.39 - 0.29 (m, 2H), 0.24 - 0.15 (m, 2H); MS (M+H)⁺ = 628.

Example 66

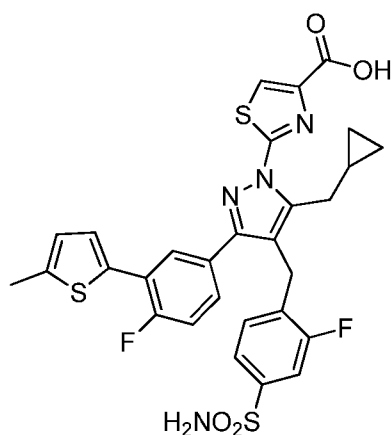
[0290] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(2-methylthiazol-5-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **232** in an embodiment of the invention.

**232**

[0291] According to similar procedures described above for **230**, the title compounds were prepared to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(2-methylthiazol-5-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **232**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.97 (s, 1H), 7.68 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.57 (m, 3H), 7.39 (dd, *J* = 10.8, 8.7 Hz, 1H), 7.17 (d, *J* = 11.3 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 4.15 (s, 2H), 3.16 (d, *J* = 6.9 Hz, 2H), 2.66 (s, 3H), 1.18 - 1.01 (m, 1H), 0.37 - 0.27 (m, 2H), 0.21 (d, *J* = 4.9 Hz, 2H); MS (M+H)⁺ = 628.

Example 67

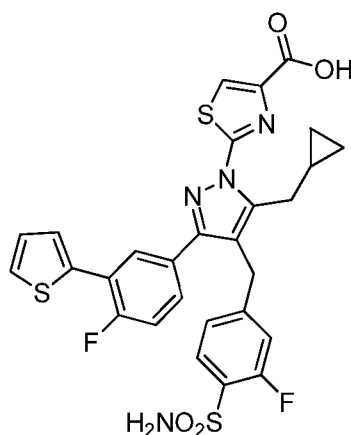
[0292] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **233** in an embodiment of the invention.

**233**

[0293] According to similar procedures described above for **230**, the title compounds were prepared to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **233**. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.09 (s, 1H), 8.29 (s, 1H), 7.63 (dd, $J = 7.5, 2.2$ Hz, 1H), 7.56 (dd, $J = 9.6, 1.8$ Hz, 1H), 7.53 - 7.49 (m, 1H), 7.49 - 7.44 (m, 1H), 7.42 (s, 2H), 7.34 (dd, $J = 11.3, 8.6$ Hz, 1H), 7.19 - 7.11 (m, 2H), 6.81 (dt, $J = 3.6, 1.1$ Hz, 1H), 4.08 (s, 2H), 3.16 (d, $J = 6.9$ Hz, 2H), 2.44 (d, $J = 1.1$ Hz, 3H), 1.17 - 1.02 (m, 1H), 0.35 - 0.27 (m, 2H), 0.22 - 0.14 (m, 2H); MS (M+H) $^+$ = 627.

Example 68

[0294] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(thiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **234** in an embodiment of the invention.

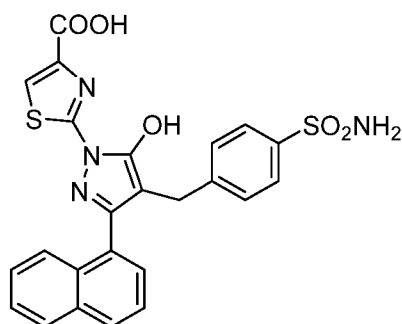
**234**

[0295] According to similar procedures described above for **230**, the title compounds were prepared and the final product was purified by reverse phase HPLC chromatography to give 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(thiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **234**. MS (M+H) $^+$ = 613.

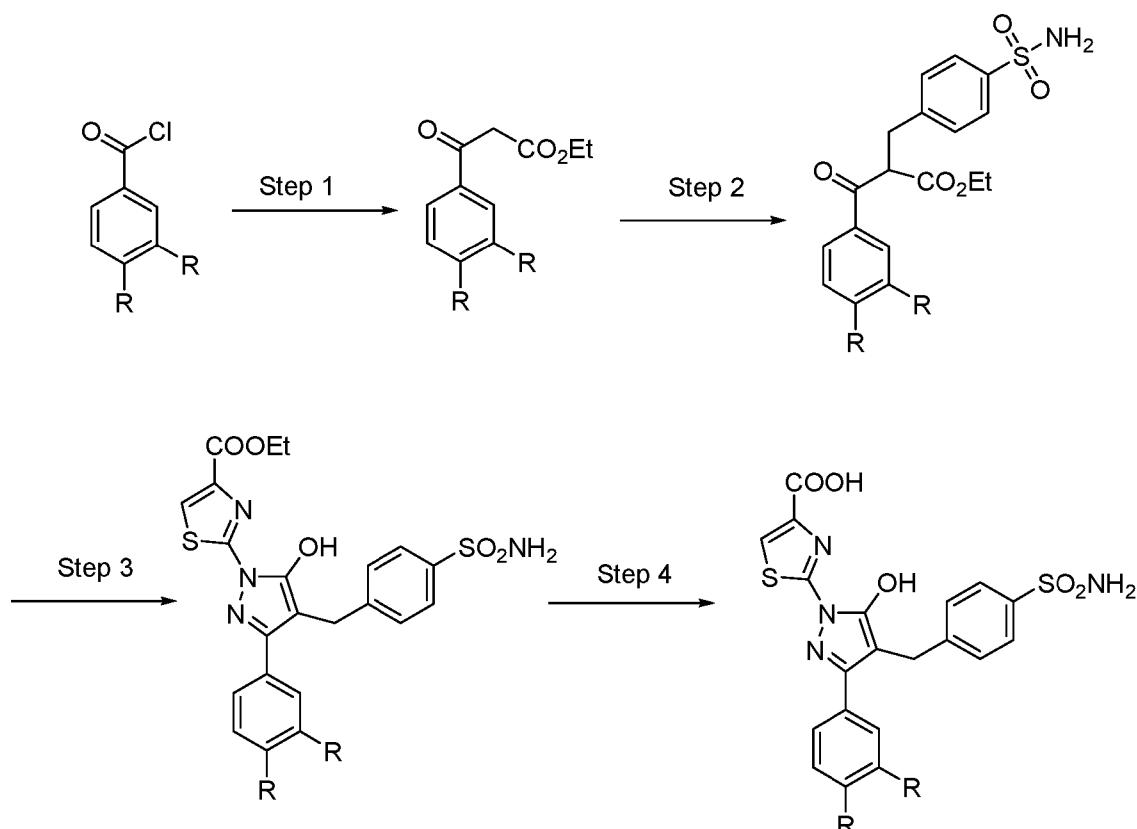
Example 69

2-(5-(hydroxy-3-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **451**:

[0296]



Route A



STEP 1. Synthesis of ethyl 3-(naphthalen-1-yl)-3-oxopropanoate.

[0297] Lithium hexamethyldisiloxane (LHMDS) (1 M in hexane, 7.8 mL, 7.8 mmol) was dissolved in dry THF (5 mL) and cooled down at -78°C . Ethyl acetate (760 μL , 7.8 mmol) was added dropwise and the reaction mixture was stirred for 30 min at -78°C . 1-Naphthoyl chloride (1 mL, 5.2 mmol) was dissolved in dry THF (5 mL) and was cooled down at -78°C . To this solution, the ethyl acetate/LHMDS solution was added dropwise and the reaction mixture was warmed to ambient temperature over 2h. Reaction was quenched with ammonium chloride, diluted with ethyl acetate (50 mL). The organic layer was separated and washed with water (50 mL), brine (50 mL) and dried with anhydrous magnesium sulfate. The residue was purified by flash chromatography (Combi-flash Rf, hexane ethyl/acetate = 5% isocratic) to give ethyl 3-(naphthalen-1-yl)-3-oxopropanoate (300 mg, 24%).

STEP 2. Synthesis of ethyl 3-(naphthalen-1-yl)-3-oxo-2-(4-sulfamoylbenzyl)propanoate.

[0298] Ethyl 3-(naphthalen-1-yl)-3-oxopropanoate (300 mg, 1.24 mmol) was dissolved in dry 1,4-dioxane (2 mL) and sodium hydride (70 mg, 1.74 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and

4-(bromomethyl)benzenesulfonamide (372 mg, 1.48 mmol) was added. The reaction mixture was stirred overnight at room temperature. The residue was purified by flash chromatography (Combi-flash Rf, hexane/methanol, 0-60% gradient) to give ethyl 3-(naphthalen-1-yl)-3-oxo-2-(4-sulfamoylbenzyl)propanoate (380 mg, 75%).

STEP 3. Synthesis of ethyl 2-(5-hydroxy-3-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0299] Ethyl 3-(naphthalen-1-yl)-3-oxo-2-(4-sulfamoylbenzyl)propanoate (260 mg, 0.63 mmol), tert-butyl 2-hydrazinylthiazole-4-carboxylate (137 mg, 0.63 mmol), *p*-toluene sulfonic acid (120 mg, 0.63 mmol) and ethanol (6 mL) were placed in microwave vial and irradiated at 110 °C for 3h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with saturated sodium bicarbonate (20 mL), brine (50 mL) and dried with anhydrous magnesium sulfate. The residue was purified by flash chromatography (Combi-flash Rf, DCM/methanol, 0-10% gradient) to give ethyl 2-(5-hydroxy-3-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (210 mg, 60%).

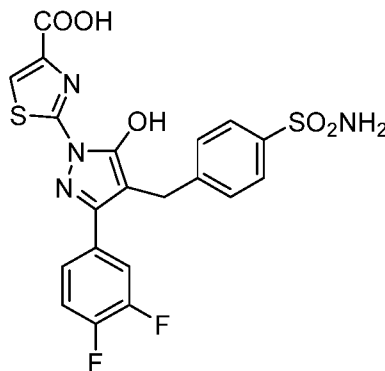
STEP 4. 2-(5-hydroxy-3-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **451**

[0300] Ethyl 2-(5-hydroxy-3-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (50 mg, 0.096 mmol) was dissolved in THF/MeOH (1mL:1mL) and LiOH (5 M, 500 µL) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was neutralized by addition of hydrochloric acid (1.2 M), diluted with ethyl acetate (15 mL), washed with water (10 mL) and dried with anhydrous magnesium sulfate. The organic layer was concentrated down using rotary evaporator and dissolved in a mixture of DMSO and MeOH and purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 20% to 85% CH₃CN for 4 min, 0.1% TFA) to give the title compound **451** (76%). ¹H-NMR (d⁶-DMSO) δ 8.19 (s, 1H), 8.09 (d, 2H, *J* = 1.6 Hz), 8.00 (d, 1H, *J* = 8 Hz), 7.86 (d, 1H, *J* = 8 Hz) 7.63-7.51 (m, 6H), 7.12 (d, 1H, *J* = 8 Hz), 3.69 (s, 2H); MS (ES) 506.9 (M+H)⁺ LCMS RT = 0.88 min.

Example 70

2-(3-(3,4-difluorophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **452**

[0301]



[0302] Using procedures analogous to that described for the preparation of **451**, the title compounds were prepared and purified by HPLC: 2-(3-(3,4-difluorophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **452** ¹H-NMR (d⁶-DMSO) δ 8.18 (s, 1H), 7.85 (d, 2H, *J* = 8.4 Hz), 7.56 (m, 1H), 7.45-7.41 (m, 4H), 3.99 (s, 2H); MS (ES) 492.9 (M+H)⁺ LCMS RT = 0.88 min.

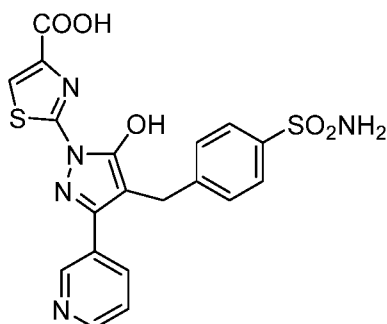
Example 71

2-(5-hydroxy-3-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **453**

[0303]

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[0304] Using procedures analogous to that described for the preparation of **451**, the title compounds were prepared and purified by HPLC: 2-(5-hydroxy-3-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **453**. MS (ES) 457.9 (M+H)⁺ LCMS RT = 0.30 min.

Example 72

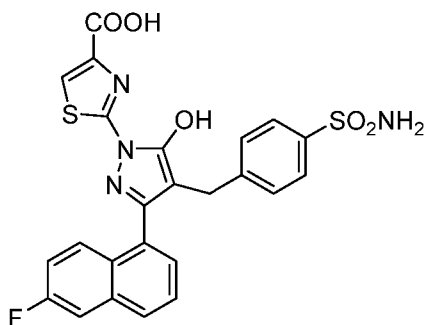
20

2-(3-(6-fluoronaphthalen-1-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **454**

[0305]

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[0306] Using procedures analogous to that described for the preparation of **451**, the title compounds were prepared and purified by HPLC: 2-(3-(6-fluoronaphthalen-1-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **454**. ¹H-NMR (d⁶-DMSO) δ 8.20 (m, 2H), 7.88 (d, 2H, *J* = 8 Hz), 7.70-7.55 (m, 5H), 7.32 (m, 1H), 7.12 (d, 1H, *J* = 8Hz), 3.69 (s, 2H); MS (ES) 524.9 (M+H)⁺ LCMS RT = 0.94 min.

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Example 73

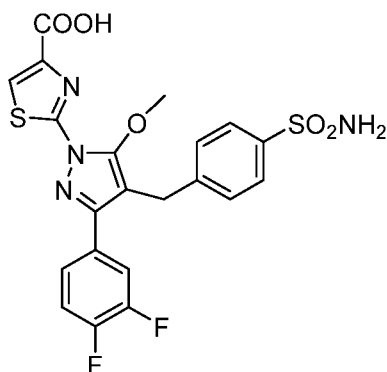
2-(3-(3,4-difluorophenyl)-5-methoxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **455**

[0307]

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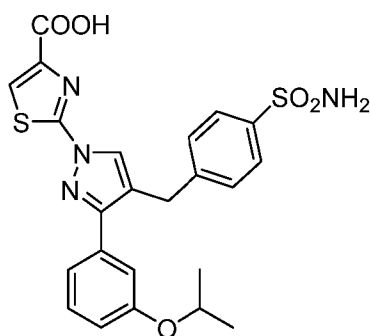


[0308] 2-(3-(3,4-Difluorophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **452** (20 mg, 0.038 mmol) was dissolved in anhydrous DMF (300 μ L). Anhydrous potassium carbonate (16 mg, 0.114 mmol) and methyl iodide (3 μ L, 0.05 mmol) were added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (5 mL) and washed with water (3x 1 mL). The organic layers were concentrated by rotary evaporator and THF (500 μ L) and sodium hydroxide (5 N, 200 μ L) were added. After 1 h, the reaction mixture was neutralized with hydrochloric acid (0.1 M) and the residue was purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 20% to 95% CH₃CN for 4 min, 0.1% TFA) to give the title compound **455** (85%). ¹H-NMR (δ^6 -DMSO) δ 8.20 (s, 1H), 7.81 (d, 2H, *J* = 8 Hz), 7.54-7.50 (m, 2H), 7.39-7.36 (m, 3H), 3.69 (s, 2H), 3.49 (s, 3H); MS (ES) 506.9 (M+H)⁺ LCMS RT = 0.89 min.

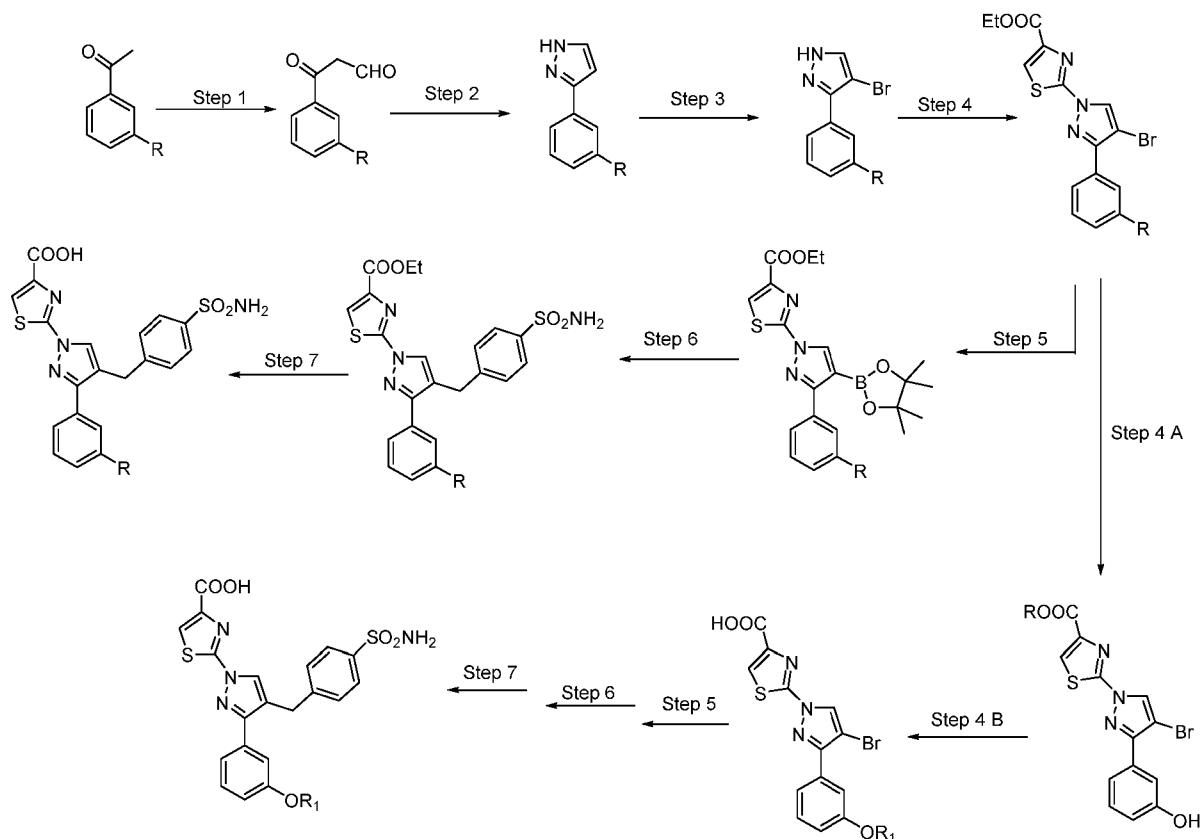
Example 74

2-(3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **459**

[0309]



Route B



STEP 1. Synthesis of 3-(3-methoxyphenyl)-3-oxopropanal.

[0310] 3-Methoxyphenyl acetophenone (3 g, 0.17 mol) was dissolved in anhydrous THF (25 mL) and cooled to 0 °C. Sodium hydride (930 mg, 0.23 mol) and ethyl formate (4.3 mL, 0.53 mol) were added. The reaction mixture was stirred overnight at room temperature, quenched with sodium hydroxide (2 N), and washed with diethyl ether. The water layers were acidified with hydrochloric acid (2 N) and extracted with diethyl ether (3 x 50 mL). The organic layers were dried with anhydrous magnesium sulfate and concentrated down with rotary evaporator to give 3-(3-methoxyphenyl)-3-oxopropanal (quantitative yield) which was sufficiently pure to be used in subsequent reaction.

STEP 2. Synthesis of 3-(3-methoxyphenyl)-1H-pyrazole

[0311] To a stirred solution of 3-(3-methoxyphenyl)-3-oxopropanal in ethanol, hydrazine (1 mL, 0.3 mmol) was added and the reaction mixture was refluxed for 3h. The reaction mixture was concentrated to half of its original volume, water (50 mL) and sodium hydroxide (1 M, 100 mL) were added. The mixture was extracted with ethyl acetate (3 x 50 mL) and dried with anhydrous magnesium sulfate. The organic layers were filtered off and concentrated by rotary evaporator to give a yellow liquid (3 g, 92%). The product was sufficiently pure for the subsequent reaction.

STEP 3. Synthesis of 4-bromo-3-(3-methoxyphenyl)-1H-pyrazole.

[0312] 3-(3-Methoxyphenyl)-1H-pyrazole (3 g, 0.017 mol) was dissolved in anhydrous DMF (30 mL) and cooled to 0°C. NBS (3.20 g, 0.018 mol) was added in three portions and the reaction mixture was stirred at room temperature for overnight. The reaction mixture was poured into a mixture of ethyl acetate and saturated sodium bicarbonate (1:1, 300 mL) and organic layer was separated, washed with brine (2 x 100 mL) and dried with anhydrous magnesium sulfate. The solvents were removed by rotary evaporator and purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-50% gradient) to give 4-bromo-3-(3-methoxyphenyl)-1H-pyrazole (3 g, 70%).

STEP 4. Synthesis of ethyl 2-(4-bromo-3-(3-methoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0313] 4-Bromo-3-(3-methoxyphenyl)-1H-pyrazole (3 g, 0.012 mol) was dissolved in anhydrous DMSO (15 mL) and anhydrous potassium carbonate (2.46 g, 0.018 mol) and ethyl 2-bromothiazole-4-carboxylate (2.8 g, 0.012) were added. The reaction mixture was heated at 120 °C for 6 h. After cooling down, the reaction mixture was poured into water and the precipitate was filtered off to give ethyl 2-(4-bromo-3-(3-methoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (3.54 g, 73%).

STEP 4A. Synthesis of ethyl 2-(4-bromo-3-(3-hydroxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid.

[0314] Ethyl 2-(4-bromo-3-(3-methoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (3 g, 0.008 mol) was dissolved in anhydrous DCM (20 mL). Boron tribromide (1 M in DCM, 9.5 mL, 0.0096 mol) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. The precipitate was filtered off and washed with DCM to give ethyl 2-(4-bromo-3-(3-hydroxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (2 g, 60 %).

STEP 4B. Synthesis of isopropyl 2-(4-bromo-3-(3-isopropoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0315] Ethyl 2-(4-bromo-3-(3-hydroxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (500 mg, 0.1 mmol) was dissolved in anhydrous DMF. Potassium carbonate (2.1 g, 15 mmol) and isopropyl bromide (1.4 mL, 10 mmol) were added and the reaction was irradiated at 130 °C for 40 min in a microwave reactor. The reaction mixture was poured into water and extracted with ethyl acetate (3 x 40 mL). The organic layers were washed with brine (2 x 50 mL) and dried with anhydrous magnesium sulfate. The solvents were removed by rotary evaporator and purified by purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-20% gradient) to give isopropyl 2-(4-bromo-3-(3-isopropoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (520 mg, 84%).

STEP 5. Synthesis of isopropyl 2-(3-(3-isopropoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0316] Isopropyl 2-(4-bromo-3-(3-isopropoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (520 mg, 1.15 mmol) was dissolved in anhydrous THF (5 mL) and potassium acetate (340 mg, 3.46 mmol), PdCl₂(dppf) (0.9 mg, 0.0011 mmol) and bis(pinacolato)diborane (408 mg, 1.61 mmol) were added. The vial was purged with argon for 5 min. The reaction was heated at 100 °C for 2h. The reaction mixture was diluted with ethyl acetate and filtered through a plug of celite.

The solvent was removed by rotary evaporator and purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-40% gradient) to give a mixture of isopropyl 2-(3-(3-isopropoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate and isopropyl 2-(3-(3-isopropoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

STEP 6. Synthesis of isopropyl 2-(3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0317] A mixture of isopropyl 2-(3-(3-isopropoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylate and 2-(3-(3-isopropoxyphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (500 mg, 1 mmol), potassium carbonate (414 mg, 3 mmol), Pd(PPh₃)₄ (1.2 mg, 0.001 mmol), and 4-(bromomethyl)benzenesulfonamide (275 mg, 1.1 mmol) were added to a microwave vial, followed by THF (8 mL) and water (3 mL). The vial was sealed and heated at 100 °C for 1h. The reaction mixture was cooled, poured into water, and extracted with ethyl acetate (3 x 20 mL). The organic layers were washed with brine (2 x 20 mL) and dried with anhydrous magnesium sulfate. The solvents were removed by rotary evaporator and purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-70% gradient) to give the title compound (150 mg, 27%).

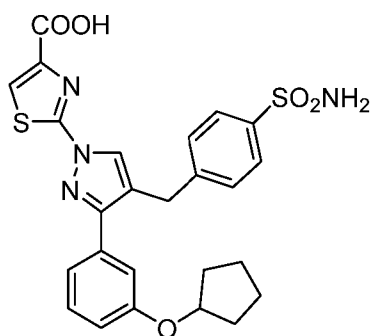
STEP 7. Synthesis of 2-(3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **459**

[0318] Isopropyl 2-(3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (50 mg, 0.09 mmol) was dissolved in THF/MeOH (1 mL : 1 mL) and LiOH (5 M, 500 µL) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was neutralized by addition of hydrochloric acid (1.2 M), diluted with ethyl acetate (15 mL), washed with water (10 mL), and dried with anhydrous magnesium sulfate. The organic layer was concentrated using a rotary evaporator, dissolved in a mixture of DMSO and MeOH, and purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 45% to 85% CH₃CN for 7 min, 0.1% TFA) to give the title compound **459** (34 mg, 76%). ¹H-NMR (d⁶-DMSO) δ 8.24 (m, 2H), 7.78 (d, 2H, J = 8 Hz), 7.44 (d, 2H, J = 8 Hz), 7.39-7.30 (m, 3H), 7.22 (d, 1H, J = 8 Hz), 7.09 (d, 1H, J = 4 Hz), 6.99-6.96 (m, 1H), 4.51 (m, 1H), 4.15 (s, 2H), 1.27 (d, 6H, J = 8 Hz); MS (ES) 499.0 (M+H)⁺ LCMS RT = 1.07 min.

Example 75

2-(3-(3-(cyclopentyloxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **460**

[0319]

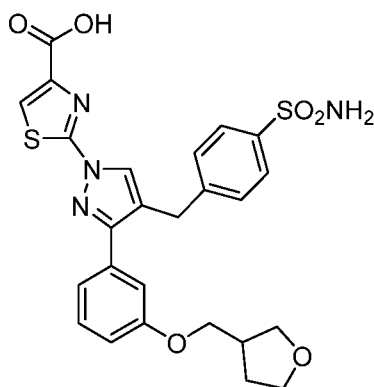


[0320] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(3-(3-(cyclopentyloxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **460** ¹H-NMR (d⁶-DMSO) δ 8.55 (m, 2H), 8.25 (d, 2H, J = 4 Hz), 7.77 (d, 2H, J = 4 Hz), 7.55-7.26 (m, 3H), 7.22 (d, 1H, J = 8 Hz), 7.09 (d, 1H, J = 8 Hz), 6.99-6.96 (m, 1H), 4.74 (m, 1H), 4.15 (s, 2H), 1.91-1.82 (m, 2H), 1.69-1.58 (m, 4H), 1.23 (m, 2H); MS (ES) 525.0 (M+H)⁺ LCMS RT = 1.15 min.

Example 76

2-(4-(4-sulfamoylbenzyl)-3-(3-((tetrahydrofuran-3-yl)methoxy)phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **461**

[0321]

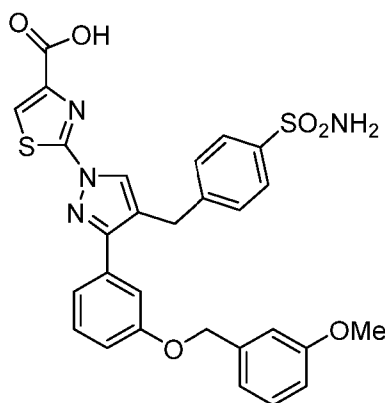


[0322] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(4-(4-sulfamoylbenzyl)-3-((tetrahydrofuran-3-yl)methoxy)phenyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid **461** MS (ES) 540.7 (M+H)⁺ LCMS RT = 1.13 min.

Example 77

2-(3-(3-((3-methoxybenzyl)oxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **462**

[0323]

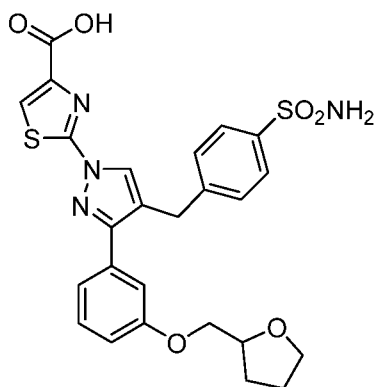


[0324] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(3-(3-((3-methoxybenzyl)oxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **462** MS (ES) 576.9 (M+H)⁺ LCMS RT = 1.02 min.

Example 78

2-(4-(4-sulfamoylbenzyl)-3-((tetrahydrofuran-2-yl)methoxy)phenyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid **463**.

[0325]

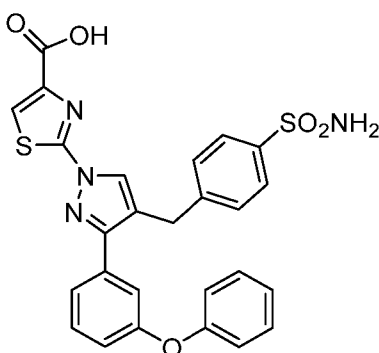


[0326] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(4-(4-sulfamoylbenzyl)-3-((tetrahydrofuran-2-yl)methoxy)phenyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid **463**. MS (ES) 540.9 (M+H)⁺ LCMS RT = 0.76 min.

Example 79

2-(3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **464**

[0327]

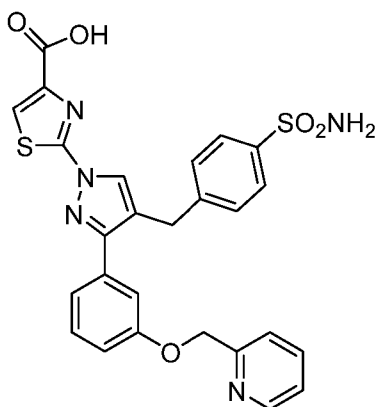


[0328] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **464** MS (ES) 532.9(M+H)⁺ LCMS RT = 0.98 min.

Example 80

2-(3-(3-(pyridin-3-ylmethoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **465**

[0329]

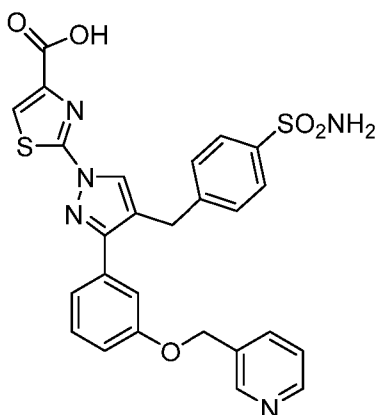


[0330] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(3-(3-(pyridin-3-ylmethoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **465** MS (ES) 548.0 (M+H)⁺ LCMS RT = 0.68 min.

Example 81

2-(3-(3-(pyridin-2-ylmethoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **466**

[0331]

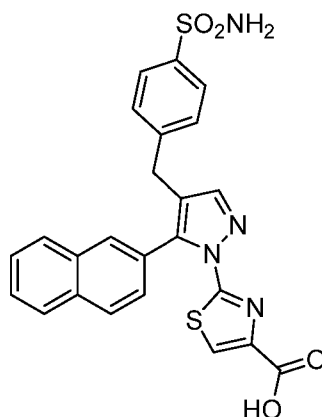


[0332] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(3-(3-(pyridin-2-ylmethoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA **466** MS (ES) 547.9 (M+H)⁺ LCMS RT = 0.68 min.

Example 82

2-(5-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **474**

[0333]

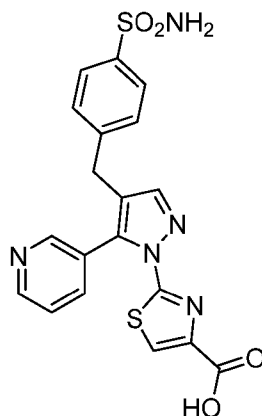


[0334] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(5-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **474** ¹H-NMR (*α*⁶-DMSO) δ 8.24(s, 1H), 8.13(s, 1H), 7.91-8.03(m, 4H), 7.80(d, *J*=8.2 Hz, 2H), 7.52-7.58(m, 3H), 7.32(s, 2H), 4.25(s, 2H); MS (ES) 491 (M+H)⁺ LCMS RT 1.04 min.

Example 83

2-(5-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **475**

[0335]

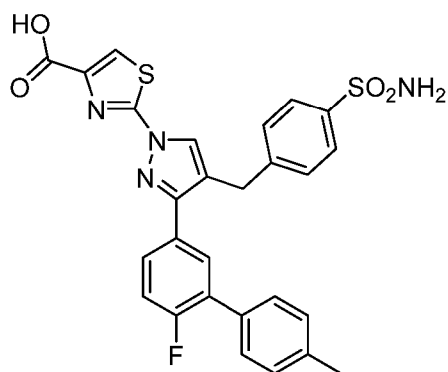


[0336] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(5-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **475** MS (ES) 442 (M+H)⁺ LCMS RT 0.64 min.

Example 84

2-(3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **476**.

[0337]

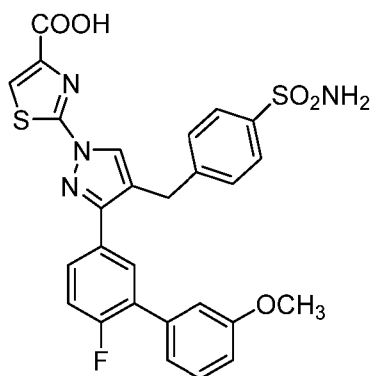


[0338] Using procedures analogous to that described for the preparation of **459**, the title compound was prepared and purified by HPLC: 2-(3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **476**. $^1\text{H-NMR}$ (d^6 -DMSO) δ 8.27(d, J = 9.24 Hz, 2H), 7.76-7.78(m, 4H), 7.29-7.46(m, 8H), 4.2(s, 2H), 2.35(s, 3H); MS (ES) 549 (M+H) $^+$ LCMS RT 1.27 min.

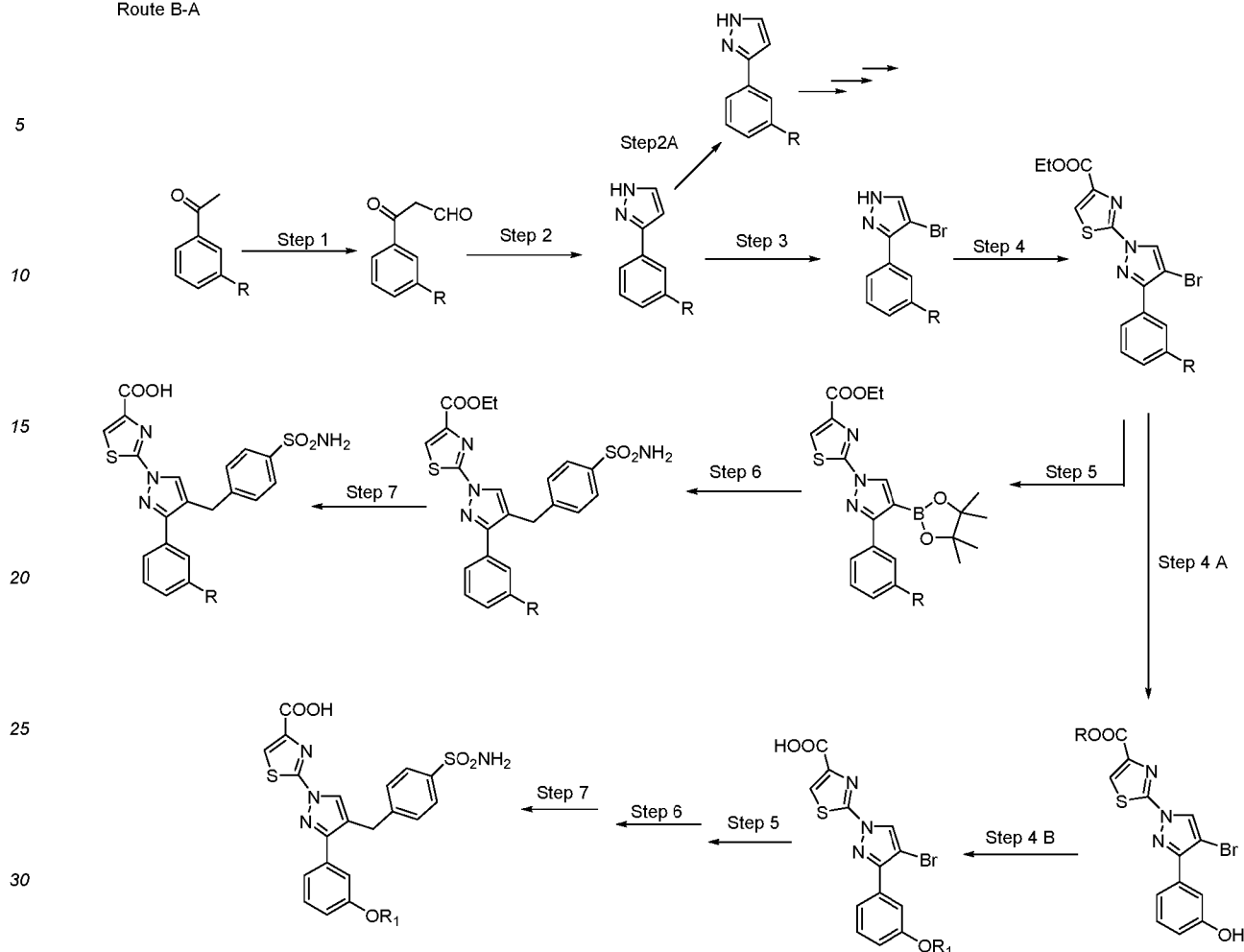
Example 85

2-(3-(6-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **456**

[0339]



Route B-A



[0340] Using procedures analogous to those described in the preparation of **459**, Step 1-2, 3-(3-bromo-4-fluorophenyl)-1H-pyrazole was prepared.

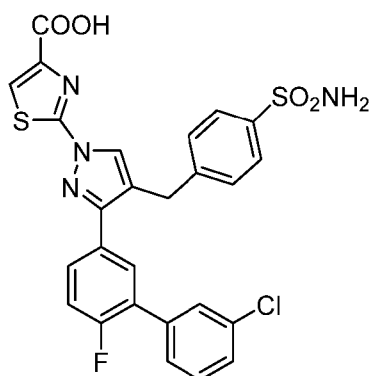
[0341] Step 2A: 3-(3-bromo-4-fluorophenyl)-1H-pyrazole (100 mg, 0.415 mmol), 3-methoxyphenyl boronic acid (95 mg, 0.622 mmol), K_2CO_3 (678 mg, 4.977 mmol), and a 2:1 mixture of dioxane/ H_2O (8.0 mL) were combined in a microwave vial and then degassed and purged with argon (3x). $Pd(dppf)Cl_2$ was added and the reaction mixture was heated to 120 °C for 1 h. The reaction mixture was cooled to room temperature, NaOH (8 mL, 1M) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The crude product was purified by flash chromatography (Combi-flash Rf, dichloromethane/methanol, 0-10% gradient) to give 3-[4-fluoro-3-(3-methoxyphenyl)phenyl]-1H-pyrazole (419 mg, 94%). ^1H -NMR ($CDCl_3$) δ 7.69 (1H, d, J = 2.2 Hz), 7.71 (1H, m), 7.63 (1H, d, J = 2.2 Hz), 7.37 (1H, t, J = 8.0 Hz), 7.21-7.09 (3H, m), 6.78 (1H, dd, J = 8.2, 2.3 Hz), 6.61 (1H, d, J = 2.3 Hz), 3.84 (3H, s). MS ($M+H$) $^+$ = 270.1.

[0342] Using procedures analogous to those described in the preparation of **459**, Steps 3-7, the title compound was prepared and purified by HPLC: 2-(3-(6-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **456** MS (ES) 565.0 ($M+H$) $^+$ LCMS RT = 1.08 min.

Example 86

2-(3-(3'-chloro-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **457**

[0343]

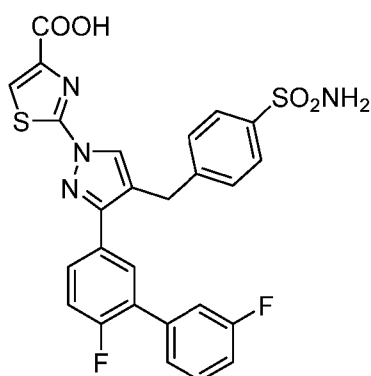


[0344] Using procedures analogous to those described in the preparation of **456**, the title compound was prepared and purified by HPLC: 2-(3-(3'-chloro-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **457** MS (ES) 568.9 (M+H)⁺ LCMS RT = 1.16 min.

Example 87

2-(3-(3',6-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **458**

[0345]

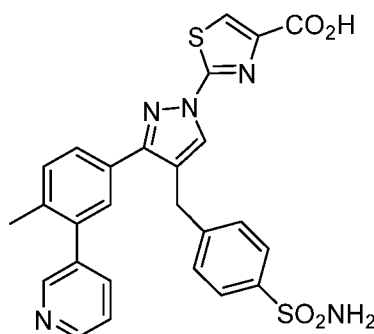


[0346] Using procedures analogous to those described in the preparation of **456**, the title compound was prepared and purified by HPLC: 2-(3-(3',6-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **458** MS (ES) 552.9 (M+H)⁺ LCMS RT = 1.12 min.

Example 88

2-(3-(4-methyl-3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **486**.

[0347]



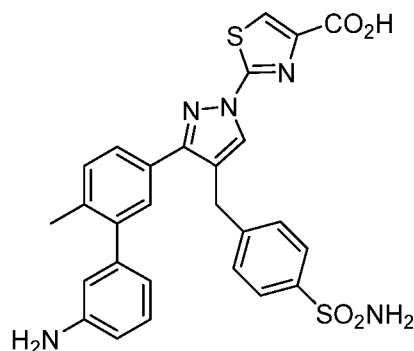
[0348] Using procedures analogous to those described in the preparation of **459**, Steps 1-6, 2-(3-(3-chloro-4-methylphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid was prepared.

[0349] Modified Step 7: A flame dried flask was charged with bis(tri-tert-butylphosphine)palladium (5.1 mg, 10 mol%), cesium carbonate (1 mL, 1 M solution), pyridin-3-ylboronic acid (25 mg, 0.2 mmol), 2-(3-(3-chloro-4-methylphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (51 mg, 0.1 mmol), and THF (2 mL). The reaction mixture was microwave irradiated at 120 °C for 20 min and the solvent was removed by rotary evaporator. The residue was filtered through celite pad with MeOH, then solvent was removed by rotary evaporator. The residue was purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 25% to 85% CH₃CN for 4 min, 0.1% TFA) to give the title compound **486** (32 mg, 60%). ¹H-NMR (MeOD) δ 8.77 (s, 1H), 8.72 (s, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 7.92 (dd, *J* = 7.6, 5.6 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.74 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.21 (s, 2H), 2.34 (s, 3H); MS (ES) 532.7 (M+H)⁺, LCMS RT = 0.82 min.

Example 89

2-(3-(3'-amino-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **487**

[0350]

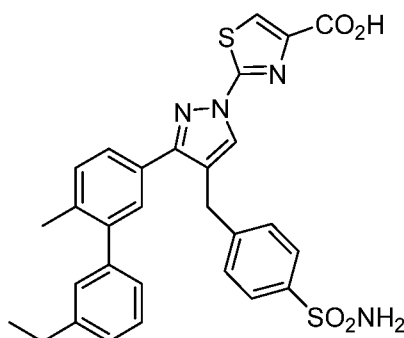


[0351] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(3'-amino-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **487** ¹H-NMR (MeOD) δ 8.37 (s, 1H), 8.16 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 7.6, 6.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 1.6 Hz, 1H), 7.40 (s, 2H), 7.38 (s, 1H), 7.27-7.20 (m, 2H), 7.15 (s, 1H), 4.19 (s, 2H), 2.30 (s, 3H); MS (ES) 546.7 (M+H)⁺; LCMS RT = 0.87 min.

Example 90

2-(3-(3'-ethyl-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **488**

[0352]

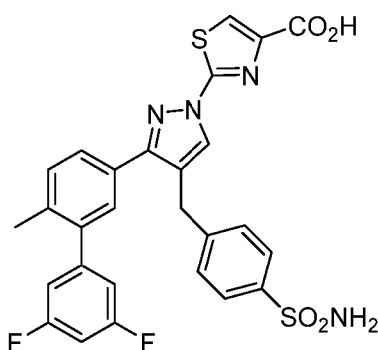


[0353] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(3'-ethyl-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **488** ¹H-NMR (MeOD) δ 8.34 (s, 1H), 8.13 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 8.0, 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 4.20 (s, 2H), 2.73 (q, J = 8.0 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J = 8.0 Hz, 3H); MS (ES) 559.4 (M+H)⁺; LCMS RT = 1.28 min.

Example 91

2-(3-(3',5'-difluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **489**

[0354]

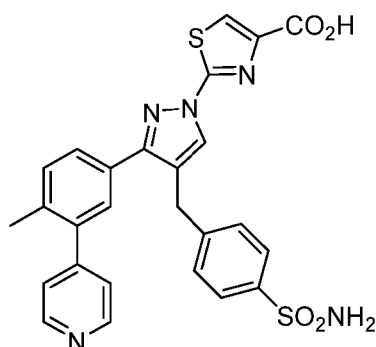


[0355] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(3',5'-difluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **489**; MS (ES) 569.6 (M+H)⁺; LCMS RT = 1.24 min.

Example 92

2-(3-(4-methyl-3-(pyridin-4-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **490**

[0356]

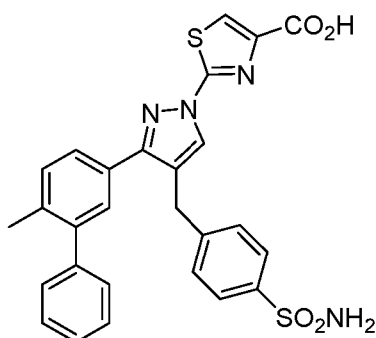


[0357] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(4-methyl-3-(pyridin-4-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **490**; $^1\text{H-NMR}$ (MeOD) δ 8.80 (br s, 2H), 8.44 (s, 1H), 8.17 (s, 1H), 7.85-7.76 (m, 5H), 7.49 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 4.21 (s, 2H), 2.39 (s, 3H); MS (ES) 533.6 (M+H) $^+$; LCMS RT = 0.83 min.

Example 93

2-(3-(6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **491**

[0358]

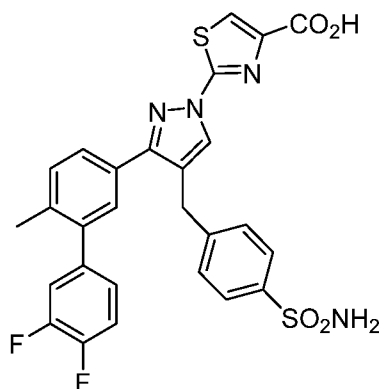


[0359] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **491** $^1\text{H-NMR}$ (MeOD) δ 8.34 (s, 1H), 8.14 (s, 1H), 7.89-7.82 (m, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 8.0, 2.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.49-7.35 (m, 4H), 7.29 (d, J = 8.0 Hz, 2H), 4.20 (s, 2H), 2.30 (s, H); MS (ES) 531.6 (M+H) $^+$; LCMS RT = 1.18 min.

Example 94

2-(3-(3',4'-difluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **492**

[0360]

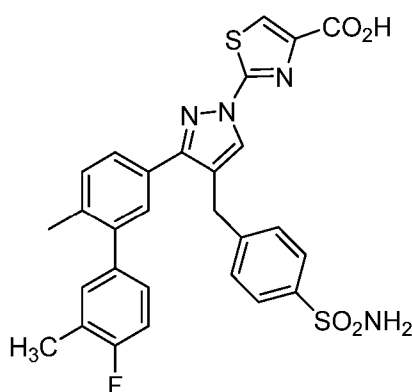


[0361] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(3',4'-difluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **492** MS (ES) 567.9 (M+H)⁺; LCMS RT = 1.20 min.

Example 95

2-(3-(4'-fluoro-3',6-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **493**

[0362]

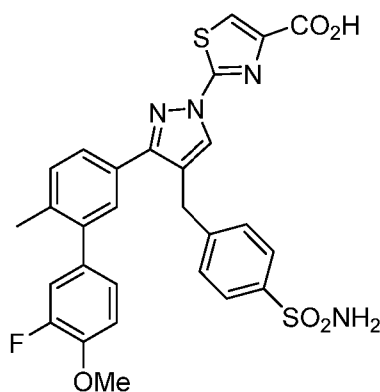


[0363] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(4'-fluoro-3',6-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **493** MS (ES) 563.9 (M+H)⁺; LCMS RT = 1.25 min.

Example 96

2-(3-(3'-fluoro-4'-methoxy-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **494**

[0364]

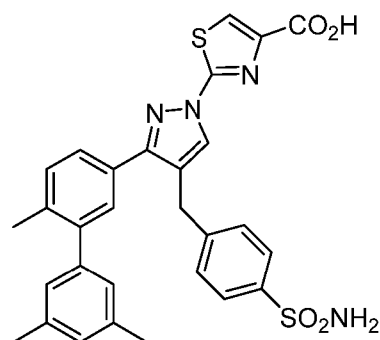


[0365] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(3'-fluoro-4'-methoxy-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **494** MS (ES) 579.6 (M+H)⁺; LCMS RT = 1.18 min.

Example 97

2-(4-(4-sulfamoylbenzyl)-3-(3',5',6-trimethyl-[1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **495**

[0366]

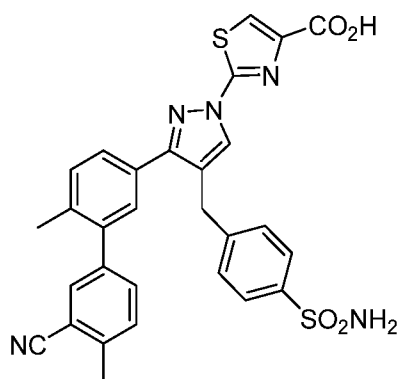


[0367] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(4-(4-sulfamoylbenzyl)-3-(3',5',6-trimethyl-[1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **495** MS (ES) 559.9 (M+H)⁺; LCMS RT = 1.29 min.

Example 98

2-(3-(3'-cyano-4',6-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **496**

[0368]

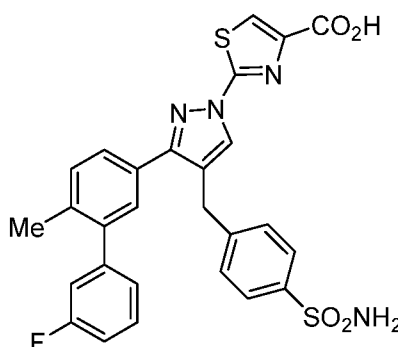


[0369] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(3'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **496** MS (ES) 549.6 (M+H)⁺; LCMS RT = 1.18 min.

Example 99

2-(3-(3'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **497**

[0370]

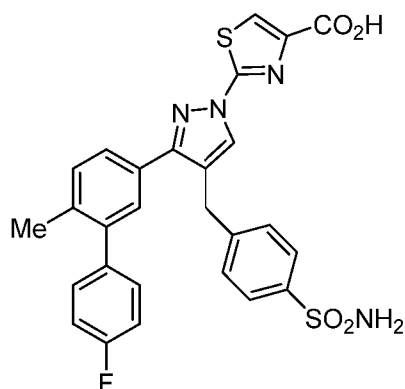


[0371] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(4'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **497** MS (ES) 549.6 (M+H)⁺; LCMS RT = 1.18 min.

Example 100

2-(3-(4'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **498** (Compound VV)

[0372]

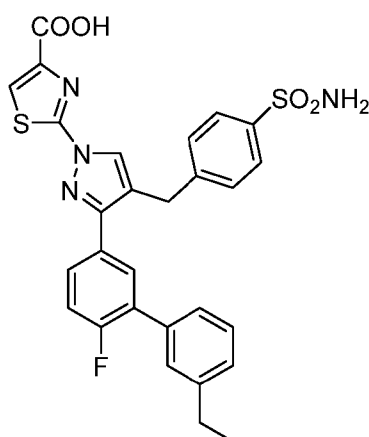


[0373] Using procedures analogous to those described in the preparation of **486**, the title compound was prepared and purified by HPLC: 2-(3-(4'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **498** MS (ES) 549.6 (M+H)⁺; LCMS RT = 1.16 min.

Example 101

2-(3-(3'-ethyl-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **513**

[0374]



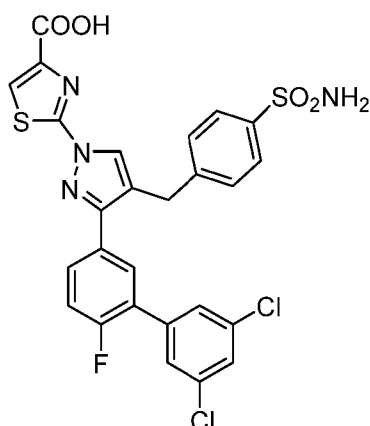
[0375] Using procedures analogous to those described in the preparation of **459**, Steps 1-6, 2-(3-(3-chloro-4-fluorophenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid was prepared.

[0376] Modified Step 7: To 2-(3-(3-chloro-4-fluorophenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (50 mg, 0.10 mmol) in dioxane / water (2.5 mL, 4:1) was added 3-ethylphenylboronic acid (23 mg, 0.15 mmol), followed by Cs₂CO₃ (68 mg, 0.20 mmol), Pd₂(dba)₃ (10.0 mg, 0.01 mmol), and *t*-Bu₃P (5 μL, 0.03 mmol). This solution was capped and purged with argon. The reaction mixture was heated at 95°C for 24 h. The reaction mixture was cooled down and diluted with HCl (10 mL, 1M) and extracted with ethyl acetate (3x 15mL). The combined organic layers were then dried with MgSO₄ and concentrated by rotary evaporator. The crude product was then purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 25% to 85% CH₃CN for 4 min, 0.1% TFA) to give 2-(3-(3'-ethyl-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **513** (12 mg, 21%). ¹H-NMR (MeOD) δ 8.37 (s, 1H), 8.17 (s, 1H), 7.86 (d, *J* = 8.24 Hz, 2H), 7.77 (d, *J* = 6.4 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 9.62 Hz, 1H), 7.16 (d, *J* = 7.79 Hz, 2H), 7.03 (m, 1H), 4.23 (s, 2H), 3.63 (q, *J* = 7.1, 14.2 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); MS (ES) 562.9 (M+H)⁺; LCMS RT = 1.24 min.

Example 102

2-(3-(3'-ethyl-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **514**

[0377]

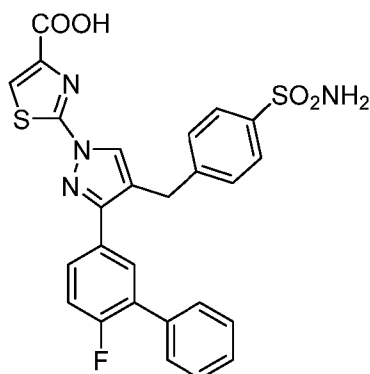


[0378] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(3'-ethyl-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **514** $^1\text{H-NMR}$ (MeOD) δ 8.36 (s, 1H), 8.16 (s, 1H), 7.87 (d, J = 6.4 Hz, 2H), 7.81 (m, 2H), 7.75 (d, J = 8.1 Hz, 2H), 7.46 (m, 2H), 7.34 (m, 2H), 4.24 (s, 2H); MS (ES) 602.9 (M+H) $^+$; LCMS RT = 1.30 min.

Example 103

2-(3-(6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **515**

[0379]

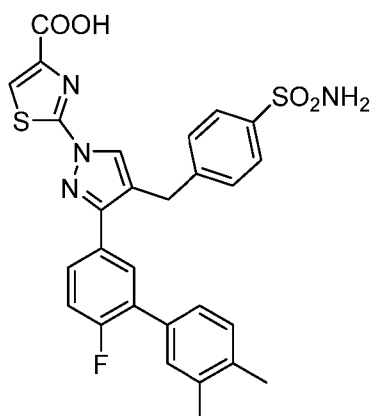


[0380] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **515** MS (ES) 544.0 (M+H) $^+$; LCMS RT = 1.18 min.

Example 104

2-(3-(6-fluoro-3',4'-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **516**

[0381]

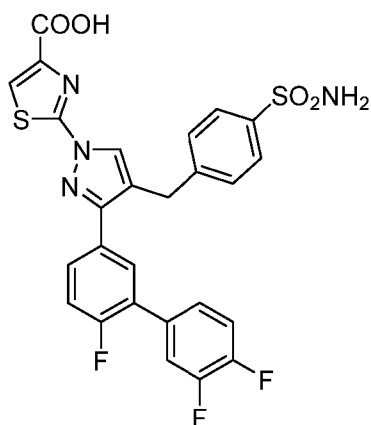


[0382] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(6-fluoro-3',4'-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **516** MS (ES) 562.9 (M+H)⁺; LCMS RT = 1.23 min.

Example 105

2-(4-(4-sulfamoylbenzyl)-3-(3',4',6-trifluoro-[1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **517**

[0383]

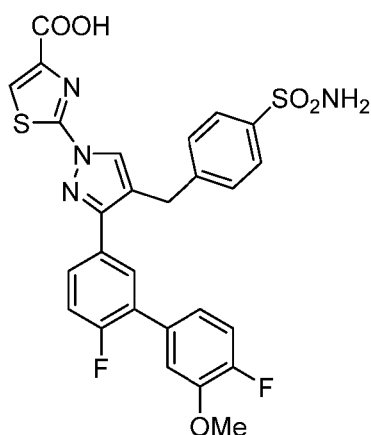


[0384] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(4-(4-sulfamoylbenzyl)-3-(3',4',6-trifluoro-[1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **517** MS (ES) 571.0 (M+H)⁺; LCMS RT = 1.18 min.

Example 106

2-(3-(4',6-difluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **518**

[0385]

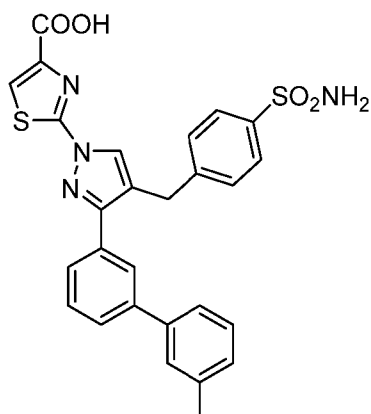


[0386] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(4',6-difluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **518** MS (ES) 582.9 (M+H)⁺; LCMS RT = 1.14 min.

Example 107

2-(3-(3'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **519**

[0387]

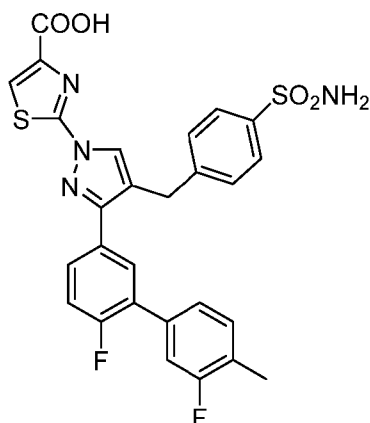


[0388] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(3'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **519** MS (ES) 530.9 (M+H)⁺; LCMS RT = 1.00 min.

Example 108

2-(3-(3',6-difluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **520**

[0389]

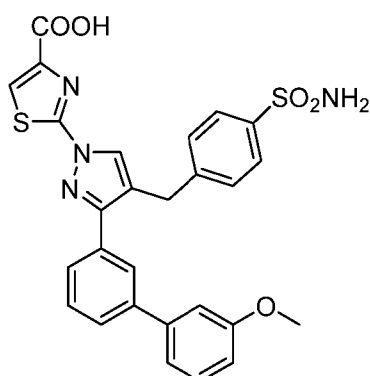


[0390] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(3',6-difluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **520** MS (ES) 566.9 (M+H)⁺; LCMS RT = 1.22 min.

Example 109

2-(3-(3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **521**

[0391]

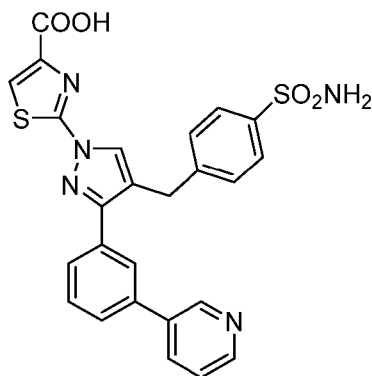


[0392] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **521** MS (ES) 546.9 (M+H)⁺; LCMS RT = 0.89 min.

Example 110

2-(3-(3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **522**

[0393]

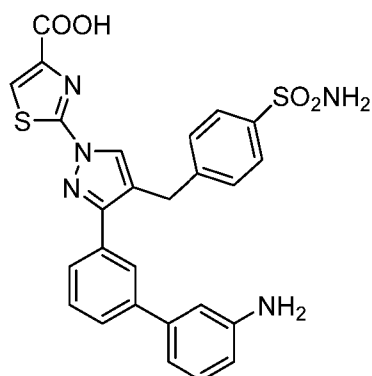


[0394] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **522** MS (ES) 517.9 (M+H)⁺; LCMS RT = 0.82 min.

Example 111

2-(3-(3'-amino-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **523**

[0395]

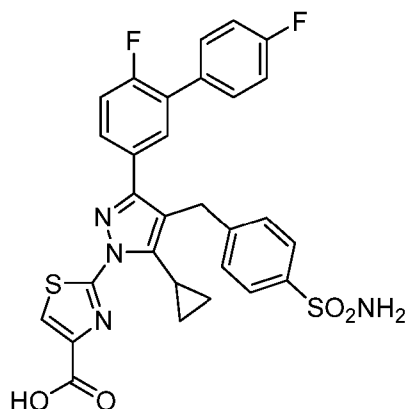


[0396] Using procedures analogous to those described in the preparation of **513**, the title compound was prepared and purified by HPLC: 2-(3-(3'-amino-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **524** MS (ES) 532.0 (M+H)⁺; LCMS RT = 0.70 min.

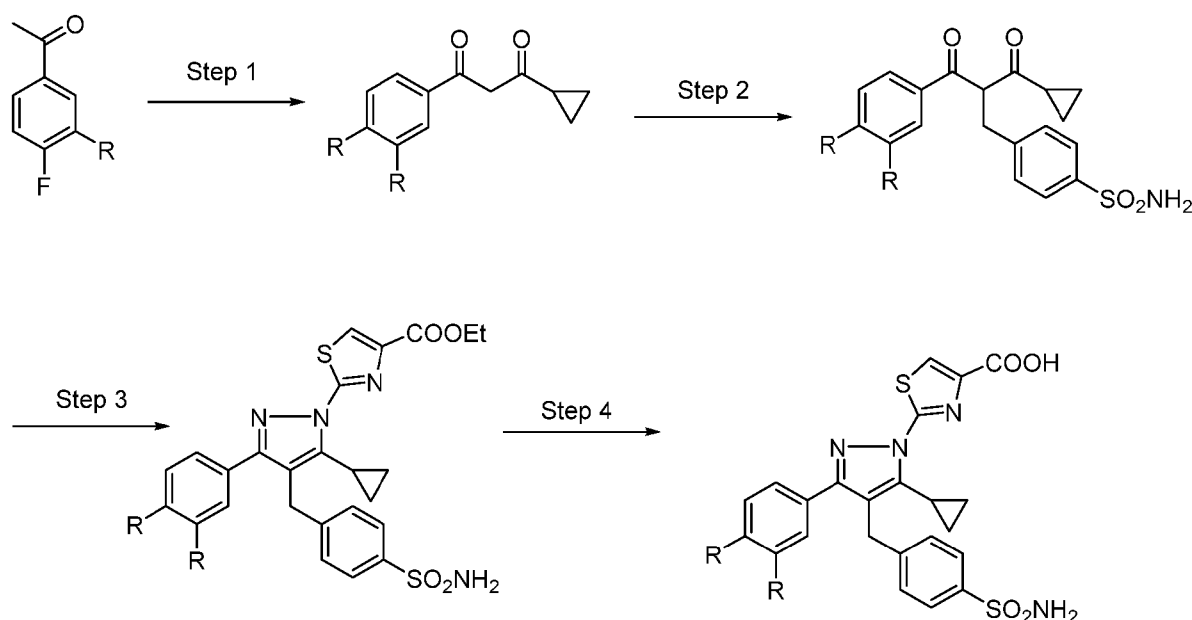
Example 112

2-(5-cyclopropyl-3-(4',6-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **482**

[0397]



Route C

**STEP 1. Synthesis of 1-(3-chloro-4-fluorophenyl)-3-cyclopropylpropane-1,3-dione.**

[0398] 1-(3-Chloro-4-fluorophenyl)ethan-1-one (1.5 g, 8.72 mmol, 1 eq) was dissolved in THF and cooled to -78 °C. After 10 minutes of stirring, LHMDS (1 M in hexanes, 12.2 mL, 1.4 eq) was added dropwise over 20 minutes. This was allowed to stir for an additional 20 minutes then cyclopropanecarbonyl chloride (1.1 mL, 12.2 mmol, 1.4 eq) was added dropwise. The reaction was allowed to stir for 3 h at which time it was brought to room temperature. Reaction was quenched with 1 M HCl and extracted with ethyl acetate. The aqueous layer was back extracted three times with ethyl acetate. The organic layer was washed with brine and dried over MgSO₄. The reaction mixture was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-20% gradient) to give 1-(3-chloro-4-fluorophenyl)-3-cyclopropylpropane-1,3-dione (1 g, 50%). MS (ES) 241 (M+H)⁺; LCMS RT 1.357 min.

STEP 2. Synthesis of 4-(2-(3-chloro-4-fluorobenzoyl)-3-cyclopropyl-3-oxopropyl)benzenesulfonamide

[0399] 1-(3-Chloro-4-fluorophenyl)-3-cyclopropylpropane-1,3-dione (1 g, 4.16 mmol, 1 eq) was dissolved in DMSO (10 mL) and stirred. 4-(bromomethyl)benzenesulfonamide (1.34 g, 5.4 mmol, 1.3 eq), Cs₂CO₃ (1.75 g, 5.4 mmol, 1.3 eq), and sodium iodide (624 mg, 4.16 mmol, 1 eq) were added. The reaction was stirred at 50 °C for 1 hour. After this time, the reaction was poured into 1 M HCl and extracted with ethyl acetate. The aqueous layer was back extracted three times with ethyl acetate. The combined organics were washed with brine and dried over MgSO₄. The reaction was

purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-80% gradient) to give 4-(2-(3-chloro-4-fluorobenzoyl)-3-cyclopropyl-3-oxopropyl)benzenesulfonamide (750 mg, 45%). MS: (ES) 410 (M+H)⁺; LCMS RT 1.14 min.

STEP 3. Synthesis of ethyl 2-(3-(3-chloro-4-fluorophenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0400] 4-(2-(3-Chloro-4-fluorobenzoyl)-3-cyclopropyl-3-oxopropyl)benzenesulfonamide (700 mg, 1.7 mmol, 1 eq) was added to a microwave vial with ethyl 2-hydrazinylthiazole-4-carboxylate (300 mg, 1.7 mmol, 1 eq) and *p*-toluenesulfonic acid (650 mg, 3.4 mmol, 2 eq). The reactants were purged with argon gas then dissolved with ethanol (4 mL). The reaction was run in the microwave reactor for 15 minutes at 100 °C. The reaction was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate = 0-80% gradient) to give ethyl 2-(3-(3-chloro-4-fluorophenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (300 mg).

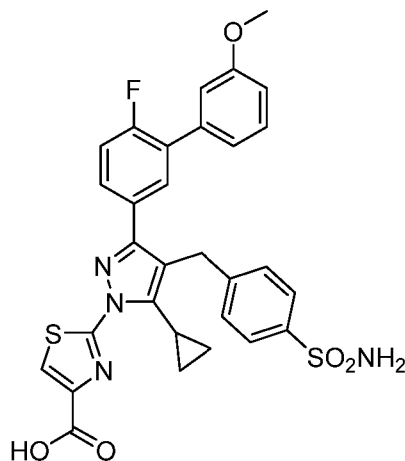
STEP 4. 2-(5-cyclopropyl-3-(4',6-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **482**

[0401] Ethyl 2-(3-(3-chloro-4-fluorophenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (15 mg, 0.03 mmol) was placed into a microwave vial along with (4-fluorophenyl)boronic acid (8 mg, 0.06 mmol, 2 eq) and the Pd(P(*t*-Bu)₃)₂ (5 mg). The reaction mixture was purged with vacuum and argon gas. Following this, Cs₂CO₃ (1 M, 1 mL) and THF (2 mL) were added. The reaction was heated in the microwave for 15 minutes at 100 °C. After LC/MS showed complete conversion to product along with hydrolysis of the ester, solvent was removed by rotary evaporation and the reaction was purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 45% to 85% CH₃CN for 7 min, 0.1% TFA) to give the title compound **482** (5 mg). ¹H-NMR (MeOD): δ 8.27(s, 1H), 7.85(d, *J*= 12 Hz, 2H), 7.57-7.63(m, 1H), 7.5(d, *J*= 16 Hz, 1H), 7.29-7.42(m, 4H), 7.12-7.25(m, 4H), 4.25(s, 2H), 2.32-2.41(m, 1H), 1.15(d, *J*=12 Hz, 2H), 0.7(d, *J*= 9 Hz, 2H); (ES) 593 (M+H)⁺ LCMS RT = 1.28 min.

Example 113

2-(5-cyclopropyl-3-(6-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **483**

[0402]

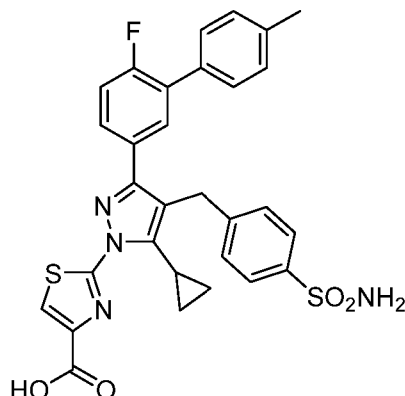


[0403] Using procedures analogous to those described in the preparation of **482**, the title compound was prepared and purified by HPLC: 2-(5-cyclopropyl-3-(6-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **483** ¹H-NMR (CDCl₃) δ 8.13(s, 1H), 7.85(d, *J*=8 Hz, 2H), 7.55-7.59(m, 1H), 7.35-7.39(m, 2H), 7.25-7.31(m, 4H), 7.17(t, *J*=18.84 Hz, 1H), 7.04(d, *J*=7.56 Hz, 1H), 6.91-6.94(dd, *J*=2, 2 Hz, 1H), 6.73(s, 1H), 5.04(s, Broad, 2H), 4.17(s, 2H), 3.87(s, 3H), 2.23-2.27(m, 1H), 1.12(d, *J*=7 Hz, 2H), 0.73(d, *J*=5 Hz, 2H), MS (ES) 605 (M+H)⁺ LCMS RT = 1.25 min.

Example 114

2-(5-cyclopropyl-3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **484**

[0404]

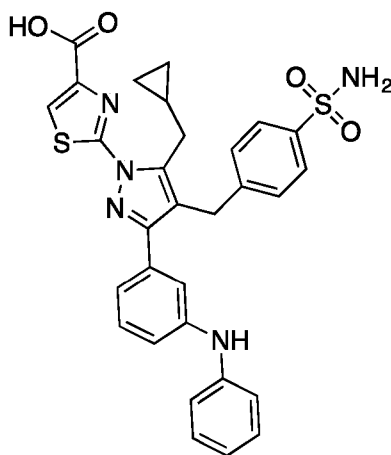


[0405] Using procedures analogous to those described in the preparation of **482**, the title compound was prepared and purified by HPLC: 2-(5-cyclopropyl-3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **484** ¹H-NMR (CDCl₃) δ 8.10(s, 1H), 7.82(d, J=8 Hz, 2H), 7.5(dd, J₁=2; J₂= 2 Hz, 1H), 7.41-7.45(m, 1H), 7.22-7.32(m, 7H), 7.13(t, J=19 Hz, 1H), 5.06(s, 2H), 4.14(s, 2H), 2.40 (s, 3H), 2.17-2.23(m, 1H), 1.07(d, J=8 Hz, 2H), 0.68(d, J=5. Hz, 2H), MS (ES) 589 (M+H)⁺ LCMS RT = 1.31 min.

Example 115

2-(5-(cyclopropylmethyl)-3-(3-(phenylamino)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **485**.

[0406]



[0407] Using procedures analogous to those described in the preparation of **482**, steps 1-3, ethyl-2-[3-(3-bromophenyl)-5-(cyclopropylmethyl)-4-[(4-sulfamoylphenyl)methyl]-1H-pyrazol-1-yl]-1,3-thiazole-4-carboxylate was prepared.

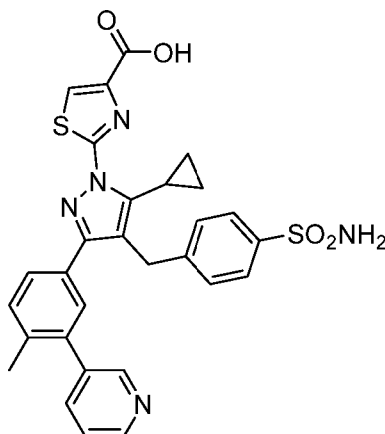
[0408] Modified Step 4: Ethyl-2-[3-(3-bromophenyl)-5-(cyclopropylmethyl)-4-[(4-sulfamoylphenyl)methyl]-1H-pyrazol-1-yl]-1,3-thiazole-4-carboxylate (80 mg, 0.139 mmol), powdered K₃PO₄ (56.6 mg, 0.267 mmol), aniline (18 μL, 0.199 mmol), and dimethylacetamide (1.3 mL) were combined in a vial. The mixture was then degassed and purged with argon (x3) after which Pd(P(tBu)₃)₂ was added. The vial was then sealed, and the mixture was stirred at 100 °C for 16 hours. After completion, the reaction mixture was cooled to room temperature, diluted with EtOAc (40 mL), washed with H₂O (2 x 10 mL), followed by brine (2 x 10 mL). The organic layer was then dried over MgSO₄, filtered, and concentrated by

rotary evaporator. The reaction was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-80% gradient) to give the title compound **485** (43 mg, 53%). ¹H-NMR (CDCl₃) δ 7.96 (1H, s), 7.72 (2H, d, *J* = 8.3 Hz), 7.23-7.18 (6H, m), 7.02-6.99 (4H, m), 6.88 (1H, t, *J* = 7.4 Hz), 4.02 (2H, s), 3.10 (2H, d, *J* = 6.8 Hz), 1.01 (1H, m), 0.33 (2H, dd, *J* = 13.8, 5.8 Hz), 0.14 (2H, dd, *J* = 10.2, 5.0 Hz); MS(ES) 585.7 (M+H)⁺.

Example 116

2-(5-cyclopropyl-3-(4-methyl-3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **499**

[0409]



[0410] Using procedures analogous to those described in the preparation of **482**, Steps 1-3, 2-(3-(3-chloro-4-methylphenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate was prepared.

[0411] Modified Step 4: A flame dried flask was charged with Bis(tri-*tert*-butylphosphine)palladium (5.1 mg, 10 mol %), cesium carbonate (1 mL, 1 M solution), pyridin-3-ylboronic acid (22 mg, 0.2 mmol), ethyl 2-(3-(3-chloro-4-methylphenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (50 mg, 0.1 mmol), and THF (2 mL). The reaction mixture was microwave irradiated at 120°C for 20 min and the solvent was removed by rotary evaporator. The residue was filtered through a celite pad with MeOH then solvent was removed by rotary evaporator. The residue was purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 35% to 85% CH₃CN for 4 min, 0.1% TFA) to give the title compound **499** (15 mg, 30%). ¹H-NMR (MeOD) δ 8.86 (d, *J* = 5.2 Hz, 1H), 8.83 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 2H), 7.27 (s, 1H), 4.25 (s, 2H), 2.42-2.34 (m, 1H), 2.33 (s, 3H), 1.10 (dt, *J* = 8.4, 4.6 Hz, 2H), 0.69 (dt, *J* = 5.6, 4.6 Hz, 2H); MS (ES) 572.9 (M+H)⁺; LCMS RT = 0.87 min.

Example 117

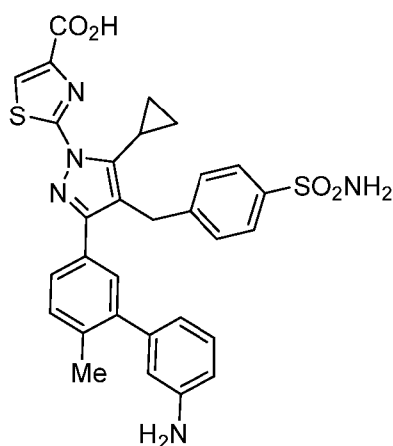
2-(3-(3'-amino-6-methyl-[1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **500**

[0412]

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[0413] Using procedures analogous to those described in the preparation of **499**, the title compound was prepared and purified by HPLC: 2-(3-(3'-amino-6-methyl-[1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **500**: $^1\text{H-NMR}$ (MeOD) δ 8.26 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.49 (dd, J = 8.0, 1.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.27 (s, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 4.23 (s, 2H), 2.41-2.33 (m, 1H), 2.27 (s, 3H), 1.08 (dt, J = 8.4, 6.4 Hz, 2H), 0.67 (dt, J = 5.6, 4.6 Hz, 2H); MS (ES) 586.9 (M+H) $^+$; LCMS RT = 0.92 min.

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Example 118

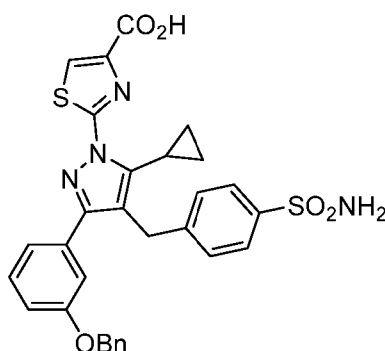
2-(3-(3-(benzyloxy)phenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **501**

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[0414]

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[0415] Using procedures analogous to those described in the preparation of **482**, the title compound was prepared and purified by HPLC: 2-(3-(3-(benzyloxy)phenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **501**: MS (ES) 549.6 (M+H) $^+$; LCMS RT = 1.16 min.

Example 119

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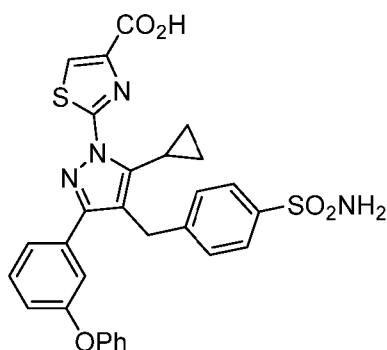
2-(5-cyclopropyl-3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **502**

[0416]

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[0417] Using procedures analogous to those described in the preparation of **482**, the title compound was prepared and purified by HPLC: 2-(5-cyclopropyl-3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **502**: $^1\text{H-NMR}$ (MeOD) δ 8.24 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.40-7.31 (m, 4H), 7.19 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 8.4 Hz, 1H), 7.07 (s, 1H), 7.00 (dd, J = 8.0, 1.6 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 4.15 (s, 2H), 2.37-2.29 (m, 1H), 1.03 (dt, J = 8.4, 6.4 Hz, 2H), 0.62 (dt, J = 5.6, 4.8 Hz, 2H); MS (ES) 573.6 (M+H) $^+$; LCMS RT = 0.94 min.

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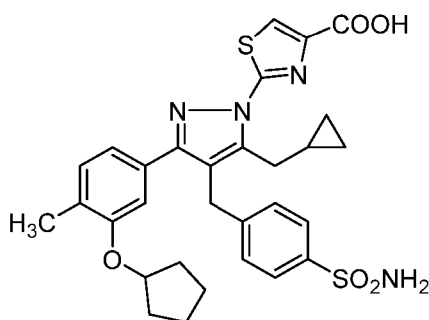
Example 120

2-(3-(3-(cyclopentyloxy)-4-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **467**

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[0418]

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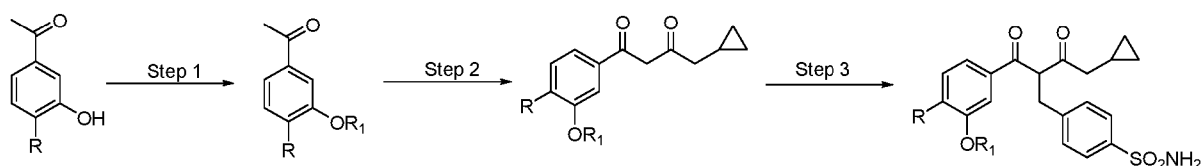


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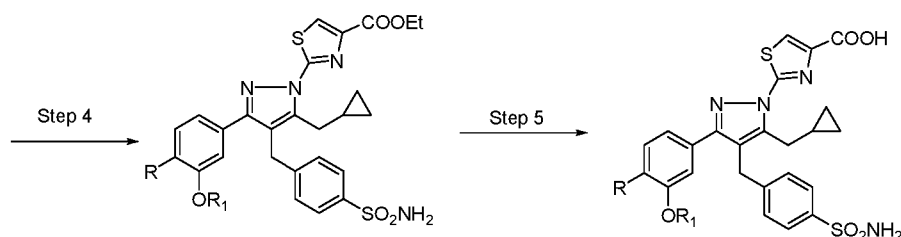
Route D

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STEP 1. Synthesis of 1-(3-(cyclopentyloxy)-4-methylphenyl)ethan-1-one

[0419] 3-Hydroxy-4-methyl acetophenone (1 g, 0.0066 mol) was dissolved in anhydrous DMF and potassium carbonate (7.35 g, 0.053 mol) and cyclopentyl bromide (2.8 mL, 0.026 mol) were added and the reaction was irradiated at 140 °C for 40 min. The reaction mixture was poured into water and extracted with ethyl acetate (3 x 40 mL). The organic layers were washed with brine (2 x 50 mL) and dried with anhydrous magnesium sulfate. The solvents were removed by rotary evaporator and purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-50% gradient) to give 1-(3-(cyclopentyloxy)-4-methylphenyl)ethan-1-one (1.20 g, 83%).

STEP 2. Synthesis of 1-(3-(cyclopentyloxy)-4-methylphenyl)-4-cyclopropylbutane-1,3-dione

[0420] To a solution of the (1H-benzo[d][1,2,3]triazol-1-yl) derivative (1.20 g, 0.0055 mol) in DCM (30 mL) was added magnesium bromide diethyletherate (3.55 g, 0.013 mol) followed by 1-(3-(cyclopentyloxy)-4-methylphenyl)ethan-1-one (1.44 g, 0.007 mol) and DIPEA (2.88 mL, 0.016 mol). The reaction mixture was stirred at rt for 2 h. The reaction mixture was cooled in an ice bath, quenched with HCl (1 M), and extracted with DCM. The DCM layer was washed with HCl (1 M), water, and brine. The crude product was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-20% gradient) to give 1-(3-(cyclopentyloxy)-4-methylphenyl)-4-cyclopropylbutane-1,3-dione (0.7 g, 42%).

STEP 3. Synthesis of 4-(2-(3-(cyclopentyloxy)-4-methylbenzoyl)-4-cyclopropyl-3-oxobutyl)-benzenesulfonamide.

[0421] 1-(3-(Cyclopentyloxy)-4-methylphenyl)-4-cyclopropylbutane-1,3-dione (0.7 g, 0.0023 mol) and cesium carbonate (0.9 g, 0.0028 mol) in DMSO (10 mL) was stirred at rt for 5 minutes then KI (0.42 g, 0.0025 mol) and 4-(bromomethyl)benzenesulfonamide (0.63 g, 0.0025 mol) were added. The reaction mixture was stirred at 50 °C for 5 min. After completion of the reaction, the mixture was poured into HCl (1 M) and extracted with ethyl acetate. The organic layer was washed with saturated ammonium chloride and brine. The crude product was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate = 0-50% gradient) to give 4-(2-(3-(cyclopentyloxy)-4-methylbenzoyl)-4-cyclopropyl-3-oxobutyl)-benzenesulfonamide (0.82 g, 76%).

STEP 4. Ethyl 2-(3-(3-(cyclopentyloxy)-4-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0422] A mixture containing 4-(2-(3-(cyclopentyloxy)-4-methylbenzoyl)-4-cyclopropyl-3-oxobutyl)benzene-sulfonamide (0.82 g, 0.0017 mol), *p*-toluene sulfonic acid (0.16 g, 0.0009 mol), pyrrolidine (71 µL, 0.0009 mol), and ethanol (7 mL) was heated at 90 °C for 1 h. Ethyl 2-hydrazinylthiazole-4-carboxylate (0.41 g, 0.0022 mol) was added and the reaction was heated until completion. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layers were dried with magnesium sulfate and concentrated. The crude product was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-80% gradient) to give ethyl 2-(3-(3-(cyclopentyloxy)-4-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate as a mixture of regioisomers (0.99 g, 93%).

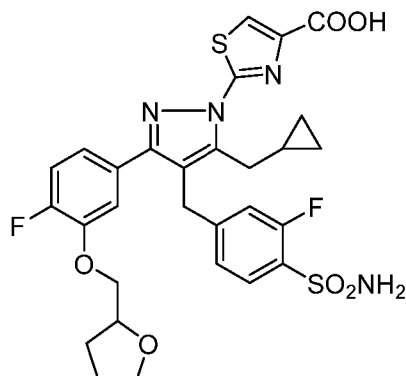
STEP 5. 2-(3-(3-(cyclopentyloxy)-4-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 467.

[0423] Ethyl 2-(3-(3-(cyclopentyloxy)-4-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (110 mg, 0.18 mmol) was dissolved in THF/MeOH (2 mL : 2 mL) and LiOH (5 M, 500 µL) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was neutralized by addition of hydrochloric acid (1.2 M), diluted with ethyl acetate (15 mL), washed with water (10 mL), and dried with anhydrous magnesium sulfate. The organic layer was concentrated using a rotary evaporator, dissolved in a mixture of DMSO and MeOH, and purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 55% to 90% CH₃CN for 4 min, 0.1% TFA) to give the title compound **467** (35 mg, 33%). ¹H-NMR (d⁶-DMSO) δ 8.07 (s, 1H), 7.53 (d, 2H, *J* = 8 Hz), 7.12-7.07 (m, 5H), 6.95 (d, 1H, *J* = 8 Hz), 6.87 (d, 1H, *J* = 8 Hz), 6.63 (s, 1H), 4.16 (m, 1H), 3.90 (s, 2H), 2.93 (m, 2H), 1.87 (s, 3H), 1.40-1.29 (m, 8H), 0.91 (m, 1H), 0.11 (m, 2H), 0.014 (m, 2H); MS (ES) 593.4 (M+H)⁺ LCMS RT = 0.81 min.

Example 121

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((tetrahydrofuran-2-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **469**

[0424]

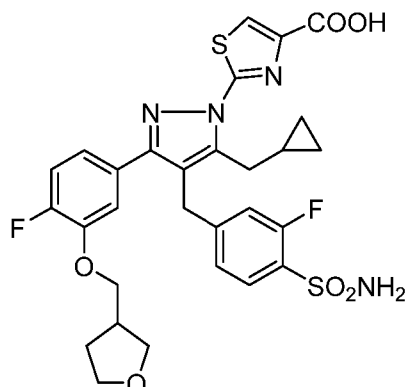


[0425] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((tetrahydrofuran-2-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **469**; $^1\text{H-NMR}$ (α^6 -DMSO) δ 8.07 (s, 1H), 7.44 (m, 1H), 7.35 (s, 2H), 7.05-6.82 (m, 5H), 3.93 (s, 2H), 3.87-3.43 (m, 6H), 2.93 (m, 2H), 1.75-1.59 (m, 3H), 1.38 (m, 1H), 0.90 (m, 1H), 0.013 (m, 2H) 0.010 (m, 2H); MS (ES) 630.9 (M+H) $^+$ LCMS RT = 1.10 min.

