

INHIBITORS OF FATTY ACID BINDING PROTEINS (FABPs), METHODS OF USE AND METHODS OF MAKING

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit to U.S. Provisional Application No. 63/471,207, filed June 5, 2023, which is hereby incorporated by reference herein.

FIELD

[0002] The present disclosure relates to compounds that inhibit fatty acid binding proteins, such as FABP3, FABP4, FABP5, and/or FABP7, pharmaceutical compositions containing these inhibitor compounds, and uses of these compounds and compositions for treating or preventing cancers that highly express any of these FABPs, in particular triple-negative breast cancer (TNBC), autoimmune diseases and disorders, viral infections, and other diseases linked to chronic inflammation including cardiovascular disease, obesity or an obesity-related disorders, diabetes, dyslipidemia, impaired glucose tolerance or impaired fasting glucose, vitiligo, psoriasis, pain and dementia.

BACKGROUND

[0003] Fatty acid binding proteins (FABP) are members of a family of small (12-15kDa), soluble proteins which contribute to the trafficking of fatty acids within the cytosolic compartments of cells. The proteins are a multigene family, well-conserved, have no catalytic function but transport hydrophobic fatty acids within the aqueous environment of the cytosol to the various destinations enabling fatty acid oxidation, membrane homeostasis or nuclear signaling. In addition, they are involved in signaling processes which are so far poorly understood [1-4]. Structurally, all members of the FABP family share a β -barrel structure that consists of a water-filled cavity and a site that binds specific lipid-ligand unique for each member. FABPs have unique tissue-expression pattern except FABP5 that is ubiquitously expressed in most tissues. Yet, in general, tissues with active lipid metabolism tend to express more than one isoform. FABP3 is mainly expressed in muscle tissues, particularly in the heart and in neurons. FABP4 is highly expressed in adipose tissue, macrophages and endothelial cells. FABP5 is also expressed in macrophages and endothelial cells, as well as in skin, adipocytes, neurons, glia cells, and several other tissues [2, 5, 6]. FABP7 is expressed in the brain, specifically in glia cells and astrocytes. Patient data that became available in recent years indicates FABP5 is highly upregulated in breast tumors, particularly in TNBC tumors. The protein was reported to induce growth and metastasis of TNBC cells, and high levels of the protein are associated with poor survival of TNBC patients. Genetic ablation of FABP5 in the breast cancer mouse model MMTV-NeuT markedly delayed formation of tumors and inhibited their growth rate [7]. And similarly, chemical inhibition of FABP5 suppressed growth of tumors in xenograft models

[8, 9]. The data indicates that inhibition of FABP5 is a promising novel approach for treatment of TNBC and perhaps other cancers that highly express this protein.

[0004] TNBC is the most aggressive and deadly breast cancer subtype and accounts for 10-20% of all breast cancer cases. Women diagnosed with TNBC are four times more likely to have cancer cells spread or metastasize to other organs within five years than patients with other types of breast cancer. TNBC are a heterogeneous group of breast tumors that are still poorly characterized at the molecular level and lack definitive prognostic markers and selective targets for therapy. This makes the treatment and management of TNBC a significant clinical problem and there is an urgent need for novel targeted therapies for this disease. Current standard of care for TNBC includes neoadjuvant systemic treatment such as anthracyclines, taxanes, and cyclophosphamide. Platinum-based chemotherapy has been proposed but is not yet recommended by available guidelines. Currently, there are no approved targeted therapies for TNBC in the neoadjuvant setting.

[0005] Genetic deletion of FABP4 and FABP5 in mice improves insulin sensitivity, lowers glucose, and protects against atherosclerosis.⁴ In a clamp study in ob/ob mice, a specific FABP4 inhibitor (BMS309403) showed a reduction of hepatic glucose production, increased glucose uptake in muscle and adipose tissue, and reduction in hepatic steatosis, but no change in body weight and energy consumption. Additionally, this compound showed a decrease in atherosclerotic plaque formation in ApoE KO mice [2, 3]. In humans, plasma levels of FABP4 are increased in patients with metabolic syndrome and atherosclerosis [10]. In addition, there is growing evidence for involvement of FABP4 in angiogenesis [11] and growth of certain tumors [12]. The global prevalence of obesity is increasing epidemically. Obesity causes an array of health problems, reduces life expectancy, and costs over US\$100 billion annually. More than a quarter of the population suffers from an aggregation of co-morbidities, including obesity, atherosclerosis, insulin resistance, dyslipidemias, coagulopathies, hypertension, and a pro-inflammatory state known as the metabolic syndrome. Patients with metabolic syndrome have high risk of athero-sclerosis as well as Type-2 diabetes and other health problems. Like obesity, atherosclerosis has very limited therapeutic options.

[0006] Atherosclerosis is the leading cause of death in the United States. At the core of this syndrome is the dysregulation of lipid metabolism and aberrant inflammatory responses. Although mechanistic roles for fatty acids have been put forward in the formation of obesity and diabetes by modifying glucose and lipid metabolism as well as inflammatory cascades, little is known about the mechanisms that link fatty acids or other lipid signals to inflammatory responses and the formation of atherosclerotic lesions.

[0007] The ability to modulate the immune system offers the prospect of treating wide range of conditions including those caused by chronic inflammation and cancer. Beyond its established role in vaccine development, immunomodulation has therapeutic potential for various conditions including autoimmunity and cancer, as well as inflammatory, fibrotic and infectious diseases.

[0008] The immune cells play a crucial role in the tumor microenvironment (TME). The tumor-infiltrating immune cells are involved in the regulation of tumor development, progression, and response to treatment. The cellular and molecular profile of the immune TME impacts the disease response to therapy and its outcome by regulating the balance between suppressive versus cytotoxic responses in the vicinity of the tumor [13]. Specific immune cells, such as T cells and natural killer cells, can help suppress tumors' growth and contribute to the elimination of cancer cells. Conversely, the accumulation of immunosuppressive immune cells, such as regulatory T cells and myeloid-derived suppressor cells, can create an environment permissive to tumor growth and progression. The balance between immune-stimulating and immune-suppressive cells in the tumor microenvironment is crucial to the success of immunotherapy and other cancer treatments. Therefore, the ability to manipulate the complex interplay between immune cells and the tumor microenvironment is crucial for the development of more effective cancer therapies.

[0009] Targeting immune cells in the tumor microenvironment is a promising strategy for improving the effectiveness of cancer treatments [13-15]. This approach aims to shift the balance of immune cells in the microenvironment from pro-tumor to anti-tumor. One way to do this is by enhancing the activity of immune cells that can recognize and eliminate cancer cells, such as T cells, natural killer cells and the pro-inflammatory M1 macrophages (classically activated macrophages). This can be achieved through the use of immune checkpoint inhibitors, which release the brakes that generally prevent immune cells from attacking the tumor. Another strategy is to reduce the number or activity of immune cells that suppress the immune response, such as regulatory T cells, myeloid-derived suppressor cells or the anti-inflammatory M2 macrophages (alternatively activated macrophages). This can be done through the use of drugs that specifically target these cell types. Combining these and other approaches, such as vaccines or CAR-T cell therapy, may provide a more comprehensive and effective way to target the immune cells in the tumor microenvironment and improve cancer treatment outcomes.

[0010] One of the mechanisms by which FABPs regulate immune cells was suggested to be through their role in mediating immune cell metabolism, which is critical for the proper functioning of the immune system. By affecting the utilization of fatty acids, FABPs regulate energy production and the signaling pathways involved in the activation and function of immune cells. For example, FABP5 was found to regulate lipid metabolism and function in T-cells in the TME by mediating the uptake and oxidation of long-chain FAs in the cells. Activated T-cells mainly rely on aerobic glycolysis to facilitate their proliferation and anti-tumor function. However, tumor-infiltrating T lymphocytes (TIL) that express high FABP5 levels usually exhibit an exhausted phenotype and impaired anti-tumor activity due to the limited availability of glucose and high levels of long-chain FAs. Inhibition of FABP5 in TILs is therefore expected to activate the anti-tumor activity of the cell by shifting their energy balance [16, 17].

[0011] Another Example for regulation of immune cells by FABP5 and FABP4 is regulation of tissue resident T-cells (Trm). Trm cells are a subset of memory T cells which are self-sustaining in non-lymphoid tissues such as the gut, lung, reproductive tract and skin for longer period without circulation and provide the first line of defense against antigens and pathogens through rapid recall responses [18-20]. Trm cells have the ability to regulate local immune homeostasis in tissues and participate in immune responses mediated by pathogens, cancer, and possibly autoantigens during autoimmunity [21]. It has become evident recently that this unique T-cell population contributes to the pathogenesis of autoimmune disorders such as psoriasis, vitiligo, autoimmune hepatitis and rheumatoid arthritis [19]. Due to their specialized function and location within tissues, gene expression signature of Trm cell, as well as their metabolic needs are distinctive from other types of T-cells [20, 22-24]. One of the most distinctive characteristics of Trm cells is they rely on exogenous free fatty acids (FFA), that are internalized from the surrounding environment and metabolized within the cell to produce ATP needed for their maintenance and survival [20]. Recently, it was reported that Trm cells selectively express the fatty acid binding proteins FABP4 and FABP5 that are essential for uptake of FFA into the cells [20]. T-cell-specific deficiency of FABP4/5 impaired uptake of FFA by Trm cells and significantly reduced their longevity and survival *in vivo*, while having no effect on survival of central memory T (TCM) cells in lymph nodes [20]. Hence, FABP4/5 inhibitors can be used to specifically target Trm in autoimmune diseases.

[0012] FABP4 and FABP5 are expressed in macrophages and were shown to regulate their function by facilitating uptake and metabolism of fatty acids and lipid in the cells [25]. FABP4 is highly expressed in Ly6C⁺MHCII⁺CD36⁺ circulating monocyte/macrophages to facilitate oxidative lipid uptake, foam cell formation, angiogenesis, tissue remodeling and pro-tumor functions [25]. FABP5 is highly expressed in Ly6C⁺MHCII⁺CD36⁻ macrophages where it was shown to be involved in formation of lipid droplets (LD) in macrophages [26], and in CD11c⁺ macrophages where it was shown to promote secretion of pro-inflammatory cytokine IL-1b [27, 28], and cause ER stress, exhaustion and ferroptosis [28, 29] and therefor affect immune cell fate and disease progression. This suggests that inhibition of FABP4/5 in macrophages will be beneficial in treating multiple diseases. It is expected to enhance anti-tumor responses in cancer, block formation of foam cells and chronic inflammation in obesity and atherosclerosis, and will promote anti-inflammatory response in cases of inflammatory and autoimmune disease as well as infections. In cases of viral infections, FABP4 was shown to be involved in virus replication and propagation in the case of SARS-Cov2 (COVID-19) and OCT43 (common cold coronavirus) viruses [30]. FABP4 was shown to be recruited to the ER membrane in infected cells and its inhibition was shown to ameliorate viral replication and viral load in cell culture models and to improve disease symptoms *in vivo* [30]. Overall, the role of FABPs in immune cell regulation highlights the importance of lipid metabolism in the regulation of the immune system and imply that targeting FABPs may be a promising strategy for improving immune cell function and treating immune-related diseases.

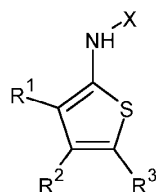
[0013] Descriptions of FABP inhibitor compounds in the art include the following. US Pat. No. 6,919,323 B2 (Sulsky *et al.*) describes certain pyridazinone compounds that inhibit the FABP aP2 (FABP4), and the use of these compounds for the treatment of Type-2 diabetes and related diseases. US Pat. No. 8,748,470 B2 (Lengyel *et al.*) describes methods for reducing or inhibiting cancer that include administering to a subject an inhibitor of FABP4 and/or FABP5, where the inhibitor is selected from a list of known compounds, including carbazole butanoic acid, aryl sulfonamide, sulfonylthiophene, 4-hydroxypyrimidine, 2,3-dimethylindole, benzoylbenzene, biphenyl-alkanoic acid, 2-oxazole-alkanoic acid, tetrahydropyrimidone, pyridone, pyrazinone, aryl carboxylic acid, tetrazole, triazolopyrimidinone, indole, or BMS480404. US Pat. No. 8,815,875 B2 (Shipps, Jr. *et al.*) describes certain heterocyclic compounds that inhibit FABP, and the use of these compounds for the treatment of diseases or disorders including cardiovascular disease, a metabolic disorder, obesity, diabetes, dyslipidemia, and impaired glucose tolerance. US Pat. No. 9,278,918 B2 (Buettelmann, *et al.*) describes certain urea derivative compounds that inhibit FABP4 and/or FABP5, and the use of these compounds for the treatment of diseases or disorders including Type-2 diabetes, atherosclerosis, chronic kidney diseases, and cancer. PCT publication WO2023043803A1 (Levi, *et al.*) describes certain aniline derivative compounds that inhibit FABP4 and/or FABP5, and the use of these compounds for the treatment of diseases relating to fatty acid metabolism, including cancer.

[0014] There remains a need for improved FABP inhibitor compounds, including compounds that inhibit one or more of FABP3, FABP4, FABP5, and FABP7, and uses of these compounds in the treatment of diseases and disorders, including cancer.

SUMMARY

[0015] The present disclosure generally relates to compounds based on a substituted 2-amino-thiophene structure that are inhibitors of one or more of FABP3, FABP4, FABP5, and FABP7 (i.e., “FABP3/4/5/7 inhibitors”), and the use of these inhibitors, methods for preparing these inhibitors, and uses of these inhibitors in pharmaceutical compositions for treating diseases relating to fatty acid metabolism. This summary is intended to introduce the subject matter of the present disclosure, but does not cover each and every embodiment, combination, or variation that is contemplated and described within the present disclosure. Further embodiments are contemplated and described by the disclosure of the detailed description, drawings, and claims.

[0016] In at least one embodiment, the present disclosure provides a FABP3/4/5/7 inhibitor compound of structural formula **I** or pharmaceutically acceptable salt thereof:



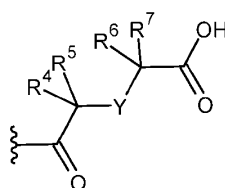
(I)

wherein,

R^1 is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, , trifluoromethyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro;

X is a moiety of formula:



wherein,

Y is a heteroatom selected from $-S-$, and $-O-$, or is $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

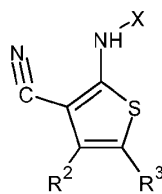
R^4 , R^5 , R^6 and R^7 is each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, and/or

R^4 and R^5 together or R^6 and R^7 together form a cyclopropyl ring or a cyclobutyl ring, or

R^5 and R^6 together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring.

[0017] In at least one embodiment of the compound of structural formula **I** of the present disclosure, the compound excludes the specific compounds as shown in Table 1 (shown elsewhere herein).

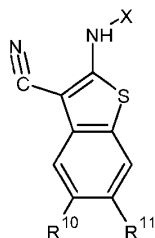
[0018] In at least one embodiment of the compound of structural formula **I** of the present disclosure, the chemical group at position R^1 is a cyano group, and the compound has a structural formula **Ia**:



(Ia).

[0019] In at least one embodiment, the compound of structural formula **Ia** is a compound having a structural formula selected from **Ij**, **Ik**, **Il**, **Im**, **In**, **Io**, **Ip**, **Iq**, **Ir**, **Is**, and **It** as shown in Table 2 (elsewhere herein).

[0020] In at least one embodiment of the compound of structural formula **I** of the present disclosure, the chemical substituents at positions R^2 and R^3 together form a 5- to 8-membered aryl or heteroaryl ring, and the compound has structural formula **Ib**



(Ib)

wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl.

[0021] In at least one embodiment, the compound of structural formula **Ib** is a compound having a structural formula selected from **Iu**, **Iv**, and **Iw** as shown in Table 3 (elsewhere herein).

[0022] In at least one embodiment of the compound of structural formula **I** of the present disclosure, the chemical group at R^1 is a 5-membered heteroaryl ring (e.g., 3-substituted 1,2,4-oxadiazol), and the compound has a structural formula selected from **Ic**, **Id**, **Ie**, **If**, **Ig**, **Ih**, and **Ii**:

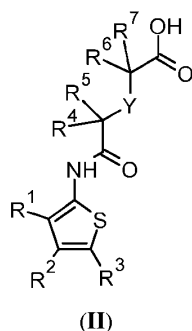
(Ic)	(Id)	(Ie)
(If)	(Ig)	(Ih)
(Ii)		

wherein R^{12} is selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl.

[0023] In at least one embodiment, the compound of structural formulas **Ic**, **Id**, **Ie**, **If**, **Ig**, **Ih**, and **Ii**, include but are not limited to the compounds having structural formulas **Ix**, **Iy**, **Iz**, **Iaa**, **Ibb**, **Icc**, **Idd**, **Iee**, **Iff**, **Igg**, **Ihh**, **Iii**, **Ijj**, **Ikk**, **Ill**, **Imm**, **Inn**, **Ioo**, **Ipp**, **Iqq**, and **Irr** shown in Table 5 (shown elsewhere herein).

[0024] In at least one embodiment of the compounds of structural formulas **I**, **Ia**, **Ib**, **Ic**, **Id**, **Ie**, **If**, **Ig**, **Ih**, **Ii**, **Ij**, **Ik**, **Il**, **Im**, **In**, **Io**, **Ip**, **Iq**, **Ir**, **Is**, **It**, **Iu**, **Iv**, **Iw**, **Ix**, **Iy**, **Iz**, **Iaa**, **Ibb**, **Icc**, **Idd**, **Iee**, **Iff**, **Igg**, **Ihh**, **Iii**, **Ijj**, **Ikk**, **Ill**, **Imm**, **Inn**, **Ioo**, **Ipp**, **Iqq**, and **Irr**, the X moiety is selected from the exemplary moieties shown in Tables 6, 7, or 8 (elsewhere herein).

[0025] In at least one embodiment, the present disclosure provides a FABP3/4/5/7 inhibitor compound of structural formula **II** and any pharmaceutically acceptable salt thereof:



wherein,

R^1 is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro;

Y is a heteroatom selected from $-S-$, and $-O-$, or is $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

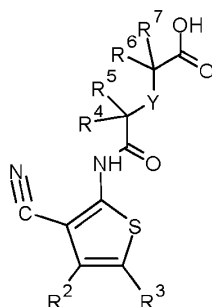
R^4 , R^5 , R^6 and R^7 is each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, and/or

R^4 and R^5 together or R^6 and R^7 together form a cyclopropyl ring or a cyclobutyl ring, or

R^5 and R^6 together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring.

[0026] In at least one embodiment of the compound of structural formula **II** of the present disclosure, the compound excludes the compounds as shown in Table 1.

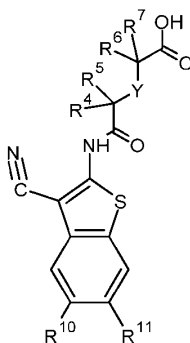
[0027] In at least one embodiment of the compound of structural formula **II**, the chemical group at position R¹ is a cyano group, and the compound has structural formula **IIa**



(IIa)

wherein the chemical groups R², R³, R⁴, R⁵, R⁶ and R⁷ are as defined for the compound of structural formula **II**. In at least one embodiment, the compounds of having the substructure of structural formula **IIa** can have a structural formula **IIj**, **IIk**, **IIl**, **IIm**, **IIo**, **IIn**, **IIp**, **IIq**, **IIr**, **IIs**, or **IIt** as shown in Table 9 (elsewhere herein).

[0028] In at least one embodiment of the compound of structural formula **II**, the chemical group at position R¹ is a cyano group. R² and R³ together form a 6-membered aryl ring, and the compound has structural formula **IIb**

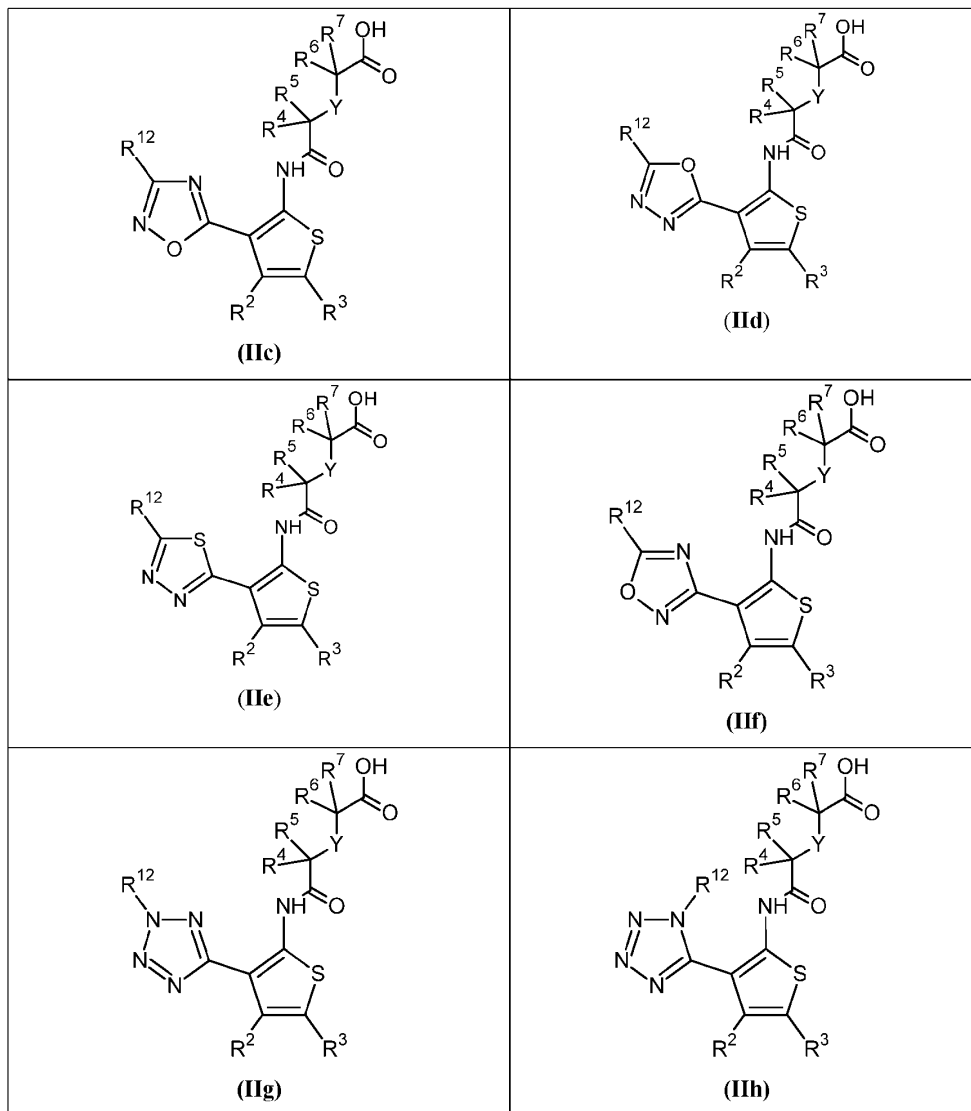


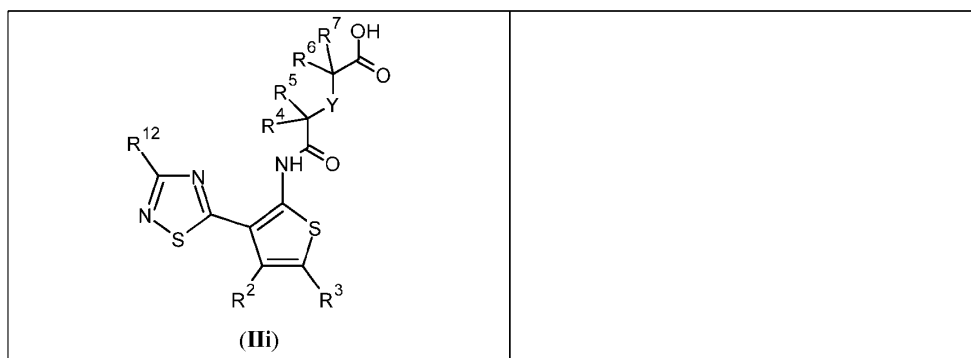
(IIb)

wherein the chemical groups R², R³, R⁴, R⁵, R⁶ and R⁷ are as defined for the compound of structural formula **II**, and R¹⁰ and R¹¹ are each independently selected from hydrogen, halogen, C₁-C₄ linear or branched alkyl, cyclopropyl, and cyclobutyl. In at least one embodiment, the compounds of structural formula **IIb** can have a structural formula **IIu**, **IIv**, or **IIw**, as shown in Table 10 (elsewhere herein).

[0029] In at least one embodiment of the compound of structural formula **II**, the chemical group at position R¹ is a 5-membered heteroaryl ring, the chemical groups at R² and R³ are each independently

selected from hydrogen, C₁-C₄ linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl, and the compound has structural formula **IIc**, **IId**, **IIf**, **Ilg**, **Iih**, or **III**





wherein the chemical groups R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II**, and the chemical group R^{12} is a hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, or phenyl. In at least one embodiment, the compound of structural formulas **IIc**, **IId**, **Ile**, **IIf**, **Ilg**, **IIh**, and **Iii**, is a compound having a structural formula **IIx**, **Ily**, **IIz**, **IIaa**, **IIbb**, **IIcc**, **IIdd**, **IIee**, **IIff**, **IIgg**, **IIhh**, **IIii**, **IIjj**, **IIkk**, **IIll**, **IImm**, **IInn**, **IIoo**, **IIpp**, **IIqq**, **IIrr**, and **IIss** as shown in Table 12 (elsewhere herein).

[0030] In at least one embodiment of the compound of structural formula **I** or the compound structural formula **II** of the present disclosure, the compound is selected from any of exemplary compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, and 65, as shown in Table 13 (elsewhere herein).

[0031] In another embodiment, the present disclosure provides a pharmaceutical composition comprising a compound of structural formula **I** or formula **II** and one or more adjunct ingredients.

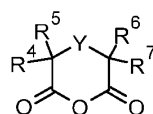
[0032] In another embodiment, the present disclosure provides uses of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or formula **II** in method of making medicament or pharmaceutical composition for the treatment of a disease or condition affected by any one or more of the FABPs, FABP3, FABP4, FABP5, and FABP7 (i.e., “conditions affected by FABP3/4/5/7”).

[0033] In another embodiment, the present disclosure provides a method for treating a subject having a disease or condition affected by FABP3/4/5/7, comprising administering to a subject in need thereof a therapeutically effective amount of compound of structural formula **I** or formula **II**, or a pharmaceutical composition comprising a compound of structural formula **I** or formula **II** and one or more adjunct ingredients.

[0034] In at least one embodiment, the diseases or conditions affected by FABP3/4/5/7 present in a subject which the compounds of structural formula **I** or formula **II** can be used to treat can be selected from: atherosclerosis, coronary atherosclerosis, arterial fibrosis, pulmonary hypertension, heart failure, obesity, Type-2 diabetes, Type-1-diabetes, gestational diabetes, polycystic ovary syndrome, endometriosis, conditions affected by lipid metabolism and free fatty acid serum levels, metabolic

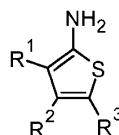
disorders, fatty liver disease, kidney fibrosis, systemic inflammation, acute inflammation, allergic inflammation, airway inflammation, viral infection (e.g., COVID-19, common cold), skin diseases (e.g., vitiligo, psoriasis, atopic dermatitis, allergic contact dermatitis, mycosis fungoides, alopecia areata, cicatricial alopecia, graft vs. host disease (GvHD), contact dermatitis, chronic eczema, dermatitis herpetiformis, cutaneous lupus, scleroderma, dermatomyositis, vasculitis, pemphigus, epidermolysis bullosa, linear IgA, blistering disease), neurological conditions and diseases (e.g., pain, multiple sclerosis (MS), Parkinson's disease, autoimmune diseases (e.g., experimental autoimmune encephalomyelitis (EAE), asthma, type-1-diabetes, autoimmune lung disease, autoimmune hepatitis, rheumatoid arthritis (RA), spondyloarthropathy, vesicular stomatitis virus infection, multiple sclerosis (MS), lupus nephritis, Crohn's disease, ulcerative colitis, and food allergy), ischemic stroke, graft versus host disease (GvHD) and cancer (e.g., breast cancer, prostate cancer, ovarian cancer, skin cancer, gastric cancer, glioma, cholangiocarcinoma, bladder cancer, multiple myeloma, colorectal cancer, hepatocellular cancer, cervical cancer, oral squamous cell carcinoma, and/or non-small cell lung cancer (NSCLC)).

[0035] In another embodiment, the present disclosure also provides methods for preparing the compounds of structural formula **I** or formula **II**, the method comprising: (a) combining in a solvent a substituted anhydride compound of formula **III**:



(III)

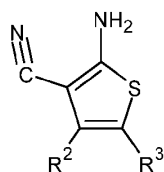
wherein Y, R⁴, R⁵, R⁶ and R⁷ are as defined above for compounds of formula **I** and **II**; with a substituted 2-amino-thiophene compound of formula **IV**:



(IV)

wherein, R¹, R² and R³ are as defined above for compounds of formula **I** and **II**; and (b) removing the solvent to obtain a compound having the structural formula **I** or formula **II**.

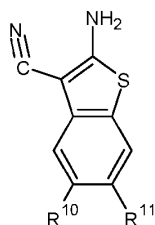
[0036] In at least one embodiment of the compound of formula **IV**, the compound is a compound of structural formula **IVa**:



(IVa)

wherein the chemical groups R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula II. In at least one embodiment, the compounds of structural formula IVa is selected from the compounds 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4j, and 4k, shown in Tables 14 and 15 (elsewhere herein).

[0037] In at least one embodiment of the compound of formula IV, the compound has structural formula IVb:



(IVb)

wherein the chemical groups R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula II, and wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl. In at least one embodiment, the compound of structural formula IVb is selected from compounds 4l, 4m, and 4n shown in Table 16 (elsewhere herein).