Example 122

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((tetrahydrofuran-3-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **470**

[0426]

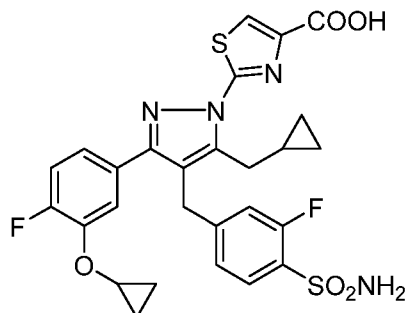


[0427] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((tetrahydrofuran-3-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **470** $^1\text{H-NMR}$ (α^6 -DMSO) δ 8.07 (s, 1H), 7.44 (m, 1H), 7.35 (s, 2H), 7.04-7.01 (m, 1H), 6.95-6.91 (m, 3H), 6.84-6.82 (m, 1H), 3.92 (s, 2H), 3.52-3.50 (m, 4H), 3.40-3.35 (m, 2H), 3.20 (m, 1H), 2.93 (m, 2H), 2.4 (m, 1H), 1.77 (m, 1H), 1.39 (m, 1H), 0.91 (m, 1H), 0.013 (m, 2H) 0.010 (m, 2H); MS (ES) 552.9 (M+H) $^+$ LCMS RT = 1.12 min.

Example 123

2-(3-(3-cyclopropoxy-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **471**

[0428]

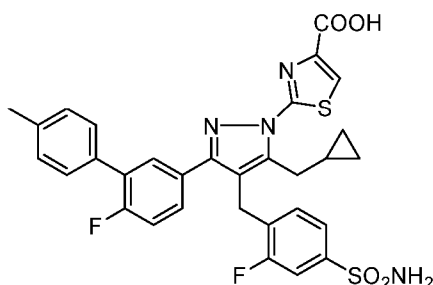


[0429] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(3-(3-cyclopropoxy-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **471** $^1\text{H-NMR}$ (δ^6 -DMSO) δ 8.07 (s, 1H), 7.46 (m, 1H), 7.37 (s, 2H), 7.19 (m, 1H), 7.05-6.85 (m, 5H), 3.92 (s, 2H), 3.50 (m, 1H), 2.93 (m, 2H), 0.91 (m, 1H), 0.013 (m, 2H) 0.010 (m, 2H); MS (ES) 586.9 (M+H) $^+$ LCMS RT = 1.12 min.

Example 124

2-(5-(cyclopropylmethyl)-3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **472**

[0430]



STEP 1: 1-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)ethan-1-one.

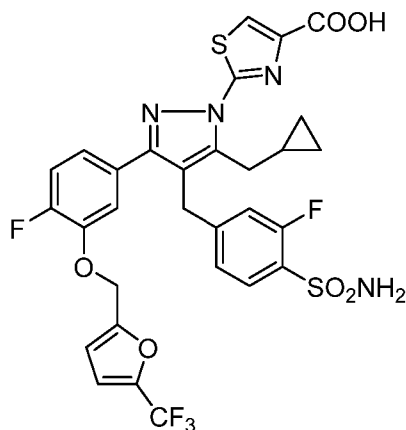
[0431] In a 20 mL microwave vial, 3-bromo-4-fluoroacetophenone (1 g, 0.0046 mol), 4-methylphenyl boronic acid (0.75 g, 0.0055 mol), potassium carbonate (1.27 g, 0.009 mol), bis-(di-*t*-butylphosphinoferrocene)dichloropalladium(II) (150 mg, 5 % mol), DMSO (12 mL), and water (4 mL) were added and the vial was purged with argon for 5 min. The vial was irradiated at 150 °C for 15 min. After completion of the reaction, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine and dried with magnesium sulfate. The crude product was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-20% gradient) to give 1-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)ethan-1-one (1 g, 90%).

[0432] Using procedures analogous to the procedures described to prepare **467**, Steps 2-5, the title compound was prepared from 1-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)ethan-1-one: 2-(5-(cyclopropylmethyl)-3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **472**; $^1\text{H-NMR}$ (δ^6 -DMSO) δ 8.31 (s, 1H), 7.59-7.35 (m, 11H), 7.17 (m, 1H), 4.13 (s, 2H), 3.02 (m, 2H), 2.35 (s, 3H), 1.15 (m, 1H), 0.033 (m, 2H) 0.021 (m, 2H); MS (ES) 621.4 (M+H) $^+$ LCMS RT = 0.79 min.

Example 125

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((5-(trifluoromethyl)furan-2-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **473**

[0433]



STEP 1 : 1-(4-fluoro-3-((5-(trifluoromethyl)furan-2-yl)methoxy)phenyl)ethan-1-one.

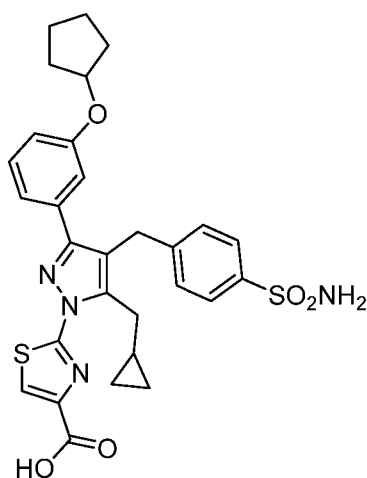
[0434] A solution of di-*t*-butyl diazocarboxylate (480 mg, 2 mmol) in THF (11 mL) was cooled to 0°C and triphenyl phosphine (553 mg, 2 mmol) was added. (5-(Trifluoromethyl)furan-2-yl)methanol (350 mg, 2 mmol) and 3-hydroxy-4-fluoroacetophenone (250 mg, 1.6 mmol) were sequentially added and the cooling was removed. The reaction mixture was stirred for 30 min, concentrated by rotary evaporator and purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-30% gradient) to give 1-(4-fluoro-3-((5-(trifluoromethyl)furan-2-yl)methoxy)phenyl)ethan-1-one (0.66 g, 95%).

[0435] Using procedures analogous to the procedures described to prepare **467**, Steps 2-5, the title compound **473** was prepared from 1-(4-fluoro-3-((5-(trifluoromethyl)furan-2-yl)methoxy)phenyl)ethan-1-one; MS (ES) 694.9 (M+H)⁺ LC-MS RT = 1.20 min.

Example 126

2-(3-(3-(cyclopentyloxy)phenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **477**

[0436]

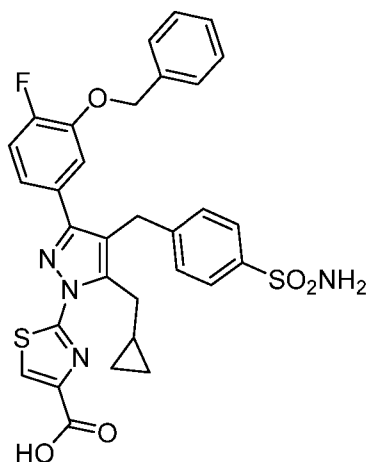


[0437] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(3-(3-(cyclopentyloxy)phenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **477** ¹H-NMR (CDCl₃) δ 8.10(s, 1H), 7.84(d, J=8.4 Hz, 2H), 7.23-7.31(m, 4H), 7.02-7.07(m, 2H), 6.88(dd, J=1.76, 1.8 Hz, 1H), 4.97(s, 2H), 4.11(s, 2H), 3.15(d, J=6.64 Hz, 2H), 1.58-1.79(m, 9H), 1.12-1.16(m, 1H), 0.43(d, J=8Hz, 2H), 0.21(d, J= 5.4 Hz, 2H), MS (ES) 579 (M+H)⁺ LCMS RT 1.15 min.

Example 127

2-(3-(3-(benzyloxy)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **480**

[0438]

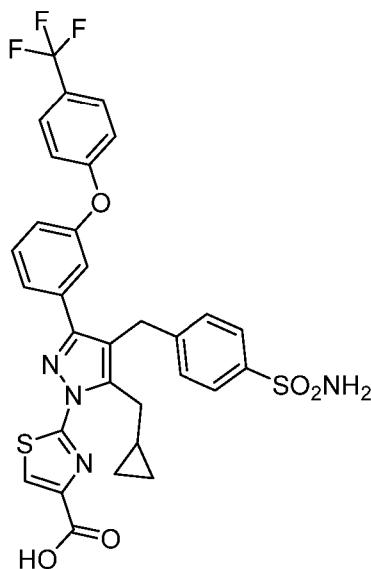


[0439] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(3-(3-(benzyloxy)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **480** ¹H-NMR (CDCl₃) δ 8.11(s, 1H), 7.84(d, J= 8 Hz, 2H), 7.24-7.38(m, 8H), 7.15(d, J= 7.4 Hz, 1H), 7.08(d, J=8 Hz, 2H), 5.01(s, 2H), 4.95(s, 3H), 4.02(s, 2H), 3.16(d, J=6.7 Hz, 2H), 1.11-1.15(m, 1H), 0.42(d, J=7 Hz, 2H), 0.21(d, J=5.24 Hz, 2H); MS (ES) 619 (M+H)⁺ LCMS RT = 1.28 min.

Example 128

2-(5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-3-(3-(4-(trifluoromethyl)phenoxy)-phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **481**

[0440]

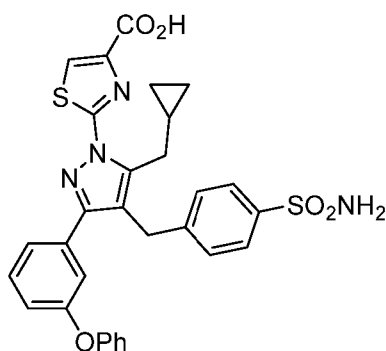


[0441] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-3-(3-(4-(trifluoromethyl)phenoxy)-phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **481**: ^1NMR (CDCl_3) δ 8.11(s, 1H), 7.8(d, J = 8Hz, 2H), 7.6(d, J = 8 Hz, 2H), 7.21-7.40(m, 5H), 7.01-7.06(m, 3H), 5.04(s, 2H), 4.08(s, 2H), 3.16(d, J = 6 Hz, 2H), 1.09-1.15(m, 1H) 0.42(d, J = 8. Hz, 2H), 0.21 (d, J = 5 Hz, 2H), MS (ES) 655 (M+H) $^+$ LCMS RT = 1.38 min.

Example 129

2-(5-(cyclopropylmethyl)-3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **503**

[0442]

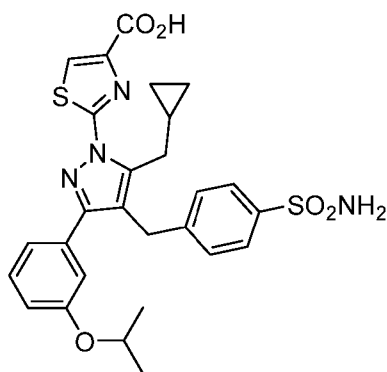


[0443] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **503**; $^1\text{H-NMR}$ (MeOD) δ 8.19 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.38-7.31 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 7.15-7.10 (m, 2H), 7.02-6.97 (m, 1H), 7.00 (dd, J = 8.0, 1.2 Hz, 2H), 4.10 (s, 2H), 3.22 (d, J = 6.8 Hz, 2H), 1.12-1.06 (m, 1H), 0.39-0.33 (m, 2H), 0.21 (dt, J = 6.0, 5.2 Hz, 2H); MS (ES) 587.7 (M+H) $^+$; LCMS RT = 1.00 min.

Example 130

2-(5-(cyclopropylmethyl)-3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **504**

[0444]

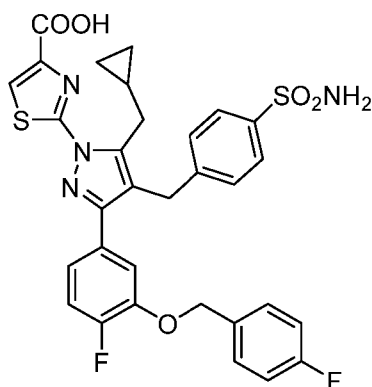


[0445] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **504**; MS (ES) 552.6 (M+H)⁺; LCMS RT = 0.98 min.

Example 131

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((4-fluorobenzyl)oxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **527**

[0446]

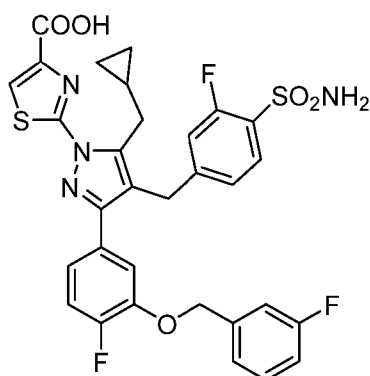


[0447] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((4-fluorobenzyl)oxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **527**; ¹H-NMR (MeOD) δ 8.21 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.40 (m, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.23 (m, 1H), 7.17 (m, 1H), 7.107 (m, 3H), 4.96 (s, 2H), 4.13 (s, 2H), 3.25 (d, *J* = 6.83 Hz, 2H), 1.12 (m, 1H), 0.38 (d, *J* = 8.1 Hz, 2H), 0.23 (d, *J* = 5.1 Hz, 2H); MS (ES) 636.9 (M+H)⁺; LCMS RT = 1.12 min.

Example 132

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((3-fluorobenzyl)oxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **528**

[0448]

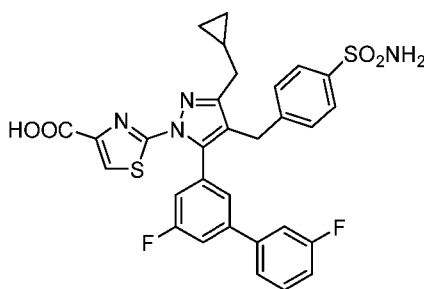


[0449] Using procedures analogous to those described in the preparation of **467**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((3-fluorobenzyl)oxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **528**; $^1\text{H-NMR}$ (MeOD) δ 8.19 (s, 1H), 7.77 (t, $J = 7.7$ Hz, 1H), 7.40 (m, 1H), 7.23 (m, 3H), 7.16 (m, 2H), 7.04 (m, 3H), 5.08 (s, 2H), 4.11 (s, 2H), 3.25 (d, $J = 6.5$ Hz), 1.11 (m, 1H), 0.39 (d, $J = 7.8$ Hz), 0.23 (d, $J = 4.6$ Hz); MS (ES) 655.0 (M+H) $^+$; LCMS RT = 1.19 min.

Example 133

4-((3-(cyclopropylmethyl)-5-(3',5-difluoro-[1,1'-biphenyl]-3-yl)-1-(4-((oxo-13-methyl)-13-oxidanyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide **525**

[0450]



[0451] Using procedures analogous to those described in the preparation of **482**, the title compound was prepared and purified by HPLC: 4-((3-(cyclopropylmethyl)-5-(3',5-difluoro-[1,1'-biphenyl]-3-yl)-1-(4-((oxo-13-methyl)-13-oxidanyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide **525**; $^1\text{H-NMR}$ (CDCl₃) δ 7.96 (s, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.39 (m, 2H), 7.24 (m, 4H), 7.06 (m, 4H), 3.93 (s, 2H), 2.53 (d, $J = 6.8$ Hz, 2H), 1.05 (m, 1H), 0.55 (m, 2H), 0.22 (d, $J = 5.8$ Hz, 2H); MS (ES) 607.0 (M+H) $^+$; LCMS RT = 0.95 min.

Example 134

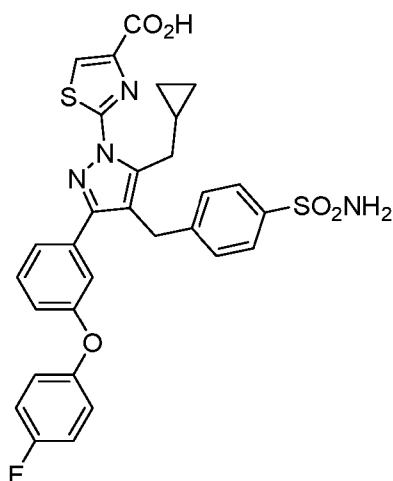
2-(5-(cyclopropylmethyl)-3-(3-(4-fluorophenoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **507**

[0452]

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Step 1: 1-(3-(4-fluorophenoxy)phenyl)ethan-1-one:

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[0453] A mixture of 1-(3-hydroxyphenyl) ethan-1-one (1.0 g, 7.34 mmol), (4-fluorophenyl)boronic acid (2.06 g, 14.7 mmol), $\text{Cu}(\text{OAc})_2$ (2.67 g, 14.7 mmol), and pyridine (1.18 mL, 14.7 mmol) in dichloromethane (20 mL) was stirred at room temperature for 48 h then quenched with water (25 mL), extracted with dichloromethane, and dried over MgSO_4 . The residue was purified by flash chromatography (Combi-flash Rf, hexane/ethyl acetate, 0-40% gradient) to give the title compound (0.56 g, 30%). $^1\text{H-NMR}$ (CDCl_3) δ (ppm) 7.67 (dt, $J = 7.6, 1.2$ Hz, 1H), 7.53 (t, $J = 2.0$ Hz, 1H), 7.42 (t, $J = 8.0$ Hz, 1H), 7.67 (dq, $J = 8.0, 0.8$ Hz, 1H), 7.08-6.97 (m, 4H), 2.58 (s, 3H).

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[0454] Step 2: Using procedures analogous to those described in the preparation of **467**, Steps 2-5, the title compound was prepared from 1-(3-(4-fluorophenoxy)phenyl)ethan-1-one and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(3-(4-fluorophenoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **507** $^1\text{H-NMR}$ (MeOD) δ (ppm) 8.14 (s, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.10-7.04 (m, 2H), 7.01-6.96 (m, 4H), 6.84 (t, $J = 2.0$ Hz, 1H), 3.92 (s, 2H), 2.46 (d, $J = 7.2$ Hz, 2H), 1.00-0.90 (m, 1H), 0.44 (ddd, $J = 8.4, 6.0, 4.4$ Hz, 2H), 0.13 (dd, $J = 10.0, 4.4$ Hz, 2H); MS (ES) 605.2 ($\text{M}+\text{H}^+$); LCMS RT = 1.20 min.

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Example 135

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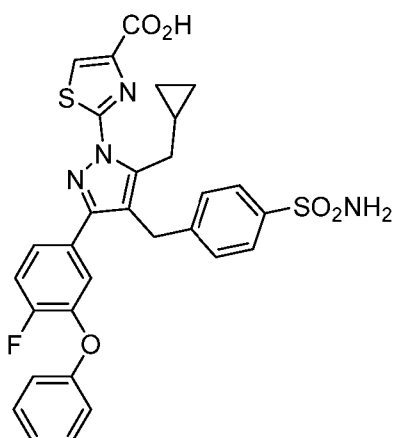
2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **508**

[0455]

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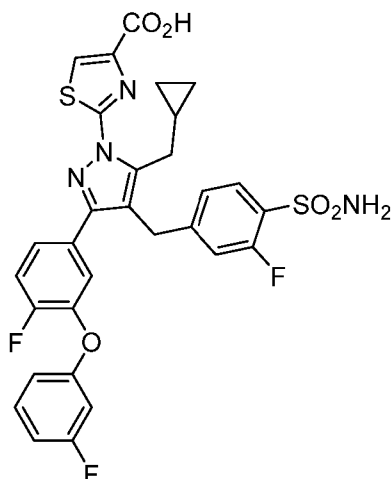
[0456] Using procedures analogous to those described in the preparation of **507**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **508**; $^1\text{H-NMR}$ (d^6 -DMSO) δ 7.63 (d, $J = 8.4$ Hz, 2H), 7.42-7.33 (m, 4H), 7.23 (s, 2H), 7.25

(d, $J = 8.8$ Hz, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 7.6$ Hz, 2H), 4.06 (s, 2H), 3.12 (d, $J = 6.8$ Hz, 2H), 0.87-0.80 (m, 1H), 0.30 (ddd, $J = 10.0, 6.0, 4.4$ Hz, 2H), 0.13 (dd, $J = 10.0, 5.2$ Hz, 2H); MS (ES) 605.2 (M+H)⁺; LCMS RT = 1.18 min.

Example 136

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(3-fluorophenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **509**

[0457]

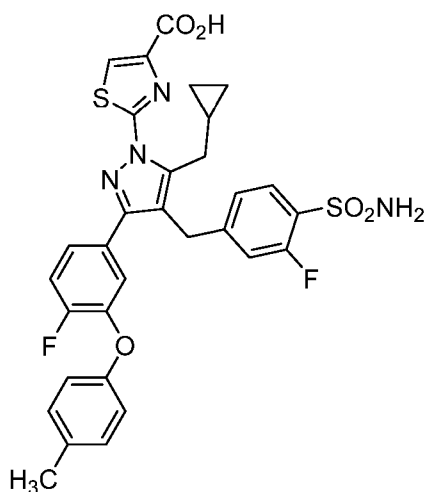


[0458] Using procedures analogous to those described in the preparation of 507, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(3-fluorophenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **509**; ¹H-NMR (MeOD) δ 8.20 (s, 1H), 7.72 (t, $J = 8.0$ Hz, 1H), 7.50-7.46 (m, 1H), 7.37-7.25 (m, 3H), 6.99 (s, 1H), 6.98 (d, $J = 16.8$ Hz, 1H), 6.88 (dt, $J = 8.4, 2.0$ Hz, 1H), 6.73 (dt, $J = 10.0, 2.0$ Hz, 1H), 6.66 (dd, $J = 8.4, 2.4$ Hz, 1H), 4.13 (s, 2H), 3.24 (d, $J = 6.8$ Hz, 2H), 1.13-1.05 (m, 1H), 0.44 (ddd, $J = 8.0, 5.6, 4.0$ Hz, 2H), 0.22 (dd, $J = 10.4, 5.2$ Hz, 2H); MS (ES) 640.9 (M+H)⁺; LCMS RT = 1.19 min.

Example 137

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(p-tolyloxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **510**

[0459]

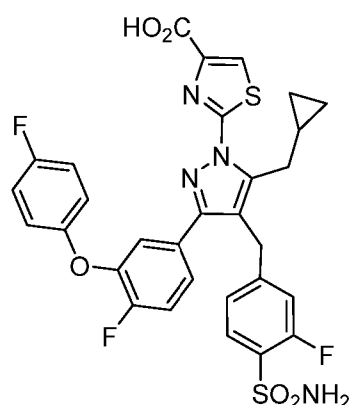


[0460] Using procedures analogous to those described in the preparation of **507**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(p-tolyloxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **510**; $^1\text{H-NMR}$ (MeOD) δ 8.19 (s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.44-7.40 (m, 1H), 7.25 (dd, J = 10.8, 8.8 Hz, 1H), 7.17-7.12 (m, 3H), 6.93 (s, 1H), 6.92 (d, J = 17.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 4.07 (s, 2H), 3.22 (d, J = 6.8 Hz, 2H), 1.11-1.04 (m, 1H), 0.37 (ddd, J = 8.0, 6.0, 4.8 Hz, 2H), 0.21 (dd, J = 10.4, 5.2 Hz, 2H); MS (ES) 636.9 (M+H) $^+$; LCMS RT = 1.12 min.

Example 138

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-fluorophenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **511**

[0461]

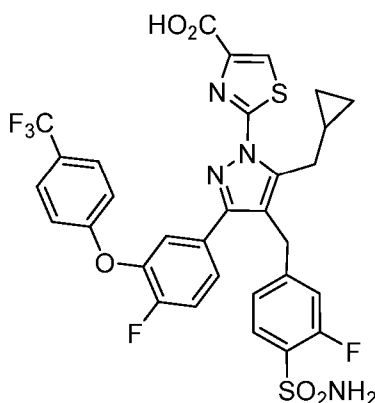


[0462] Using procedures analogous to those described in the preparation of **507**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-fluorophenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **511**; $^1\text{H-NMR}$ (MeOD): δ 8.19 (s, 1H), 7.71 (t, J = 8.8 Hz, 1H), 7.45-7.41 (m, 1H), 7.26 (dd, J = 8.8, 11.0 Hz, 1H), 7.15 (dd, J = 2.2, 7.9 Hz, 1H), 7.09 (dd, J = 8.5, 9.0 Hz, 2H), 6.98-6.89 (m, 4H), 4.09 (s, 2H), 3.23 (d, J = 7.05 Hz, 2H), 1.13-1.04 (m, 1H), 0.40-0.35 (m, 2H), 0.23-0.19 (m, 2H); MS (ES) 641.0 (M+H) $^+$; LCMS RT = 1.18 min.

Example 139

2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-(trifluoromethyl)phenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **512**

[0463]



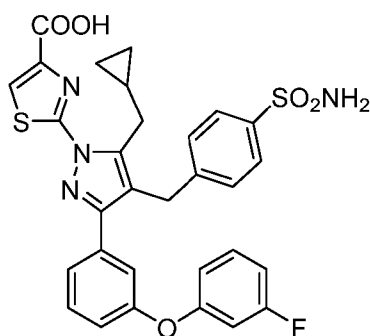
[0464] Using procedures analogous to those described in the preparation of **507**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-(trifluoromethyl)phenoxy)phenyl)-4-(3-fluoro-4-sulfa-

moylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **512**; $^1\text{H-NMR}$ (MeOD) δ 8.28 (s, 1H), 7.73-7.67 (m, 3H), 7.52-7.48 (m, 1H), 7.38 (dd, J = 2.1, 7.6 Hz, 1H), 7.30 (dd, J = 8.5, 10.5 Hz, 1H), 7.03-6.96 (m, 4H), 4.16 (s, 2H), 3.27 (d, J = 6.8 Hz, 2H), 1.18-1.08 (m, 1H), 0.42-0.38 (m, 2H), 0.26-0.23 (m, 2H); MS (ES) 691.0 (M+H) $^+$; LCMS RT = 1.24 min.

Example 140

2-(5-(cyclopropylmethyl)-3-(3-(3-fluorophenoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **526**

[0465]

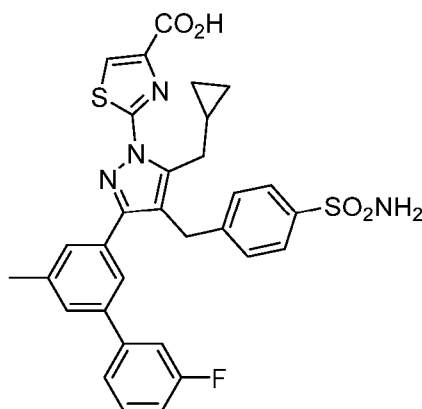


Using procedures analogous to those described in the preparation of **507**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(3-(3-fluorophenoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **526**; $^1\text{H-NMR}$ (MeOD) δ 7.89 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.42 (m, 2H), 7.34 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.12 (m, 1H), 8.87 (m, 2H), 6.70 (m, 2H), 4.13 (s, 2H), 3.25 (d, J = 6.7 Hz, 2H), 0.32 (d, J = 8.2 Hz, 2H), 0.12 (d, J = 4.39 Hz, 2H); MS (ES) 605.2 (M+H) $^+$; LCMS RT = 1.21 min.

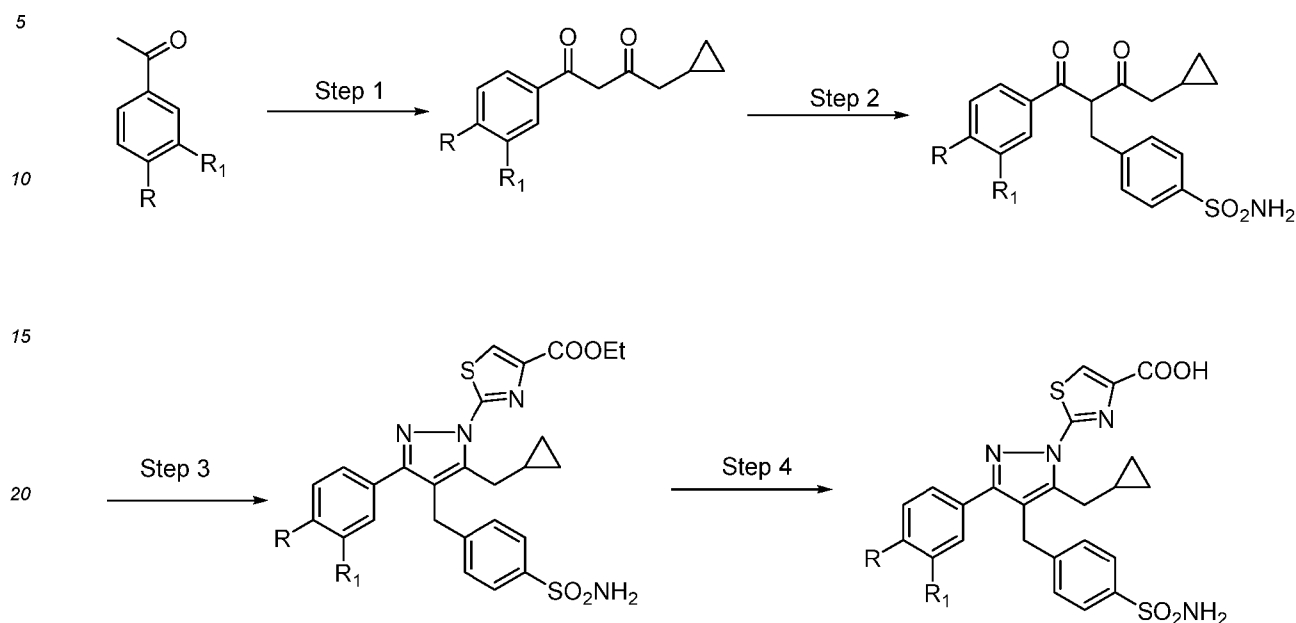
Example 141

2-(5-(cyclopropylmethyl)-3-(3'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **505**

[0467]



Route E



[0468] Using procedures similar to the procedures described to prepare **467**, Steps 1-3, ethyl 2-(3-(3-bromo-5-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate was prepared.

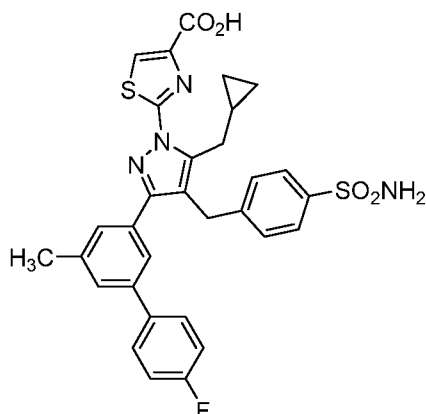
STEP 4. 2-(5-(cyclopropylmethyl)-3-(3'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

[0469] A flame dried flask was charged with bis(tri-*tert*-butylphosphine)palladium (4.0 mg, 10 mol%), cesium carbonate (0.5 mL, 1 M solution), (3-fluorophenyl)boronic acid (23 mg, 0.162 mmol), pyrazole regioisomer (50 mg, 0.081 mmol), and THF (2 mL). The reaction mixture was microwave irradiated at 120 °C for 20 min and the solvent was removed by rotary evaporator. After saponification and neutralization, the residue was purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 40% to 90% CH₃CN for 4 min, 0.1% TFA) to give the title compound **505** (10 mg, 21%). MS (ES) 603.7 (M+H)⁺; LCMS RT = 1.26 min.

Example 142

2-(5-(cyclopropylmethyl)-3-(4'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **506**

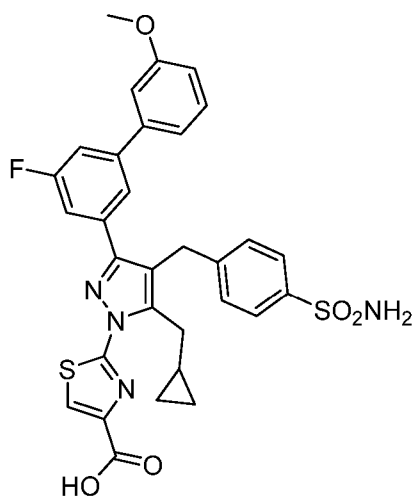
[0470]



[0471] Using procedures similar to the procedures described to prepare **505**, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(4'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **506**; MS (ES) 603.4 (M+H)⁺; LCMS RT = 1.26 min.

Example 143

2-(5-(cyclopropylmethyl)-3-(5-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **478**

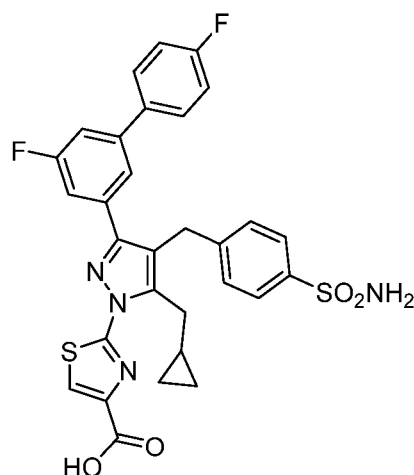


[0473] Using procedures similar to the procedures described to prepare **505**, the title compound **478** was prepared and purified by HPLC; ¹NMR (CDCl₃) δ 8.10 (s, 1H) 7.86 (d, J=8.32 Hz, 2H,) 7.23-7.29 (m, 7H), 7.00 (d, J=7.12 Hz, 1H), 6.91 (dd, J= 1.88 1.88 Hz, 1H), 6.60 (t, J=3.92 Hz, 1H), 4.96 (s, 2H), 4.11(s, 2H),), 3.87(s, 3H), 3.21(d, J=6.64 Hz, 2H) 1.17-1.25(m, 1H) 0.47(d, J=7.28 Hz, 2H), 0.24(d, J=5.2 Hz, 2H), MS: (ES) 619 (M+H)⁺ LCMS RT 1.32 min.

Example 144

2-(5-(cyclopropylmethyl)-3-(4',5-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **479**

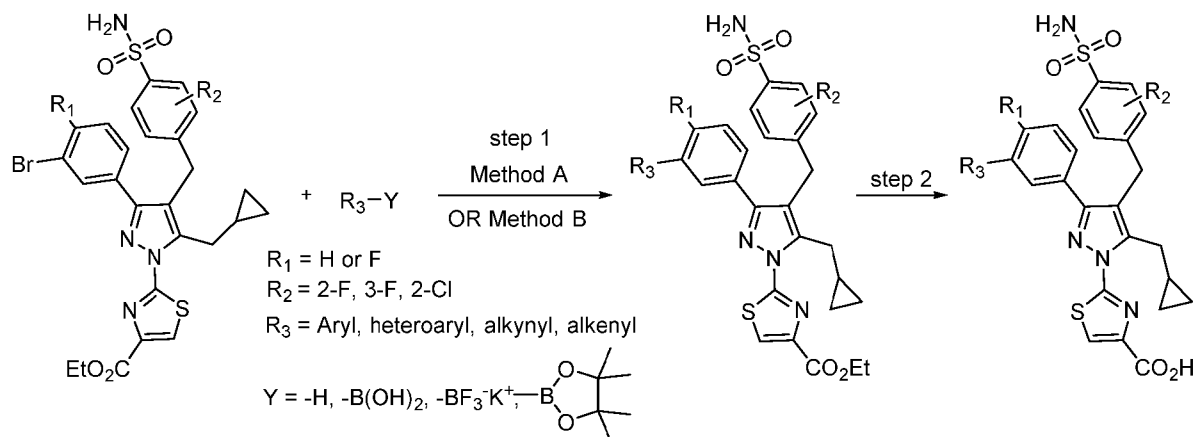
[0474]



[0475] Using procedures similar to the procedures described to prepare 505, the title compound was prepared and purified by HPLC: 2-(5-(cyclopropylmethyl)-3-(5-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **479**; MS (ES) 607 (M+H)⁺ LCMS RT 1.35 min.

Example 145

[0476]



STEP 1: General Synthesis of ethyl 2-(3-(3-substituted-4-substitutedphenyl)-5-(cyclopropylmethyl)-4-(3-substituted-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0477] Method A - Dioxane (2 mL) and water (0.5 mL) were added to a mixture of ethyl 2-(3-(3-bromo-4-substituted-phenyl)-5-(cyclopropylmethyl)-4-(3-substituted-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.2 mmol, 1 eq), potassium phosphate (0.4 mmol, 2 eq), S-PHOS (5 mol%), SPhos Palladacycle G3 (2.5 mol%) and appropriate boronic acid/ester or potassium trifluoroborate in a sealed microwave vial. The reaction mixture was bubbled with argon for few minutes then stirred at 100 °C in a preheated heating block for 1-6 h. Upon completion of the reaction as detected by LCMS, the reaction mixture was cooled and stirred with a metal scavenger for 1 h. The reaction mixture was then diluted with ethyl acetate and filtered through a pad of celite. The filtrate was concentrated and purified directly on silica using gradient elution (20-40 % ethyl acetate in hexanes).

[0478] Method B - A mixture of ethyl 2-(3-(3-bromo-4-substituted phenyl)-5-(substituted)-4-(3/4-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (1 mmol), tri(tert-butylphosphonium)tetrafluoroborate (10 mol %), allyl-palladium chloride dimer (5 mol %) and DABCO (2 mmol, 2 eq) in dioxane (0.5 molar concentration) was bubbled with argon for 5 minutes. The appropriate alkyne (1.5 mmol, 1.5 eq) was added and the reaction mixture was stirred at room temperature overnight. After completion of the reaction, silica bound palladium scavenger was added and the slurry was stirred at room temperature for 1 hr, subsequently diluted with ethyl acetate and filtered through a pad of celite. The filtrate was concentrated and the residue was purified directly on silica using gradient elution (20-40 % ethyl acetate in

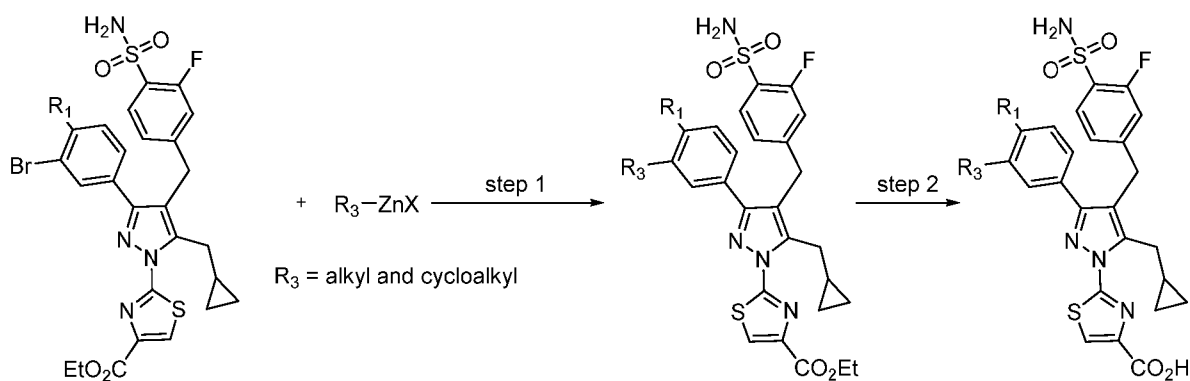
hexanes) yielding the desired compound which was taken to the next step.

STEP 2: 2-(3-(3-substituted-4-substitutedphenyl)-5-(cyclopropylmethyl)-4-(3-substituted-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

[0479] The titled compound was synthesized and purified in a similar manner as described in Example 18.

Example 146

[0480]



STEP 1: General Synthesis of ethyl 2-(3-(3-substituted-4-substitutedphenyl)-5-(cyclopropylmethyl)-4-(3-substituted-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate using Negishi coupling

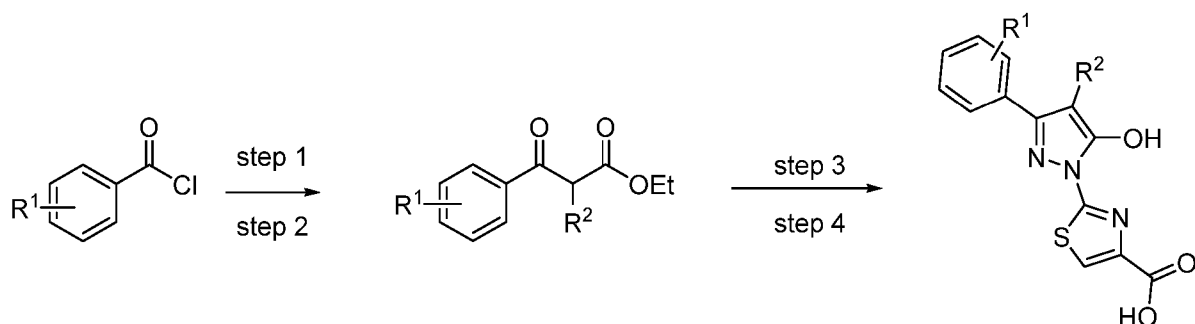
[0481] A mixture of ethyl 2-(3-(3-bromo-4-substitutedphenyl)-5-(cyclopropylmethyl)-4-(3-substituted-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (1 eq) (0.1 g, 0.157 mmol), CPhos (5 mol %), CPhos Pdcycle G3 (Sigma cat # 763004, 2.5 mol %) in a Biotage microwave vial was backfilled with argon then added a THF solution of appropriate alkyl/cycloalkyl zinc halide (3-5 eq) under argon. The reaction mixture was stirred at room temperature or at 60 °C for 0.5- 3 h. After completion, the reaction mixture was quenched with 1 molar HCl and extracted with ethyl acetate. The organic layer was washed with bicarbonate and brine subsequently dried under magnesium sulfate. The crude material was purified directly on silica using gradient elution (10-40 % EA in hexanes over 20 column volumes).

STEP 2: General Synthesis of ethyl 2-(3-(3-substituted-4-substitutedphenyl)-5-(cyclopropylmethyl)-4-(3-substituted-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids

[0482] The titled compound was synthesized and purified in a similar manner as described in Example 18.

Example 147

[0483] This example describes the synthesis of 2-(5-(hydroxy)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids.



STEP 1: Synthesis of ethyl 3-oxo-3-phenylpropanoates

[0484] Ethyl acetate (102 mmol) was added dropwise to a cooled solution of lithium stirred for 30 minutes at which time the appropriate benzoyl chloride (56.6 mmol) was added after which the reaction was allowed to attain rt. Upon completion as detected by LCMS, the reaction was quenched with sat. aq. NH_4Cl . The product was extracted with ethyl acetate and the organic layer washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on silica using gradient elution (5-50 % ethyl acetate in hexanes over 12 CV). The resulting yellow oils were used in the next step without further purification or characterization.

STEP 2: Synthesis of ethyl 3-oxo-3-phenyl-2-(4-sulfamoylbenzyl)propanoates

[0485] Ethyl 3-oxo-3-phenylpropanoate (150 mmol) and cesium carbonate (Cs_2CO_3 , 226 mmol) were dissolved in DMSO (50 ml). The reaction mixture was stirred at rt for 10 minutes at which time potassium iodide were added (KI, 150 mmol) and 4-(bromomethyl)-benzenesulfonamides (165 mmol). The resulting mixture was stirred at rt for 1 h. Upon completion as detected by LCMS, the reaction mixture was diluted with a large excess of ethyl acetate and filtered through celite. The filtrate was washed with 1 M HCl, sat aq NH_4Cl and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on silica using gradient elution (20-40 % ethyl acetate in hexanes over 16 CV).

STEP 3: ethyl 2-(5-hydroxy-3-phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylates

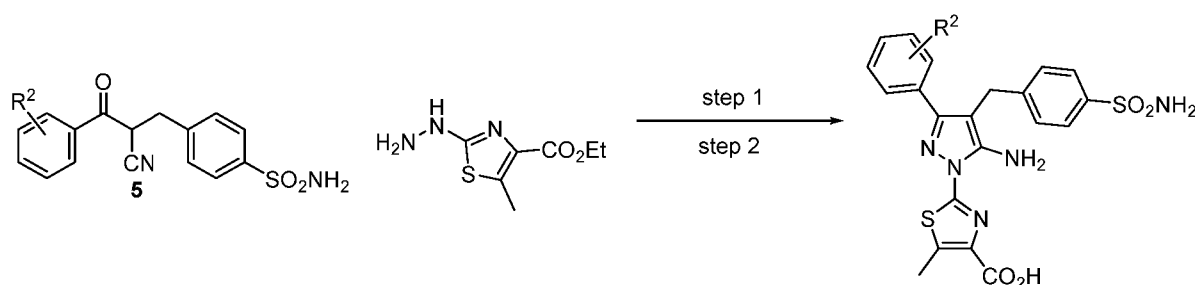
[0486] A solution of ethyl 3-oxo-3-phenyl-2-(4-sulfamoylbenzyl)propanoate (6.7 mmol), ethyl 2-hydrazinylthiazole-4-carboxylate, 2 HBr (7.3 mmol) and *p*-toluene sulfonic acid (pTsOH , 20 mmol) in dioxane was heated in a sealed vessel in the microwave for 15 min at 160 °C. Upon completion as detected by LCMS, the reaction mixture was diluted with ethyl acetate and filtered through celite. The solvent was removed under reduced pressure and the crude product was purified directly on silica using gradient elution (0-100 % ethyl acetate in hexanes over 15 CV).

STEP 4: Synthesis of 2-(5-hydroxy-3-phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acids

[0487] To a solution of ethyl 2-(5-hydroxy-3-phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylate (0.07 mmol) in THF/MeOH was added 1.5 M LiOH (0.27 mmol). The reaction mixture was stirred at rt for 1 h. Upon completion as detected by LCMS, the solvent was removed by forced air. The residue was taken into DMSO and purified directly via preparative reverse phase using gradient elution (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA). The product fractions were directly frozen and lyophilized overnight, yielding an off-white powder.

Example 148

[0488] This example describes the synthesis of 2-(5-(hydroxy)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acids.

STEP 1: Synthesis of 4-((5-amino-1-substituted-3-phenyl-1H-pyrazol-4-yl)methyl) benzenesulfonamide

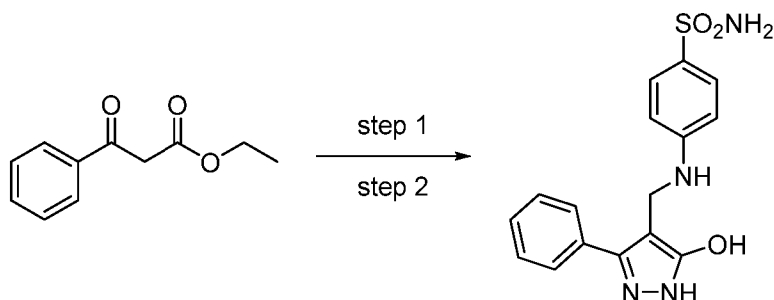
[0489] A solution of ethyl 2-hydrazinyl-5-methylthiazole-4-carboxylate (0.267 mmol), 4-(2-cyano-3-oxo-3-phenylpropyl)benzenesulfonamide (0.267 mmol) and tosic acid (0.534 mmol) in MeOH was heated in the microwave for 15 min. The crystals upon cooling was collected by filtration and washed with ethanol and dried used as such in the next step.

STEP 2: 2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-5-methylthiazole-4-carboxylic acid

[0490] The titled compound was synthesized and purified in a similar manner as described in Example 18

Example 149

[0491] This example describes the synthesis of 4-(((5-hydroxy-3-phenyl-1H-pyrazol-4-yl)methyl)amino)benzenesulfonamide in an embodiment of the invention.

STEP 1: Synthesis of 3-phenyl-1H-pyrazol-5-ol

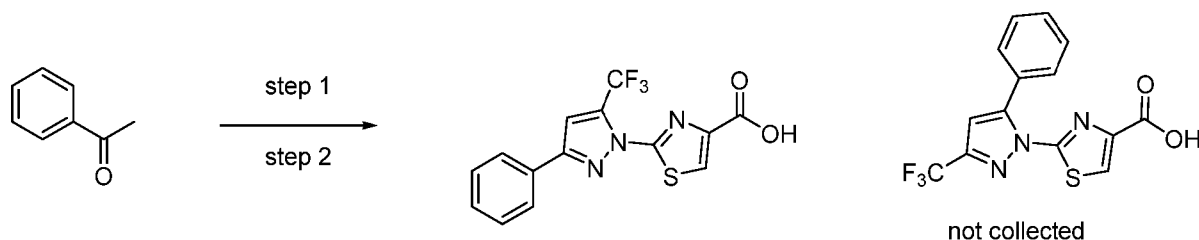
[0492] To a solution of ethyl 3-oxo-3-phenylpropanoate (24.7 mmol) in ethanol (15 ml) was added hydrazine hydrate (49 mmol) at 0 °C, then stirred at rt for 1 h. Upon completion, the product was extracted with ethyl acetate, washed with water, bicarbonate and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product obtained after evaporating the solvent was used as such in the next step.

STEP 2: 4-(((5-hydroxy-3-phenyl-1H-pyrazol-4-yl)methyl)amino)-benzenesulfonamide

[0493] 3-phenyl-1H-pyrazol-5-ol (0.5 g, 3.12 mmol) and 4-aminobenzenesulfonamide (0.538 g, 3.12 mmol) in EtOH (Volume: 6.24 ml) was stirred in a sealed tube at 100 °C for 1h. The product precipitated upon cooling, and the slurry was sonicated for 5 minutes and filtered. The precipitate was washed with ethanol, re-suspended in DMSO and purified directly on reverse phase using gradient elution (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

Example 150

[0494] This example describes the synthesis of 2-(3-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid.

STEP 1: Synthesis of 1-(3,4-difluorophenyl)-4,4,4-trifluorobutane-1,3-dione

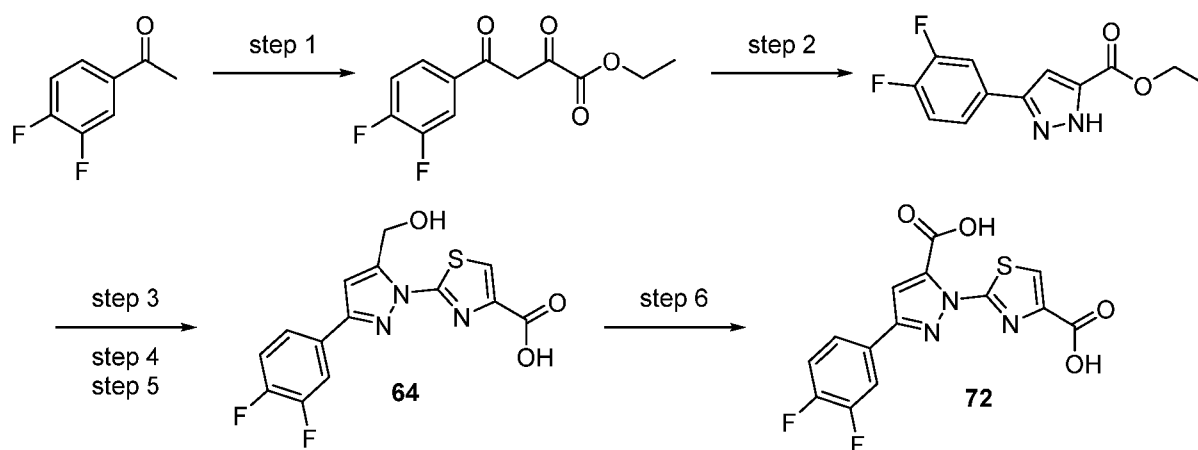
[0495] A stirring solution of 1-(3,4-difluorophenyl)ethanone (3.20 mmol) in DMF (6 ml) was chilled to 0 °C before NaH (3.8 mmol) was added portionwise. The reaction mixture was stirred for 30 minutes at which time ethyl 2,2,2-trifluoroacetate (3.84 mmol) was added and the reaction mixture was allowed to attain rt. Upon completion the reaction was quenched with water the pH was adjusted with 1 N HCl and the product was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified directly on silica using gradient elution (5-50 % ethyl acetate in hexanes over 12 CV) to provide a yellow oil.

STEP 2: Synthesis of 2-(3-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

[0496] A solution of 1-(4-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (3.99 mmol) and hydrazinecarbothioamide (3.99 mmol) in EtOH was refluxed for 12 h. The solvent was removed under reduced pressure and the residue was boiled in chloroform and filtered. The filtrate was concentrated and taken up EtOH then added ethyl 3-bromo-2-oxopropanoate (3.99 mmol) and refluxed for 1 h. Added concentrated sulfuric acid and refluxed overnight. The solvent was concentrated and the product extracted with ethyl acetate. The organic layer was washed with bicarbonate and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product containing the mixture of products was purified on reverse phase preparative column. The second peak was collected and hydrolyzed with HCl/AcOH at 120 °C in a sealed tube for 1 h. After removing the solvent with forced air the crude product were purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

Example 151

[0497] This example describes the synthesis of 2-(3-(3,4-difluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid and 3-(3,4-difluorophenyl)-1-(4-(methoxycarbonyl)thiazol-2-yl)-1H-pyrazole-5-carboxylic acid

STEP 1: Synthesis of ethyl 4-(3,4-difluorophenyl)-2,4-dioxobutanoate

[0498] A solution of NaOEt (144 mmol) in ethanol was added 1-(3,4-difluorophenyl)ethanone (96 mmol) was stirred for 5 minutes at which time diethyl oxalate (106 mmol) was added. The reaction mixture was stirred for 10 minutes and a thick ppt was formed. The reaction mixture was poured into ice water containing 7 mL of conc HCl. A precipitate formed and was collected by filtration and washed with water and dried under air. The crude product was used as such in the next step.

STEP 2: Synthesis of ethyl 3-(3,4-difluorophenyl)-1H-pyrazole-5-carboxylate

[0499] To a solution of ethyl 4-(3,4-difluorophenyl)-2,4-dioxobutanoate (90 mmol) in ethanol was added hydrazine monohydrate (99 mmol) and the reaction mixture was stirred at rt for 12 h. The reaction becomes clear solution and eventually the product precipitates. The solvent was removed and the desired compound was purified by recrystallization in ethanol.

STEP 3: Synthesis of (3-(3,4-difluorophenyl)-1H-pyrazol-5-yl)methanol

[0500] To a solution of ethyl 3-(3,4-difluorophenyl)-1H-pyrazole-5-carboxylate (5.67 mmol) in THF (20 ml) was added lithium aluminum hydride (11.34 mmol, 1.0 M in THF) slowly dropwise at 0 °C. The reaction mixture was stirred for 1 h then quenched with sat. aq. NH₄Cl. The product was extracted with ethyl acetate and the organic layer washed with water and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified directly on silica using gradient elution (50-100 % EA in hexanes).

STEP 4: Synthesis of tert-butyl 2-(3-(3,4-difluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0501] A solution of (3-(3,4-difluorophenyl)-1H-pyrazol-5-yl)methanol (0.952 mmol), tert-butyl 2-bromothiazole-4-carboxylate (1.047 mmol), (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (0.190 mmol), CuI (0.095 mmol) and K₃PO₄ (2.093 mmol) in dioxane was stirred at 110 °C in a sealed tube for 12 h. Upon completion the reaction mixture was stirred with thiol resin and filtered through celite and the celite pad was washed with ethyl acetate. After concentration the crude product was purified directly on silica using gradient elution (10-50 % ethyl acetate in hexanes) providing a white solid.

STEP 5: Synthesis of 2-(3-(3,4-difluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

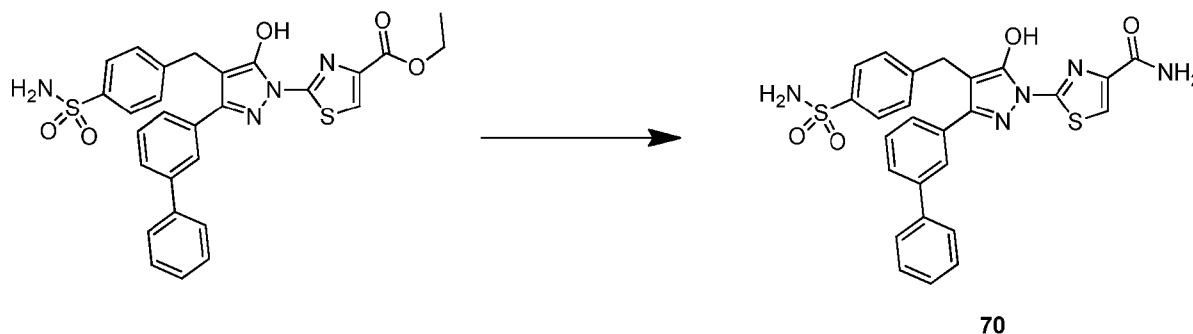
[0502] Tert-butyl 2-(3-(3,4-difluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate was deprotected with TFA/DCM. The product was purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

STEP 6: Synthesis of 3-(3-(3,4-difluorophenyl)-1-(4-(methoxycarbonyl)thiazol-2-yl)-1H-pyrazole-5-carboxylic acid

[0503] To a 5 dram vial were added methyl 2-(3-(3,4-difluorophenyl)-5-formyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.014 g, 0.04 mmol) and Oxone (0.025 g, 0.04 mmol). The reaction mixture was stirred at rt for 16 hr. The reaction was complete by LCMS. The reaction mixture was diluted with water and the product was extracted with EtOAc. The org layer was dried with brine and Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

Example 152

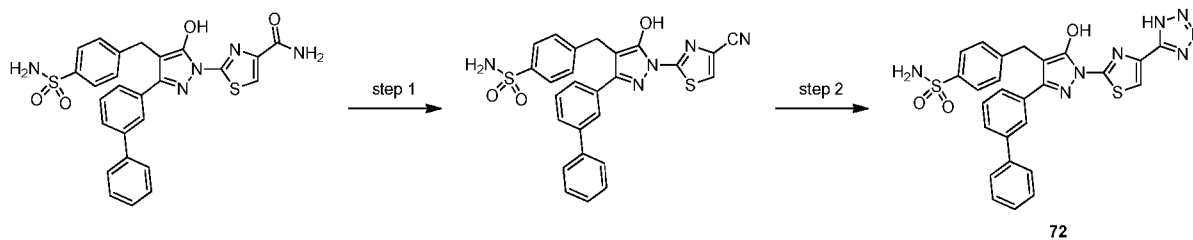
[0504] This example describes the synthesis of 2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxamide **70** in an embodiment of the invention.



[0505] A stirring solution of ethyl 2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.019 mmol) and MeOH (0.5 ml) at 0 °C was bubbled with ammonia gas for 1 min. The reaction mixture was heated to 60 °C for 30 min. Upon completion, the reaction mixture was purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

Example 153

[0506] This example describes the synthesis of 4-((1-(4-(1H-tetrazol-5-yl)thiazol-2-yl)-3-([1,1'-biphenyl]-3-yl)-5-hydroxy-1H-pyrazol-4-yl)methyl)benzenesulfonamide **72** in an embodiment of the invention.



STEP 1: Synthesis of 4-((3-([1,1'-biphenyl]-3-yl)-1-(4-cyanothiazol-2-yl)-5-hydroxy-1H-pyrazol-4-yl)methyl)benzenesulfonamide

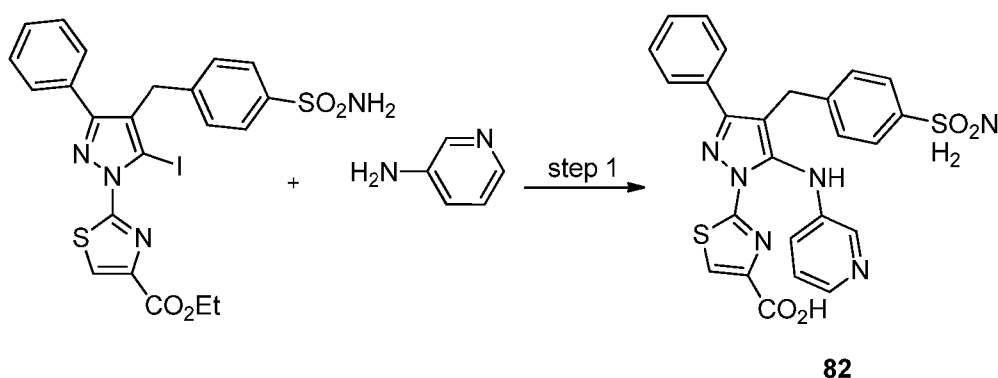
[0507] To a stirring solution of 2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxamide (0.344 mmol) and diisopropylethylamine (1.030 mmol) in CH_2Cl_2 (3.4 mL) was added TFAA (0.687 mmol) dropwise at 0 °C. The reaction mixture was stirred at rt for 5 hr. An additional 2 eq. of TFAA (0.687 mmol) and 3 eq of diisopropylethylamine (1.030 mmol) were added and the reaction mixture was stirred overnight. Upon completion, the reaction was diluted with CH_2Cl_2 , washed with water, NaHCO_3 , and brine. The organic layer was dried over MgSO_4 and concentrated under reduced pressure and the residue was purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

STEP 2: Synthesis of 4-((1-(4-(1H-tetrazol-5-yl)thiazol-2-yl)-3-([1,1'-biphenyl]-3-yl)-5-hydroxy-1H-pyrazol-4-yl)methyl)benzenesulfonamide

[0508] A solution of N-((4-((3-([1,1'-biphenyl]-3-yl)-1-(4-cyanothiazol-2-yl)-5-hydroxy-1H-pyrazol-4-yl)methyl)phenyl)sulfonyl)-2,2,2-trifluoroacetamide (0.036 mmol), sodium azide (0.108 mmol) and NH_4Cl (0.072 mmol) heated to 125 °C in DMF (0.4 ml) for 2 h. Upon completion, the reaction mixture was purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

Example 154

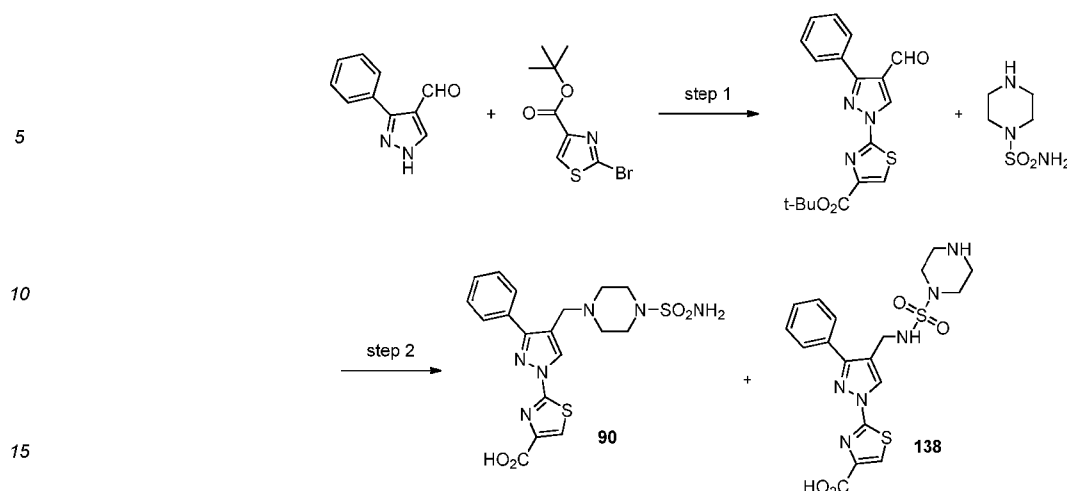
[0509] This example describes the synthesis of 2-(3-phenyl-5-(pyridin-3-ylamino)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **80** in an embodiment of the invention.



[0510] A mixture of ethyl 2-(5-iodo-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.168 mmol), pyridin-3-amine (0.252 mmol), XantPhos (0.168 mmol), $\text{Pd}_2(\text{dba})_3$ (0.168 mmol) and sodium tert-butoxide (0.370 mmol) in a microwave vial was degassed with argon. 2 mL of dioxane was added and stirred at 100 °C overnight. The solvent was removed by forced air. The contents were suspended in DMSO and stirred with silica palladium scavenger at 70 °C for 1 h then filtered through a syringe filter. The crude product was hydrolyzed according to Example 18 and was purified directly on reverse phase preparative column (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA).

Example 155

[0511] This example describes the synthesis of 2-(3-phenyl-4-((4-sulfamoylpiperazin-1-yl)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **90** and 2-(3-phenyl-4-((piperazine-1-sulfonamido)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **138**.



STEP 1: Synthesis of tert-butyl 2-(4-formyl-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate

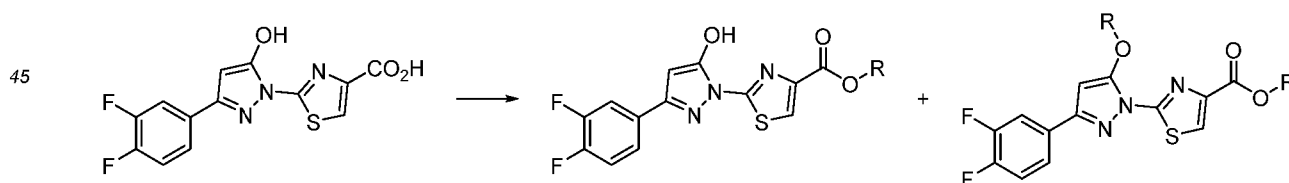
20 **[0512]** A solution of 3-phenyl-1H-pyrazole-4-carbaldehyde (2.323 mmol), K_2CO_3 (3.48 mmol), and tert-butyl 2-bromothiazole-4-carboxylate (2.439 mmol) in DMSO was stirred for 3 h. Upon completion the product was extracted with ethyl acetate, washed with sat. aq. NH_4Cl , water and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on silica using gradient elution (50-100 % EA in hexanes) providing a yellow solid.

STEP 2: Synthesis of 2-(3-phenyl-4-((4-sulfamoylpiperazin-1-yl)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **90** and 2-(3-phenyl-4-((piperazine-1-sulfonamido)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid **138**

30 **[0513]** A mixture of tert-butyl 2-(4-formyl-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.422 mmol) and piperazine-1-sulfonamide (0.633 mmol) in methanol (2 mL) was stirred at 90 °C for 15 minutes in a sealed tube. The reaction mixture was cooled to room temperature then treated with sodium cyanoborohydride (0.844 mmol) and stirred at rt for another 1 h. The mixture of products was extracted with ethyl acetate. The organic layer was subsequently washed with water and brine. Upon removal of the solvent, the product was taken in dichloromethane (1 mL) and treated with TFA (0.5 mL) then stirred at rt for 1 h. The solvent was removed by forced air and the crude product was subsequently purified on a preparative HPLC.

Example 156

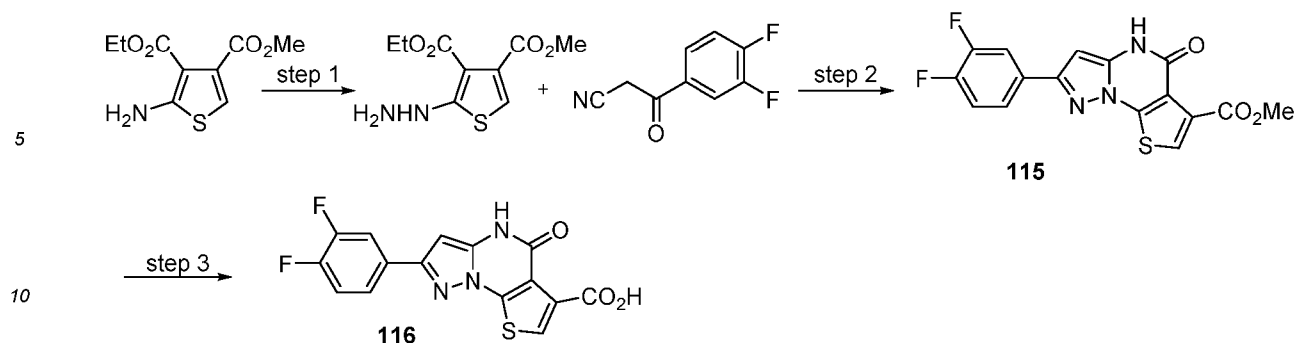
40 **[0514]** This example describes the synthesis of alkyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylate and alkyl 2-(3-(3,4-difluorophenyl)-5-alkoxy-1H-pyrazol-1-yl)thiazole-4-carboxylate in an embodiment of the invention.



50 **[0515]** To a stirring solution of 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (0.155 mmol) in DMA (0.8 mL) were added 1-chloroethyl ethyl carbonate (0.155 mmol) and K_2CO_3 (0.309 mmol). The reaction mixture was stirred at rt for 2 h. Upon completion the reaction mixture was filtered and the filtrate was subsequently purified on a preparative HPLC.

Example 157

[0516] This example describes the synthesis of 2-(3-(3,4-difluorophenyl)-5-oxo-4,5-dihydropyrazolo[1,5-a]thieno[3,2-e]pyrimidine-6-carboxylic acid **116** in an embodiment of the invention



STEP 1: Synthesis of 3-ethyl 4-methyl 2-hydrazinylthiophene-3,4-dicarboxylate

15 **[0517]** A solution of 3-ethyl 4-methyl 2-aminothiophene-3,4-dicarboxylate (4.86 g, 21.20 mmol, 1 eq) in conc. HCl (30 ml) was added sodium nitrite (1.609 g, 23.32 mmol, 1.1 eq) in 15 mL of water drop wise at 0 °C. The reaction mixture was stirred for 30 min then added a solution of tin(II) chloride (16.08 g, 85 mmol, 4 eq) in 15 mL of conc. HCl and stirred for 15 minutes. The reaction mixture was carefully neutralized with 40 % NaOH solution upon cooling in an ice bath.

20 The solid tin salt was removed by filtration and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified on a flash system using a 220 G gold silica column eluting with 20-100 % ethyl acetate in hexanes. The first peak with mass M+H = 245 was pooled and concentrated to get a light yellow solid (1.36 g in 26 % yield).

STEP 2: Synthesis of methyl 2-(3,4-difluorophenyl)-5-oxo-4,5-dihydropyrazolo[1,5-a]thieno[3,2-e]pyrimidine-6-carboxylate **115**

25 **[0518]** A thoroughly mixed mixture of 3-ethyl 4-methyl 2-hydrazinylthiophene-3,4-dicarboxylate (0.3 g, 1.228 mmol, 1 eq) and 3-(3,4-difluorophenyl)-3-oxopropanenitrile (0.222 g, 1.228 mmol, 1 eq) in an open vial was stirred neat at 130 °C for 1.5 h. The melted liquid becomes thick solid which is triturated in DCM/MeOH. The crude product was purified on flash system using a 24 g silica column eluting with 1-10 % methanol in DCM over 12 column volumes. The pure fraction was pooled and concentrated to get 0.49 g (Yield = 84 %) of white solid.

30

STEP 3: Synthesis of 2-(3,4-difluorophenyl)-5-oxo-4,5-dihydropyrazolo[1,5-a]thieno[3,2-e]pyrimidine-6-carboxylic acid **116**

35 **[0519]** A solution methyl 2-(3,4-difluorophenyl)-5-oxo-4,5-dihydropyrazolo[1,5-a]thieno[3,2-e]pyrimidine-6-carboxylate (0.1 g, 0.277 mmol, 1 eq) in a mixture of THF/MeOH (3/1) was treated with 1.5 molar solution of LiOH in water (4-5 eq) then stirred at room temperature for 1 h. The excess solvent was removed by forced air then the residue was acidified with 1 molar HCl. The crude product was taken in DMSO and purified on a preparative HPLC.

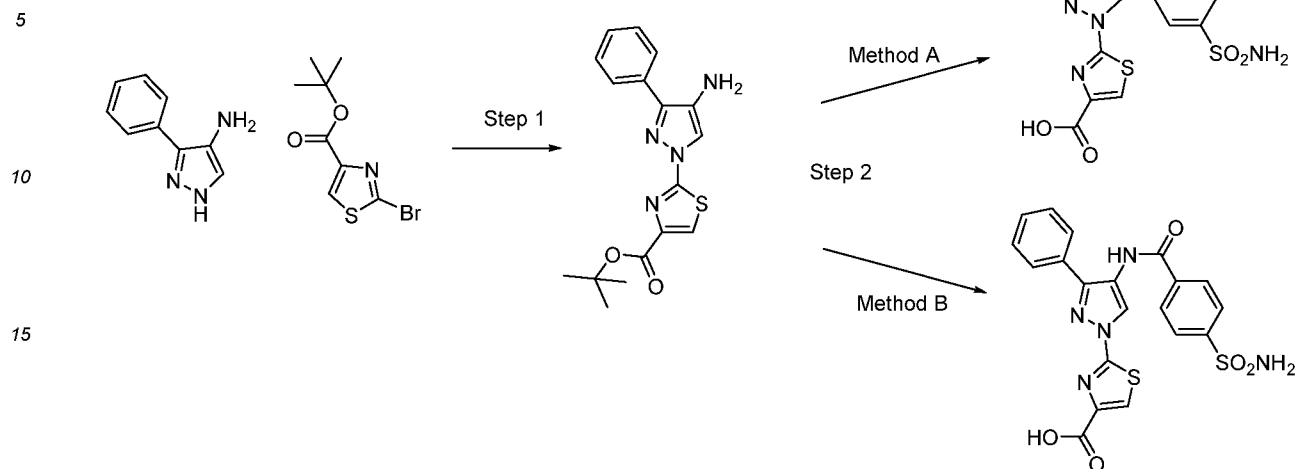
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Example 158

45 **[0520]** This example describes the synthesis of 2-(3-phenyl-4-((4-sulfamoylbenzyl)amino)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid and 2-(3-phenyl-4-(4-sulfamoylbenzamido)-1H-pyrazol-1-yl)thiazole-4-carboxylic

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STEP 1: Synthesis of tert-butyl 2-(4-amino-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate

[0521] A solution of 3-phenyl-1H-pyrazol-4-amine (0.25 g, 1.57 mmol), K_2CO_3 (0.33 g, 2.36 mmol), and tert-butyl 2-bromothiazole-4-carboxylate (0.47 g, 1.73 mmol) in DMSO was stirred for 24 h at 120 °C. Upon completion the reaction mixture was cooled, diluted with ethyl acetate and filtered through celite. The organic layer was washed with ammonium chloride and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on silica gel using gradient elution (5-80 % ethyl acetate containing 1 % TEA in hexanes over 15 CV) to afford the desired compound as a yellow solid.

STEP 2 - Method A- Synthesis of 2-(3-phenyl-4-((4-sulfamoylbenzyl)amino)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

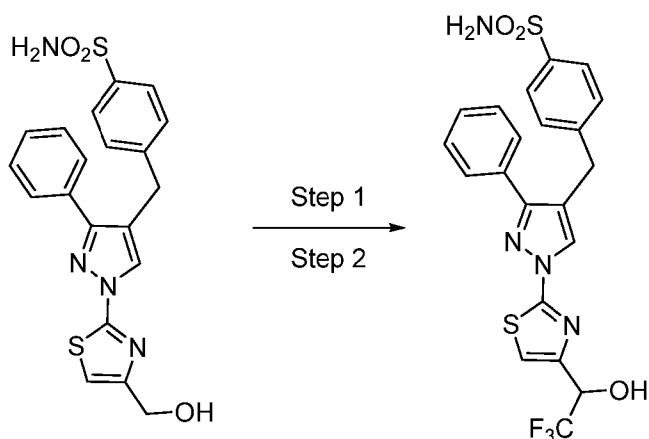
[0522] To a stirring solution of tert-butyl 2-(4-amino-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.13 g, 0.38 mmol) and 4-formylbenzenesulfonamide (0.09 g, 0.49 mmol) in MeOH (3 ml) was added few drops of acetic acid. The reaction mixture was stirred at 80 °C for 30 minutes in a sealed tube. The reaction mixture was cooled to rt then added sodium cyanoborohydride (0.048 g, 0.759 mmol) and stirred at rt for another 15 minutes. The crude reaction mixture was purified directly on reverse phase preparative chromatography without workup using gradient elution (4-100% acetonitrile modified with 0.1% TFA in water modified with 0.1% TFA). The pure product was deprotected with TFA/DCM finally purified on HPLC.

STEP 2 - Method B - Synthesis of 2-(3-phenyl-4-(4-sulfamoylbenzamido)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

[0523] A solution of 4-sulfamoylbenzoic acid (0.09 g, 0.44 mmol) and HATU (0.22 g, 0.58 mmol) in DMF was stirred at rt for 15 minutes at which time tert-butyl 2-(4-amino-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.1 g, 0.29 mmol) and Hunig'sBase (0.10 ml, 0.58 mmol) were added. The reaction mixture was stirred at 60 °C for 4 h. Upon completion the reaction mixture was cooled and extracted with ethyl acetate. The organic layer was washed with water, bicarbonate and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on silica gel using gradient elution (20-100 % ethyl acetate in hexanes over 15 CV). The first fraction was collected and dried. The pure product was deprotected with TFA/DCM, dried using forced air then taken up in DMSO and finally purified on HPLC.

Example 159

[0524] This example describes the synthesis of 4-((3-phenyl-1-(4-(2,2,2-trifluoro-1-hydroxyethyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide in an embodiment of the invention



STEP 1: Synthesis of 4-((1-(4-formylthiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide

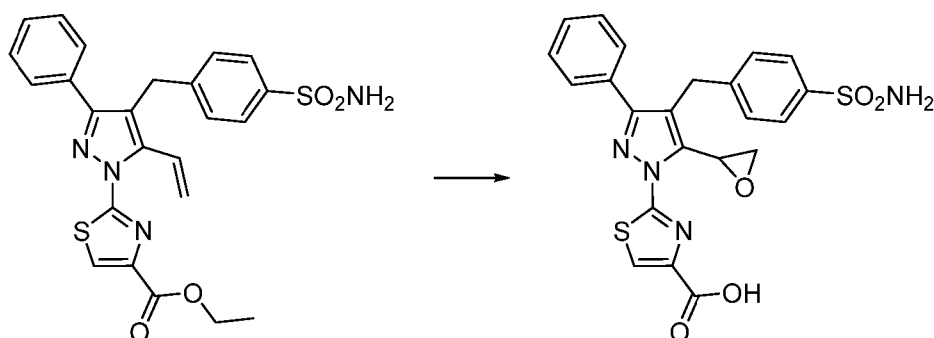
[0525] To a stirring solution of 4-((1-(4-(hydroxymethyl)thiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (0.36 g, 0.84 mmol) in CHCl_3 (10 mL) was added manganese dioxide (0.37 g, 4.2 mmol). The reaction mixture was stirred at rt for 12 h. Upon completion the solution was filtered through celite and concentrated under reduced pressure to afford the title compound. The crude product was taken to the next step without purification.

STEP 2: Synthesis of 4-((3-phenyl-1-(4-(2,2,2-trifluoro-1-hydroxyethyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide

[0526] To a stirring solution of 4-((1-(4-formylthiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (0.15 g, 0.35 mmol) in THF (2 mL) was added (trifluoromethyl)trimethylsilane (0.16 mL, 1.060 mmol) followed by TBAF (0.18 mL, 0.18 mmol) at 0 °C. The reaction mixture was stirred at rt for 4 h. Upon completion the product was extracted with ethyl acetate, washed with 1 molar HCl and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified directly on reverse phase HPLC.

Example 160

[0527] This example describes the synthesis of 2-(5-(oxiran-2-yl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid

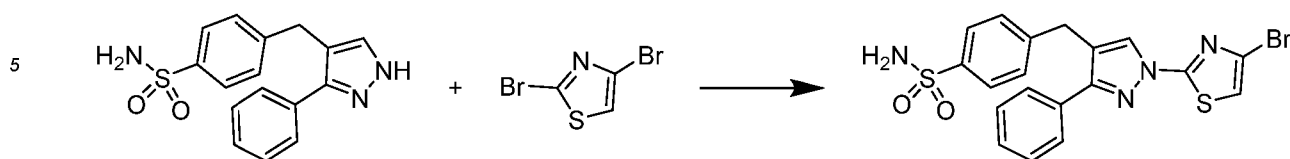


[0528] To a stirring solution of ethyl 2-(3-phenyl-4-(4-sulfamoylbenzyl)-5-vinyl-1H-pyrazol-1-yl)thiazole-4-carboxylate (0.1 g, 0.2 mmol) in ethyl acetate/acetone mixture was added a solution of sodium bicarbonate (0.09 g, 1.0 mmol) in 2 mL of water followed by addition of a solution of Oxone (0.373 g, 0.607 mmol) in 1 mL water. The reaction mixture was stirred vigorously at rt for 3 days. Upon completion the product was extracted with ethyl acetate, washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was hydrolyzed with LiOH in THF/MeOH/water then purified in HPLC without using any acid modifiers.

Example 161

[0529] This example describes the synthesis of 2-(5-(oxiran-2-yl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thi-

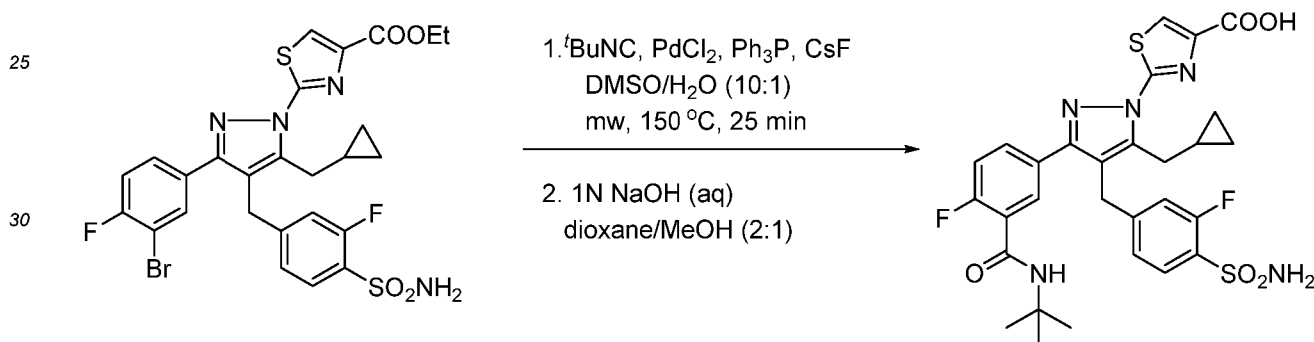
azole-4-carboxylic acid in an embodiment of the invention



10 **[0530]** To a round bottom flask were added 4-((3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (.03 g, 0.09 mmol) and DMF (0.5 ml), followed by NaH (3.6 mg, 0.09 mmol). The reaction mixture was stirred at rt for 20 mins, at which time 2,4-dibromothiazole (0.02 g, 0.09 mmol) was added. The reaction mixture was heated to 100 °C for 1 h. Reaction was predominantly finished with no visible starting material this time. The reaction was quenched with water and extracted with EtOAc and washed with water and brine, dried over Na₂SO₄, filtered, concentrated in vacuo. The residue was purified directly on silica using gradient elution (20-80% ethyl acetate in hexanes over 12 CV) to afford the title compound.

Example 162

20 **[0531]** This example describes the synthesis of 2-(3-(3-(tert-butylcarbamoyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl) thiazole-4-carboxylic acid.



35 STEP 1: Synthesis of ethyl 2-(3-(3-(tert-butylcarbamoyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate

40 **[0532]** To a mixture of ethyl 2-(3-(3-bromo-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (100.0 mg, 0.156 mmol), PdCl₂ (1.38 mg, 0.0078 mmol) and PPh₃ (4.0 mg, 0.0156 mmol) in DMSO (1.8 mL) was added CsF (26.0 mg, 0.171 mmol) and water (0.2 mL) successively. The reaction mixture was allowed to stir for 5 min at rt, and *tert*-butyl isocyanide (26.4 µL, 0.234 mmol) was added. The reaction mixture was irradiated at 150 °C for 25 min in a microwave reactor. The reaction mixture was poured into water and extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with brine (1 x 20 mL) and dried with anhydrous magnesium sulfate. The combined organic layer was concentrated in rotary evaporator and the crude (43.0 mg) was used in the next step.

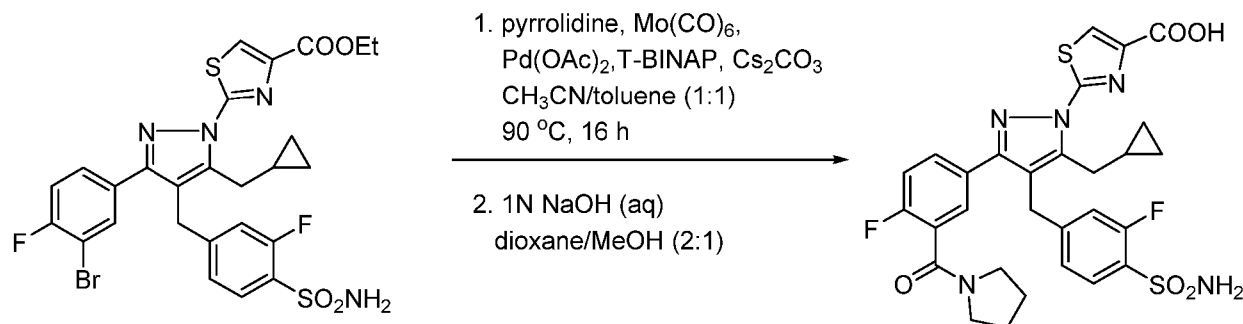
STEP 2. Synthesis of 2-(3-(3-(tert-butylcarbamoyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl) thiazole-4-carboxylic acid.

50 **[0533]** Ethyl 2-(3-(3-(tert-butylcarbamoyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate from Step 1 (43.0 mg, 0.065 mmol) was dissolved in a mixture of dioxane and MeOH (1.0 mL / 0.5 mL) and 1.0 mL of 1 N aqueous NaOH was added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized by the addition of 1.0 M aqueous hydrochloric acid, diluted with ethyl acetate (15 mL), washed with water (10 mL), and dried with anhydrous magnesium sulfate. The organic layer was concentrated using a rotary evaporator and the residue was dissolved in DMSO and purified by HPLC (Phenomenex Gemini C18, H₂O/CH₃CN gradient from 40% to 100% CH₃CN for 4 min, 0.1% TFA) to give the title compound (11.0 mg, 26%). ¹H-NMR (MeOD) δ: 8.21 (s, 1H), 7.79-7.69 (m, 3H), 7.19 (dd, *J* = 8.6, 10.0 Hz, 1H), 7.11-7.05 (m, 2H), 4.21 (s, 2H), 3.28

(d, $J = 6.8$ Hz, 2H), 1.44 (s, 9H), 1.18-1.10 (m, 1H), 0.43-0.39 (m, 2H), 0.28-0.24 (m, 2H); MS (ES) 630.1 $[M + H]^+$, LCMS RT = 1.048 min.

Example 163

[0534] This example describes the synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(pyrrolidine-1-carbonyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (Cpd. C).



STEP 1: Synthesis of ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(pyrrolidine-1-carbonyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate.

[0535] To a solution of ethyl 2-(3-(3-bromo-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (100.0 mg, 0.156 mmol) in CH_3CN (1.0 mL) and toluene (1.0 mL) were added $Mo(CO)_6$ (61.7 mg, 0.234 mmol), $Pd(OAc)_2$ (3.5 mg, 0.0156 mmol), T-BINAP (10.5 mg, 0.0156 mmol), Cs_2CO_3 (76.2 mg, 0.234 mmol) and pyrrolidine (20.0 μL , 0.234 mmol). The reaction mixture was heated at 90 °C for 16 h. The reaction mixture was poured into water and extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with brine (1 x 20 mL) and dried with anhydrous magnesium sulfate. The combined organic layer was concentrated in rotary evaporator and the crude (31.0 mg) was used for the next step.

STEP 2: Synthesis of 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(pyrrolidine-1-carbonyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid.

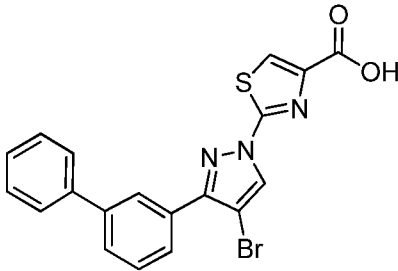
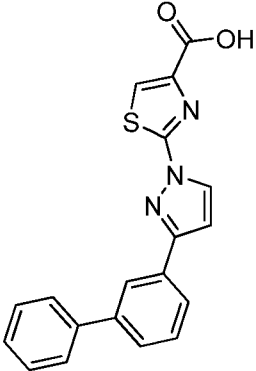
[0536] Ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(pyrrolidine-1-carbonyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate from Step 1 (31.0 mg, 0.047 mmol) was dissolved in a mixture of dioxane and MeOH (1.0 mL/ 0.5 mL) and 1.0 mL of 1 N aqueous NaOH was added. The reaction mixture was stirred at room temperature 2 h. The reaction mixture was neutralized by addition of 1.0 M aqueous hydrochloric acid diluted with ethyl acetate (15 mL), washed with water (10 mL), and dried with anhydrous magnesium sulfate. The organic layer was concentrated using a rotary evaporator, and the residue was dissolved in DMSO and purified by HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient from 40% to 100% CH_3CN for 4 min, 0.1% TFA) to give the title compound (10.0 mg, 24%). ^1H -NMR (MeOD) δ : 8.22 (s, 1H), 7.75-7.71 (m, 2H), 7.54 (dd, $J = 2.2, 6.4$ Hz, 1H), 7.24 (t, $J = 8.8$ Hz, 1H), 7.07 (t, $J = 7.4$ Hz, 2H), 4.20 (s, 2H), 3.59 (t, $J = 7.1$ Hz, 2H), 3.30 (d, $J = 6.9$ Hz, 2H), 3.19 (t, $J = 2$ Hz), 2.03-1.91 (m, 4H), 0.95-0.86 (m, 1H), 0.45-0.40 (m, 2H), 0.29-0.25 (m, 2H); MS (ES) 628.0 $[M + H]^+$, LCMS RT = 0.968 min.