[0038] In at least one embodiment of the compound of formula IV, the chemical group at R^1 is a 5-membered heteroaryl ring (e.g., 3-substituted 1,2,4-oxadiazol), and the compound is selected from the compounds of structural formula IVc, IVd, IVe, IVf, IVg, IVh, and IVi shown in Table 17 (elsewhere herein). In at least one embodiment, the compounds of structural formulas IVc, IVd, IVe, IVf, IVg, IVh, and IVi are selected from compounds 4o, 4p, 4q, 4r, 4s, 4t, 4u, 4v, 4w, 4x, 4y, 4z, 4aa, 4bb, 4cc, 4dd, 4ee, 4ff, 4gg, 4hh, and 4ii shown in Table 18 (elsewhere herein).

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] A better understanding of the novel features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings (also “Figure” and “FIG.” herein), of which:

[0040] FIG. 1A, FIG. 1B, and FIG. 1C depict plots of results showing that inhibitor compounds **FTS005**, **FTS030**, **FTS031**, **FTS037**, and **FTS039** do not activate transcription by PPAR α , PPAR γ , or PPAR δ . Transcriptional activation assays in COS7 cells co-transfected with vectors encoding either PPAR α (FIG. 1A), PPAR γ (FIG. 1B), or PPAR δ (FIG. 1C), together with a PPAR response element (PPRE), and a vector harboring β -galactosidase, serving as a transfection control. Cells were treated with PPARs' specific agonists Wy-134643 (5 μ M), rosiglitazone (5 μ M), and GW0742 (5 μ M) or one of the compounds **FTS005**, **FTS030**, **FTS031**, **FTS037**, and **FTS039** (10 μ M). Data is mean $\pm$ SD from 3 independent experiments.

[0041] FIG. 2A, FIG. 2B, and FIG. 2C depict plots of results showing that the FABP3/4/5/7 inhibitor compound **FTS005**, which exhibits specificity for FABP4/5, inhibits growth of TNBC cells in an FABP5-dependent manner and more efficiently than the FABP5/7 inhibitor, SBF-126. Cells in all experiments were treated with one of the denoted compounds at indicated concentrations for 4 days. Cells confluency was measured using Incucyte software. FIG. 2A: Results indicating that compound **FTS005** at different concentrations inhibits proliferation of MB-231 and BT-549 cell lines. IC₅₀ values were calculated using GraphPad fitting algorithms. FIG. 2B: Plots of results indicating that compound **FTS005** at different concentrations inhibits proliferation of wild type MB-231 cell line but not those cells stably expressing the FABP5 shRNA ("shF5"). FIG. 2C: Plots of results indicating that compound **FTS005** at different concentrations inhibits proliferation of MB-231 cell lines better than the commercially available FABP5/7 inhibitor SBF-126. Data is mean $\pm$ SD from 3 independent experiments.

[0042] FIG. 3A, FIG. 3B, and FIG. 3C depict plots of results indicating that the FABP3/4/5/7 inhibitor compound **FTS005** inhibits growth of mouse mammary carcinoma cell lines expressing high levels of FABP5 relative to those expressing low levels of the gene. Cells in all experiments were treated with the denoted compound at indicated concentrations for 4 days. Cells confluency was measured using Incucyte software. FIG. 3A: Levels of FABP5 mRNA in the donated cell lines was measured by QPCR. FIG. 3B: Results indicating that compound **FTS005** inhibits proliferation of MB-231 and 4T1 cell lines in correlation to expression levels of FABP5 in the cells. IC₅₀ values were calculated using GraphPad fitting algorithms. FIG. 3C: Results indicating that compound **FTS005** inhibit cell proliferation only in cells that express FABP5. Data is mean $\pm$ SD from 3 independent experiments.

[0043] FIG. 4A and FIG. 4B depict plots of results indicating that the FABP3/4/5/7 inhibitors compounds **FTS005**, **FTS040**, **FTS041**, **FTS042**, **FTS043**, **FTS044**, **FTS045**, and **FTS049** inhibit proliferation of ovarian cancer cells OVCAR8. Cells in all experiments were treated with the denoted compounds at indicated concentrations for 4 days. Cells confluency was measured using Incucyte software.: FIG. 4A Results indicating that compounds **FTS005**, **FTS040**, **FTS041**, **FTS042**, **FTS043**, **FTS044**, **FTS045**, and **FTS049** inhibit proliferation of OVCAR8 cell line. FIG. 4B: IC₅₀ values for all

compounds were calculated using GraphPad fitting algorithms. Data is mean±SD from 3 independent experiments.

[0044] **FIG. 5A, FIG. 5B, and FIG. 5C** depict results showing that the FABP3/4/5/7 inhibitor **FTS005** inhibits growth of neuroblastoma and sensitize cells to all-trans retinoic acid (atRA) treatments. NPG human neuroblastoma cells were treated with **FTS005** at indicated concentrations in the presence or absence of retinoic acid (1 mM) for 4 days. Cells confluency was measured using Incucyte software. **FIG. 5A**: Results indicating that compound **FTS005** inhibits proliferation of NPG cells but shows synergistic effect when combined with atRA. **FIG. 5B, FIG. 5C**: Results indicating that compound **FTS005** in combination with atRA inhibit cell proliferation more efficiently than atRA mono-treatment. IC₅₀ values were calculated using GraphPad fitting algorithms. Data is mean±SD from 3 independent experiments.

[0045] **FIG. 6A, FIG. 6B, FIG. 6C, FIG. 6D, FIG. 6E, FIG. 6F, and FIG. 6G** depict results showing FABP3/4/5/7 inhibitor **FTS005** suppresses tumor growth *in vivo* in xenograft model. **FIG. 6A**: Tumor growth in MB-231 xenograft model. MB-231 cells (5×10⁶) were transplanted into the right flank of 7-week-old female NOD scid gamma (NSG) mice. One day later **FTS005** treatment started by gavage 5 times a week (20, or 40 mg/kg) or vehicle. Tumor growth was monitored twice a week. Mean±SD (n=5) (by unpaired t-test). **FIG. 6B**: Data plotted represents the weight of tumors in each mouse at the end point (day 24). Statistical significance between the control and treated mice in all experiments was evaluated using a Student's t-test. **FIG. 6C**: Representative histological sections of paraffin embedded section from tumors stained with antibodies for Ki67, VEGFA, and F4/80. **FIG. 6D, FIG. 6E, and FIG. 6F**: Plots indicating the intensity of the immunohistology staining for each sample. **FIG. 6G**: Expression levels of the denoted PPARδ target genes in samples from collected tumors. Data in FIG 5C, FIG 5D, and FIG 5G is mean±SD of 3 mice/group. Statistical analyses were carried out using two-tailed Student's t-test. *p<0.05, **p<0.01.

[0046] **FIG. 7A, FIG. 7B, FIG. 7C, FIG. 7D, FIG. 7E, and FIG. 7F** depict results showing FABP3/4/5/7 inhibitor **FTS005** suppresses tumor growth *in vivo* in syngeneic mouse model. **FIG. 7A**: Tumor growth in 4T1 syngeneic xenograft model. 4T1 cells (1×10⁵) were transplanted into the mammary fat pad of 7-week-old female BALB/c mice. One day later **FTS005** treatment started by gavage 5 times a week (40 mg/kg) or vehicle. Tumor growth was monitored twice a week. Mean±SD (n=4) (by unpaired t-test). **FIG. 7B**: Data plotted represents the weight of individual tumors in each mouse at the end point (day 32). Statistical significance between the control and treated mice in all experiments was evaluated using a Student's t-test. **FIG. 7C**: Expression levels of the known PPARδ direct targets VEGFA, ACSL1, and PLIN2 that are involved in tumor growth and FA storage and oxidation, in tumor samples collected from treated and untreated mice. **FIG. 7D**: Representative histological sections of paraffin embedded section from treated and untreated tumors stained with antibodies for the proliferation marker Ki67 and VEGFA. **FIG. 7E and FIG. 7F**: Plots indicating the

percentage of positive immunohistology staining of Ki67 (**FIG. 7E**) and VEGFA (**FIG. 6F**) out of the total section area for each sample. * $p < 0.05$.

[0047] **FIG. 8A, FIG. 8B, FIG. 8C, and FIG. 8D** depict results of metabolomic analysis for metabolites of glycolysis, TCA cycle, FA oxidation, long-chain fatty acids, and ADP and ATP, that were measured by LC/MS/MS in tumor samples collected from the treated and untreated mice. **FIG. 8A**: Amounts of long chain fatty acids in the tumor cells. **FIG. 8B**: Amount of TCA cycle metabolites in treated and untreated tumors. **FIG. 8C**: Amount of ADP, ATP and their calculated ratio in treated and untreated tumors. **FIG. 8D**: Amount of glycolysis metabolites in treated and untreated tumors. Data is mean $\pm$ SD of 3 mice/group. Statistical analyses were carried out using two-tailed Student's t-test. * $p < 0.05$, ** $p < 0.01$.

[0048] **FIG. 9A, FIG. 9B, FIG. 9C, FIG. 9D, FIG. 9E, and FIG. 9F** depict results showing FABP3/4/5/7 inhibitor **FTS005** regulates tumor associated macrophages within the tumor microenvironment in 4T1 syngeneic mouse model. **FIG. 9A, FIG. 9B, and FIG. 9C**: Representative histological sections of paraffin embedded section from treated and untreated tumors stained with antibodies for F4/80 (**FIG. 9A**), CD68 (**FIG. 9B**), and CD163 (**FIG. 9C**). **FIG. 9D, FIG. 9E, and FIG. 9F**: Plots indicating the percentage of positive immunohistology staining with each antibody for each sample. Data in **FIG. 9D, FIG. 9E, and FIG. 9F** is mean $\pm$ SD of 3 mice/group. Statistical analyses were carried out using two-tailed Student's t-test. * $p < 0.05$.

[0049] **FIG. 10A, FIG. 10B, FIG. 10C, FIG. 10D, FIG. 10E, and FIG. 10F** depict results showing FABP3/4/5/7 inhibitor **FTS005** regulates T cells within the tumor microenvironment in 4T1 syngeneic mouse model. **FIG. 10A**: Representative histological sections of paraffin embedded section from treated and untreated tumors stained with antibodies for CD3 (A), CD4 (B), and CD8 (C). **FIG. 10B**: Plots indicating the percentage of positive immunohistology staining with each antibody for each sample. Data is mean $\pm$ SD of 3 mice/group. Statistical analyses were carried out using two-tailed Student's t-test. * $p < 0.05$. **FIG. 10C, FIG. 10D**: Plots indicating the frequency of CD4 and CD8 splenic T-cells (**FIG. 10C**) and activated CD4 and CD8 T-cells (TNF α + CD4 CD8T cells) (**FIG. 10D**) harvested from untreated and treated syngeneic mice. **FIG. 10E**: Harvested splenocytes were stimulated in vitro (IVS) with Luc2 peptides (2 μ g/mL) in T-cell media supplemented with 20 ng/mL IL-7 and 20 U/mL IL-2 (5 $\times 10^6$ cells/well). After 2 weeks of IVS, the cells were counted (n=5). **FIG. 10F**: After 2wks-IVS, the splenic T-cells co-cultured with 4T1Luc2-CFSE high (target, Balb/c origin) and F420Luc2-CFSE low (control, B6 origin) (Target:Effector=1:5) overnight. Next day, the live CFSE+ cells were counted by Flow cytometry and calculate the percent of specific lysis using the formula: (% = 100(1-live CFSE high/live CFSE low)), normalized by control. The statistical significance was measured by two-way student t-test: ns, non-specific, * $p < 0.05$.

[0050] **FIG. 11** depict results of immune cell profiling done by utilizing nCounter PanCancer Immune Profiling Panel showing that treatment with FABP3/4/5/7 inhibitor **FTS005** modulates multiple immune cells within the tumor microenvironment in 4T1 syngeneic mouse model. **FIG. 11**:

immune cells profile indicating all immune cell types that were found to be significantly different in the analysis (P-value<0.05, fold change>1.5).

[0051] **FIG. 12A** and **FIG. 12B** depict results showing that **FTS005** inhibits lipid uptake in cell culture models of steatosis and mature adipocytes. **FIG. 12A:** Plots indicating the intensity of Nile Red staining in hepatic HepG2 cells that were treated with designated concentrations of **FTS005** or the known FABP4 inhibitor BMS309403 for 4 h followed by oleic acid treatment (OA) (1mM, 24 h). Lipid accumulation was only measure in live cells that were positive for Dapi staining. Quantification of total lipid uptake was done using Biotech Cytation 5 plate reader. **FIG. 12B:** Histogram depicting the color intensity of Nile Red staining in viable mature adipocytes following treatment with **FTS005**. 3T3-L1 pre-adipocytes were differentiated in culture. Cells were treated with FTS005 or the known FABP4 inhibitor BMS309403 (BMS) on day six and stained with Nile Red on day 12.

[0052] **FIG. 13A, FIG. 13B, FIG. 13C, FIG. 13D, FIG. 13E, FIG. 13F, FIG. 13G, FIG. 13H, FIG. 13I, FIG. 13J, and FIG. 13K** depict results showing that FABP inhibitor **FTS005** modulate differentiation of macrophages in culture. **FIG. 13A, FIG. 13C, FIG. 13D:** Frequency of the M1 marker MHC-II (**FIG. 13A**), and the M2 markers CD36 (**FIG. 13C**) and CD206 (**FIG. 13D**) in naïve macrophages following their differentiated into M1- or M2-macrophages. **FIG. 13B, FIG. 13E:** Levels of the cytokines IL-12 (**FIG. 13B**) and IL-10 (**FIG. 13E**) secreted from M1 and M2 macrophages, respectively, during differentiation. **FIG. 13F, FIG. 13G, FIG. 13H:** Expression levels of CD206 (**FIG. 13F**), and levels of IL-10 (**FIG. 13G**) and IL-12 (**FIG. 13H**) in macrophages differentiated from naïve status to M2-macrophages in the absence and presence of FABP4/5 inhibitor **FTS005**. **FIG. 13I, FIG. 13J, FIG. 13K:** Frequency (**FIG. 13I**) and expression levels of CD206 (**FIG. 13J**), and levels of IL-12 (**FIG. 13K**) in M1-macrophages differentiated into M2-macrophages in the absence and presence of **FTS005**.

DETAILED DESCRIPTION

[0053] In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

[0054] General Definitions

[0055] In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

[0056] All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (°C) unless otherwise specified.

[0057] The terms “a” and “an” are defined as one or more unless this disclosure explicitly requires otherwise.

[0058] Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another aspect includes from the one

particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint.

The terms “comprise” (and any form of comprise, such as “comprises” and “comprising”), “have” (and any form of have, such as “has” and “having”), “include” (and any form of include, such as “includes” and “including”) and “contain” (and any form of contain, such as “contains” and “containing”) are open-ended linking verbs. As a result, an apparatus that “comprises,” “has,” “includes” or “contains” one or more elements possesses those one or more elements but is not limited to possessing only those elements. Likewise, a method that “comprises,” “has,” “includes” or “contains” one or more steps possesses those one or more steps but is not limited to possessing only those one or more steps.

[0059] Any embodiment of any of the disclosed methods or compositions can consist of or consist essentially of – rather than comprise/include/contain/have – any of the described steps, elements, and/or features. Thus, in any of the claims, the term “consisting of” or “consisting essentially of” can be substituted for any of the open-ended linking verbs recited above, in order to change the scope of a given claim from what it would otherwise be using the open-ended linking verb.

The feature or features of one embodiment may be applied to other embodiments, even though not described or illustrated, unless expressly prohibited by this disclosure or the nature of the embodiments.