Example 164

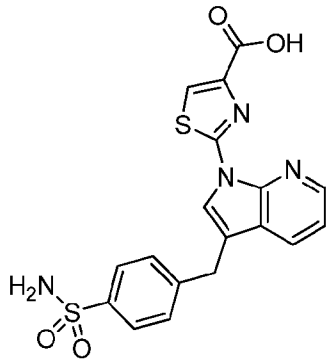
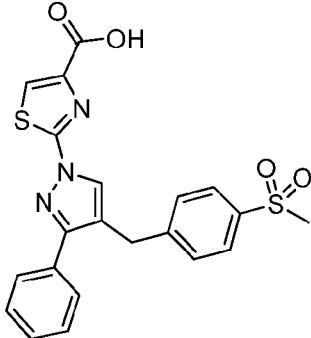
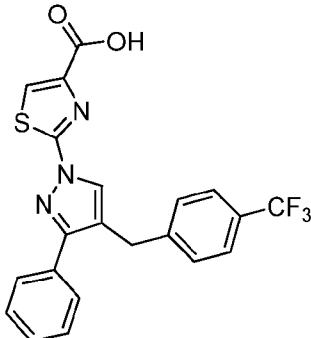
[0537] This example describes the LDHA inhibitory activity, as measured by the assay set forth in Example 1, of exemplified compounds of formula (I) as embodiments. See Table 7. The compounds are assigned and activity level based on IC_{50} as follows: +++ < 100 nM; ++ 100 nM - 1000 nM; + > 1000 nM - 57000 nM; and - > 57000 nM.

Table 7

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
19		2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.18 (s, 1H), 8.21 (s, 2H), 7.80 – 7.71 (m, 2H), 7.72 – 7.63 (m, 2H), 7.52 – 7.37 (m, 5H), 7.28 (s, 2H), 4.15 (s, 2H); MS (M+H)⁺ = 441	+++	28
20		2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.20 (s, 1H), 8.29 (s, 1H), 8.24 (s, 1H), 7.81 (d, <i>J</i> = 1.8 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.74 – 7.67 (m, 2H), 7.57 (d, <i>J</i> = 7.6 Hz, 3H), 7.50 – 7.42 (m, 4H), 7.37 (dd, <i>J</i> = 8.4, 6.3 Hz, 1H), 7.30 (s, 2H), 4.21 (s, 2H); MS	+++	29

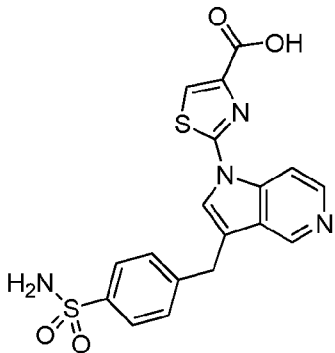
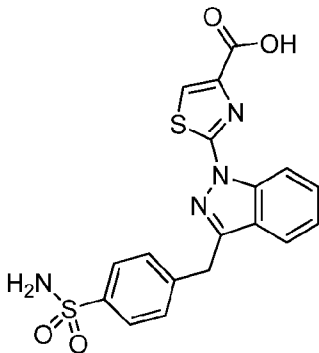
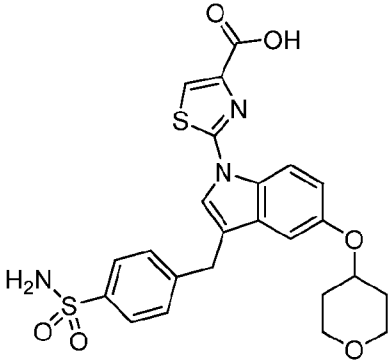
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(M+H) ⁺ = 517		
21		2-(3-([1,1'-biphenyl]-3-yl)-4-bromo-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.25 (s, 1H), 8.93 (s, 1H), 8.28 (s, 1H), 8.12 (d, <i>J</i> = 1.8 Hz, 1H), 7.85 (dd, <i>J</i> = 7.7, 1.5 Hz, 1H), 7.79 (dd, <i>J</i> = 7.9, 1.5 Hz, 1H), 7.72 (dd, <i>J</i> = 7.5, 1.7 Hz, 2H), 7.63 (t, <i>J</i> = 7.8 Hz, 1H), 7.50 (t, <i>J</i> = 7.6 Hz, 2H), 7.40 (t, <i>J</i> = 7.4 Hz, 1H); MS (M+H)⁺ = 427	+	30
22		2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H)⁺ = 348	+	31

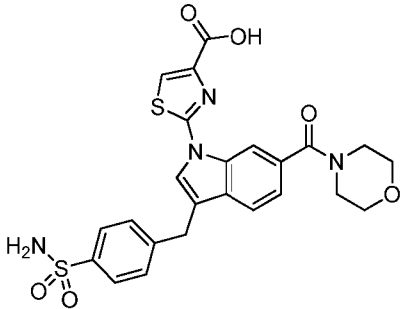
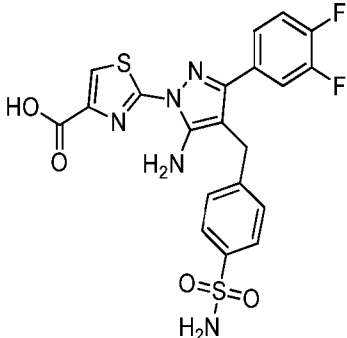
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
23		2-(3-(3,4-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 358	-	32
24		2-(5-hydroxy-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 459	++	33
25		2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.16 (s, 1H), 8.88 – 8.78 (m, 2H), 8.33 (s, 1H), 8.15 (ddd, <i>J</i> = 11.7, 7.7, 2.2 Hz, 1H), 8.05 – 7.97 (m, 1H), 7.68 (dt, <i>J</i> = 10.8, 8.5 Hz, 1H), 7.60 (dd, <i>J</i> = 8.1, 4.6 Hz, 1H); MS (M+H) ⁺ = 359	-	34

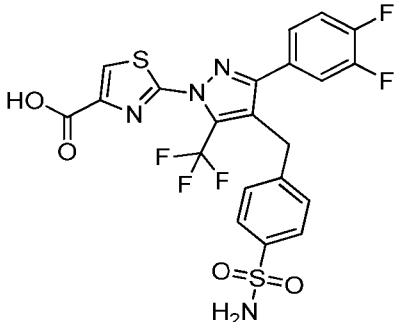
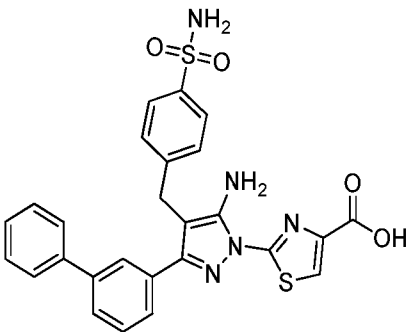
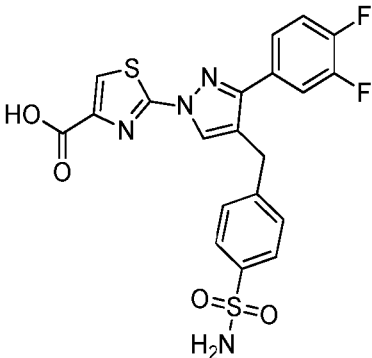
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
26		2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.04 (s, 1H), 8.46 (dd, <i>J</i> = 4.8, 1.5 Hz, 1H), 8.19 (s, 1H), 8.09 (dd, <i>J</i> = 7.8, 1.5 Hz, 1H), 8.07 (s, 1H), 7.80 – 7.72 (m, 2H), 7.58 (d, <i>J</i> = 8.2 Hz, 2H), 7.32 (dd, <i>J</i> = 7.9, 4.8 Hz, 1H), 7.27 (s, 2H), 4.23 (s, 2H); MS (M+H) ⁺ = 415	++	35
27		2-(4-(4-(methylsulfonyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (s, 1H), 8.34 (s, 1H), 8.23 (d, <i>J</i> = 1.7 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.70 – 7.62 (m, 2H), 7.53 – 7.37 (m, 5H), 4.19 (s, 2H), 3.17 (s, 3H); MS (M+H) ⁺ = 440	-	36
28		2-(3-phenyl-4-(4-(trifluoromethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (s, 1H), 8.33 (s, 1H), 8.23 (s, 1H), 7.69 – 7.59 (m, 4H), 7.50 – 7.36 (m, 5H), 4.18 (s, 2H); MS (M+H) ⁺ = 430	-	37

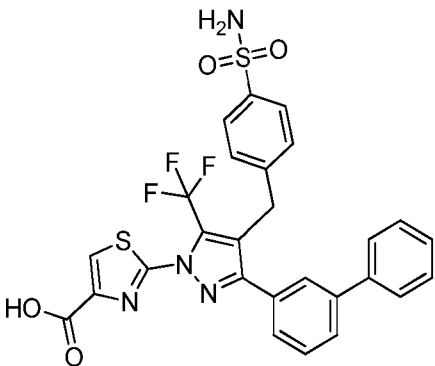
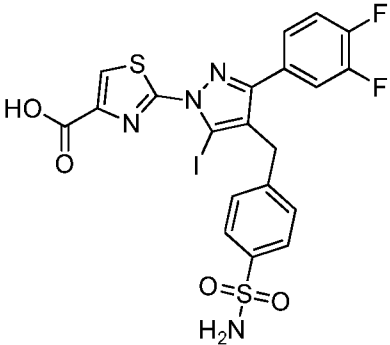
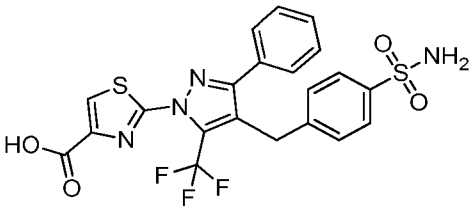
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
29		2-(3-([1,1'-biphenyl]-3-yl)-1H-pyrrolo[2,3-b]pyridin-1-yl)thiazole-4-carboxylic acid, TFA ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.08 (s, 1H), 8.68 (s, 1H), 8.57 (d, <i>J</i> = 4.7 Hz, 1H), 8.55 – 8.50 (m, 1H), 8.28 (s, 1H), 8.07 (d, <i>J</i> = 2.0 Hz, 1H), 7.83 (m, 3H), 7.68 (d, <i>J</i> = 7.7 Hz, 1H), 7.61 (t, <i>J</i> = 7.6 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.43 – 7.35 (m, 1H); MS (M+H) ⁺ = 398	-	38
30		2-(5-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.20 (s, 1H), 8.40 (d, <i>J</i> = 8.5 Hz, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.73 (d, <i>J</i> = 8.0 Hz, 2H), 7.61 (s, 1H), 7.55 (d, <i>J</i> = 8.0 Hz, 2H), 7.43 (d, <i>J</i> = 8.6 Hz, 1H), 7.25 (s, 2H), 4.21 (s, 2H), 3.76 – 3.34 (m, 8H); MS (M+H) ⁺ = 527	+	39
31		2-(5-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.17 (s, 1H), 8.40 (dd, <i>J</i> = 9.2, 4.5 Hz, 1H), 8.19 (d, <i>J</i> = 1.0 Hz, 1H),	++	40

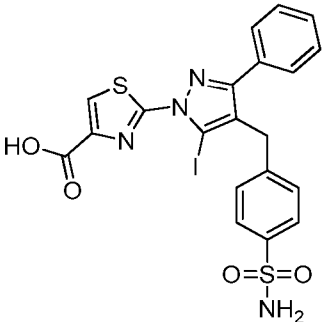
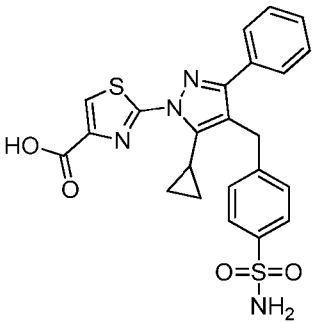
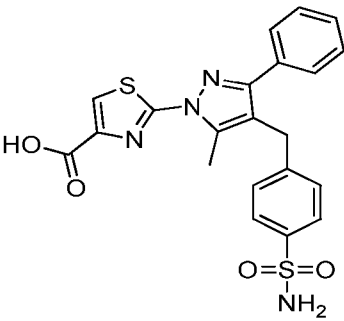
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		7.93 (s, 1H), 7.73 (d, <i>J</i> = 8.0 Hz, 2H), 7.56 (d, <i>J</i> = 8.0 Hz, 2H), 7.37 (dd, <i>J</i> = 9.2, 2.6 Hz, 1H), 7.27 – 7.18 (m, 3H), 4.16 (s, 2H); MS (M+H) ⁺ = 432		
32		2-(5-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.11 (s, 1H), 8.25 (d, <i>J</i> = 8.5 Hz, 1H), 8.17 (s, 1H), 7.77 (s, 1H), 7.75 – 7.69 (m, 2H), 7.55 – 7.49 (m, 2H), 7.45 (d, <i>J</i> = 1.8 Hz, 1H), 7.32 (dd, <i>J</i> = 8.5, 1.6 Hz, 1H), 7.23 (s, 2H), 4.17 (s, 2H), 3.58 – 3.46 (m, 6H), 2.35 – 2.23 (m, 4H); MS (M+H) ⁺ = 513	+	41
33		2-(3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.22 (s, 1H), 8.71 (s, 1H), 8.28 (s, 1H), 7.86 – 7.81 (m, 2H), 7.81 – 7.75 (m, 2H), 7.48 – 7.35 (m, 3H), 7.33 – 7.29 (m, 2H), 7.27 (s, 2H); MS (M+H) ⁺ = 443	+++	42

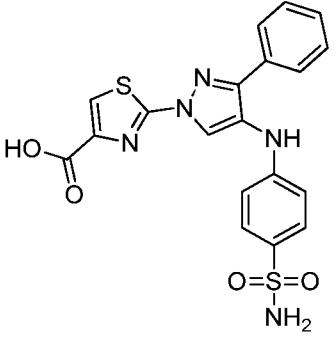
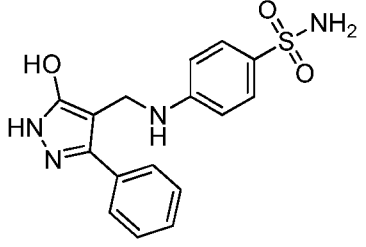
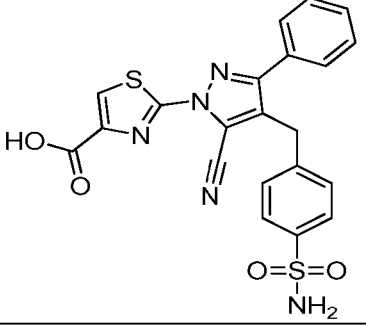
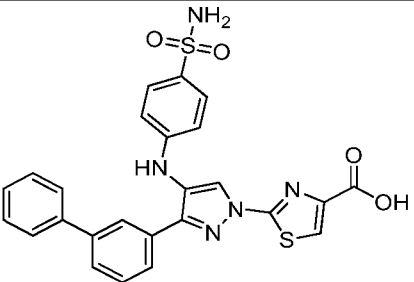
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
34		2-(3-(4-sulfamoylbenzyl)-1H-pyrrolo[3,2-c]pyridin-1-yl)thiazole-4-carboxylic acid, NH ₃ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.83 (d, <i>J</i> = 1.0 Hz, 1H), 8.46 (d, <i>J</i> = 5.8 Hz, 1H), 8.27 (s, 1H), 8.21 (dd, <i>J</i> = 5.8, 1.0 Hz, 1H), 7.95 (s, 1H), 7.74 (d, <i>J</i> = 8.3 Hz, 2H), 7.57 (d, <i>J</i> = 8.4 Hz, 2H), 7.23 (s, 2H), 4.25 (s, 2H) (acid OH not shown); MS (M+H) ⁺ = 415	++	43
35		2-(3-(4-sulfamoylbenzyl)-1H-indazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.15 (s, 1H), 8.51 (d, <i>J</i> = 8.4 Hz, 1H), 8.18 (s, 1H), 7.80 (dd, <i>J</i> = 8.0, 1.0 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.67 (ddd, <i>J</i> = 8.3, 7.0, 1.1 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.35 (ddd, <i>J</i> = 8.1, 7.0, 0.9 Hz, 1H), 7.27 (s, 2H), 4.49 (s, 2H); MS (M+H) ⁺ = 415	+	44
36		2-(3-(4-sulfamoylbenzyl)-5-((tetrahydro-2H-pyran-4-yl)oxy)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH ₃ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.22 (d, <i>J</i> = 8.9 Hz, 1H), 8.04 (s, 1H), 7.74 (d, <i>J</i> = 3.6 Hz, 2H), 7.71 (d,	++	

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		<i>J</i> = 1.9 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.23 (s, 2H), 7.06 (d, <i>J</i> = 2.4 Hz, 1H), 7.01 (dd, <i>J</i> = 9.0, 2.4 Hz, 1H), 4.57 – 4.41 (m, 1H), 4.14 (s, 2H), 3.83 (dt, <i>J</i> = 11.7, 4.4 Hz, 2H), 3.44 (ddd, <i>J</i> = 11.8, 9.5, 2.8 Hz, 2H), 1.90 (dd, <i>J</i> = 13.1, 3.5 Hz, 2H), 1.54 (ddd, <i>J</i> = 13.0, 8.8, 4.0 Hz, 2H) (acid OH not shown); MS (M+H) ⁺ = 514		
37		2-(6-(morpholine-4-carbonyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH ₃ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.45 (dd, <i>J</i> = 1.4, 0.7 Hz, 1H), 7.98 (s, 1H), 7.93 (s, 1H), 7.75 – 7.67 (m, 2H), 7.58 (dd, <i>J</i> = 8.1, 0.7 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.28 – 7.16 (m, 3H), 4.19 (s, 2H), 3.54 (d, <i>J</i> = 41.1 Hz, 8H) (acid OH not shown); MS (M+H) ⁺ = 527	+	46
38		2-(5-amino-3-(3,4-difluorophenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid MS (M+H) ⁺ = 492	+++	12, 18

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
39		2-(3-(3,4-difluorophenyl)-4-(4-sulfamoylbenzyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.29 (s, 1H), 8.47 (d, J = 1.2 Hz, 1H), 7.87 – 7.66 (m, 2H), 7.69 – 7.46 (m, 2H), 7.48 – 7.19 (m, 5H), 4.24 (s, 2H); MS (M+H) ⁺ = 545	+++	14, 18
40		2-(3-([1,1'-biphenyl]-3-yl)-5-amino-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.06 (s, 1H), 8.21 (d, J = 1.1 Hz, 1H), 7.79 – 7.74 (m, 2H), 7.70 – 7.62 (m, 2H), 7.59 – 7.47 (m, 2H), 7.46 – 7.32 (m, 7H), 7.29 (s, 2H), 6.94 (s, 2H), 4.05 (s, 2H); (M+H) ⁺ = 532	+++	12, 18
41		2-(3-(3,4-difluorophenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 8.24 (s, 1H), 7.86 – 7.62 (m, 2H), 7.55 (q, J = 5.7, 4.9 Hz, 2H), 7.47 – 7.38 (m, 2H), 7.31 (s, 1H), 4.18 (s, 2H); (M+H) ⁺ = 477	+++	28

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
42		2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.27 (s, 1H), 8.45 (d, J = 1.2 Hz, 1H), 7.77 (tt, J = 6.6, 1.5 Hz, 3H), 7.67 (q, J = 1.6 Hz, 1H), 7.62 – 7.28 (m, 13H), 4.27 (s, 2H); (M+H) ⁺ = 589	+++	14, 18
43		2-(3-(3,4-difluorophenyl)-5-iodo-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.23 (s, 1H), 8.41 (d, J = 1.1 Hz, 1H), 7.83 – 7.65 (m, 2H), 7.63 – 7.47 (m, 2H), 7.42 – 7.35 (m, 1H), 7.32 – 7.25 (m, 4H), 4.15 (s, 2H); (M+H) ⁺ = 603	+++	13, 18
44		2-(3-phenyl-4-(4-sulfamoylbenzyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.27 (s, 1H), 8.46 (d, J = 0.9 Hz, 1H), 7.79 – 7.66 (m, 2H), 7.58 – 7.41 (m, 5H), 7.30 (s, 3H), 7.33 – 7.26 (m, 1H), 4.23 (s, 2H); (M+H) ⁺ = 509	+++	14, 18

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
45		2-(5-iodo-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.19 (s, 1H), 8.37 (d, J = 1.2 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.57 – 7.49 (m, 2H), 7.51 – 7.36 (m, 3H), 7.31 – 7.24 (m, 4H), 4.12 (s, 2H); (M+H) ⁺ = 567	+++	13, 18
46		2-(5-cyclopropyl-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.32 (s, 1H), 7.74 – 7.70 (m, 2H), 7.53 – 7.49 (m, 2H), 7.43 – 7.37 (m, 3H), 7.31 – 7.26 (m, 4H), 4.14 (s, 2H), 2.25 (tt, J = 8.5, 5.6 Hz, 1H), 1.02 – 0.92 (m, 2H), 0.71 – 0.62 (m, 2H); (M+H) ⁺ = 481	+++	112
47		2-(5-methyl-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.29 – 8.19 (m, 1H), 7.78 – 7.65 (m, 2H), 7.53 (dq, J = 6.8, 1.3 Hz, 2H), 7.49 – 7.33 (m, 3H), 7.32 – 7.23 (m, 4H), 4.08 (s, 2H), 2.67 (d, J = 1.1 Hz, 3H); (M+H) ⁺ = 455	+++	49

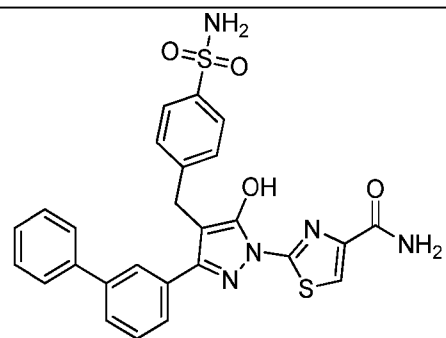
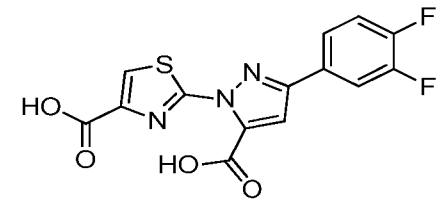
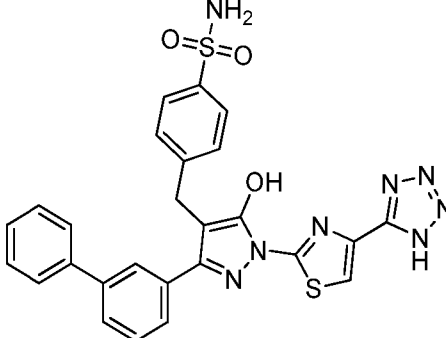
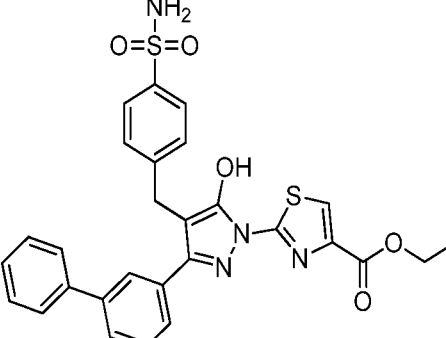
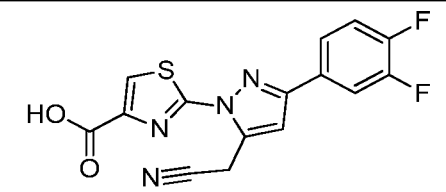
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
48		2-(3-phenyl-4-((4-sulfamoylphenyl)amino)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.20 (s, 1H), 8.57 (s, 1H), 8.25 (d, J = 2.4 Hz, 2H), 7.82 (dt, J = 8.1, 1.3 Hz, 3H), 7.55 (dd, J = 8.7, 1.2 Hz, 3H), 7.48 – 7.33 (m, 4H), 6.98 (s, 2H), 6.85 – 6.76 (m, 2H); (M+H) ⁺ = 442	+++	27
49		4-(((5-hydroxy-3-phenyl-1H-pyrazol-4-yl)methyl)amino)benzenesulfonamide (M+H) ⁺ = 345	-	149
50		2-(5-carbamoyl-3-phenyl-4-((4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 466	+++	17, 18
51		2-(3-([1,1'-biphenyl]-3-yl)-4-((4-sulfamoylphenyl)amino)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid. (M+H) ⁺ = 518	+++	27

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
52		2-(3-([1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 7.80 – 7.73 (m, 2H), 7.73 – 7.59 (m, 2H), 7.60 – 7.47 (m, 2H), 7.42 (d, J = 4.3 Hz, 4H), 7.43 – 7.28 (m, 5H), 4.19 (s, 2H), 2.30 (tt, J = 8.6, 5.6 Hz, 1H), 1.04 – 0.95 (m, 2H), 0.73 – 0.64 (m, 2H); (M+H) ⁺ = 557	+++	112
53		2-(3-(3,4-difluorophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 493	++	147
54		2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 533	++	147
55		2-(3-(2'-fluoro-[1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 551	++	147

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
56		ethyl 2-(3-([1,1'-biphenyl]-3-yl)-5-amino-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 560	+	12, 18
57		2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-5-methylthiazole-4-carboxylic acid. 1H NMR (400 MHz, DMSO-d ₆) δ 12.94 (s, 1H), 7.81 – 7.65 (m, 2H), 7.48 (dq, J = 6.8, 1.3 Hz, 2H), 7.49 – 7.26 (m, 5H), 7.24 (s, 2H), 6.82 (s, 2H), 3.97 (s, 2H), 2.68 (d, J = 1.2 Hz, 3H), 2.52 (d, J = 1.2 Hz, 1H); (M+H) ⁺ = 470	++	148
58		ethyl 2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 484	+	12
59		2-(5-(cyanomethyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 8.28 (s, 1H), 7.70 – 7.63 (m, 2H), 7.59 – 7.49 (m, 2H), 7.46 – 7.34 (m, 3H), 7.30 – 7.22 (m, 4H), 4.67 (s, 2H),	++	19, 20

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		4.22 (s, 2H); (M+H) ⁺ = 480		
60		2-(3-(3,4-difluorophenyl)-5-methoxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 507	++	73
61		2-(3-(3,4-difluorophenyl)-5-ethoxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	++	73
62		2-(3-phenyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 340	+	150
63		2-(3-(2'-fluoro-[1,1'-biphenyl]-3-yl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 382	-	147
64		2-(3-(3,4-difluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid. (M+H) ⁺ = 338	-	151

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
65		2-(3-(3,4-difluorophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
66		2-(5-hydroxy-3-methyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
67		2-(3-([1,1'-biphenyl]-3-yl)-4-(4-carbamoylbenzyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
68		2-(3-([1,1'-biphenyl]-3-yl)-4-(4-carboxybenzyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
69		2-(3-(3-bromophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	+	147

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
70		2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxamide	-	152
71		2-(5-carboxy-3-(3,4-difluorophenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	151
72		4-((1-(4-(1H-tetrazol-5-yl)thiazol-2-yl)-3-([1,1'-biphenyl]-3-yl)-5-hydroxy-1H-pyrazol-4-yl)methyl)benzenesulfonamide	+	153
73		ethyl 2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate	+	147
74		2-(5-(cyanomethyl)-3-(3,4-difluorophenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	+	19, 20

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
75		2-(5-((1H-tetrazol-5-yl)methyl)-3-(3,4-difluorophenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	+	21, 20
76		2-(3-phenyl-4-(4-sulfamoylphenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 427	+	69
77		ethyl 2-(3-phenyl-4-(4-sulfamoylbenzyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 537	+	14
78		2-(5-iodo-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxamide	+	152

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
79		2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxamide	+	152
80		2-(3-phenyl-5-(pyridin-3-ylamino)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 533	+	154
81		2-(5-hydroxy-3-(naphthalen-1-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	+	69
82		2-(5-hydroxy-3-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	+	147

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
83		4-((5-amino-1-(6-chloropyridazin-3-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	+	148
84		4-((5-amino-1-(3-methylbenzoyl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	+	148
85		4-((5-amino-1-(3-fluorobenzoyl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	+	148
86		4-((5-amino-1-(4-methylthiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	+	148

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
87		2-(5-((1H-tetrazol-5-yl)methyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 523	+	21, 18
88		4-((1-(4-(hydroxymethyl)thiazol-2-yl)-3-phenyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide	+	22
89		2-(3-(6-fluoronaphthalen-1-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	69
90		2-(3-phenyl-4-((4-sulfamoylpiperazin-1-yl)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 449	+	155
91		2-(5-hydroxy-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
92		2-(5-hydroxy-3-(3-(methylsulfonyl)phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
93		2-(5-hydroxy-3-(3-morpholinophenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
94		2-(3-(4-fluoro-3-(methylsulfonyl)phenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
95		2-(3-(3,5-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
96		2-(3-(2,3-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
97		2-(3-(2,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
98		1-((ethoxycarbonyl)oxy)ethyl 2-(3-(3,4-difluorophenyl)-5-(1-((ethoxycarbonyl)oxy)ethoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
99		(pivaloyloxy)methyl 2-(3-(4-fluorophenyl)-5-((pivaloyloxy)methoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156
100		2-(3-(2,6-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
101		3-(3-fluoro-4-(methylsulfonyl)phenyl)-1-(4-(hydroxymethyl)thiazol-2-yl)-1H-pyrazol-5-ol	-	147
102		2-(3-(2,5-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
103		2-(3-(4-fluoro-3-(methylsulfonamido)phenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
104		2-(3-(3-benzyl-4-fluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
105		1-((ethoxycarbonyl)oxy)ethyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
106		2-morpholinoethyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156
107		2,3-dihydro-1H-inden-5-yl 2-(3-(3,4-difluorophenyl)-5-((dimethylcarbamoyl)oxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156
108		2,3-dihydro-1H-inden-5-yl 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156
109		(isobutyryloxy)methyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	156
110		2-(3-(3-(N-benzylsulfamoyl)-4-fluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
111		2-(3-(4-(cyclopropanesulfonamido)-3-fluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
112		2-(3-(4-(2-(cyclopropanesulfonamido)ethyl)-3-fluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
113		2-(4-benzyl-3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
114		2-(3-(4-fluoro-3-(N-methylsulfamoyl)phenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid	-	147
115		methyl 2-(3-(3,4-difluorophenyl)-5-oxo-4,5-dihydropyrazolo[1,5-a]thieno[3,2-e]pyrimidine-6-carboxylate (M+H) ⁺ = 362	-	157
116		2-(3-(3,4-difluorophenyl)-5-oxo-4,5-dihydropyrazolo[1,5-a]thieno[3,2-e]pyrimidine-6-carboxylic acid (M+H) ⁺ = 348	-	157
117		tert-butyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-4-(3-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	69
118		tert-butyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-4-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylate	-	69

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
119		2-(3-(3,4-difluorophenyl)-7-hydroxy-1H-indazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 374	-	69
120		2-(3-(3,4-difluorophenyl)-7-hydroxy-1H-indazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 352	-	34
121		ethyl 2-(3-(3,4-difluorophenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 352	-	147
122		2-(3-(4-fluoro-3-(2-(methylsulfonamido)ethyl)phenyl)-5-hydroxy-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 427	-	147
123		ethyl 2-(5-amino-3-(3,4-difluorophenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 520	+	12

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
124		2-(3-([1,1'-biphenyl]-3-yl)-5-hydroxy-4-(4-(N-methylsulfamoyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 547	-	69
125		2-(3-(3,4-difluorophenyl)-7-hydroxy-1H-indol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 373	-	32
126		2-(4-acetamido-5-hydroxy-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 345	-	33
127		2-(3-phenyl-4-(4-sulfamoylbenzyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxamide	-	152
128		4-((5-amino-1-(6-oxo-1,6-dihydropyridazin-3-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	-	148

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
129		ethyl 3-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)benzoate	-	148
130		3-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)benzoic acid	-	148
131		4-((5-amino-1-(4-(hydroxymethyl)thiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	-	148
132		4-((5-((1H-tetrazol-5-yl)methyl)-1-(4-(hydroxymethyl)thiazol-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide (M+H) ⁺ = 509	-	22

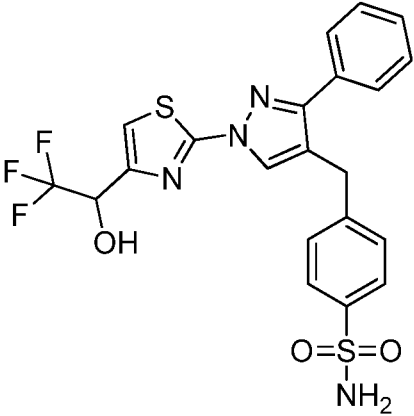
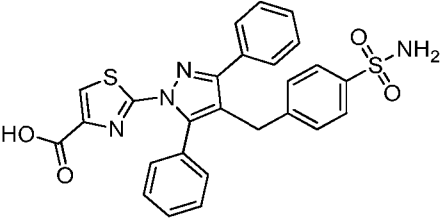
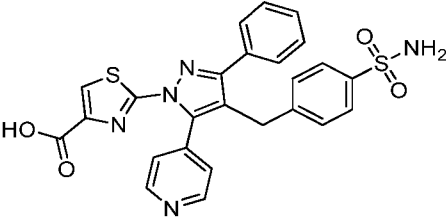
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
133		methyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 537	-	21
134		ethyl 2-(5-((1H-tetrazol-5-yl)methyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 551	-	21
135		ethyl 2-(5-(cyanomethyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 508	-	19
136		2-(3-phenyl-4-(4-sulfamoylbenzamido)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 449	-	158

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
137		4-((5-amino-3-phenyl-1-(4-(trifluoromethyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide	-	148
138		2-(3-phenyl-4-((piperazine-1-sulfonamido)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 449	-	155
139		2-(3-phenyl-4-(((4-sulfamoylphenyl)amino)methyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 456	-	155
140		ethyl 6-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)pyridazine-3-carboxylate	-	148
141		ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 585	-	14

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
142		2-(3-phenyl-4-((4-sulfamoylbenzyl)amino)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 456	-	158
143		4-((5-amino-1-(5-amino-1-methyl-1H-pyrazole-4-carbonyl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	-	148
144		6-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)picolinic acid	+	148
145		2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)isonicotinic acid	-	148

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
146		ethyl 2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-5-methylthiazole-4-carboxylate (M+H) ⁺ = 498	-	148
147		2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-5-methylthiazole-4-carboxylic acid (M+H) ⁺ = 470	+	148
148		2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 456	+	148
149		(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate	++	156

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
150		4-((5-amino-1-(1H-indole-7-carbonyl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	-	148
151		ethyl 2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)oxazole-4-carboxylate (M+H) ⁺ = 468	+	148
152		4-((5-amino-1-(4-hydroxypyrimidin-2-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide	-	148
153		2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)oxazole-4-carboxylic acid (M+H) ⁺ = 440	++	148

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
154		4-((3-phenyl-1-(4-(2,2,2-trifluoro-1-hydroxyethyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide 1H NMR (400 MHz, DMSO-d ₆) δ 8.21 (d, J = 0.8 Hz, 1H), 7.76 – 7.61 (m, 4H), 7.57 (d, J = 0.7 Hz, 1H), 7.49 – 7.35 (m, 5H), 7.26 (s, 2H), 6.99 (d, J = 6.3 Hz, 1H), 5.27 – 5.15 (m, 1H), 4.14 (s, 2H); (M+H) ⁺ = 495	++	159
155		2-(3,5-diphenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 12.86 (s, 1H), 8.23 (s, 1H), 7.75 – 7.67 (m, 0H), 7.66 – 7.55 (m, 4H), 7.40 (s, 4H), 7.47 – 7.30 (m, 4H), 7.30 – 7.15 (m, 5H), 3.98 (s, 2H); (M+H) ⁺ = 517	+++	15
156		2-(3-phenyl-5-(pyridin-4-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.64 – 8.57 (m, 2H), 8.23 (s, 1H), 7.66 – 7.54 (m, 4H), 7.47 – 7.34 (m, 5H), 7.25 – 7.16 (m, 4H), 4.05 (q, J = 5.2 Hz, 1H), 4.01 (s, 2H), 3.14 (d, J = 5.2 Hz, 2H); (M+H) ⁺ = 518	+	15

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
157		2-(3-phenyl-5-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 8.71 – 8.61 (m, 2H), 8.22 (s, 1H), 8.00 (ddd, J = 7.9, 2.2, 1.7 Hz, 1H), 7.66 – 7.57 (m, 4H), 7.52 (ddd, J = 7.9, 5.0, 0.9 Hz, 1H), 7.47 – 7.34 (m, 3H), 7.25 – 7.17 (m, 4H), 4.01 (s, 2H); (M+H) ⁺ = 518	++	15
158		2-(3-isopropyl-5-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 483	+	49
159		2-(5-isopropyl-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (600 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.28 (s, 1H), 7.74 – 7.68 (m, 2H), 7.51 – 7.45 (m, 2H), 7.42 – 7.34 (m, 3H), 7.31 – 7.25 (m, 4H), 4.21 – 4.12 (m, 1H), 4.15 (s, 2H), 1.28 – 1.24 (m, 6H); (M+H) ⁺ = 483	++	49

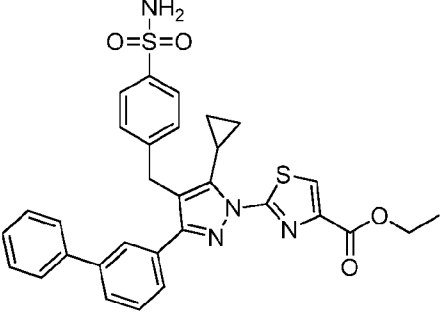
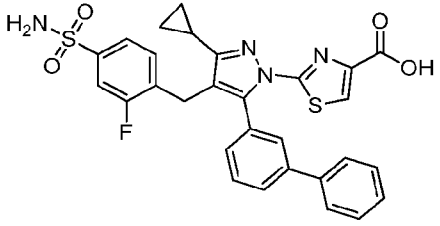
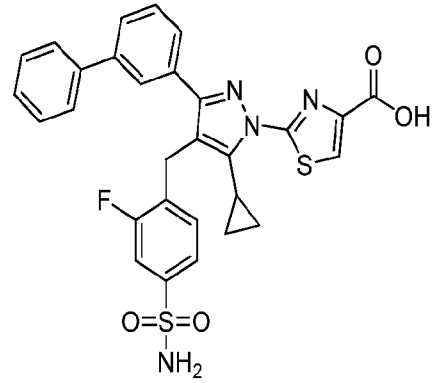
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
160		2-(5-(cyclopropylethynyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.31 (s, 1H), 7.76 – 7.68 (m, 2H), 7.65 – 7.55 (m, 2H), 7.50 – 7.37 (m, 3H), 7.36 – 7.21 (m, 4H), 4.17 (s, 2H), 1.60 (tt, J = 7.7, 5.3 Hz, 1H), 1.00 – 0.86 (m, 4H); (M+H) ⁺ = 505	+++	16
161		4-((3-([1,1'-biphenyl]-3-yl)-1H-pyrazol-4-yl)amino)benzenesulfonamide (M+H) ⁺ = 391	-	25
162		ethyl 2-(3-([1,1'-biphenyl]-3-yl)-4-((4-sulfamoylphenyl)amino)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 546	+	26
163		ethyl 2-(3-cyclopropyl-5-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 511	-	33

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC_{50} (μ M)	Example Method
164		ethyl 2-(5-cyclopropyl-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 511	+	33
165		cyclopropyl-5-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-ylthiazole-4-carboxylic acid (M+H) ⁺ = 483	+	33
166		2-(5-cyclopropyl-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.16 (s, 1H), 8.35 (s, 1H), 7.83 – 7.71 (m, 4H), 7.45 – 7.31 (m, 3H), 7.29 – 7.15 (m, 4H), 3.31 (s, 2H), 2.63 (tt, J = 8.5, 5.5 Hz, 1H), 0.99 – 0.80 (m, 4H); (M+H) ⁺ = 483	+++	33

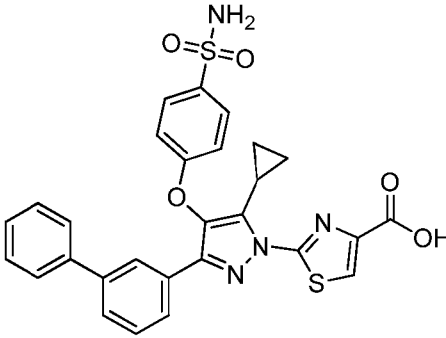
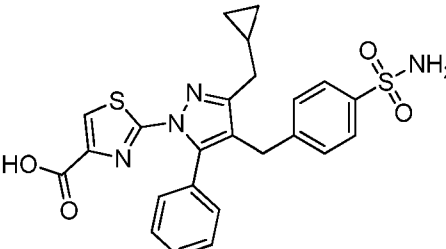
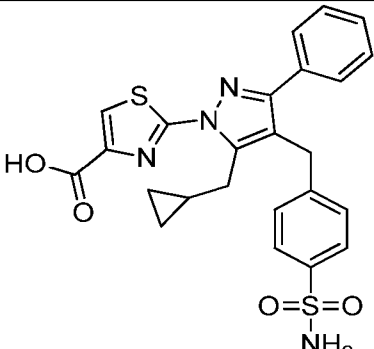
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
167		2-(3-phenyl-4-(4-sulfamoylbenzyl)-5-vinyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.18 (s, 1H), 8.32 (s, 1H), 7.80 – 7.72 (m, 2H), 7.65 (dd, J = 18.1, 11.9 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.55 – 7.26 (m, 8H), 5.63 – 5.54 (m, 1H), 5.45 (dd, J = 18.1, 1.1 Hz, 1H), 4.21 (s, 2H); (M+H) ⁺ = 467	+++	15
168		ethyl 2-(3-cyclopentyl-5-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 539	-	33
169		ethyl 2-(5-(3-cyclopentyl-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 539	-	33
170		2-(3-cyclopentyl-5-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 511	+	33

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
171		2-(5-cyclopentyl-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 511	++	33
172		2-(3-cyclohexyl-5-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 525	+	33
173		2-(5-cyclohexyl-3-phenyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 525	+	33
174		2-(3-cyclopentyl-5-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 508	+	49
175		2-(5-cyclopentyl-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 508	++	49
176		2-(3-cyclohexyl-5-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 523	+	49

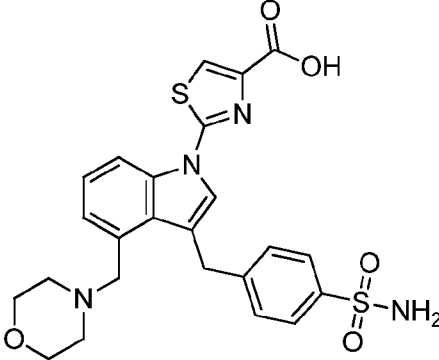
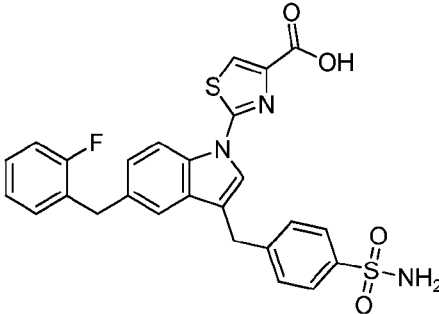
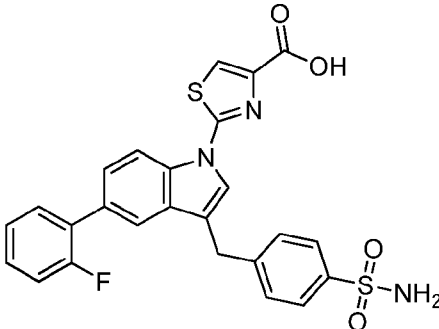
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
177		2-(5-cyclohexyl-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 523	+	49
178		2-(5-(oxiran-2-yl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 483	+	160
179		2-(3-phenyl-5-(phenylethynyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 541	+	16
180		ethyl 2-(5-([1,1'-biphenyl]-3-yl)-3-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate (M+H) ⁺ = 585	-	49

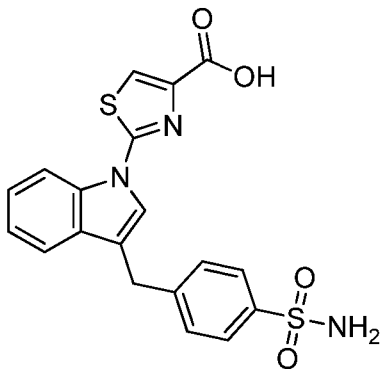
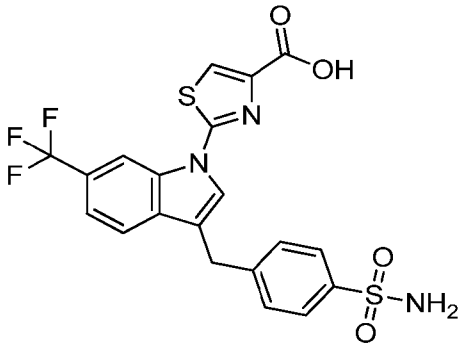
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
181		ethyl 2-(3-([1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate 1H NMR (400 MHz, DMSO-d ₆) δ 8.40 (s, 1H), 7.80 – 7.73 (m, 2H), 7.73 – 7.47 (m, 4H), 7.47 – 7.28 (m, 9H), 4.33 (q, J = 7.1 Hz, 2H), 4.20 (s, 2H), 3.35 – 3.25 (m, 1H), 2.25 (tt, J = 8.5, 5.6 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.06 – 0.96 (m, 2H), 0.75 – 0.65 (m, 2H); (M+H) ⁺ = 585	-	49
182		cyclopropyl-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid (M+H) ⁺ = 575	+	49
183		2-(3-([1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.34 (s, 1H), 7.70 (dt, J = 6.6, 2.1 Hz, 1H), 7.62 (dt, J = 2.7, 1.4 Hz, 2H), 7.61 – 7.49 (m, 4H), 7.49 – 7.40 (m, 6H), 7.39 – 7.33 (m, 1H), 7.28 – 7.19 (m, 1H), 4.14 (s, 2H), 2.24 (tt, J = 8.5, 5.6 Hz, 1H), 1.13 – 0.90 (m, 2H), 0.78 – 0.60 (m, 2H);	+++	49

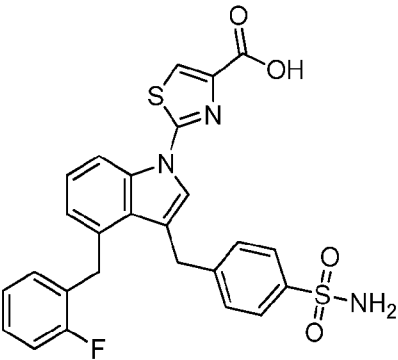
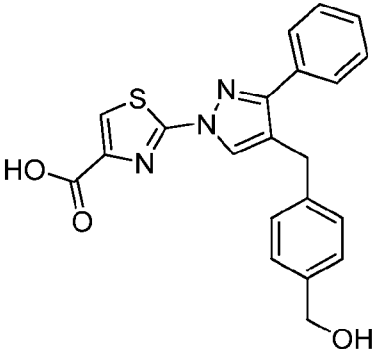
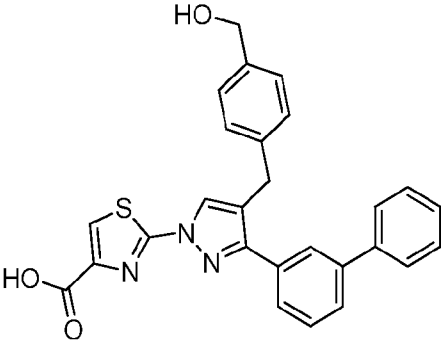
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(M+H) ⁺ = 575		
184		2-(5-([1,1'-biphenyl]-3-yl)-3-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 557	+	49
185		2-(5-benzyl-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 7.66 – 7.53 (m, 4H), 7.45 – 7.33 (m, 3H), 7.28 – 7.06 (m, 10H), 4.69 (s, 2H), 4.18 (s, 2H), 4.11 – 4.03 (m, 1H), 3.17 (d, J = 4.6 Hz, 2H); (M+H) ⁺ = 531	++	49
186		2-(5-([1,1'-biphenyl]-3-yl)-3-cyclopropyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 559	+	33

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
187		2-(3-([1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(4-sulfamoylphenoxy)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid 1H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.36 (s, 1H), 7.93 (td, J = 1.8, 0.5 Hz, 1H), 7.85 – 7.71 (m, 3H), 7.66 (ddd, J = 7.8, 1.9, 1.1 Hz, 1H), 7.56 – 7.32 (m, 6H), 7.30 – 7.21 (m, 4H), 2.73 – 2.61 (m, 1H), 1.02 – 0.90 (m, 2H), 0.93 – 0.83 (m, 2H); (M+H) ⁺ = 559	+++	33
188		2-(3-(cyclopropylmethyl)-5-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 495	++	141
189		2-(5-(cyclopropylmethyl)-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 495	+++	141

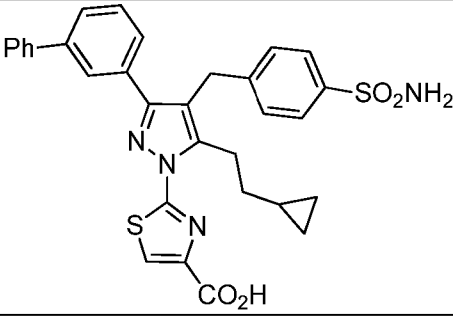
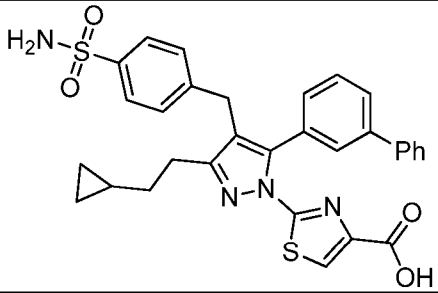
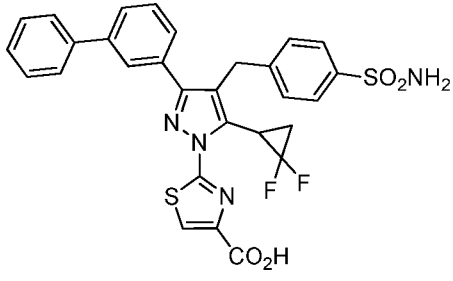
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
190		methyl 2-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-4-(trifluoromethyl)pyrimidine-5-carboxylate	-	148
191		6-(5-amino-3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)pyridazine-3-carboxylic acid	-	148
192		2-(6-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH ₃ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.13 (s, 1H), 7.76 – 7.71 (m, 2H), 7.69 (s, 1H), 7.56 – 7.50 (m, 2H), 7.50 – 7.46 (m, 1H), 7.45 (s, 1H), 7.23 (s, 2H), 7.14 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 4.15 (s, 2H), 3.55 (dd, <i>J</i> = 8.9, 4.4 Hz, 6H), 2.34 (t, <i>J</i> = 4.6 Hz, 4H) (acid OH not shown); MS (M+H) ⁺ = 513	++	41

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
193		2-(4-(morpholinomethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH ₃ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.27 (d, <i>J</i> = 8.4 Hz, 1H), 7.79 – 7.70 (m, 2H), 7.48 (s, 1H), 7.46 (s, 1H), 7.41 – 7.34 (m, 2H), 7.31 – 7.23 (m, 3H), 7.06 (dd, <i>J</i> = 7.3, 1.0 Hz, 1H), 4.51 (s, 2H), 3.51 (dd, <i>J</i> = 9.5, 4.9 Hz, 6H), 2.35 – 2.21 (m, 4H) (acid OH not shown); MS (M+H) ⁺ = 513	++	41
194		2-(5-(2-fluorobenzyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid, NH ₃ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.23 – 8.17 (m, 1H), 8.03 (s, 1H), 7.74 (s, 1H), 7.73 – 7.67 (m, 2H), 7.52 – 7.45 (m, 2H), 7.42 (d, <i>J</i> = 1.6 Hz, 1H), 7.23 (m, 5H), 7.17 – 7.05 (m, 2H), 4.12 (s, 2H), 4.02 (s, 2H) (acid OH not shown); MS (M+H) ⁺ = 522	++	40
195		2-(5-(2-fluorophenyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.14 (s, 1H), 8.42 (dd, <i>J</i> = 8.6, 0.6 Hz, 1H), 8.22	+++	40

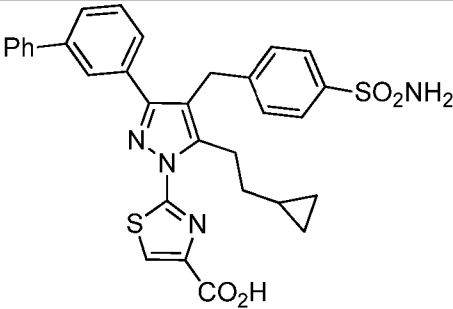
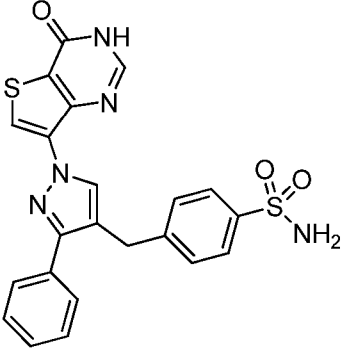
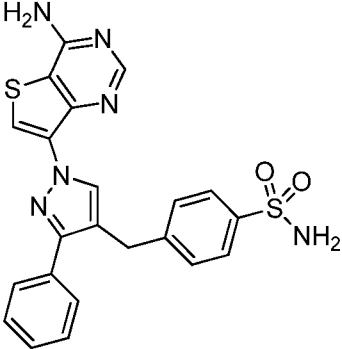
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(s, 1H), 7.89 (s, 1H), 7.77 – 7.68 (m, 3H), 7.59 – 7.54 (m, 3H), 7.52 (td, <i>J</i> = 7.8, 1.7 Hz, 1H), 7.39 (tdd, <i>J</i> = 7.8, 5.1, 1.8 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.21 (s, 2H), 4.22 (s, 2H); MS (M+H) ⁺ = 508		
196		2-(3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.13 (s, 1H), 8.34 (dt, <i>J</i> = 8.4, 0.9 Hz, 1H), 8.18 (s, 1H), 7.83 (s, 1H), 7.75 – 7.67 (m, 2H), 7.57 – 7.48 (m, 3H), 7.37 (ddd, <i>J</i> = 8.4, 7.1, 1.2 Hz, 1H), 7.22 (s, 2H), 7.21 – 7.16 (m, 1H), 4.18 (s, 2H); MS (M+H) ⁺ = 414	++	40
197		2-(3-(4-sulfamoylbenzyl)-6-(trifluoromethyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.20 (s, 1H), 8.79 (dd, <i>J</i> = 1.7, 0.9 Hz, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 7.78 – 7.68 (m, 3H), 7.59 – 7.49 (m, 3H), 7.23 (s, 2H), 4.23 (s, 2H); MS (M+H) ⁺ = 482	++	40

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
198		2-(4-(2-fluorobenzyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.15 (s, 1H), 8.34 (dd, <i>J</i> = 8.4, 0.9 Hz, 1H), 8.18 (s, 1H), 7.75 – 7.70 (m, 2H), 7.69 (s, 1H), 7.35 – 7.21 (m, 6H), 7.17 (ddd, <i>J</i> = 9.6, 8.2, 1.3 Hz, 1H), 7.04 (td, <i>J</i> = 7.4, 1.3 Hz, 1H), 6.81 (d, <i>J</i> = 7.4 Hz, 1H), 6.78 – 6.71 (m, 1H), 4.17 (s, 2H), 4.14 (s, 2H); MS (M+H) ⁺ = 522	++	40
199		2-(4-(4-(hydroxymethyl)benzyl)-3-phenyl-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.15 (s, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 7.73 – 7.65 (m, 2H), 7.50 – 7.36 (m, 3H), 7.27 – 7.15 (m, 4H), 5.07 (t, <i>J</i> = 5.8 Hz, 1H), 4.44 (d, <i>J</i> = 5.5 Hz, 2H), 4.02 (s, 2H); MS (M+H) ⁺ = 392	-	28
200		2-(3-([1,1'-biphenyl]-3-yl)-4-(4-(hydroxymethyl)benzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.16 (s, 1H), 8.21 (d, <i>J</i> = 2.9 Hz, 2H), 7.83 (t, <i>J</i> = 1.8 Hz, 1H), 7.70 (ddt, <i>J</i> = 7.7, 6.0, 1.4 Hz, 2H), 7.61 – 7.49	+	29

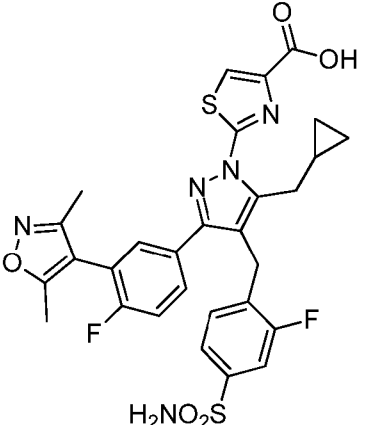
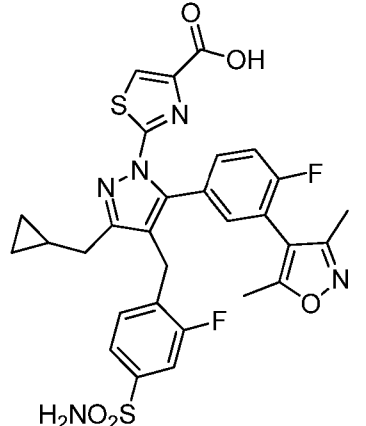
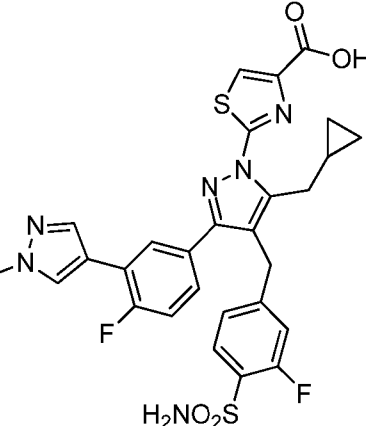
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(m, 3H), 7.44 (s, 1H), 7.45 – 7.31 (m, 2H), 7.29 – 7.17 (m, 4H), 5.09 (t, <i>J</i> = 5.8 Hz, 1H), 4.45 (d, <i>J</i> = 5.3 Hz, 2H), 4.09 (s, 2H); MS (M+H) ⁺ = 468		
201		2-(6-(hydroxymethyl)-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.11 (s, 1H), 8.27 – 8.23 (m, 1H), 8.19 (s, 1H), 7.79 (d, <i>J</i> = 0.9 Hz, 1H), 7.74 – 7.69 (m, 2H), 7.55 – 7.49 (m, 2H), 7.49 – 7.43 (m, 1H), 7.22 (s, 2H), 7.15 (dd, <i>J</i> = 8.1, 1.4 Hz, 1H), 5.22 (t, <i>J</i> = 5.7 Hz, 1H), 4.59 (d, <i>J</i> = 4.6 Hz, 2H), 4.16 (s, 2H); MS (M+H)⁺ = 444	++	40
202		2-(7-fluoro-3-(4-sulfamoylbenzyl)-1H-indol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 13.16 (s, 1H), 8.37 (s, 1H), 7.72 (m, 3H), 7.52 (d, <i>J</i> = 7.5 Hz, 2H), 7.39 (d, <i>J</i> = 7.5 Hz, 1H), 7.24 (s, 2H), 7.21 – 7.07 (m, 2H), 4.17 (s, 2H); MS (M+H)⁺ = 432	++	40

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
203		2-(3-([1,1'-biphenyl]-3-yl)-5-(2-cyclopropylethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 585	+++	49
204		2-(5-([1,1'-biphenyl]-3-yl)-3-(2-cyclopropylethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 585	+	49
205		2-(3-([1,1'-biphenyl]-3-yl)-5-(2,2-difluorocyclopropyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.29 – 12.98 (m, 1H), 8.34 (s, 1H), 7.78 – 7.73 (m, 2H), 7.73 – 7.66 (m, 2H), 7.63 – 7.49 (m, 2H), 7.49 – 7.40 (m, 2H), 7.39 – 7.32 (m, 4H), 7.30 (s, 2H), 4.22 (s, 2H), 3.30 – 3.24 (m, 1H), 2.24 – 1.98 (m, 1H), 1.81 – 1.60 (m, 1H); (M+H) ⁺ = 593	+++	49

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
206		2-(5-([1,1'-biphenyl]-3-yl)-3-(2,2-difluorocyclopropyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 593	+	49
207		2-(3-([1,1'-biphenyl]-3-yl)-5-((2,2-difluorocyclopropyl)methyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.30 (s, 1H), 7.77 – 7.67 (m, 4H), 7.61 (dt, J = 7.8, 1.4 Hz, 1H), 7.52 (td, J = 7.6, 0.8 Hz, 1H), 7.48 – 7.40 (m, 4H), 7.38 – 7.33 (m, 3H), 7.30 (s, 2H), 4.19 (s, 2H), 3.40 (td, J = 19.2, 17.2, 7.3 Hz, 2H), 2.28 – 2.11 (m, 1H), 1.55 – 1.32 (m, 1H); (M+H) ⁺ = 607	+++	49
208		2-(5-([1,1'-biphenyl]-3-yl)-3-((2,2-difluorocyclopropyl)methyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 607	+	49

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
209		2-(3-([1,1'-biphenyl]-3-yl)-5-(2-cyclopropylethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 585	+++	49
210		4-((1-(4-oxo-3,4-dihydrothieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide ¹ H NMR (400 MHz, DMSO-d ₆) δ 12.79 (s, 1H), 8.71 (s, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 7.74 – 7.68 (m, 2H), 7.68 – 7.62 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 3H), 7.25 (s, 2H), 4.16 (s, 2H); MS (M+H) ⁺ = 464	-	51
211		4-((1-(4-aminothieno[3,2-d]pyrimidin-7-yl)-3-phenyl-1H-pyrazol-4-yl)methyl)benzenesulfonamide, TFA ¹ H NMR (400 MHz, DMSO-d ₆) δ 8.92 (d, J = 4.9 Hz, 1H), 8.47 (d, J = 1.6 Hz, 1H), 8.32 (d, J = 2.2 Hz, 1H), 7.87 (s, 2H), 7.69 (m, 4H), 7.49 – 7.30 (m, 5H), 7.26 (s, 2H), 4.17 (s, 2H); MS (M+H) ⁺ = 463	+	52

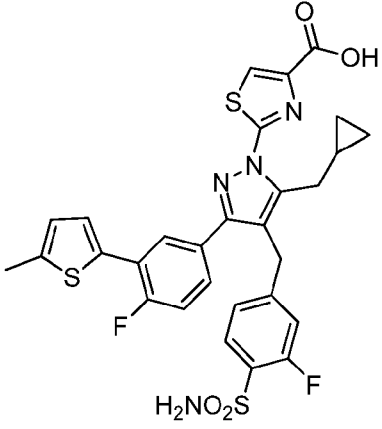
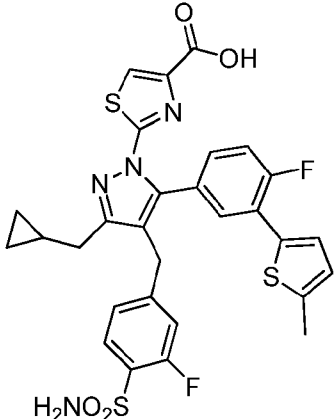
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
212		1-methyl-2-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)-1H-imidazole-5-carboxylic acid, TFA ; MS (M+H) ⁺ = 438	-	53
213		5-(3-phenyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiophene-3-carboxylic acid, TFA ¹ H NMR (400 MHz, DMSO-d ₆) δ 12.88 (s, 1H), 8.45 (s, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.63 – 7.55 (m, 3H), 7.44 – 7.32 (m, 5H), 7.26 (s, 2H), 4.08 (s, 2H); MS (M+H) ⁺ = 440	+	54
214		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.29 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.52 (dd, J = 9.6, 1.8 Hz, 1H), 7.46 (dd, J = 8.0, 1.8 Hz, 1H), 7.40 (s, 2H), 7.34 (ddd, J = 8.5, 5.0, 2.2 Hz, 1H), 7.26 (dd, J = 11.0, 8.5 Hz, 1H), 7.12 (t, J = 7.8	+++	55

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		Hz, 1H), 4.10 (s, 2H), 3.85 (s, 3H), 3.15 (d, J = 7.0 Hz, 2H), 1.14 – 1.01 (m, 1H), 0.37 – 0.14 (m, 4H); MS (M+H) ⁺ = 611		
215		2-(5-(cyclopropylmethyl)-3-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 626	+++	56
216		2-(3-(cyclopropylmethyl)-5-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 626	-	56
217		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 611	+++	57

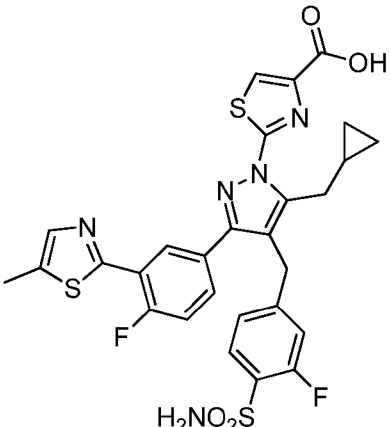
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
218		2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(1-methyl-1H-pyrazol-4-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 611	-	57
219		2-(5-(cyclopropylmethyl)-3-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 626	+++	58
220		2-(3-(cyclopropylmethyl)-5-(3-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 626	-	58

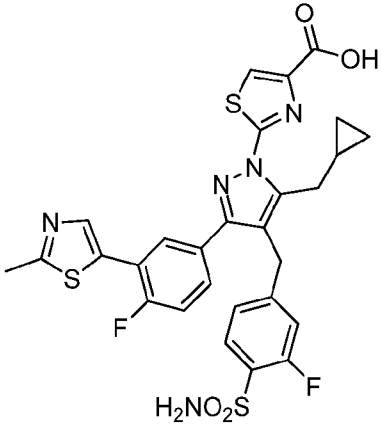
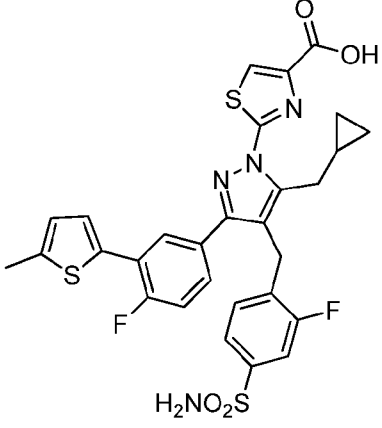
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
221		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 627	+++	59
222		2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 627	-	59
223		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 627	+++	60

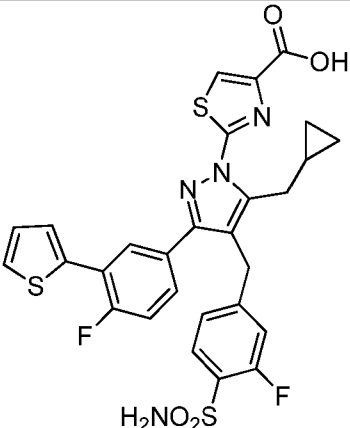
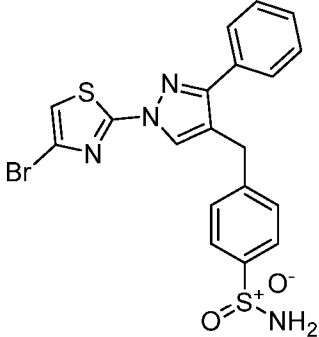
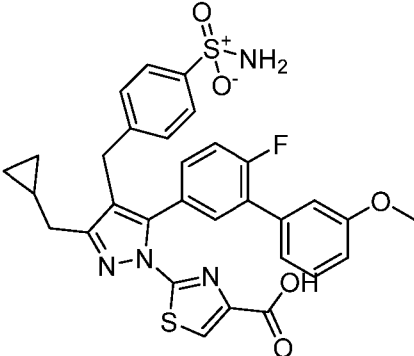
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
224		2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(4-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 627	-	60
225		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 627	NA	61
226		2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H) ⁺ = 627	-	61

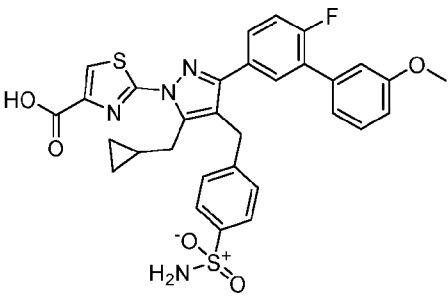
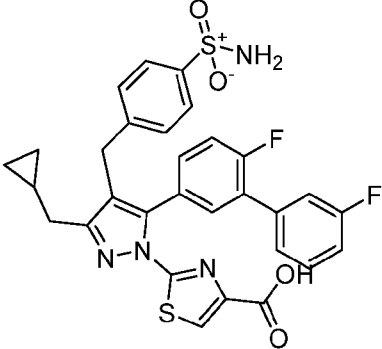
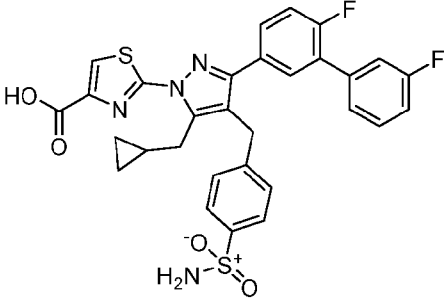
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
227		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H)⁺ = 627 NMR (HCl salt) from YSM14-67 ¹H NMR (400 MHz, DMSO-d₆) δ 13.13 (s, 1H), 8.29 (s, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.62 (dd, J = 7.6, 2.2 Hz, 1H), 7.58 (s, 2H), 7.50 (ddd, J = 8.5, 4.8, 2.2 Hz, 1H), 7.34 (dd, J = 11.3, 8.6 Hz, 1H), 7.19 (dd, J = 11.3, 1.6 Hz, 1H), 7.13 (dd, J = 3.6, 0.9 Hz, 1H), 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 6.81 (dt, J = 3.6, 1.1 Hz, 1H), 4.14 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.44 (d, J = 1.1 Hz, 3H), 1.19 – 1.03 (m, 1H), 0.39 – 0.28 (m, 2H), 0.24 – 0.14 (m, 2H)	+++	62
228		2-(3-(cyclopropylmethyl)-5-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA MS (M+H)⁺ = 627	-	62

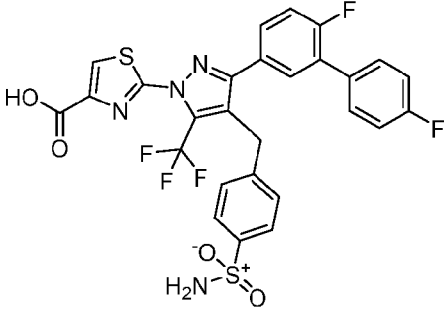
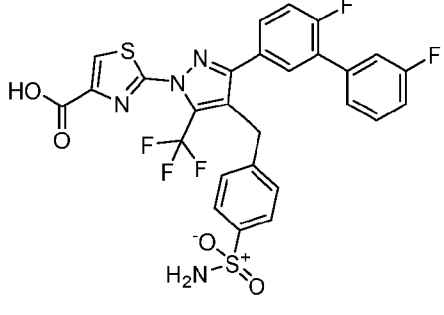
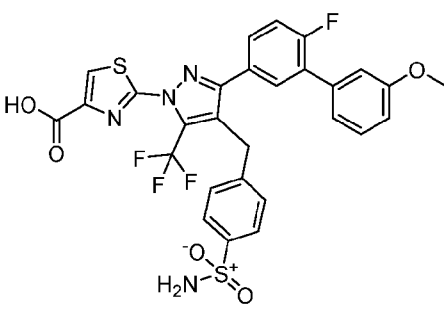
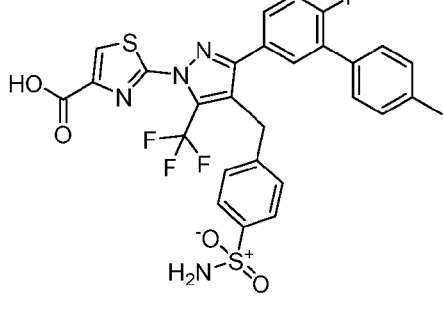
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
229		ethyl 2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate ¹H NMR (400 MHz, Chloroform-d) δ 7.96 (s, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.55 (dd, J = 7.4, 2.2 Hz, 1H), 7.37 (ddd, J = 8.5, 4.7, 2.2 Hz, 1H), 7.15 – 7.04 (m, 3H), 7.00 (dd, J = 11.1, 1.6 Hz, 1H), 6.73 (dt, J = 3.7, 1.0 Hz, 1H), 4.93 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.07 (s, 2H), 3.21 (d, J = 6.8 Hz, 2H), 2.49 (d, J = 1.1 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H), 1.19 – 1.06 (m, 1H), 0.49 – 0.38 (m, 2H), 0.28 (dt, J = 6.1, 4.7 Hz, 2H); MS (M+H)⁺ = 655	-	63
230		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylfuran-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-d₆) δ 13.10 (s, 1H), 8.29 (s, 1H), 7.76 (dd, J = 7.4, 2.3 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.57 (s,	+++	64

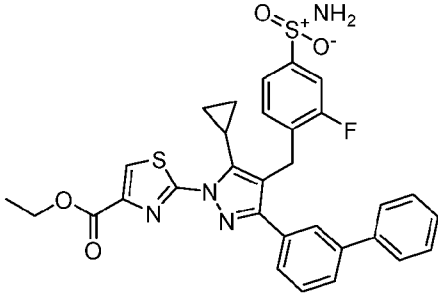
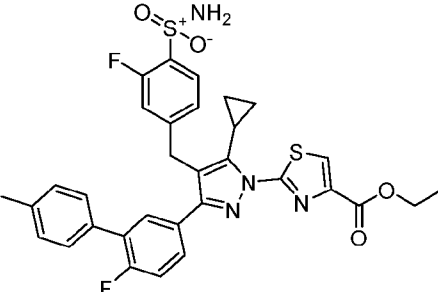
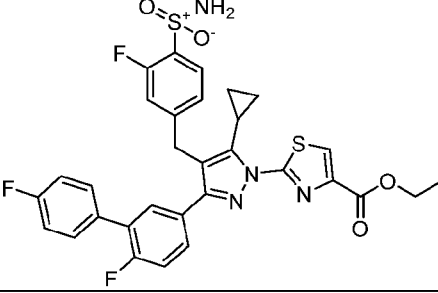
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		2H), 7.54 (ddd, J = 8.6, 4.8, 2.3 Hz, 1H), 7.33 (dd, J = 11.2, 8.6 Hz, 1H), 7.20 (dd, J = 11.3, 1.6 Hz, 1H), 7.07 (dd, J = 8.1, 1.6 Hz, 1H), 6.70 (t, J = 3.5 Hz, 1H), 6.22 (dt, J = 3.1, 1.0 Hz, 1H), 4.15 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.27 (s, 3H), 1.17 – 1.06 (m, 1H), 0.38 – 0.28 (m, 2H), 0.24 – 0.14 (m, 2H); MS (M+H) ⁺ = 611		
231		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiazol-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.30 (dd, J = 7.2, 2.3 Hz, 1H), 8.28 (s, 1H), 7.70 – 7.59 (m, 3H), 7.54 (s, 2H), 7.43 (dd, J = 11.1, 8.7 Hz, 1H), 7.16 (dd, J = 11.4, 1.6 Hz, 1H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 4.14 (s, 2H), 3.19 – 3.14 (m, 2H), 2.49 (d, J = 1.2 Hz, 3H), 1.18 – 1.05 (m, 1H), 0.39 – 0.29 (m, 2H), 0.24 – 0.15 (m, 2H); MS (M+H) ⁺ = 628	+++	65

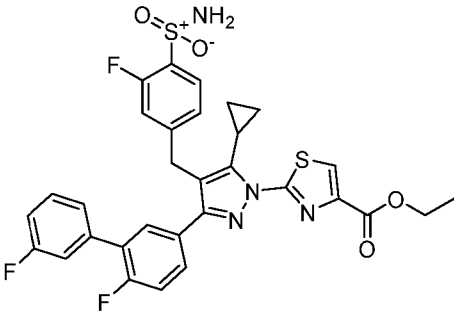
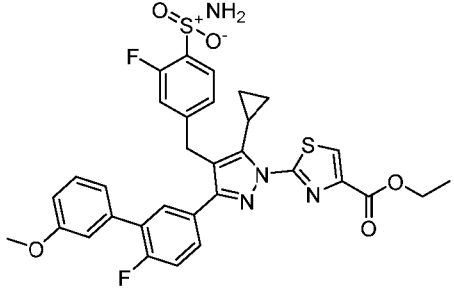
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
232		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(2-methylthiazol-5-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-d₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.97 (s, 1H), 7.68 (dd, J = 7.4, 2.0 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.57 (m, 3H), 7.39 (dd, J = 10.8, 8.7 Hz, 1H), 7.17 (d, J = 11.3 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 4.15 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.66 (s, 3H), 1.18 – 1.01 (m, 1H), 0.37 – 0.27 (m, 2H), 0.21 (d, J = 4.9 Hz, 2H); MS (M+H)⁺ = 628	+++	66
233		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(5-methylthiophen-2-yl)phenyl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid ¹H NMR (400 MHz, DMSO-d₆) δ 13.09 (s, 1H), 8.29 (s, 1H), 7.63 (dd, J = 7.5, 2.2 Hz, 1H), 7.56 (dd, J = 9.6, 1.8 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.49 – 7.44 (m, 1H), 7.42 (s, 2H), 7.34 (dd, J =	+++	67

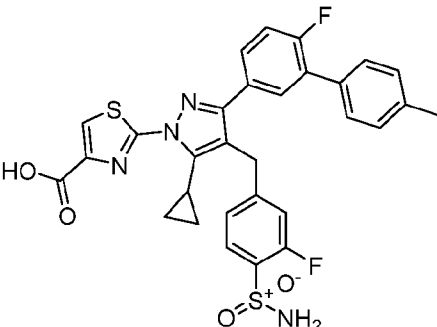
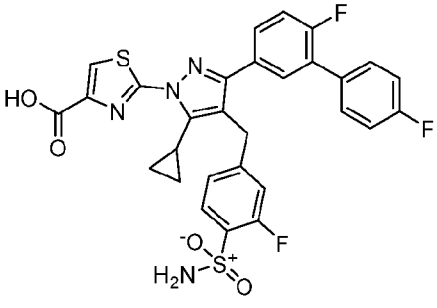
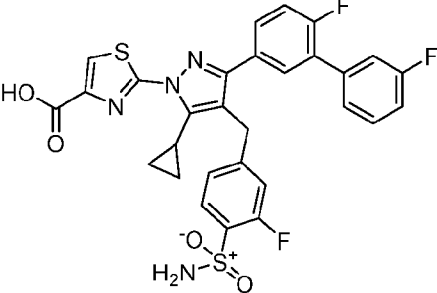
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		11.3, 8.6 Hz, 1H), 7.19 – 7.11 (m, 2H), 6.81 (dt, J = 3.6, 1.1 Hz, 1H), 4.08 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.44 (d, J = 1.1 Hz, 3H), 1.17 – 1.02 (m, 1H), 0.35 – 0.27 (m, 2H), 0.22 – 0.14 (m, 2H); MS (M+H) ⁺ = 627		
234		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(thiophen-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA ; MS (M+H) ⁺ = 613	+++	68
235		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.30 (d, J = 0.8 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.67 – 7.63 (m, 2H), 7.62 (s, 1H), 7.47 – 7.41 (m, 2H), 7.41 – 7.37 (m, 2H), 7.26 (s, 2H), 4.13 (s, 2H); (M+H) ⁺ = 476.4	+	161
236		(M+H) ⁺ = 619.7	-	141

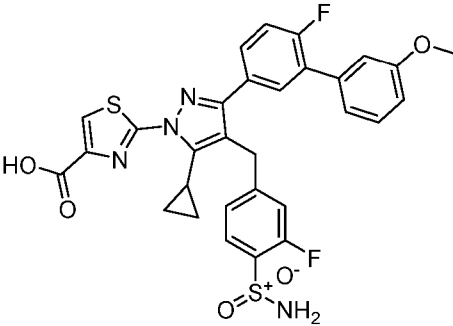
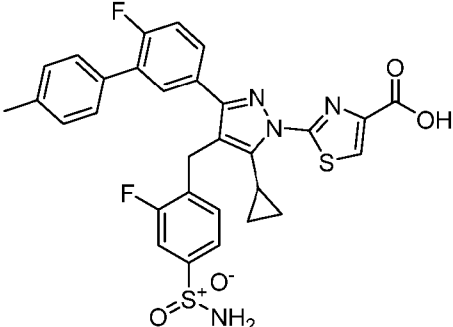
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
237		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.27 (s, 1H), 7.71 – 7.64 (m, 2H), 7.63 – 7.55 (m, 2H), 7.37 – 7.23 (m, 6H), 6.99 (dt, J = 2.9, 1.6 Hz, 1H), 6.95 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.89 (dtd, J = 7.6, 1.6, 0.9 Hz, 1H), 4.14 (s, 2H), 3.75 (s, 3H), 3.13 (d, J = 6.9 Hz, 2H), 1.17 – 1.04 (m, 1H), 0.36 – 0.27 (m, 2H), 0.22 – 0.15 (m, 2H); (M+H) ⁺ = 619.7	+++	141
238		(M+H) ⁺ = 607.7	+	141
239		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.30 (s, 1H), 7.73 – 7.68 (m, 2H), 7.68 – 7.64 (m, 1H), 7.62 (dd, J = 7.6, 2.3 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.39 (dd, J = 10.8, 8.6 Hz, 1H), 7.35 (dd, J = 2.7, 1.4 Hz, 0H), 7.34 – 7.27 (m, 5H), 7.26 – 7.22 (m, 1H), 7.18 (dq, J = 7.8, 1.3 Hz, 1H), 4.18 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 1.14 (ddd, J = 12.8, 7.7, 4.9 Hz, 0H), 0.45 – 0.27 (m, 2H), 0.28 – 0.14 (m, 2H); (M+H) ⁺ = 607.7	+++	141

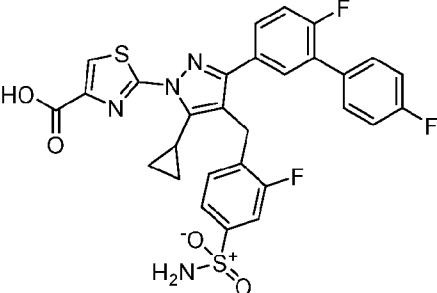
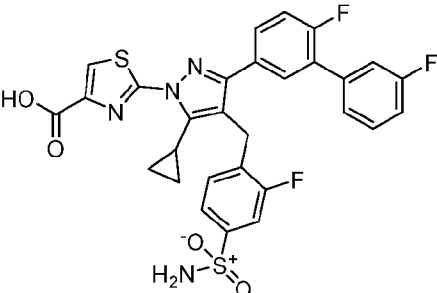
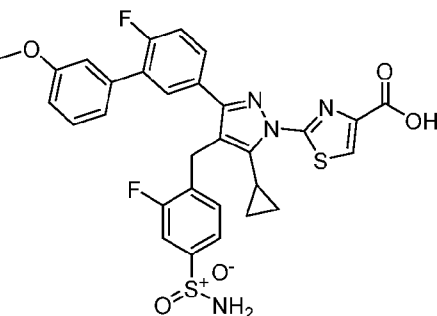
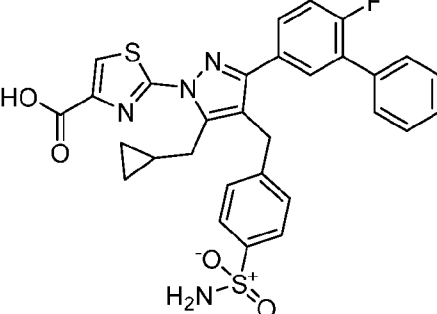
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
240		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.29 (s, 1H), 8.46 (s, 1H), 7.80 – 7.72 (m, 2H), 7.59 (ddd, J = 8.5, 4.8, 2.3 Hz, 1H), 7.56 (dd, J = 7.5, 2.3 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.36 – 7.25 (m, 6H), 4.27 (s, 2H); (M+H) ⁺ = 621.6	+++	14
241		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.27 (s, 1H), 8.44 (s, 1H), 7.75 – 7.69 (m, 2H), 7.62 (dd, J = 7.5, 2.3 Hz, 1H), 7.58 (ddd, J = 8.5, 4.8, 2.3 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.39 – 7.33 (m, 1H), 7.32 – 7.26 (m, 4H), 7.27 – 7.20 (m, 2H), 4.25 (s, 2H); (M+H) ⁺ = 621.6	+++	14
242		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.30 (s, 1H), 8.45 (s, 1H), 7.78 – 7.72 (m, 2H), 7.63 (dd, J = 7.5, 2.3 Hz, 1H), 7.58 (ddd, J = 8.5, 4.7, 2.3 Hz, 1H), 7.46 (dd, J = 10.6, 8.5 Hz, 1H), 7.40 – 7.29 (m, 6H), 7.04 (q, J = 1.8 Hz, 1H), 7.01 – 6.95 (m, 2H), 4.27 (s, 2H), 3.76 (s, 3H); (M+H) ⁺ = 633.6	+++	14
243		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.27 (s, 1H), 8.42 (s, 1H), 7.77 – 7.70 (m, 2H), 7.56 – 7.50 (m, 2H), 7.41 (dd, J = 10.7, 9.1 Hz, 1H), 7.33 – 7.26 (m, 6H), 7.23 (dd, J = 8.4, 0.8 Hz, 2H), 4.23 (s, 2H), 2.31 (s, 3H); (M+H) ⁺ = 617.6	+++	14

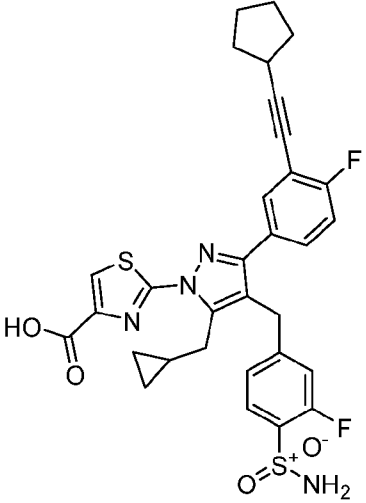
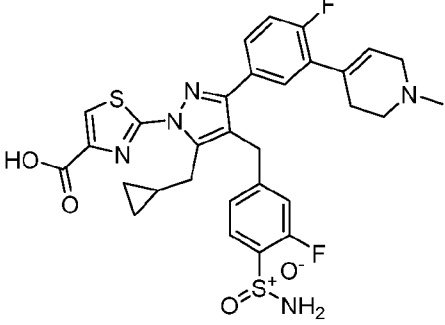
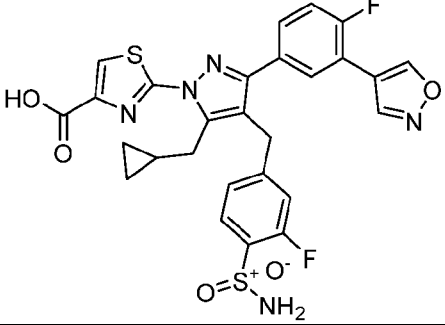
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
244		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.37 (d, J = 0.8 Hz, 1H), 7.66 (dt, J = 6.7, 2.1 Hz, 1H), 7.59 (q, J = 1.6 Hz, 2H), 7.55 (dd, J = 10.9, 1.8 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.36 (m, 6H), 7.33 (ddd, J = 6.7, 4.9, 2.8 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 2.17 (tt, J = 8.6, 5.6 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.97 (dt, J = 11.2, 3.2 Hz, 2H), 0.73 – 0.58 (m, 2H); (M+H) ⁺ = 603.7	-	112
245		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.37 (d, J = 0.3 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.58 (s, 2H), 7.54 (ddd, J = 8.5, 4.8, 2.3 Hz, 1H), 7.44 (dd, J = 7.6, 2.3 Hz, 1H), 7.33 (dd, J = 10.7, 8.5 Hz, 1H), 7.23 (d, J = 0.7 Hz, 4H), 7.23 – 7.17 (m, 1H), 7.05 (dd, J = 8.2, 1.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.16 (s, 2H), 2.31 (s, 3H), 2.19 (tt, J = 8.6, 5.6 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.03 – 0.91 (m, 2H), 0.70 – 0.60 (m, 2H); (M+H) ⁺ = 635.7	+	112
246		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.37 (d, J = 0.4 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.60 – 7.43 (m, 5H), 7.38 (dd, J = 10.7, 8.5 Hz, 1H), 7.34 – 7.27 (m, 1H), 7.27 – 7.13 (m, 3H), 7.06 (dd, J =	+	112

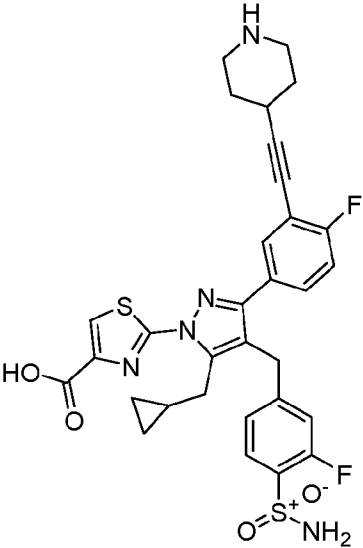
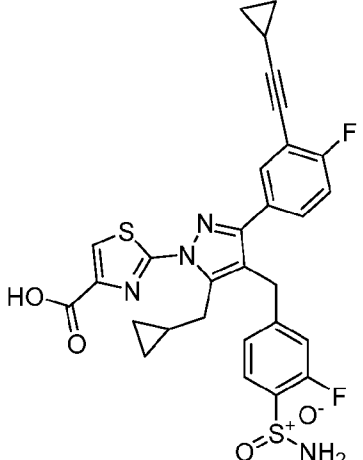
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		8.2, 1.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.17 (s, 2H), 2.26 – 2.09 (m, 1H), 1.35 – 1.22 (m, 3H), 1.03 – 0.90 (m, 2H), 0.65 (td, J = 6.1, 4.4 Hz, 2H); (M+H) ⁺ = 639.7		
247		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.40 (s, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.64 – 7.55 (m, 3H), 7.47 (dd, J = 7.6, 2.3 Hz, 1H), 7.44 – 7.35 (m, 3H), 7.28 (t, J = 8.9 Hz, 2H), 7.22 (d, J = 11.2 Hz, 1H), 7.08 (dd, J = 8.1, 1.6 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 4.19 (s, 2H), 2.22 (tt, J = 8.5, 5.7 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.08 – 0.92 (m, 2H), 0.73 – 0.64 (m, 2H); (M+H) ⁺ = 639.7	+	112
248		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.39 (d, J = 0.5 Hz, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.62 – 7.50 (m, 4H), 7.42 – 7.33 (m, 2H), 7.24 – 7.16 (m, 1H), 7.09 (dd, J = 8.2, 1.6 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.92 (dt, J = 7.7, 1.4 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.19 (s, 2H), 3.78 (s, 3H), 3.17 (dd, J = 5.2, 0.5 Hz, 1H), 2.21 (tt, J = 8.5, 5.6 Hz, 1H), 1.36 – 1.27 (m, 3H), 1.06 – 0.95 (m, 2H), 0.67 (td, J = 6.2, 4.4 Hz, 2H); (M+H) ⁺ = 651.7	-	112

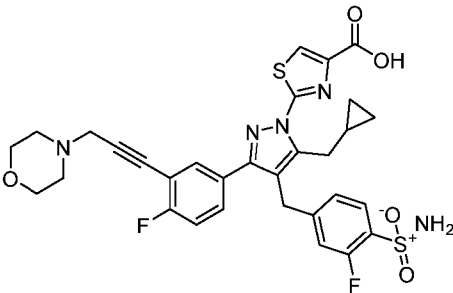
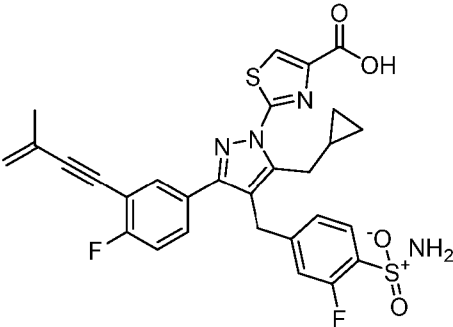
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
249		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.28 (s, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.58 (s, 2H), 7.53 (ddd, J = 8.5, 4.8, 2.3 Hz, 1H), 7.44 (dd, J = 7.7, 2.3 Hz, 1H), 7.33 (dd, J = 10.7, 8.6 Hz, 1H), 7.23 (s, 4H), 7.20 (dd, J = 11.3, 1.6 Hz, 1H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 4.15 (s, 2H), 3.14 (d, J = 3.9 Hz, 1H), 2.31 (s, 3H), 2.23 (tt, J = 8.6, 5.6 Hz, 1H), 1.01 – 0.89 (m, 2H), 0.68 – 0.59 (m, 2H); (M+H) ⁺ = 607.7	+++	112
250		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.29 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.52 (dd, J = 7.5, 2.3 Hz, 1H), 7.47 (td, J = 8.0, 6.1 Hz, 1H), 7.37 (dd, J = 10.7, 8.5 Hz, 1H), 7.31 (dd, J = 10.2, 2.2 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.20 (s, 0H), 7.05 (dd, J = 8.0, 1.5 Hz, 1H), 4.17 (s, 2H), 2.23 (tt, J = 8.5, 5.5 Hz, 1H), 1.03 – 0.90 (m, 2H), 0.68 – 0.52 (m, 2H); (M+H) ⁺ = 611.6	+++	112
251		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.31 (s, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.64 – 7.57 (m, 3H), 7.55 (dd, J = 7.6, 2.3 Hz, 1H), 7.50 (td, J = 8.1, 6.2 Hz, 1H), 7.40 (dd, J =	+++	112

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		10.7, 8.5 Hz, 1H), 7.34 (d, J = 10.2 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.23 (s, 0H), 7.08 (dd, J = 8.0, 1.6 Hz, 1H), 4.20 (s, 2H), 2.38 – 2.17 (m, 1H), 1.08 – 0.86 (m, 2H), 0.76 – 0.52 (m, 2H); (M+H) ⁺ = 611.6		
252		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.30 (s, 1H), 7.69 (t, J = 7.9 Hz, 1H), 7.58 (d, J = 4.8 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.41 – 7.34 (m, 2H), 7.24 – 7.17 (m, 1H), 7.08 (dd, J = 8.1, 1.6 Hz, 1H), 7.02 – 6.99 (m, 1H), 6.98 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.92 (dd, J = 7.7, 1.3 Hz, 1H), 4.19 (s, 2H), 3.78 (s, 3H), 2.34 – 2.13 (m, 1H), 1.10 – 0.93 (m, 2H), 0.71 – 0.61 (m, 2H); (M+H) ⁺ = 623.7	+++	112
253		¹ H NMR (400 MHz, DMSO-d ₆) δ 7.59 – 7.44 (m, 3H), 7.42 (s, 2H), 7.33 (dd, J = 10.7, 8.5 Hz, 1H), 7.24 (d, J = 1.6 Hz, 3H), 7.17 (t, J = 7.8 Hz, 1H), 4.10 (s, 2H), 2.34 – 2.27 (m, 3H), 2.19 (s, 0H), 0.95 (d, J = 9.0 Hz, 2H), 0.62 (d, J = 5.6 Hz, 2H); (M+H) ⁺ = 607.7	+++	112

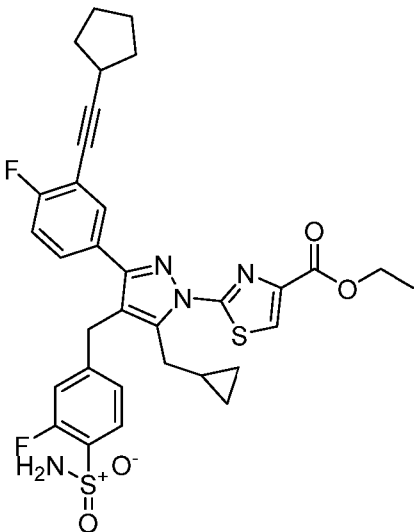
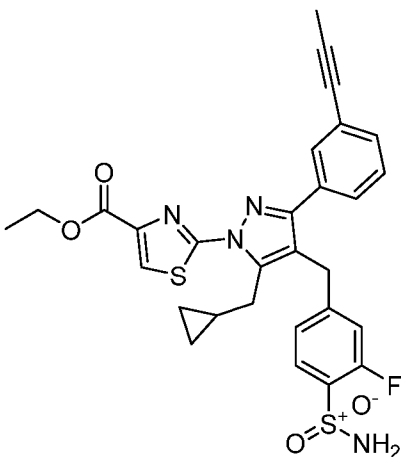
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
254		(M+H) ⁺ = 611.6	+++	112
255		¹ H NMR (400 MHz, DMSO-d ₆) δ 7.62 – 7.44 (m, 4H), 7.44 – 7.27 (m, 3H), 7.28 – 7.11 (m, 3H), 4.11 (s, 2H), 2.18 (s, 0H), 0.96 (d, J = 8.1 Hz, 2H), 0.62 (d, J = 5.6 Hz, 2H); (M+H) ⁺ = 611.6	+++	112
256		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.30 (s, 1H), 7.60 – 7.46 (m, 4H), 7.40 (s, 2H), 7.40 – 7.29 (m, 2H), 7.17 (t, J = 7.8 Hz, 1H), 7.05 – 6.83 (m, 3H), 4.11 (s, 2H), 3.75 (s, 3H), 2.18 (tt, J = 8.5, 5.6 Hz, 1H), 1.03 – 0.89 (m, 2H), 0.68 – 0.55 (m, 2H); (M+H) ⁺ = 623.7	+++	112
257		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.29 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.64 (ddd, J = 8.6, 4.7, 2.3 Hz, 1H), 7.57 (dd, J = 7.6, 2.3 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.42 – 7.34 (m, 4H), 7.32 (d, J = 9.4 Hz, 4H), 4.17 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 1.14 (h, J = 5.9, 5.3 Hz, 1H), 0.33 (dt, J = 8.3, 2.8 Hz, 2H), 0.28 – 0.15 (m, 2H); (M+H) ⁺ = 589.7	+++	112

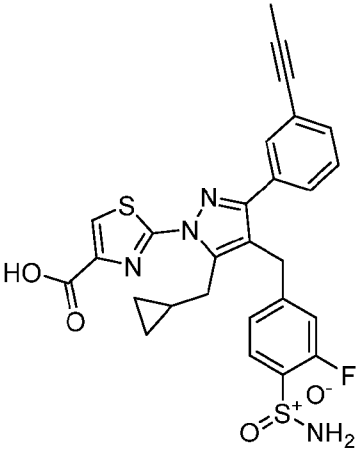
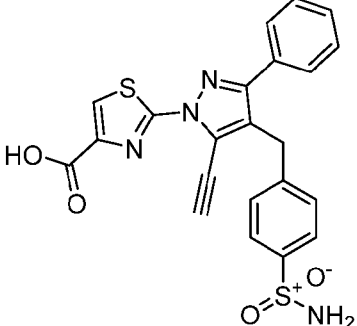
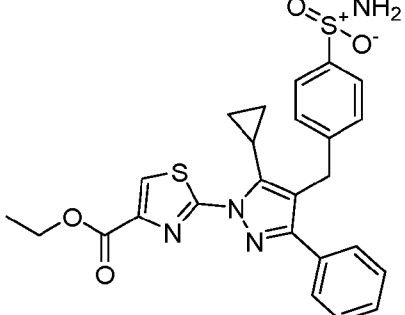
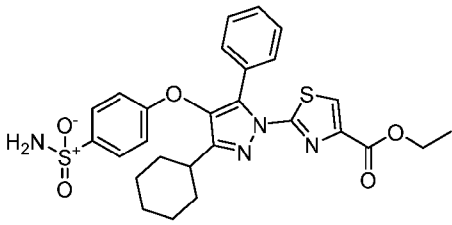
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
258		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.16 (s, 1H), 8.29 (d, J = 2.7 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.60 – 7.49 (m, 4H), 7.35 – 7.23 (m, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.5 Hz, 1H), 4.13 (s, 2H), 3.15 (d, J = 6.8 Hz, 2H), 2.87 (p, J = 7.3 Hz, 1H), 2.05 – 1.86 (m, 2H), 1.69 (tdd, J = 9.3, 5.2, 2.7 Hz, 1H), 1.58 (dddd, J = 11.9, 10.4, 6.0, 2.9 Hz, 3H), 1.11 (pd, J = 7.7, 3.7 Hz, 1H), 0.39 – 0.29 (m, 2H), 0.21 (dd, J = 5.0, 1.6 Hz, 2H); (M+H) ⁺ = 623.7	+++	145
259		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.23 (s, 1H), 7.73 – 7.53 (m, 3H), 7.49 (ddd, J = 8.5, 4.8, 2.3 Hz, 1H), 7.37 – 7.09 (m, 3H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 5.93 – 5.74 (m, 1H), 4.11 (s, 2H), 3.21 – 3.05 (m, 4H), 2.62 (t, J = 5.7 Hz, 2H), 2.31 (d, J = 13.8 Hz, 5H), 1.11 (dd, J = 9.3, 3.9 Hz, 1H), 0.31 (dt, J = 8.2, 2.8 Hz, 2H), 0.27 – 0.12 (m, 2H); (M+H) ⁺ = 626.7	+++	145
260		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (d, J = 0.7 Hz, 1H), 7.76 (dd, J = 7.3, 2.2 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.30 (dd, J = 9.8, 8.6 Hz, 1H), 7.14 – 7.07 (m, 1H), 7.06 – 6.99 (m, 1H), 4.37	+	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		– 4.24 (m, 2H), 4.16 (s, 2H), 4.08 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.31 (td, J = 7.1, 0.8 Hz, 3H), 1.18 – 1.05 (m, 1H), 0.33 (dt, J = 8.2, 2.8 Hz, 2H), 0.27 – 0.19 (m, 2H); (M+H) ⁺ = 599		
261		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.29 (s, 1H), 8.15 (s, 1H), 7.64 (td, J = 7.9, 3.0 Hz, 2H), 7.61 – 7.53 (m, 5H), 7.50 (dd, J = 6.9, 2.2 Hz, 1H), 7.44 (ddd, J = 8.6, 5.1, 2.3 Hz, 1H), 7.31 (td, J = 9.0, 3.6 Hz, 2H), 7.16 – 6.98 (m, 4H), 4.13 (s, 2H), 3.80 (s, 2H), 3.25 – 3.12 (m, 6H), 3.02 (q, J = 8.8, 3.4 Hz, 6H), 2.42 (d, J = 6.8 Hz, 2H), 2.11 – 1.93 (m, 4H), 1.75 (ddq, J = 13.6, 9.1, 4.3 Hz, 4H), 1.19 – 1.04 (m, 1H), 1.00 – 0.85 (m, 1H), 0.43 – 0.37 (m, 2H), 0.36 – 0.30 (m, 2H), 0.24 – 0.18 (m, 2H), 0.14 – 0.08 (m, 2H); (M+H) ⁺ = 639	+++	145
262		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.29 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.56 – 7.47 (m, 2H), 7.27 (t, J = 9.0 Hz, 1H), 7.13 (dd, J = 11.2, 1.5 Hz, 1H), 7.02 (dd, J = 8.2, 1.6 Hz, 1H), 4.12 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.57 (tt, J = 8.3, 5.0 Hz, 1H), 1.11 (ddd, J = 13.1, 9.1,	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		5.9 Hz, 1H), 0.95 – 0.86 (m, 2H), 0.78 – 0.70 (m, 2H), 0.37 – 0.27 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 597		
263		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.82 (s, 1H), 8.16 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.58 (s, 2H), 7.55 – 7.46 (m, 1H), 7.36 (t, J = 9.0 Hz, 1H), 7.12 – 6.99 (m, 2H), 3.81 (s, 2H), 3.63 (s, 8H), 2.41 (d, J = 6.8 Hz, 2H), 0.99 – 0.86 (m, 1H), 0.45 – 0.35 (m, 2H), 0.16 – 0.05 (m, 2H); (M+H) ⁺ = 654.7	+++	145
264		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.28 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.54 (dd, J = 7.3, 1.9 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.27 (t, J = 9.0 Hz, 1H), 7.13 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 4.12 (s, 2H), 3.15 (d, J = 6.8 Hz, 2H), 1.57 (tt, J = 8.3, 5.0 Hz, 1H), 1.11 (ddd, J = 12.8, 7.9, 5.4 Hz, 1H), 0.98 – 0.84 (m, 2H), 0.79 – 0.67 (m, 2H), 0.32 (dt, J = 8.2, 2.8 Hz, 2H), 0.23 – 0.14 (m, 2H); (M+H) ⁺ = 595.6	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
265		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.16 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.59 – 7.52 (m, 4H), 7.30 (t, J = 9.4 Hz, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 5.53 (s, 1H), 4.14 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.45 (s, 6H), 1.20 – 1.05 (m, 1H), 0.37 – 0.27 (m, 2H), 0.26 – 0.12 (m, 2H); (M+H) ⁺ = 613.7	+++	145
266		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (d, J = 2.5 Hz, 1H), 7.71 – 7.52 (m, 6H), 7.47 (td, J = 7.6, 2.2 Hz, 1H), 7.34 (dd, J = 8.2, 2.3 Hz, 2H), 7.27 – 7.16 (m, 3H), 7.08 (d, J = 8.0 Hz, 1H), 4.30 (qd, J = 7.1, 2.3 Hz, 2H), 4.17 (s, 2H), 3.21 – 3.08 (m, 2H), 2.30 (d, J = 2.1 Hz, 3H), 1.30 (td, J = 7.1, 2.3 Hz, 3H), 1.15 (ddd, J = 9.8, 5.2, 2.0 Hz, 1H), 0.32 (td, J = 5.8, 5.4, 2.7 Hz, 2H), 0.24 (d, J = 4.9 Hz, 2H); (M+H) ⁺ = 631.8	+	145
267		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.27 (s, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.59 (s, 2H), 7.26 (t, J = 7.9 Hz, 1H), 7.17 (dd, J = 11.4, 1.6 Hz, 1H), 7.04 (ddd, J = 14.9, 7.5, 1.5 Hz, 2H), 6.95 (dd, J = 8.3, 2.5 Hz, 1H), 6.81 (t, J = 2.0 Hz, 1H), 4.10 (s, 2H), 3.72 – 3.60 (m, 4H),	+++	145

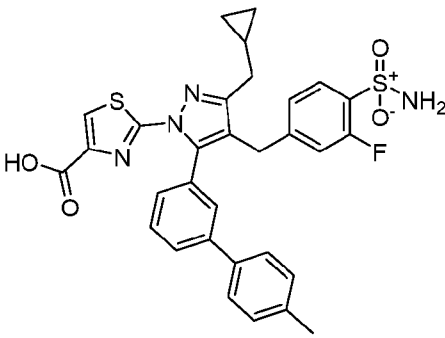
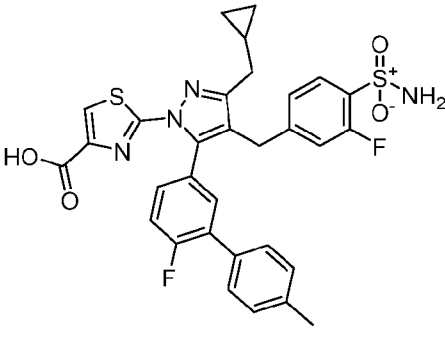
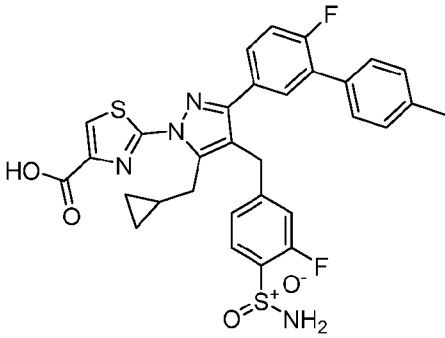
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		3.15 (d, J = 6.9 Hz, 2H), 2.95 – 2.83 (m, 4H), 1.12 (dt, J = 14.8, 7.2, 3.7 Hz, 1H), 0.37 – 0.27 (m, 2H), 0.24 – 0.17 (m, 2H); (M+H) ⁺ = 598.7		
268		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (d, J = 0.7 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.59 – 7.49 (m, 4H), 7.31 – 7.23 (m, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.5 Hz, 1H), 4.30 (qd, J = 7.1, 0.8 Hz, 2H), 4.13 (s, 2H), 3.15 (d, J = 6.8 Hz, 2H), 2.87 (p, J = 7.2 Hz, 1H), 2.05 – 1.90 (m, 2H), 1.79 – 1.66 (m, 1H), 1.64 – 1.50 (m, 4H), 1.31 (td, J = 7.1, 0.7 Hz, 3H), 1.18 – 1.02 (m, 2H), 0.33 (dt, J = 8.1, 2.8 Hz, 2H), 0.28 – 0.17 (m, 2H); (M+H) ⁺ = 651.8	-	145
269		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (d, J = 0.7 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.53 (d, J = 6.7 Hz, 3H), 7.51 – 7.44 (m, 0H), 7.41 – 7.30 (m, 2H), 7.12 (d, J = 11.3 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.13 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.02 (s, 3H), 1.41 – 1.22 (m, 3H), 1.12 (s, 2H), 0.43 – 0.29 (m, 2H), 0.23 (q, J = 4.9 Hz, 2H); (M+H) ⁺ = 579.7	+	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
270		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.25 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.50 – 7.44 (m, 1H), 7.39 – 7.30 (m, 2H), 7.12 (dd, J = 11.5, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.13 (s, 2H), 3.19 – 3.07 (m, 3H), 2.02 (s, 3H), 1.19 – 0.97 (m, 1H), 0.38 – 0.27 (m, 2H), 0.27 – 0.10 (m, 2H); (M+H) ⁺ = 551.6	+++	145
271		(M+H) ⁺ = 465	+	16
272		(M+H) ⁺ = 509	-	112
273		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.28 (s, 1H), 7.74 – 7.64 (m, 2H), 7.45 – 7.35 (m, 2H), 7.34 – 7.27 (m, 3H), 7.22 (s, 2H), 7.14 – 7.07 (m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.55 – 2.49 (m, 1H), 1.94 – 1.39 (m, 7H), 1.26 – 1.11 (m, 6H); (M+H) ⁺ = 553	-	33

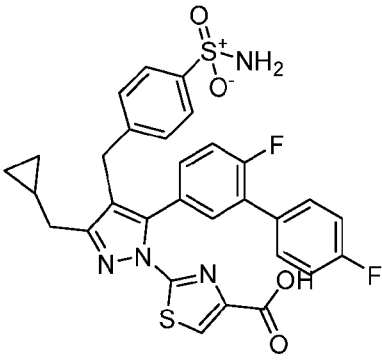
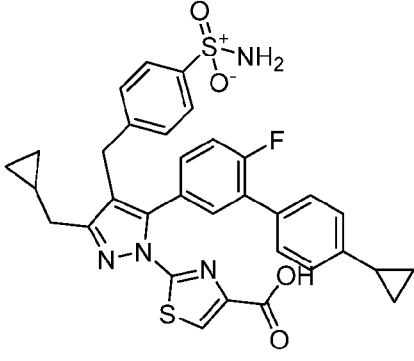
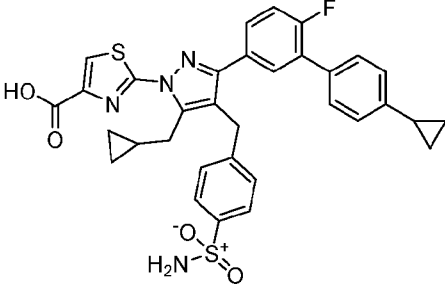
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
274		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.38 (s, 1H), 7.78 – 7.68 (m, 4H), 7.42 – 7.26 (m, 3H), 7.22 (s, 2H), 7.18 – 7.09 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.88 (tt, J = 12.0, 3.1 Hz, 1H), 1.96 – 1.44 (m, 7H), 1.39 – 0.98 (m, 6H); (M+H) ⁺ = 553	-	33
275		(M+H) ⁺ = 531	+	112
276		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.28 (s, 1H), 7.75 – 7.64 (m, 4H), 7.59 (dt, J = 7.7, 1.3 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.45 – 7.37 (m, 4H), 7.37 – 7.30 (m, 3H), 7.28 (s, 2H), 4.16 (s, 2H), 3.16 (m, 2H), 1.13 (ddtd, J = 13.0, 8.0, 6.9, 4.9 Hz, 1H), 0.37 – 0.27 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 571	+++	141
277		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.16 (s, 1H), 7.79 – 7.61 (m, 2H), 7.37 – 7.09 (m, 6H), 6.89 (ddd, J = 8.3, 4.3, 2.0 Hz, 1H), 3.84 (s, 2H), 3.71 (s, 3H), 2.40 (d, J = 6.8 Hz, 2H), 0.99 – 0.82 (m, 1H), 0.43 – 0.33 (m, 2H), 0.13 – 0.05 (m, 2H); (M+H) ⁺ = 543	+	141

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
278		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.16 (s, 1H), 7.79 – 7.61 (m, 2H), 7.37 – 7.09 (m, 6H), 6.89 (ddd, J = 8.3, 4.3, 2.0 Hz, 1H), 3.84 (s, 2H), 3.71 (s, 3H), 2.40 (d, J = 6.8 Hz, 2H), 0.99 – 0.82 (m, 1H), 0.43 – 0.33 (m, 2H), 0.13 – 0.05 (m, 2H); (M+H) ⁺ = 543	+++	141
279		(M+H) ⁺ = 599	+	141
280		(M+H) ⁺ = 585	+	141
281		(M+H) ⁺ = 585	+++	141

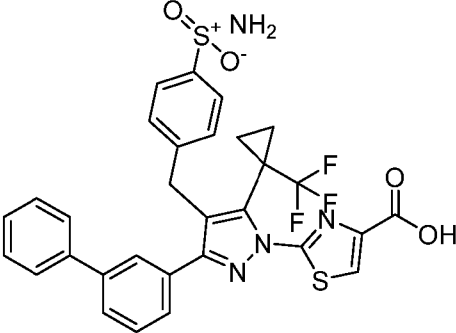
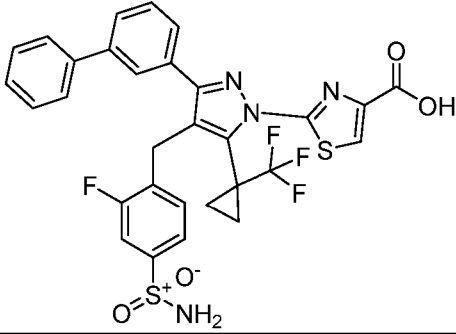
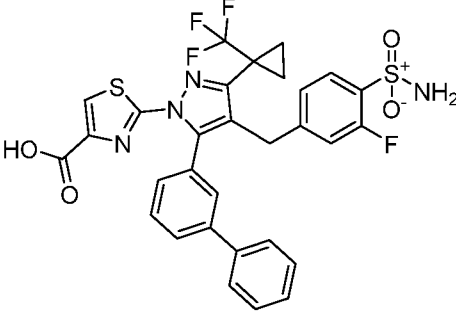
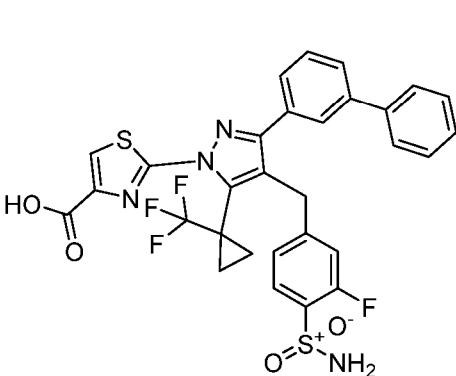
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
282		(M+H) ⁺ = 603	+++	141
283		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.16 (s, 1H), 7.70 – 7.63 (m, 2H), 7.52 (dd, J = 7.6, 2.2 Hz, 1H), 7.40 – 7.15 (m, 11H), 3.85 (s, 2H), 2.39 (d, J = 6.8 Hz, 2H), 2.29 (s, 3H), 0.91 (dddd, J = 11.6, 8.1, 5.0, 2.0 Hz, 1H), 0.42 – 0.33 (m, 2H), 0.13 – 0.04 (m, 2H); (M+H) ⁺ = 603	+	141
284		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.26 (s, 1H), 7.72 – 7.66 (m, 2H), 7.61 – 7.48 (m, 2H), 7.35 – 7.19 (m, 10H), 4.13 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.31 (s, 3H), 1.17 – 1.05 (m, 1H), 0.33 – 0.26 (m, 2H), 0.22 – 0.15 (m, 2H); (M+H) ⁺ = 603	+++	141
285		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.16 (s, 1H), 7.55 – 7.44 (m, 3H), 7.39 (s, 2H), 7.39 – 7.13 (m, 8H), 3.83 (s, 2H), 2.43 (d, J = 6.8 Hz, 2H), 2.30 (s, 3H), 0.98 – 0.86 (m, 1H), 0.43 – 0.33 (m, 2H), 0.15 – 0.06 (m, 2H); (M+H) ⁺ = 621	+	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
286		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.84 (s, 1H), 8.18 (s, 1H), 7.68 – 7.57 (m, 3H), 7.55 (s, 2H), 7.48 – 7.38 (m, 3H), 7.30 (ddd, J = 7.6, 1.8, 1.1 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.09 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 3.86 (s, 2H), 2.42 (d, J = 6.8 Hz, 2H), 2.28 (s, 3H), 1.00 – 0.87 (m, 1H), 0.44 – 0.34 (m, 2H), 0.15 – 0.06 (m, 2H); (M+H) ⁺ = 603	+	145
287		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.86 (s, 1H), 8.17 (s, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.58 – 7.47 (m, 1H), 7.40 – 7.24 (m, 5H), 7.24 – 7.17 (m, 2H), 7.22 – 7.06 (m, 2H), 7.09 – 6.97 (m, 1H), 3.86 (s, 2H), 2.41 (d, J = 6.8 Hz, 2H), 2.30 (s, 3H), 0.92 (dddd, J = 11.6, 8.1, 5.0, 1.9 Hz, 1H), 0.43 – 0.34 (m, 2H), 0.14 – 0.06 (m, 2H); (M+H) ⁺ = 621	+	145
288		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.24 (s, 1H), 7.69 – 7.53 (m, 2H), 7.57 (s, 2H), 7.49 (dd, J = 7.6, 2.3 Hz, 1H), 7.32 (dd, J = 10.7, 8.5 Hz, 1H), 7.24 (s, 3H), 7.26 – 7.12 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 4.14 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.31 (s, 3H),	+++	145

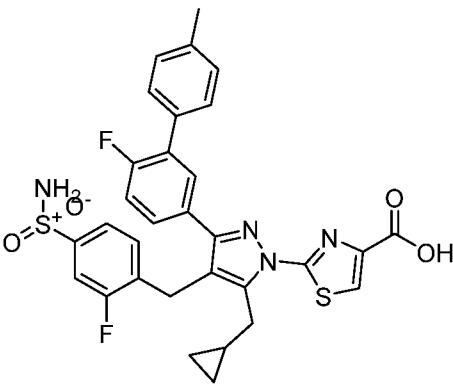
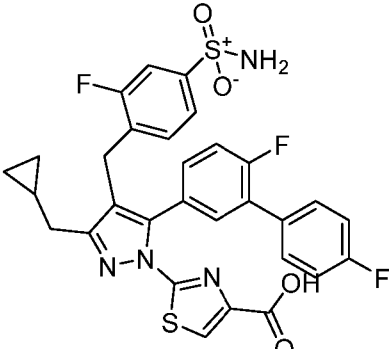
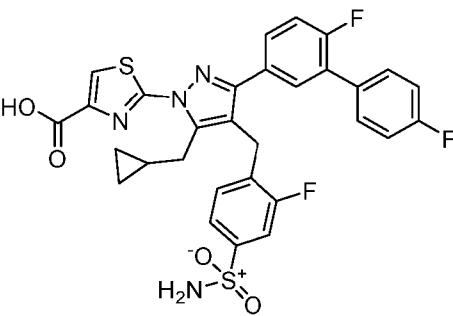
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		1.18 – 1.00 (m, 1H), 0.36 – 0.25 (m, 2H), 0.23 – 0.15 (m, 2H); (M+H) ⁺ = 621		
289		(M+H) ⁺ = 589	+	145
290		(M+H) ⁺ = 589	+++	145
291		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.86 (s, 1H), 8.18 (s, 1H), 7.71 – 7.57 (m, 3H), 7.57 – 7.49 (m, 4H), 7.46 (td, J = 7.7, 0.6 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.37 – 7.26 (m, 2H), 7.13 – 6.99 (m, 2H), 3.87 (s, 2H), 2.43 (d, J = 6.8 Hz, 2H), 1.02 – 0.86 (m, 1H), 0.44 – 0.34 (m, 2H), 0.15 – 0.07 (m, 2H); (M+H) ⁺ = 589	+	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
292		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.89 (s, 1H), 8.16 (s, 1H), 7.70 – 7.63 (m, 2H), 7.68 – 7.43 (m, 3H), 7.42 – 7.27 (m, 2H), 7.28 – 7.17 (m, 6H), 3.85 (s, 2H), 2.39 (d, J = 6.8 Hz, 2H), 0.92 (dddd, J = 13.3, 8.1, 5.0, 2.0 Hz, 1H), 0.42 – 0.33 (m, 2H), 0.13 – 0.04 (m, 2H); (M+H) ⁺ = 607	+	145
293		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.89 (s, 1H), 8.16 (s, 1H), 7.72 – 7.63 (m, 2H), 7.50 (dd, J = 7.6, 2.2 Hz, 1H), 7.40 – 7.26 (m, 4H), 7.29 – 7.20 (m, 4H), 7.12 – 7.04 (m, 2H), 3.85 (s, 2H), 2.39 (d, J = 6.8 Hz, 2H), 1.90 (tt, J = 8.3, 5.1 Hz, 1H), 0.98 – 0.88 (m, 3H), 0.73 – 0.62 (m, 2H), 0.42 – 0.31 (m, 2H), 0.15 – 0.04 (m, 2H); (M+H) ⁺ = 629	+	145
294		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.30 (s, 1H), 7.77 – 7.64 (m, 2H), 7.60 (ddd, J = 8.5, 4.7, 2.3 Hz, 1H), 7.52 (dd, J = 7.7, 2.3 Hz, 1H), 7.41 – 7.28 (m, 4H), 7.31 – 7.18 (m, 2H), 7.18 – 7.08 (m, 2H), 4.16 (s, 2H), 3.21 – 3.14 (m, 2H), 1.94 (tt, J = 8.3, 5.0 Hz, 1H), 1.21 – 1.07 (m, 1H), 1.05 – 0.92 (m, 2H), 0.79 – 0.65 (m, 2H), 0.38 – 0.30 (m, 2H), 0.25 – 0.18 (m, 2H); (M+H) ⁺ =	+++	145

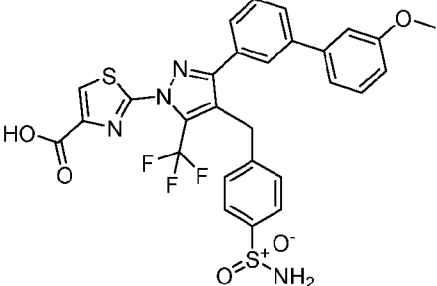
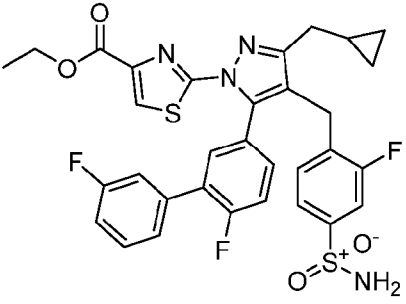
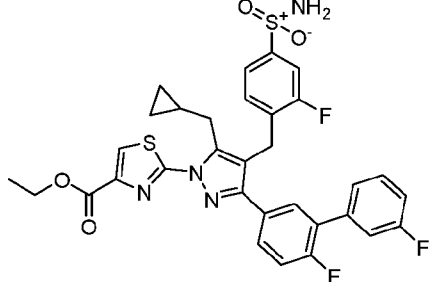
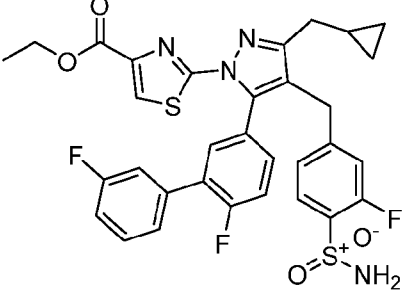
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		629		
295		(M+H) ⁺ = 592	+	141
296		(M+H) ⁺ = 592	+++	141
297		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.41 (s, 1H), 7.76 – 7.70 (m, 2H), 7.69 – 7.62 (m, 3H), 7.48 (td, J = 7.6, 0.7 Hz, 1H), 7.45 – 7.31 (m, 8H), 7.30 (s, 2H), 4.40 – 4.35 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 7H); (M+H) ⁺ = 653	-	49
298		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.95 (s, 1H), 7.68 – 7.58 (m, 4H), 7.49 – 7.43 (m, 2H), 7.44 – 7.33 (m, 3H), 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 4H), 3.99 (s, 2H), 1.37 – 1.24 (m, 2H), 1.04 (s, 2H); (M+H) ⁺ = 653	+	49

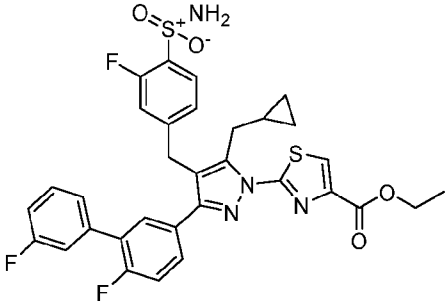
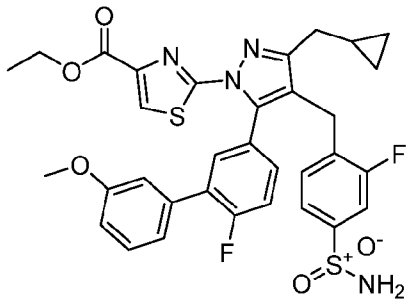
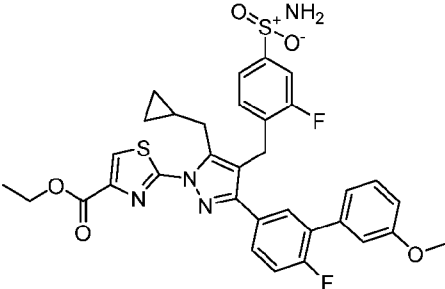
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
299		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.07 (s, 1H), 8.31 (s, 1H), 7.73 – 7.65 (m, 2H), 7.70 – 7.57 (m, 3H), 7.49 – 7.40 (m, 1H), 7.43 – 7.24 (m, 10H), 4.33 (s, 2H), 1.81 – 0.93 (m, 4H); (M+H) ⁺ = 625	+	49
300		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.07 (s, 1H), 8.31 (s, 1H), 7.68 – 7.48 (m, 4H), 7.50 – 7.36 (m, 8H), 7.39 – 7.28 (m, 1H), 7.09 (t, J = 7.8 Hz, 1H), 4.27 (s, 2H), 1.73 – 1.10 (m, 4H); (M+H) ⁺ = 643	++	49
301		(M+H) ⁺ = 643	+	49
302		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.09 (s, 1H), 8.30 (s, 1H), 7.67 – 7.54 (m, 6H), 7.50 – 7.40 (m, 1H), 7.44 – 7.34 (m, 4H), 7.39 – 7.27 (m, 1H), 7.19 (dd, J = 11.4, 1.6 Hz, 1H), 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 4.34 (s, 2H), 1.81 – 0.93 (m, 4H); (M+H) ⁺ = 643	+	49

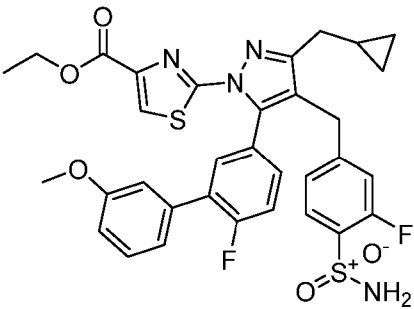
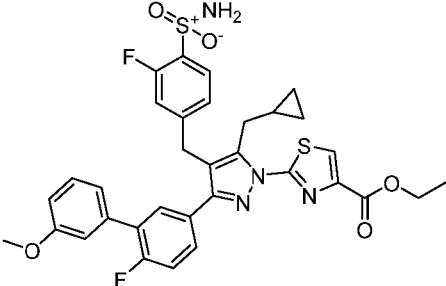
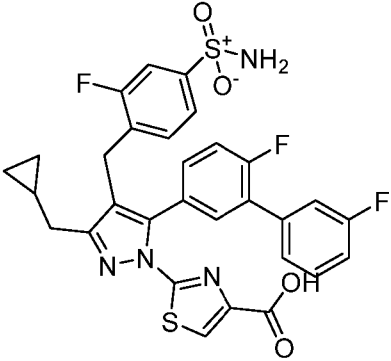
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
303		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.93 (s, 1H), 8.23 (s, 1H), 7.72 – 7.56 (m, 4H), 7.54 – 7.28 (m, 7H), 7.32 – 7.16 (m, 4H), 3.93 (s, 2H), 3.70 (q, J = 11.2 Hz, 2H); (M+H) ⁺ = 599	+	49
304		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.20 (s, 1H), 8.30 (s, 1H), 7.72 – 7.57 (m, 5H), 7.47 (td, J = 7.7, 0.6 Hz, 1H), 7.45 – 7.23 (m, 9H), 4.66 (q, J = 10.5 Hz, 2H), 4.26 (s, 2H); (M+H) ⁺ = 599	++	49
305		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.88 (s, 1H), 7.71 – 7.63 (m, 2H), 7.53 (dd, J = 7.6, 2.2 Hz, 1H), 7.40 – 7.26 (m, 4H), 7.29 – 7.21 (m, 6H), 3.85 (s, 2H), 2.88 (hept, J = 6.9 Hz, 1H), 2.39 (d, J = 6.8 Hz, 2H), 1.19 (s, sH), 1.18 (s, 3H), 0.92 (dddd, J = 11.8, 6.8, 5.6, 2.9 Hz, 1H), 0.44 – 0.31 (m, 2H), 0.15 – 0.04 (m, 2H); (M+H) ⁺ = 631	+	145
306		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.73 – 7.66 (m, 2H), 7.61 – 7.46 (m, 2H), 7.38 – 7.20 (m, 10H), 4.13 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.89 (hept, J = 6.9 Hz, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.15 – 1.04 (m, 1H), 0.35 – 0.26 (m, 2H), 0.23 – 0.14 (m, 2H); (M+H) ⁺ = 631	+++	145

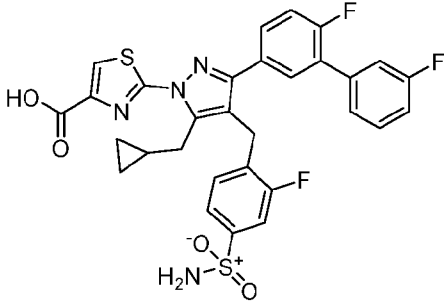
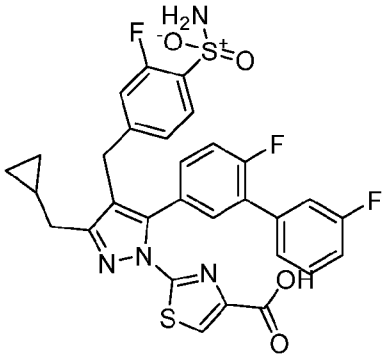
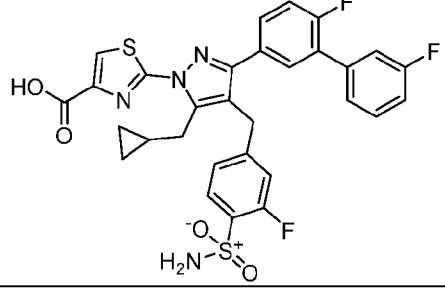
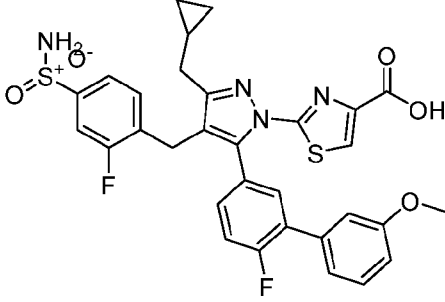
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
307		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.27 (s, 1H), 7.59 – 7.44 (m, 4H), 7.42 (s, 2H), 7.32 (dd, J = 10.8, 8.5 Hz, 1H), 7.24 (s, 1H), 7.24 (s, 3H), 7.14 (t, J = 7.8 Hz, 1H), 4.09 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.50 (s, 1H), 2.31 (s, 3H), 1.15 – 1.02 (m, 1H), 0.35 – 0.14 (m, 4H); (M+H) ⁺ = 621	+++	145
308		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.89 (s, 1H), 8.17 (s, 1H), 7.60 – 7.41 (m, 5H), 7.44 – 7.14 (m, 7H), 3.84 (s, 2H), 2.52–2.51 (m, 2H), 0.99 – 0.84 (m, 1H), 0.43 – 0.34 (m, 2H), 0.15 – 0.06 (m, 2H); (M+H) ⁺ = 625	+	145
309		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.28 (s, 1H), 7.62 – 7.49 (m, 2H), 7.49 (ddd, J = 8.4, 6.3, 2.1 Hz, 2H), 7.42 (s, 2H), 7.39 (ddd, J = 8.9, 5.4, 1.4 Hz, 2H), 7.34 (dd, J = 10.7, 8.6 Hz, 1H), 7.31 – 7.21 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 4.09 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.15 – 1.02 (m, 1H), 0.35 – 0.26 (m, 2H), 0.29 – 0.15 (m, 2H); (M+H) ⁺ = 625	+++	145

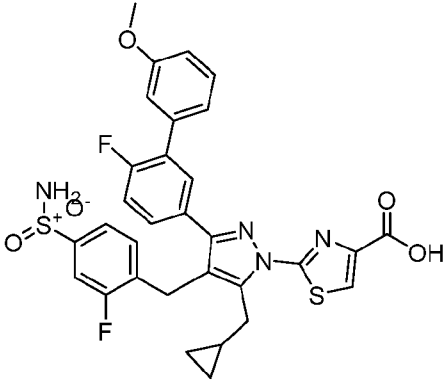
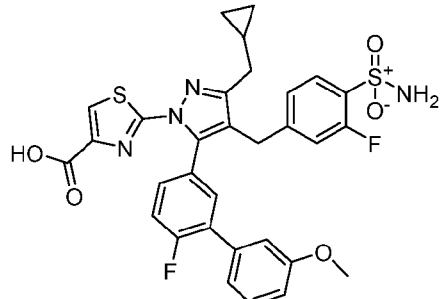
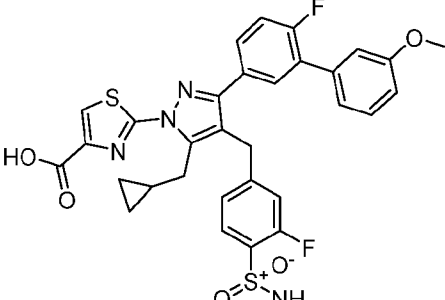
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
310		¹ H NMR (400 MHz, DMSO-d6) δ 13.12 (s, 1H), 8.26 (s, 1H), 7.73 – 7.65 (m, 2H), 7.62 (ddd, J = 8.6, 4.7, 2.3 Hz, 1H), 7.49 (dd, J = 7.6, 2.3 Hz, 1H), 7.41 – 7.29 (m, 3H), 7.32 – 7.19 (m, 6H), 4.13 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.50 (s, 1H), 1.19 – 1.02 (m, 1H), 0.35 – 0.24 (m, 2H), 0.27 – 0.15 (m, 2H); (M+H) ⁺ = 607	+++	145
311		(M+H) ⁺ = 599	+++	14, 18
312		(M+H) ⁺ = 603	+++	14, 18
313		(M+H) ⁺ = 603	+++	14, 18

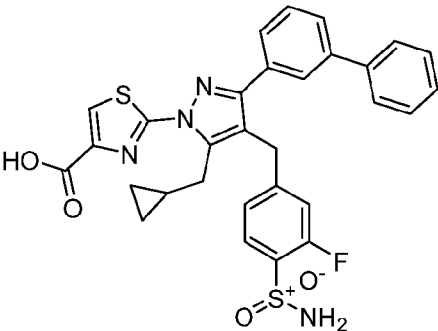
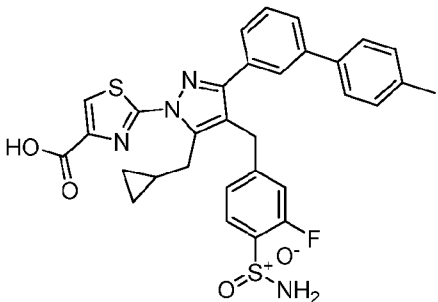
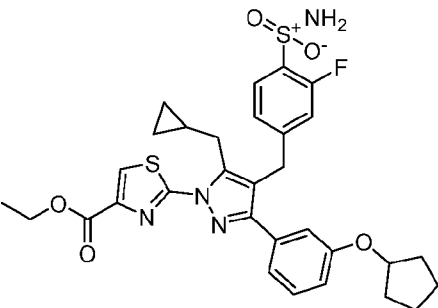
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
314		(M+H) ⁺ = 615	+++	14, 18
315		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.22 (s, 1H), 7.66 (dd, J = 7.6, 2.2 Hz, 1H), 7.52 – 7.36 (m, 5H), 7.40 – 7.27 (m, 4H), 7.26 – 7.16 (m, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.85 (s, 2H), 2.44 (d, J = 6.8 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H), 0.99 – 0.86 (m, 1H), 0.44 – 0.34 (m, 2H), 0.16 – 0.07 (m, 2H); (M+H) ⁺ = 653	-	141
316		(M+H) ⁺ = 653	+	141
317		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.22 (s, 1H), 7.69 (dd, J = 7.6, 2.2 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.52 – 7.34 (m, 2H), 7.38 – 7.31 (m, 1H), 7.35 – 7.27 (m, 2H), 7.21 (dddd, J = 9.0, 8.3, 2.6, 1.0 Hz, 1H), 7.11 (dd, J = 11.4, 1.5 Hz, 1H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.88 (s, 2H), 2.41 (d, J = 6.8 Hz, 2H), 1.10	-	141

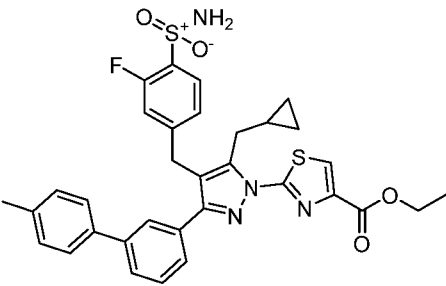
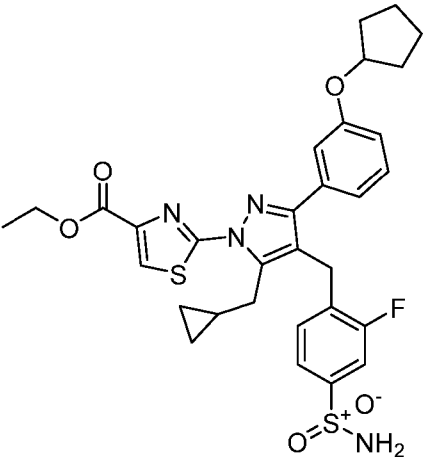
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(t, J = 7.1 Hz, 3H), 0.99 – 0.87 (m, 1H), 0.44 – 0.34 (m, 2H), 0.15 – 0.06 (m, 2H); (M+H) ⁺ = 653		
318		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (s, 1H), 7.68 – 7.55 (m, 3H), 7.56 (s, 2H), 7.48 (ddd, J = 8.4, 7.7, 6.2 Hz, 1H), 7.42 – 7.29 (m, 2H), 7.34 – 7.16 (m, 2H), 7.21 – 7.11 (m, 2H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.17 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.25 – 0.96 (m, 1H), 0.37 – 0.19 (m, 4H); (M+H) ⁺ = 653	-	141
319		(M+H) ⁺ = 665	-	141
320		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (s, 1H), 7.61 – 7.44 (m, 4H), 7.43 – 7.29 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 7.02 – 6.94 (m, 1H), 6.99 – 6.87 (m, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 3.76 (s, 3H), 3.15 (d, J = 6.9 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.20 – 0.95 (m, 0H), 0.36 – 0.17	-	141

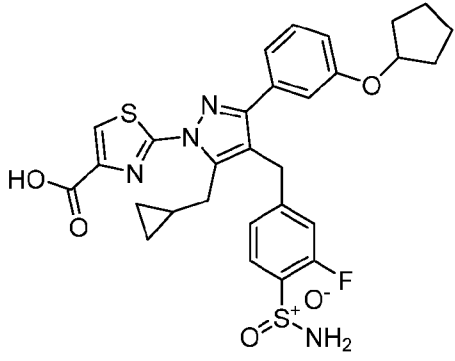
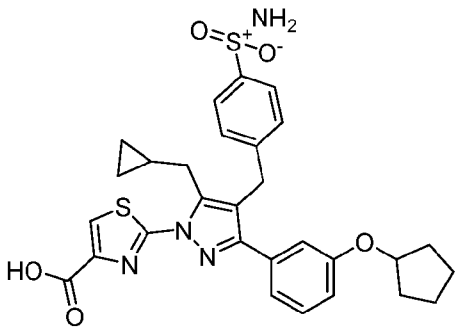
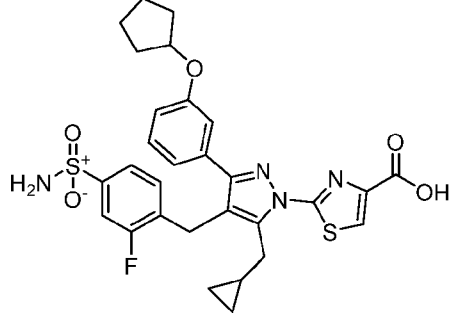
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(m, 4H); (M+H) ⁺ = 665		
321		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.22 (s, 1H), 7.67 – 7.58 (m, 2H), 7.55 (s, 2H), 7.44 – 7.27 (m, 3H), 7.15 – 6.89 (m, 6H), 4.10 (q, J = 7.1 Hz, 2H), 3.88 (s, 2H), 3.72 (s, 3H), 2.41 (d, J = 6.8 Hz, 2H), 1.11 (t, J = 7.1 Hz, 3H), 1.01 – 0.78 (m, 1H), 0.43 – 0.34 (m, 2H), 0.15 – 0.06 (m, 2H); (M+H) ⁺ = 665	-	141
322		(M+H) ⁺ = 665	+	141
323		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.91 (s, 1H), 8.18 (s, 1H), 7.66 (dd, J = 7.6, 2.2 Hz, 1H), 7.52 – 7.25 (m, 7H), 7.39 (s, 2H), 7.26 – 7.15 (m, 2H), 3.85 (s, 2H), 2.44 (d, J = 6.8 Hz, 2H), 1.00 – 0.85 (m, 1H), 0.44 – 0.34 (m, 2H), 0.15 – 0.07 (m, 2H); (M+H) ⁺ = 625	+	141

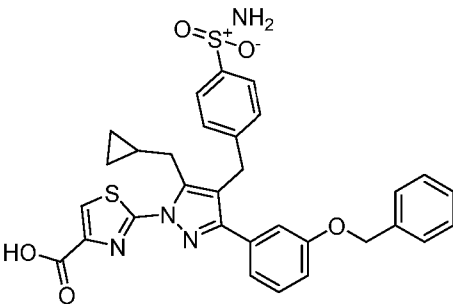
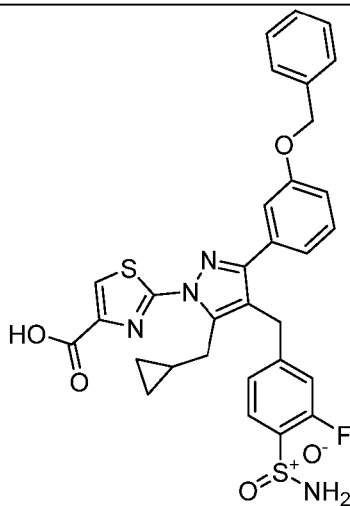
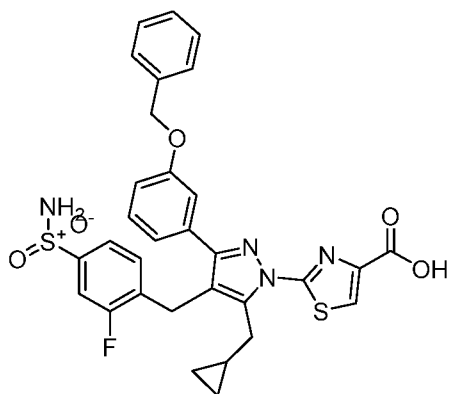
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
324		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.27 (s, 1H), 7.64 – 7.55 (m, 2H), 7.55 – 7.43 (m, 3H), 7.43 – 7.09 (m, 7H), 4.11 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.21 – 0.95 (m, 1H), 0.36 – 0.25 (m, 2H), 0.28 – 0.15 (m, 2H); (M+H) ⁺ = 625	+++	141
325		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.91 (s, 1H), 8.17 (s, 1H), 7.73 – 7.58 (m, 2H), 7.55 (s, 2H), 7.50 – 7.40 (m, 1H), 7.44 – 7.33 (m, 2H), 7.37 – 7.29 (m, 2H), 7.21 (dddd, J = 9.1, 8.3, 2.6, 1.0 Hz, 1H), 7.14 – 6.99 (m, 2H), 3.88 (s, 2H), 2.41 (d, J = 6.8 Hz, 2H), 1.00 – 0.85 (m, 1H), 0.44 – 0.34 (m, 2H), 0.15 – 0.06 (m, 2H); (M+H) ⁺ = 625	+	141
326		(M+H) ⁺ = 625	+++	141
327		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.89 (s, 1H), 8.18 (s, 1H), 7.57 (dd, J = 7.6, 2.2 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.42 – 7.23 (m, 5H), 7.20 (t, J = 7.9 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.92 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 3.85 (s, 2H), 3.72 (s, 3H), 2.43 (d,	+	141

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		J = 6.8 Hz, 2H), 1.06 – 0.78 (m, 1H), 0.43 – 0.32 (m, 2H), 0.17 – 0.04 (m, 2H); (M+H) ⁺ = 637		
328		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.27 (s, 1H), 7.61 – 7.44 (m, 4H), 7.41 (s, 2H), 7.39 – 7.29 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.02 – 6.87 (m, 3H), 4.11 (s, 2H), 3.76 (s, 3H), 3.15 (d, J = 6.9 Hz, 2H), 1.20 – 0.98 (m, 1H), 0.35 – 0.26 (m, 2H), 0.29 – 0.15 (m, 2H); (M+H) ⁺ = 637	+++	141
329		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.88 (s, 1H), 8.17 (s, 1H), 7.67 – 7.57 (m, 2H), 7.55 (s, 2H), 7.43 – 7.26 (m, 3H), 7.15 – 6.97 (m, 4H), 6.92 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 3.88 (s, 2H), 3.72 (s, 3H), 2.40 (d, J = 6.8 Hz, 2H), 0.92 (dddd, J = 14.8, 8.0, 5.0, 1.9 Hz, 1H), 0.43 – 0.34 (m, 2H), 0.14 – 0.06 (m, 2H); (M+H) ⁺ = 637	+	141
330		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.68 – 7.54 (m, 3H), 7.56 (s, 2H), 7.39 – 7.29 (m, 2H), 7.15 (dd, J = 11.3, 1.6 Hz, 1H), 7.09 – 6.86 (m, 4H), 4.16 (s, 2H), 3.75 (s, 3H), 3.14 (d, J = 6.9 Hz, 2H), 1.11	+++	141

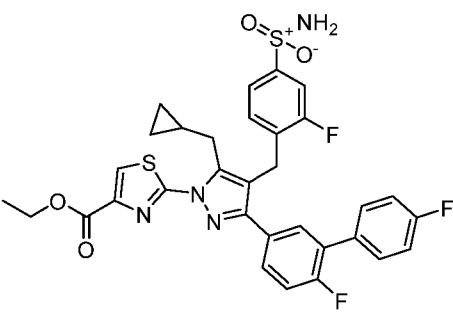
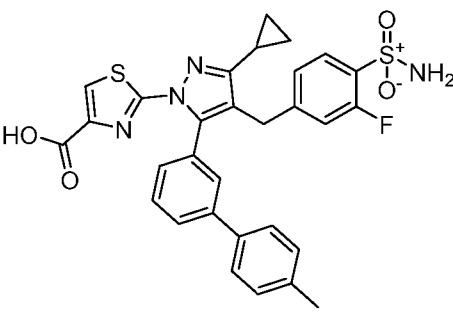
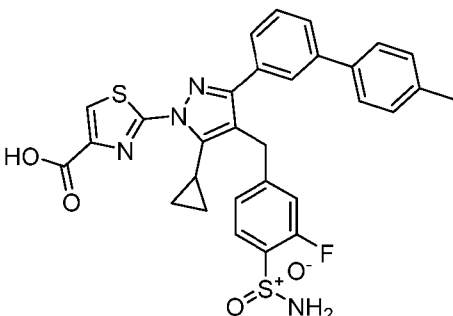
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(s, 1H), 0.36 – 0.27 (m, 2H), 0.24 – 0.15 (m, 2H); (M+H) ⁺ = 637		
331		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.71 – 7.62 (m, 2H), 7.66 – 7.53 (m, 2H), 7.58 (s, 2H), 7.56 – 7.29 (m, 6H), 7.19 (dd, J = 11.4, 1.6 Hz, 1H), 7.08 (dd, J = 8.1, 1.6 Hz, 1H), 4.17 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.23 – 1.07 (m, 1H), 0.37 – 0.28 (m, 2H), 0.31 – 0.17 (m, 2H); (M+H) ⁺ = 589	+++	141
332		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.71 – 7.53 (m, 4H), 7.58 (s, 2H), 7.57 – 7.40 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.26 – 7.15 (m, 3H), 7.08 (dd, J = 8.1, 1.6 Hz, 1H), 4.16 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.30 (s, 3H), 1.23 – 1.01 (m, 1H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 603	+++	141
333		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.33 (s, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.56 (s, 2H), 7.32 – 7.23 (m, 1H), 7.14 (dd, J = 11.3, 1.5 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.94 – 6.83 (m, 2H), 4.58 (dq, J = 6.0, 3.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 3.12 (d, J = 6.9 Hz, 2H), 1.80 – 1.68 (m, 2H), 1.68	+	120

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		– 1.59 (m, 3H), 1.59 – 1.47 (m, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.16 – 1.04 (m, 1H), 0.36 – 0.27 (m, 2H), 0.27 – 0.17 (m, 2H); (M+H) ⁺ = 625		
334		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.33 (s, 1H), 7.73 – 7.65 (m, 2H), 7.32 – 7.22 (m, 5H), 7.09 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 6.95 – 6.83 (m, 2H), 4.54 (dq, J = 6.1, 3.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 3.11 (d, J = 6.9 Hz, 2H), 1.78 – 1.41 (m, 8H), 1.30 (t, J = 7.1 Hz, 3H), 1.14 – 1.10 (m, 1H), 0.35 – 0.25 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 607	-	141
335		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.49 – 8.24 (m, 1H), 7.60 – 7.45 (m, 2H), 7.41 (s, 2H), 7.27 (ddd, J = 8.2, 7.7, 0.5 Hz, 1H), 7.18 – 7.02 (m, 2H), 6.96 – 6.83 (m, 2H), 4.57 (dq, J = 5.9, 3.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 3.13 (d, J = 7.0 Hz, 2H), 1.92 – 1.40 (m, 8H), 1.30 (t, J = 7.1 Hz, 3H), 1.23 – 0.93 (m, 1H), 0.39 – 0.26 (m, 2H), 0.24 – 0.13 (m, 2H); (M+H) ⁺ = 625	+	120

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
336		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 0H), 8.27 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.27 (t, J = 7.9 Hz, 1H), 7.18 – 7.07 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 6.94 – 6.83 (m, 2H), 4.58 (tt, J = 5.7, 2.5 Hz, 1H), 4.11 (s, 2H), 3.12 (d, J = 6.9 Hz, 2H), 1.78 – 1.46 (m, 8H), 1.23 – 0.93 (m, 1H), 0.35 – 0.14 (m, 4H); (M+H) ⁺ = 597	+++	120
337		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.27 (s, 1H), 7.72 – 7.65 (m, 2H), 7.32 – 7.19 (m, 6H), 7.09 (ddd, J = 7.6, 1.6, 1.0 Hz, 1H), 6.95 – 6.82 (m, 3H), 4.54 (dq, J = 6.1, 3.1 Hz, 1H), 4.09 (s, 2H), 3.11 (d, J = 6.9 Hz, 2H), 1.78 – 1.69 (m, 2H), 1.69 – 1.57 (m, 4H), 1.57 – 1.46 (m, 4H), 1.21 – 0.93 (m, 1H), 0.34 – 0.25 (m, 2H), 0.22 – 0.13 (m, 2H); (M+H) ⁺ = 579	+++	120
338		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 7.58 – 7.45 (m, 2H), 7.41 (s, 2H), 7.27 (t, J = 7.9 Hz, 1H), 7.16 – 7.02 (m, 2H), 6.93 – 6.83 (m, 2H), 4.56 (tt, J = 5.6, 2.5 Hz, 1H), 4.05 (s, 2H), 3.13 (d, J = 6.9 Hz, 2H), 1.80 – 1.46 (m, 8H), 1.20 – 0.82 (m, 1H), 0.34 – 0.26 (m, 2H), 0.26 – 0.14 (m, 2H); (M+H) ⁺ =	+++	120

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		597		
339		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.27 (s, 1H), 7.72 – 7.64 (m, 2H), 7.42 – 7.20 (m, 10H), 7.16 – 7.07 (m, 2H), 7.00 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 5.01 (s, 2H), 4.09 (s, 2H), 3.11 (d, J = 6.9 Hz, 2H), 1.09 (ddtd, J = 13.0, 7.9, 6.9, 5.0 Hz, 1H), 0.35 – 0.25 (m, 2H), 0.22 – 0.13 (m, 2H); (M+H) ⁺ = 601	+++	120
340		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.42 – 7.24 (m, 6H), 7.16 – 7.05 (m, 3H), 7.00 (ddt, J = 8.3, 2.6, 1.2 Hz, 2H), 5.03 (s, 2H), 4.10 (s, 2H), 3.12 (d, J = 6.9 Hz, 2H), 1.14 – 0.98 (m, 1H), 0.35 – 0.24 (m, 2H), 0.25 – 0.14 (m, 2H); (M+H) ⁺ = 619	+++	120
341		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.58 – 7.43 (m, 2H), 7.43 – 7.24 (m, 8H), 7.16 – 6.96 (m, 4H), 5.04 (s, 2H), 4.05 (s, 2H), 3.12 (d, J = 6.9 Hz, 2H), 1.18 – 0.96 (m, 1H), 0.34 – 0.25 (m, 2H), 0.22 – 0.13 (m, 2H); (M+H) ⁺ = 619	+++	120

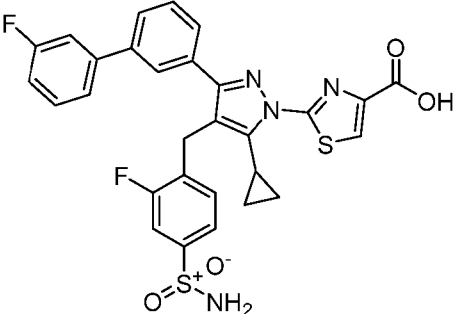
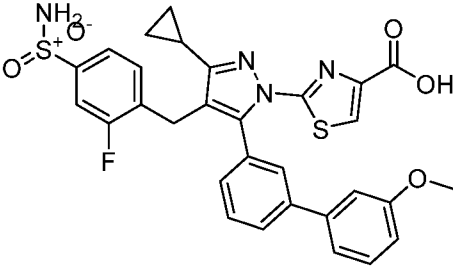
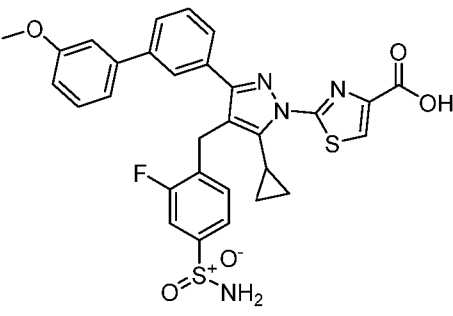
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
342		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.91 (s, 1H), 8.18 (s, 1H), 7.73 – 7.63 (m, 2H), 7.50 – 7.05 (m, 12H), 7.03 (ddd, J = 8.4, 2.6, 1.0 Hz, 1H), 6.90 (dt, J = 7.6, 1.1 Hz, 1H), 5.05 (s, 2H), 3.79 (s, 2H), 2.36 (d, J = 6.8 Hz, 2H), 0.98 – 0.83 (m, 1H), 0.43 – 0.31 (m, 2H), 0.12 – 0.03 (m, 2H); (M+H) ⁺ = 601	+	120
343		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.34 (s, 1H), 7.69 – 7.54 (m, 2H), 7.58 (s, 2H), 7.50 (dd, J = 7.6, 2.3 Hz, 1H), 7.33 (dd, J = 10.7, 8.6 Hz, 1H), 7.24 (s, 3H), 7.29 – 7.13 (m, 2H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.32 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.21 – 1.00 (m, 1H), 0.37 – 0.26 (m, 2H), 0.23 (dt, J = 5.1, 2.6 Hz, 2H); (M+H) ⁺ = 649	+	141
344		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (s, 1H), 7.67 – 7.41 (m, 9H), 7.38 – 7.29 (m, 2H), 7.26 – 7.13 (m, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 3.15 (dd, J = 9.8, 6.1 Hz, 3H), 2.30 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.25 – 0.96 (m, 0H), 0.37 – 0.19 (m, 4H); (M+H) ⁺ = 631	-	145

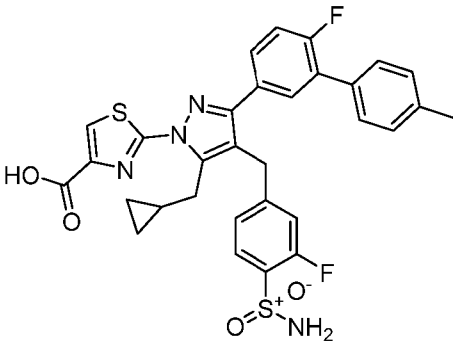
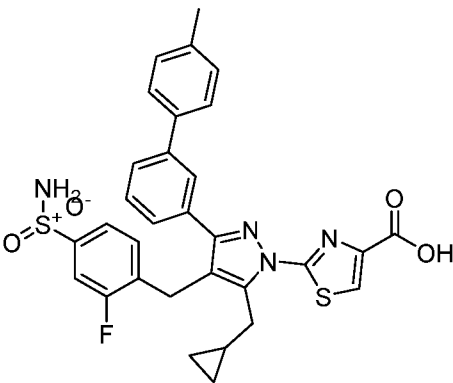
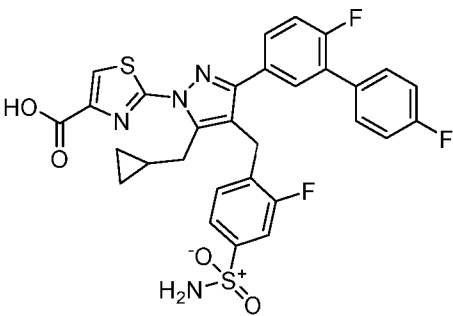
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
345		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (s, 1H), 7.63 – 7.45 (m, 4H), 7.43 (s, 2H), 7.45 – 7.30 (m, 3H), 7.32 – 7.21 (m, 2H), 7.15 (t, J = 7.8 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.20 – 0.91 (m, 0H), 0.37 – 0.18 (m, 4H); (M+H) ⁺ = 653	+	145
346		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.84 (s, 1H), 8.15 (s, 1H), 7.70 – 7.54 (m, 5H), 7.50 – 7.40 (m, 3H), 7.30 (dt, J = 7.7, 1.3 Hz, 1H), 7.24 – 7.08 (m, 3H), 7.13 – 7.02 (m, 1H), 3.92 (s, 2H), 2.29 (s, 3H), 1.77 (tt, J = 7.5, 5.6 Hz, 1H), 0.85 (ddd, J = 6.9, 3.5, 1.6 Hz, 4H); (M+H) ⁺ = 589	+	112
347		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.09 (s, 1H), 8.31 (s, 1H), 7.73 – 7.41 (m, 7H), 7.31 (d, J = 8.2 Hz, 2H), 7.26 – 7.17 (m, 3H), 7.08 (dd, J = 8.2, 1.6 Hz, 1H), 4.16 (s, 2H), 2.30 (s, 3H), 2.30 – 2.19 (m, 1H), 1.02 – 0.92 (m, 2H), 0.70 – 0.61 (m, 2H); (M+H) ⁺ = 589	+++	112

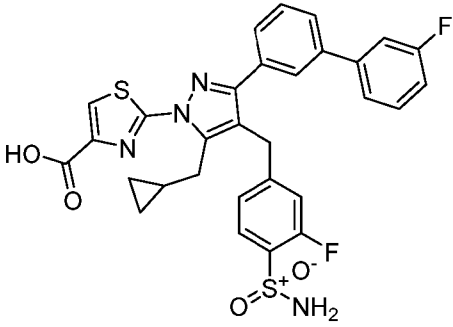
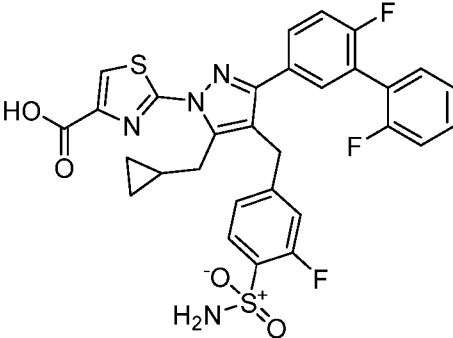
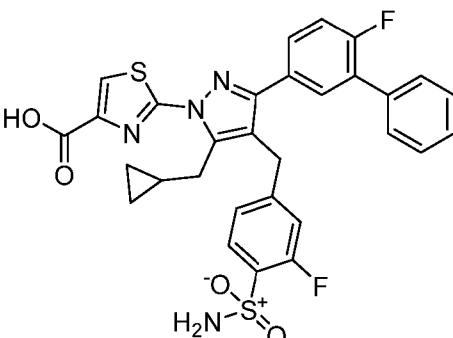
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
348		(M+H) ⁺ = 593	+	112
349		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.31 (s, 1H), 7.74 – 7.60 (m, 2H), 7.60 (s, 2H), 7.59 – 7.39 (m, 5H), 7.27 – 7.18 (m, 3H), 7.08 (dd, J = 8.1, 1.6 Hz, 1H), 4.17 (s, 2H), 2.25 (tt, J = 8.5, 5.5 Hz, 1H), 1.04 – 0.93 (m, 2H), 0.73 – 0.62 (m, 2H); (M+H) ⁺ = 593	+++	112
350		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.85 (s, 1H), 8.15 (s, 1H), 7.78 – 7.69 (m, 2H), 7.64 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.52 – 7.39 (m, 4H), 7.43 – 7.32 (m, 1H), 7.20 – 7.02 (m, 3H), 3.93 (s, 2H), 1.76 (tt, J = 7.6, 5.5 Hz, 1H), 0.90 – 0.78 (m, 4H); (M+H) ⁺ = 593	+	112
351		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.31 (s, 1H), 7.74 – 7.61 (m, 3H), 7.59 – 7.44 (m, 4H), 7.49 – 7.35 (m, 2H), 7.26 – 7.04 (m, 4H), 4.18 (s, 2H), 2.24 (tt, J = 8.5, 5.6 Hz, 1H), 1.04 – 0.91 (m, 2H), 0.72 – 0.61 (m, 2H); (M+H) ⁺ = 593	+++	112

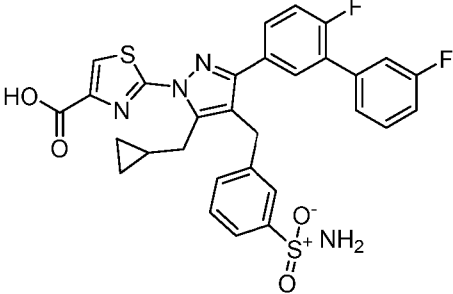
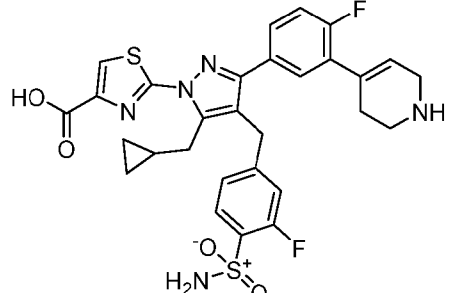
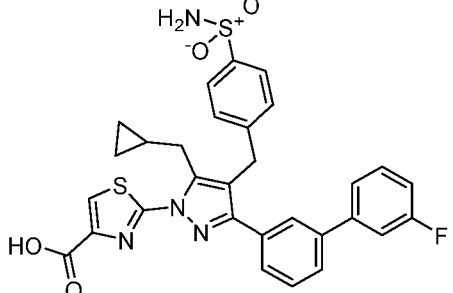
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
352		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.84 (s, 1H), 8.15 (s, 1H), 7.73 – 7.60 (m, 3H), 7.55 (s, 2H), 7.48 (td, J = 7.7, 0.5 Hz, 1H), 7.37 – 7.25 (m, 2H), 7.17 – 7.03 (m, 4H), 6.88 (ddd, J = 8.2, 2.5, 1.0 Hz, 1H), 3.93 (s, 2H), 3.29 (s, 9H), 1.75 (tt, J = 7.5, 5.6 Hz, 1H), 0.90 – 0.78 (m, 4H); (M+H) ⁺ = 605	+	112
353		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.30 (s, 1H), 7.72 – 7.59 (m, 3H), 7.59 – 7.40 (m, 4H), 7.36 – 7.25 (m, 1H), 7.20 (dd, J = 11.3, 1.6 Hz, 1H), 7.12 – 7.03 (m, 2H), 6.93 (dddd, J = 21.2, 8.3, 2.2, 0.9 Hz, 2H), 4.17 (s, 2H), 3.76 (s, 3H), 2.24 (tt, J = 8.5, 5.6 Hz, 1H), 1.01 – 0.90 (m, 2H), 0.71 – 0.58 (m, 2H); (M+H) ⁺ = 605	+++	112
354		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.85 (s, 1H), 8.16 (s, 1H), 7.69 – 7.49 (m, 3H), 7.54 – 7.46 (m, 1H), 7.50 – 7.39 (m, 5H), 7.33 – 7.15 (m, 4H), 3.90 (s, 2H), 2.29 (s, 3H), 1.76 (p, J = 6.8 Hz, 1H), 0.87 – 0.80 (m, 4H); (M+H) ⁺ = 589	+	112

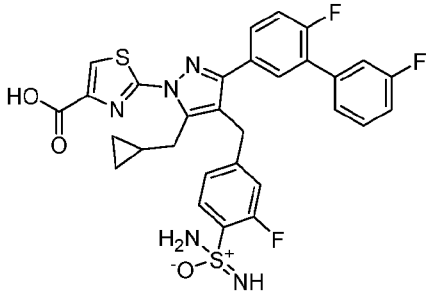
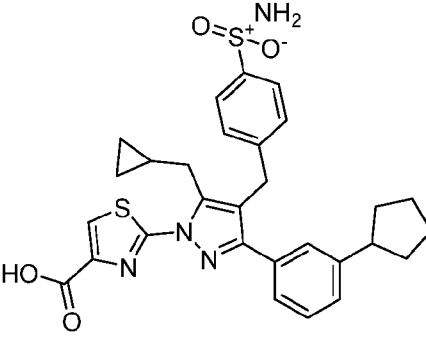
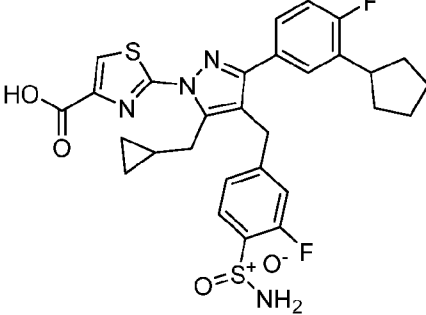
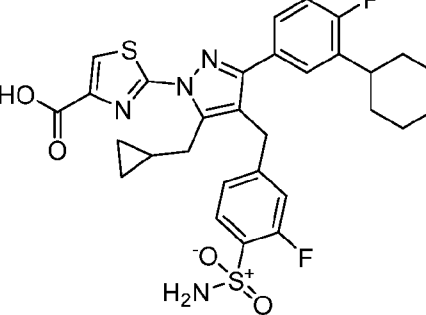
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
355		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.31 (s, 1H), 7.69 – 7.49 (m, 4H), 7.52 – 7.42 (m, 2H), 7.43 (s, 2H), 7.37 – 7.28 (m, 2H), 7.25 – 7.16 (m, 3H), 4.11 (s, 2H), 2.30 (s, 3H), 2.21 (tt, J = 8.5, 5.6 Hz, 1H), 1.02 – 0.92 (m, 2H), 0.69 – 0.60 (m, 2H); (M+H) ⁺ = 589	+++	112
356		(M+H) ⁺ = 593	+	112
357		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.30 (s, 1H), 7.65 (dt, J = 6.6, 2.1 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.58 – 7.46 (m, 3H), 7.50 – 7.41 (m, 4H), 7.29 – 7.16 (m, 3H), 4.11 (s, 2H), 2.21 (tt, J = 8.6, 5.6 Hz, 1H), 1.02 – 0.91 (m, 2H), 0.71 – 0.60 (m, 2H); (M+H) ⁺ = 593	+++	112
358		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.85 (s, 1H), 8.15 (s, 1H), 7.72 (ddd, J = 9.7, 1.8, 0.9 Hz, 2H), 7.55 – 7.46 (m, 1H), 7.50 (s, 1H), 7.51 – 7.38 (m, 4H), 7.40 (s, 2H), 7.36 – 7.10 (m, 3H), 3.91 (s, 2H), 1.82 – 1.70 (m, 1H), 0.89 – 0.78 (m, 4H); (M+H) ⁺ = 593	+	112

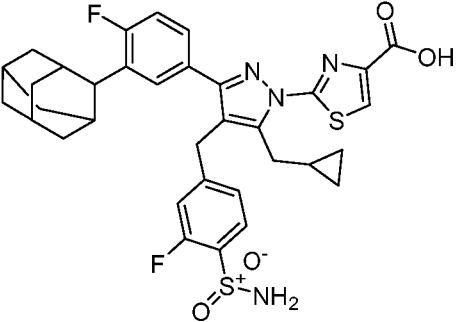
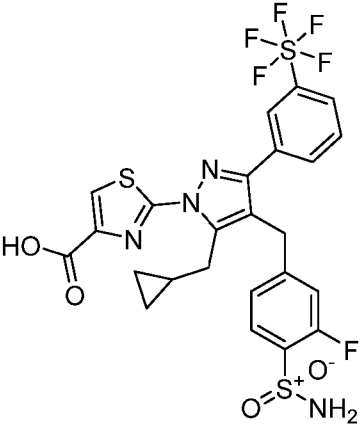
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
359		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.30 (s, 1H), 7.65 (dt, J = 6.6, 2.1 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.58 – 7.46 (m, 3H), 7.50 – 7.41 (m, 4H), 7.29 – 7.16 (m, 3H), 4.11 (s, 2H), 3.14 (d, J = 2.7 Hz, 1H), 2.21 (tt, J = 8.6, 5.6 Hz, 1H), 1.02 – 0.91 (m, 2H), 0.71 – 0.60 (m, 2H); (M+H) ⁺ = 593	+++	112
360		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.84 (s, 1H), 8.16 (s, 1H), 7.72 – 7.61 (m, 2H), 7.55 – 7.43 (m, 3H), 7.39 (s, 2H), 7.34 – 7.21 (m, 3H), 7.10 (dd, J = 6.9, 1.3 Hz, 2H), 6.92 – 6.84 (m, 1H), 3.90 (s, 2H), 3.74 (s, 3H), 1.81 – 1.69 (m, 1H), 0.89 – 0.79 (m, 4H); (M+H) ⁺ = 605	+	112
361		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.31 (s, 1H), 7.72 – 7.60 (m, 2H), 7.64 – 7.48 (m, 2H), 7.53 – 7.43 (m, 2H), 7.41 (s, 2H), 7.36 – 7.27 (m, 1H), 7.20 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 2.5, 1.7 Hz, 1H), 6.93 (dddd, J = 24.5, 8.3, 2.1, 0.9 Hz, 2H), 4.12 (s, 2H), 3.76 (s, 3H), 2.20 (tt, J = 8.5, 5.6 Hz, 1H), 1.01 – 0.90 (m, 2H), 0.70 – 0.57 (m, 2H); (M+H) ⁺ = 605	+++	112

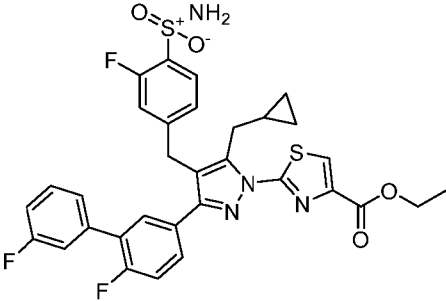
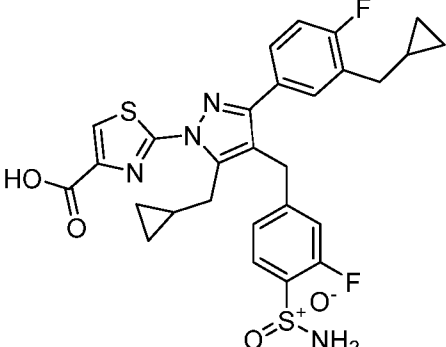
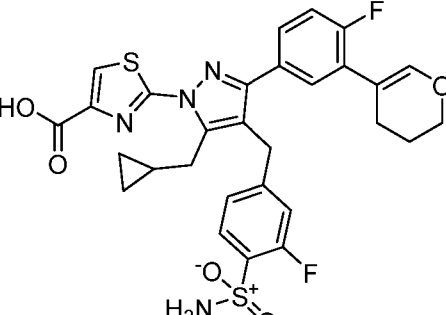
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
362		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.69 – 7.54 (m, 2H), 7.58 (s, 2H), 7.50 (dd, J = 7.6, 2.3 Hz, 1H), 7.33 (dd, J = 10.7, 8.6 Hz, 1H), 7.24 (s, 3H), 7.29 – 7.13 (m, 2H), 7.04 (dd, J = 8.2, 1.6 Hz, 1H), 4.15 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.32 (s, 3H), 1.20 – 0.96 (m, 1H), 0.37 – 0.27 (m, 2H), 0.28 – 0.16 (m, 2H); (M+H) ⁺ = 621	+++	145
363		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.25 (s, 1H), 7.67 – 7.59 (m, 2H), 7.61 – 7.42 (m, 4H), 7.43 (s, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.26 – 7.12 (m, 3H), 4.11 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.30 (s, 3H), 1.18 – 1.01 (m, 1H), 0.36 – 0.27 (m, 2H), 0.24 – 0.17 (m, 2H); (M+H) ⁺ = 603	+++	145
364		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.28 (s, 1H), 7.63 – 7.45 (m, 4H), 7.43 (s, 2H), 7.44 – 7.21 (m, 5H), 7.14 (t, J = 7.8 Hz, 1H), 4.10 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.15 – 1.02 (m, 0H), 0.36 – 0.15 (m, 4H); (M+H) ⁺ = 625	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
365		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.27 (s, 1H), 7.74 – 7.62 (m, 3H), 7.66 – 7.56 (m, 1H), 7.55 (s, 2H), 7.54 – 7.43 (m, 1H), 7.47 – 7.38 (m, 2H), 7.29 – 7.16 (m, 2H), 7.21 – 7.12 (m, 1H), 7.07 (dd, J = 8.1, 1.6 Hz, 1H), 4.18 (s, 2H), 3.15 (dd, J = 9.4, 5.6 Hz, 2H), 1.23 – 1.06 (m, 1H), 0.37 – 0.17 (m, 4H); (M+H) ⁺ = 607	+++	145
366		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.27 (s, 1H), 7.70 – 7.58 (m, 2H), 7.55 (s, 2H), 7.56 – 7.41 (m, 2H), 7.41 – 7.23 (m, 4H), 7.17 – 6.99 (m, 2H), 4.15 (s, 2H), 3.15 (dd, J = 5.8, 4.1 Hz, 2H), 1.21 – 1.00 (m, 1H), 0.37 – 0.25 (m, 2H), 0.27 – 0.16 (m, 2H); (M+H) ⁺ = 625	+++	145
367		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.69 – 7.30 (m, 11H), 7.17 (dd, J = 11.3, 1.6 Hz, 1H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 4.16 (s, 2H), 3.19 – 3.11 (m, 2H), 1.19 – 1.05 (m, 1H), 0.37 – 0.26 (m, 2H), 0.26 – 0.16 (m, 2H); (M+H) ⁺ = 607	+++	145