[0060] Any embodiment of any of the disclosed compounds or methods can consist of or consist essentially of – rather than comprise/include/contain/have – any of the described steps, elements, and/or features. Thus, in any of the claims, the term “consisting of” or “consisting essentially of” can be substituted for any of the open-ended linking verbs recited above, in order to change the scope of a given claim from what it would otherwise be using the open-ended linking verb.

[0061] The feature or features of one embodiment may be applied to other embodiments, even though not described or illustrated, unless expressly prohibited by this disclosure or the nature of the embodiments.

[0062] As used herein, the term “subject” refers to a human or an animal that would benefit from being administered with the FABP3/4/5/7 inhibitor compounds discussed in the present application, such as those suffering from, without limitation a disease affected by expression of one or more of the FABPs, FABP3, FABP4, FABP5, and FABP7, lack of control of free fatty acid serum levels, cancer, metabolic syndrome, or atherosclerosis.

[0063] As used herein, the terms “treat,” “treating,” “treatment,” and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith. It will be appreciated that, although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated.

[0064] As used herein, the terms “prevent,” “preventing,” “prevention,” “prophylactic treatment” and the like are encompassed within the term “treating,” and refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

[0065] As used herein, “pharmaceutically acceptable” means physiologically tolerable, for either human or veterinary applications. In addition, “pharmaceutically acceptable” is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to a subject without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. Essentially, the pharmaceutically acceptable material is nontoxic to the recipient. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art. For a discussion of pharmaceutically acceptable carriers and other components of pharmaceutical compositions, see, e.g., Remington’s Pharmaceutical Sciences, 18th ed., Mack Publishing Company, 1990.

[0066] “Test agents” or otherwise “test compounds” as used herein refers to an agent or compound that is to be screened in one or more of the assays described herein. Test agents include compounds of a variety of general types including, but not limited to, small organic molecules, known pharmaceuticals, polypeptides; carbohydrates such as oligosaccharides and polysaccharides; polynucleotides; lipids or phospholipids; fatty acids; steroids; or amino acid analogs. Test agents can be obtained from libraries, such as natural product libraries and combinatorial libraries. In addition, methods of automating assays are known that permit screening of several thousands of compounds in a short period.

[0067] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the described invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. Details associated with the embodiments described above and others are described below.

The herein disclosed aryl, heterocyclic, and heteroaryl units can have one or more hydrogen atoms substituted therefor. Non-limiting examples of substitutions for hydrogen include the following:

[0068] Substituted and unsubstituted linear, branched, or cyclic alkyl units include the following non-limiting examples: methyl (C₁), ethyl (C₂), n-propyl (C₃), *iso*-propyl (C₃), cyclopropyl (C₃), n-butyl (C₄), *sec*-butyl (C₄), *iso*-butyl (C₄), *tert*-butyl (C₄), cyclobutyl (C₄), cyclopentyl (C₅), cyclohexyl (C₆), and the like; whereas substituted linear, branched, or cyclic alkyl, non-limiting examples of which includes, hydroxymethyl (C₁), chloromethyl (C₁), trifluoromethyl (C₁), aminomethyl (C₁), 1-

chloroethyl (C₂), 2-hydroxyethyl (C₂), 1,2-difluoroethyl (C₂), 2,2,2-trifluoroethyl (C₃), 3-carboxypropyl (C₃), 2,3-dihydroxycyclobutyl (C₄), and the like.

[0069] Substituted and unsubstituted linear, branched, or cyclic alkenyl include, ethenyl (C₂), 3-propenyl (C₃), 1-propenyl (*also* 2-methylethenyl) (C₃), isopropenyl (*also* 2-methylethen-2-yl) (C₃), buten-4-yl (C₄), and the like; substituted linear or branched alkenyl, non-limiting examples of which include, 2-chloroethenyl (*also* 2-chlorovinyl) (C₂), 4-hydroxybuten-1-yl (C₄), 7-hydroxy-7-methyloct-4-en-2-yl (C₉), 7-hydroxy-7-methyloct-3,5-dien-2-yl (C₉), and the like.

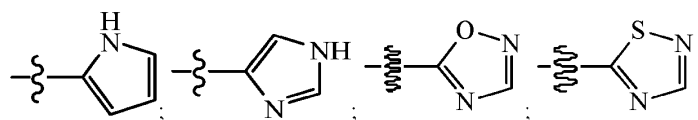
[0070] Substituted and unsubstituted linear or branched alkynyl include, ethynyl (C₂), prop-2-ynyl (*also* propargyl) (C₃), propyn-1-yl (C₃), and 2-methyl-hex-4-yn-1-yl (C₇); substituted linear or branched alkynyl, non-limiting examples of which include, 5-hydroxy-5-methylhex-3-ynyl (C₇), 6-hydroxy-6-methylhept-3-yn-2-yl (C₈), 5-hydroxy-5-ethylhept-3-ynyl (C₉), and the like.

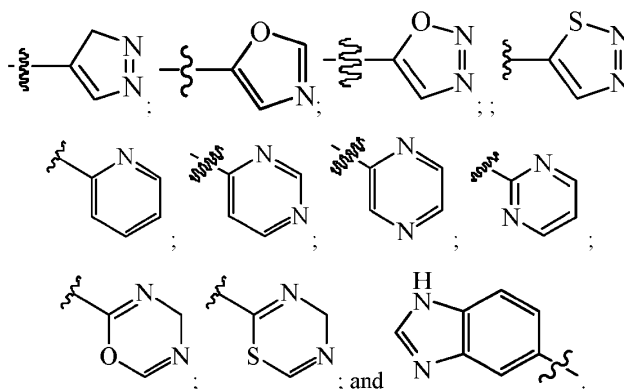
[0071] Substituted and unsubstituted “alkoxy” are used herein denotes a unit having the general formula –OR¹⁰⁰ wherein R¹⁰⁰ is an alkyl, alkenyl, or alkynyl unit as defined herein above, for example, methoxy, methoxymethyl, methoxymethyl.

[0072] Substituted and unsubstituted “haloalkyl” are used herein denotes an alkyl unit having a hydrogen atom substituted by one or more halogen atoms, for example, trifluoromethyl, 1,2-dichloroethyl, and 3,3,3-trifluoropropyl.

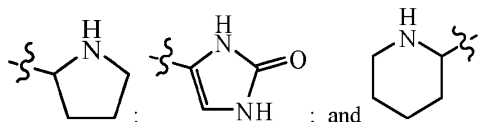
[0073] The term “aryl” as used herein denotes cyclic organic units that comprise at least one benzene ring having a conjugated and aromatic six-membered ring, non-limiting examples of which include phenyl (C₆), naphthyl-1-yl (C₁₀), naphthyl-2-yl (C₁₀). Aryl rings can have one or more hydrogen atoms substituted by another organic or inorganic radical. Non-limiting examples of substituted aryl rings include: 4-fluorophenyl (C₆), 2-hydroxyphenyl (C₆), 3-methylphenyl (C₆), 2-amino-4-fluorophenyl (C₆), 2-(*N,N*-diethylamino)phenyl (C₆), 2-cyanophenyl (C₆), 2,6-di-*tert*-butylphenyl (C₆), 3-methoxyphenyl (C₆), 8-hydroxynaphthyl-2-yl (C₁₀), 4,5-dimethoxynaphthyl-1-yl (C₁₀), and 6-cyanonaphthyl-1-yl (C₁₀).

[0074] The term “heteroaryl” denotes an organic unit comprising a five or six membered conjugated and aromatic ring wherein at least one of the ring atoms is a heteroatom selected from nitrogen, oxygen, or sulfur. The heteroaryl rings can comprise a single ring, for example, a ring having 5 or 6 atoms wherein at least one ring atom is a heteroatom not limited to nitrogen, oxygen, or sulfur, such as a pyridine ring, a furan ring, or thiofuran ring. A “heteroaryl” can also be a fused multicyclic and heteroaromatic ring system having wherein at least one of the rings is an aromatic ring and at least one atom of the aromatic ring is a heteroatom including nitrogen, oxygen, or sulfur. The following are non-limiting examples of heteroaryl rings according to the present disclosure:



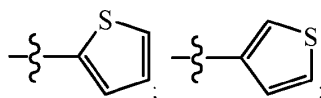


[0075] The term “heterocyclic” denotes a ring system having from 3 to 10 atoms wherein at least one of the ring atoms is a heteroatom not limited to nitrogen, oxygen, or sulfur. The rings can be single rings, fused rings, or bicyclic rings. Non-limiting examples of heterocyclic rings include:



[0076] All of the aforementioned heteroaryl or heterocyclic rings can be optionally substituted with one or more substitutes for hydrogen as described herein further.

Throughout the description of the present disclosure the terms having the spelling “thiophene-2-yl and thiophene-3-yl” are used to describe the heteroaryl units having the respective formulae:



whereas in naming the compounds of the present disclosure, the chemical nomenclature for these moieties are typically spelled “thiophen-2-yl and thiophen-3-yl” respectively. Herein the terms “thiophene-2-yl and thiophene-3-yl” are used when describing these rings as units or moieties which make up the compounds of the present disclosure solely to make it unambiguous to the artisan of ordinary skill which rings are referred to herein.

[0077] The following are non-limiting examples of units which can substitute for hydrogen atoms on a hydrocarbyl (C_1 - C_{20} linear, branched or cyclic alkyl), aryl, heterocyclic or heteroaryl ring:

- i) linear, branched, or cyclic alkyl, alkenyl, and alkynyl; for example, methyl (C_1), ethyl (C_2), n-propyl (C_3), *iso*-propyl (C_3), cyclopropyl (C_3), propylene-2-yl (C_3), propargyl (C_3), n-butyl (C_4), *iso*-butyl (C_4), *sec*-butyl (C_4), *tert*-butyl (C_4), cyclobutyl (C_4), n-pentyl (C_5), cyclopentyl (C_5), n-hexyl (C_6), and cyclohexyl (C_6);

- ii) substituted or unsubstituted aryl; for example, phenyl, 2-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 2-aminophenyl, 3-hydroxyphenyl, 4-trifluoromethylphenyl, and biphenyl-4-yl;
- iii) substituted or unsubstituted heterocyclic; examples of which are provided herein below;
- iv) substituted or unsubstituted heteroaryl; examples of which are provided herein below;
- v) alkoxy; for example, $-\text{OH}$, $-\text{CH}_2\text{OH}$, $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, and $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_3$;
- vi) keto; for example, $-\text{COCH}_3$, $-\text{CH}_2\text{COCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{COCH}_2\text{CH}_3$, $-\text{COCH}_2\text{CH}_2\text{CH}_3$, and $-\text{CH}_2\text{COCH}_2\text{CH}_2\text{CH}_3$;
- vii) alkyl carboxyl; for example, $-\text{CO}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$, and $-\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$;
- viii) alkyl amido; for example, $-\text{CONH}_2$, $-\text{CH}_2\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CH}_2\text{CONHCH}_3$, $-\text{CON}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CON}(\text{CH}_3)_2$;
- ix) alkyl carbamate; for example, $-\text{OC}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{OC}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{NHCH}_3$, $-\text{OC}(\text{O})\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{OC}(\text{O})\text{N}(\text{CH}_3)_2$;
- x) alkylamino; for example, $-\text{NH}_2$, $-\text{CH}_2\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{NH}(\text{CH}_2\text{CH}_3)$;
- xi) halogen: $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, and $-\text{I}$;
- xii) $-\text{CH}_m\text{X}_n$; wherein X is halogen, m is from 0 to 2, $m+n=3$; for example, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CCl}_3$, or $-\text{CBr}_3$;
- xiii) alkyl-cyano; for example; $-\text{CN}$, $-\text{CH}_2\text{CN}$, and $-\text{CH}_2\text{CH}_2\text{CN}$;
- xiv) alkyl-nitro; for example; $-\text{NO}_2$, $-\text{CH}_2\text{NO}_2$, and $-\text{CH}_2\text{CH}_2\text{NO}_2$;
- xv) alkylsulfonylethyl alkyl; for example, $-\text{SO}_2\text{H}$, $-\text{CH}_2\text{SO}_2\text{H}$, $-\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{C}_6\text{H}_5$, and $-\text{CH}_2\text{SO}_2\text{C}_6\text{H}_5$; xvi) alkylene sulfonic acid; for example, $-\text{SO}_3\text{H}$, $-\text{CH}_2\text{SO}_3\text{H}$;
- xvii) hydroxyl groups or thiol groups, or
- xviii) amino groups, monosubstituted amino, or disubstituted amino.

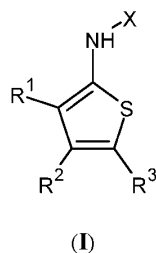
[0078] For the purposes of the present disclosure the terms “compound,” “analog,” and “composition of matter” stand equally well for the HIF-1 α prolyl hydroxylase enzyme inhibitors described herein, including all enantiomeric forms, diastereomeric forms, salts, and the like, and the terms “compound,” “analog,” and “composition of matter” are used interchangeably throughout the present specification.

[0079] The compounds disclosed herein include all salt forms, for example, salts of both basic groups, *inter alia*, amines, as well as salts of acidic groups, *inter alia*, carboxylic acids. The following are non-limiting examples of anions that can form pharmaceutically acceptable salts with basic groups: chloride, bromide, iodide, sulfate, bisulfate, carbonate, bicarbonate, phosphate, formate,

acetate, propionate, butyrate, pyruvate, lactate, oxalate, malonate, maleate, succinate, tartrate, fumarate, citrate, and the like. The following are non-limiting examples of cations that can form pharmaceutically acceptable salts of the anionic form of acidic substituent groups on the compounds described herein: sodium, lithium, potassium, calcium, magnesium, zinc, bismuth, and the like.

[0080] FABP3/4/5/7 Inhibitor Compounds

[0081] Disclosed herein are compounds that inhibit one or more of the FABP3, FABP4, FABP5, and FABP7 (i.e., an “FABP3/4/5/7 inhibitor”). These FABP3/4/5/7 inhibitor compounds of the present disclosure are based on a substituted thiophene ring having the general structural formula I:

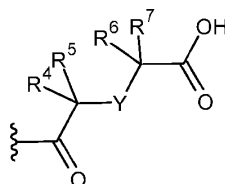


wherein,

R¹ is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R² and R³ are each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl, or R² and R³ together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C₁-C₄-alkyl, methoxy, or fluoro;

X is a moiety of formula:



wherein,

Y is a heteroatom selected from -S-, and -O-, or is -CR⁸R⁹-, wherein R⁸ and R⁹ are each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, phenyl, and benzyl, or R⁸ and R⁹ together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

R⁴, R⁵, R⁶ and R⁷ is each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, phenyl, and benzyl, and/or

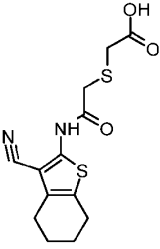
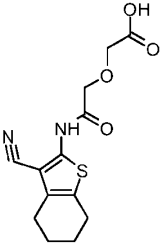
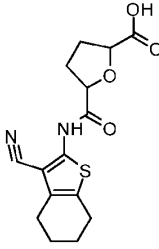
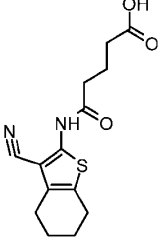
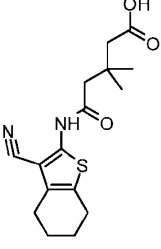
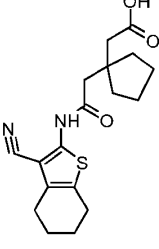
R⁴ and R⁵ together or R⁶ and R⁷ together form a cyclopropyl ring or a cyclobutyl ring, or

R⁵ and R⁶ together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring.