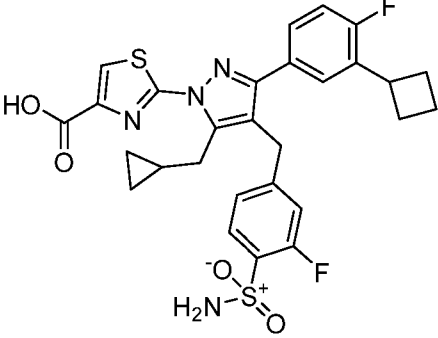
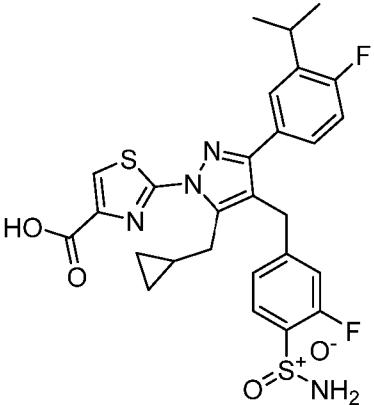
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
368		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.26 (s, 1H), 7.65 – 7.17 (m, 11H), 7.27 (s, 2H), 4.14 (s, 2H), 3.19 – 3.11 (m, 3H), 1.18 – 0.96 (m, 1H), 0.37 – 0.27 (m, 2H), 0.23 – 0.14 (m, 2H); (M+H) ⁺ = 607	+	145
369		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.80 (s, 2H), 8.27 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.60 – 7.47 (m, 3H), 7.39 – 7.21 (m, 2H), 7.12 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 5.93 – 5.87 (m, 1H), 4.14 – 4.01 (m, 3H), 3.75 – 3.68 (m, 2H), 3.25 (t, J = 6.0 Hz, 2H), 3.15 (dd, J = 7.2, 5.8 Hz, 4H), 1.12 (dddd, J = 15.0, 10.0, 5.0, 2.1 Hz, 1H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 612	+++	145
370		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.29 (s, 1H), 7.76 – 7.66 (m, 4H), 7.65 – 7.57 (m, 1H), 7.55 – 7.38 (m, 3H), 7.36 – 7.13 (m, 6H), 4.18 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 1.23 – 0.98 (m, 1H), 0.38 – 0.17 (m, 4H); (M+H) ⁺ = 589	+++	141

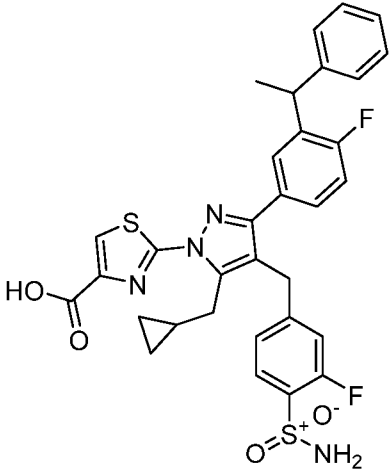
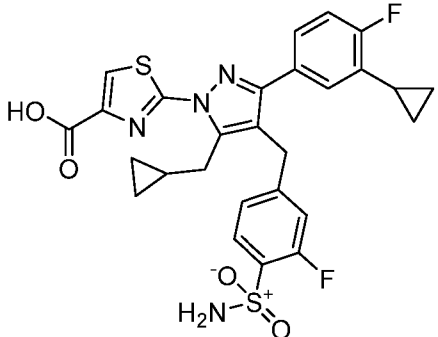
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
371		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.29 (s, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.64 (ddq, J = 7.3, 3.5, 2.3, 1.8 Hz, 2H), 7.59 – 7.46 (m, 1H), 7.43 – 7.29 (m, 2H), 7.30 – 7.12 (m, 3H), 7.12 – 7.02 (m, 1H), 4.20 (s, 2H), 3.20 – 3.09 (m, 2H), 1.23 – 0.93 (m, 0H), 0.38 – 0.25 (m, 2H), 0.29 – 0.16 (m, 2H); (M+H) ⁺ = 624	+++	141
372		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.10 (s, 1H), 7.74 – 7.65 (m, 2H), 7.36 (dt, J = 7.6, 1.5 Hz, 1H), 7.33 – 7.18 (m, 7H), 4.09 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.89 (tt, J = 9.8, 7.5 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.71 – 1.48 (m, 3H), 1.42 – 1.25 (m, 1H), 1.16 – 1.03 (m, 1H), 0.36 – 0.15 (m, 4H); (M+H) ⁺ = 563	+++	146
373		(M+H) ⁺ = 599	+++	146
374		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.44 (ddd, J = 8.5, 5.0, 2.3 Hz, 1H), 7.27 – 7.16 (m, 2H), 7.20 – 7.11 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz,	+++	146

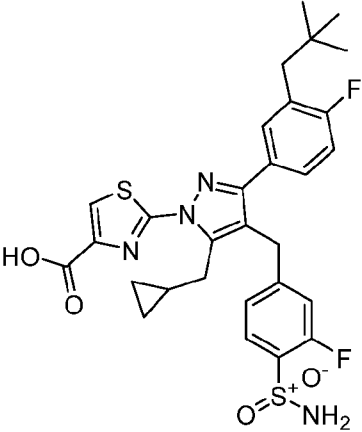
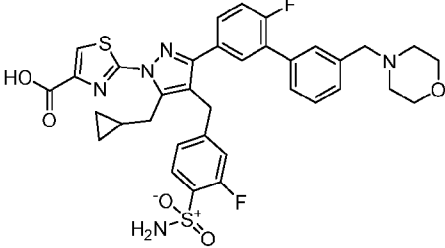
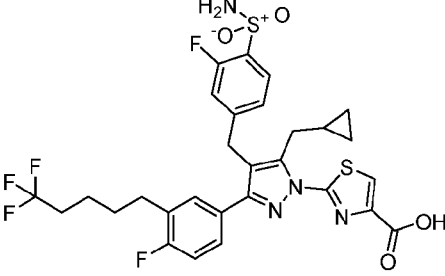
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		¹ H), 4.10 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 2.78 – 2.66 (m, 1H), 1.72 (dd, J = 9.7, 6.4 Hz, 2H), 1.61 (d, J = 11.8 Hz, 3H), 1.37 – 1.23 (m, 2H), 1.15 (s, 2H), 1.20 – 1.03 (m, 2H), 0.38 – 0.29 (m, 2H), 0.26 – 0.17 (m, 2H); (M+H) ⁺ = 613		
375		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.12 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.52 – 7.38 (m, 2H), 7.23 – 7.09 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 4.09 (s, 2H), 3.16 – 3.09 (m, 3H), 2.07 (d, J = 3.8 Hz, 2H), 1.90 – 1.79 (m, 2H), 1.85 (s, 4H), 1.69 – 1.64 (m, 3H), 1.52 (d, J = 12.9 Hz, 3H), 1.42 (d, J = 12.6 Hz, 2H), 1.18 – 1.02 (m, 1H), 0.35 – 0.24 (m, 2H), 0.25 – 0.14 (m, 2H); (M+H) ⁺ = 665	++	146
376		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.31 (s, 1H), 7.96 – 7.81 (m, 3H), 7.64 (td, J = 7.9, 5.8 Hz, 2H), 7.56 (s, 2H), 7.13 (dd, J = 11.4, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 4.17 (s, 2H), 3.18 (d, J = 6.9 Hz, 2H), 1.31 – 1.00 (m, 1H), 0.39 – 0.25 (m, 2H), 0.29 – 0.18 (m, 2H); (M+H) ⁺ = 639	+++	141

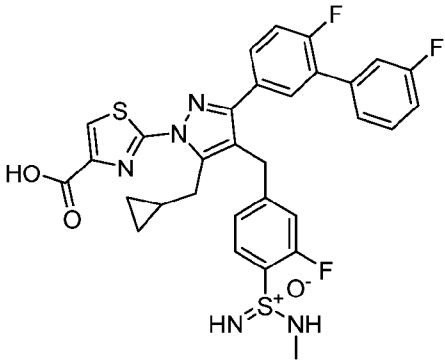
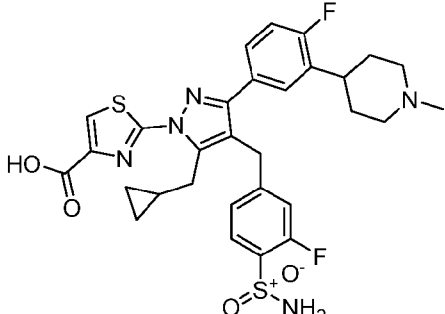
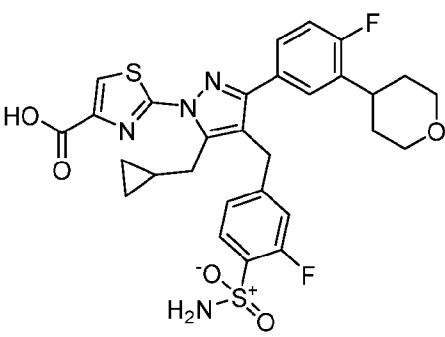
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
377		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (s, 1H), 7.69 – 7.56 (m, 3H), 7.58 (s, 2H), 7.49 (ddd, J = 8.4, 7.7, 6.2 Hz, 1H), 7.43 – 7.29 (m, 2H), 7.30 – 7.13 (m, 3H), 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.31 (s, 1H), 3.16 (d, J = 6.9 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.15 (td, J = 7.4, 5.6 Hz, 1H), 0.38 – 0.20 (m, 4H); (M+H) ⁺ = 653	-	141
378		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.27 (s, 1H), 7.67 – 7.54 (m, 1H), 7.55 (s, 2H), 7.46 – 7.36 (m, 2H), 7.22 – 7.06 (m, 2H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 5.81 – 5.66 (m, 1H), 5.00 – 4.87 (m, 2H), 4.13 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.27 – 2.17 (m, 2H), 1.24 – 1.05 (m, 1H), 0.38 – 0.26 (m, 2H), 0.29 – 0.16 (m, 2H); (M+H) ⁺ = 585	+++	146
379		(M+H) ⁺ = 613	+++	145

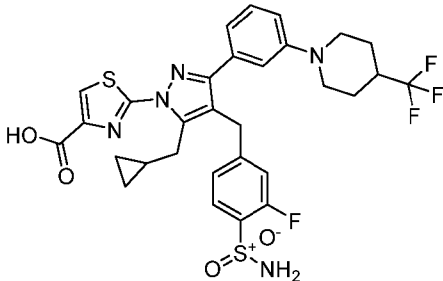
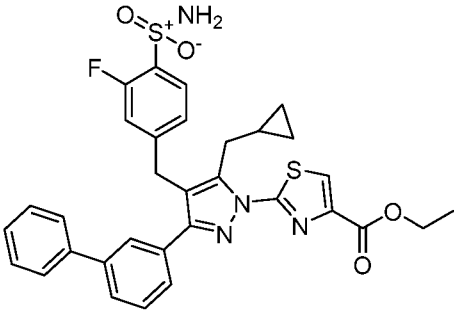
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
380		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.27 (s, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.60 – 7.47 (m, 3H), 7.32 (s, 1H), 7.29 – 7.13 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 5.91 (d, J = 16.9 Hz, 1H), 4.33 (s, 1H), 4.13 (s, 2H), 4.06 (s, 1H), 3.79 (s, 1H), 3.61 (s, 1H), 3.16 (d, J = 6.9 Hz, 2H), 2.25 (s, 1H), 2.02 (s, 1H), 2.11 – 1.75 (m, 1H), 1.22 – 1.05 (m, 1H), 0.74 (s, 3H), 0.72 (s, 1H), 0.38 – 0.28 (m, 2H), 0.26 – 0.17 (m, 2H); (M+H) ⁺ = 680	+++	145
381		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.54 (s, 2H), 7.48 – 7.30 (m, 2H), 7.21 – 7.05 (m, 2H), 7.01 (dd, J = 8.2, 1.6 Hz, 1H), 4.13 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.60 – 2.49 (m, 1H), 2.32 (dd, J = 13.2, 7.9 Hz, 1H), 1.48 (dp, J = 13.5, 6.9 Hz, 1H), 1.37 – 1.18 (m, 1H), 1.17 – 1.00 (m, 1H), 0.89 – 0.77 (m, 3H), 0.70 (d, J = 6.6 Hz, 3H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 601	+++	146

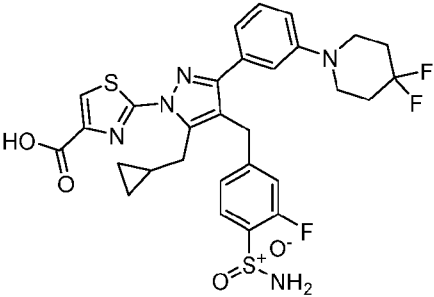
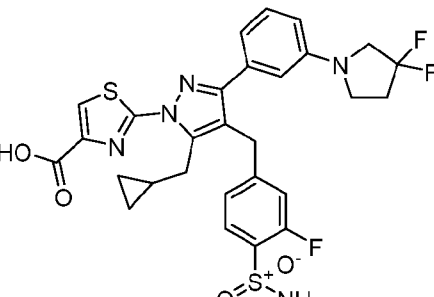
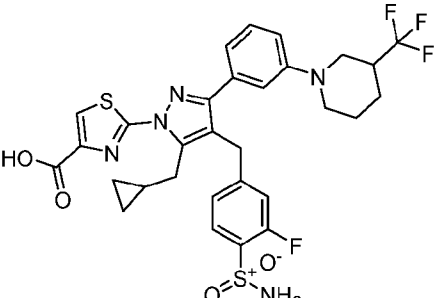
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
382		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.54 (s, 2H), 7.48 – 7.30 (m, 2H), 7.21 – 7.05 (m, 2H), 7.01 (dd, J = 8.2, 1.6 Hz, 1H), 4.13 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.60 – 2.49 (m, 1H), 2.32 (dd, J = 13.2, 7.9 Hz, 1H), 1.48 (dp, J = 13.5, 6.9 Hz, 1H), 1.37 – 1.18 (m, 1H), 1.17 – 1.00 (m, 1H), 0.89 – 0.77 (m, 3H), 0.70 (d, J = 6.6 Hz, 3H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 585	+++	146
383		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.68 – 7.58 (m, 1H), 7.56 (s, 2H), 7.46 – 7.30 (m, 2H), 7.20 – 7.06 (m, 2H), 7.03 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 4.12 (d, J = 5.3 Hz, 2H), 3.19 – 3.02 (m, 3H), 1.09–1.02 (d, J = 6.9 Hz, 6H), 0.81 (t, J = 7.3 Hz, 1H), 0.38 – 0.28 (m, 2H), 0.25 – 0.17 (m, 2H); (M+H) ⁺ = 573	+++	146

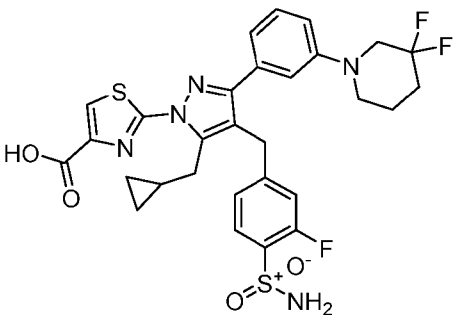
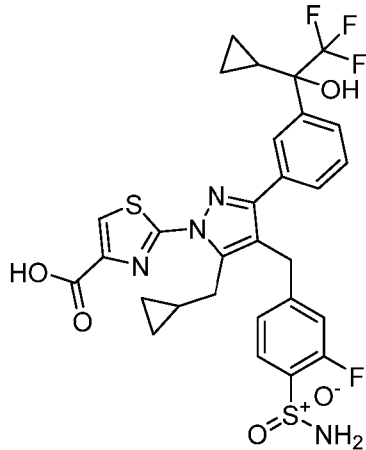
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
384		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.25 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.58 (s, 2H), 7.50 – 7.35 (m, 2H), 7.28 – 7.19 (m, 2H), 7.21 – 7.11 (m, 2H), 7.16 – 7.01 (m, 3H), 6.98 (dd, J = 8.1, 1.6 Hz, 1H), 4.35 (q, J = 7.2 Hz, 1H), 4.08 (s, 2H), 3.13 (dd, J = 7.0, 4.0 Hz, 2H), 1.41 (d, J = 7.2 Hz, 3H), 1.20 – 0.96 (m, 1H), 0.31 (dt, J = 9.1, 2.9 Hz, 2H), 0.24 – 0.15 (m, 2H); (M+H) ⁺ = 635	+++	146
385		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.38 (ddd, J = 8.5, 5.0, 2.3 Hz, 1H), 7.21 – 7.08 (m, 2H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 6.94 (dd, J = 7.4, 2.2 Hz, 1H), 4.09 (s, 2H), 3.13 (d, J = 6.9 Hz, 2H), 1.97 (tt, J = 8.5, 5.2 Hz, 1H), 1.18 – 1.04 (m, 1H), 0.94 – 0.83 (m, 2H), 0.54 – 0.40 (m, 2H), 0.36 – 0.25 (m, 2H), 0.26 – 0.15 (m, 2H); (M+H) ⁺ = 571	+++	146

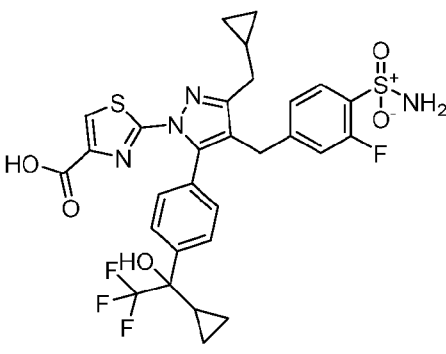
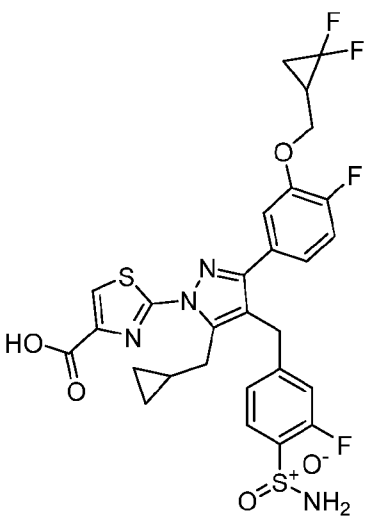
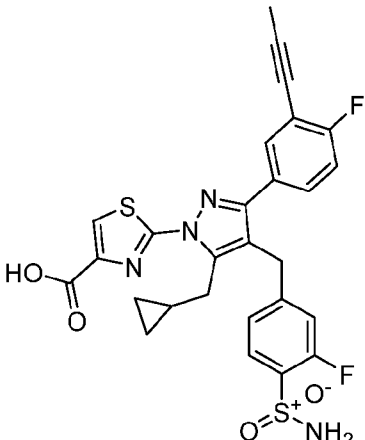
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
386		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.47 (ddd, J = 8.5, 5.0, 2.3 Hz, 1H), 7.30 – 7.14 (m, 2H), 7.12 – 6.98 (m, 2H), 4.11 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.44 (d, J = 1.6 Hz, 2H), 1.11 (ddt, J = 10.3, 7.7, 2.9 Hz, 1H), 0.80 – 0.75 (m, 9H), 0.36 – 0.25 (m, 2H), 0.27 – 0.15 (m, 2H); (M+H) ⁺ = 601	+++	146
387		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.16 (s, 1H), 9.84 (s, 1H), 8.30 (s, 1H), 7.69 – 7.56 (m, 3H), 7.58 (s, 2H), 7.56 – 7.49 (m, 4H), 7.39 (dd, J = 10.6, 8.5 Hz, 1H), 7.16 (dd, J = 11.4, 1.5 Hz, 1H), 7.06 (dd, J = 8.1, 1.6 Hz, 1H), 4.39 (s, 2H), 4.16 (s, 2H), 3.95 (d, J = 12.9 Hz, 2H), 3.60 (t, J = 11.9 Hz, 2H), 3.26 (s, 1H), 3.17 (d, J = 6.8 Hz, 2H), 3.07 (s, 1H), 1.22 – 1.04 (m, 1H), 0.38 – 0.29 (m, 2H), 0.26 – 0.17 (m, 2H); (M+H) ⁺ = 706	+++	146
388		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.43 (ddd, J = 10.1, 5.8, 2.4 Hz, 2H), 7.24 – 7.09 (m, 2H), 7.03 (dd, J = 8.2, 1.5 Hz, 1H), 4.14 (s, 2H), 3.17 (d, J = 6.9 Hz,	+++	146

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		2H), 2.72 – 2.56 (m, 3H), 2.36 – 2.17 (m, 2H), 1.65 – 1.39 (m, 5H), 1.25 – 1.05 (m, 1H), 0.40 – 0.30 (m, 2H), 0.26 – 0.18 (m, 2H); (M+H) ⁺ = 655		
389		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.29 (s, 1H), 7.74 – 7.61 (m, 2H), 7.58 – 7.44 (m, 2H), 7.37 (dd, J = 10.7, 8.6 Hz, 1H), 7.31 (ddt, J = 10.3, 2.9, 1.5 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.17 – 7.04 (m, 2H), 4.18 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 2.32 (s, 3H), 1.21 – 1.06 (m, 1H), 0.38 – 0.26 (m, 2H), 0.28 – 0.17 (m, 2H); (M+H) ⁺ = 638	++	141
390		(M+H) ⁺ = 628	+++	146
391		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.26 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.45 (ddd, J = 8.5, 5.0, 2.2 Hz, 1H), 7.31 (dd, J = 7.3, 2.3 Hz, 1H), 7.23 – 7.09 (m, 2H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.12 (s, 2H), 3.89 (dt, J = 11.3, 2.9 Hz, 2H), 3.39 (td, J = 11.2, 3.5 Hz, 2H), 3.16 (d, J =	+++	146

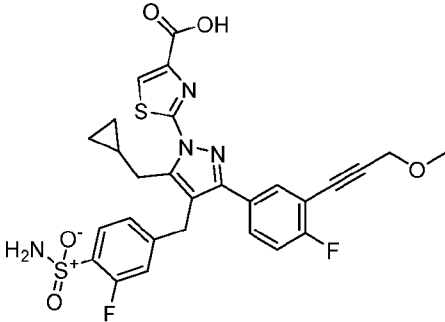
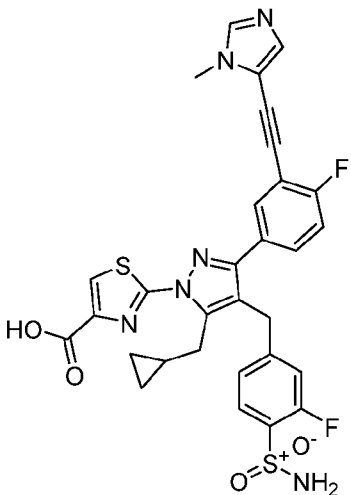
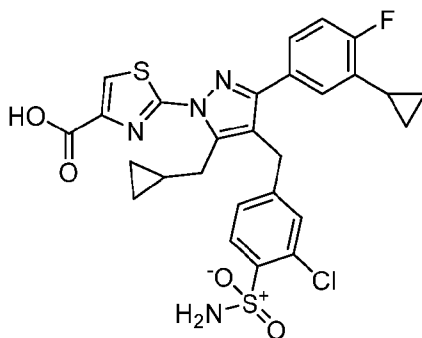
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		6.9 Hz, 2H), 2.98 (tt, J = 10.2, 5.0 Hz, 1H), 1.50 (td, J = 11.4, 10.3, 4.0 Hz, 4H), 1.25 – 1.00 (m, 1H), 0.38 – 0.29 (m, 2H), 0.30 – 0.17 (m, 2H); (M+H) ⁺ = 615		
392		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.27 (s, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.24 (dd, J = 8.3, 7.6 Hz, 1H), 7.15 (dd, J = 11.3, 1.6 Hz, 1H), 7.05 (dd, J = 8.2, 1.6 Hz, 1H), 7.03 – 6.92 (m, 2H), 6.85 (t, J = 1.9 Hz, 1H), 4.10 (s, 2H), 3.48–3.3 (m, 1H), 3.14 (d, J = 6.9 Hz, 2H), 2.68 – 2.53 (m, 2H), 2.47 – 2.27 (m, 2H), 1.80 (d, J = 12.4 Hz, 2H), 1.45 (qd, J = 12.4, 4.0 Hz, 2H), 1.19 – 1.04 (m, 1H), 0.36 – 0.28 (m, 2H), 0.23 – 0.16 (m, 2H); (M+H) ⁺ = 664	+++	145
393		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.35 (s, 1H), 7.72 – 7.64 (m, 2H), 7.68 – 7.54 (m, 2H), 7.59 (s, 2H), 7.55 – 7.30 (m, 6H), 7.21 (dd, J = 11.4, 1.6 Hz, 1H), 7.10 (dd, J = 8.1, 1.6 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.18 (s, 2H), 3.29 (s, 2H), 3.18 (d, J = 6.9 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.23 – 1.08 (m, 1H), 0.39 – 0.28 (m, 2H), 0.32 – 0.21 (m, 2H); (M+H) ⁺ = 617	-	141

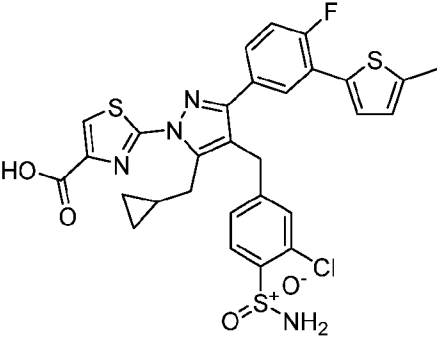
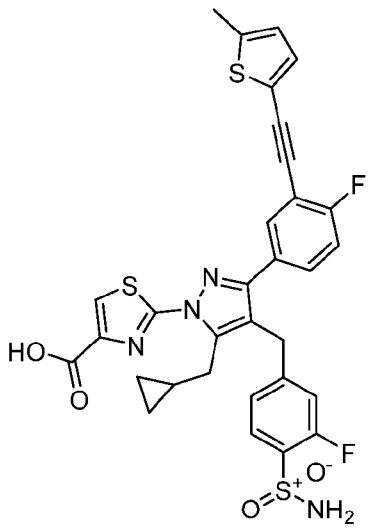
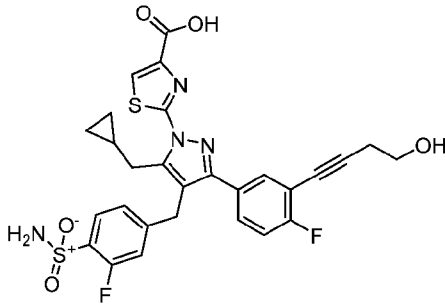
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
394		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.10 (s, 1H), 8.27 (s, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.59 (s, 2H), 7.25 (dd, J = 8.3, 7.6 Hz, 1H), 7.16 (dd, J = 11.4, 1.6 Hz, 1H), 7.10 – 6.96 (m, 3H), 6.87 (dd, J = 2.6, 1.5 Hz, 1H), 4.10 (s, 2H), 3.18 – 3.09 (m, 6H), 1.95 (tt, J = 14.1, 5.7 Hz, 4H), 1.23 – 1.00 (m, 1H), 0.37 – 0.27 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 632	+++	141
395		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.26 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 6.90 (dt, J = 7.7, 1.1 Hz, 1H), 6.70 – 6.50 (m, 2H), 4.12 (s, 2H), 3.59 (t, J = 13.3 Hz, 2H), 3.4 – 3.29 (m, 2H), 2.31 – 2.29 (m, 2H), 3.14 (d, J = 6.9 Hz, 2H), 1.21 – 1.02 (m, 1H), 0.38 – 0.26 (m, 2H), 0.24 – 0.14 (m, 2H); (M+H) ⁺ = 618	+	141
396		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.27 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.29 – 7.20 (m, 1H), 7.13 (dd, J = 11.4, 1.6 Hz, 1H), 7.08 – 6.90 (m, 4H), 4.11 (s, 2H), 3.36 (d, J = 12.8 Hz, 1H), 3.13 (d, J = 6.9 Hz, 2H), 2.68 (dd, J =	+++	141

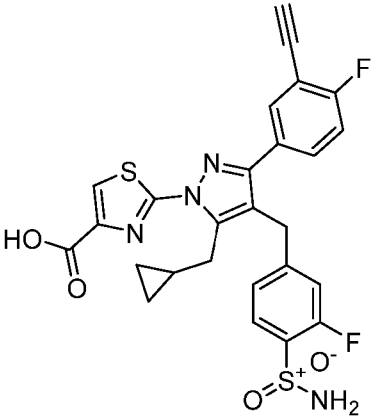
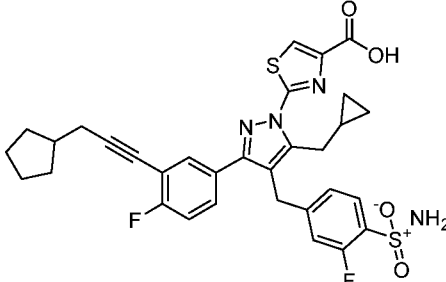
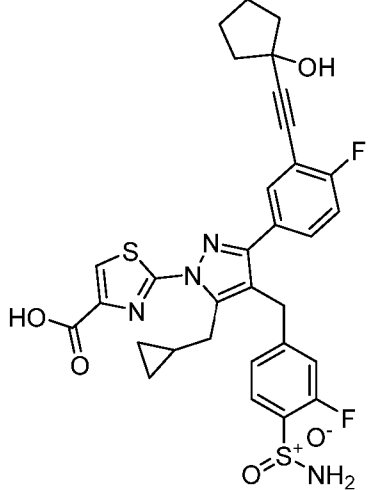
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		12.1, 11.0 Hz, 1H), 2.62 – 2.49 (m, 3H), 2.01 – 1.75 (m, 0H), 1.69 (d, J = 12.9 Hz, 1H), 1.57 – 1.32 (m, 3H), 1.19 – 1.04 (m, 1H), 0.36 – 0.27 (m, 2H), 0.24 – 0.15 (m, 2H); (M+H) ⁺ = 664		
397		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 8.27 (s, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.24 (dd, J = 8.2, 7.6 Hz, 1H), 7.18 – 6.94 (m, 4H), 6.89 (dd, J = 2.6, 1.5 Hz, 1H), 4.11 (s, 2H), 3.37 (t, J = 11.9 Hz, 2H), 3.19 – 3.08 (m, 2H), 3.00 (t, J = 5.5 Hz, 2H), 1.98 (tt, J = 13.8, 6.4 Hz, 2H), 1.72 – 1.52 (m, 2H), 1.18 – 1.04 (m, 1H), 0.37 – 0.25 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 632	+++	141
398		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.27 (s, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.57 – 7.50 (m, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.12 – 6.99 (m, 2H), 6.11 (s, 1H), 4.12 (s, 1H), 3.14 (d, J = 6.8 Hz, 2H), 1.39 (tt, J = 8.4, 5.3 Hz, 1H), 1.18 – 1.04 (m, 1H), 0.70 (dq, J = 10.0, 5.1 Hz, 1H), 0.54 – 0.42 (m, 1H), 0.37 – 0.09 (m, 5H); (M+H) ⁺ = 651	+++	141

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
399		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.87 (s, 1H), 8.21 (s, 1H), 7.70 – 7.63 (m, 2H), 7.63 – 7.56 (m, 1H), 7.56 (s, 2H), 7.49 – 7.36 (m, 2H), 7.06 – 6.95 (m, 2H), 6.03 (s, 1H), 3.85 (s, 2H), 2.42 (d, J = 6.8 Hz, 2H), 1.48 (tt, J = 8.3, 5.3 Hz, 1H), 1.01 – 0.86 (m, 2H), 0.67 (dq, J = 10.0, 5.1 Hz, 1H), 0.49 – 0.33 (m, 4H), 0.27 – 0.04 (m, 5H); (M+H) ⁺ = 651	+	141
400		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.27 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.31 – 7.09 (m, 4H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.16 – 4.05 (m, 3H), 3.85 (ddd, J = 10.6, 8.6, 1.6 Hz, 1H), 3.15 (d, J = 6.7 Hz, 2H), 2.29 – 1.99 (m, 0H), 1.70 (ttdd, J = 12.0, 8.0, 4.9 Hz, 2H), 1.43 (dtd, J = 13.8, 7.8, 4.2 Hz, 1H), 1.26 – 0.93 (m, 1H), 0.37 – 0.16 (m, 4H); (M+H) ⁺ = 637	+++	120
401		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.68 – 7.46 (m, 5H), 7.28 (dd, J = 9.5, 8.7 Hz, 1H), 7.12 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 4.12 (s, 2H), 3.14 (d, J = 6.2 Hz, 3H), 2.07 (s, 3H), 1.11 (dddd, J = 12.5, 8.0, 4.9, 1.9 Hz, 1H), 0.37 – 0.27 (m, 2H),	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		0.27 – 0.16 (m, 2H); (M+H) ⁺ = 569		
402		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.69 – 7.44 (m, 6H), 7.27 (dd, J = 9.4, 8.7 Hz, 1H), 7.15 (dd, J = 11.4, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.13 (s, 2H), 3.16 (d, J = 6.8 Hz, 2H), 1.27 (s, 9H), 1.18 – 0.96 (m, 1H), 0.37 – 0.27 (m, 2H), 0.27 – 0.16 (m, 2H); (M+H) ⁺ = 611	+++	145
403		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.16 (s, 1H), 8.29 (s, 1H), 7.78 – 7.68 (m, 2H), 7.68 – 7.58 (m, 2H), 7.56 (s, 2H), 7.47 (dd, J = 3.7, 1.2 Hz, 1H), 7.37 (dd, J = 9.4, 8.7 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 4.16 (s, 2H), 3.16 (d, J = 7.0 Hz, 2H), 1.20 – 1.05 (m, 1H), 0.38 – 0.27 (m, 2H), 0.27 – 0.17 (m, 2H); (M+H) ⁺ = 637	+++	145

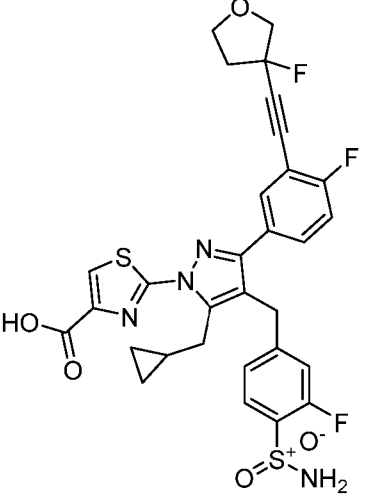
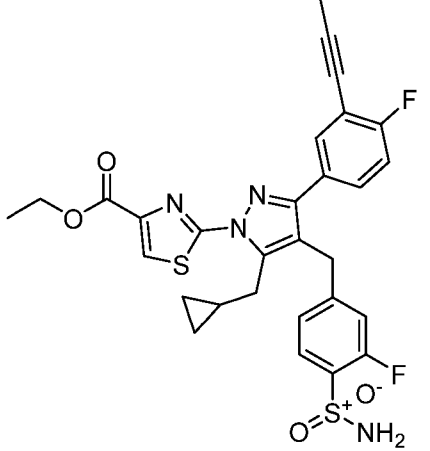
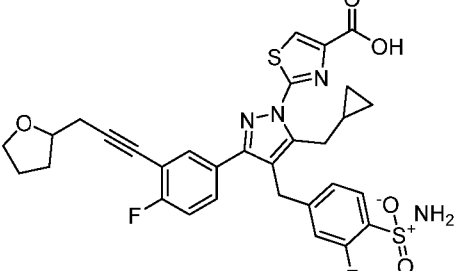
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
404		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.27 (s, 1H), 7.68 – 7.56 (m, 3H), 7.56 (s, 1H), 7.38 – 7.29 (m, 1H), 7.13 (dd, J = 11.3, 1.5 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.34 (s, 2H), 4.14 (s, 2H), 3.31 (s, 3H), 3.15 (d, J = 6.5 Hz, 2H), 1.33 – 0.83 (m, 0H), 0.37 – 0.27 (m, 2H), 0.24 – 0.16 (m, 2H); (M+H) ⁺ = 599	+++	145
405		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 7.74 – 7.60 (m, 3H), 7.57 (s, 2H), 7.43 – 7.34 (m, 2H), 7.16 (dd, J = 11.3, 1.6 Hz, 1H), 7.04 (dd, J = 8.2, 1.6 Hz, 1H), 4.16 (s, 2H), 3.67 (d, J = 0.5 Hz, 3H), 3.16 (d, J = 6.9 Hz, 2H), 1.26 – 0.96 (m, 1H), 0.38 – 0.28 (m, 2H), 0.25 – 0.17 (m, 2H); (M+H) ⁺ = 635	+++	145
406		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.26 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.52 (s, 2H), 7.42 – 7.31 (m, 2H), 7.21 – 7.11 (m, 2H), 6.94 (dd, J = 7.4, 2.2 Hz, 1H), 4.08 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 1.97 (tt, J = 8.4, 5.2 Hz, 1H), 1.19 – 1.04 (m, 2H), 0.96 – 0.83 (m, 2H), 0.54 – 0.40 (m, 2H), 0.37 – 0.26 (m, 2H), 0.26 – 0.15 (m, 2H);	+++	146

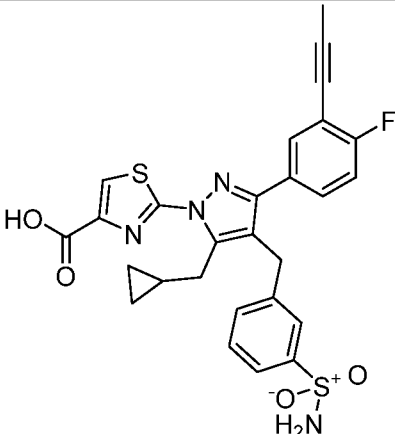
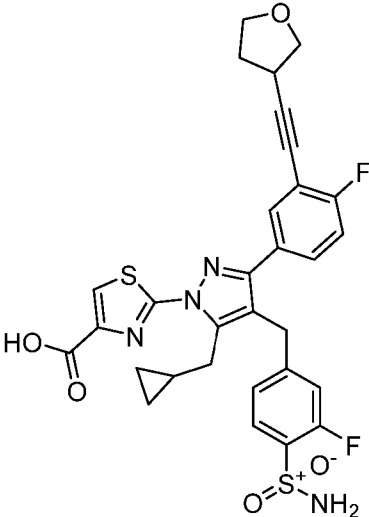
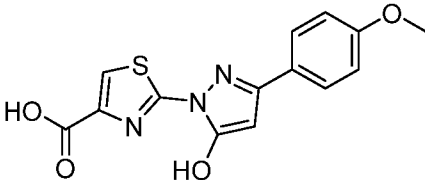
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(M+H) ⁺ = 588		
407		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.28 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.61 – 7.43 (m, 6H), 7.35 (dd, J = 11.3, 8.6 Hz, 1H), 7.22 – 7.10 (m, 2H), 6.82 (dt, J = 3.6, 1.1 Hz, 1H), 4.15 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 1.20 – 0.98 (m, 1H), 0.38 – 0.29 (m, 2H), 0.28 – 0.17 (m, 2H); (M+H) ⁺ = 644	+++	145
408		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.29 (s, 1H), 7.72 (dd, J = 6.9, 2.3 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.56 (s, 2H), 7.36 (dd, J = 9.4, 8.7 Hz, 1H), 7.27 (d, J = 3.4 Hz, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 6.83 (dt, J = 3.4, 1.1 Hz, 1H), 4.16 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.20 – 1.05 (m, 1H), 0.38 – 0.27 (m, 2H), 0.27 – 0.16 (m, 2H); (M+H) ⁺ = 651	+++	145
409		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.28 (s, 1H), 7.68 – 7.57 (m, 2H), 7.56 (s, 2H), 7.52 (ddd, J = 8.7, 5.0, 2.3 Hz, 1H), 7.28 (dd, J = 9.4, 8.7 Hz, 1H), 7.12 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.2, 1.6 Hz, 1H), 4.89 (d, J = 6.3 Hz, 1H), 4.13 (s, 2H), 3.57 (q, J = 6.6 Hz, 2H), 3.15 (d, J = 6.7 Hz, 2H), 2.58 (t, J	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		= 6.8 Hz, 2H), 1.11 (dddd, J = 15.0, 10.0, 5.0, 2.2 Hz, 1H), 0.37 – 0.27 (m, 2H), 0.24 – 0.16 (m, 2H); (M+H) ⁺ = 599		
410		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.29 (s, 1H), 7.72 – 7.57 (m, 3H), 7.55 (s, 2H), 7.33 (t, J = 9.0 Hz, 1H), 7.12 (dd, J = 11.4, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.53 (s, 1H), 4.14 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.18 – 1.04 (m, 1H), 0.37 – 0.27 (m, 2H), 0.24 – 0.16 (m, 2H); (M+H) ⁺ = 556	+++	145
411		(M+H) ⁺ = 637	+++	145
412		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.09 (s, 1H), 7.68 – 7.51 (m, 4H), 7.30 (dd, J = 9.4, 8.6 Hz, 1H), 7.13 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 5.39 (s, 1H), 4.13 (s, 2H), 3.18 – 3.11 (m, 2H), 1.96 – 1.79 (m, 4H), 1.79 – 1.59 (m, 4H), 1.10 (s, 1H), 0.36 – 0.15 (m, 4H); (M+H) ⁺ = 639	+++	145

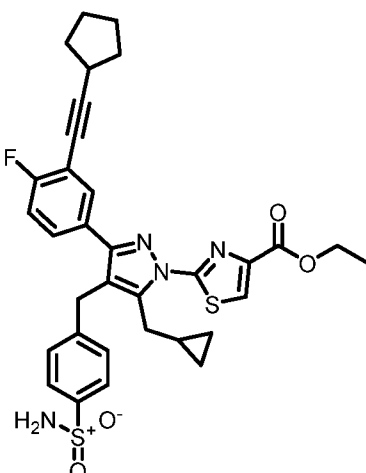
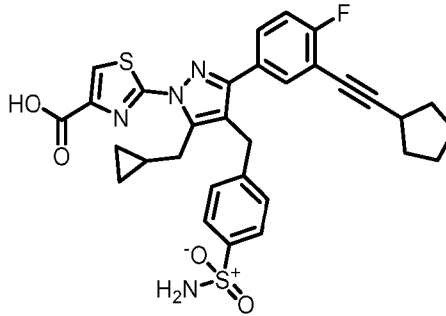
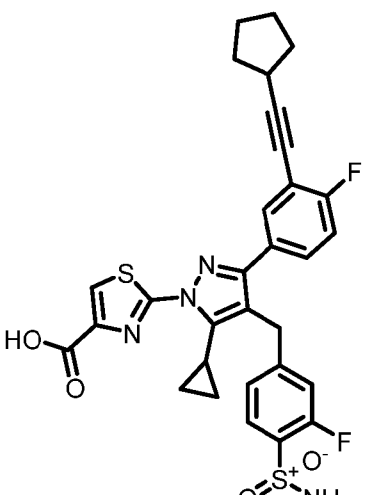
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
413		(M+H) ⁺ = 641	+++	145
414		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.30 (s, 1H), 7.76 (dd, J = 6.7, 2.3 Hz, 1H), 7.72 – 7.58 (m, 2H), 7.57 (s, 2H), 7.39 (t, J = 9.0 Hz, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.2, 1.6 Hz, 1H), 4.99 – 4.81 (m, 4H), 4.15 (s, 2H), 3.16 (d, J = 7.2 Hz, 2H), 1.20 – 1.05 (m, 1H), 0.38 – 0.27 (m, 2H), 0.27 – 0.17 (m, 2H); (M+H) ⁺ = 629	+++	145
415		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.18 (s, 1H), 7.74 – 7.53 (m, 4H), 7.39 – 7.26 (m, 1H), 7.13 (dd, J = 11.4, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 6.69 (s, 1H), 4.78 – 4.71 (m, 2H), 4.62 – 4.55 (m, 2H), 4.15 (s, 2H), 3.15 (d, J = 6.5 Hz, 2H), 1.18 – 1.03 (m, 1H), 0.37 – 0.25 (m, 2H), 0.25 – 0.13 (m, 2H); (M+H) ⁺ = 627	+++	145

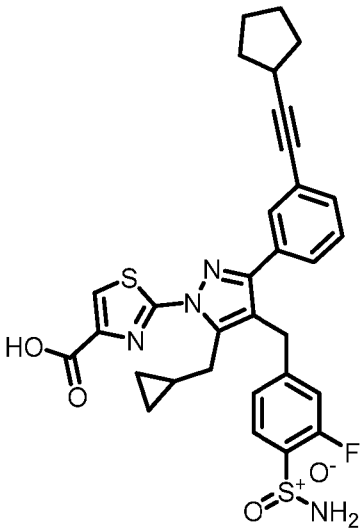
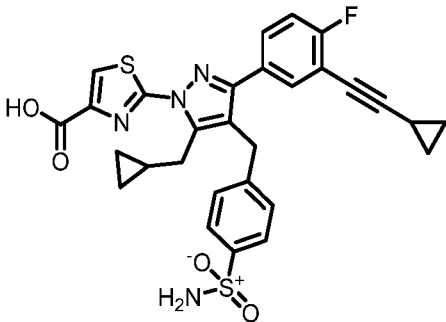
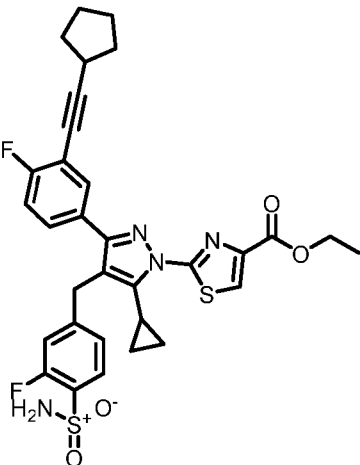
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
416		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.29 (s, 1H), 7.68 – 7.58 (m, 2H), 7.58 – 7.54 (m, 3H), 7.36 – 7.26 (m, 1H), 7.15 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.72 (d, J = 5.5 Hz, 2H), 4.43 (d, J = 5.7 Hz, 2H), 4.14 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.62 (s, 3H), 1.12 (s, 1H), 0.38 – 0.28 (m, 2H), 0.25 – 0.17 (m, 2H); (M+H) ⁺ = 625	+++	145
417		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.20 (s, 1H), 10.36 (s, 1H), 8.32 (s, 1H), 7.79 – 7.55 (m, 5H), 7.40 (t, J = 9.0 Hz, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.04 (dd, J = 8.2, 1.6 Hz, 1H), 4.40 (s, 2H), 4.16 (s, 2H), 3.17 (d, J = 6.9 Hz, 2H), 1.96 (s, 4H), 1.23 – 1.00 (m, 0H), 0.39 – 0.29 (m, 2H), 0.26 – 0.18 (m, 2H); (M+H) ⁺ = 638	+++	145
418		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.27 (s, 1H), 7.68 – 7.58 (m, 3H), 7.57 (d, J = 4.7 Hz, 2H), 7.37 – 7.27 (m, 1H), 7.13 (dd, J = 11.5, 1.5 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 5.92 (s, 1H), 4.14 (s, 2H), 3.91 – 3.83 (m, 2H), 3.83 – 3.72 (m, 2H), 3.15 (d, J = 6.7 Hz, 2H), 2.24 – 2.13 (m, 2H), 0.98 (s, 1H), 0.57 (s, 1H),	+++	145

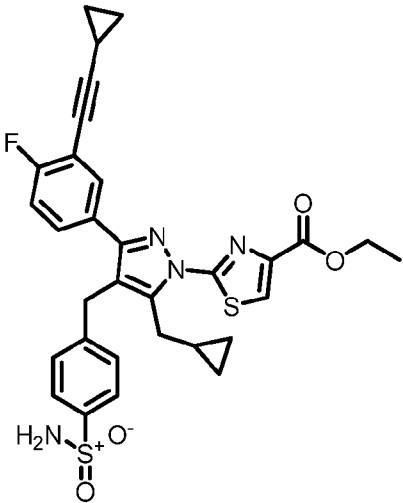
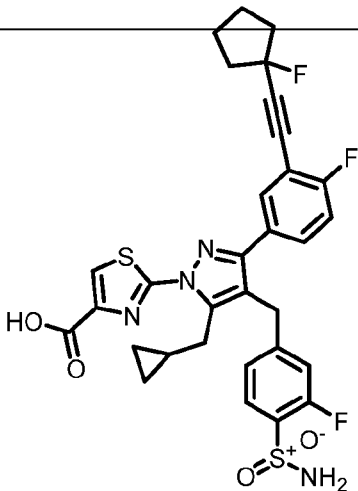
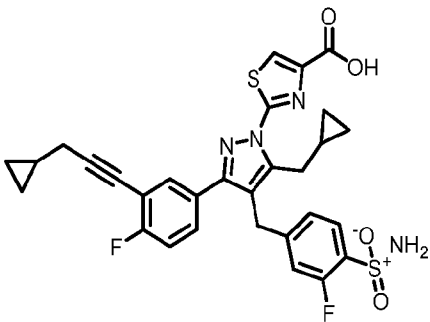
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 641		
419		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.17 (s, 1H), 8.29 (s, 1H), 7.72 – 7.59 (m, 3H), 7.57 (s, 2H), 7.37 (t, J = 9.3 Hz, 1H), 7.15 (dd, J = 11.4, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 4.23 – 4.10 (m, 3H), 4.00 – 3.85 (m, 3H), 3.16 (d, J = 7.0 Hz, 2H), 2.61 – 2.33 (m, 13H), 1.12 (dddd, J = 13.0, 8.0, 4.9, 1.9 Hz, 1H), 0.38 – 0.17 (m, 4H); (M+H) ⁺ = 643	+++	145
420		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.51 (ddd, J = 8.6, 5.0, 2.3 Hz, 1H), 7.28 (dd, J = 9.4, 8.7 Hz, 1H), 7.13 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.2, 1.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.07 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.18 – 1.07 (m, 1H), 0.38 – 0.29 (m, 2H), 0.25 – 0.17 (m, 2H); (M+H) ⁺ = 597	+	145
421		(M+H) ⁺ = 639	+++	145

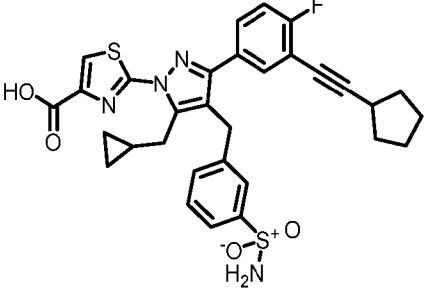
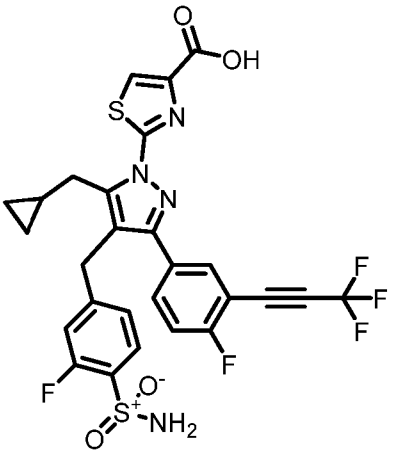
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
422		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.27 (s, 1H), 7.65 – 7.38 (m, 5H), 7.34 – 7.21 (m, 4H), 4.11 (s, 2H), 3.14 (dd, J = 5.8, 3.3 Hz, 2H), 2.06 (s, 3H), 1.17 – 1.03 (m, 1H), 0.36 – 0.25 (m, 2H), 0.25 – 0.14 (m, 2H); (M+H) ⁺ = 551	+++	145
423		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.29 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.60 – 7.51 (m, 4H), 7.34 – 7.24 (m, 1H), 7.14 (dd, J = 11.4, 1.6 Hz, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 4.13 (s, 2H), 3.95 (dd, J = 8.1, 7.3 Hz, 1H), 3.87 – 3.68 (m, 2H), 3.58 (dd, J = 8.1, 6.5 Hz, 1H), 3.34 – 3.22 (m, 6H), 3.15 (d, J = 6.9 Hz, 2H), 2.25 (dddd, J = 12.1, 8.5, 7.4, 6.0 Hz, 1H), 1.92 (ddt, J = 12.1, 7.8, 6.6 Hz, 1H), 1.12 (s, 1H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 625	+++	145
424		¹ H NMR (400 MHz, DMSO-d ₆) δ 12.98 (s, 1H), 8.14 (s, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.05 (s, 2H), 5.96 (s, 1H), 3.81 (s, 3H); (M+H) ⁺ = 318	-	147

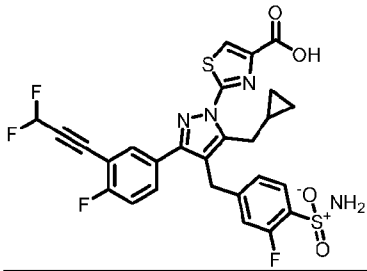
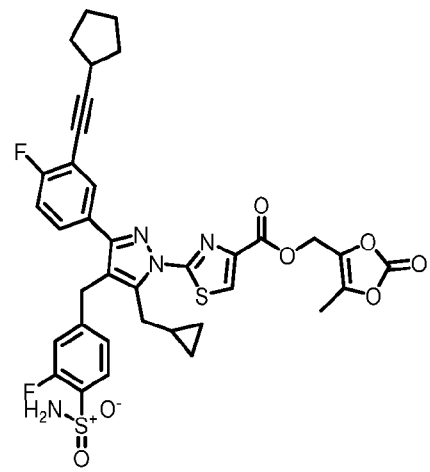
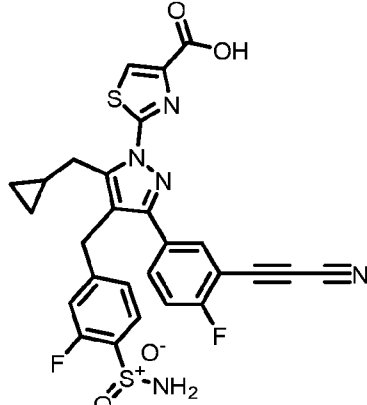
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
425		(M+H) ⁺ = 306	-	147
426		¹ H NMR (400 MHz, DMSO-d ₆) δ 6.09 – 7.99 (m, 2H), 7.92 (s, 1H), 7.41 – 7.30 (m, 2H); (M+H) ⁺ = 358	+	150
427		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.25 (s, 1H), 8.40 (s, 1H), 8.05 – 7.93 (m, 4H), 7.63 – 7.52 (m, 2H); (M+H) ⁺ = 374	+	150
428		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.34 (d, J = 0.5 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.57 – 7.44 (m, 4H), 7.37 – 7.31 (m, 2H), 7.13 (dd, J = 11.3, 1.5 Hz, 1H), 7.04 (dd, J = 8.2, 1.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.13 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.82 (p, J = 7.3 Hz, 1H), 2.00 – 1.87 (m, 2H), 1.75 – 1.47 (m, 6H), 1.35 – 1.28 (m, 2H), 1.26 (d, J = 19.9 Hz, 1H), 1.18 – 1.07 (m, 1H), 0.38 – 0.28 (m, 2H), 0.28 – 0.19 (m, 2H); (M+H) ⁺ = 633	-	145

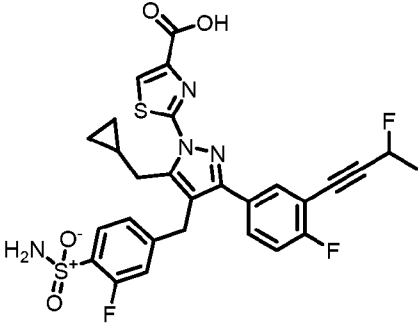
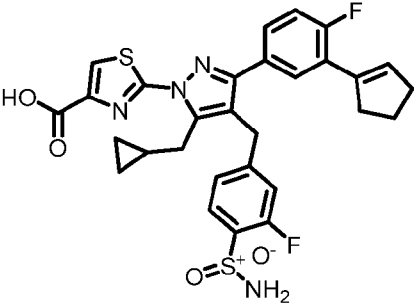
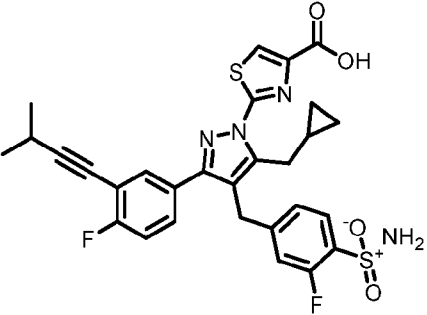
Cmpd ID	Structure	Compound name and physical data		Inhibitory activity IC ₅₀ (μM)	Example Method
429		(M+H) ⁺ = 633		+	145
430		(M+H) ⁺ = 605		+++	145
431		(M+H) ⁺ = 609		+++	145

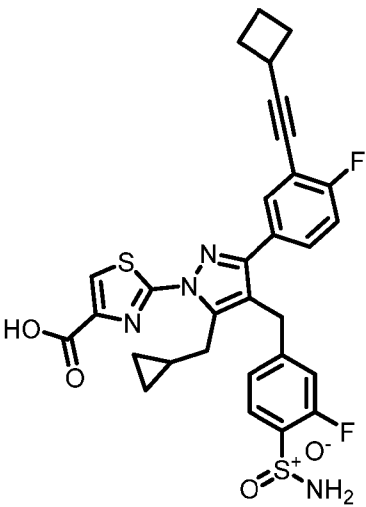
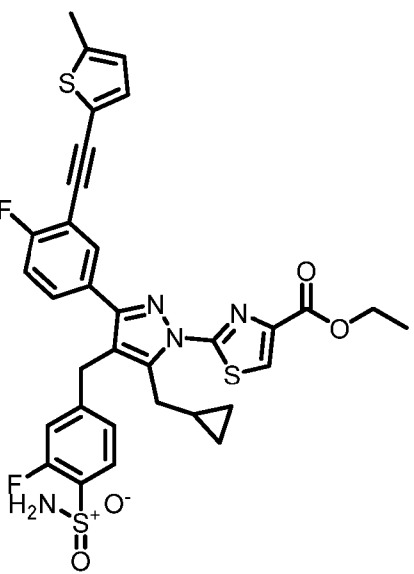
Cmpd ID	Structure	Compound name and physical data		Inhibitory activity IC ₅₀ (μM)	Example Method
432		(M+H) ⁺ = 605		+++	145
433		(M+H) ⁺ = 577		+++	145
434		(M+H) ⁺ = 637		+	145

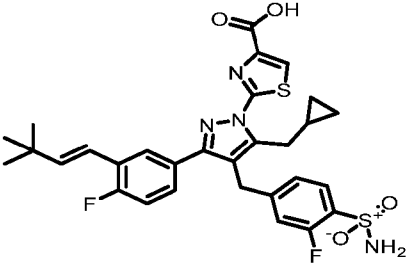
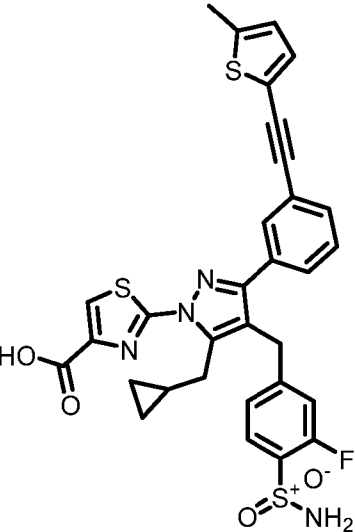
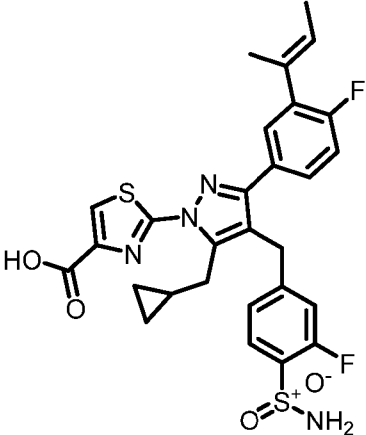
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
435		(M+H) ⁺ = 605	+	145
436		(M+H) ⁺ = 641	+++	145
437		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.29 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.29 (dd, J = 9.4, 8.5 Hz, 1H), 7.13 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 4.13 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.51 (d, J = 5.9 Hz, 2H), 1.11 (dddd, J = 15.0, 10.0, 5.1, 2.2 Hz, 1H), 1.05 – 0.92 (m, 1H), 0.51	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		– 0.41 (m, 2H), 0.37 – 0.28 (m, 2H), 0.27 – 0.16 (m, 4H); (M+H) ⁺ = 609		
438		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.28 (s, 1H), 7.61 (dt, J = 7.9, 1.4 Hz, 1H), 7.56 – 7.38 (m, 4H), 7.32 (dt, J = 7.7, 1.4 Hz, 1H), 7.27 (s, 2H), 7.24 (d, J = 8.9 Hz, 1H), 4.10 (s, 2H), 3.15 (d, J = 6.8 Hz, 2H), 2.87 (p, J = 7.2 Hz, 1H), 2.02 – 1.49 (m, 8H), 1.10 (tdd, J = 12.0, 7.1, 2.4 Hz, 1H), 0.37 – 0.27 (m, 2H), 0.23 – 0.14 (m, 2H); (M+H) ⁺ = 605	++	145
439		(M+H) ⁺ = 641	++	145

Cmpd ID	Structure	Compound name and physical data		Inhibitory activity IC ₅₀ (μM)	Example Method
440		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.83 (dd, J = 6.7, 2.3 Hz, 1H), 7.72 (ddd, J = 8.7, 5.1, 2.3 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.55 (s, 2H), 7.42 (t, J = 9.1 Hz, 1H), 7.15 – 7.07 (m, 1H), 7.06 – 6.97 (m, 1H), 4.16 (s, 2H), 3.16 (d, J = 7.0 Hz, 2H), 1.18 – 1.02 (m, 1H), 0.36 – 0.28 (m, 2H), 0.24 – 0.17 (m, 2H); (M+H) ⁺ = 606		+++	145
441		¹ H NMR (400 MHz, Chloroform-d) δ 8.03 (s, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.51 (dd, J = 6.8, 2.3 Hz, 1H), 7.33 (ddd, J = 8.6, 4.9, 2.3 Hz, 1H), 7.08 – 6.90 (m, 3H), 5.30 (s, 2H), 5.10 (s, 2H), 4.99 (s, 2H), 4.05 (s, 2H), 3.18 (d, J = 6.8 Hz, 2H), 2.85 (p, J = 7.4 Hz, 1H), 2.25 (s, 3H), 2.12 – 1.93 (m, 1H), 1.86 – 1.54 (m, 7H), 1.17 – 1.02 (m, 1H), 0.47 – 0.39 (m, 2H), 0.28 – 0.22 (m, 2H); (M+H) ⁺ = 735		-	145
442		(M+H) ⁺ = 580		+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
443		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.34 – 12.89 (m, 1H), 8.29 (s, 1H), 7.71 – 7.58 (m, 3H), 7.56 (s, 2H), 7.36 (t, J = 8.9 Hz, 1H), 7.18 – 6.96 (m, 2H), 5.77 – 5.53 (m, 1H), 4.14 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.60 (dd, J = 23.0, 6.5 Hz, 3H), 1.12 (tq, J = 9.8, 3.4, 2.4 Hz, 1H), 0.38 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 601	+++	145
444		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.28 (s, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.35 (dd, J = 7.6, 2.3 Hz, 1H), 7.29 – 7.01 (m, 3H), 6.25 (p, J = 2.1 Hz, 1H), 4.12 (s, 2H), 3.18 – 3.11 (m, 2H), 2.49 – 2.38 (m, 4H), 1.85 (p, J = 7.6 Hz, 2H), 1.12 (tdd, J = 11.3, 6.4, 2.0 Hz, 1H), 0.37 – 0.27 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 597	+++	145
445		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.60 – 7.48 (m, 4H), 7.28 (t, J = 9.0 Hz, 1H), 7.14 (dd, J = 11.4, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 4.12 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.82 (hept, J = 6.8 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H), 1.12 (tq, J = 9.9, 3.5, 2.2 Hz, 1H), 0.38 – 0.28	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(m, 2H), 0.25 – 0.17 (m, 2H); (M+H) ⁺ = 597		
446		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.14 (s, 1H), 8.29 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.58 – 7.49 (m, 4H), 7.28 (dd, J = 9.5, 8.3 Hz, 1H), 7.14 (dd, J = 11.3, 1.6 Hz, 1H), 7.03 (dd, J = 8.2, 1.6 Hz, 1H), 4.13 (s, 2H), 3.36 – 3.23 (m, 1H), 3.15 (d, J = 6.6 Hz, 2H), 2.34 – 2.23 (m, 2H), 2.19 – 2.07 (m, 2H), 2.01 – 1.81 (m, 2H), 1.19 – 1.04 (m, 1H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); (M+H) ⁺ = 609	+++	145
447		¹ H NMR (400 MHz, DMSO-d ₆) δ 8.37 (s, 1H), 7.72 (dd, J = 6.9, 2.3 Hz, 1H), 7.69 – 7.51 (m, 4H), 7.36 (t, J = 9.0 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.15 (dd, J = 11.3, 1.6 Hz, 1H), 7.04 (dd, J = 8.2, 1.6 Hz, 1H), 6.83 (dt, J = 3.6, 1.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.16 (s, 2H), 3.16 (d, J = 6.9 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.19 – 1.04 (m, 1H), 0.40 – 0.29 (m, 2H), 0.27 – 0.19 (m, 2H); (M+H) ⁺ = 679	-	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
448		(M+H) ⁺ = 613	+++	145
449		¹ H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.29 (s, 1H), 7.69 – 7.60 (m, 2H), 7.59 – 7.47 (m, 4H), 7.42 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 3.6 Hz, 1H), 7.14 (dd, J = 11.3, 1.5 Hz, 1H), 7.04 (dd, J = 8.1, 1.5 Hz, 1H), 6.81 (dd, J = 3.6, 1.3 Hz, 1H), 4.16 (s, 2H), 3.16 (d, J = 7.1 Hz, 2H), 2.47 – 2.44 (m, 3H), 1.13 (dq, J = 14.8, 7.2, 5.0 Hz, 1H), 0.38 – 0.28 (m, 2H), 0.26 – 0.15 (m, 2H); (M+H) ⁺ = 633	+++	145
450		(M+H) ⁺ = 585	+++	145

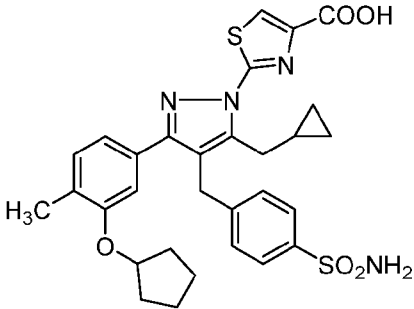
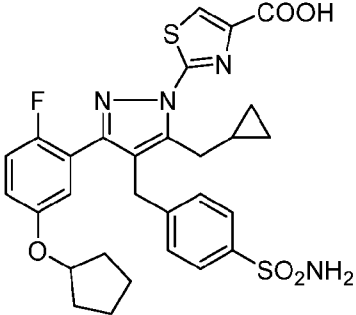
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
451		2-(5-hydroxy-3-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d6-DMSO) δ 8.19 (s, 1H), 8.09 (d, 2H, J = 1.6 Hz), 8.00 (d, 1H, J = 8Hz), 7.86 (d, 1H, J = 8Hz), 7.63-7.51 (m, 6H), 7.12 (d, 1H, J = 8Hz), 3.69 (s, 2H); MS (ES) 506.9 (M+H) ⁺ LCMS RT = 0.88 min.	+	Example 69
452		2-(3-(3,4-difluorophenyl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d6-DMSO) δ 8.18 (s, 1H), 7.85 (d, 2H, J = 8.4 Hz), 7.56 (m, 1H), 7.45-7.41 (m, 4H), 3.99 (s, 2H); MS (ES) 492.9 (M+H) ⁺ LCMS RT = 0.88 min.	++	Example 70
453		2-(5-hydroxy-3-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, TFA: VU0657478 (PC-6-098); MS (ES) 457.9 (M+H) ⁺ LCMS RT = 0.30 min.	+	Example 71

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
454		2-(3-(6-fluoronaphthalen-1-yl)-5-hydroxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d6-DMSO) δ 8.20 (m, 2H), 7.88 (d, 2H, J = 8 Hz), 7.70-7.55 (m, 5H), 7.32 (m, 1H), 7.12 (d, 1H, J = 8Hz), 3.69 (s, 2H); MS (ES) 524.9 (M+H) ⁺ LCMS RT = 0.94 min.	+	Example 72
455		2-(3-(3,4-difluorophenyl)-5-methoxy-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d6-DMSO) δ 8.20 (s, 1H), 7.81 (d, 2H, J = 8 Hz), 7.54-7.50 (m, 2H), 7.39-7.36 (m, 3H), 3.69 (s, 2H), 3.49 (s, 3H); MS (ES) 506.9 (M+H) ⁺ LCMS RT = 0.89 min.	++	Example 73
456		2-(3-(6-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 565.0 (M+H) ⁺ LCMS RT = 1.08 min.	+++	Example 85

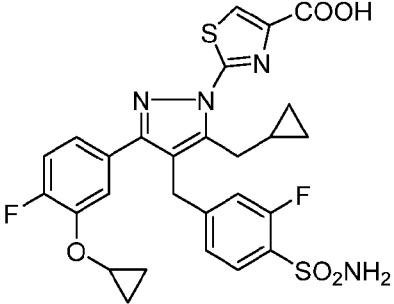
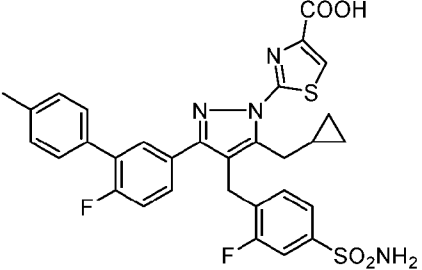
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
457		2-(3-(3'-chloro-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 568.9 (M+H) ⁺ LCMS RT = 1.16 min.	+++	Example 86
458		2-(3-(3',6-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 552.9 (M+H) ⁺ LCMS RT = 1.12 min.	+++	Example 87
459		2-(3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d ₆ -DMSO) δ 8.24 (m, 2H), 7.78 (d, 2H, J = 8 Hz), 7.44 (d, 2H, J = 8Hz), 7.39-7.30 (m, 3H), 7.22 (d, 1H, J = 8Hz), 7.09 (d, 1H, J = 4 Hz), 6.99-6.96 (m, 1H), 4.51 (m, 1H), 4.15 (s, 2H), 1.27 (d, 6H, J = 8 Hz); MS (ES) 499.0 (M+H) ⁺ LCMS RT = 1.07 min.	+++	Example 74

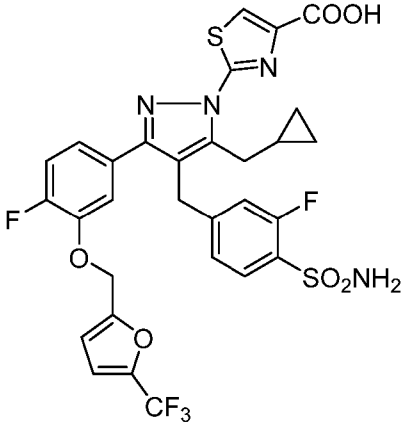
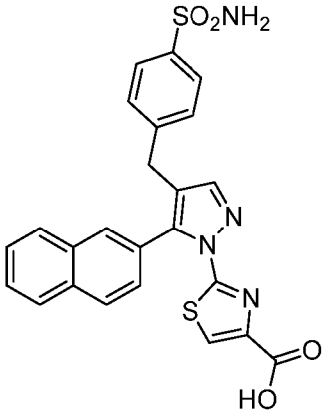
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
460		2-(3-(3-(cyclopentyloxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d ₆ -DMSO) δ 8.55 (m, 2H), 8.25 (d, 2H, J = 4 Hz), 7.77 (d, 2H, J = 4 Hz), 7.55-7.26 (m, 3H), 7.22 (d, 1H, J = 8Hz), 7.09 (d, 1H, J = 8 Hz), 6.99-6.96 (m, 1H), 4.74 (m, 1H), 4.15 (s, 2H), 1.91-1.82 (m, 2H), 1.69-1.58 (m, 4H), 1.23 (m, 2H); MS (ES) 525.0 (M+H) ⁺ LCMS RT = 1.15 min.	+++	Example 75
461		2-(4-(4-sulfamoylbenzyl)-3-((tetrahydrofuran-3-yl)methoxy)phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 540.7 (M+H) ⁺ LCMS RT = 1.13 min.	+++	Example 76
462		2-(3-(3-((3-methoxybenzyl)oxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 576.9 (M+H) ⁺ LCMS RT = 1.02 min.	+++	Example 77

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
463		2-(4-(4-sulfamoylbenzyl)-3-((tetrahydrofuran-2-yl)methoxy)phenyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid; MS (ES) 540.9 (M+H) ⁺ LCMS RT = 0.76 min.	+++	Example 78
464		2-(3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid; MS (ES) 532.9(M+H) ⁺ LCMS RT = 0.98 min.	+++	Example 79
465		2-(3-(3-(pyridin-3-ylmethoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid, TFA MS (ES) 548.0 (M+H) ⁺ LCMS RT = 0.68 min.	+++	Example 80
466		2-(3-(3-(pyridin-2-ylmethoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-ylthiazole-4-carboxylic acid TFA; MS (ES) 547.9 (M+H) ⁺ , LCMS RT = 0.68 min.	+++	Example 81

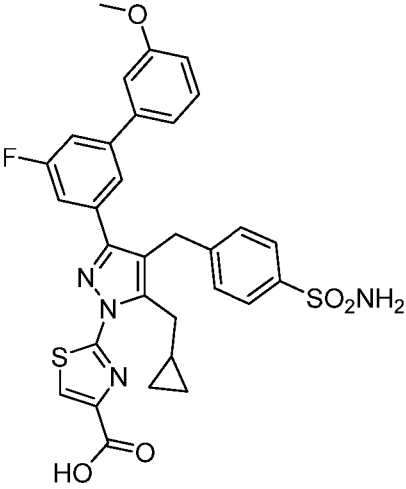
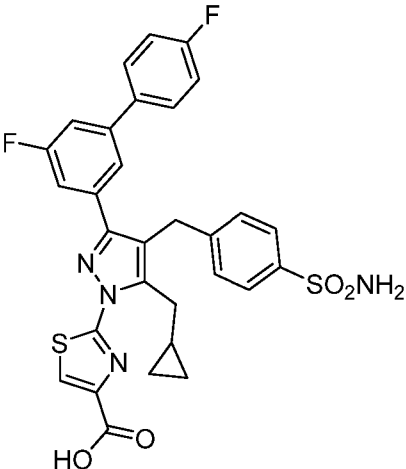
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
467		Synthesis of 2-(3-(3-(cyclopentyloxy)-4-methylphenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H-NMR (d6-DMSO) δ 8.07 (s, 1H), 7.53 (d, 2H, J = 8 Hz), 7.12-7.07 (m, 5H), 6.95 (d, 1H, J = 8 Hz), 6.87 (d, 1H, J = 8 Hz), 6.63 (s, 1H), 4.16 (m, 1H), 3.90 (s, 2H), 2.93 (m, 2H), 1.87 (s, 3H), 1.40-1.29 (m, 8H), 0.91 (m, 1H), 0.11 (m, 2H), 0.014 (m, 2H) ; MS (ES) 593.4 (M+H)⁺, LCMS RT = 0.81 min.	+++	Example 120
468		2-(3-(5-(cyclopentyloxy)-2-fluorophenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H-NMR (d6-DMSO) δ 8.07 (s, 1H), 7.43 (d, 2H, J = 8 Hz), 7.02-6.93 (m, 5H), 6.73 (m, 1H), 6.60 (m, 1H), 4.40 (m, 1H), 2.93 (m, 2H), 1.59-1.54 (m, 2H), 1.52-1.32 (m, 6H), 0.91 (m, 1H), 0.013 (m, 2H), 0.010 (m, 2H); MS (ES) 597.4 (M+H)⁺, LCMS RT = 0.67 min.	++	By analogy with Example 120

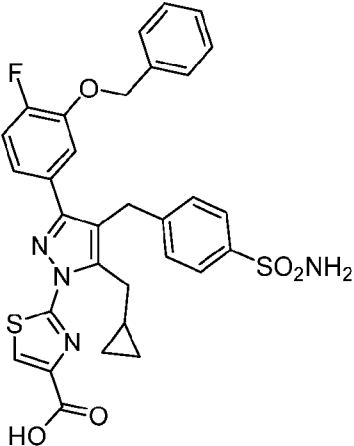
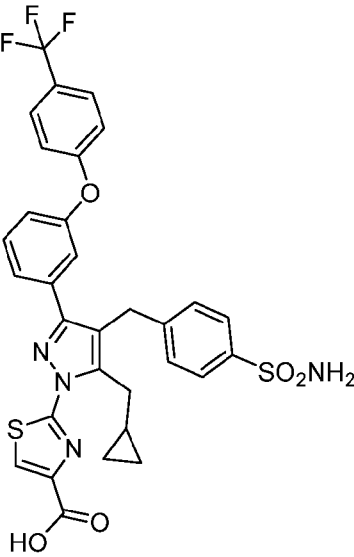
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
5				
10				
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469		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((tetrahydrofuran-2-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d ₆ -DMSO) δ 8.07 (s, 1H), 7.44 (m, 1H), 7.35 (s, 2H), 7.05-6.82 (m, 5H), 3.93 (s, 2H), 3.87-3.43 (m, 6H), 2.93 (m, 2H), 1.75-1.59 (m, 3H), 1.38 (m, 1H), 0.90 (m, 1H), 0.013 (m, 2H) 0.010 (m, 2H); MS (ES) 630.9 (M+H) ⁺ , LCMS RT = 1.10 min.	+++	Example 121
470		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((tetrahydrofuran-3-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d ₆ -DMSO) δ 8.07 (s, 1H), 7.44 (m, 1H), 7.35 (s, 2H), 7.04-7.01 (m, 1H),	+++	Example 122

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		6.95-6.91 (m, 3H), 6.84-6.82 (m, 1H), 3.92 (s, 2H), 3.52-3.50 (m, 4H), 3.40-3.35 (m, 2H), 3.20(m, 1H), 2.93 (m, 2H), 2.4 (m, 1H), 1.77(m, 1H), 1.39 (m, 1H), 0.91 (m, 1H), 0.013 (m, 2H) 0.010 (m, 2H); MS (ES) 552.9 (M+H) ⁺ , LCMS RT = 1.12 min.		
471		2-(3-(3-cyclopropoxy-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d ₆ -DMSO) δ 8.07 (s, 1H), 7.46 (m, 1H), 7.37 (s, 2H), 7.19 (m, 1H), 7.05-6.85 (m, 5H), 3.92 (s, 2H), 3.50 (m, 1H), 2.93 (m, 2H), 0.91 (m, 1H), 0.013 (m, 2H) 0.010 (m, 2H); MS (ES) 586.9 (M+H) ⁺ , LCMS RT = 1.12 min.	+++	Example 123
472		2-(5-(cyclopropylmethyl)-3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(2-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d ₆ -DMSO) δ 8.31 (s, 1H), 7.59-7.35 (m, 11H), 7.17 (m, 1H), 4.13 (s, 2H),		Example 124

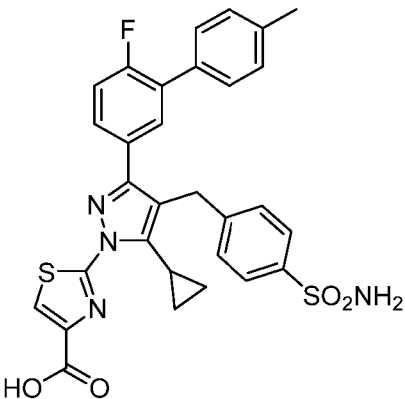
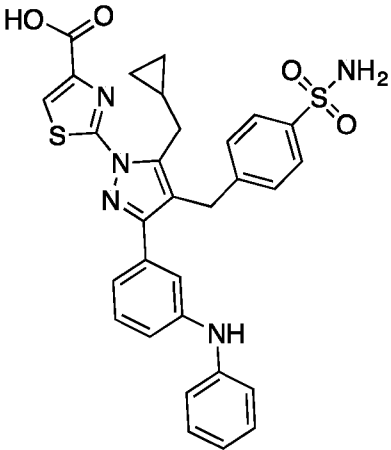
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		3.02 (m, 2H), 2.35 (s, 3H), 1.15 (m, 1H), 0.033 (m, 2H) 0.021 (m, 2H); MS (ES) 621.4 (M+H) ⁺ , LCMS RT = 0.79 min.		
473		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((5-(trifluoromethyl)furan-2-yl)methoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 694.9 (M+H) ⁺ , LCMS RT = 1.20 min.	+++	Example 125
474		2-(5-(naphthalen-2-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d6-DMSO) δ 8.24(s, 1H). 8.13(s, 1H), 7.91-8.03(m, 4H), 7.80(d, J=8.2 Hz, 2H), 7.52-7.58(m, 3H), 7.32(s, 2H), 4.25(s, 2H); MS (ES) 491 (M+H) ⁺ LCMS RT 1.04 min.	+++	Example 82

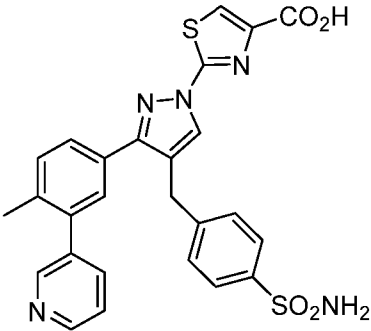
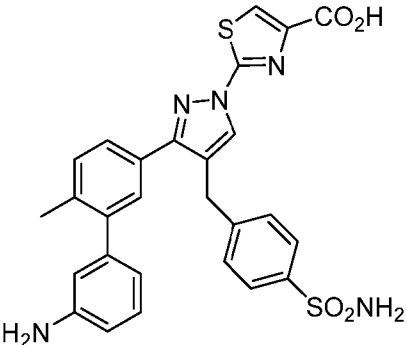
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
475		2-(5-(pyridin-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 442 (M+H) ⁺ LCMS RT 0.64 min.	++	Example 83
476		2-(3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (d6-DMSO) δ 8.27 (d, J= 9.24 Hz, 2H), 7.76-7.78 (m, 4H), 7.29-7.46 (m, 8H), 4.2 (s, 2H), 2.35 (s, 3H); MS (ES) 549 (M+H) ⁺ LCMS RT 1.27 min.	+++	Example 84
477		2-(3-(3-(cyclopentyloxy)phenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (CDCl ₃) δ 8.10 (s, 1H), 7.84(d, J=8.4 Hz, 2H), 7.23-7.31(m, 4H), 7.02-7.07(m, 2H), 6.88(dd, J=1.76, 1.8 Hz, 1H) 4.97(s, 2H), 4.11(s, 2H), 3.15(d, J=6.64 Hz, 2H), 1.58-1.79(m, 9H), 1.12-1.16(m, 1H), 0.43 (d,		Example 126

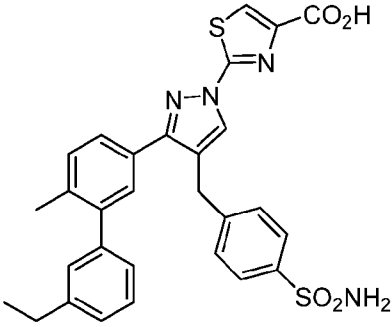
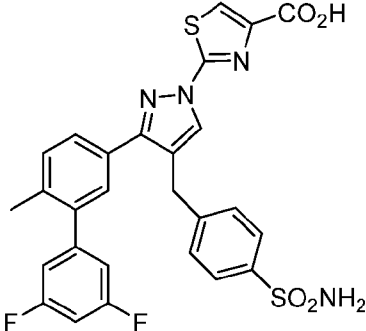
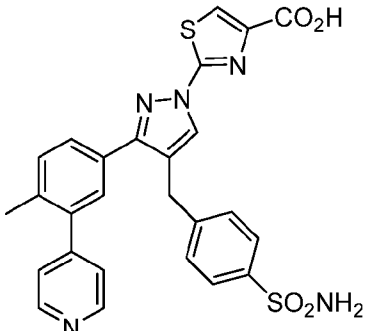
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		J=8Hz, 2H), 0.21 (d, J= 5.4 Hz, 2H), MS (ES) 579 (M+H) ⁺ LCMS RT 1.15 min.		
478		2-(5-(cyclopropylmethyl)-3-(5-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (CDCl ₃) δ 8.10(s, 1H) 7.86(d, J=8.32 Hz, 2H,) 7.23-7.29(m, 7H), 7.00 (d, J=7.12 Hz, 1H), 6.91(dd, J= 1.88 1.88 Hz, 1H), 6.60(t, J=3.92 Hz, 1H), 4.96(s, 2H), 4.11(s, 2H),), 3.87(s, 3H), 3.21(d, J=6.64 Hz, 2H) 1.17-1.25(m, 1H) 0.47(d, J=7.28 Hz, 2H), 0.24 (d, J=5.2 Hz, 2H), MS: (ES) 619 (M+H) ⁺ LCMS RT 1.32 min.	+++	Example 143
479		2-(5-(cyclopropylmethyl)-3-(4',5-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 607 (M+H) ⁺ LCMS RT 1.35 min.	+++	Example 144

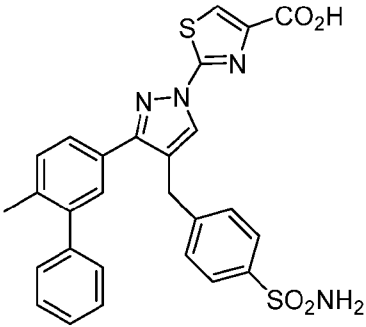
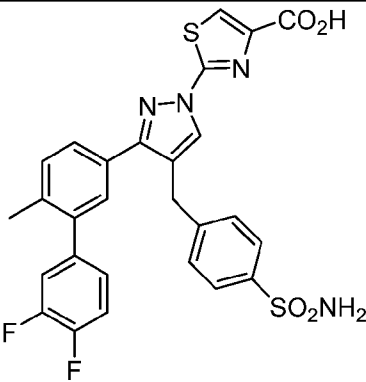
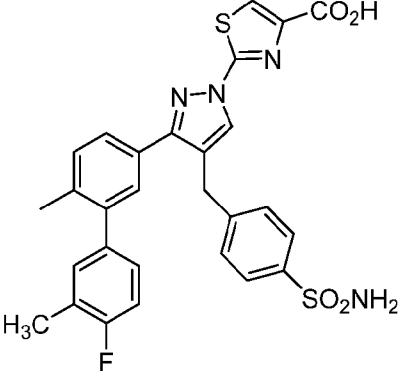
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
480		2-(3-(3-(benzyloxy)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H-NMR (CDCl₃) δ 8.11(s, 1H), 7.84(d, J= 8 Hz, 2H), 7.24-7.38(m, 8H), 7.15(d, J= 7.4 Hz, 1H) 7.08(d, J=8 Hz, 2H), 5.01(s, 2H), 4.95(s, 3H), 4.02(s, 2H), 3.16(d, J=6.7 Hz, 2H), 1.11-1.15(m, 1H), 0.42(d, J=7 Hz, 2H), 0.21(d, J=5.24 Hz, 2H); MS (ES) 619 (M+H)⁺ LCMS RT = 1.28 min.	+++	Example 127
481		2-(5-(cyclopropylmethyl)-4-(4-sulfamoylbenzyl)-3-(3-(4-(trifluoromethyl)phenoxy)phenyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H-NMR (CDCl₃) δ 8.11(s, 1H), 7.8(d, J= 8Hz, 2H), 7.6(d, J=8 Hz, 2H), 7.21-7.40(m, 5H), 7.01-7.06(m, 3H), 5.04(s, 2H), 4.08(s, 2H), 3.16(d, J= 6 Hz, 2H), 1.09-1.15(m, 1H) 0.42(d, J= 8. Hz, 2H), 0.21 (d, J=5 Hz, 2H), MS (ES) 655 (M+H)⁺ LCMS RT = 1.38 min in 2 min method.	+++	Example 128

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
482		2-(5-cyclopropyl-3-(4',6-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD): δ 8.27(s, 1H) 7.85(d, J=12 Hz, 2H),; 7.57-7.63(m, 1H), 7.5(d, J=16 Hz, 1H), 7.29-7.42(m, 4H), 7.12-7.25(m, 4H), 4.25(s, 2H), 2.32-2.41(m, 1H), 1.15 (d, J=12 Hz, 2H), 0.7(d, J=9 Hz, 2H); (ES) 593 (M+H) ⁺ LCMS RT = 1.28 min in 2 min method.	+++	Example 112
483		2-(5-cyclopropyl-3-(6-fluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (CDCl ₃) δ 8.13(s, 1H) , 7.85 (d, J=8 Hz, 2H), 7.55-7.59 (m, 1H), 7.35-7.39(m, 2H), 7.25-7.31 (m, 4H), 7.17(t, J=18.84 Hz, 1H), 7.04 (d, J=7.56 Hz, 1H), 6.91-6.94 (dd, J=2, 2 Hz, 1H), 6.73 (s, 1H), 5.04 (s, Broad, 2H), 4.17 (s, 2H), 3.87(s, 3H), 2.23-2.27(m, 1H), 1.12 (d, J=7 Hz, 2H), 0.73 (d, J=5 Hz, 2H), MS (ES) 605 (M+H) ⁺ LCMS RT = 1.25 min in 2 min method.	+++	Example 113

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
484		2-(5-cyclopropyl-3-(6-fluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (CDCl ₃) δ 8.10(s, 1H), 7.82(d, J=8. Hz, 2H), 7.5(dd, J1=2; J2= 2 Hz, 1H), 7.41-7.45(m, 1H), 7.22-7.32(m, 7H), 7.13(t, J=19 Hz, 1H), 5.06(s, 2H), 4.14(s, 2H), 2.40 (s, 3H), 2.17-2.23(m, 1H), 1.07(d, J=8 Hz, 2H), 0.68(d, J=5. Hz, 2H), MS (ES) 589 (M+H) ⁺ LCMS RT = 1.31 min in 2 min method.	+++	Example 114
485		2-(5-(cyclopropylmethyl)-3-(3-(phenylamino)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (CDCl ₃) δ 7.96 (1H, s), 7.72 (2H, d, J = 8.3 Hz), 7.23-7.18 (6H, m), 7.02-6.99 (4H, m), 6.88 (1H, t, J = 7.4 Hz), 4.02 (2H, s), 3.10 (2H, d, J = 6.8 Hz), 1.01 (1H, m), 0.33 (2H, dd, J = 13.8, 5.8 Hz), 0.14 (2H, dd, J = 10.2, 5.0 Hz); MS(ES) 587.7 (M+H) ⁺ ; LCMS RT =1.06 min.	+++	Example 115

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
486		2-(3-(4-methyl-3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.77 (s, 1H), 8.72 (s, 1H), 8.40 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.16 (s, 1H), 7.92 (dd, J = 7.6, 5.6 Hz, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.74 (dd, J = 7.6, 1.6 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.21 (s, 2H), 2.34 (s, 3H); MS (ES) 532.7 (M+H) ⁺ , LCMS RT = 0.82 min.	+++	Example 88
487		2-(3-(3'-amino-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.37 (s, 1H), 8.16 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 7.6, 6.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.40 (s, 2H), 7.38 (s, 1H), 7.27-7.20 (m, 2H), 7.15 (s, 1H), 4.19 (s, 2H), 2.30 (s, 3H); MS (ES) 546.7 (M+H) ⁺ ; LCMS RT = 0.87 min.	+++	Example 89

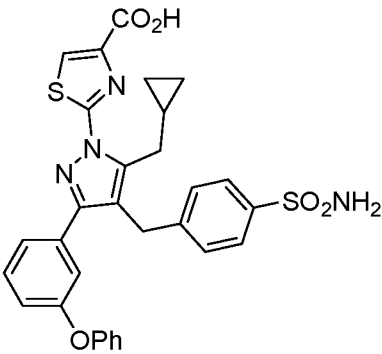
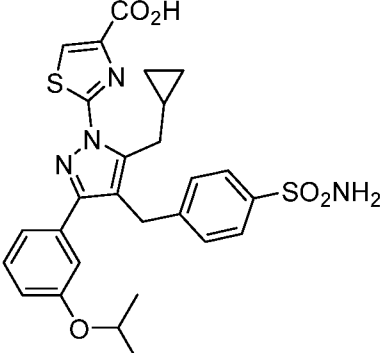
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
488		2-(3-(3'-ethyl-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.34 (s, 1H), 8.13 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.59 (dd, J = 8.0, 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 4.20 (s, 2H), 2.73 (q, J = 8.0 Hz, 2H), 2.29 (s, 3H), 1.30 (t, J = 8.0 Hz, 3H); MS (ES) 559.4 (M+H) ⁺ ; LCMS RT = 1.28 min.	++	Example 90
489		2-(3-(3',5'-difluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 569.6 (M+H) ⁺ ; LCMS RT = 1.24 min.	++	Example 91
490		2-(3-(4-methyl-3-(pyridin-4-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.80 (br s, 2H), 8.44 (s, 1H), 8.17 (s, 1H), 7.85-7.76 (m, 5H), 7.49 (d, J = 6.0 Hz, 1H), 7.41 (d, J = 2.0	++	Example 92

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		Hz, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 4.21 (s, 2H), 2.39 (s, 3H); MS (ES) 533.6 (M+H) ⁺ ; LCMS RT = 0.83 min.		
491		2-(3-(6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ; ¹ H-NMR (MeOD) δ 8.34 (s, 1H), 8.14 (s, 1H), 7.89-7.82 (m, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 8.0, 2.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.49-7.35 (m, 4H), 7.29 (d, J = 8.0 Hz, 2H), 4.20 (s, 2H), 2.30 (s, H); MS (ES) 531.6 (M+H) ⁺ ; LCMS RT = 1.18 min.	++	Example 93
492		2-(3-(3',4'-difluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 567.9 (M+H) ⁺ ; LCMS RT = 1.20 min.	++	Example 94
493		2-(3-(4'-fluoro-3',6-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 563.9 (M+H) ⁺ ; LCMS RT = 1.25 min.	++	Example 95

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
494		2-(3-(3'-fluoro-4'-methoxy-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 579.6 (M+H) ⁺ ; LCMS RT = 1.18 min.	++	Example 96
495		2-(4-(4-sulfamoylbenzyl)-3-(3',5',6-trimethyl-[1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 559.9 (M+H) ⁺ ; LCMS RT = 1.29 min.	++	Example 97
496		2-(3-(3'-cyano-4',6-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 570.9 (M+H) ⁺ ; LCMS RT = 1.16 min.	++	Example 98
497		2-(3-(3'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 549.6 (M+H) ⁺ ; LCMS RT = 1.18 min.	++	Example 99

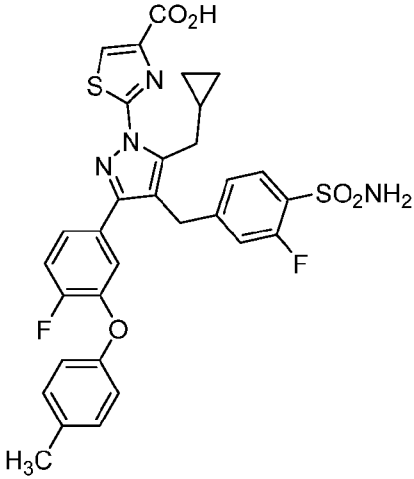
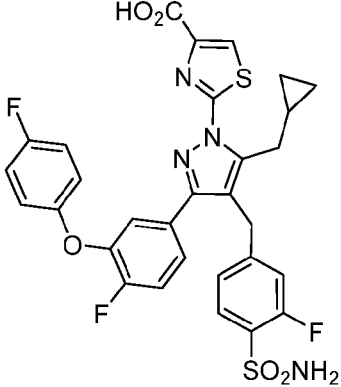
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
498		2-(3-(4'-fluoro-6-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 549.6 (M+H) ⁺ ; LCMS RT = 1.16 min.	++	Example 100
499		2-(5-cyclopropyl-3-(4-methyl-3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.86 (d, J = 5.2 Hz, 1H), 8.83 (s, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H), 8.13 (dd, J = 8.0, 1.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.64 (dd, J = 8.0, 1.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.29 (s, 2H), 7.27 (s, 1H), 4.25 (s, 2H), 2.42-2.34 (m, 1H), 2.33 (s, 3H), 1.10 (dt, J = 8.4, 4.6 Hz, 2H), 0.69 (dt, J = 5.6, 4.6 Hz, 2H); MS (ES) 572.9 (M+H) ⁺ ; LCMS RT = 0.87 min.	+++	Example 116
500		2-(3-(3'-amino-6-methyl-[1,1'-biphenyl]-3-yl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ; ¹ H-NMR (MeOD) δ 8.26 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.49 (dd, J = 8.0, 1.6 Hz,	+++	Example 117

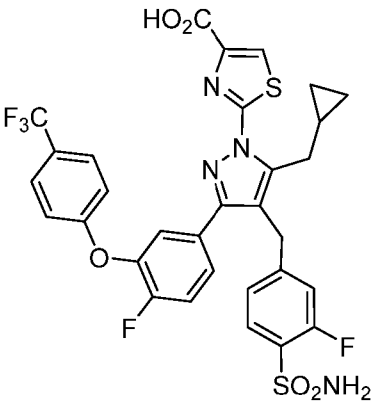
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		1H), 7.32 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.27 (s, 3H), 7.18 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 4.23 (s, 2H), 2.41-2.33 (m, 1H), 2.27 (s, 3H), 1.08 (dt, J = 8.4, 6.4 Hz, 2H), 0.67 (dt, J = 5.6, 4.6 Hz, 2H); MS (ES) 586.9 (M+H) ⁺ ; LCMS RT = 0.92 min.		
501		2-(3-(3-(benzyloxy)phenyl)-5-cyclopropyl-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.24 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.40-7.34 (m, 4H), 7.31-7.22 (m, 4H), 7.14-7.09 (m, 2H), 6.99 (dd, J = 8.0, 2.0 Hz, 1H), 4.96 (s, 2H), 4.16 (s, 2H), 2.37-2.28 (m, 1H), 1.04 (dt, J = 8.4, 6.4 Hz, 2H), 0.63 (dt, J = 5.6, 4.8 Hz, 2H); MS (ES) 586.9 (M+H) ⁺ ; LCMS RT = 0.92 min.	+++	Example 118
502		2-(5-cyclopropyl-3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.24 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.40-7.31 (m, 4H), 7.19 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 8.4 Hz, 1H), 7.07 (s, 1H), 7.00	+++	Example 119

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(dd, J = 8.0, 1.6 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 4.15 (s, 2H), 2.37-2.29 (m, 1H), 1.03 (dt, J = 8.4, 6.4 Hz, 2H), 0.62 (dt, J = 5.6, 4.8 Hz, 2H); MS (ES) 573.6 (M+H) ⁺ ; LCMS RT = 0.94 min.		
503		2-(5-(cyclopropylmethyl)-3-(3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.19 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.38-7.31 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 7.15-7.10 (m, 2H), 7.02-6.97 (m, 1H), 7.00 (dd, J = 8.0, 1.2 Hz, 2H), 4.10 (s, 2H), 3.22 (d, J = 6.8 Hz, 2H), 1.12-1.06 (m, 1H), 0.39-0.33 (m, 2H), 0.21 (dt, J = 6.0, 5.2 Hz, 2H); MS (ES) 587.7 (M+H) ⁺ ; LCMS RT = 1.00 min.	+++	Example 129
504		2-(5-(cyclopropylmethyl)-3-(3-isopropoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 552.6 (M+H) ⁺ ; LCMS RT = 0.98 min.	+++	Example 130

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
505		2-(5-(cyclopropylmethyl)-3-(3'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 603.7 (M+H) ⁺ ; LCMS RT = 1.26 min.	+++	Example 141
506		2-(5-(cyclopropylmethyl)-3-(4'-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 603.4 (M+H) ⁺ ; LCMS RT = 1.26 min.	+++	Example 142
507		2-(5-(cyclopropylmethyl)-3-(3-(4-fluorophenoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ (ppm) 8.14 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.10-7.04 (m, 2H), 7.01-6.96 (m, 4H), 6.84 (t, J = 2.0 Hz, 1H), 3.92 (s, 2H), 2.46 (d, J = 7.2 Hz, 2H), 1.00-0.90 (m, 1H), 0.44 (ddd, J = 8.4, 6.0, 4.4 Hz, 2H), 0.13 (dd, J = 10.0, 4.4 Hz, 2H); MS (ES) 605.2 (M+H) ⁺ ; LCMS RT =	+++	Example 134

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		1.20 min.		
508		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-phenoxyphenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H-NMR (d₆-DMSO) δ 7.63 (d, J = 8.4 Hz, 2H), 7.42-7.33 (m, 4H), 7.23 (s, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 7.6 Hz, 2H), 4.06 (s, 2H), 3.12 (d, J = 6.8 Hz, 2H), 0.87-0.80 (m, 1H), 0.30 (ddd, J = 10.0, 6.0, 4.4 Hz, 2H), 0.13 (dd, J = 10.0, 5.2 Hz, 2H); MS (ES) 605.2 (M+H)⁺; LCMS RT = 1.18 min.	+++	Example 135
509		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(3-fluorophenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ; ¹H-NMR (MeOD) δ 8.20 (s, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.50-7.46 (m, 1H), 7.37-7.25 (m, 3H), 6.99 (s, 1H), 6.98 (d, J = 16.8 Hz, 1H), 6.88 (dt, J = 8.4, 2.0 Hz, 1H), 6.73 (dt, J = 10.0, 2.0 Hz, 1H), 6.66 (dd, J = 8.4, 2.4 Hz, 1H), 4.13 (s, 2H), 3.24 (d, J = 6.8 Hz, 2H), 1.13-	+++	Example 136

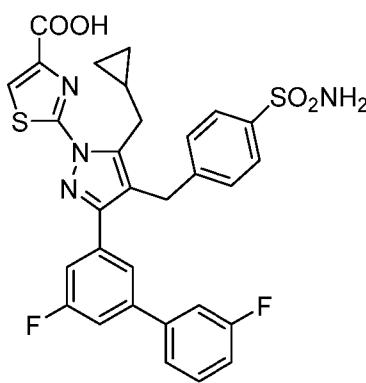
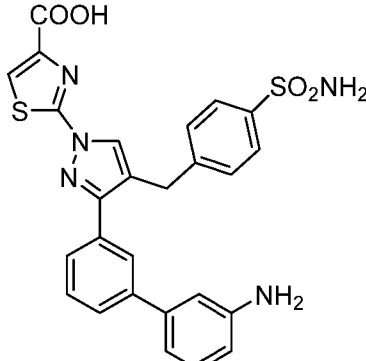
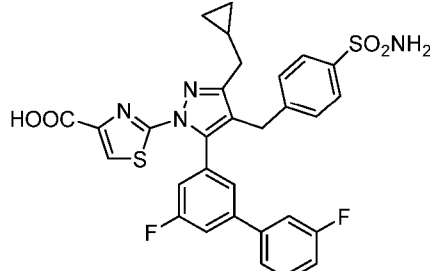
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		1.05 (m, 1H), 0.44 (ddd, J = 8.0, 5.6, 4.0 Hz, 2H), 0.22 (dd, J = 10.4, 5.2 Hz, 2H); MS (ES) 640.9 (M+H) ⁺ ; LCMS RT = 1.19 min.		
510		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(p-tolyloxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.19 (s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.44-7.40 (m, 1H), 7.25 (dd, J = 10.8, 8.8 Hz, 1H), 7.17-7.12 (m, 3H), 6.93 (s, 1H), 6.92 (d, J = 17.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 4.07 (s, 2H), 3.22 (d, J = 6.8 Hz, 2H), 1.11-1.04 (m, 1H), 0.37 (ddd, J = 8.0, 6.0, 4.8 Hz, 2H), 0.21 (dd, J = 10.4, 5.2 Hz, 2H); MS (ES) 636.9 (M+H) ⁺ ; LCMS RT = 1.12 min.	+++	Example 137
511		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-fluorophenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD): δ 8.19 (s, 1H), 7.71 (t, J = 8.8 Hz, 1H), 7.45-	+++	Example 138

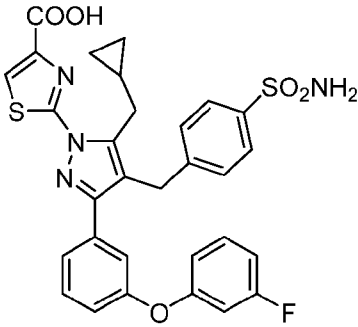
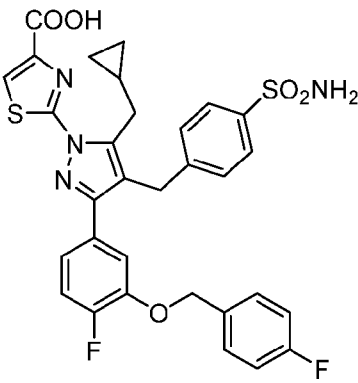
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		7.41 (m, 1H), 7.26 (dd, J = 8.8, 11.0 Hz, 1H), 7.15 (dd, J = 2.2, 7.9 Hz, 1H), 7.09 (dd, J = 8.5, 9.0 Hz, 2H), 6.98-6.89 (m, 4H), 4.09 (s, 2H), 3.23 (d, J = 7.05 Hz, 2H), 1.13-1.04 (m, 1H), 0.40-0.35 (m, 2H), 0.23-0.19 (m, 2H); MS (ES) 641.0 (M+H) ⁺ ; LCMS RT = 1.18 min.		
512		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-(trifluoromethyl)phenoxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.28 (s, 1H), 7.73-7.67 (m, 3H), 7.52-7.48 (m, 1H), 7.38 (dd, J = 2.1, 7.6 Hz, 1H), 7.30 (dd, J = 8.5, 10.5 Hz, 1H), 7.03-6.96 (m, 4H), 4.16 (s, 2H), 3.27 (d, J = 6.8 Hz, 2H), 1.18-1.08 (m, 1H), 0.42-0.38 (m, 2H), 0.26-0.23 (m, 2H); MS (ES) 691.0 (M+H) ⁺ ; LCMS RT = 1.24 min.	+++	Example 139

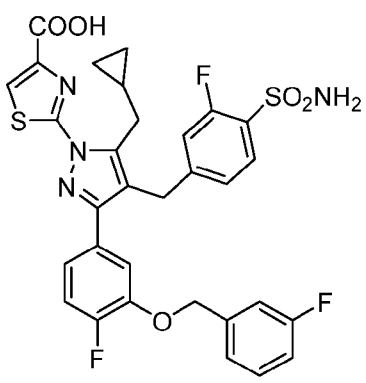
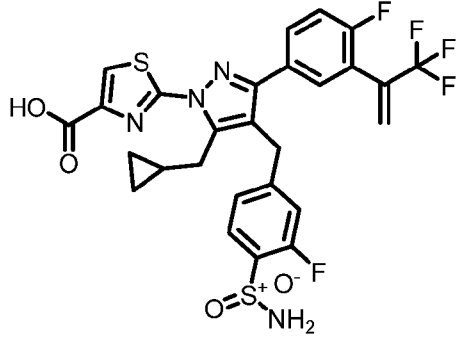
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
513		2-(3-(3'-ethyl-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.37 (s, 1H), 8.17 (s, 1H), 7.86 (d, J = 8.24 Hz, 2H), 7.77 (d, J = 6.4 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.33 (t, J = 9.62 Hz, 1H), 7.16 (d, J = 7.79 Hz, 2H), 7.03 (m, 1H), 4.23 (s, 2H), 3.63 (q, J = 7.1, 14.2 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); MS (ES) 562.9 (M+H) ⁺ ; LCMS RT = 1.24 min.	++	Example 101
514		2-(3-(3',5'-dichloro-6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.36 (s, 1H), 8.16 (s, 1H), 7.87 (d, J = 6.4 Hz, 2H), 7.81 (m, 2H), 7.75 (d, J = 8.1 Hz, 2H), 7.46 (M, 2H), 7.34 (m, 2H), 4.24 (s, 2H); MS (ES) 602.9 (M+H) ⁺ ; LCMS RT = 1.30 min.	+	Example 102

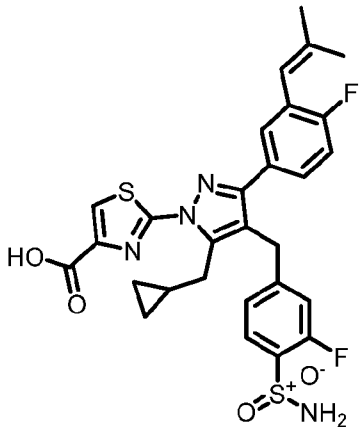
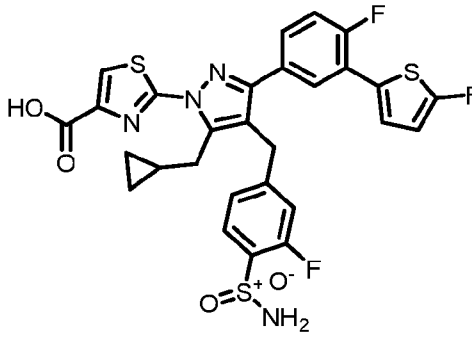
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
515		2-(3-(6-fluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 544.0 (M+H) ⁺ ; LCMS RT = 1.18 min.	+++	Example 103
516		2-(3-(6-fluoro-3',4'-dimethyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 562.9 (M+H) ⁺ ; LCMS RT = 1.23 min.	++	Example 104
517		2-(4-(4-sulfamoylbenzyl)-3-(3',4',6-trifluoro-[1,1'-biphenyl]-3-yl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 571.0 (M+H) ⁺ ; LCMS RT = 1.18 min.	++	Example 105
518		2-(3-(4',6-difluoro-3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 582.9 (M+H) ⁺ ; LCMS RT = 1.14 min.	+++	Example 106

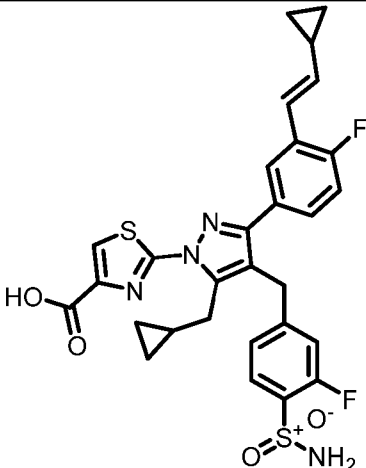
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
519		2-(3-(3'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 530.9 (M+H) ⁺ ; LCMS RT = 1.00 min.	+++	Example 107
520		2-(3-(3',6-difluoro-4'-methyl-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 566.9 (M+H) ⁺ ; LCMS RT = 1.22 min.	++	Example 108
521		2-(3-(3'-methoxy-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 546.9 (M+H) ⁺ ; LCMS RT = 0.89 min.	+++	Example 109
522		2-(3-(3-(pyridin-3-yl)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 517.9 (M+H) ⁺ ; LCMS RT = 0.82 min.	++	Example 110

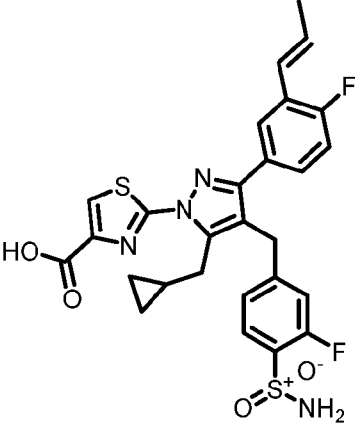
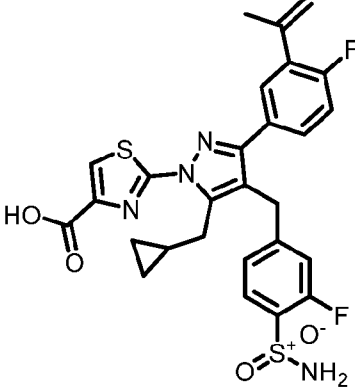
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
523		2-(5-(cyclopropylmethyl)-3-(3',5-difluoro-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 607.0 (M+H) ⁺ ; LCMS RT = 1.10 min.	++	
524		2-(3-(3'-amino-[1,1'-biphenyl]-3-yl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; MS (ES) 532.0 (M+H) ⁺ ; LCMS RT = 0.70 min.	++	Example 111
525		4-((3-(cyclopropylmethyl)-5-(3',5-difluoro-[1,1'-biphenyl]-3-yl)-1-(4-((oxo-13-methyl)-13-oxidanyl)thiazol-2-yl)-1H-pyrazol-4-yl)methyl)benzenesulfonamide; ¹ H-NMR (CDCl ₃) δ 7.96 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.39 (m, 2H), 7.24 (m, 4H) 7.06 (m, 4H), 3.93 (s, 2H) 2.53 (d, J = 6.8 Hz, 2H), 1.05 (m, 1H), 0.55 (m, 2H), 0.22 (d, J = 5.8 Hz, 2H); MS (ES) 607.0 (M+H) ⁺ ; LCMS RT = 0.95 min.	+	Example 133

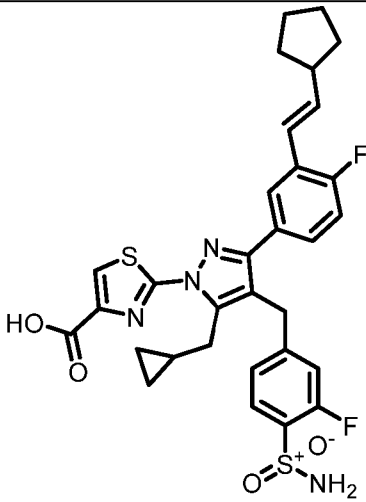
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
526		2-(5-(cyclopropylmethyl)-3-(3-(3-fluorophenoxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 7.89 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.42 (m, 2H), 7.34 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.12 (m, 1H), 8.87 (m, 2H), 6.70 (m, 2H), 4.13 (s, 2H), 3.25 (d, J = 6.7 Hz, 2H), 0.32 (d, J = 8.2 Hz, 2H), 0.12 (d, J = 4.39 Hz, 2H); MS (ES) 605.2 (M+H) ⁺ ; LCMS RT = 1.21 min.	++	Example 140
527		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((4-fluorobenzyl)oxy)phenyl)-4-(4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.21 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.40 (m, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.23 (m, 1H), 7.17 (m, 1H), 7.107 (m, 3H), 4.96 (s, 2H), 4.13 (s, 2H), 3.25 (d, J = 6.83 Hz, 2H), 1.12 (m, 1H), 0.38 (d, J = 8.1 Hz, 2H), 0.23 (d, J = 5.1 Hz, 2H); MS (ES) 636.9 (M+H) ⁺ ; LCMS RT = 1.12 min.	+++	Example 131

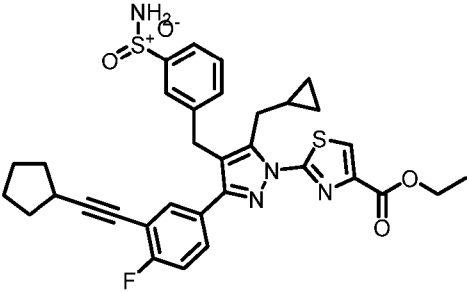
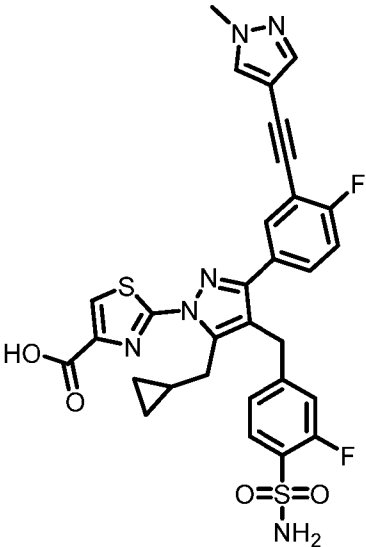
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
528		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((3-fluorobenzyl)oxy)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹ H-NMR (MeOD) δ 8.19 (s, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.40 (m, 1H), 7.23 (m, 3H), 7.16 (m, 2H), 7.04 (m, 3H), 5.08 (s, 2H), 4.11 (s, 2H), 3.25 (d, J = 6.5 Hz), 1.11 (m, 1H), 0.39 (d, J = 7.8 Hz), 0.23 (d, J = 4.6 Hz); MS (ES) 655.0 (M+H) ⁺ ; LCMS RT = 1.19 min.	+++	Example 132
529		2-(3-(3,4-difluorophenyl)-1H-pyrazolo[3,4-b]pyridin-1-yl)thiazole-4-carboxylic acid, ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.18 (s, 1H), 8.24 (s, 1H), 7.70 – 7.59 (m, 2H), 7.57 (s, 2H), 7.49 (dd, J = 7.2, 2.3 Hz, 1H), 7.37 (dd, J = 10.0, 8.6 Hz, 1H), 7.10 (dd, J = 11.3, 1.6 Hz, 1H), 7.01 (dd, J = 8.1, 1.6 Hz, 1H), 6.30 (dt, J = 2.1, 1.0 Hz, 1H), 5.95 (s, 1H), 4.12 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.18 – 0.99 (m, 0H), 0.38 – 0.27 (m, 2H), 0.25 – 0.15 (m, 2H); MS (M+H) ⁺ = 625	+++	145

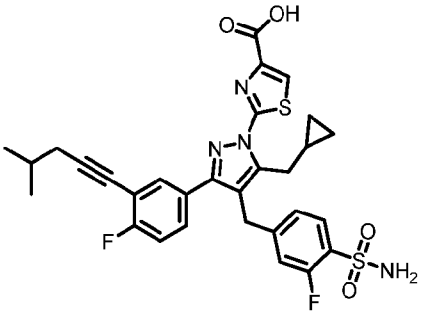
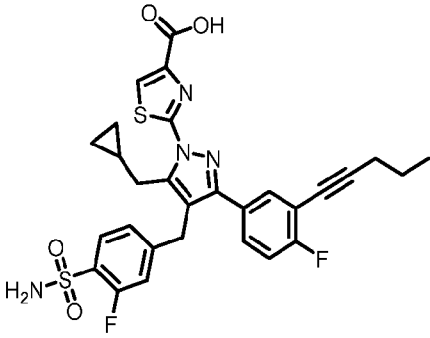
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
530		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(2-methylprop-1-en-1-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H NMR (400 MHz, DMSO-d₆) δ 13.14 (s, 1H), 8.26 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.56 (s, 2H), 7.45 (ddd, J = 8.4, 5.0, 2.3 Hz, 1H), 7.34 (dd, J = 7.5, 2.2 Hz, 1H), 7.21 (dd, J = 10.0, 8.5 Hz, 1H), 7.14 – 6.99 (m, 2H), 6.23 – 6.09 (m, 1H), 4.11 (s, 2H), 3.13 (d, J = 6.9 Hz, 2H), 1.85 (d, J = 1.4 Hz, 3H), 1.54 (t, J = 1.1 Hz, 3H), 1.18 – 1.04 (m, 1H), 0.36 – 0.27 (m, 2H), 0.24 – 0.15 (m, 2H); MS (M+H)⁺=585	+++	145
531		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(prop-1-en-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid; ¹H NMR (400 MHz, DMSO-d₆) δ 13.17 (s, 1H), 8.28 (s, 1H), 7.73 – 7.61 (m, 2H), 7.61 – 7.49 (m, 3H), 7.37 (dd, J = 11.3, 8.6 Hz, 1H), 7.17 (dd, J = 11.3, 1.6 Hz, 1H), 7.07 (s, 1H), 7.10 – 7.02 (m, 1H), 6.79	+++	145

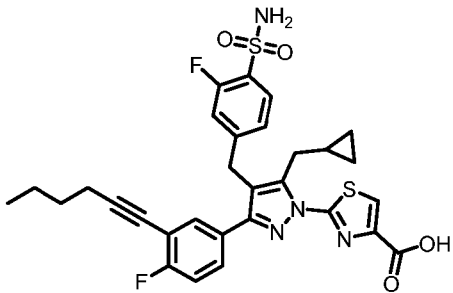
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(ddd, J = 4.2, 2.2, 1.1 Hz, 1H), 4.16 (s, 2H), 3.16 (d, J = 7.0 Hz, 2H), 1.24 – 1.06 (m, 1H), 0.38 – 0.28 (m, 2H), 0.32 – 0.17 (m, 2H); MS (M+H)+ = 632		
532		(E)-2-(5-(cyclopropylmethyl)-3-(3-(2-cyclopropylvinyl)-4-fluorophenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d ₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.51 (dd, J = 7.4, 2.3 Hz, 1H), 7.42 (ddd, J = 8.6, 5.0, 2.2 Hz, 1H), 7.23 – 7.10 (m, 2H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 5.64 (dd, J = 15.9, 9.4 Hz, 1H), 4.13 (s, 2H), 3.14 (d, J = 6.7 Hz, 2H), 1.59 (dddd, J = 12.8, 9.4, 8.1, 4.7 Hz, 1H), 1.24 – 0.96 (m, 1H), 0.84 – 0.74 (m, 2H), 0.55 – 0.46 (m, 2H), 0.37 – 0.16 (m, 4H); MS (M+H)+ = 597	+++	145

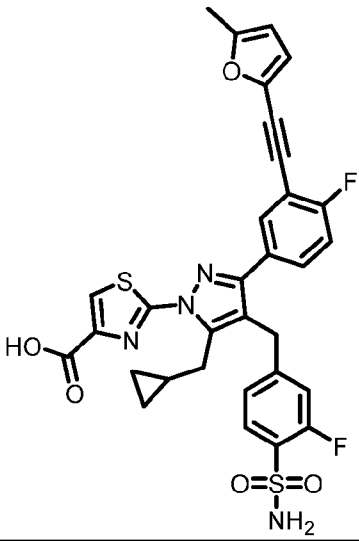
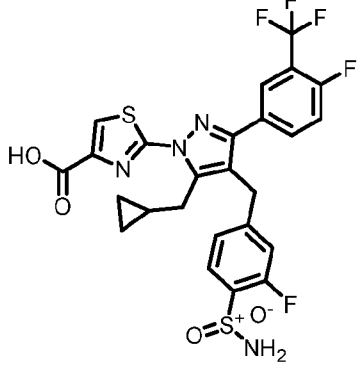
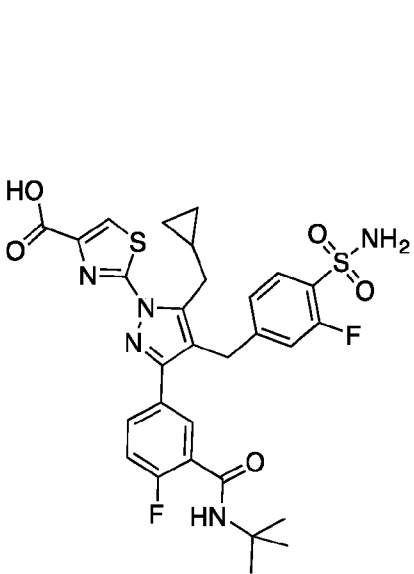
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
533		(E)-2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(prop-1-en-1-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.43 (ddd, J = 8.5, 5.0, 2.3 Hz, 1H), 7.24 – 7.11 (m, 2H), 7.04 (dd, J = 8.1, 1.6 Hz, 1H), 6.45 (dq, J = 15.8, 1.6 Hz, 1H), 6.11 (dq, J = 16.0, 6.6 Hz, 1H), 4.12 (s, 2H), 3.16 (d, J = 7.0 Hz, 2H), 1.83 (dd, J = 6.6, 1.7 Hz, 3H), 1.20 – 1.06 (m, 1H), 0.38 – 0.28 (m, 2H), 0.25 – 0.17 (m, 2H); MS (M+H)⁺ = 571	+++	145
534		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(prop-1-en-2-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.50 (ddd, J = 8.6, 4.8, 2.3 Hz, 1H), 7.40 (dd, J = 7.5, 2.3 Hz, 1H), 7.23 (dd, J = 11.1, 8.5 Hz, 1H), 7.13 (dd, J = 11.4, 1.6 Hz, 1H), 7.04 (dd, J =	+++	145

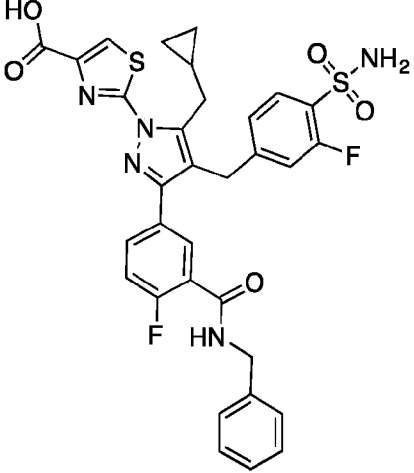
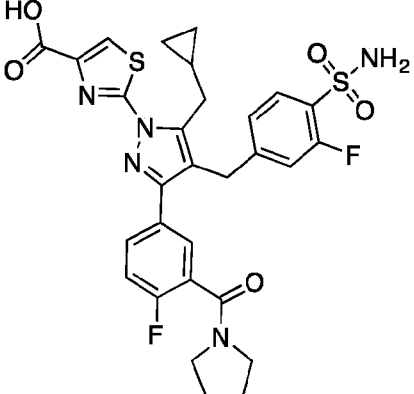
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		8.1, 1.6 Hz, 1H), 5.24 (dp, J = 2.4, 1.2 Hz, 1H), 5.14 (dq, J = 1.8, 0.9 Hz, 1H), 4.12 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 1.96 (q, J = 1.0 Hz, 3H), 1.24 – 0.93 (m, 1H), 0.37 – 0.28 (m, 2H), 0.25 – 0.16 (m, 2H); MS (M+H)+ = 571		
535		(E)-2-(3-(3-(2-cyclopentylvinyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d₆) δ 13.15 (s, 1H), 8.28 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.59 – 7.43 (m, 4H), 7.25 – 7.12 (m, 2H), 7.05 (dd, J = 8.1, 1.6 Hz, 1H), 6.41 (dd, J = 16.0, 1.1 Hz, 1H), 6.08 (dd, J = 16.0, 8.0 Hz, 1H), 4.14 (s, 2H), 3.15 (d, J = 6.9 Hz, 2H), 2.63 – 2.49 (m, 1H), 1.83 – 1.62 (m, 2H), 1.66 – 1.48 (m, 2H), 1.31 (s, 1H), 1.39 – 1.24 (m, 1H), 1.20 – 1.05 (m, 1H), 0.37 – 0.28 (m, 2H), 0.29 – 0.16 (m, 2H); MS (M+H)+ = 625	+++	145

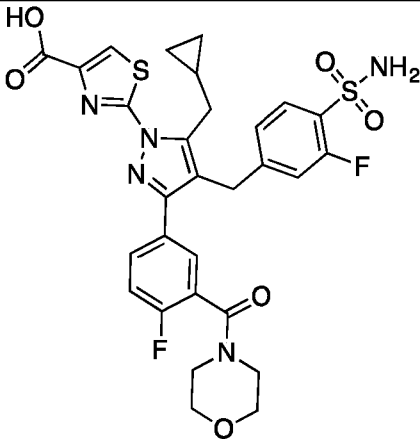
Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
536		ethyl 2-(3-(3-(cyclopentylethynyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylate, ¹ H NMR (400 MHz, DMSO-d ₆) δ 8.36 (s, 1H), 7.61 (dt, J = 7.9, 1.4 Hz, 1H), 7.53 (s, 1H), 7.56 – 7.49 (m, 1H), 7.53 – 7.38 (m, 2H), 7.36 – 7.21 (m, 2H), 7.28 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 3.14 (d, J = 6.9 Hz, 2H), 2.87 (p, J = 7.3 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.94 (s, 1H), 1.72 – 1.50 (m, 7H), 1.30 (t, J = 7.1 Hz, 3H), 1.12 (s, 1H), 0.37 – 0.17 (m, 4H); MS (M+H) ⁺ = 633	-	145
537		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((1-methyl-1H-pyrazol-4-yl)ethynyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, MS (M+H) ⁺ = 635		145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
538		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(4-methylpent-1-yn-1-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d₆) δ 13.16 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.59 – 7.49 (m, 4H), 7.29 (ddd, J = 9.2, 8.0, 1.1 Hz, 1H), 7.13 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 4.12 (s, 2H), 3.14 (d, J = 6.8 Hz, 3H), 2.34 (d, J = 6.4 Hz, 2H), 1.83 (dp, J = 13.2, 6.6 Hz, 1H), 1.11 (dddd, J = 14.9, 8.0, 4.9, 1.9 Hz, 1H), 0.97 (d, J = 6.7 Hz, 6H), 0.37 – 0.25 (m, 2H), 0.26 – 0.15 (m, 2H); MS (M+H)⁺ = 611	+++	145
539		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(pent-1-yn-1-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d₆) δ 13.16 (s, 1H), 8.28 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.57 (s, 2H), 7.58 – 7.49 (m, 2H), 7.33 – 7.24 (m, 1H), 7.13 (dd, J = 11.3, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 4.12	+++	145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		(s, 2H), 3.17 – 3.11 (m, 3H), 2.42 (t, J = 6.9 Hz, 2H), 1.54 (q, J = 7.1 Hz, 2H), 1.18 – 1.03 (m, 1H), 0.97 (t, J = 7.4 Hz, 3H), 0.37 – 0.27 (m, 2H), 0.24 – 0.15 (m, 2H); MS (M+H)+ = 597		
540		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(hex-1-yn-1-yl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, 1H NMR (400 MHz, DMSO-d6) δ 13.16 (s, 1H), 8.28 (s, 1H), 7.57 (s, 2H), 7.69 – 7.48 (m, 3H), 7.28 (dd, J = 9.4, 8.6 Hz, 1H), 7.13 (dd, J = 11.4, 1.6 Hz, 1H), 7.02 (dd, J = 8.1, 1.6 Hz, 1H), 4.12 (s, 2H), 3.18 – 3.11 (m, 3H), 2.44 (t, J = 6.9 Hz, 2H), 1.57 – 1.34 (m, 4H), 1.18 – 1.03 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H), 0.37 – 0.27 (m, 2H), 0.24 – 0.16 (m, 2H); MS (M+H)+ = 611	+++	145
541		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-((5-methylfuran-2-yl)ethynyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid, MS (M+H)+ = 635		145

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
				
542		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(trifluoromethyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid (M+H) ⁺ = 599	+++	49
543		2-(3-(3-(tert-butylcarbamoyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid: ¹ H-NMR (MeOD) δ: 8.21 (s, 1H), 7.79-7.69 (m, 3H), 7.19 (dd, J = 8.6, 10.0 Hz, 1H), 7.11-7.05 (m, 2H), 4.21 (s, 2H), 3.28 (d, J = 6.8 Hz, 2H), 1.44 (s, 9H), 1.18-1.10 (m, 1H), 0.43-0.39 (m, 2H), 0.28-0.24 (m,	+++	162

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		2H); MS (ES) 630.1 (M + H) ⁺ , LCMS RT = 1.048 min.		
544		2-(3-(3-(benzylcarbamoyl)-4-fluorophenyl)-5-(cyclopropylmethyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid: MS (ES) 664.0 (M + H) ⁺ , LCMS RT = 1.052 min.	+++	162
545		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(pyrrolidine-1-carbonyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid: ¹ H-NMR (MeOD) δ: 8.22 (s, 1H), 7.75-7.71 (m, 2H), 7.54 (dd, J = 2.2, 6.4 Hz, 1H), 7.24 (t, J = 8.8 Hz, 1H), 7.07 (t, J = 7.4 Hz, 2H), 4.20 (s, 2H), 3.59 (t, J = 7.1 Hz, 2H), 3.30 (d, J = 6.9 Hz, 2H), 3.19 (t, J = 2H), 2.03-1.91 (m, 4H), 0.95-0.86 (m, 1H), 0.45-0.40 (m, 2H), 0.29-0.25 (m, 2H); MS (ES) 628.0 (M + H) ⁺ , LCMS RT	+++	163

Cmpd ID	Structure	Compound name and physical data	Inhibitory activity IC ₅₀ (μM)	Example Method
		= 0.968 min.		
546		2-(5-(cyclopropylmethyl)-3-(4-fluoro-3-(morpholine-4-carbonyl)phenyl)-4-(3-fluoro-4-sulfamoylbenzyl)-1H-pyrazol-1-yl)thiazole-4-carboxylic acid: MS (ES) 644.0 [M + H] ⁺ , LCMS RT = 0.977 min.	163	

Example 165

[0538] This example describes the inhibition of lactate production, as measured by the assay set forth in Example 1, of exemplary compounds of formula (I). See Table 8. The lactate activity in Table 8 is represented by 0 to 3 pluses as follows: +++ <1 μM; ++ 1-10 μM; + 10-57 μM; and - >57 μM.

TABLE 8

Cmpd ID	Lactate activity
42	++
43	+
47	-
52	++
53	-
54	-
160	++
183	+++
189	++
203	+++

Cmpd ID	Lactate activity
206	++
207	++
212	-
213	-
214	++
215	+
217	++
219	++
221	+++
223	+++

Cmpd ID	Lactate activity
227	+++
229	-
230	+++
231	+++
232	+++
233	+++
234	+++
237	++
239	+++
251	++

5

Cmpd ID	Lactate activity
252	++
257	+++
258	+++
259	+
260	++
261	++
262	+++
263	+
264	+++
265	++
266	-
267	+
268	-
269	+++
276	+++
281	+++
284	+++
288	+++
290	+++
294	+++
296	++
304	+
306	+++
307	+++
309	+++
310	+++
324	+++
326	+++
327	+
330	+++
331	+++
332	+++
336	+++
337	+++
338	+++
364	+++
365	+++
366	+++
367	+++
368	+
369	+
370	++

10

15

20

25

30

35

40

45

50

55

Cmpd ID	Lactate activity
371	+++
372	++
373	+++
374	+++
375	++
376	+++
377	-
378	+++
379	+++
380	++
381	+++
382	+++
383	+++
384	+++
385	+++
386	+++
387	++
388	++
389	++
390	-
391	+++
393	-
394	+
395	+
396	++
397	++
398	+
399	-
400	+++
401	+++
402	+++
403	+++
404	+++
405	+++
406	++
407	+++
408	+++
409	++
410	+++
411	+++
412	++
413	+++

Cmpd ID	Lactate activity
414	++
415	++
416	++
417	++
418	++
419	+++
420	-
421	++
422	+
423	+++
428	-
429	-
430	+++
431	+++
432	+++
433	+++
434	-
435	-
436	+++
437	+++
438	++
439	-
440	++
442	++
443	+++
444	+++
445	+++
446	+++
458	++
467	+++
468	++
469	++
470	++
471	++
472	+++
473	+++
477	+++
478	++
479	+++
480	+++
481	++
485	++

Cmpd ID	Lactate activity
501	++
502	++
503	++
504	++
505	++
506	++
507	++
508	++
509	+++
510	+++
511	++
512	+++
523	++
526	+
527	++
528	+++
542	++
543	++
544	++
545	+

Example 167

[0539] This example evaluates the pharmacokinetics (PK) of compound **42** when administered orally as the ethyl ester prodrug (compound **141**).

[0540] Compound **141** is the ethyl ester prodrug of compound **42**. A dose formulation was freshly prepared comprising either compound **42** or compound **141**, in a solution of 10% *N*-methyl-2-pyrrolidone (NMP), 40% PEG400, and 50% of Solutol™ (30%) in water to provide a concentration of 1 mg/mL of compound **42** or **141**. The dose formulation was stirred at room temperature and used within 30 minutes after preparing.

[0541] Male CD1 mice obtained from Si Bei Fu Laboratory Animal Technology Co. Ltd were fed prior to dosing. On the first day of dosing, the mice ranged in age from about 7-9 weeks and weighed approximately 20-30 g. The mice were orally administered 10 mL/kg (10 mg/kg) of the formulation comprising either compound **42** or **141**.

[0542] PK measurements were taken at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h post dose. For sample collections, approximately 0.03 mL blood was collected by the dorsal metatarsal vein at each time point. All blood samples were transferred into plastic micro centrifuge tubes containing 2 microliters (μL) of 1,000 IU heparin as anti-coagulant. Collection tubes with blood samples and anticoagulant were inverted several times for proper mixing of the tube contents and then placed on wet ice prior to centrifugation for plasma. Blood samples were centrifuged at 4,000 g for 5 minutes at 4 °C to obtain plasma. Plasma samples were stored in polypropylene tubes, quickly frozen in an ice box, and kept at -75 ± 15 °C. Plasma samples were analyzed using an LC/MS/MS method. The peak concentration (C_{max}), area under the curve (AUC_{last}), and the fraction of the dose that enters systemic circulation (F) of compounds **42** and **142** are set forth below in Table 9.

Table 9

Compound	C_{max} (ng/mL)	AUC_{last} (h·ng/mL)	F(%)
42	159	1214	34
141	851	2409	69

[0543] DELETED

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

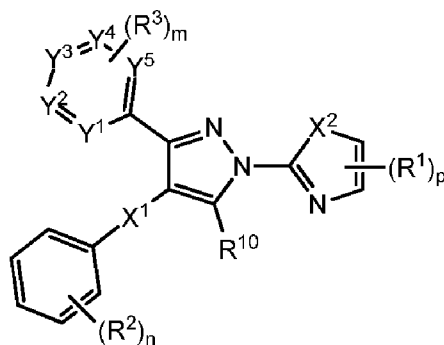
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Patentkrav

1. Forbindelse med formelen (Ia):



(Ia)

hvor

Y¹, Y², Y³, Y⁴ og Y⁵ hver uafhængigt er CH eller N;

R¹ er valgt uafhængigt fra halo, -C(O)R⁴, -CH₂OH, -C(O)NHCN, -C(O)NHSO₂H, -C(S)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -(C₁-C₈hydrokarbyl), -C(O)NHOH, -C(O)OCR⁵R⁶OC(O)OR⁴, -P(O)(OH)₂, -B(OR¹³)(OR¹⁴), -SO₂(OH), -C(O)NHS(O)₂Me, -SO₂NR⁵R⁶, -(C₀-C₄hydrokarbyl)(mono- eller bicyklisk heterocyclus, der har 1 til 4 heteroatomer valgt uafhængigt fra N, O og S), og -C(O)O-(C₀-C₄hydrokarbyl)(mono- eller bicyklisk heterocyclus, der har 1 til 4 heteroatomer valgt uafhængigt fra N, O og S), hver af hvilken R¹ undtagen halo, -P(O)(OH)₂ og -SO₂(OH), er substitueret eller ikke-substitueret;

R² er valgt uafhængigt fra hydroxyl, halo, -CN, -NO₂, C₁-C₈hydrokarbyl, -O(C₁-C₈hydrokarbyl), -(C₀-C₄hydrokarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrokarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrokarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrokarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrokarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrokarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrokarbyl)(mono- og bicyklisk heterocyclus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), -(C₀-C₄hydrokarbyl)(mono- og bicyklisk heterocyclus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), -C(O)R⁴, -CO₂R⁴, -

- $C(O)NR^5R^6$, $-NR^5C(O)R^4$, $-(CH_2)_qNR^5(SO_2)R^4$, $-(CH_2)_qNR^5C(O)R^4$, $-(CH_2)_qNR^7C(O)NR^5R^6$, $-(CH_2)_qNR^5R^6$, $-(CH_2)_qSO_2NR^5R^6$, $-(CH_2)_qSO_2R^4$,
 hvorved hver C_1 -C8hydrocarbyl, $-O(C_1-C_8hydrocarbyl)$, $-(C_0-C_4hydrocarbyl)C_3-C_8cycloalkyl$, $-O(C_0-C_4hydrocarbyl)C_3-C_8cycloalkyl$, $-(C_0-C_4hydrocarbyl)C_3-C_8cycloalkenyl$, $-O(C_0-C_4hydrocarbyl)C_3-C_8cycloalkenyl$, $-O(C_0-C_4hydrocarbyl)C_6-C_{12}aryl$, $-(C_0-C_4hydrocarbyl)C_6-C_{12}aryl$, $-O(C_0-C_4hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S)$, $-(C_0-C_4hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S)$ er substitueret eller ikke-substitueret;
- R^3 er valgt uafhængigt fra hydroxyl, halo, $-CN$, $-NO_2$, $-SF_5$, $C_1-C_8hydrocarbyl$, $-O(C_1-C_8hydrocarbyl)$, $-(C_0-C_4hydrocarbyl)C_3-C_8cycloalkyl$, $-O(C_0-C_4hydrocarbyl)C_3-C_8cycloalkyl$, $-(C_0-C_4hydrocarbyl)C_3-C_8cycloalkenyl$, $-O(C_0-C_4hydrocarbyl)C_3-C_8cycloalkenyl$, $-O(C_0-C_4hydrocarbyl)C_6-C_{12}aryl$, $-(C_0-C_4hydrocarbyl)C_6-C_{12}aryl$, $-O(C_0-C_4hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S)$, $-(C_0-C_4hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S)$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^5R^6$, $-NR^5C(O)R^4$, $-(CH_2)_qNR^5(SO_2)R^4$, $-(CH_2)_qNR^5C(O)R^4$, $-(CH_2)_qNR^7C(O)NR^5R^6$, $-(CH_2)_qNR^5R^6$, $-(CH_2)_qSO_2NR^5R^6$, $-(CH_2)_qSO_2R^4$,
 hvorved hver C_1 -C8hydrocarbyl, $-O(C_1-C_8hydrocarbyl)$, $-(C_0-C_4hydrocarbyl)C_3-C_8cycloalkyl$, $-O(C_0-C_4hydrocarbyl)C_3-C_8cycloalkyl$, $-(C_0-C_4hydrocarbyl)C_3-C_8cycloalkenyl$, $-O(C_0-C_4hydrocarbyl)C_3-C_8cycloalkenyl$, $-O(C_0-C_4hydrocarbyl)C_6-C_{12}aryl$, $-(C_0-C_4hydrocarbyl)C_6-C_{12}aryl$, $-O(C_0-C_4hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S)$, $-(C_0-C_4hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S)$ er substitueret eller ikke-substitueret; eller

to R³-molekyledele og fenylgruppen, som de er forbundet med, danner en naphthyl-gruppe eller dens heterocykliske analog, der eventuelt er substitueret;

hver R⁴, R⁵, R⁶, R⁷, R⁸ og R⁹ er de samme eller forskellige, og hver er hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂aryl, C₁-C₁₂heteroaryl eller C₁-C₁₂heterocycloalkyl, hvorved hver C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂aryl, C₁-C₁₂heteroaryl eller C₁-C₁₂heterocycloalkyl er substitueret eller ikke-substitueret;

R¹⁰ er hydrogen, halo, -CN, -NO₂, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵(SO₂)R⁴, -NR⁵C(O)R⁴, -NR⁷C(O)NR⁵R⁶, -NR⁵R⁶, -SO₂NR⁵R⁶, -SO₂R⁴, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, O(C₀-C₄hydrocarbyl)C₃-C₈cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), -(C₀-C₄hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), hvorved hver R¹⁰ bortset fra hydrogen, halo, -CN og -NO₂ er substitueret eller ikke-substitueret;

hver R¹³ og R¹⁴ er de samme eller forskellige, og hver er hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₆ cycloalkyl, C₆-C₁₂ aryl, hvori R¹³ og R¹⁴ eventuelt er forbundet med hinanden for at danne en ring;

X¹ er en binding, -CR⁸R⁹-, -NR⁵-, -CR⁸NR⁵-, -NR⁵CR⁸-, -NR⁵C(O)- -O-, -CO-, -SO-, -SO₂- eller -S-;

X² er -NR⁵-, -O-, -SO₂-, eller -S-;

m, n og q er de samme eller forskellige, og hver er 0, 1, 2, 3, 4 eller 5; og p er 1 eller 2

eller et farmakologisk acceptabelt salt deraf,

hvor "substitueret" betyder, at enhver eller flere hydrogen på det angivne atom eller den angivne gruppe erstattes med én, der er valgt fra en halogen, en cyano-gruppe, en hydroxyl-gruppe, en nitro-gruppe, en alkyl-gruppe, der har 1 til 8 carbonatomer, en cycloalkyl-gruppe, der har 3 til 8 carbonatomer,

en (cycloalkyl)alkyl-gruppe, der har 4 til 8 carbonatomer, en alkenyl, der har én eller flere umættede forbindelser og 2 til 8 carbonatomer, en alkynyl-gruppe, der har én eller flere umættede forbindelser og fra 2 til 8 carbonatomer, en alkoxy-gruppe, der har én eller flere oxygen-forbindelser og 1 til 8 carbonatomer, en aryloxy-gruppe og en alkylthio-gruppe, der har én eller flere thioæter-forbindelser og 1 til 8 carbonatomer.

2. Forbindelsen eller saltet ifølge krav 1, hvori

R¹ er valgt uafhængigt fra hydroxyl, halo, -CO₂H, -SO₂NH₂, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₂haloalkyl eventuelt substitueret med halo, C₁-C₂haloalkoxy og -CO₂(C₁-C₆ alkyl),

R² er valgt fra F og -SO₂NH₂, hvor én af R² er -SO₂NH₂;

R³ er valgt uafhængigt fra

(a) halogen, hydroxyl, SF₅;

(b) C₁-C₆hydrocarbyl, hvor enhver alkylen(CH₂)-gruppe i hydrocarbyl-forbindelsen eventuelt er erstattet med NH, O eller S;

(c) -C₀-C₂hydrocarbyl (fenyl), -C₀-C₂hydrocarbyl (fenyl), -C₀-C₂hydrocarbyl (thiofenyl), -C₀-C₂hydrocarbyl (oxazolyl), -C₀-C₂hydrocarbyl (thiazolyl), -C₀-C₂hydrocarbyl (tetrahydrofuranyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkanyl), -C₀-C₂hydrocarbyl(C₃-C₆cycloalkenyl), -C₀-C₂hydrocarbyl (tetrahydropyrenyl), -C₀-C₂hydrocarbyl (imidazolyl), -C₀-C₂hydrocarbyl(thiophenyl), hvor enhver alkylen(CH₂)-gruppe i C₀-C₂hydrocarbyl-forbindelsen eventuelt er erstattet med NH, O eller S;

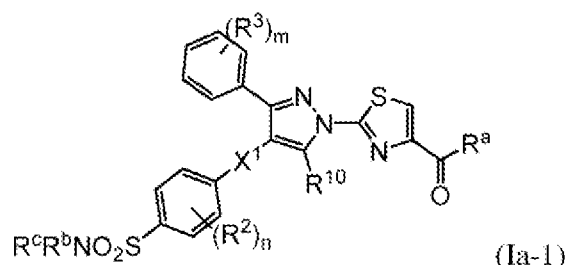
hvor hver af (b) er ikke-substitueret eller substitueret med 1 eller flere substituent, der er valgt uafhængigt fra halogen, hydroxyl, cyano, amino, C₁-C₂haloalkyl og C₁-C₂haloalkoxy;

hvor hver af (c) er ikke-substitueret eller substitueret med 1 eller flere substituent, der er valgt uafhængigt fra halogen, hydroxyl, cyano, amino, C₁-C₄alkyl, C₁-C₆cycloalkyl, mono- eller di-C₁-C₄alkylamino, C₁-C₄alkoxy, C₁-C₂haloalkyl og C₁-C₂haloalkoxy.

3. Forbindelsen eller saltet ifølge ethvert af kravene 1-2, hvori én eller flere af følgende betingelser er opfyldt:

- 5 (a) R^2 er $-\text{SO}_2\text{NR}^5\text{R}^6$ og R^5 , og R^6 er den samme eller forskellig, og hver er H eller $\text{C}_1\text{-C}_8$ alkyl.
 (b) n er 1;
 (c) R^3 er uafhængigt halo, $\text{C}_1\text{-C}_8$ haloalkyl, $\text{C}_1\text{-C}_8$ haloalkoxy, substitueret eller ikke-substitueret $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_8$ alkenyl, $\text{C}_2\text{-C}_8$ alkynyl eller
 10 substitueret eller ikke-substitueret fenyl;
 (d) m er 1 eller 2;
 (e) X^1 er $-\text{CR}^8\text{R}^9$ -, $-\text{O}-$ eller $-\text{NH}-$; og
 (f) X^2 er $-\text{S}$.

- 15 4. Forbindelsen eller salt ifølge krav 1, hvori forbindelsen er en forbindelse i formelen (-Ia-1)



- 20 hvori
 R^a er $-\text{R}^4$, $-\text{OR}^4$, eller $-\text{NR}^5\text{R}^6$, som hver især er substitueret eller ikke-substitueret;
 R^b og R^c er de samme eller forskellige, og hver er H eller substitueret eller ikke-substitueret $\text{C}_1\text{-C}_8$ alkyl;
 25 R^3 er valgt uafhængigt fra hydroxyl, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_8$ alkenyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_1\text{-C}_8$ alkoxy, $\text{C}_3\text{-C}_6$ cycloalkyloxy, aryloxy, halo, $\text{C}_1\text{-C}_8$ haloalkoxy, $\text{C}_1\text{-C}_8$ haloalkyl, haloaryl, haloaryloxy, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{R}^4$, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})\text{R}^4$, -

$(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^4$, $-(\text{CH}_2)_q\text{aryl}$, $-(\text{CH}_2)_q\text{heteroaryl}$, and $-(\text{CH}_2)_q\text{heterocycloalkyl}$, hvorved hver R^2 bortset fra hydroxyl og halo er substitueret eller ikke-substitueret;

R^3 er valgt uafhængigt fra hydroxyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, $-(\text{C}_1$ - $\text{C}_4\text{hydrocarbyl})\text{C}_3$ - $\text{C}_6\text{cycloalkyl}$, C_1 - C_8 alkoxy, $-(\text{C}_0$ - $\text{C}_4\text{alkoxy})\text{C}_3$ - $\text{C}_6\text{cycloalkyl}$, $-(\text{C}_0$ - $\text{C}_4\text{alkoxy})\text{aryl}$, halo, C_1 - C_8 haloalkoxy, C_1 - C_8 haloalkyl, haloaryl, haloaryloxy, $-\text{CN}$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{R}^4$, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^4$, $-(\text{C}_0$ - $\text{C}_4\text{hydrocarbyl})\text{aryl}$, $-(\text{C}_0$ - $\text{C}_4\text{hydrocarbyl})\text{heteroaryl}$, $-(\text{C}_0$ - $\text{C}_4\text{alkoxy})\text{heteroaryl}$, $-(\text{C}_0$ - $\text{C}_4\text{alkoxy})\text{heterocycloalkyl}$, and $-(\text{C}_0$ - $\text{C}_4\text{hydrocarbyl})\text{heterocycloalkyl}$, hvorved hver R^3 bortset fra hydroxyl og halo er substitueret eller ikke-substitueret; eller to R^3 -molekyledele og fenylgruppen, som de er forbundet med, danner en naphthyl-gruppe, der eventuelt er substitueret;

hver R^4 , R^5 , R^6 , R^7 , R^8 og R^9 er den samme eller forskellig, og hver er hydrogen, C_1 - C_8 alkyl eller C_3 - C_6 cycloalkyl, hvorved hver C_1 - C_8 alkyl og C_3 - C_6 cycloalkyl er substitueret eller ikke-substitueret;

R^{10} er hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, hydroxyalkyl, C_1 - C_8 alkoxy, halo, C_1 - C_8 haloalkyl, heteroarylalkyl, $-\text{CN}$, $-\text{CO}_2\text{R}^4$, $-\text{NR}^5\text{R}^6$ eller $-\text{SO}_2\text{R}^4$, hvorved hver R^{10} bortset fra hydrogen og halo er substitueret eller ikke-substitueret;

X^1 er en binding, $-\text{CR}^8\text{R}^9$ -, $-\text{NR}^5$ -, $-\text{O}$ -, $-\text{S}(\text{O})$ - eller $-\text{S}(\text{O})_2$ - eller $-\text{S}$ -, hvorved hver R^8 og R^9 er substitueret eller ikke-substitueret;

n er et heltal fra 0 til 4; og

m og q er de samme eller forskellige, og hver er 0 eller et heltal fra 1-5 eller et farmakologisk acceptabelt salt deraf.

5. Forbindelsen eller salt ifølge krav 4, hvori

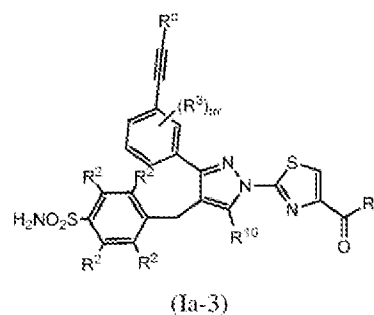
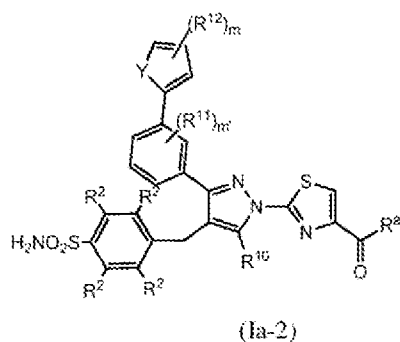
R^a er R^4 , $-\text{OR}^4$ eller $-\text{NR}^5\text{R}^6$;

R^3 er én eller flere substituent, der er valgt uafhængigt fra halo, hydroxyl, $-\text{CN}$, $-\text{NO}_2$, amino, $-\text{C}(\text{O})\text{R}^4$, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{C}(\text{O})\text{R}^4$, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, C_1 - C_2 haloalkyl og C_1 - C_2 haloalkoxy;

hver R^4 , R^5 og R^6 er den samme eller forskellig, og hver er hydrogen eller C_1 - C_2 alkyl; og R^{10} er hydrogen, halo, $-CN$, C_1 - C_4 alkyl, hydroxyl C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_2 - C_4 alkenyl, $(C_3$ - C_6 cycloalkyl) C_0 - C_2 alkyl, C_1 - C_2 haloalkyl, C_1 - C_2 haloalkoxy, $-CO_2R^4$, $-NR^5R^6$ eller $-SO_2R^4$; og

én af R^3 er valgt fra C_2 - C_6 alkynyl, $-(C_0$ - C_2 alkyl) C_3 - C_6 cycloalkyl, $-(C_2$ - C_4 alkenyl) C_3 - C_6 cycloalkyl, $-(C_2$ - C_4 alkynyl) C_3 - C_6 cycloalkyl, $-(C_0$ - C_2 alkoxy) C_3 - C_6 cycloalkyl, dihydropyranyl, $-(C_0$ - C_4 alkoxy)fenyl, $-(C_0$ - C_4 alkyl)fenyl, $-(C_2$ - C_4 alkenyl)fenyl, $-(C_2$ - C_4 alkynyl)fenyl, $-(C_0$ - C_4 alkoxy)heteroaryl, $-(C_0$ - C_4 alkyl)heteroaryl, $-(C_2$ - C_4 alkenyl)heteroaryl og $-(C_2$ - C_4 alkynyl)heteroaryl, hvor heteroaryl er valgt fra thienyl, furanyl, thiazolyl, pyrazolyl, imidazolyl; hvorved hver ene eller flere substituent er valgt fra hydroxyl, halo, $-CN$, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkynyl, C_1 - C_4 alkoxy, $(C_3$ - C_6 cycloalkyl) C_0 - C_2 alkyl, C_1 - C_2 haloalkyl og C_1 - C_2 haloalkoxy; og 0 eller 1 eller flere R^3 er valgt fra hydroxyl, halo, $-CN$, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_2 haloalkyl og C_1 - C_2 haloalkoxy.

6. Forbindelsen eller saltet ifølge krav 4, hvori forbindelsen er en forbindelse i formelen (Ia-2) eller formelen (Ia-3):



hvor

$Y = -CH=CH-$, O, S, NH;

R^a er $-R^4$, $-OR^4$ eller $-NR^5R^6$, hvorved hver R^4 , R^5 og R^6 er substitueret eller ikke-substitueret;

hver R^2 er den samme eller forskellig, og er hydrogen, hydroxyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, C_1 - C_8 alkoxy, C_3 - C_6 cycloalkyloxy, aryloxy, halo, C_1 - C_8 haloalkoxy, C_1 - C_8 haloalkyl, haloaryl, haloaryloxy, -CN, -NO₂, -C(O) R^4 , -CO₂ R^4 , -C(O)NR⁵ R^6 , -NR⁵C(O) R^4 , -(CH₂)_qNR⁵(SO₂) R^4 , -(CH₂)_qNR⁵C(O) R^4 , -
 5 (CH₂)_qNR⁷C(O)NR⁵ R^6 , - (CH₂)_qNR⁵ R^6 , -(CH₂)_qSO₂NR⁵ R^6 , -(CH₂)_qSO₂ R^4 , -(CH₂)_qaryl, -(CH₂)_qheteroaryl, eller -(CH₂)_qheterocycloalkyl, hvorved hver R^3 bortset fra hydrogen, hydroxyl og halo er substitueret eller ikke-substitueret;

10 hver R^{11} og R^{12} er uafhængigt valgt fra hydroxyl, halo, -CN, NO₂, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_1 - C_8 alkoxy, C_1 - C_2 haloalkoxy, C_1 - C_2 haloalkyl, C(O) R^4 , CO₂ R^4 , C(O)NR⁵ R^6 , NR⁵C(O) R^4 , -(CH₂)_qNR⁵(SO₂) R^4 , - (CH₂)_qNR⁵C(O) R^4 , -(CH₂)_qNR⁷C(O)NR⁵ R^6 , -(CH₂)_qNR⁵ R^6 , - (CH₂)_qSO₂NR⁵ R^6 og -(CH₂)_qSO₂ R^4 , hvorved hver R^{11} og R^{12} bortset fra

15 hydroxyl, halo, -CN og NO₂ er substitueret eller ikke-substitueret; R^d er hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, hydroxyl, hydroxyalkyl, C_1 - C_8 alkoxy, halo, C_1 - C_8 haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -CN, -CO₂ R^4 , -NR⁵ R^6 eller -SO₂ R^4 , hvorved hver R^d bortset fra halo og -CN er substitueret eller

20 ikke-substitueret; hver R^4 , R^5 , R^6 og R^7 er den samme eller forskellig, og hver er hydrogen, C_1 - C_8 alkyl eller C_3 - C_6 cycloalkyl, hvorved hver C_1 - C_8 alkyl og C_3 - C_6 cycloalkyl er substitueret eller ikke-substitueret;

25 R^{10} er hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, hydroxyalkyl, C_1 - C_8 alkoxy, halo, C_1 - C_8 haloalkyl, -CN, -CO₂ R^4 , -NR⁵ R^6 eller -SO₂ R^4 , hvorved hver R^{10} bortset fra hydrogen og halo er substitueret eller ikke-substitueret;

m og q er de samme eller forskellige, og hver er 0, 1, 2, 3, 4 eller 5;; og m' er 0 eller et heltal fra 1-4.

30

7. Forbindelsen eller saltet ifølge krav 6, hvori

R^a er hydrogen, hydroxyl, amino, C_1 - C_2 alkyl, C_1 - C_2 alkoxy og mono- eller di- C_1 - C_2 alkylamino-;

hver R^2 er den samme eller forskellig og er valgt uafhængigt fra hydrogen, halo, hydroxyl, -CN, -NO₂, amino, -C(O) R^4 , -CO₂ R^4 , -C(O)NR⁵ R^6 , -NR⁵C(O) R^4 , C_1 - C_2 alkyl, C_1 - C_2 alkoxy, C_1 - C_2 haloalkyl og C_1 - C_2 haloalkoxy;

hver R^3 er valgt uafhængigt fra hydroxyl, halo, -CN, NO₂, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, C_1 - C_2 haloalkoxy og C_1 - C_2 haloalkyl;

hver R^4 , R^5 , R^6 og R^7 er den samme eller forskellig, og hver er hydrogen eller C_1 - C_2 alkyl;

m' er 0 eller et heltal fra 1-4;

R^{10} er hydrogen, halo, -CN, C_1 - C_4 alkyl, hydroxyl C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_2 - C_4 alkenyl, (C_3 - C_6 cycloalkyl) C_0 - C_2 alkyl, C_1 - C_2 haloalkyl, C_1 - C_2 haloalkoxy, -CO₂ R^4 , -NR⁵ R^6 eller -SO₂ R^4 ;

R^d er thienyl substitueret med methyl.

8. Forbindelsen eller saltet ifølge krav 6, hvori

R^a er hydroxyl eller substitueret eller ikke-substitueret -O(C_1 - C_8 alkyl);

R^3 er hydrogen, substitueret eller ikke-substitueret C_1 - C_8 alkyl, substitueret eller ikke-substitueret C_1 - C_8 alkoxy eller halo;

R^{11} og R^{12} er hver uafhængigt valgt fra substitueret eller ikke-substitueret C_1 - C_4 alkyl, substitueret eller ikke-substitueret C_1 - C_8 alkoxy eller halo;

R^{10} er hydrogen, substitueret eller ikke-substitueret C_1 - C_8 alkyl, substitueret eller ikke-substitueret cyclopropyl, substitueret eller ikke-substitueret -CH₂-

cyclopropyl, substitueret eller ikke-substitueret -CH=CH₂, substitueret eller

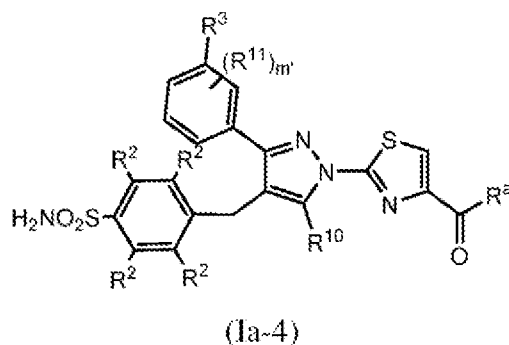
ikke-substitueret -C≡C-cyclopropyl, -I, -CF₃, -NH₂ eller -CN;

m er 0, 1 eller 2; og

m' er 0.

9. Forbindelsen eller salt ifølge krav 4, hvori forbindelsen er en forbindelse i

formlen (Ia-4):



hvor

- 5 R^a er $-R^4$, $-OR^4$ eller $-NR^5R^6$, hvorved hver R^4 , R^5 og R^6 er substitueret eller ikke-substitueret;
- hver R^2 er den samme eller forskellig og er hydrogen, hydroxyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, C_1 - C_8 alkoxy, C_3 - C_6 cycloalkyloxy, aryloxy, halo, C_1 - C_8 haloalkoxy, C_1 - C_8 haloalkyl, haloaryl, haloaryloxy, $-CN$, $-NO_2$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^5R^6$, $-NR^5C(O)R^4$, $-(CH_2)_qNR^5(SO_2)R^4$, $-(CH_2)_qN_2R^5C(O)R^4$, $-(CH_2)_qNR^7C(O)NR^5R^6$, $-(CH_2)_qNR^5R^6$, $-(CH_2)_qSO_2NR^5R^6$, $-(CH_2)_qSO_2R^4$, $-(CH)_q$ aryl, $-(CH_2)_q$ heteroaryl eller $-(CH_2)_q$ heterocycloalkyl, hvorved hver R^2 bortset fra hydrogen, hydroxyl og halo er substitueret eller ikke-substitueret;
- 15 R^3 er valgt fra C_2 - C_6 alkynyl, $-(C_0$ - C_2 alkyl) C_3 - C_6 cycloalkyl, $-(C_2$ - C_4 alkenyl) C_3 - C_6 cycloalkyl, $-(C_2$ - C_4 alkynyl) C_3 - C_6 cycloalkyl, $-(C_0$ - C_2 alkoxy) C_3 - C_6 cycloalkyl, dihydropyranyl, $-(C_0$ - C_4 alkoxy)fenyl, $-(C_0$ - C_4 alkyl)fenyl, $-(C_2$ - C_4 alkenyl)fenyl, $-(C_2$ - C_4 alkynyl)fenyl, $-(C_0$ - C_4 alkoxy)heteroaryl, $-(C_0$ - C_4 alkyl)heteroaryl, $-(C_2$ - C_4 alkenyl)heteroaryl og $-(C_2$ - C_4 alkynyl)heteroaryl, hvor heteroaryl er en 5- til 6-leddet heteroaryl, der har 1, 2, 3 eller 4 heteroatomer, der er valgt uafhængigt fra N, O og S, og hvor hver R^3 er ikke-substitueret eller substitueret med én eller flere substituent, der er valgt fra hydroxyl, halo, $-CN$, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkynyl, C_1 - C_4 alkoxy, $(C_3$ - C_6 cycloalkyl) C_0 - C_2 alkyl, C_1 - C_2 haloalkyl og C_1 - C_2 haloalkoxy;
- 20 hver R^{11} er valgt uafhængigt fra hydroxyl, halo, $-CN$, NO_2 , C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_1 - C_8 alkoxy, C_1 - C_2 haloalkoxy, C_1 - C_2 haloalkyl, $-C(O)R^4$, $-$
- 25

CO_2R^4 , $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^5(\text{SO}_2)\text{R}^4$, -
 $(\text{CH}_2)_q\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{NR}^5\text{R}^6$, -
 $(\text{CH}_2)_q\text{SO}_2\text{NR}^5\text{R}^6$ og $-(\text{CH}_2)_q\text{SO}_2\text{R}^4$, hvorved hver R^{11} og R^{12} bortset fra
hydroxyl, halo, $-\text{CN}$, NO_2 er substitueret eller ikke-substitueret;

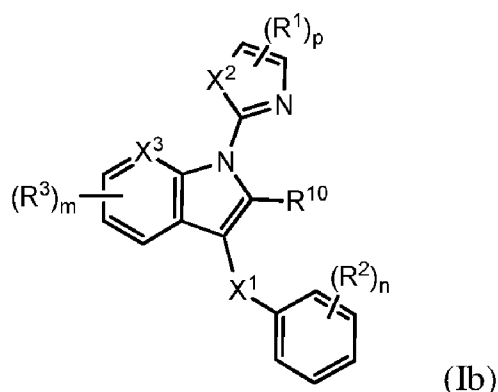
5 hver R^4 , R^5 , R^6 og R^7 er den samme eller forskellig, og hver er hydrogen,
 C_1 - C_8 alkyl eller C_3 - C_6 cycloalkyl, hvorved hver C_1 - C_8 alkyl og C_3 - C_6
cycloalkyl er substitueret eller ikke-substitueret;

R^{10} er hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6
cycloalkyl, C_3 - C_6 cycloalkylalkyl, hydroxyalkyl, C_1 - C_8 alkoxy, halo, C_1 - C_8
10 haloalkyl, $-\text{CN}$, $-\text{CO}_2\text{R}^4$, $-\text{NR}^5\text{R}^6$ eller $-\text{SO}_2\text{R}^4$, hvorved hver R^{10} bortset fra
hydrogen og halo er substitueret eller ikke-substitueret;

mis 0 eller 1, 2, 3, 4 eller 5; og

m' er 0 eller et heltal fra 1-4.

15 **10.** Forbindelsen eller saltet i formlen (Ib):



hvor

R^1 er valgt uafhængigt fra halo, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-(\text{C}_1$ - C_8 hydrocarbyl),
 $-\text{C}(\text{O})\text{NHOH}$, $-\text{C}(\text{O})\text{OCR}^5\text{R}^6\text{OC}(\text{O})\text{OR}^4$, $-(\text{C}_0$ - C_4 hydrocarbyl) (mono- eller
bicyklisk heterocyclus, der har 1 til 4 heteroatomer, der er valgt uafhængigt
fra N, O og S), $-\text{C}(\text{O})-(\text{C}_0$ - C_4 hydrocarbyl) (mono- eller bicyklisk
25 heterocyclus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O,
and S), $-\text{P}(\text{O})(\text{OH})_2$, $-\text{B}(\text{OR}^{13})(\text{OR}^{14})$, $-\text{SO}_2(\text{OH})$, $-\text{C}(\text{O})\text{NHS}(\text{O})_2\text{Me}$ og -

R³ er valgt uafhængigt af hydroxyl, halo, -CN, -NO₂, -SF₅, C₁-C₈hydrocarbyl, -O(C₁-C₈hydrocarbyl), -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkyl, -(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₃-C₈ cycloalkenyl, -O(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -(C₀-C₄hydrocarbyl)C₆-C₁₂aryl, -O(C₀-C₄hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), -(C₀-C₄hydrocarbyl)(mono- og bicyklisk heterocyklus, der har 1 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), -C(O)R⁴, -CO₂R⁴, -C(O)NR⁵R⁶, -NR⁵C(O)R⁴, -(CH₂)_qNR⁵(SO₂)R⁴, -(CH₂)_qNR⁵C(O)R⁴, -

$(\text{CH}_2)_q\text{NR}^7\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{SO}_2\text{NR}^5\text{R}^6$, $-(\text{CH}_2)_q\text{SO}_2\text{R}^4$,
 hvorved hver C_1 - C_8 hydrocarbyl, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0$ -
 $\text{C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$ cycloalkyl, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$ cycloalkyl, -
 5 $(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$ cycloalkenyl, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$
 cycloalkenyl, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})(\text{mono- og bicyklisk heterocyklus, der har 1}$
 til 4 heteroatomer, der er valgt uafhængigt fra N, O og S), $-(\text{C}_0$ -
 $\text{C}_4\text{hydrocarbyl})(\text{mono- og bicyklisk heterocyklus, der har 1 til 4}$
 heteroatomer, der er valgt uafhængigt fra N,
 10 O og S) er substitueret eller ikke-substitueret; eller
 hver R^4 , R^5 , R^6 , R^7 , R^8 og R^9 er den samme eller forskellig, og hver er
 hydrogen, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_8$ alkenyl, $\text{C}_3\text{-C}_6$ cycloalkyl, aryl, heteroaryl
 eller heterocycloalkyl, hvorved hver $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_2\text{-C}_8$ alkenyl, $\text{C}_3\text{-C}_6$
 cycloalkyl, aryl, heteroaryl eller heterocycloalkyl er substitueret eller ikke-
 15 substitueret;
 R^{10} er hydrogen, halo, $-\text{CN}$, $-\text{NO}_2$, $-\text{CO}_2\text{R}^4$, $-\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5(\text{SO}_2)\text{R}^4$, -
 $\text{NR}^5\text{C}(\text{O})\text{R}^4$, $-\text{NR}^7\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{NR}^5\text{R}^6$, $-\text{SO}_2\text{NR}^5\text{R}^6$, $-\text{SO}_2\text{R}^4$, C_1 -
 C_8 hydrocarbyl, $-\text{O}(\text{C}_1\text{-C}_8\text{hydrocarbyl})$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$
 cycloalkyl, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$ cycloalkyl, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$
 20 C_8 cycloalkenyl, $-\text{O}(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_3\text{-C}_8$ cycloalkenyl, $-\text{O}(\text{C}_0$ -
 $\text{C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-(\text{C}_0\text{-C}_4\text{hydrocarbyl})\text{C}_6\text{-C}_{12}\text{aryl}$, $-\text{O}(\text{C}_0$ -
 $\text{C}_4\text{hydrocarbyl})(\text{mono- og bicyklisk heterocyklus, der har 1 til 4}$
 heteroatomer, der er valgt uafhængigt fra N, O og S), $-(\text{C}_0$ -
 $\text{C}_4\text{hydrocarbyl})(\text{mono- og bicyklisk heterocyklus, der har 1 til 4}$
 25 heteroatomer, der er valgt uafhængigt fra N, O og S), hvorved hver R^{10}
 bortset fra hydrogen, halo, $-\text{CN}$ og $-\text{NO}_2$ er substitueret eller ikke-
 substitueret;
 hver R^{13} og R^{14} er de samme eller forskellige, og hver er hydrogen, $\text{C}_1\text{-C}_8$
 alkyl, $\text{C}_2\text{-C}_8$ alkenyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_6\text{-C}_{12}$ aryl, hvori R^{13} og R^{14}
 30 eventuelt er forbundet med hinanden for at danne en ring;
 X^1 er en binding, $-\text{CR}^8\text{R}^9$, $-\text{NR}^5$, $-\text{CR}^8\text{NR}^5$, $-\text{NR}^5\text{CR}^8$, $-\text{NR}^5\text{C}(\text{O})$, $-\text{O}$, -
 CO , $-\text{SO}$, $-\text{SO}_2$ eller $-\text{S}$;

X^2 er $-NR^5$ -, $-O$ - eller $-SO_2$ - eller $-S$ -;

X^3 er CH eller N ;

m og q er de samme eller forskellige, og hver er 0 eller et heltal fra 1-5;

n er et heltal fra 1-5; og

p er 1 eller 2

hvor "substitueret" betyder, at enhver eller flere hydrogen på det angivne atom eller den angivne gruppe erstattes med én, der er valgt fra en halogen, en cyano-gruppe, en hydroxyl-gruppe, en nitro-gruppe, en alkyl-gruppe, der har 1 til 8 carbonatomer, en cycloalkyl-gruppe, der har 3 til 8 carbonatomer, en (cycloalkyl)alkyl-gruppe, der har 4 til 8 carbonatomer, en alkenyl, der har én eller flere umættede forbindelser og 2 til 8 carbonatomer, en alkynyl-gruppe, der har én eller flere umættede forbindelser og fra 2 til 8 carbonatomer, en alkoxy-gruppe, der har én eller flere oxygen-forbindelser og 1 til 8 carbonatomer, en aryloxy-gruppe og en alkylthio-gruppe, der har én eller flere thioæter-forbindelser og 1 til 8 carbonatomer.

- 11.** Forbindelsen eller saltet ifølge krav 10, hvor én eller flere af følgende betingelser er opfyldt:

(a) R^1 er $-CO_2H$ eller $-CO_2(C_1-C_8 \text{ alkyl})$, hvor C_1-C_8 alkyl er substitueret eller ikke-substitueret;

(b) R^2 er $-SO_2NR^5R^6$ og R^5 og R^6 er de samme eller forskellige, og hver er H eller C_1-C_8 alkyl;

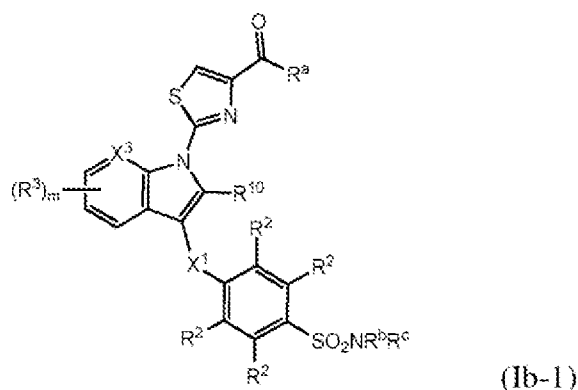
(c) hver R^3 er uafhængigt halo, C_1-C_8 haloalkyl, C_1-C_8 haloalkoxy, substitueret eller ikke-substitueret C_1-C_4 alkyl, substitueret eller ikke-substitueret C_2-C_8 alkenyl, substitueret eller ikke-substitueret C_2-C_8 alkynyl, substitueret eller ikke-substitueret $-(CH_2)_q$ aryl, substitueret eller ikke-substitueret $-(CH_2)_q$ heteroaryl eller substitueret eller ikke-substitueret $-(CH_2)_q$ heterocycloalkyl;

(d) n er 1;

(e) m er 0, 1 eller 2;

(f) R^{10} er substitueret eller ikke-substitueret C_1 - C_3 alkyl, substitueret eller ikke-substitueret cyclopropyl, substitueret eller ikke-substitueret $-(C_1$ - C_3 alkyl)-cyclopropyl, substitueret eller ikke-substitueret $-CH=CH_2$, substitueret eller ikke-substitueret $-C\equiv C$ -cyclopropyl, substitueret eller ikke-substitueret fenyl, substitueret eller ikke-substitueret benzyl, $-OH$, $-CH_2OH$, $-CF_3$, $-CF_2CF_3$, $-Cl$, $-F$, $-I$, $-CN$, $-CH_2CN$, $-NH_2$ eller $-CH_2$ -tetrazolyl;
 (g) X^1 er $-CR^8R^9$ -, $-O$ - eller $-NH$ -; og
 (h) X^2 er $-S$ -.