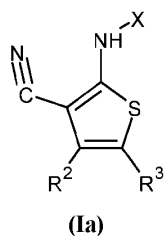
[0082] In at least one embodiment, the compound of structural formula **I** includes any pharmaceutically acceptable salt thereof.

[0083] In at least one embodiment, the compound of structural formula **I** of the present disclosure excludes the compounds shown in Table 1 below.

[0084] **TABLE 1**

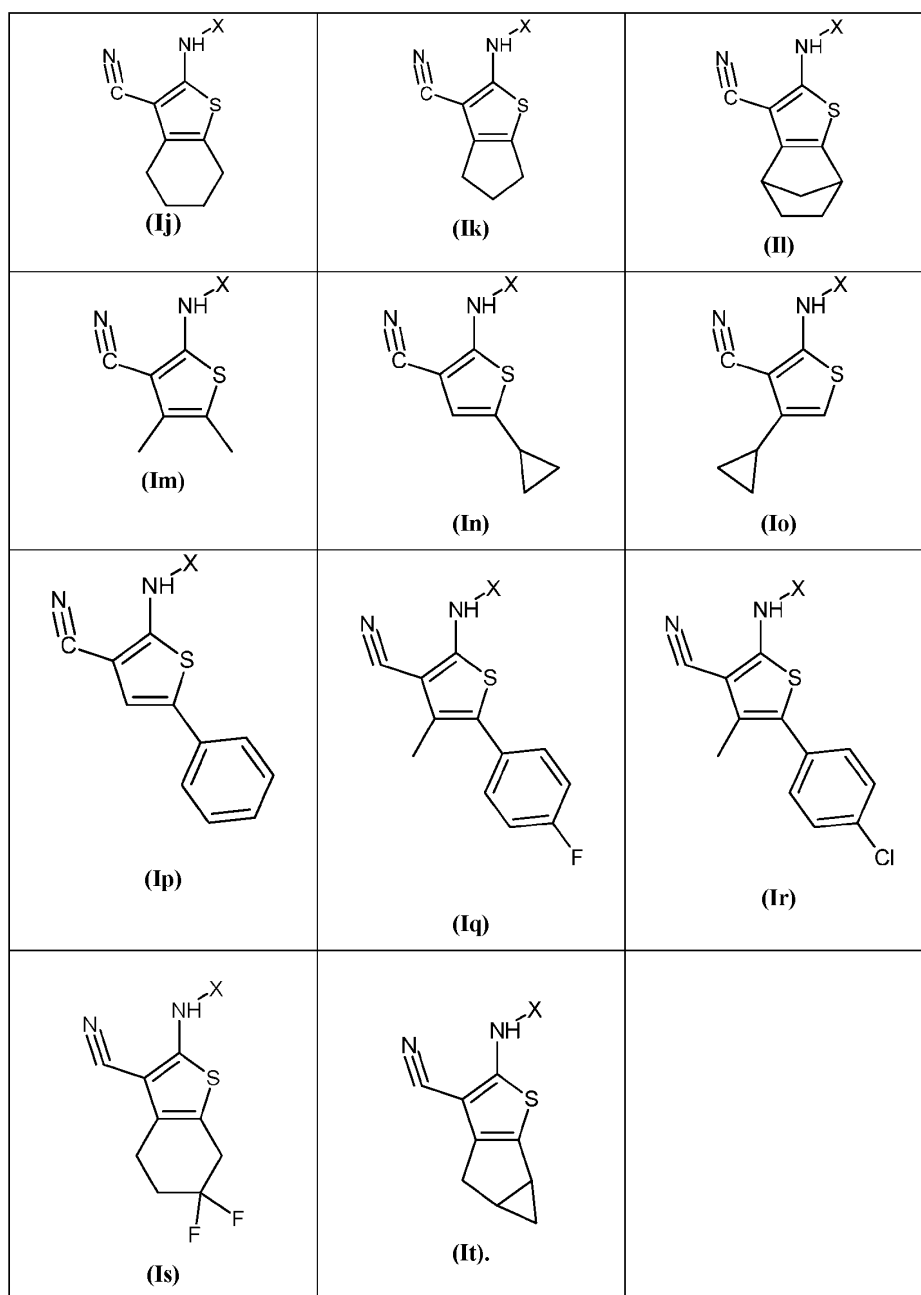
		
		

[0085] In at least one embodiment of the FABP3/4/5/7 inhibitor compounds having structural formula **I**, the chemical group at position R¹ is a cyano group. For example, the compound of formula **I** can have formula **Ia**:

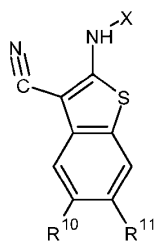


[0086] Exemplary compounds of formula **Ia**, include but are not limited to the compounds having structural formulas **Ij**, **Ik**, **Il**, **Im**, **In**, **Io**, **Ip**, **Iq**, **Ir**, **Is**, and **It** as shown in Table 2 below.

[0087] **TABLE 2**



[0088] In at least one embodiment, the chemical substituents at positions R^2 and R^3 together form a 5- to 8-membered aryl or heteroaryl ring. For example, the compound of formula **I** can have formula **Ib**



(Ib)

wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl.

[0089] Exemplary compounds of formula **Ib**, include but are not limited to the compounds having structural formulas **Iu**, **Iv**, and **Iw** shown in Table 3 below.

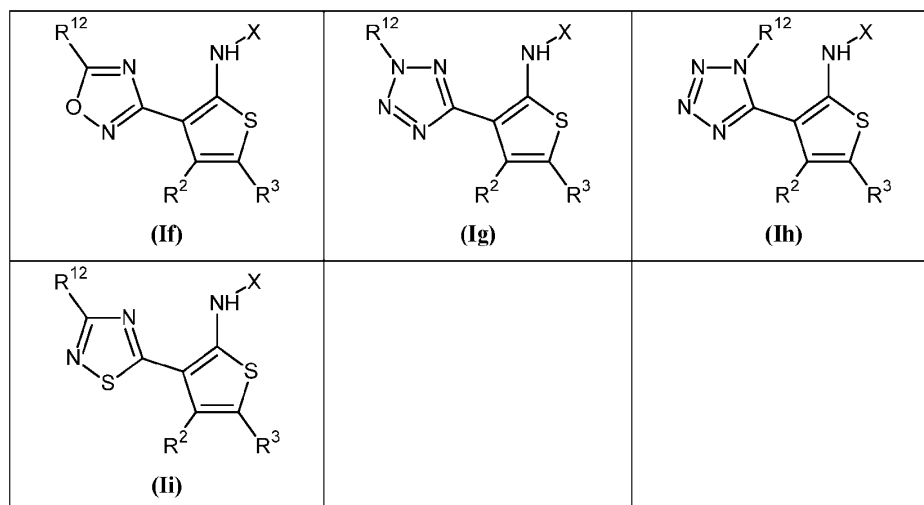
[0090] TABLE 3

(Iu)	(Iv)	(Iw)
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[0091] In at least one embodiment of the FABP3/4/5/7 inhibitor compounds having structural formula **I**, the chemical group at R^1 is a 5-membered heteroaryl ring (e.g., 3-substituted 1,2,4-oxadiazol). For example, the compound of formula **I** can be a compound structural formula **Ic**, **Id**, **Ie**, **If**, **Ig**, **Ih**, or **Ii** as shown in Table 4 below.

[0092] TABLE 4

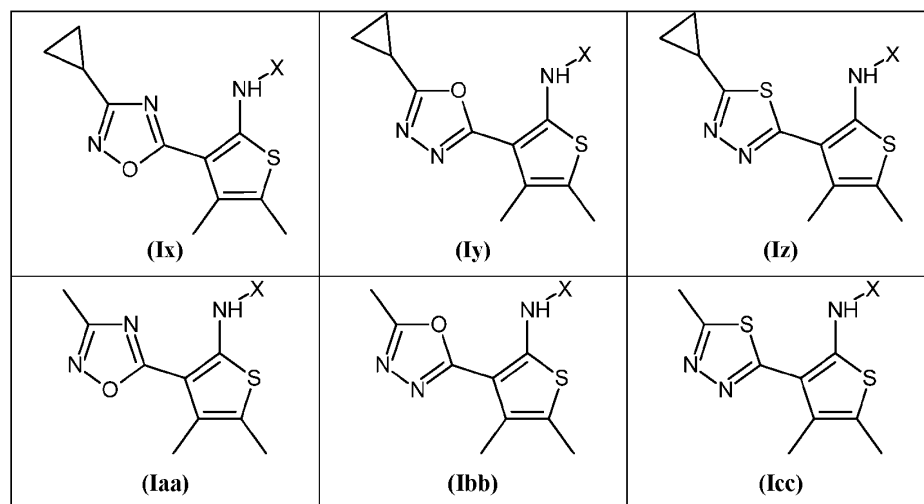
(Ic)	(Id)	(Ie)
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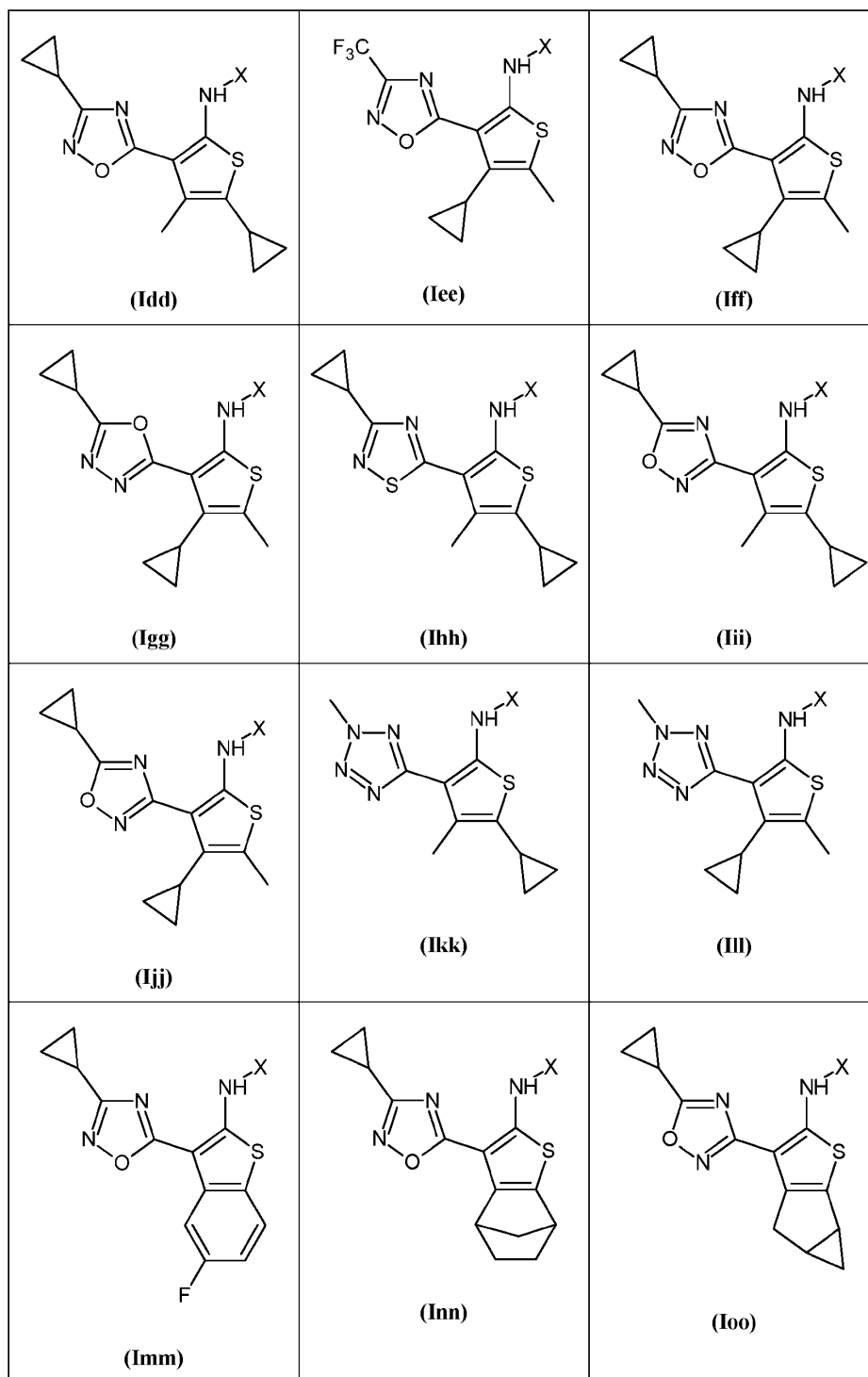


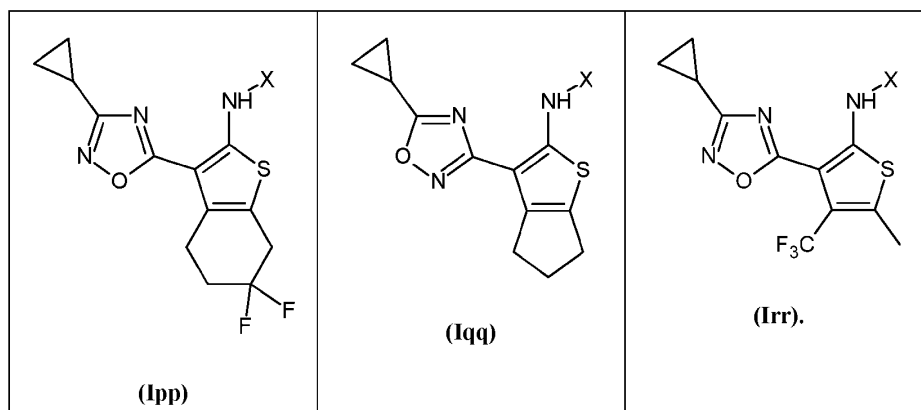
wherein R^{12} is selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl.

[0093] Exemplary compounds of formulas **Ic**, **Id**, **Ie**, **If**, **Ig**, **Ih**, or **Ii**, include but are not limited to the compounds having structural formulas **Ix**, **Iy**, **Iz**, **Iaa**, **Ibb**, **Icc**, **Idd**, **Iee**, **Iff**, **Igg**, **Ihh**, **Iii**, **Ijj**, **Ikk**, **Ill**, **Imm**, **Inn**, **Ioo**, **Ipp**, **Iqq**, and **Irr** shown in Table 5 below.