10 12. Forbindelsen eller saltet ifølge krav 10, hvori forbindelsen er en forbindelse i formelen (Ib-1)



15 hvori

R^a er $-R^4$, $-OR^4$ eller $-NR^5R^6$, hvorved hver R^4 , R^5 og R^6 er substitueret eller ikke-substitueret;

20 R^b og R^c er de samme eller forskellige, og hver er H eller substitueret eller ikke-substitueret C_1 - C_8 alkyl;

hver R^2 er den samme eller forskellig, og hver er hydrogen, hydroxyl, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, C_1 - C_8 alkoxy, C_3 - C_6 cycloalkyloxy, aryloxy, halo, C_1 - C_8 haloalkoxy, C_1 - C_8 haloalkyl, haloaryl, haloaryloxy, $-CN$, $-NO_2$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^5R^6$, $-NR^5C(O)R^4$, $-$

25 $(CH_2)_qNR^5(SO_2)R^4$, $-(CH_2)_qNR^5C(O)R^4$, $-(CH_2)_qNR^7C(O)NR^5R^6$, $-(CH_2)_qNR^5R^6$, $- (CH_2)_qSO_2NR^5R^6$, $-(CH_2)_qSO_2R^4$, $-(CH_2)_q$ aryl, $-$

$(\text{CH}_2)_q$ heteroaryl eller $-(\text{CH}_2)_q$ heterocycloalkyl, hvorved hver R^2 bortset fra hydrogen, hydroxyl, halo, $-\text{CN}$ og $-\text{NO}_2$ er substitueret eller ikke-substitueret;

R^3 er halo, $-\text{C}(\text{O})\text{R}^4$, C_2 - C_8 alkynyl, haloaryl, $-(\text{CH}_2)_q$ aryl, $-(\text{CH}_2)_q$ heteroaryl eller $-(\text{CH}_2)_q$ heterocycloalkyl, hvorved hver R^3 er substitueret eller ikke-substitueret;

hver R^4 , R^5 , R^6 , R^7 , R^8 og R^9 er den samme eller forskellig, og hver er hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, aryl, heteroaryl eller heterocycloalkyl, hvorved hver C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_3 - C_6 cycloalkyl, aryl, heteroaryl eller heterocycloalkyl er substitueret eller ikke-substitueret;

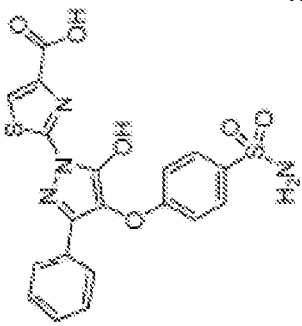
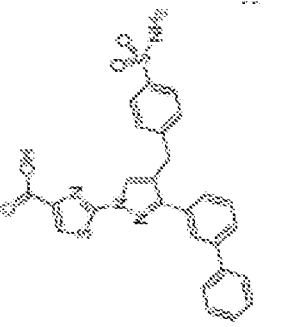
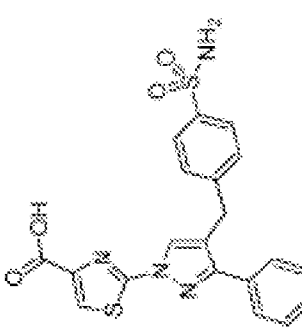
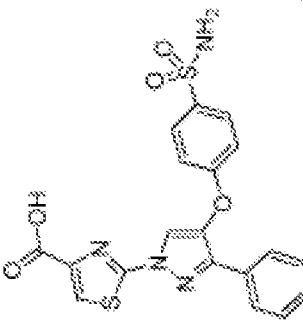
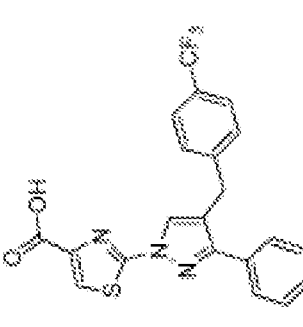
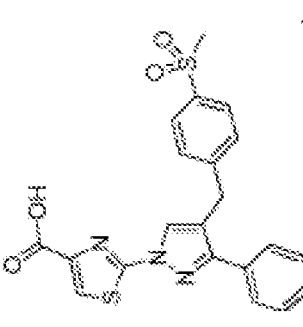
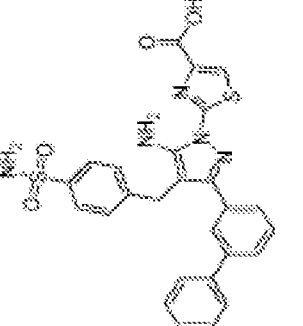
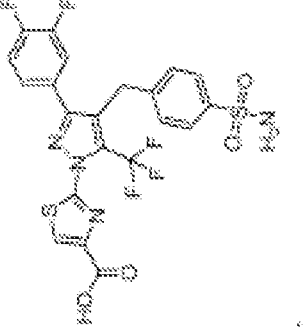
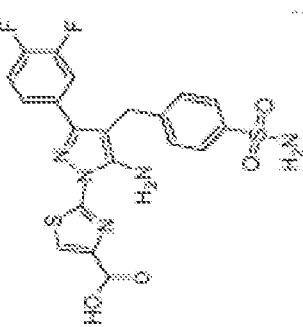
R^{10} er hydrogen, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkylalkyl, hydroxyl, hydroxyalkyl, C_1 - C_8 alkoxy, C_1 - C_8 haloalkyl, halo, aryl, arylalkyl, heteroarylalkyl, $-\text{CN}$, $-\text{CO}_2\text{R}^4$, $-\text{NR}^5\text{R}^6$ eller $-\text{SO}_2\text{R}^4$, hvorved hver R^{10} bortset fra hydrogen, hydroxyl, halo og $-\text{CN}$ er substitueret eller ikke-substitueret;

X^1 er en binding, $-\text{CR}^8\text{R}^9$ -, $-\text{NR}^5$ -, $-\text{O}$ -, $-\text{SO}$ - eller $-\text{SO}_2$ - eller $-\text{S}$ -, hvorved hver R^5 , R^8 og R^9 er substitueret eller ikke-substitueret;

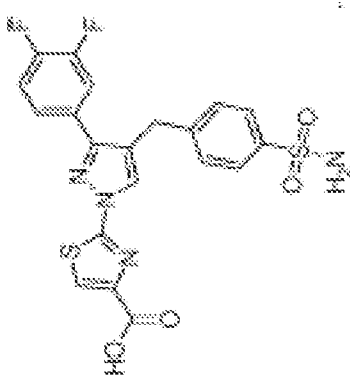
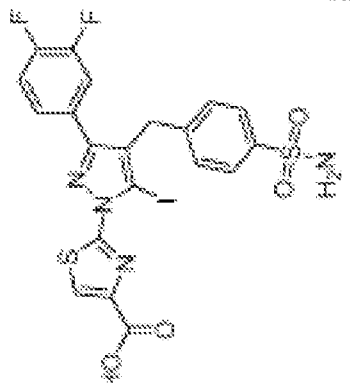
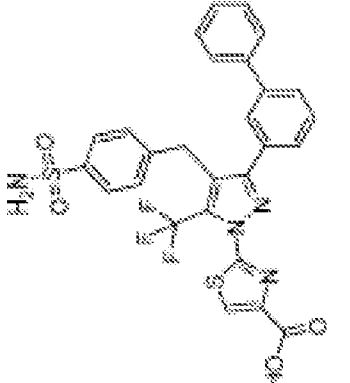
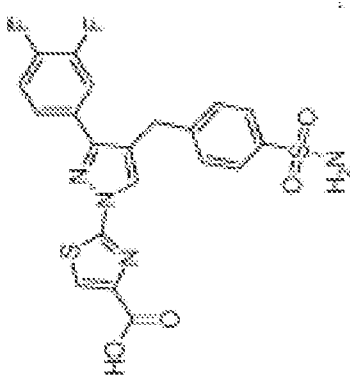
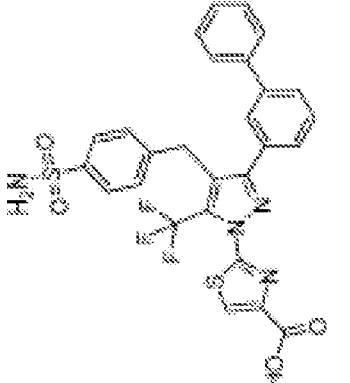
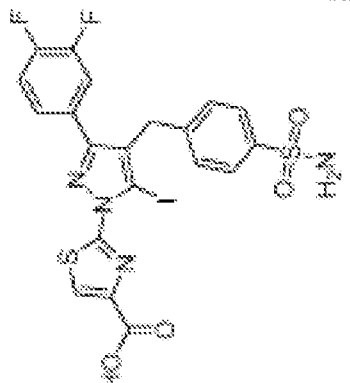
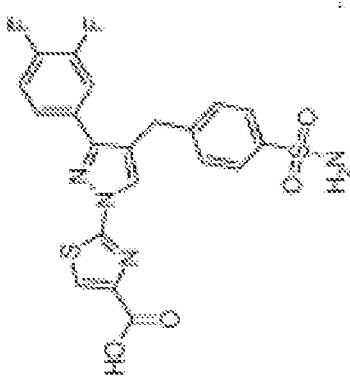
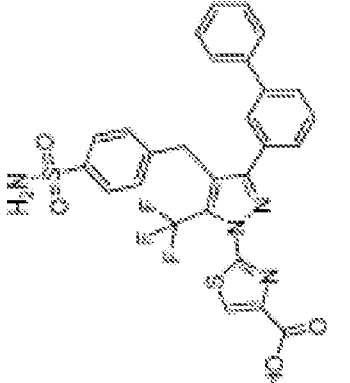
X^3 er CH eller N ; og

m og q er de samme eller forskellige, og hver er 0 eller et heltal fra 1-5.

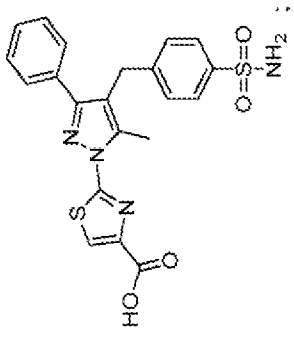
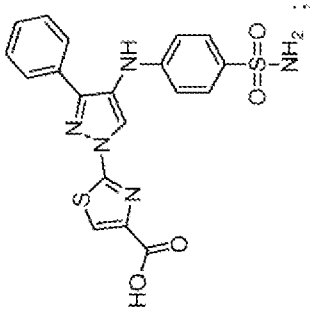
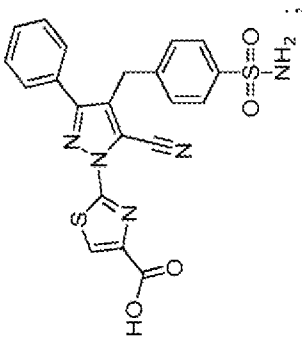
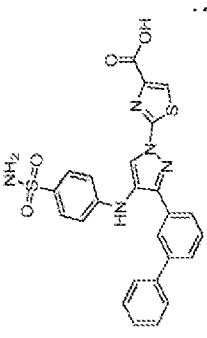
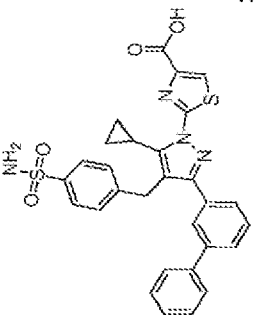
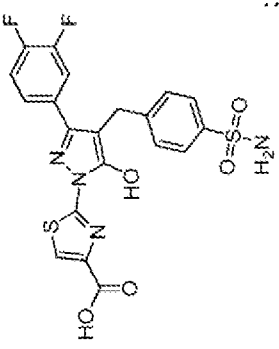
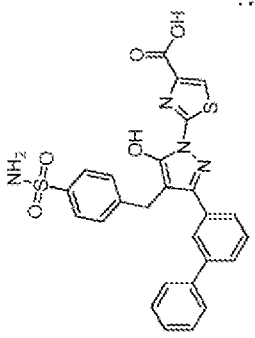
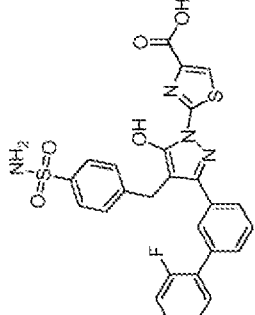
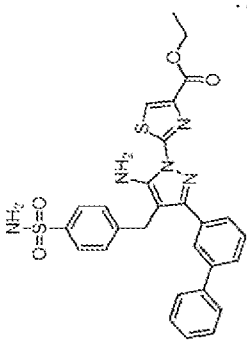
- 13.** Forbindelsen eller det farmakologisk acceptable salt deraf ifølge krav 1, som er valgt fra følgende strukturer (under hver af dem findes forbindelsesnummeret):

 ;	 ;	 ;
24	25	26
 ;	 ;	 ;
27	28	29
 ;	 ;	 ;
30	31	32

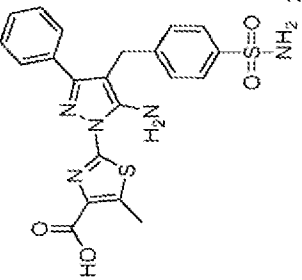
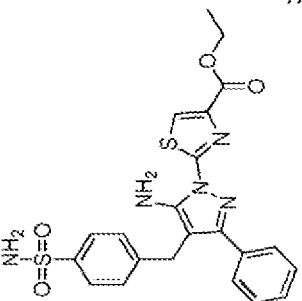
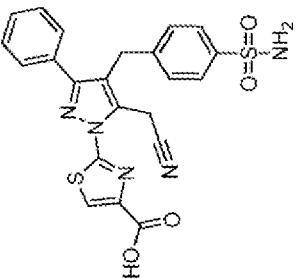
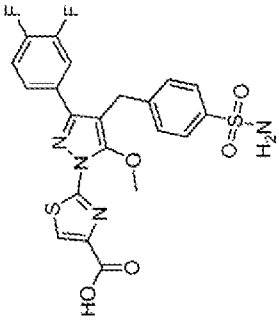
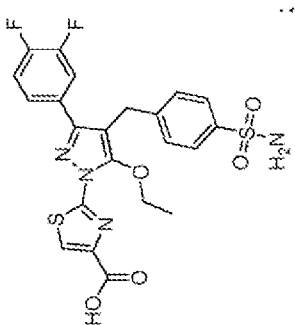
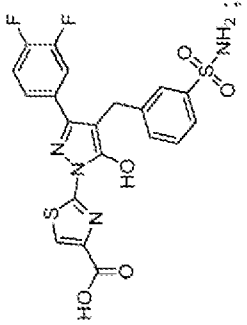
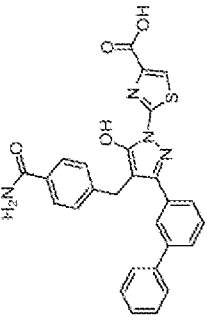
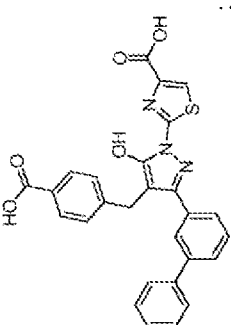
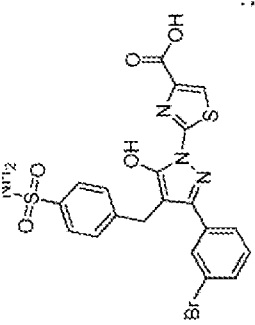
(fortsat)

38		40	
39		41	
42		43	
44		45	

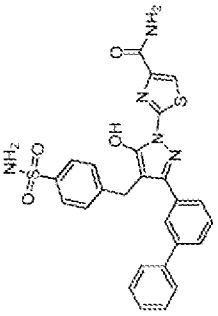
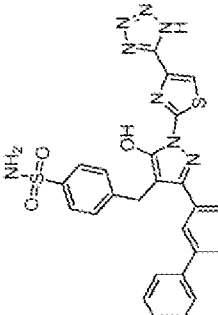
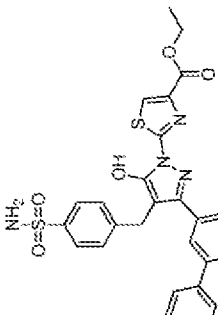
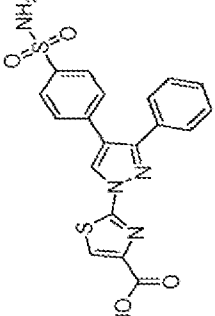
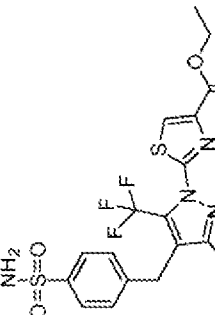
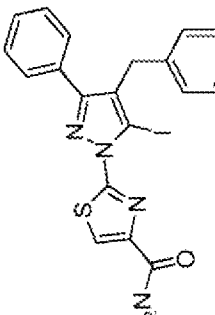
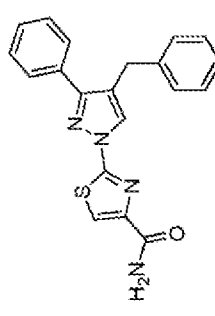
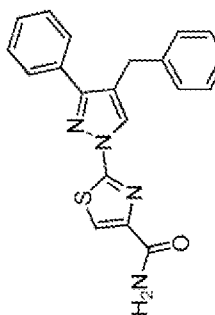
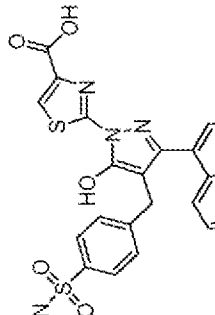
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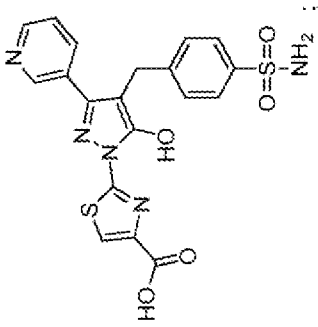
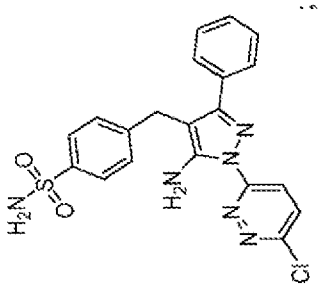
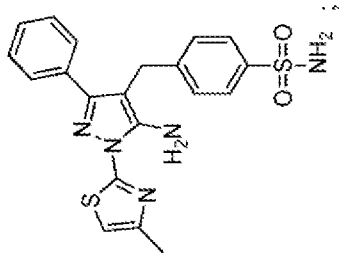
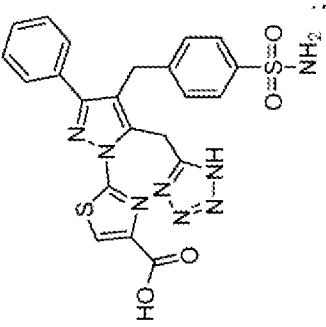
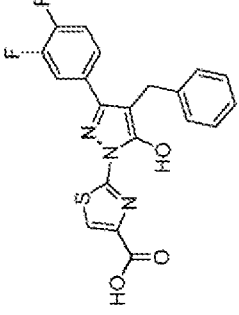
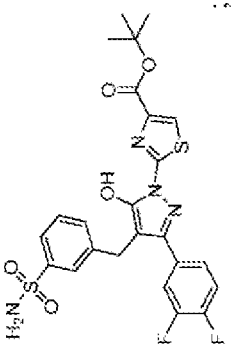
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	67		68		69

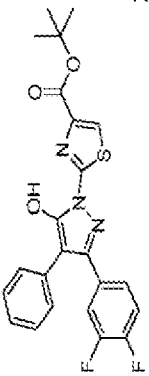
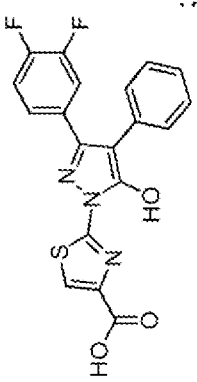
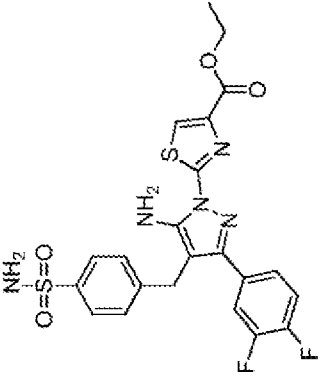
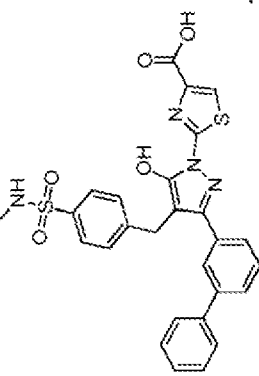
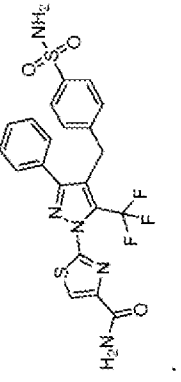
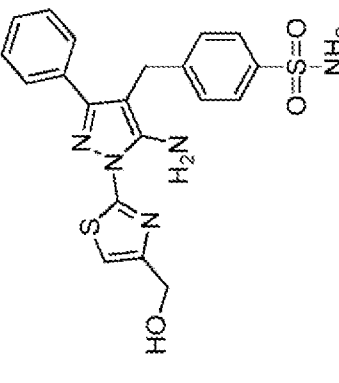
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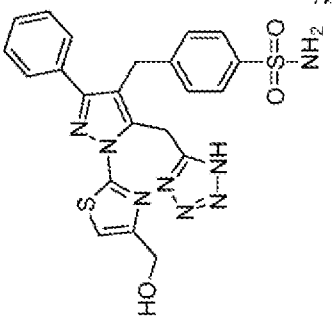
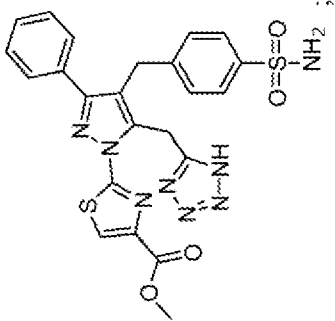
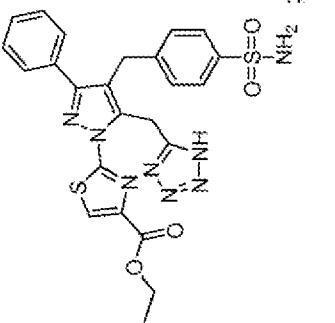
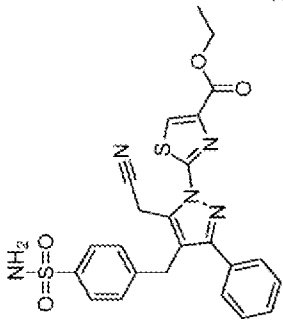
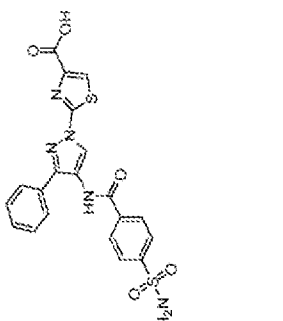
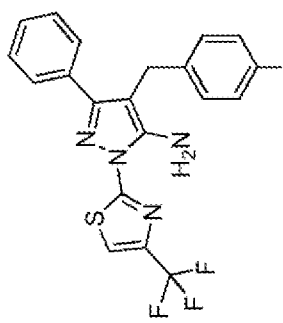
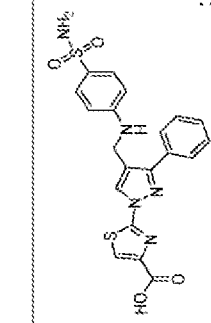
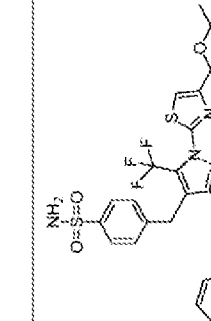
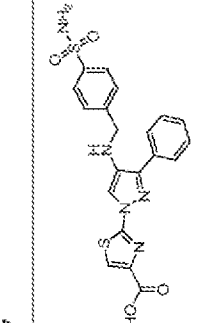
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82	83	86
		
87	88	89

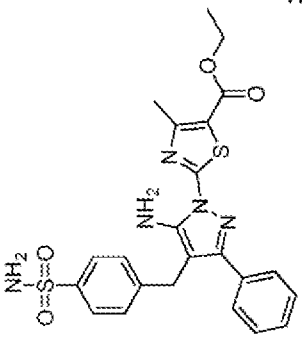
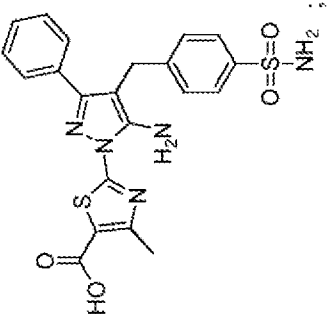
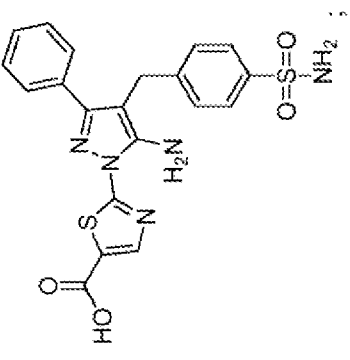
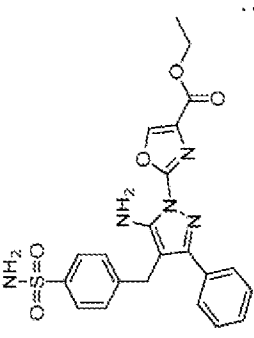
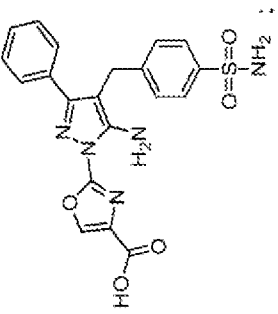
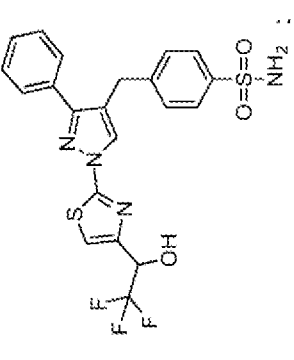
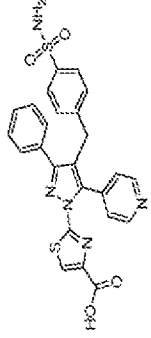
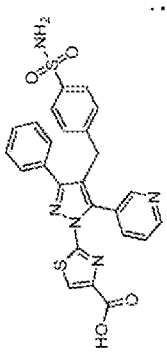
(fortsat)

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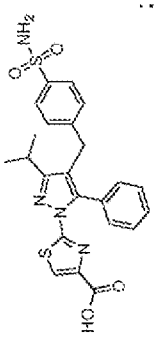
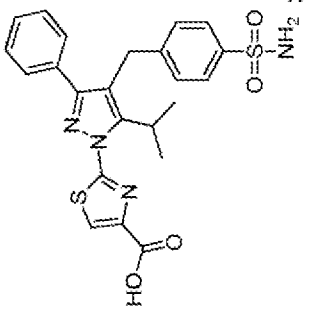
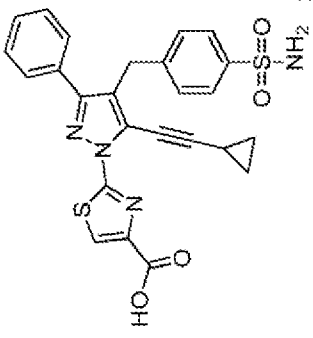
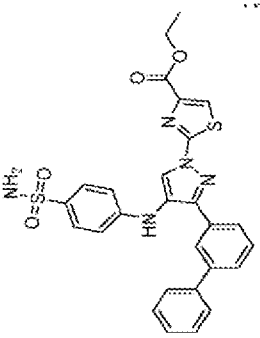
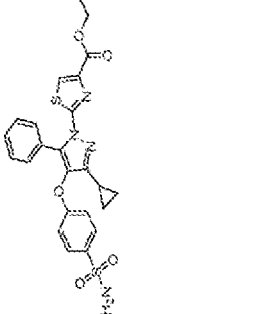
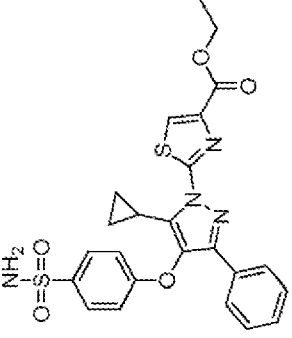
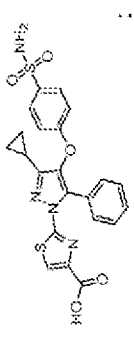
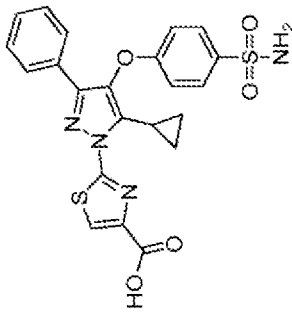
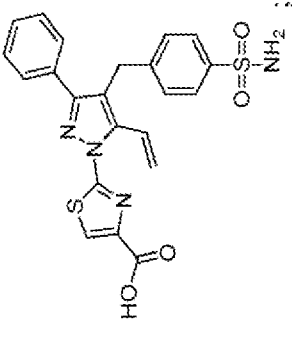
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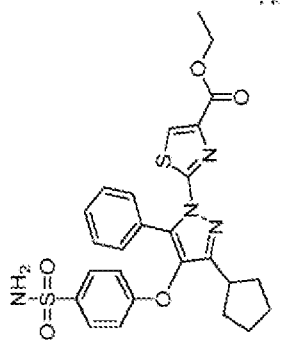
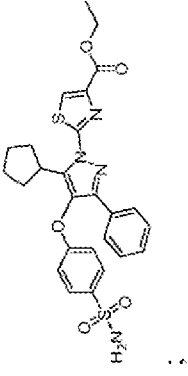
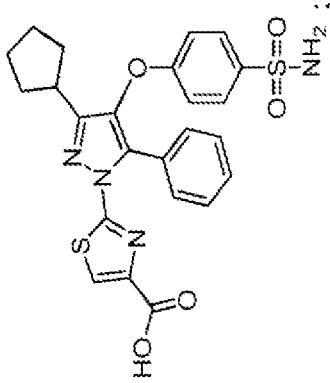
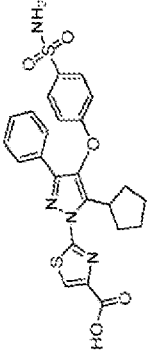
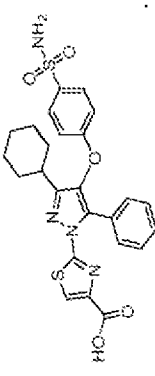
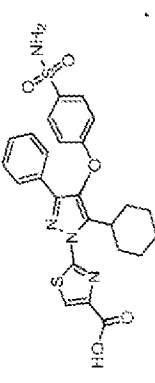
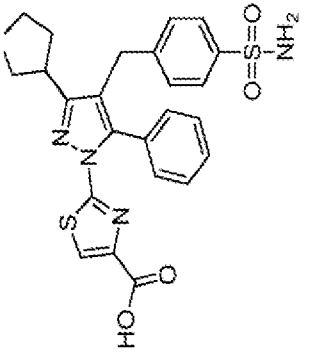
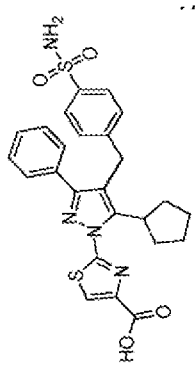
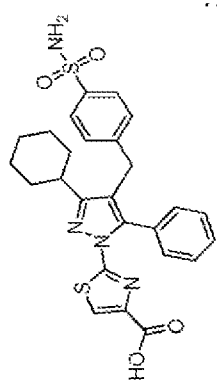
(fortsat)

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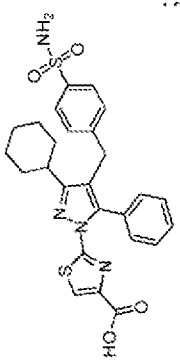
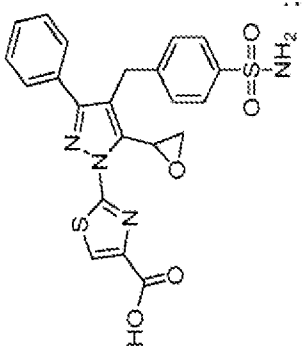
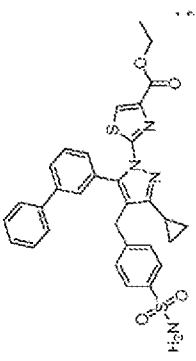
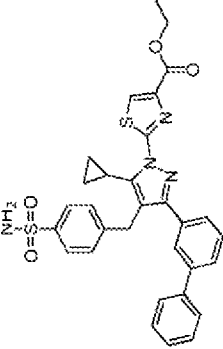
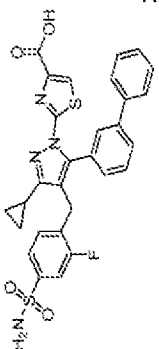
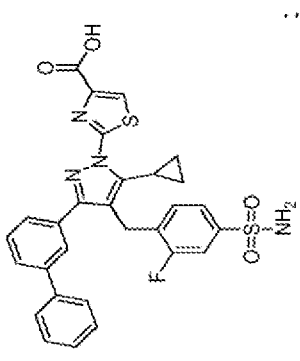
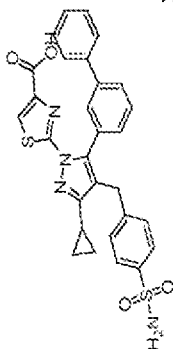
(fortsat)

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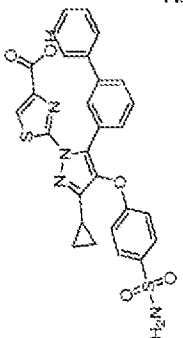
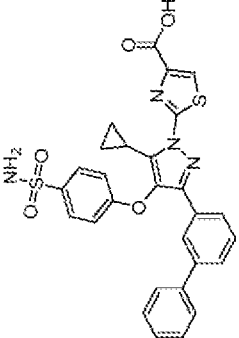
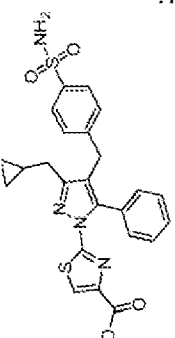
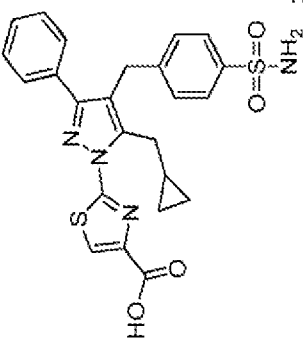
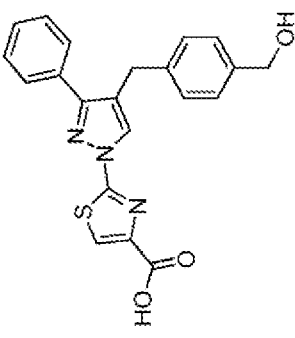
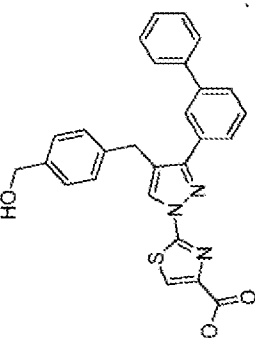
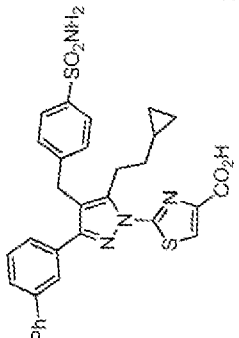
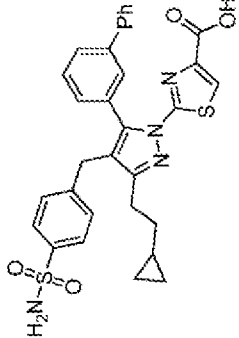
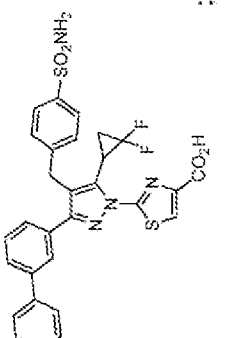
(fortsat)

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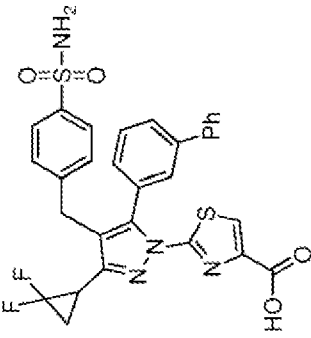
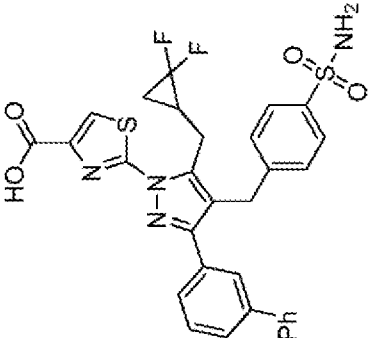
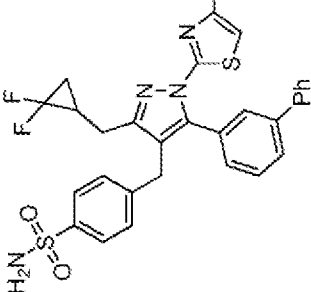
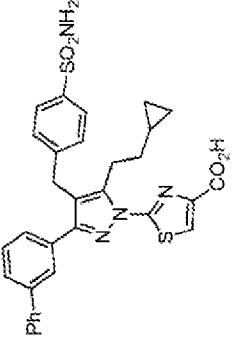
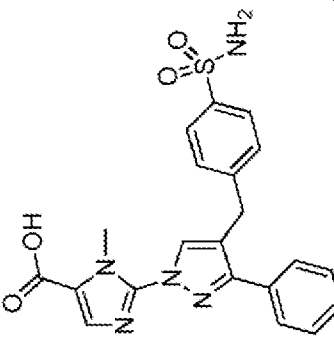
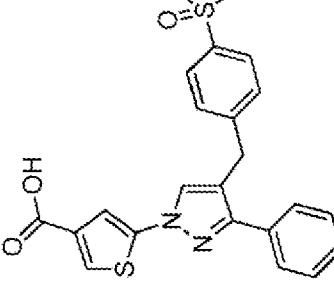
(fortsat)

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(fortsat)

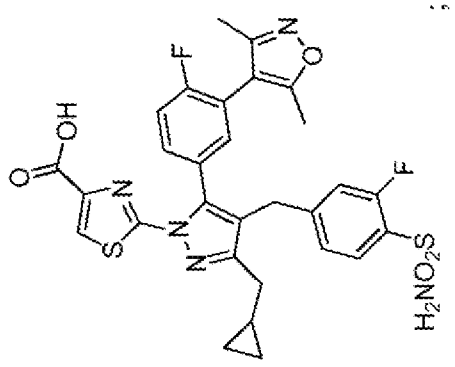
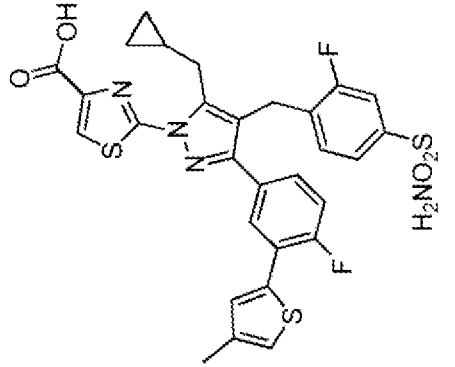
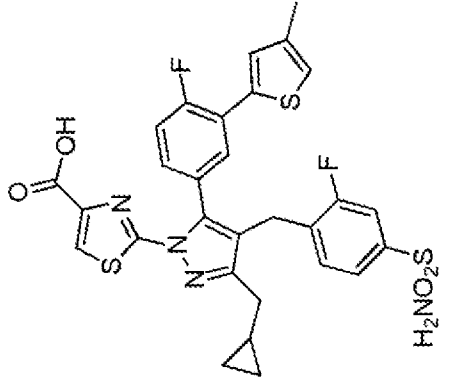
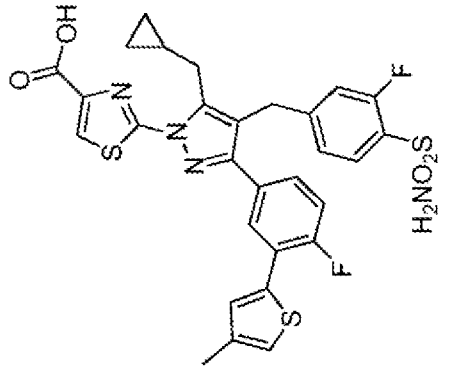
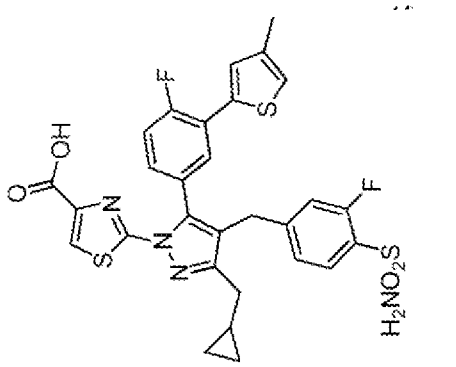
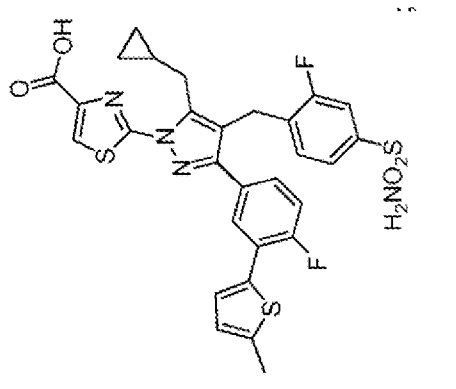
		
		
		

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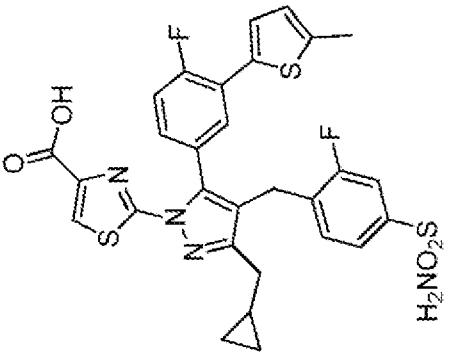
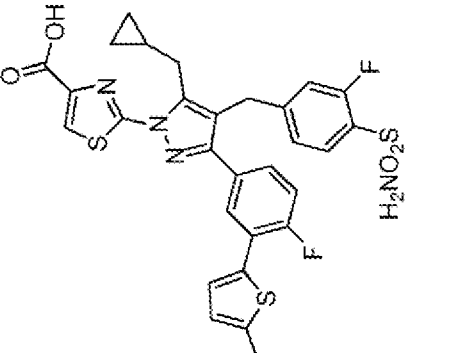
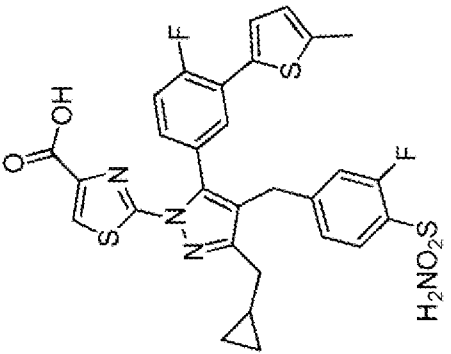
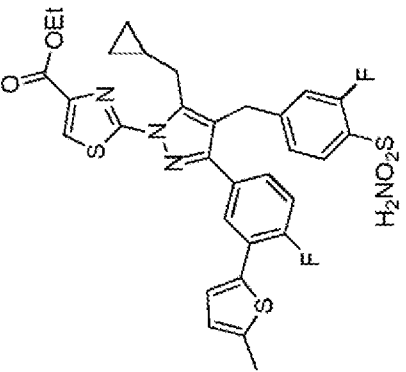
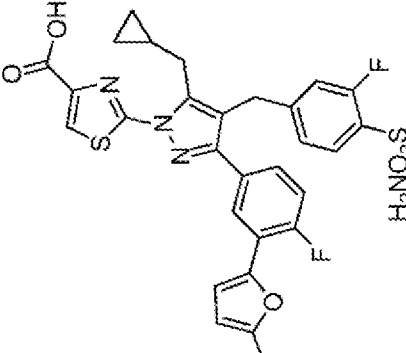
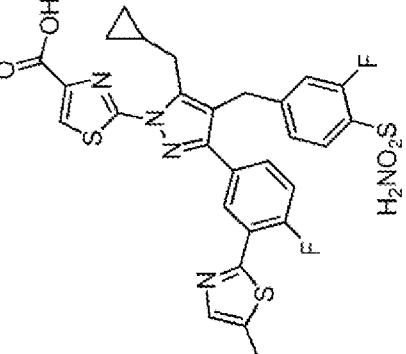
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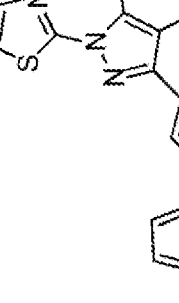
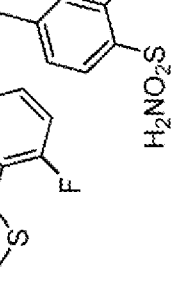
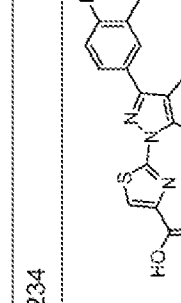
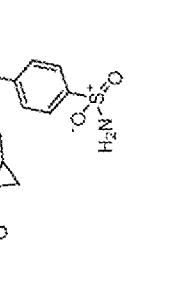
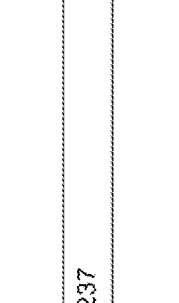
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(fortsat)

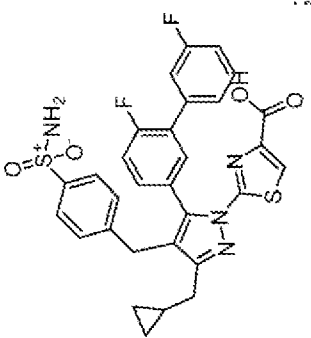
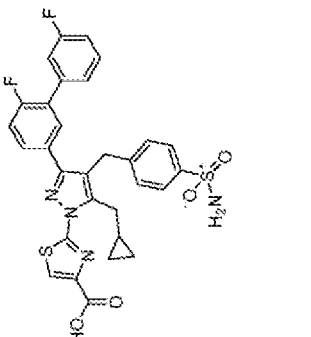
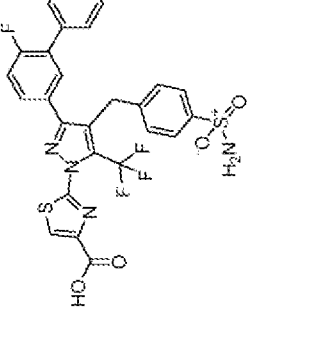
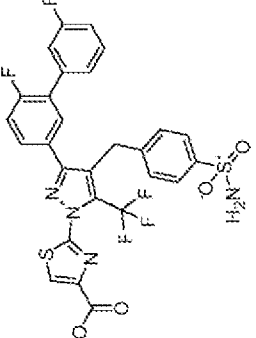
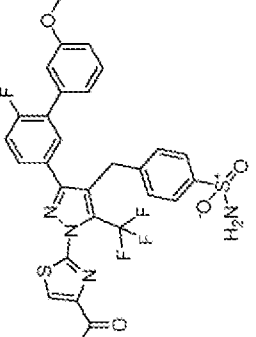
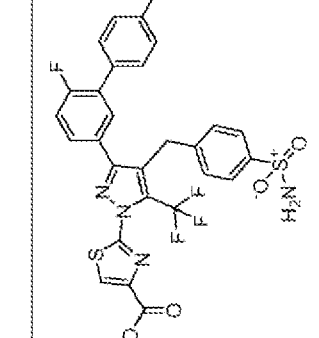
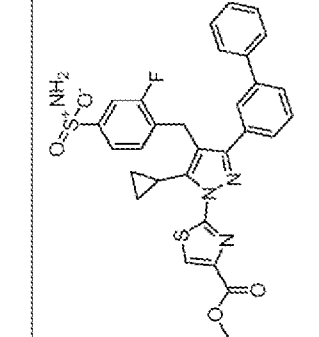
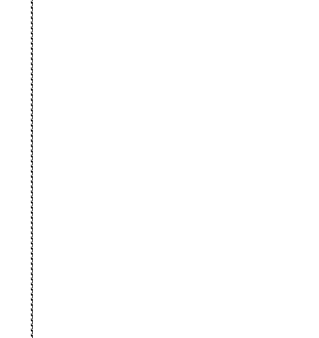
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 $\text{H}_2\text{NO}_2\text{S}$;	223	 $\text{H}_2\text{NO}_2\text{S}$;	224	 $\text{H}_2\text{NO}_2\text{S}$;	225

(fortsat)

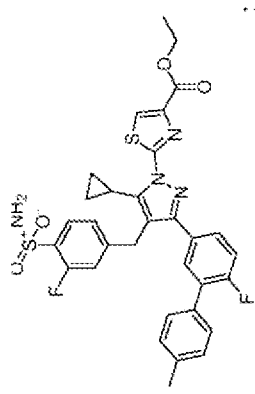
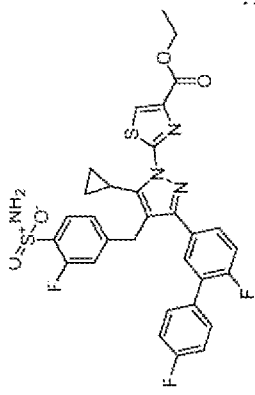
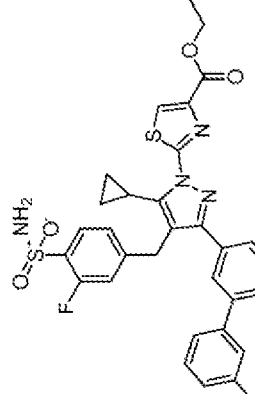
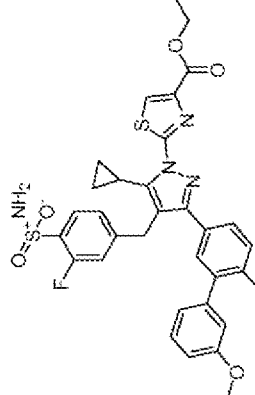
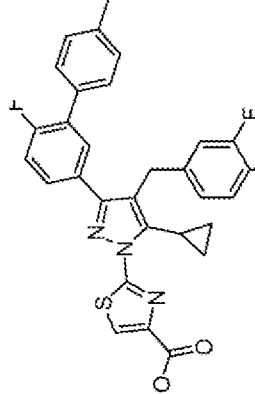
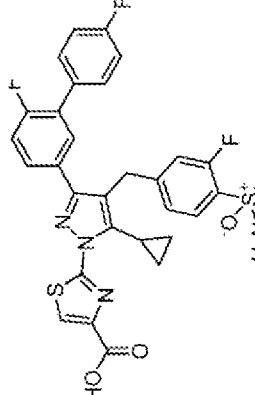
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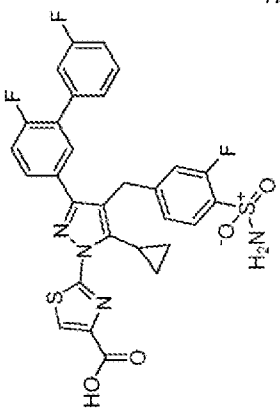
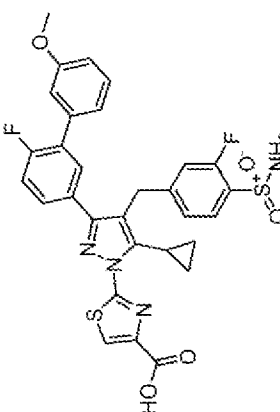
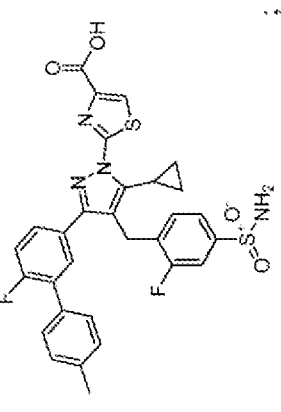
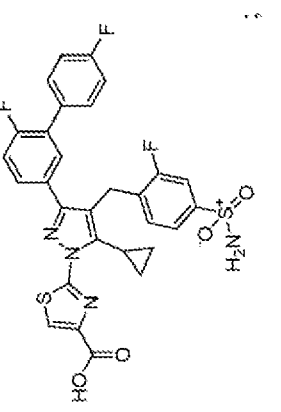
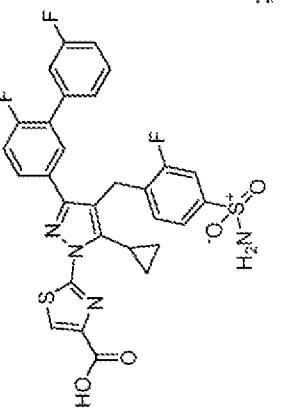
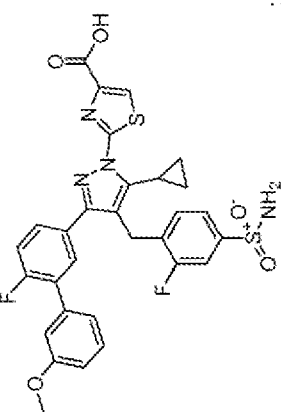
(fortsat)

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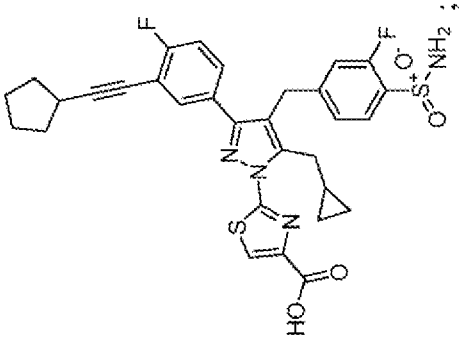
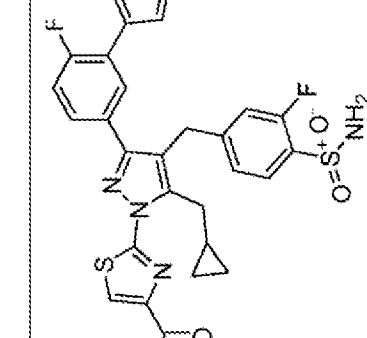
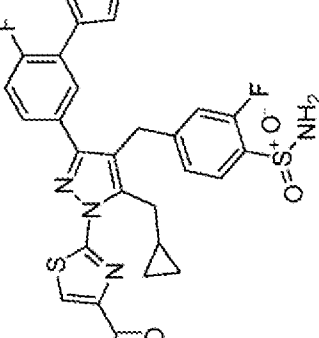
(fortsat)

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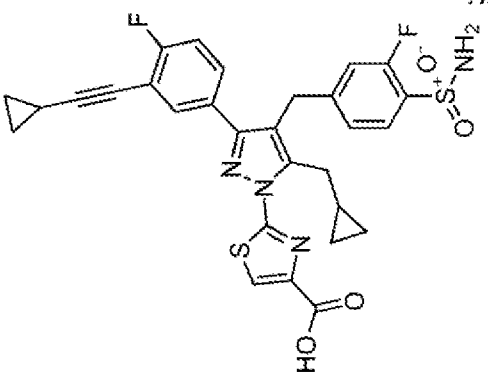
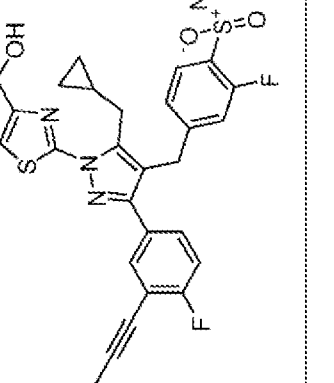
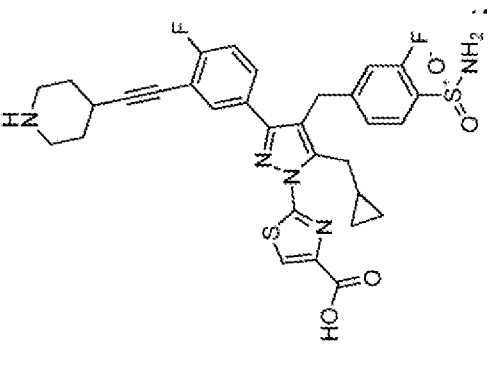
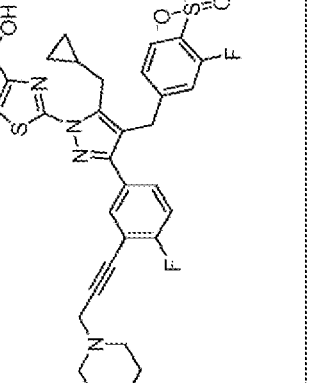
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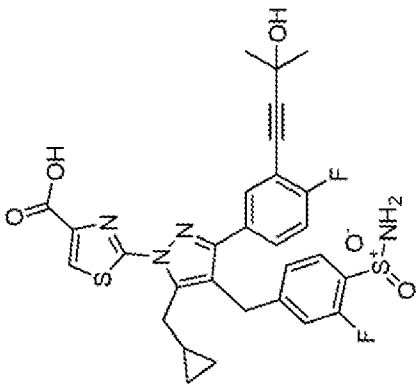
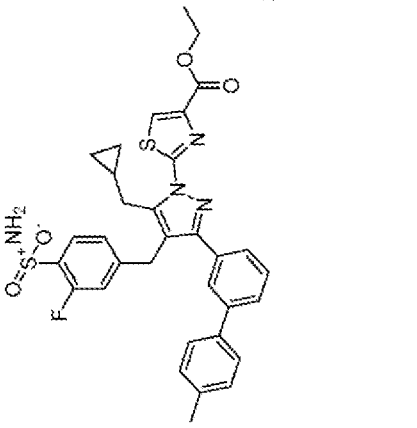
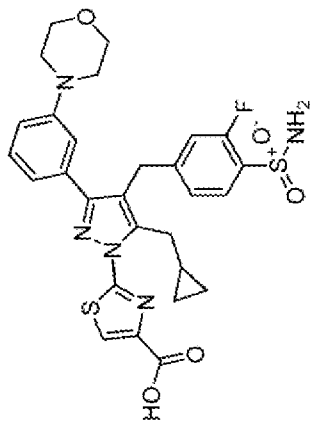
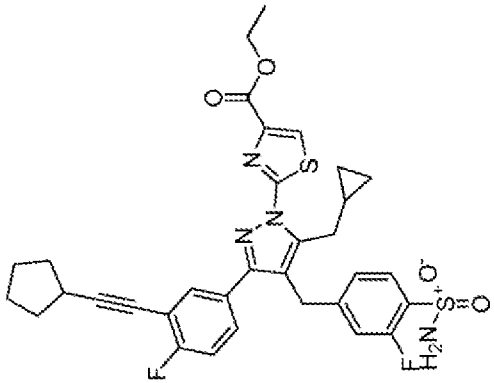
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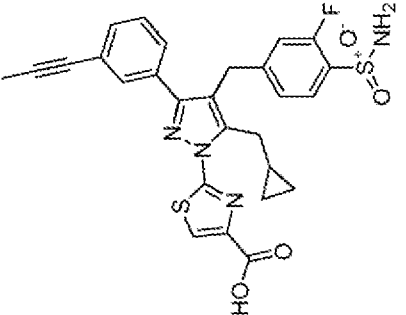
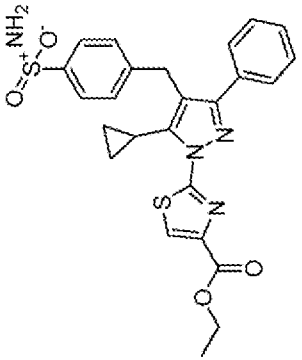
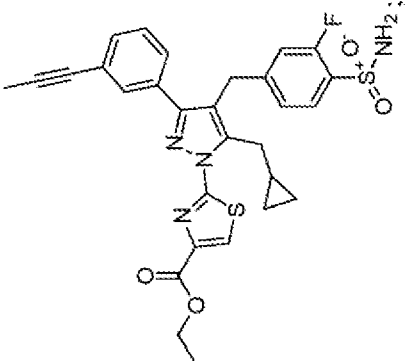
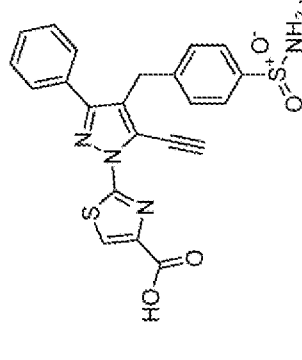
(fortsat)

	261
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(fortsat)

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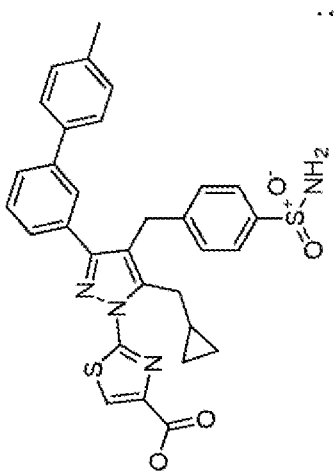
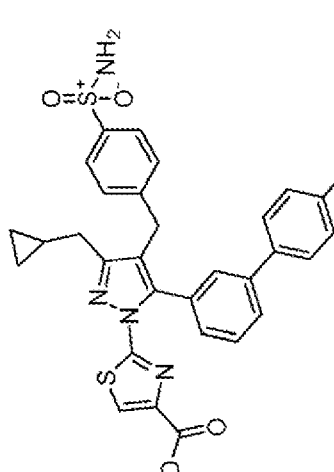
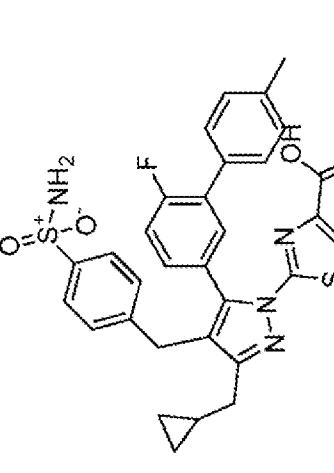
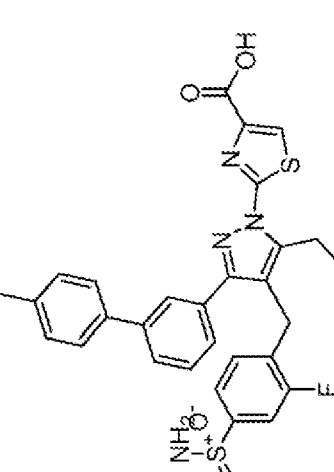
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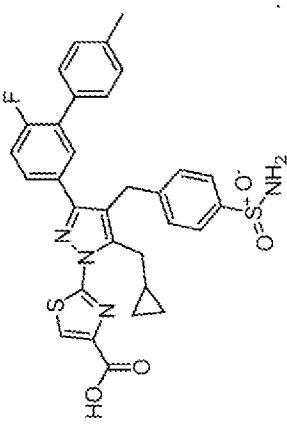
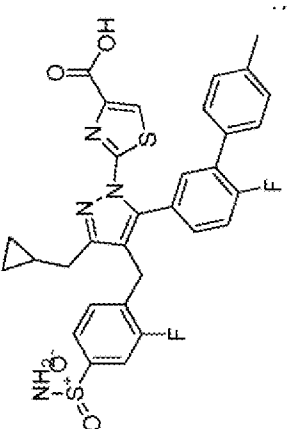
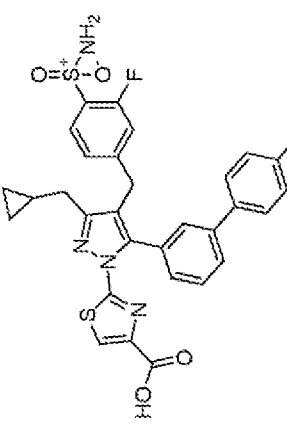
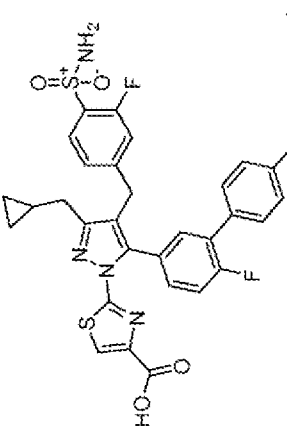
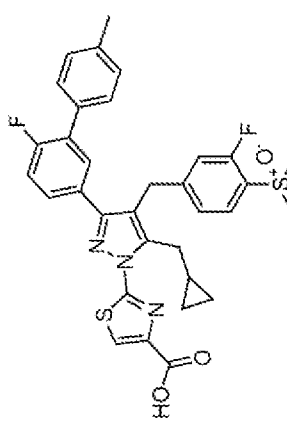
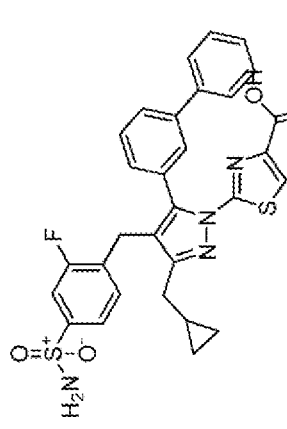
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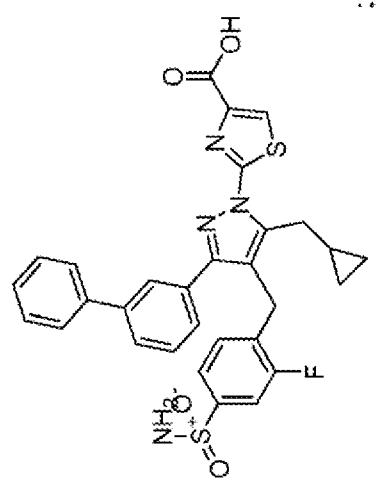
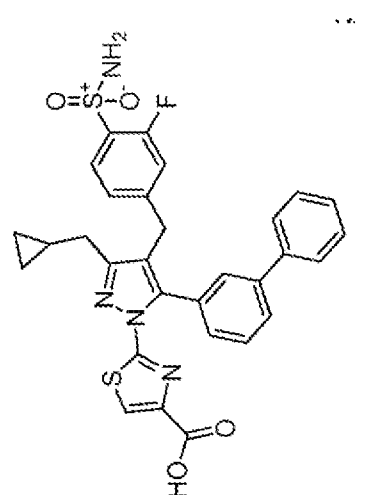
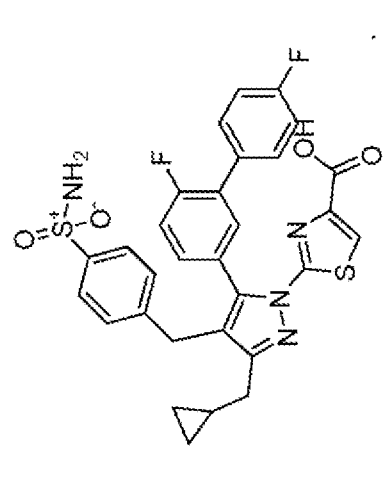
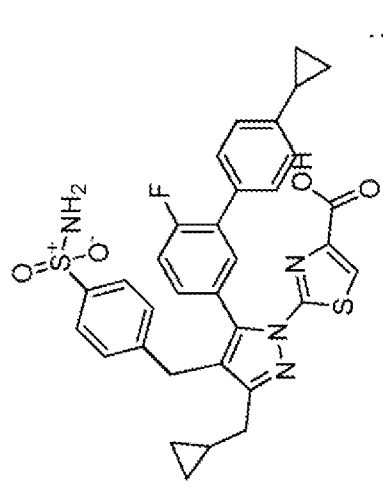
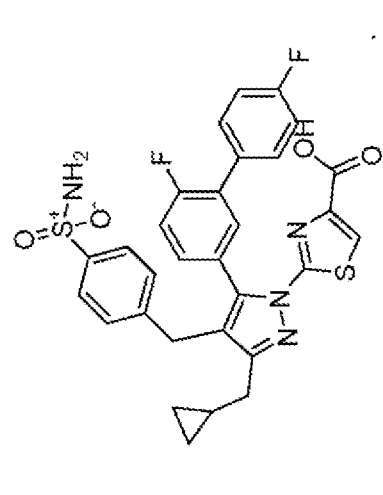
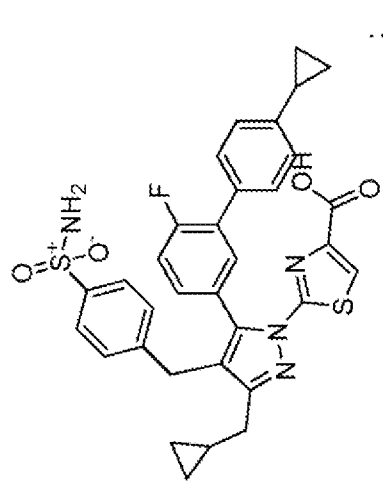
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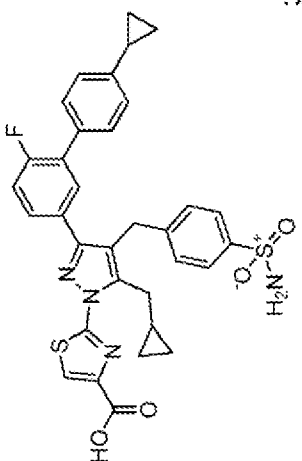
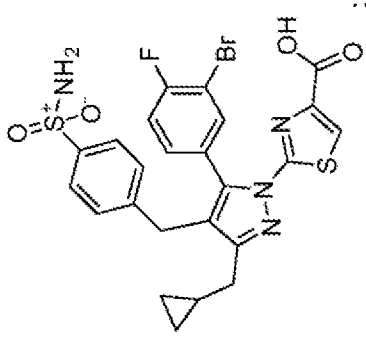
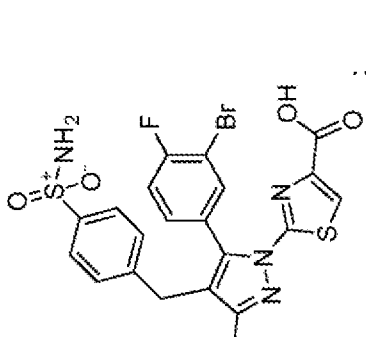
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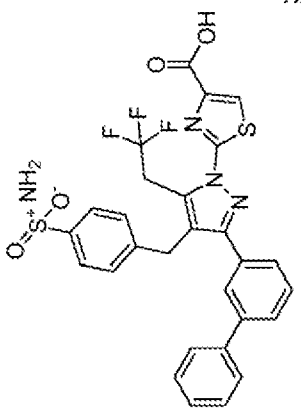
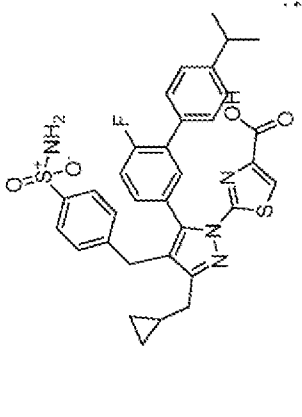
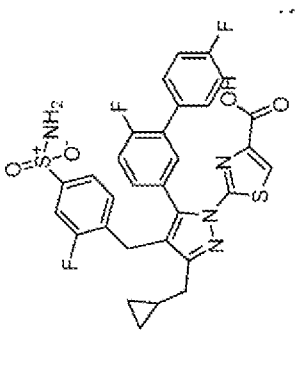
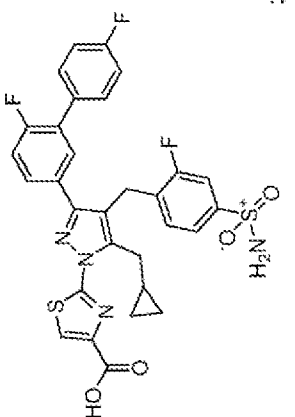
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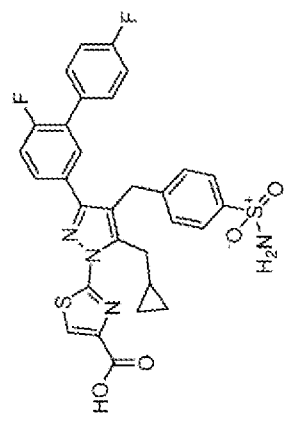
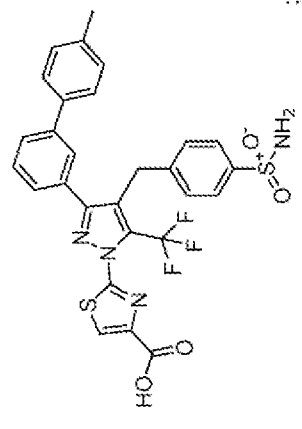
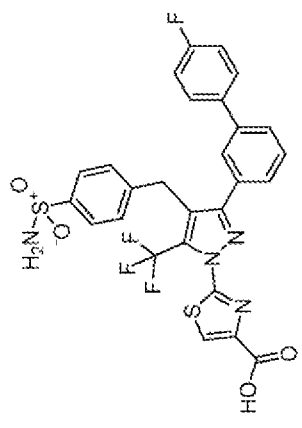
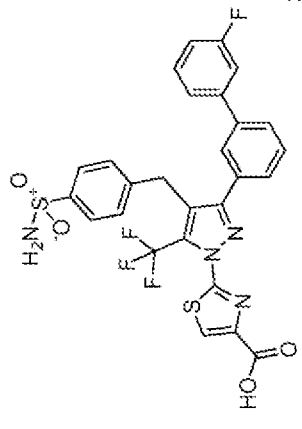
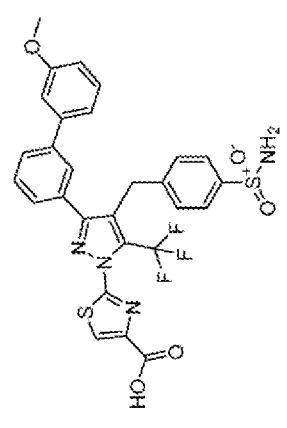
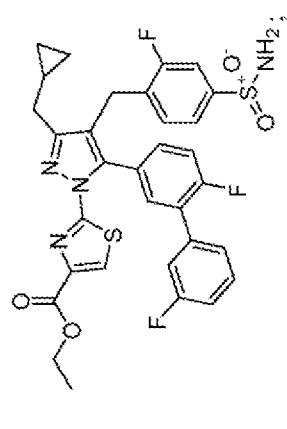
(fortsat)

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(fortsat)

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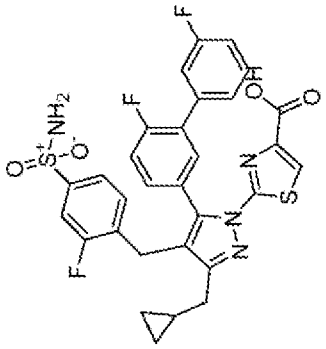
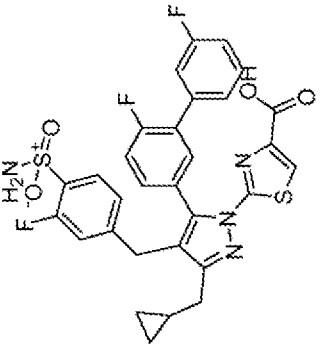
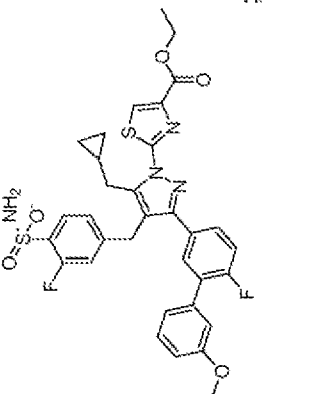
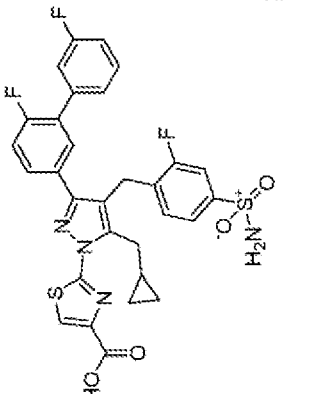
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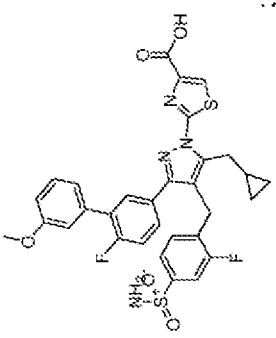
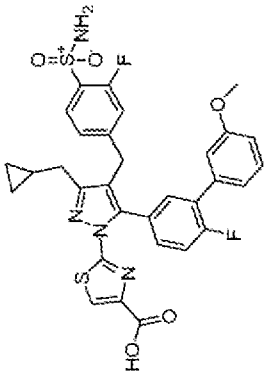
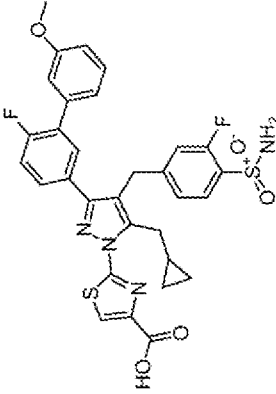
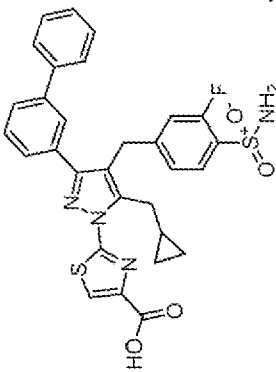
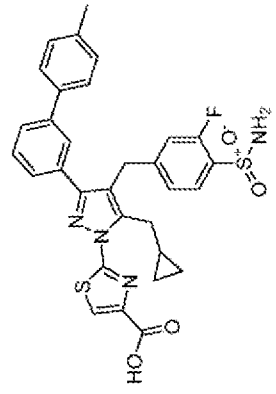
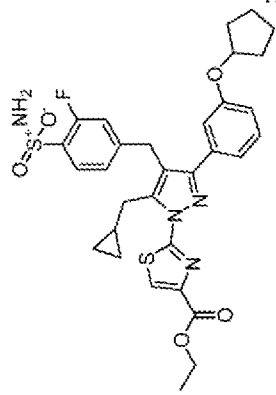
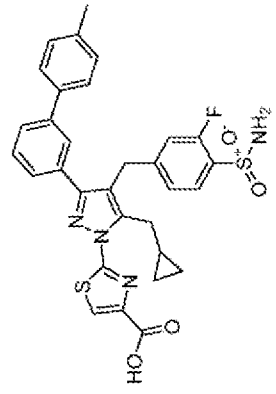
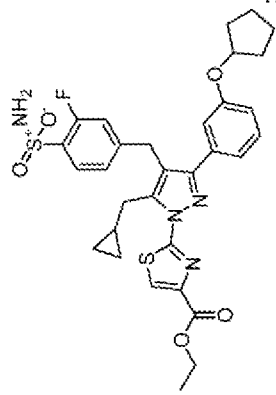
(fortsat)

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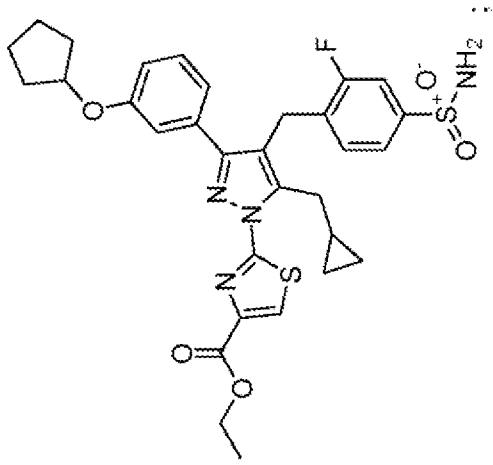
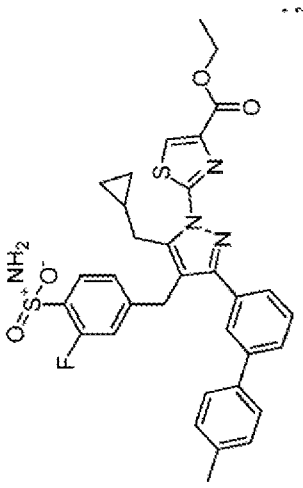
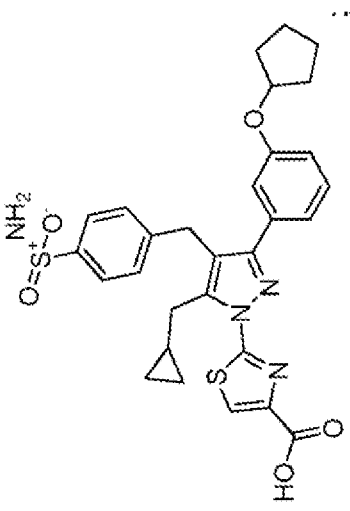
(fortsat)

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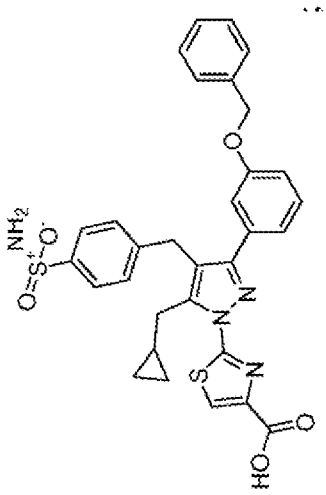
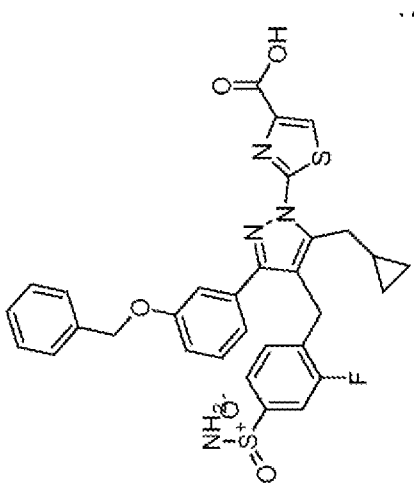
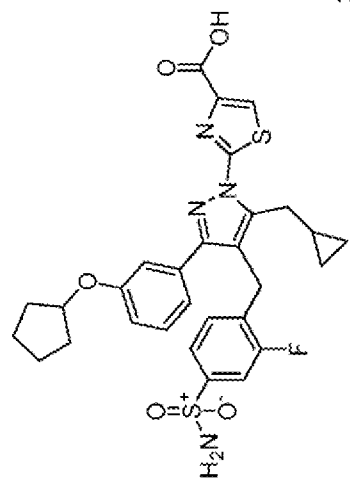
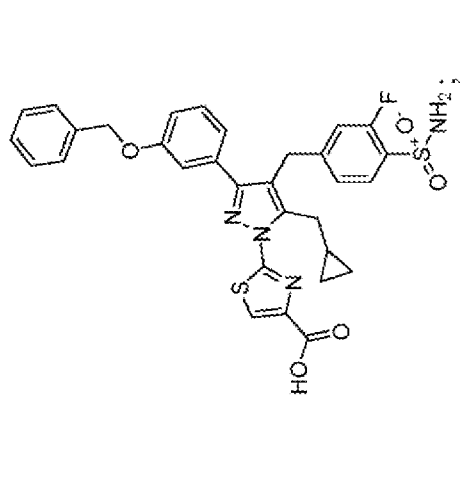
(fortsat)

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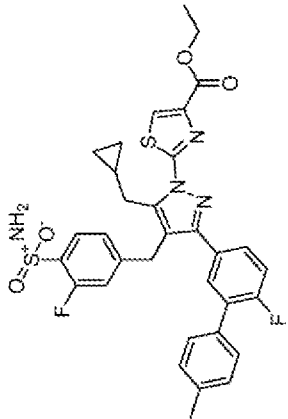
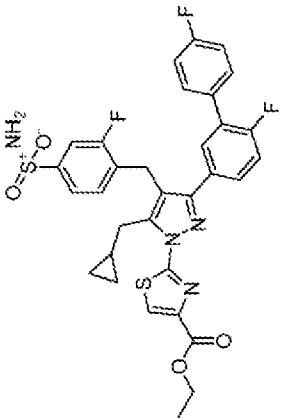
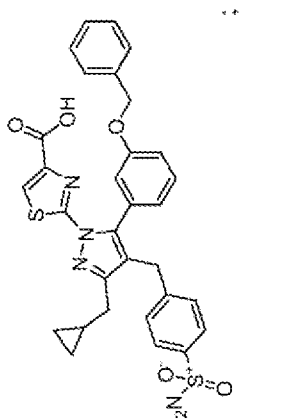
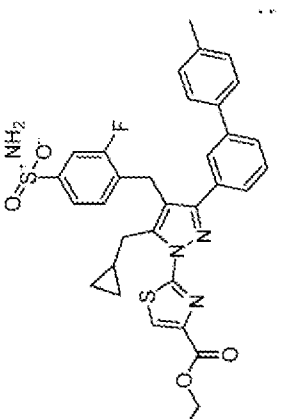
(fortsat)