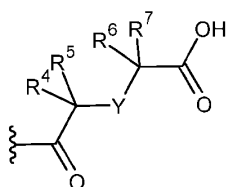
[0094] TABLE 5







[0095] The FABP3/4/5/7 inhibitor compounds having structural formula **I** of the present disclosure comprise a moiety X attached to the amine group of the thiophene. The X moiety is a chemical group of formula:



wherein,

Y is a heteroatom selected from $-S-$, and $-O-$, or is $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

R^4 , R^5 , R^6 and R^7 is each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, and/or

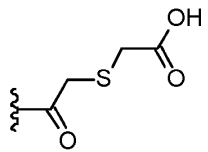
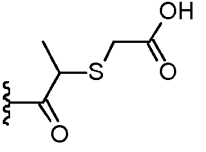
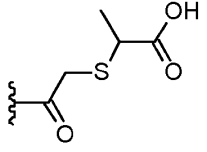
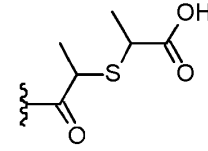
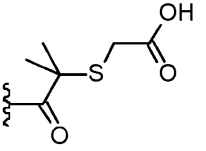
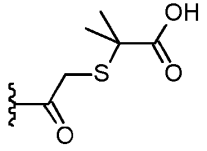
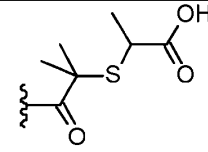
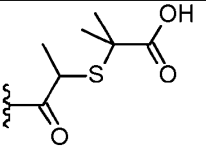
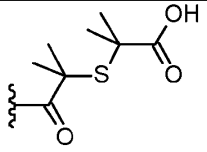
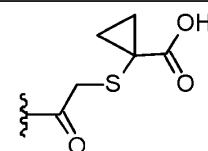
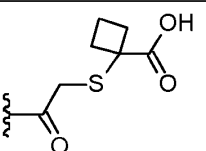
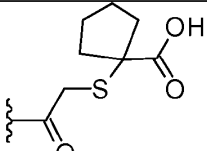
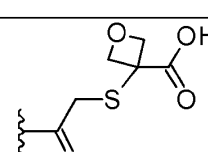
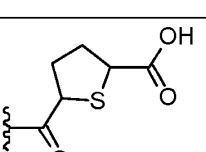
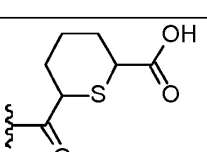
R^4 and R^5 together or R^6 and R^7 together form a cyclopropyl ring or a cyclobutyl ring, or

R^5 and R^6 together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring.

[0096] In at least one embodiment of the compounds of structural formula **I**, the chemical group Y of the X moiety is selected from $-S-$ or $-O-$ and R^4 , R^5 , R^6 and R^7 are each independently hydrogen or C_1 - C_4 linear or branched alkyl.

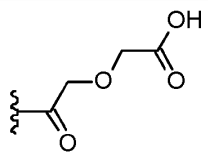
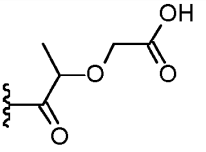
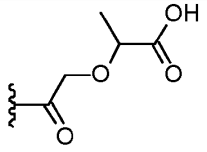
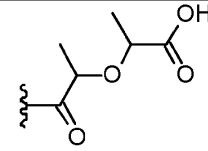
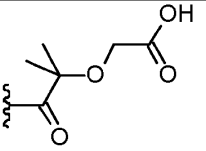
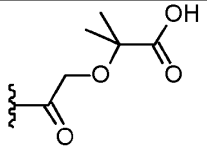
[0097] Exemplary X moieties where Y is a sulfur atom ($-S-$) can include any of the moieties shown in Table 6 below.

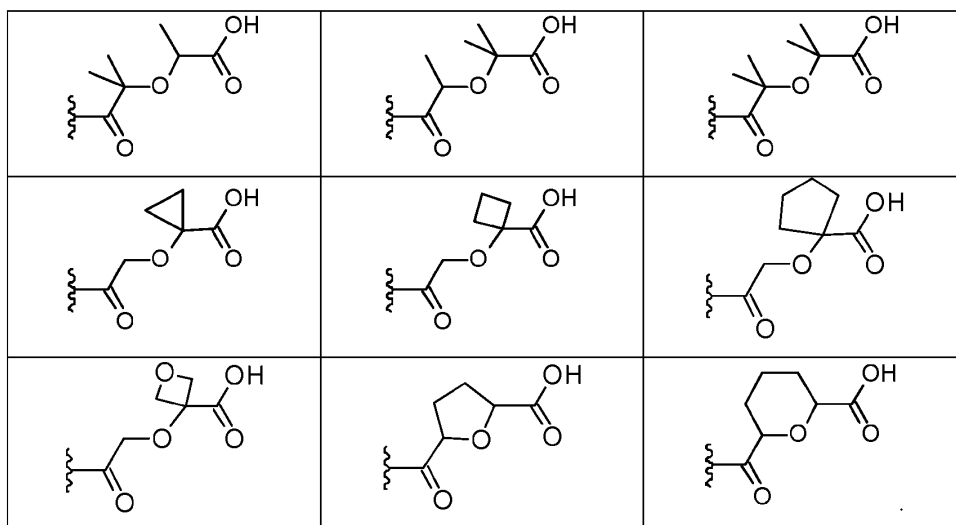
[0098] TABLE 6

[0099] Exemplary X moieties where Y is an oxygen atom (-O-) can include any of the moieties shown in Table 7 below.

[0100] TABLE 7

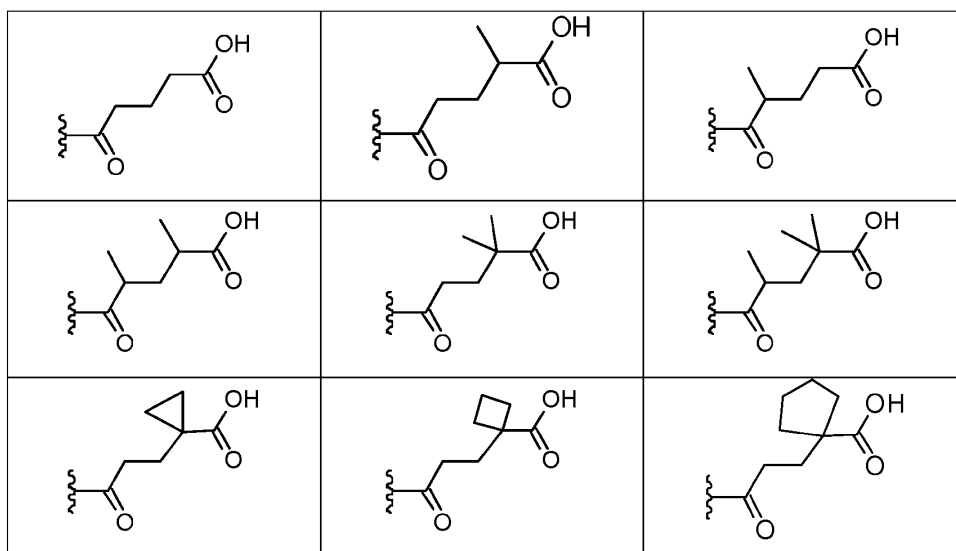
		
		

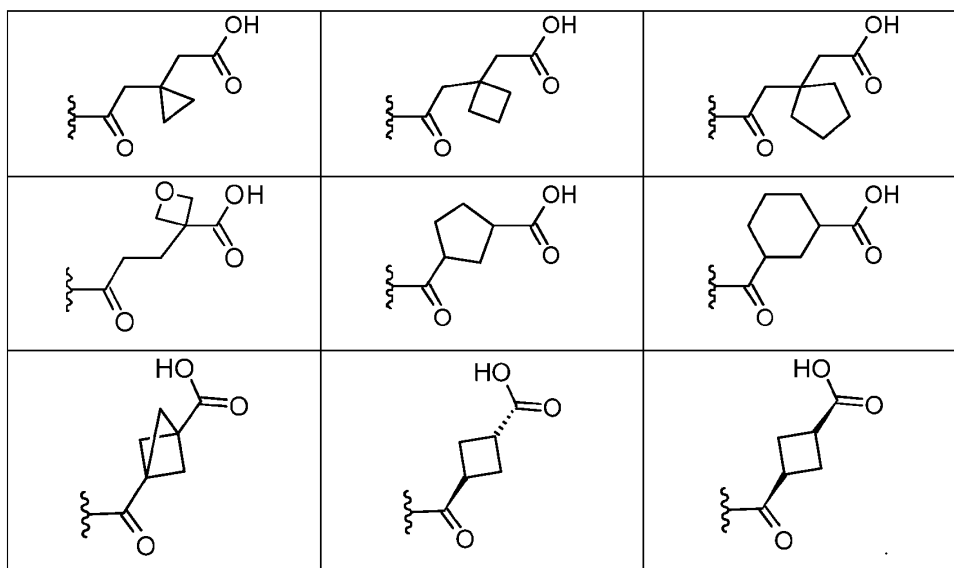


[0101] In at least one embodiment of the compounds of structural formula **I**, the chemical group Y of the X moiety is $-\text{CR}^8\text{R}^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring, and the chemical groups at positions R^1 , R^5 , R^6 and R^7 are each independently hydrogen or C_1 - C_4 linear or branched alkyl, and.

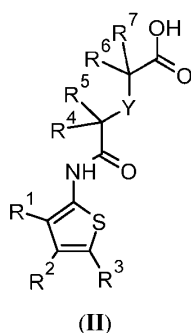
[0102] Exemplary X moieties where Y is $-\text{CR}^8\text{R}^9-$ can include any of the moieties shown in Table 8 below.

[0103] TABLE 8





[0104] The various inhibitor compounds of structural formula **I** provided in the present disclosure include a range of compounds with various substituted thiophene ring moieties combined with various X moieties. The various FABP3/4/5/7 inhibitor compounds can be represented as compounds of structural formula **II** and any pharmaceutically acceptable salt thereof:



wherein,

R^1 is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro;

Y is a heteroatom selected from –S–, and –O–, or is –CR⁸R⁹–, wherein R⁸ and R⁹ are each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, phenyl, and benzyl, or R⁸ and R⁹ together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

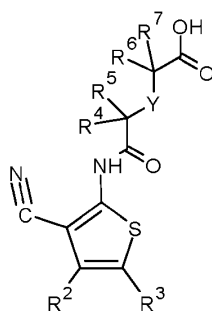
R⁴, R⁵, R⁶ and R⁷ is each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, phenyl, and benzyl, and/or

R⁴ and R⁵ together or R⁶ and R⁷ together form a cyclopropyl ring or a cyclobutyl ring, or

R⁵ and R⁶ together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring.

[0105] In at least one embodiment, the compound of structural formula **II** of the present disclosure excludes the compounds of Table 1 (see above).

[0106] Like the FABP3/4/5/7 inhibitor compounds of structural formula **I**, the compounds of structural formula **II** include a range of compounds represented by sub-structures. For example, in at least one embodiment of the FABP3/4/5/7 inhibitor compounds having structural formula **II**, the chemical group at position R¹ is a cyano group, and the compound has structural formula (**IIa**)

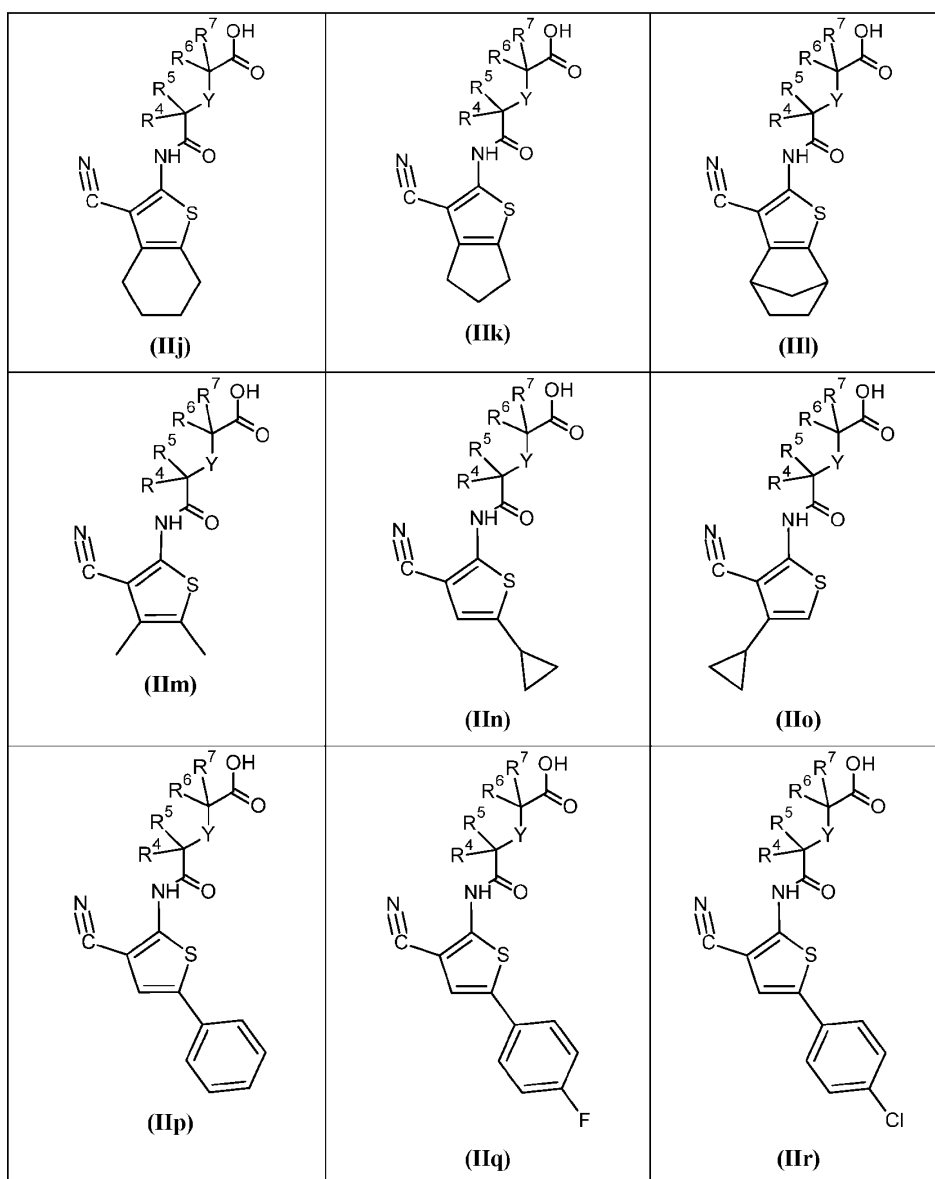


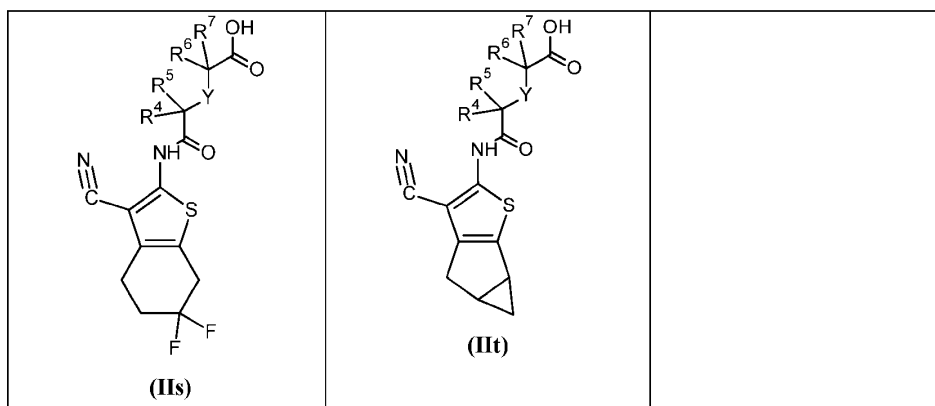
(**IIa**)

wherein the chemical groups R², R³, R⁴, R⁵, R⁶ and R⁷ are as defined for the compound of structural formula **II**.

[0107] In at least one embodiment, the compounds of having the substructure of structural formula **IIa** can have a structural formula **IIj**, **IIk**, **IIl**, **IIm**, **IIn**, **IIo**, **IIp**, **IIq**, **IIr**, **IIs**, and **IIt** as shown in Table 9 below.

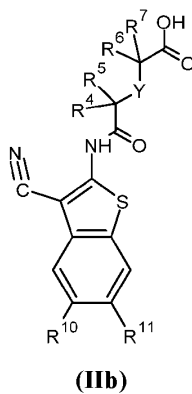
[0108] **TABLE 9**





wherein the chemical groups R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II**.

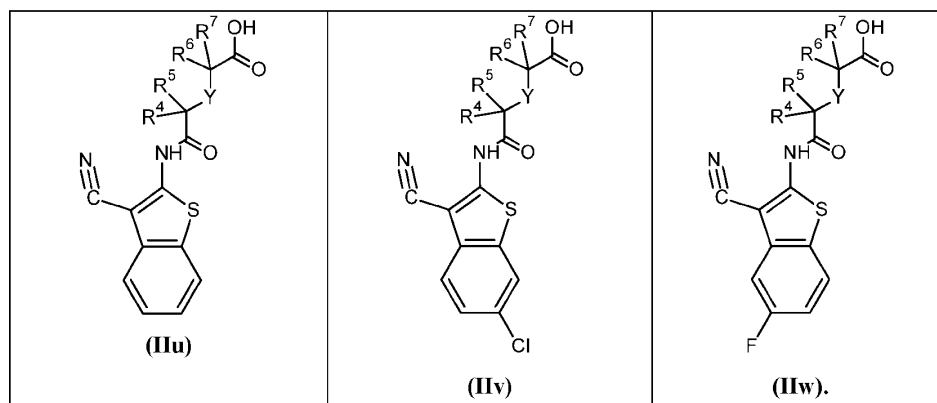
[0109] In at least one embodiment of the FABP3/4/5/7 inhibitor compounds having structural formula **II**, the chemical group at position R^1 is a cyano group, R^2 and R^3 together form a 6-membered aryl ring and the compound has structural formula **(IIb)**



wherein the chemical groups R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II**, and wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl.

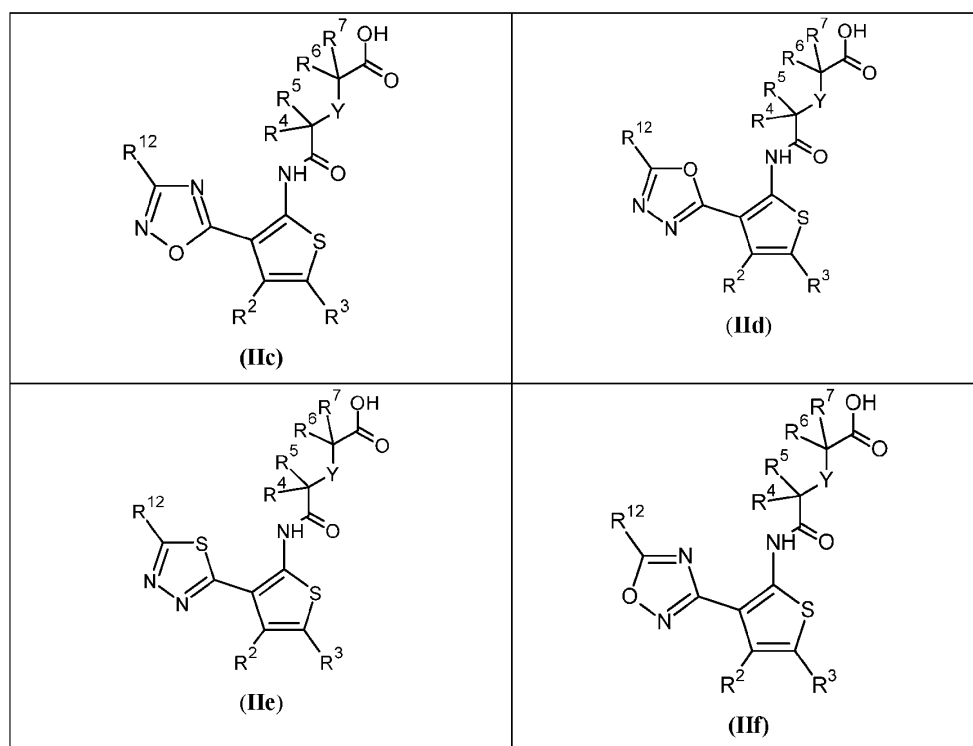
[0110] In at least one embodiment, the compounds of having the substructure of structural formula **IIb** can have a structural formula **IIu**, **IIv**, and **IIw** as shown in Table 10 below.

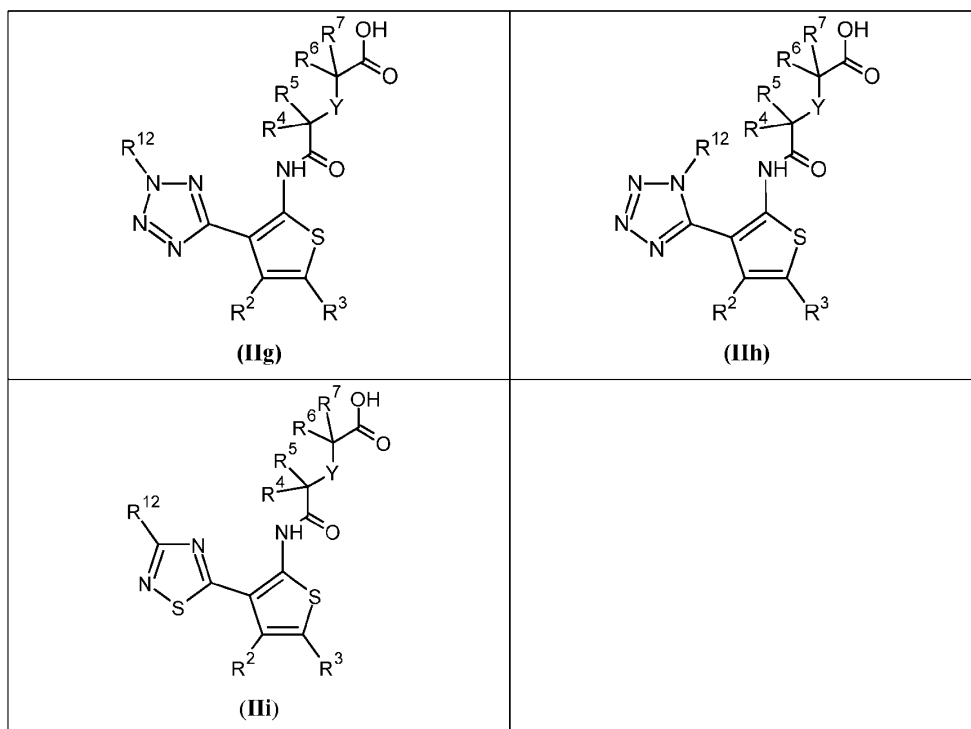
[0111] **TABLE 10**



[0112] In at least one embodiment of the compounds of structural formula **II**, the chemical group at position R^1 is a 5-membered heteroaryl ring (e.g., 3-substituted 1,2,4-oxadiazol), and the chemical groups at R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl. For example, in at least one embodiment the compound can have structural formula **IIc**, **IId**, **IIf**, **IIg**, **IIh**, and **IIi** shown in Table 11 below.

[0113] TABLE 11

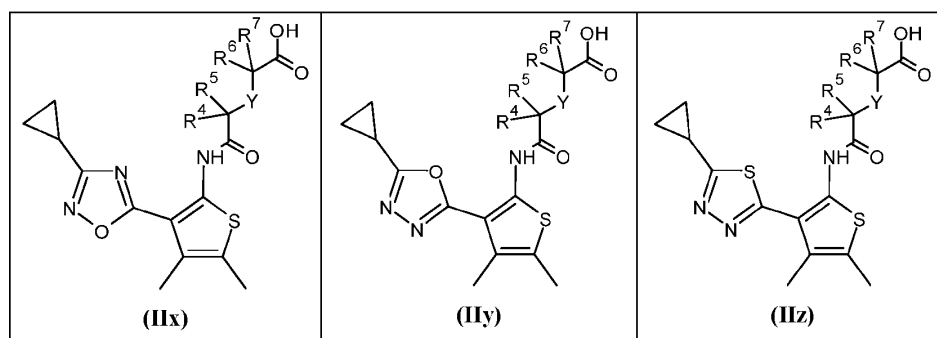


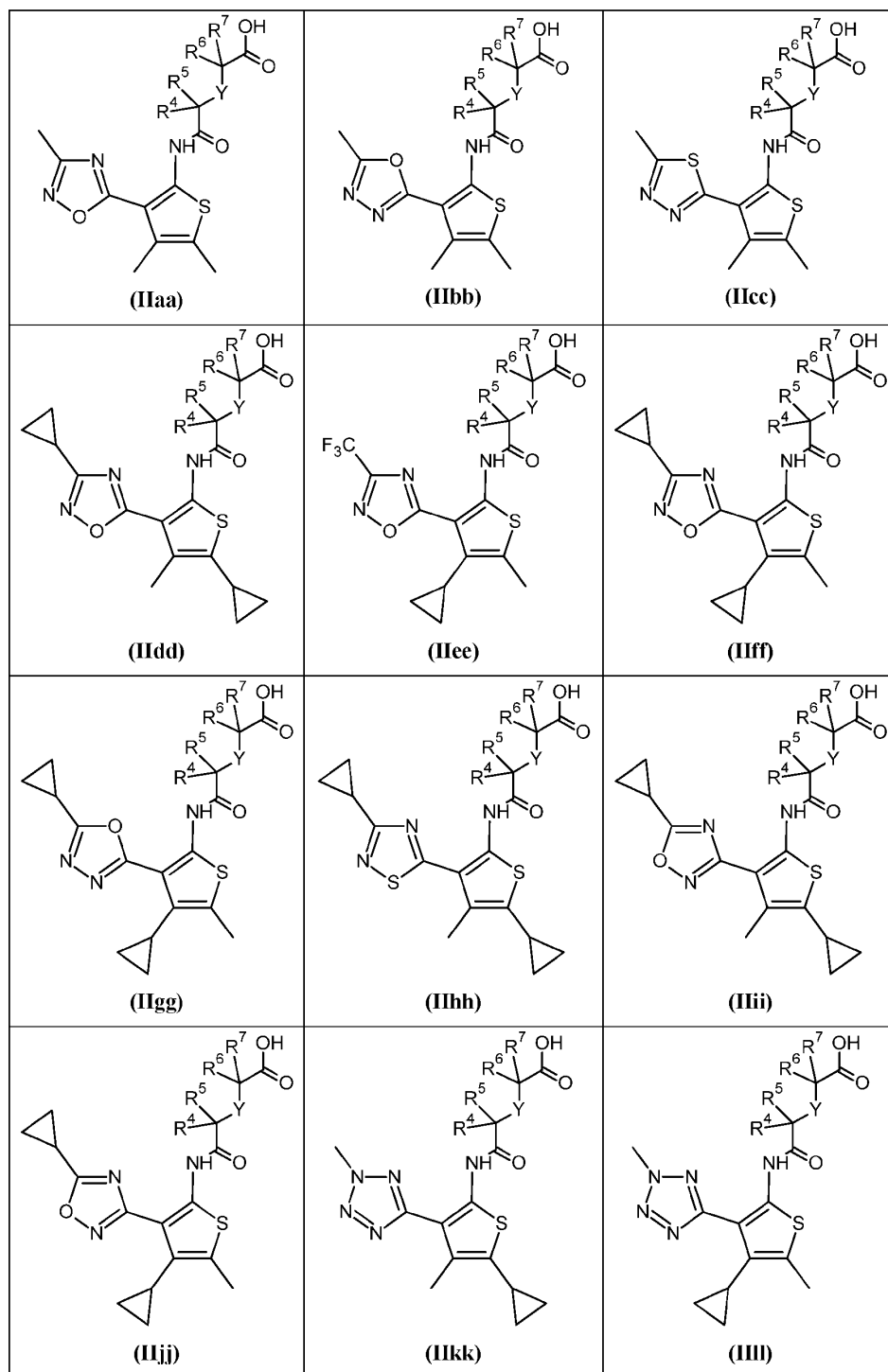


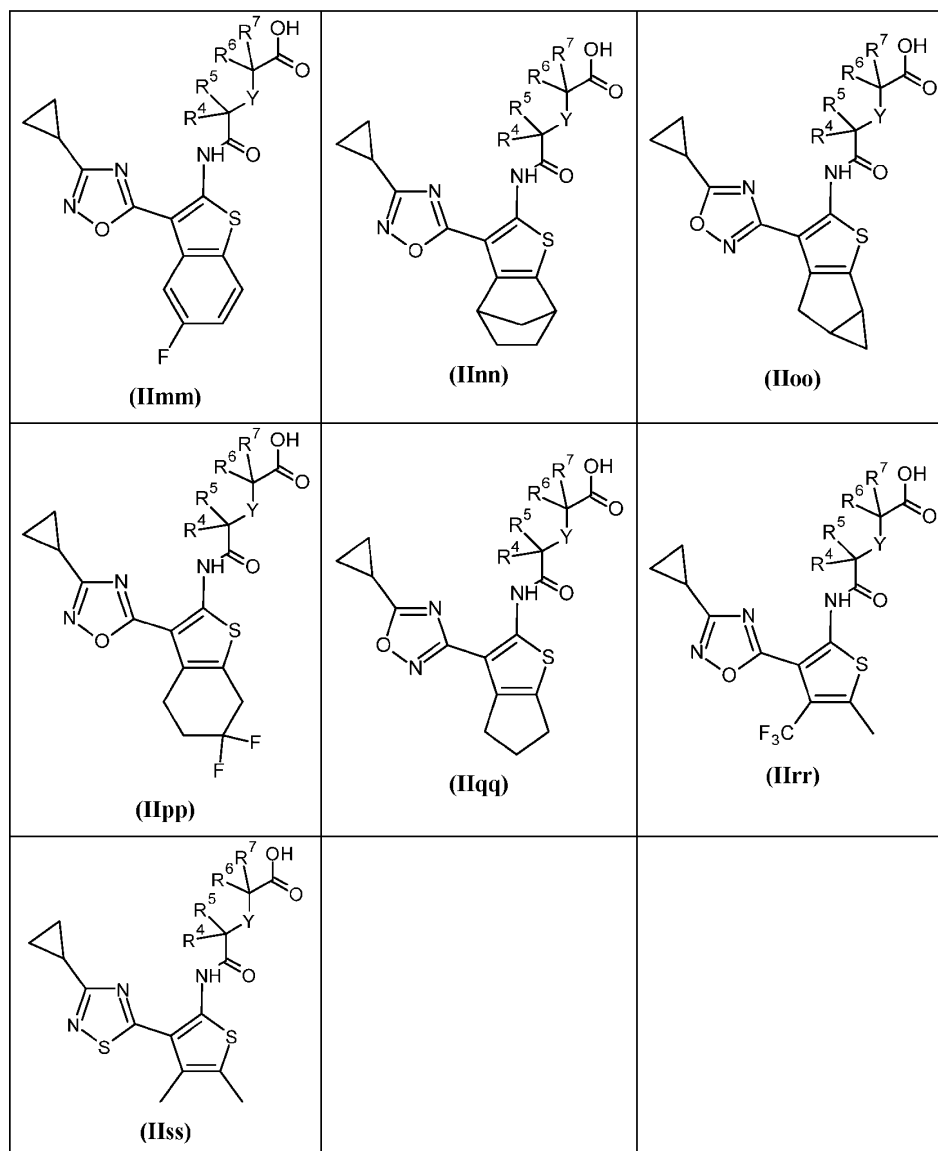
wherein the chemical groups R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II** and the chemical group R^{12} in **IIc**, **IId**, **IIf**, **IIg**, and **IIh** can be a hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, or phenyl.