		
334	335	
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	336	337

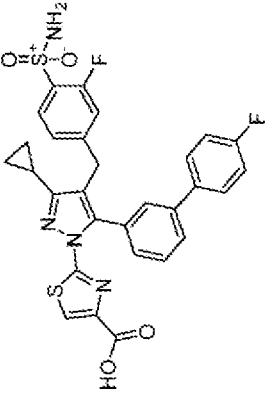
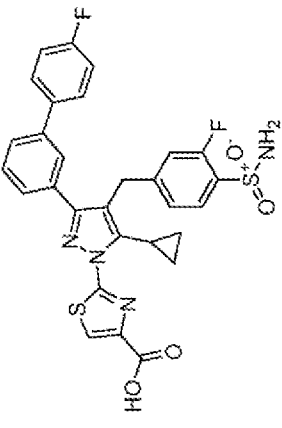
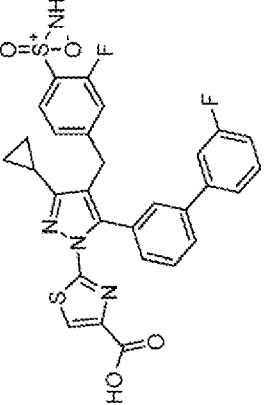
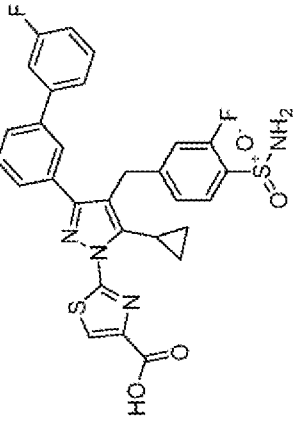
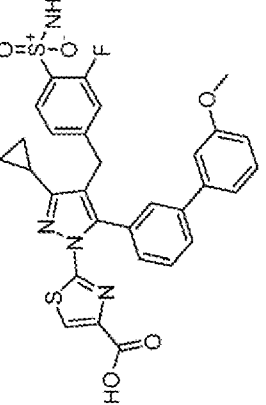
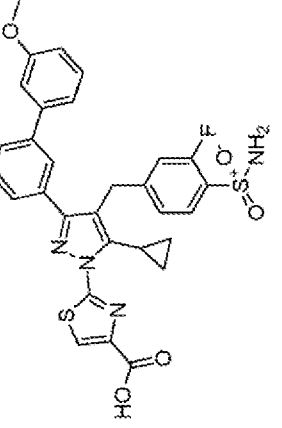
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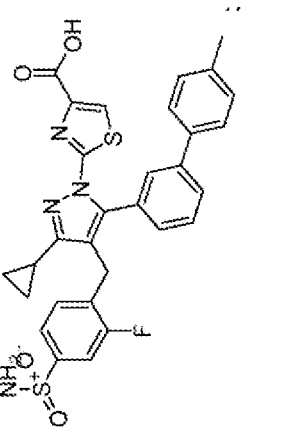
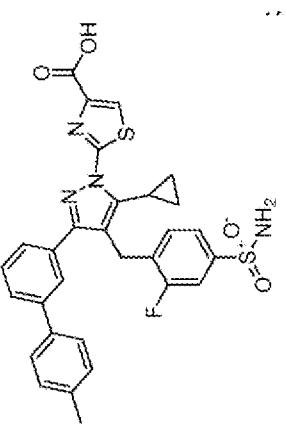
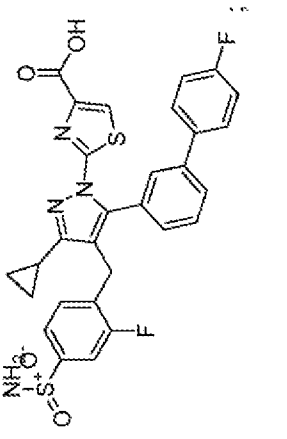
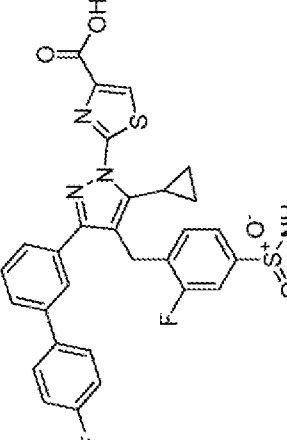
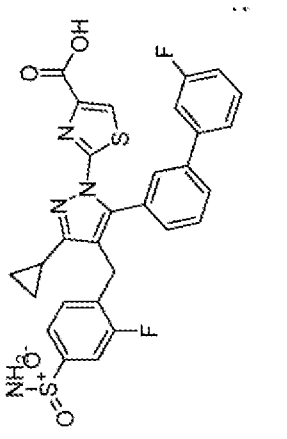
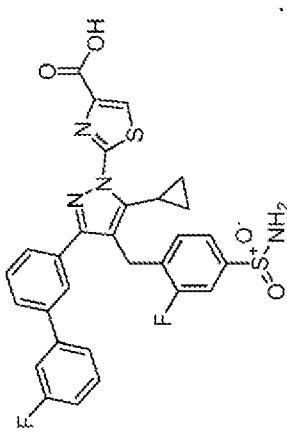
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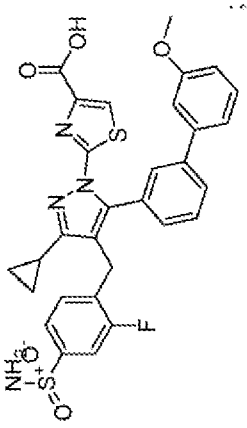
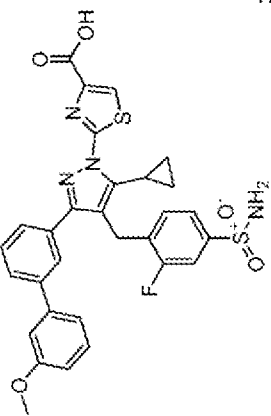
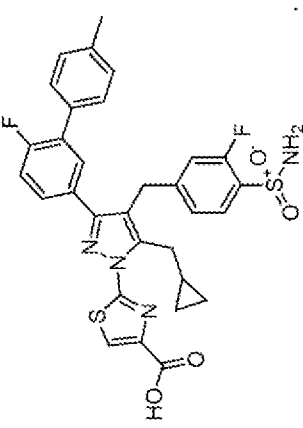
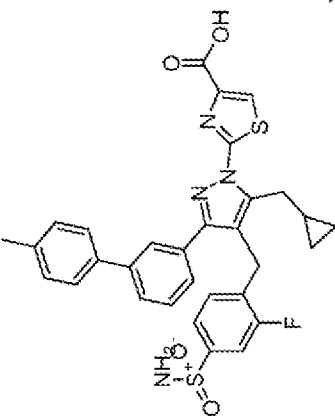
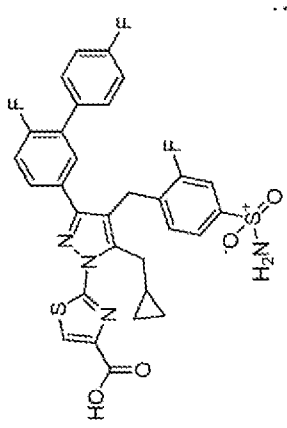
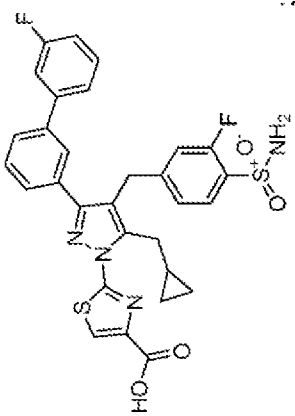
(fortsat)

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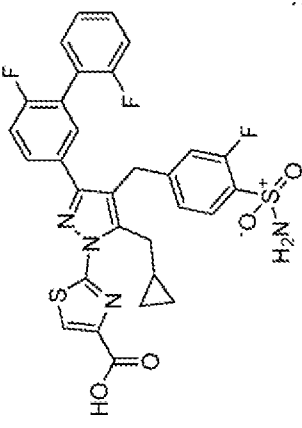
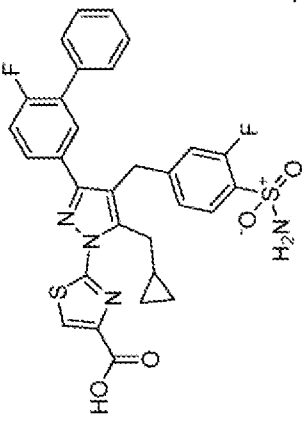
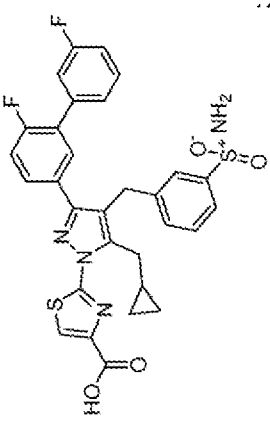
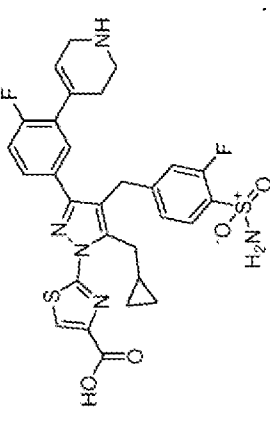
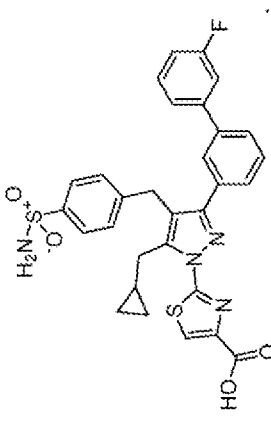
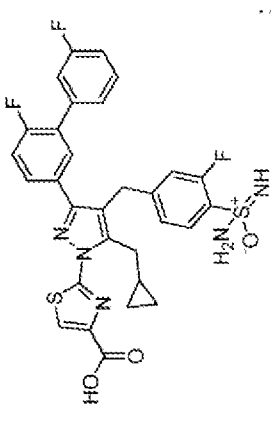
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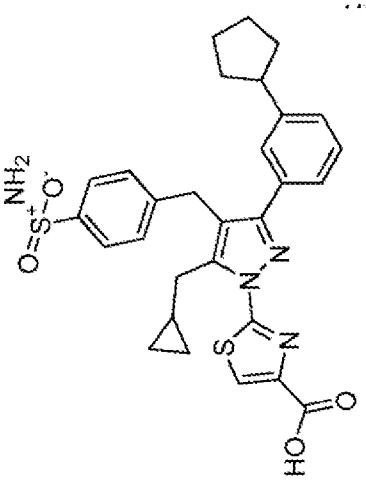
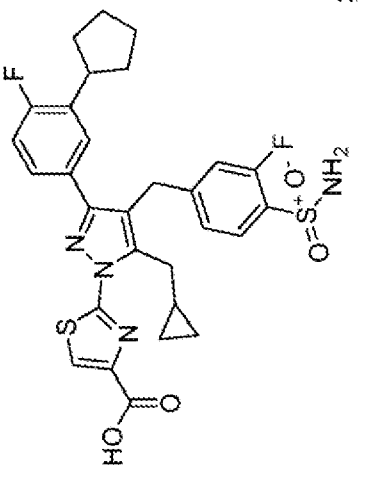
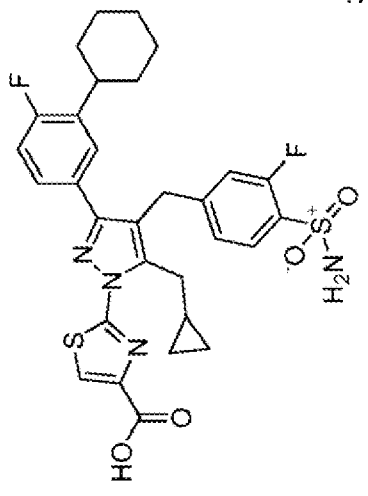
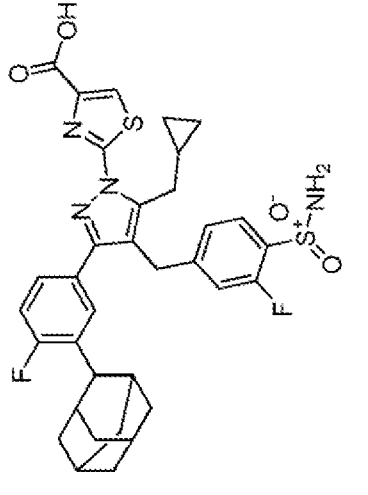
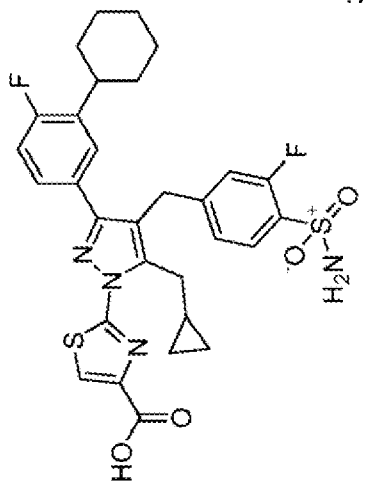
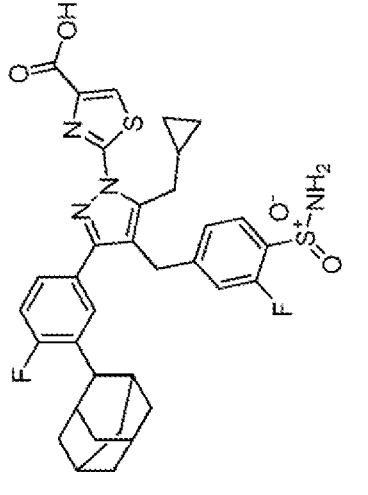
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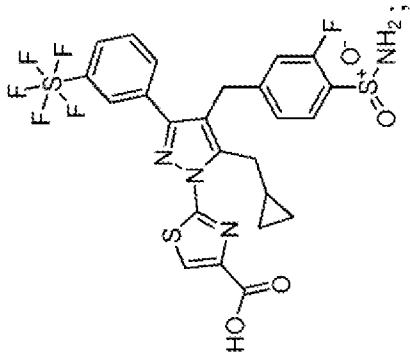
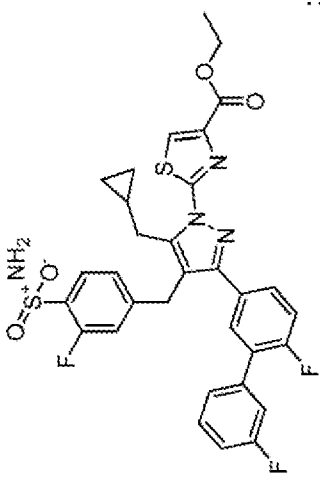
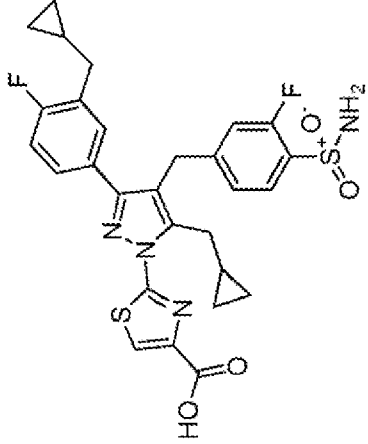
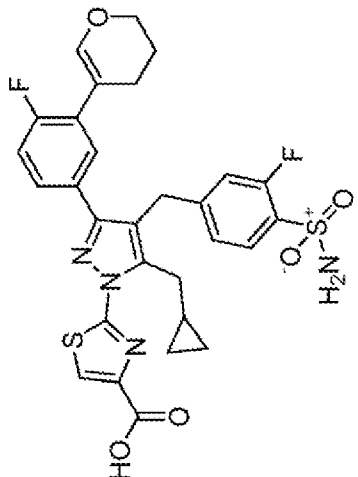
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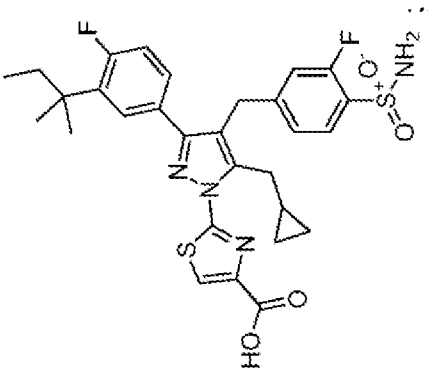
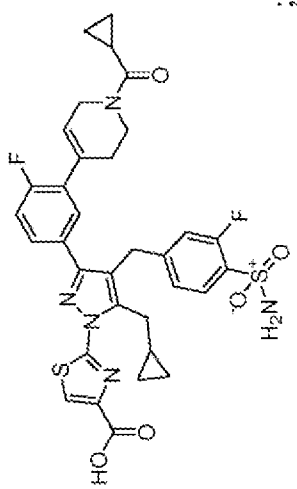
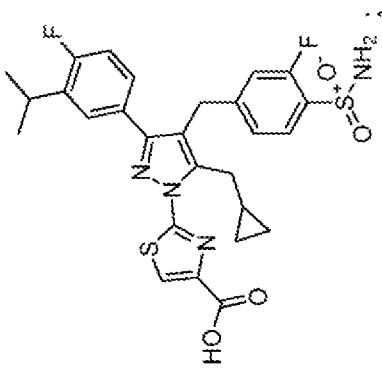
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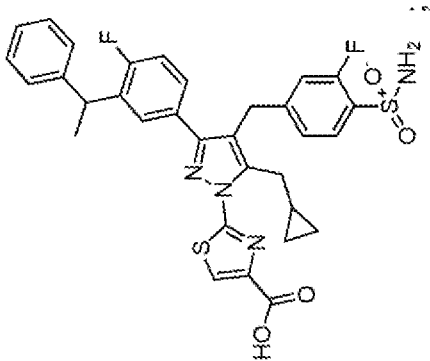
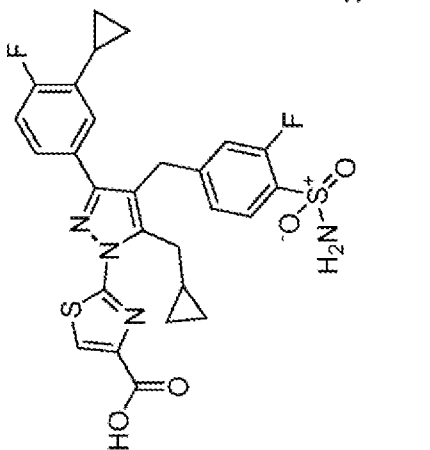
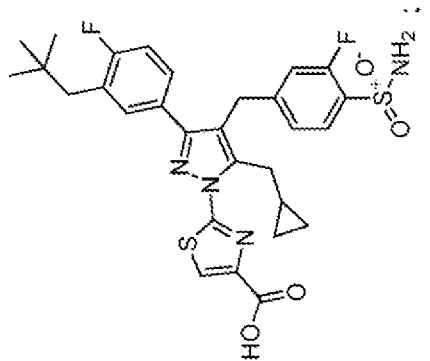
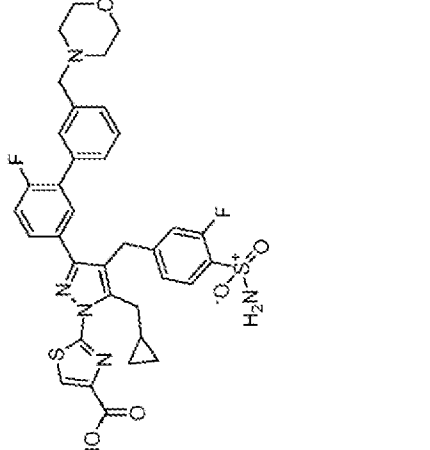
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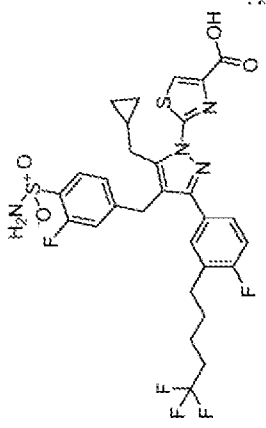
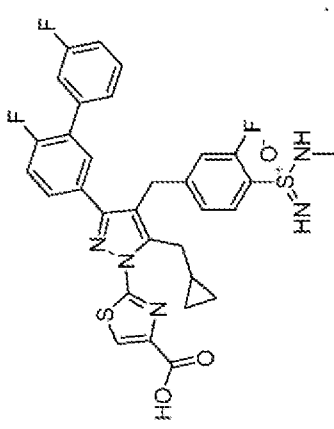
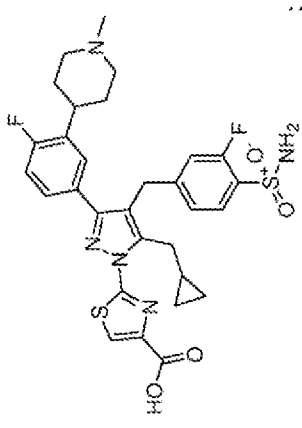
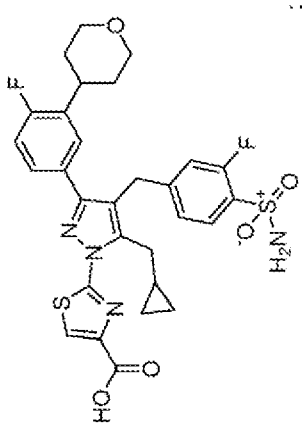
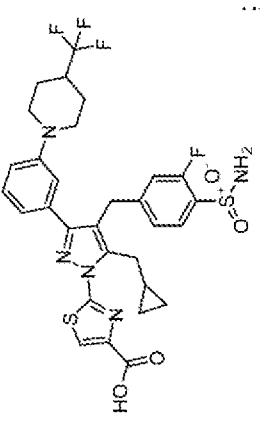
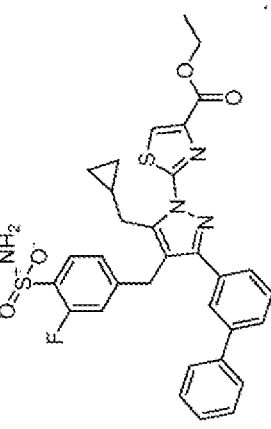
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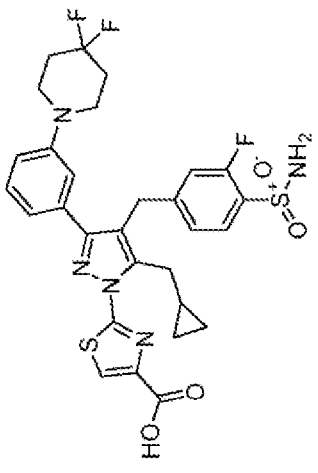
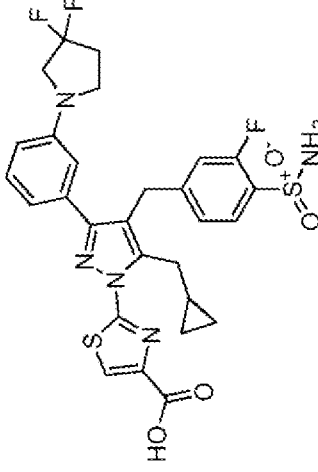
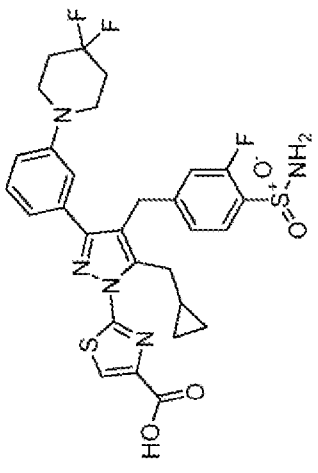
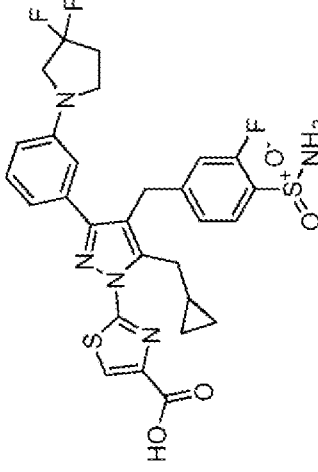
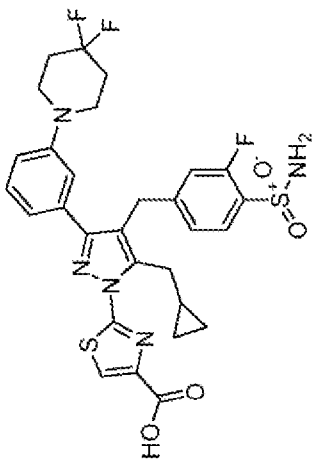
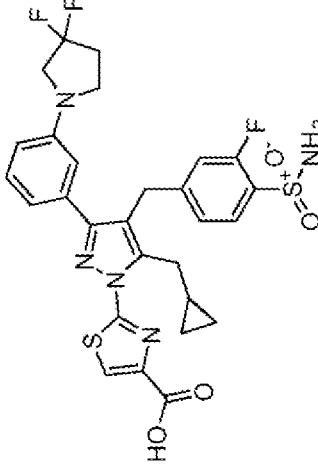
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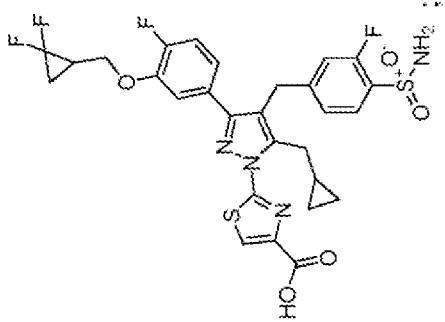
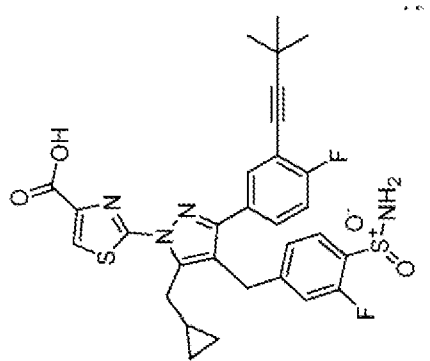
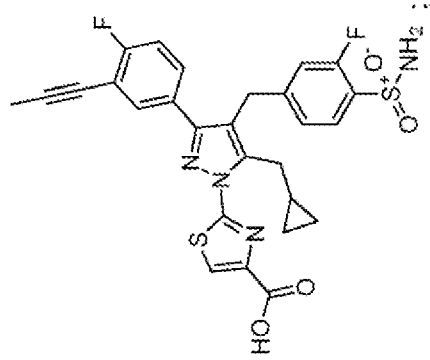
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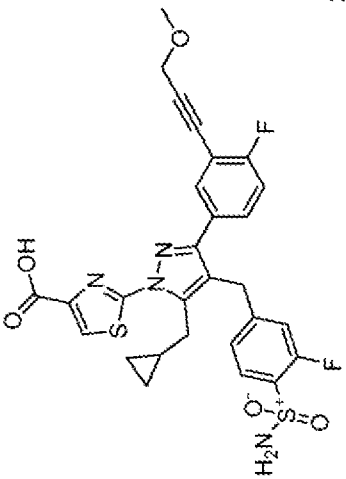
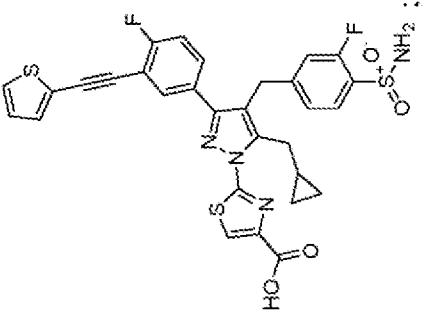
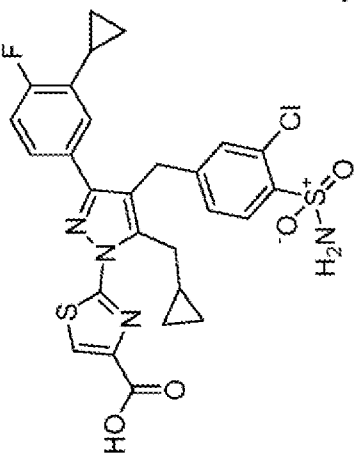
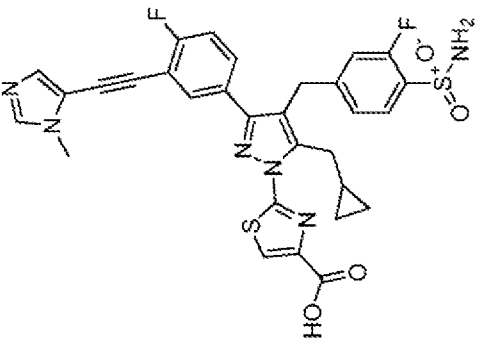
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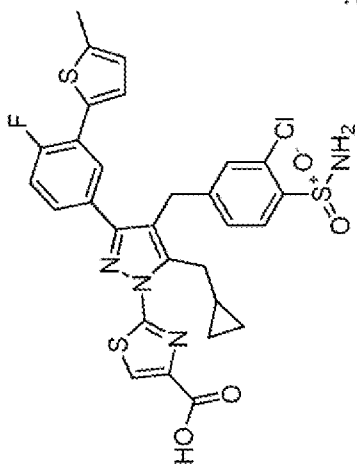
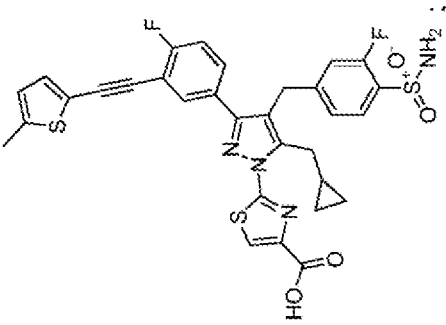
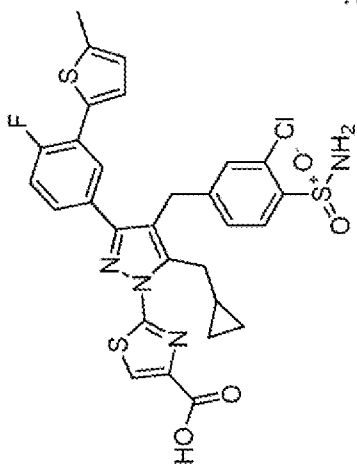
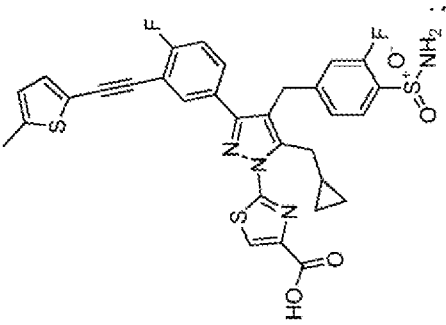
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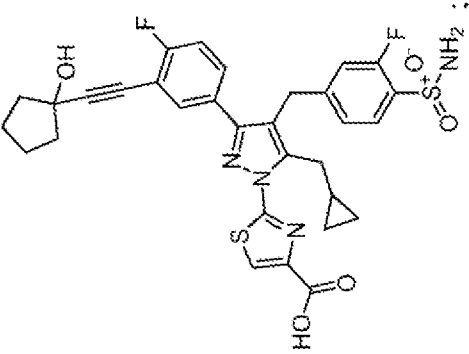
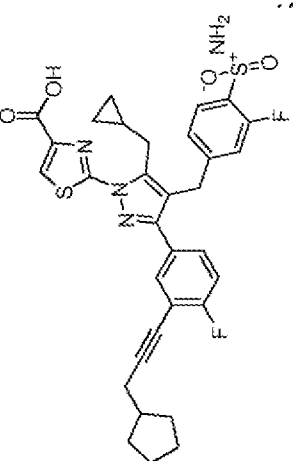
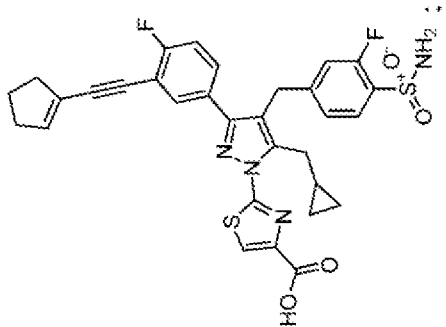
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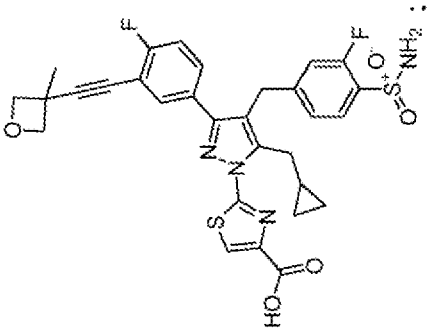
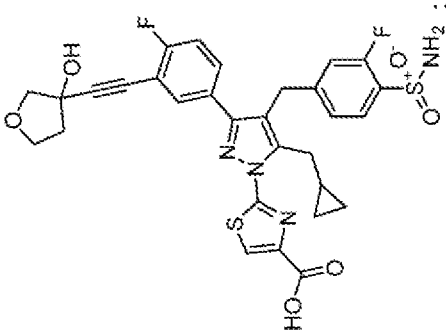
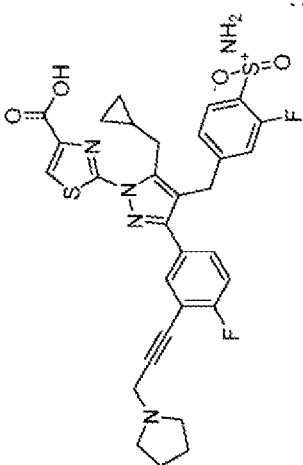
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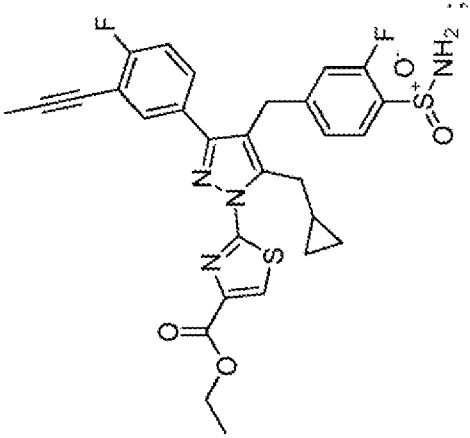
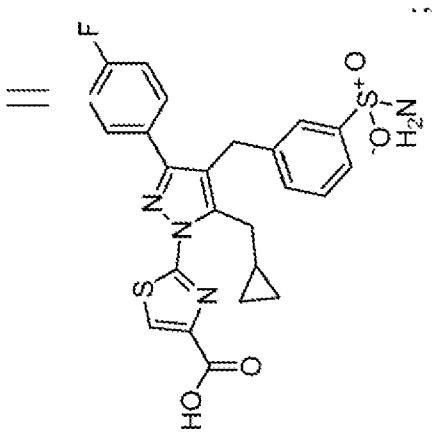
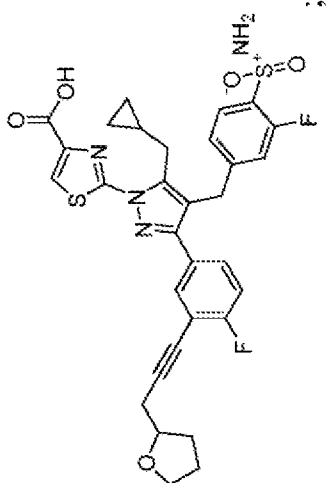
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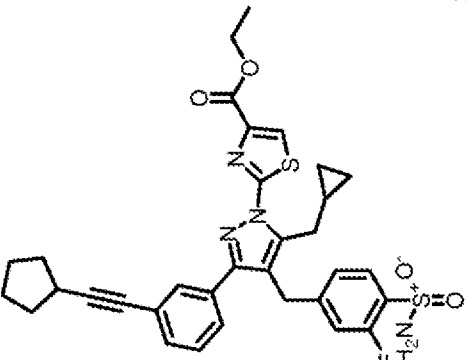
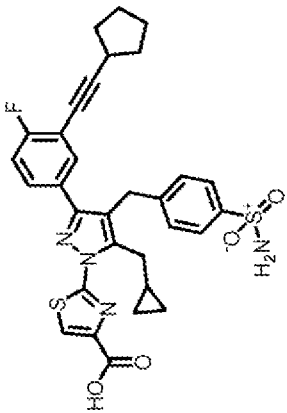
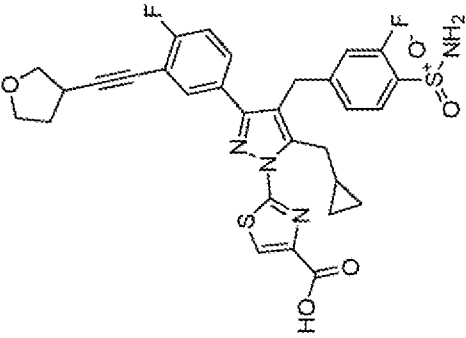
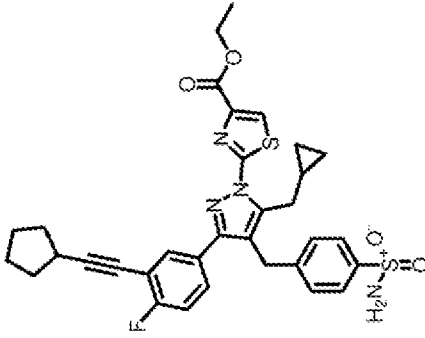
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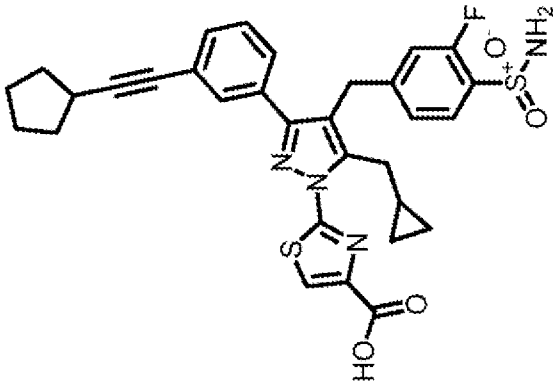
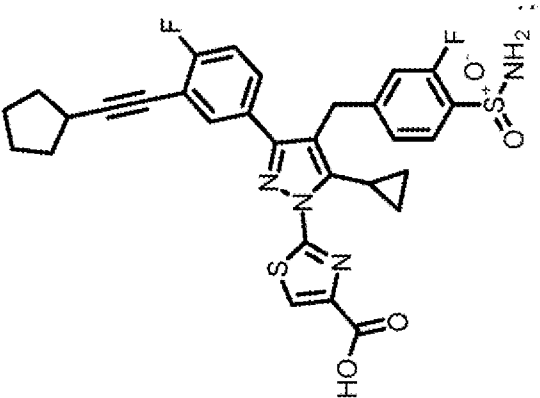
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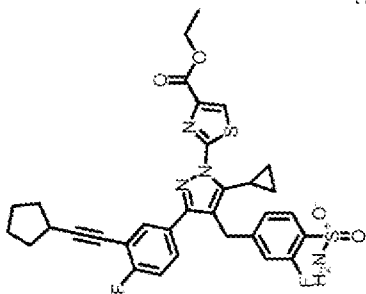
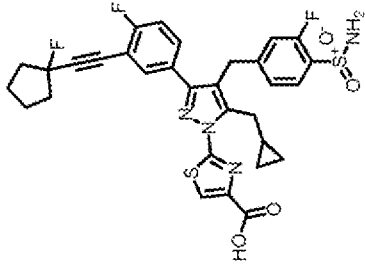
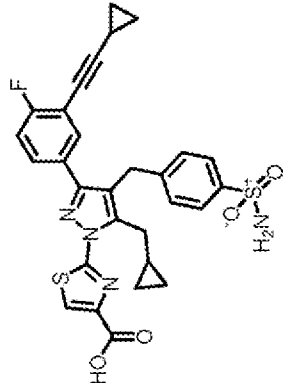
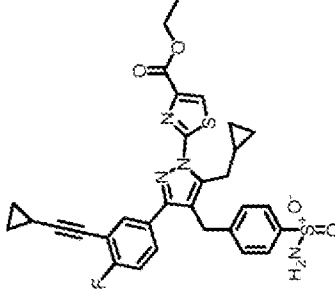
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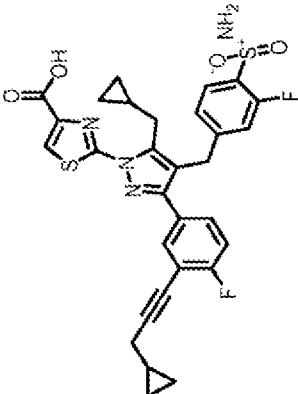
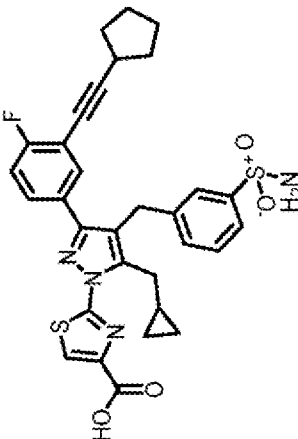
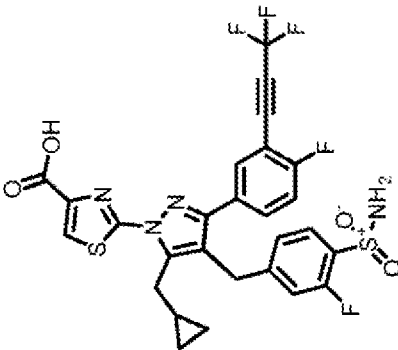
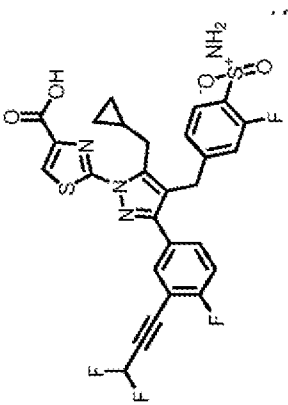
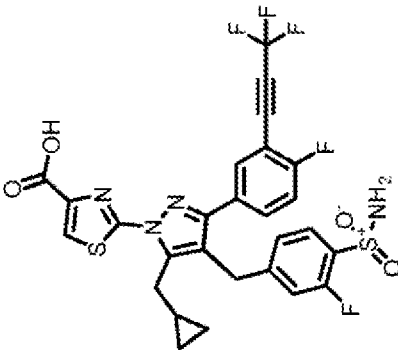
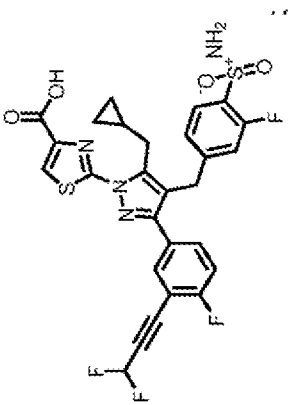
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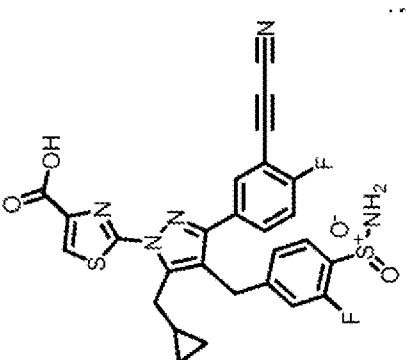
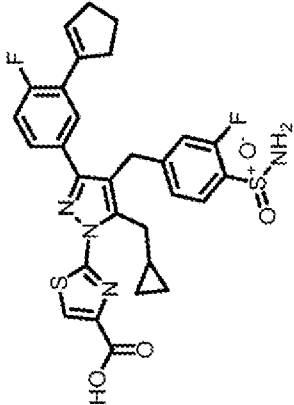
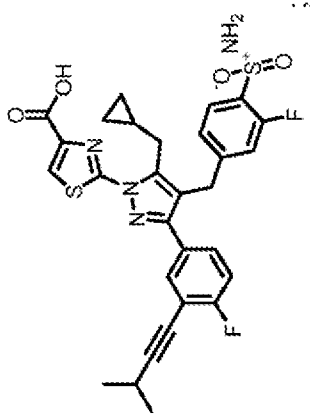
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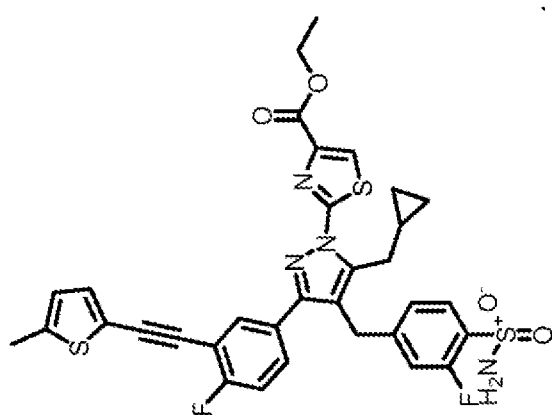
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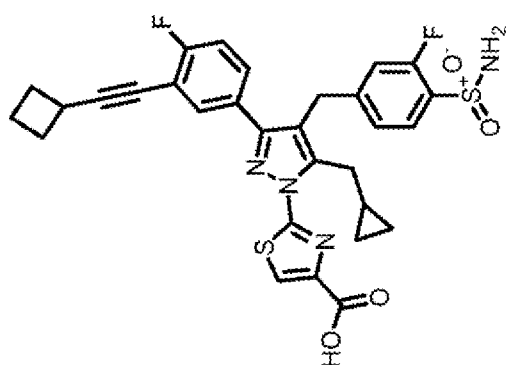
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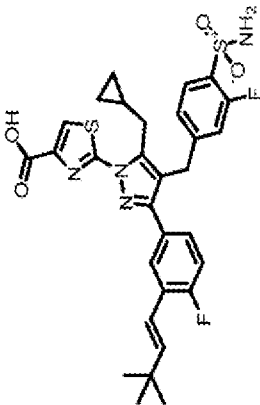
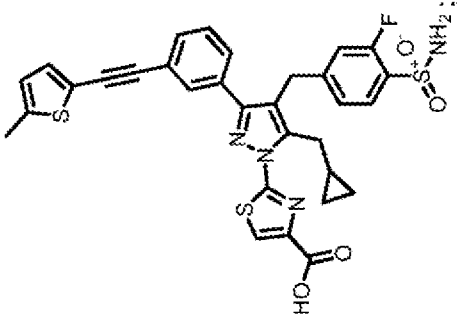
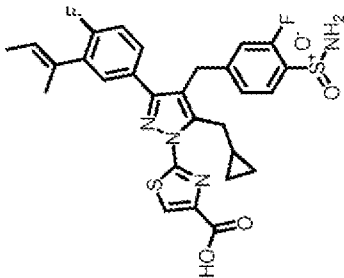
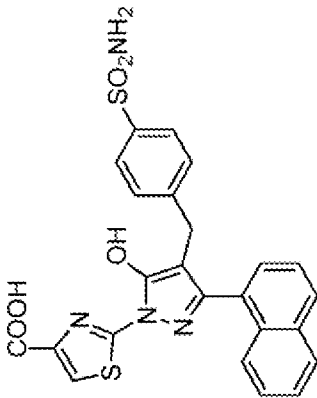


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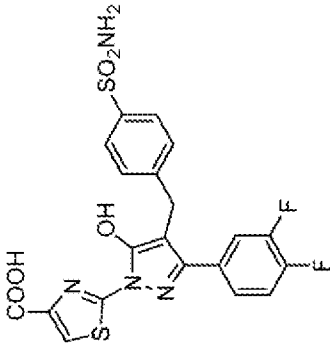
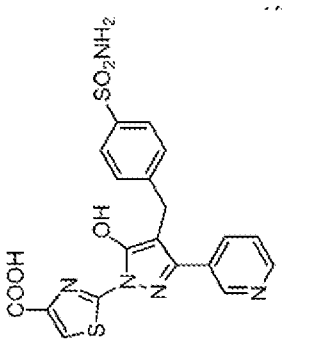
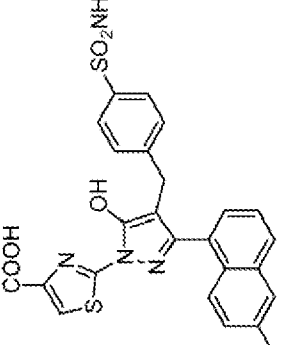
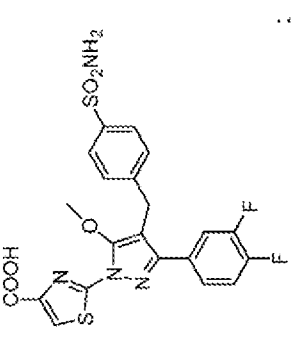
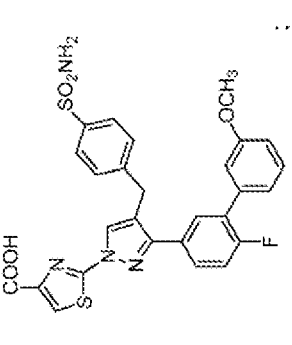
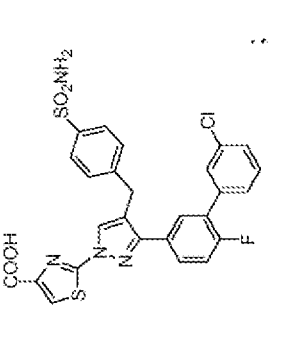


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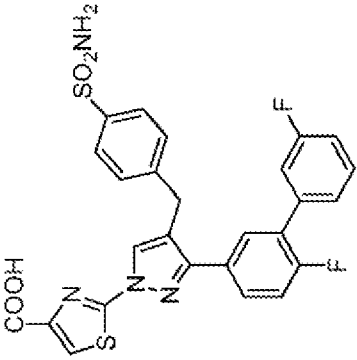
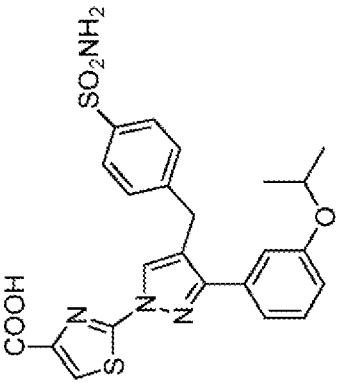
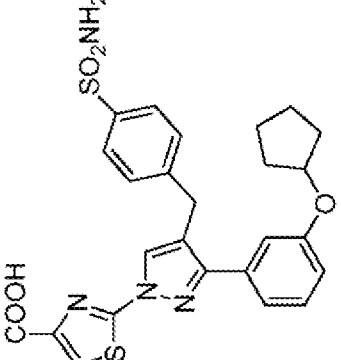
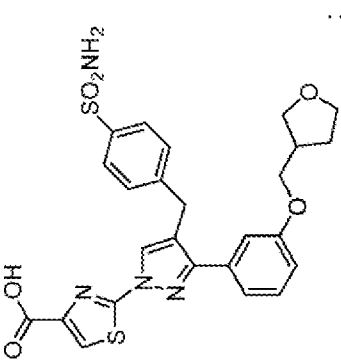
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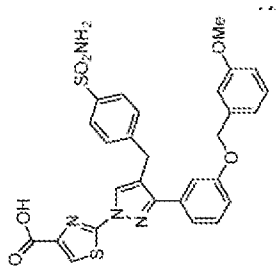
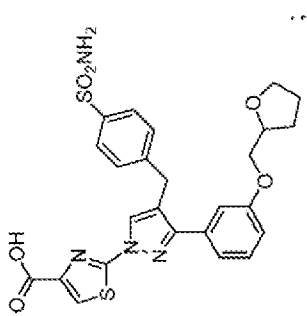
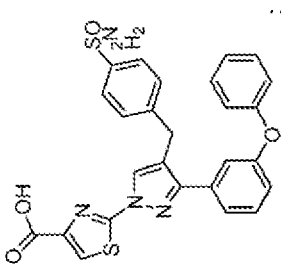
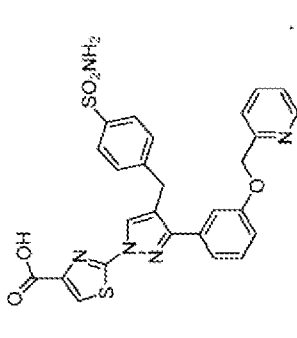
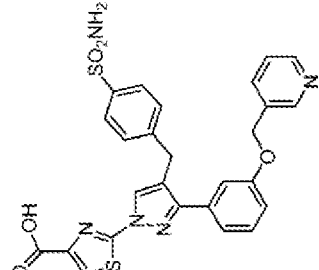
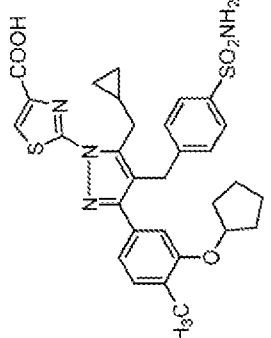
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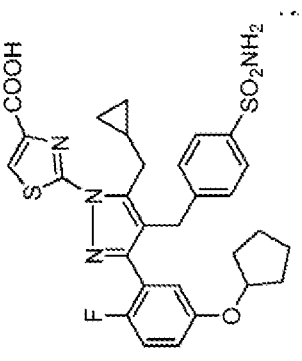
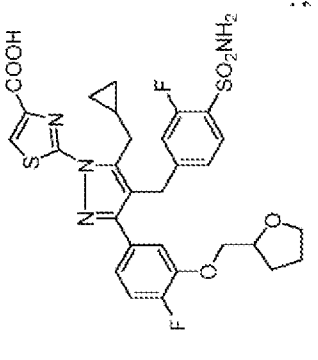
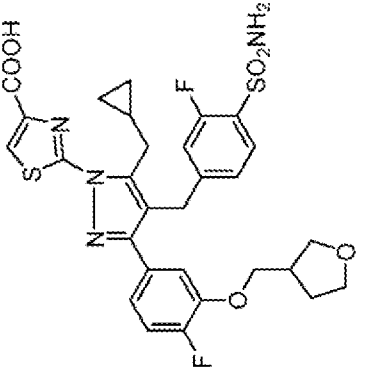
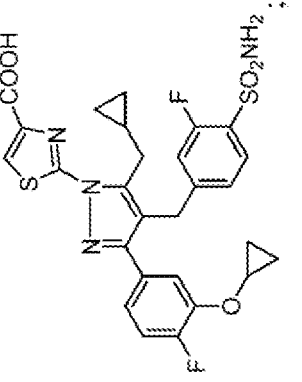
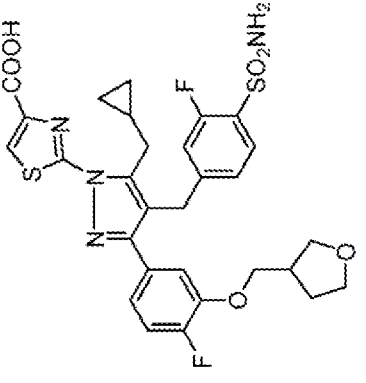
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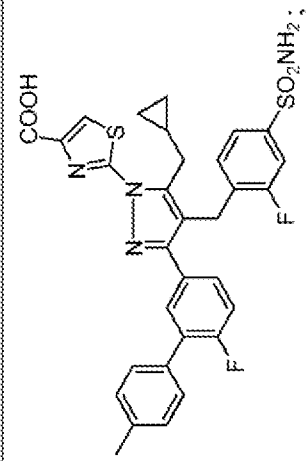
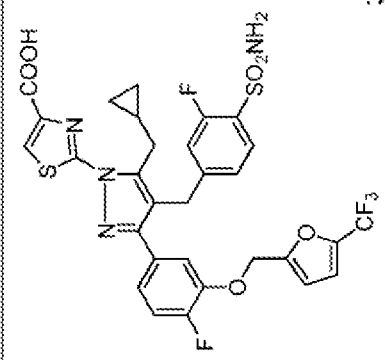
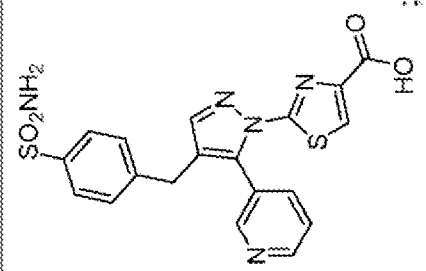
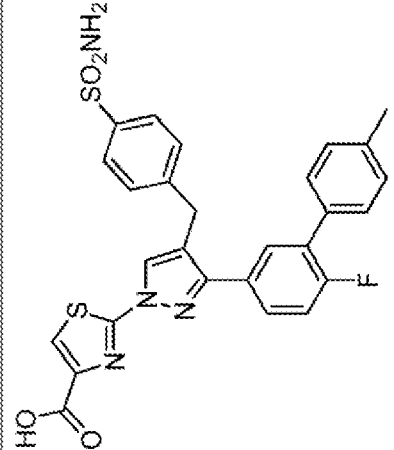
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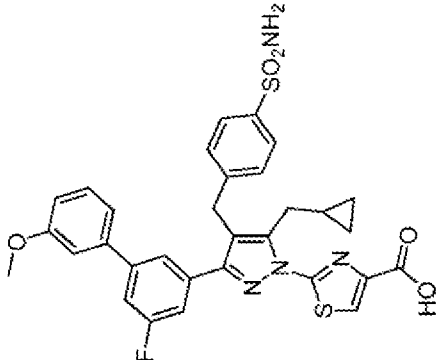
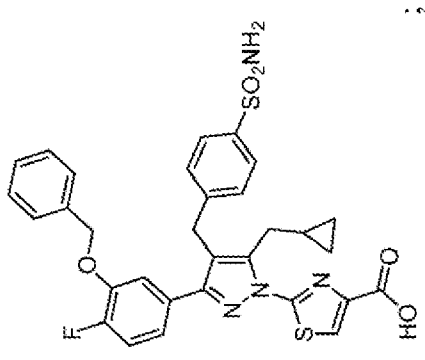
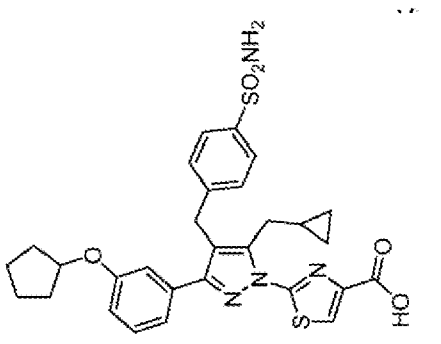
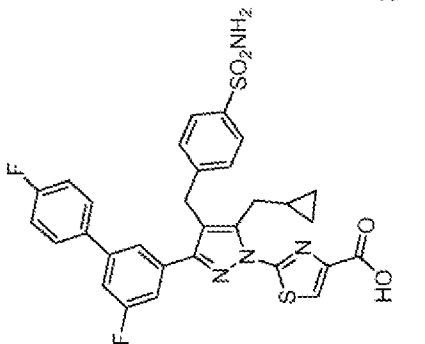
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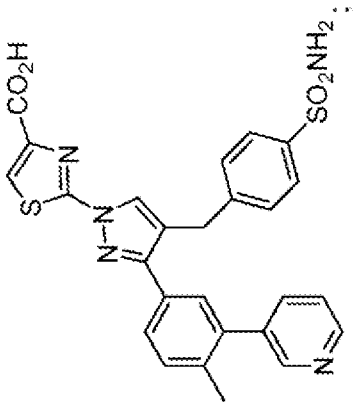
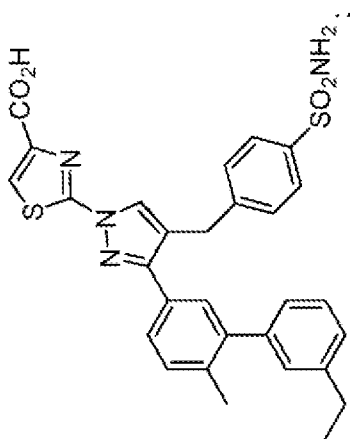
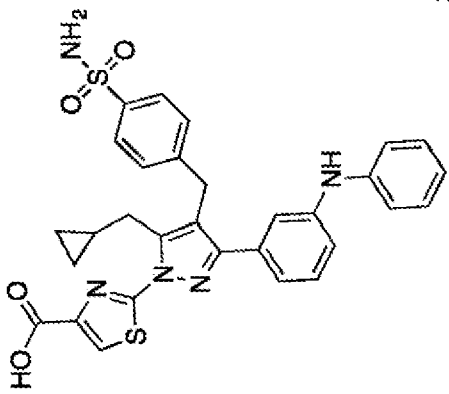
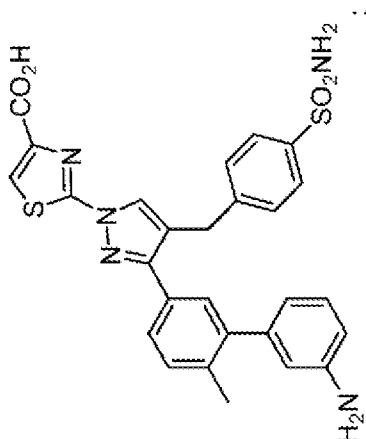
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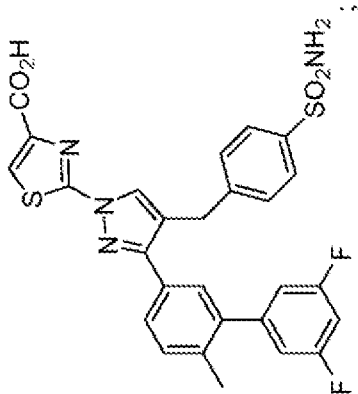
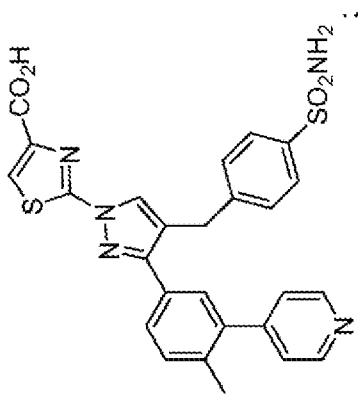
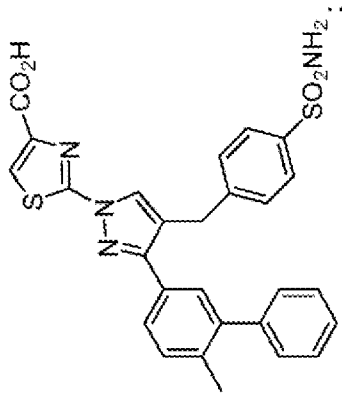
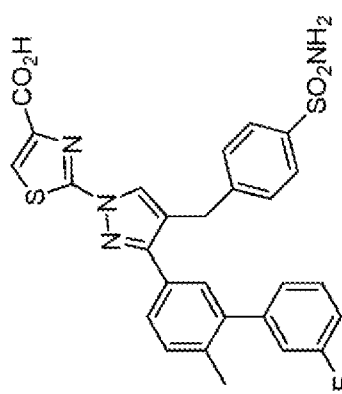
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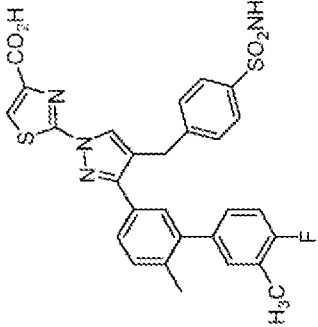
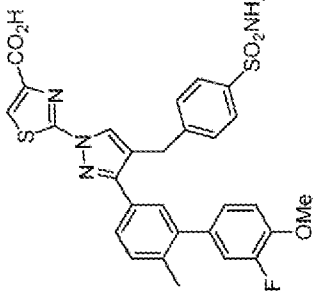
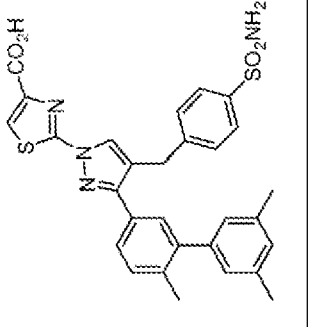
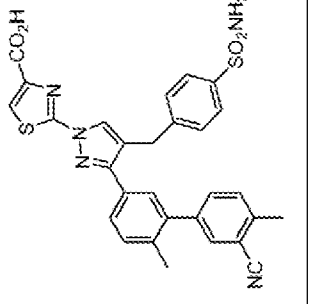
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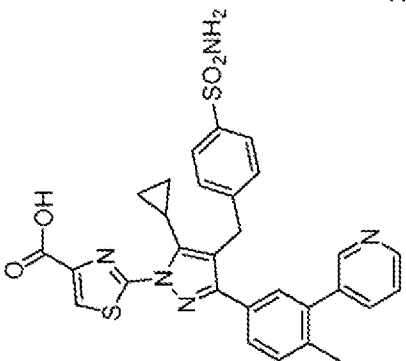
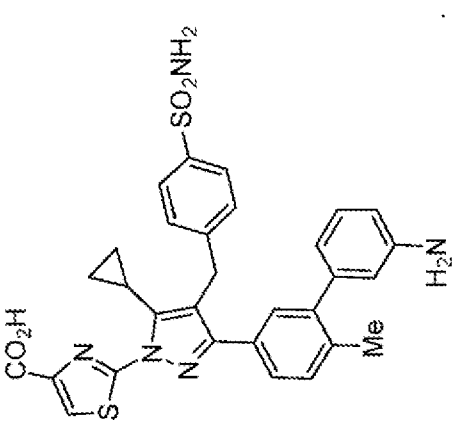
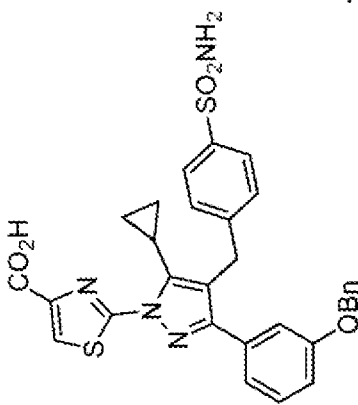
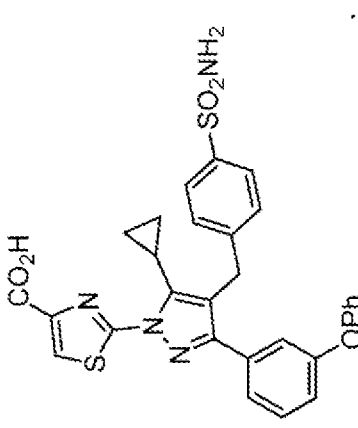
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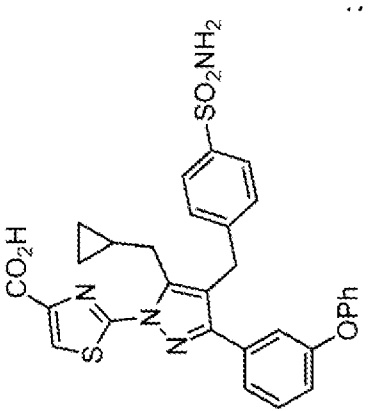
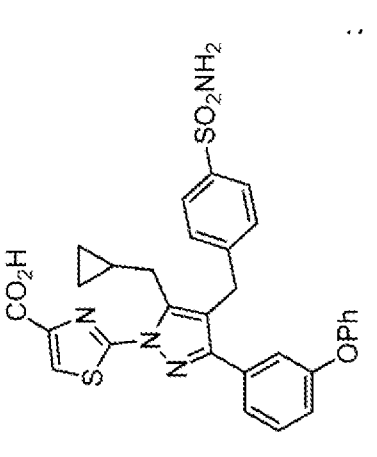
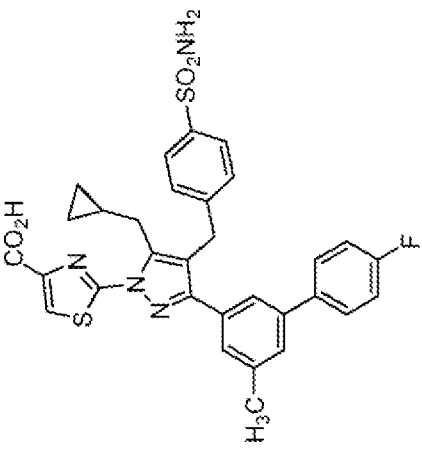
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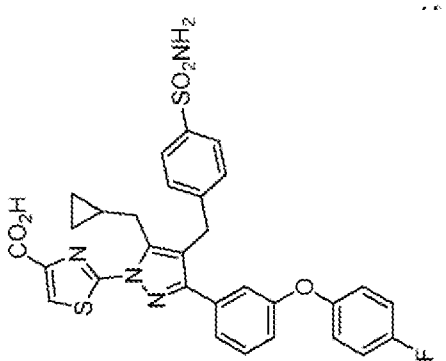
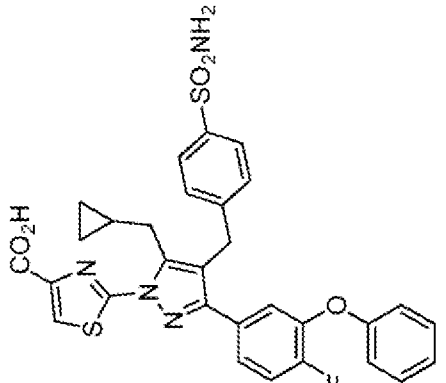
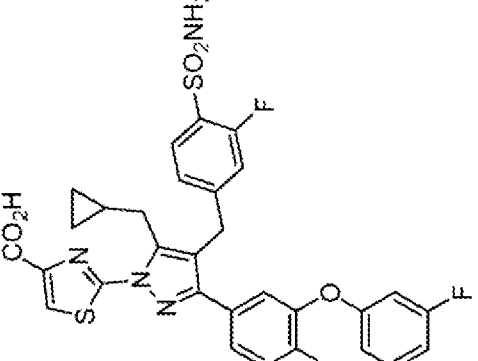
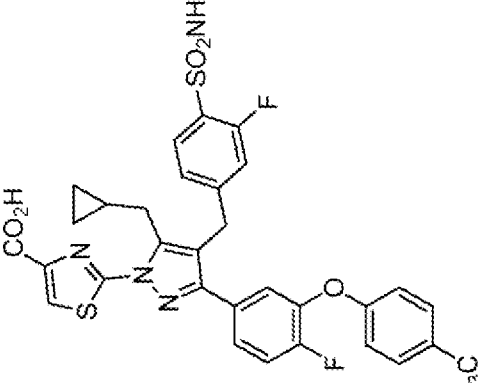
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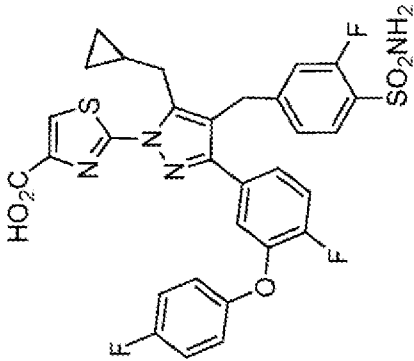
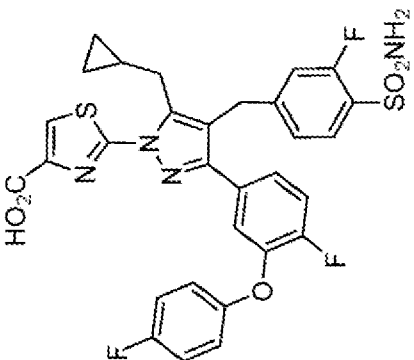
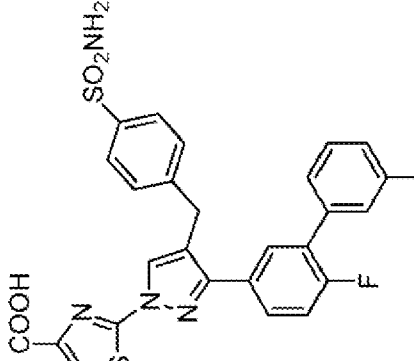
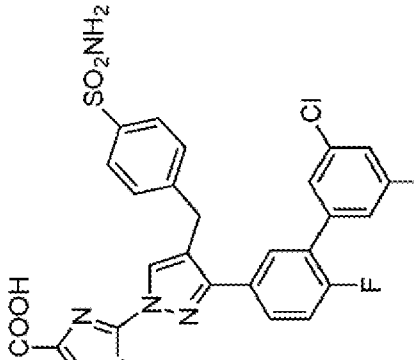
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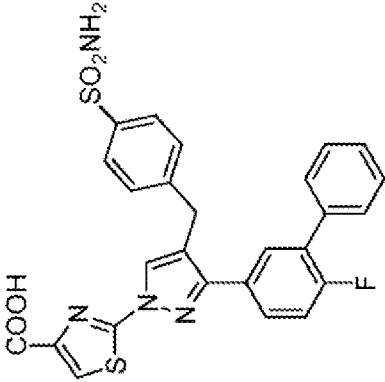
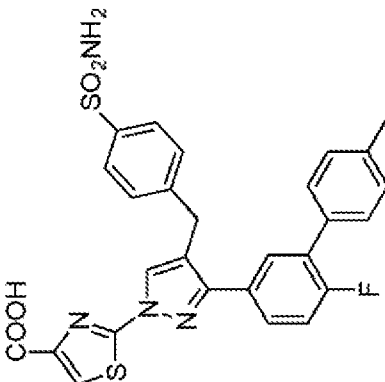
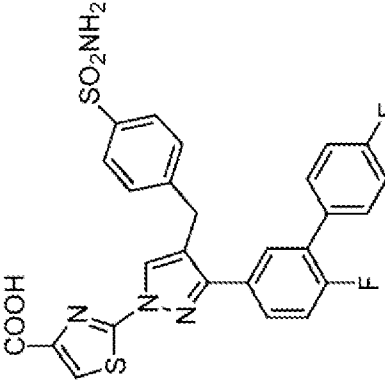
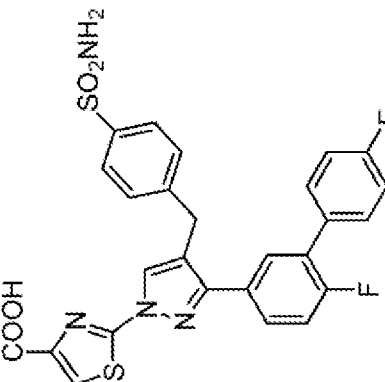
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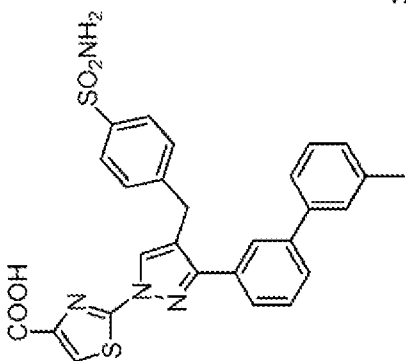
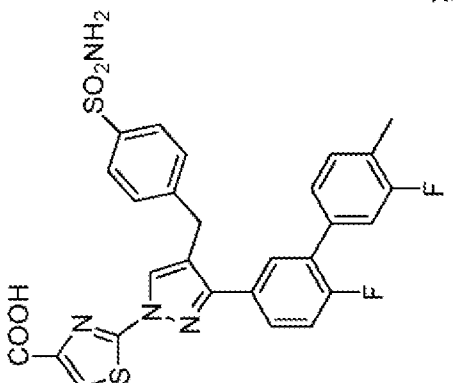
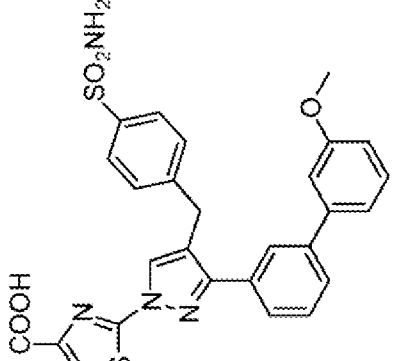
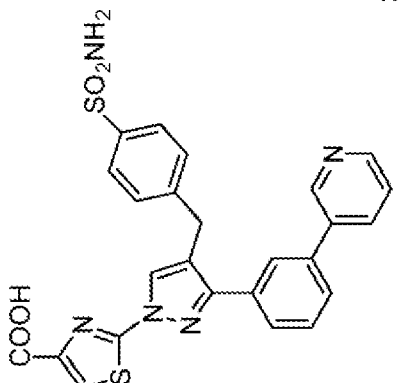
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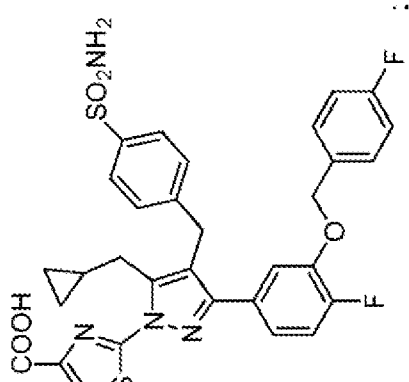
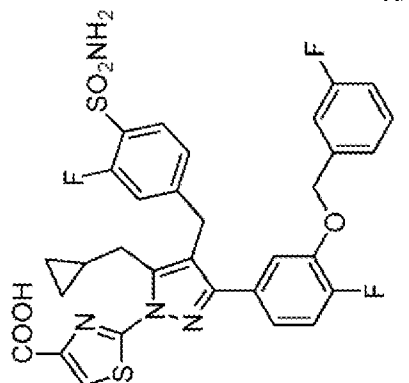
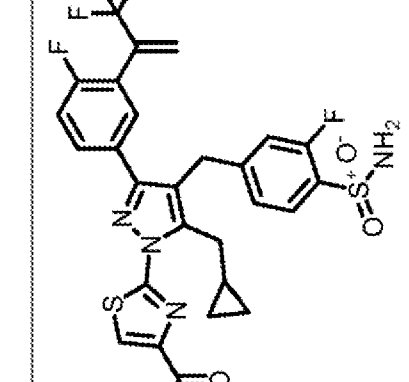
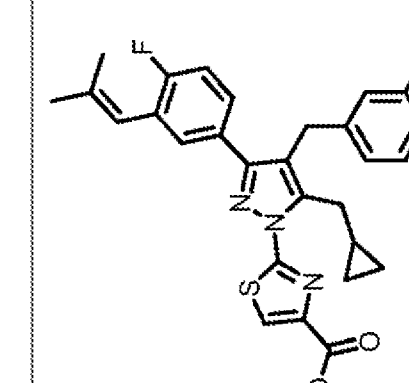
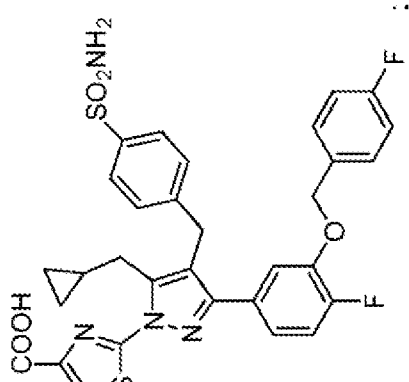
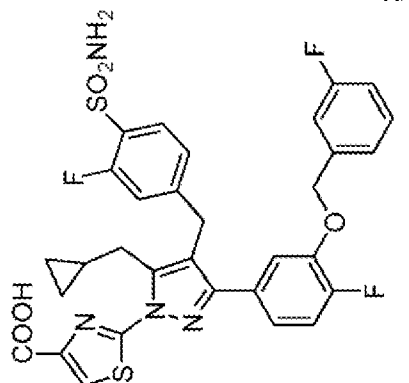
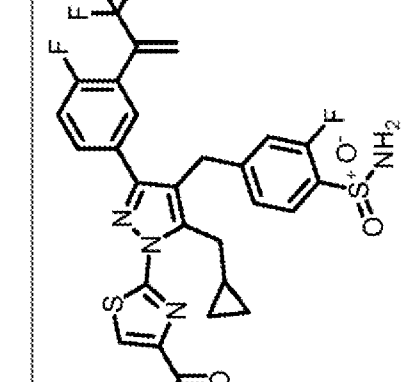
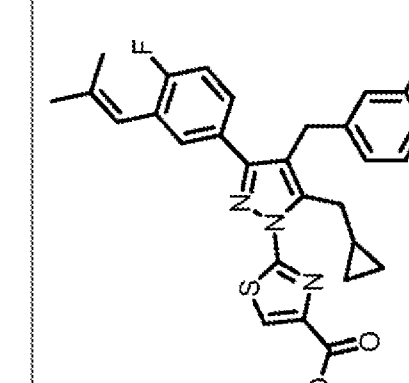
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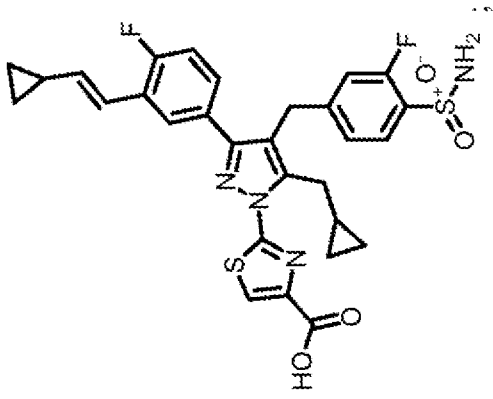
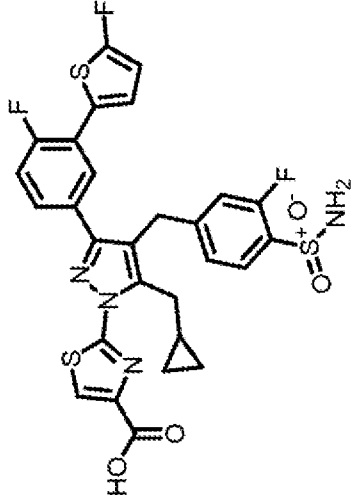
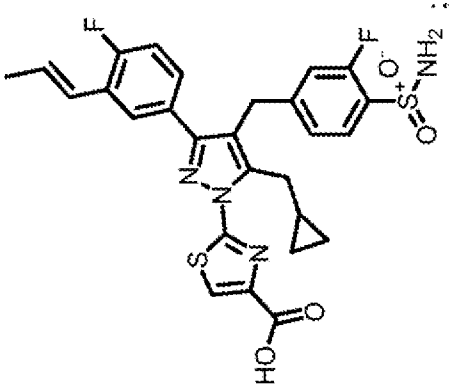
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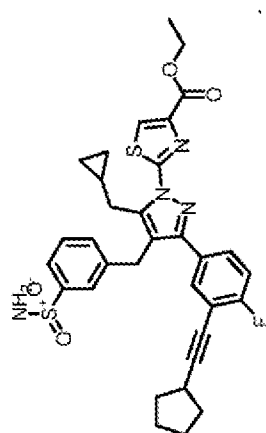
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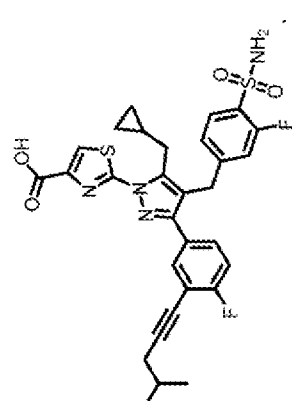
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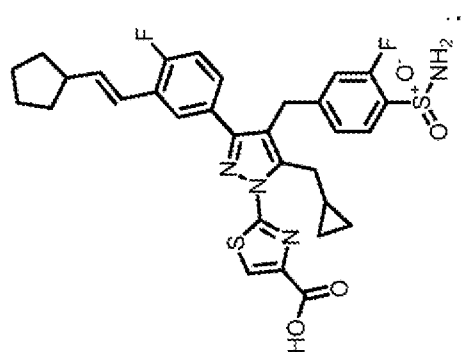
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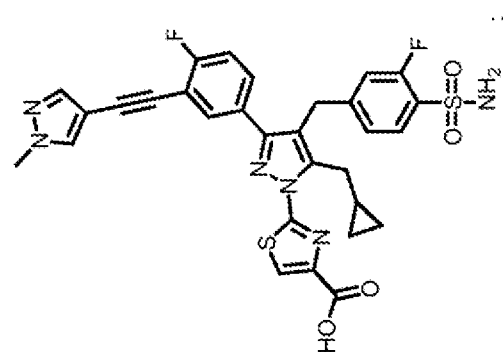
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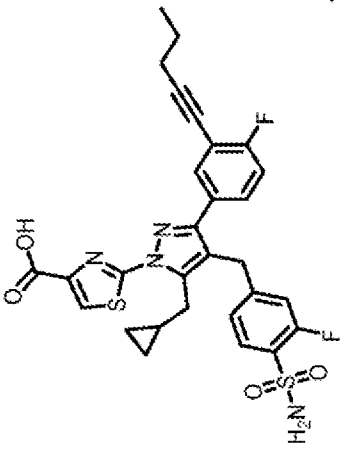
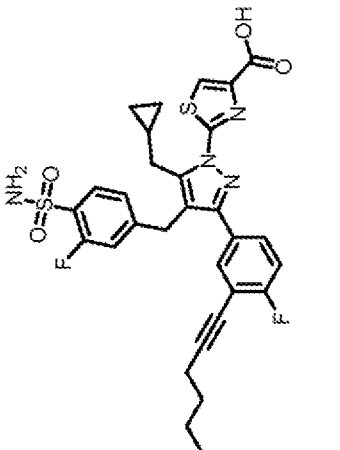
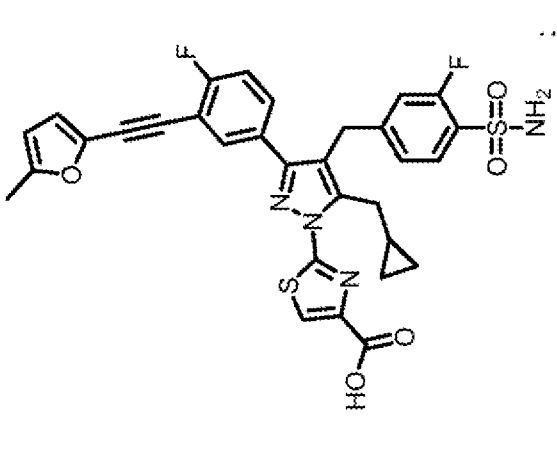
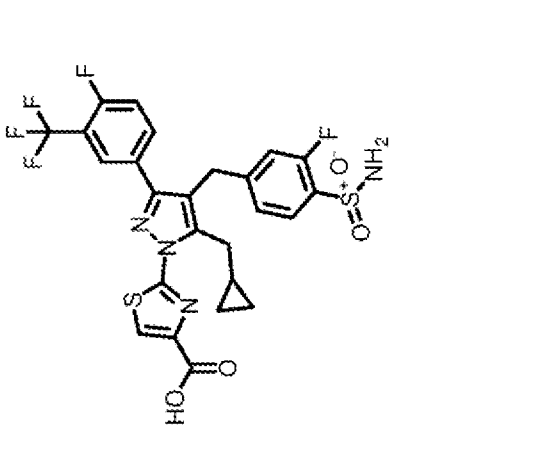


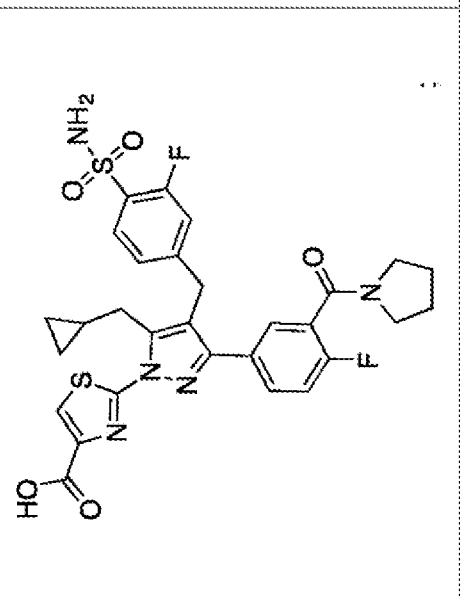
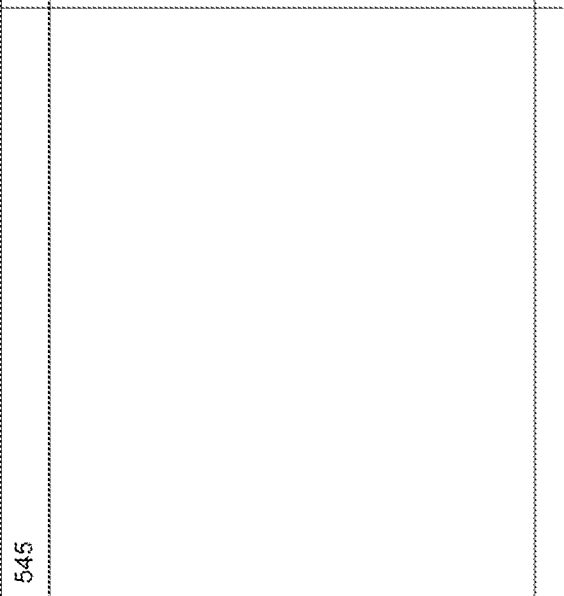
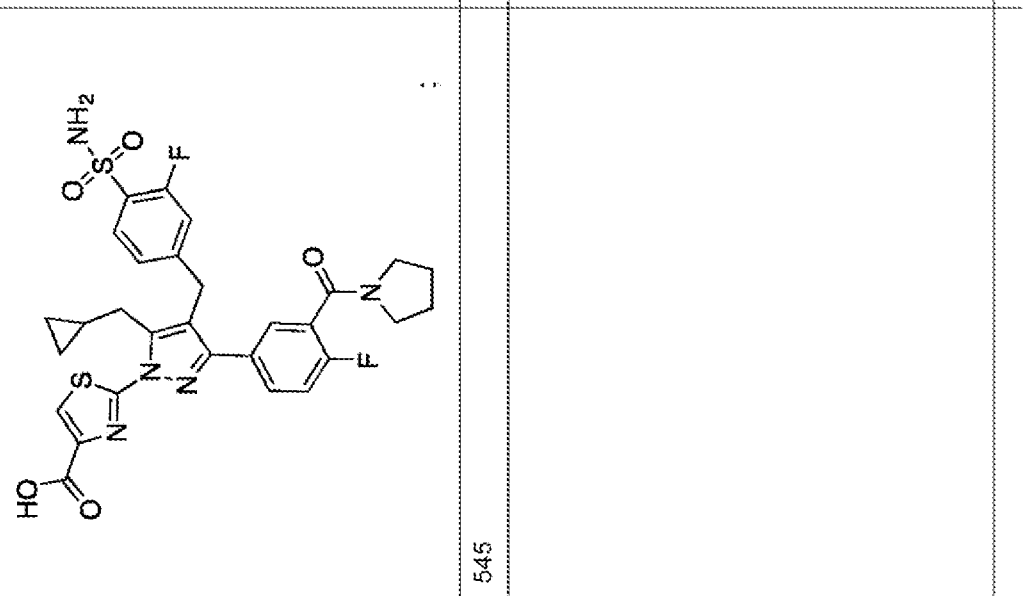
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- 5 **14.** En farmakologisk sammensætning, der omfatter mindst én forbindelse eller et farmakologisk acceptabelt salt af ethvert af kravene 1-13 og en farmakologisk acceptabel bærer.
- 10 **15.** Forbindelsen eller saltet ifølge krav 1-13, eller en forbindelse ifølge krav 14, til brug i en fremgangsmåde til behandling af en patient med kræftceller, der er resistente mod et anti-kræftmiddel, hvori, i nævnte fremgangsmåde, nævnte forbindelse eller sammensætning og nævnte anti-kræftmiddel indgives til patienten, og hvor, i nævnte fremgangsmåde, nævnte forbindelse eller sammensætning gør kræftcellerne følsomme over for nævnte anti-kræftmiddel igen.