[0114] In at least one embodiment, the compounds having the substructures of structural formulas **IIc**, **IId**, **IIf**, **IIg**, and **IIh** can have a structural formula **IIx**, **IIy**, **IIz**, **IIaa**, **IIbb**, **IIcc**, **IIdd**, **IIee**, **IIff**, **IIgg**, **IIhh**, **IIii**, **IIjj**, **IIkk**, **IIll**, **IImm**, **IInn**, **IIoo**, **IIpp**, **IIqq**, **IIrr**, and **IIss** as shown in Table 12 below.

[0115] **TABLE 12**



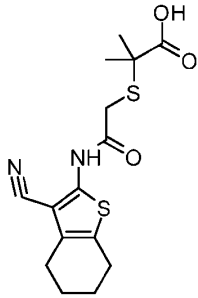
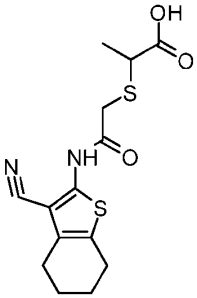
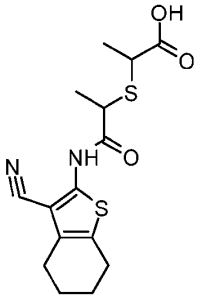
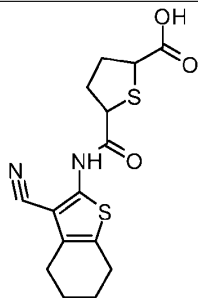
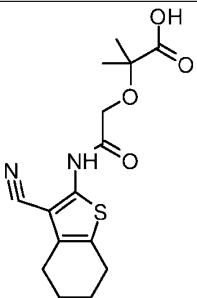
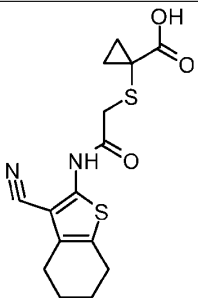
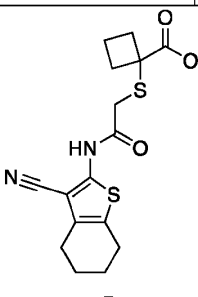
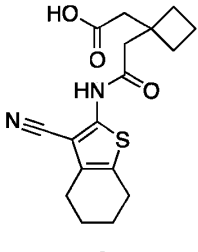
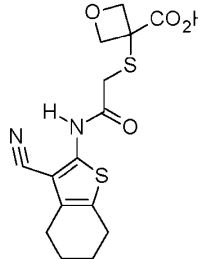
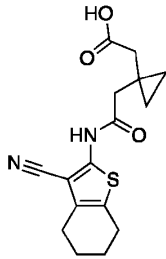


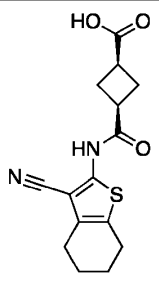
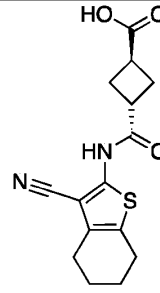
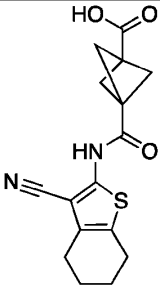
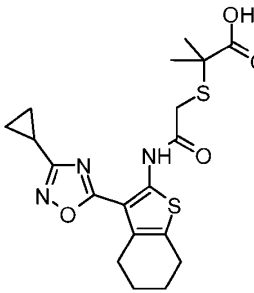
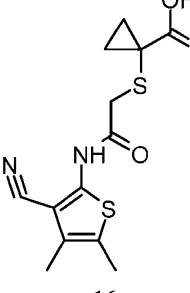
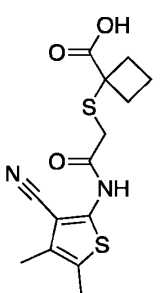
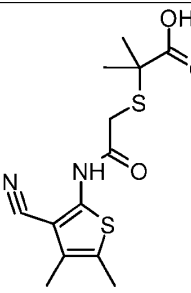
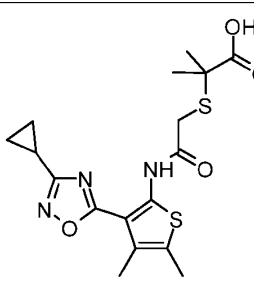
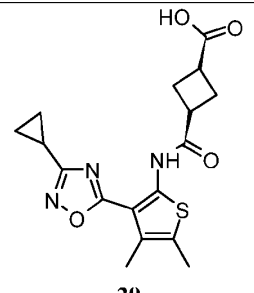
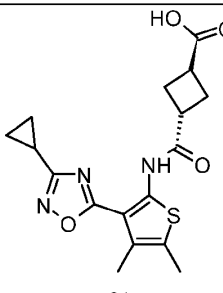
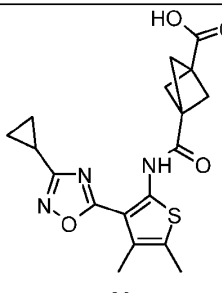
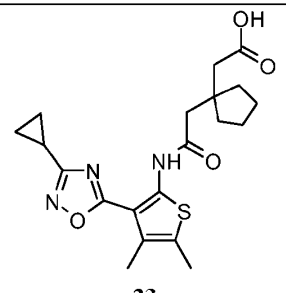


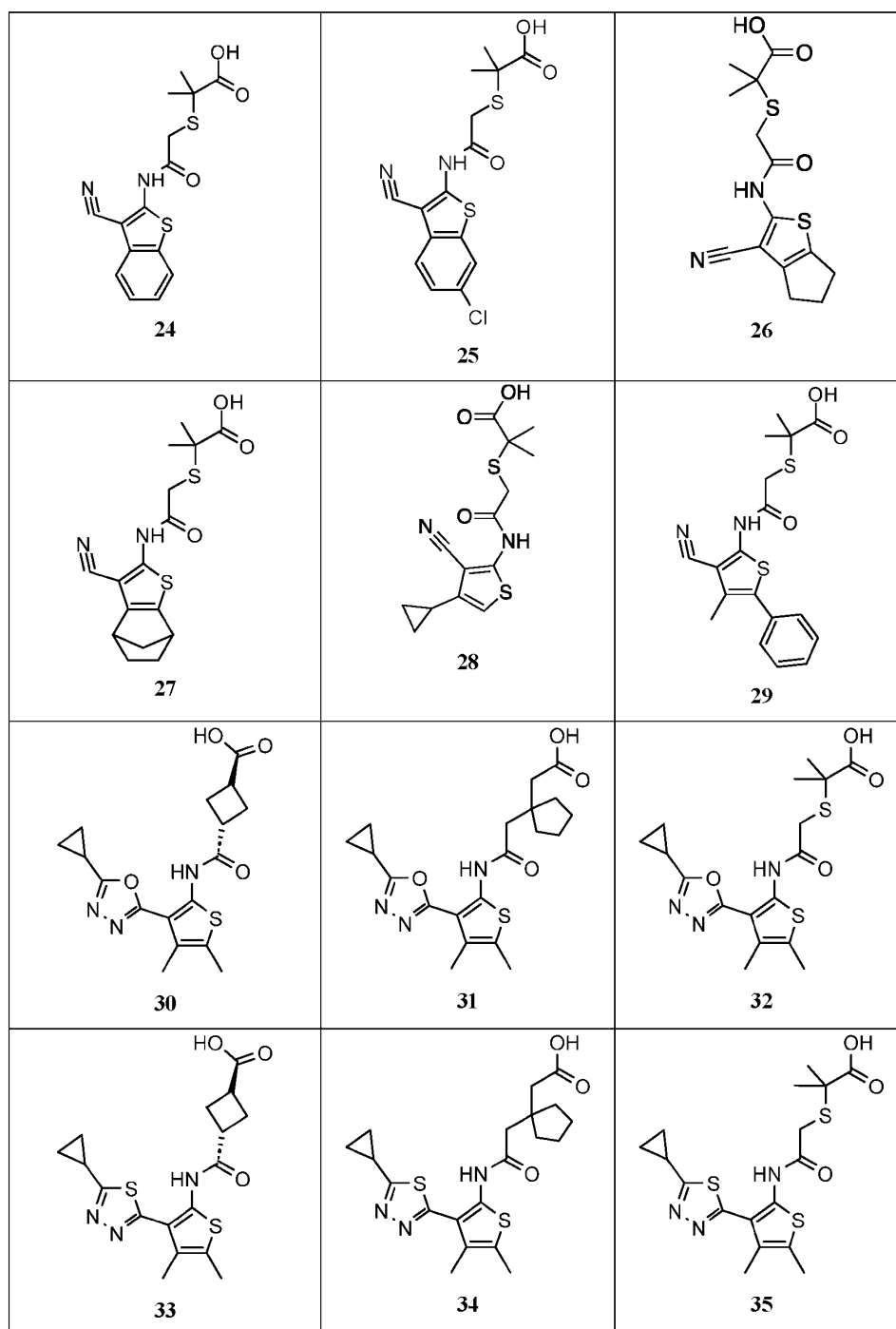
[0116] In each of the various substructure embodiments of the compound of structural formula **II**, including the compounds of structural formulas **IIa**, **IIb**, **IIc**, **IId**, **IIe**, **IIf**, **IIg**, **IIh**, **IIi**, **IIj**, **IIk**, **IIl**, **IIm**, **IIn**, **IIo**, **IIp**, **IIq**, **IIr**, **IIs**, **IIu**, **IIv**, **IIw**, **IIx**, **IIy**, **IIz**, **IIaa**, **IIbb**, **IIcc**, **IIdd**, **IIee**, **IIff**, **IIgg**, **IIhh**, **IIii**, **IIjj**, **IIkk**, **IIll**, **IImm**, **IInn**, **IIoo**, **IIpp**, **IIqq**, **IIrr**, and **IIss**, it is contemplated that the atom or chemical group represented by Y can be –S– or –O–, and the chemical groups R⁴, R⁵, R⁶ and R⁷ can each independently be hydrogen or C₁–C₄ linear or branched alkyl. Accordingly, exemplary FABP3/4/5/7 inhibitor compounds of structural formulas **I** and **II** include, but are not limited to,

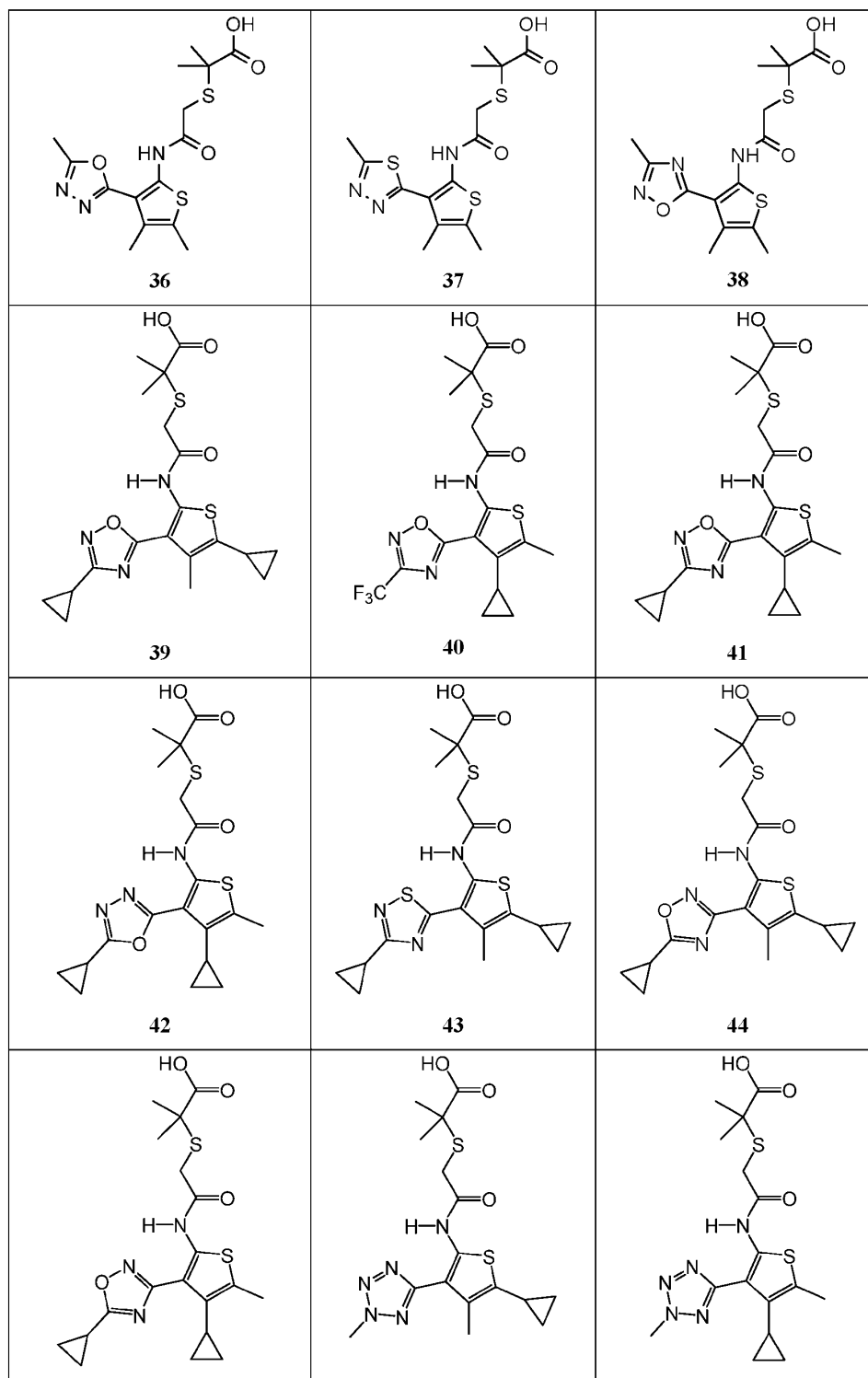
compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, and 65, which are shown in Table 13 below.

[0117] TABLE 13

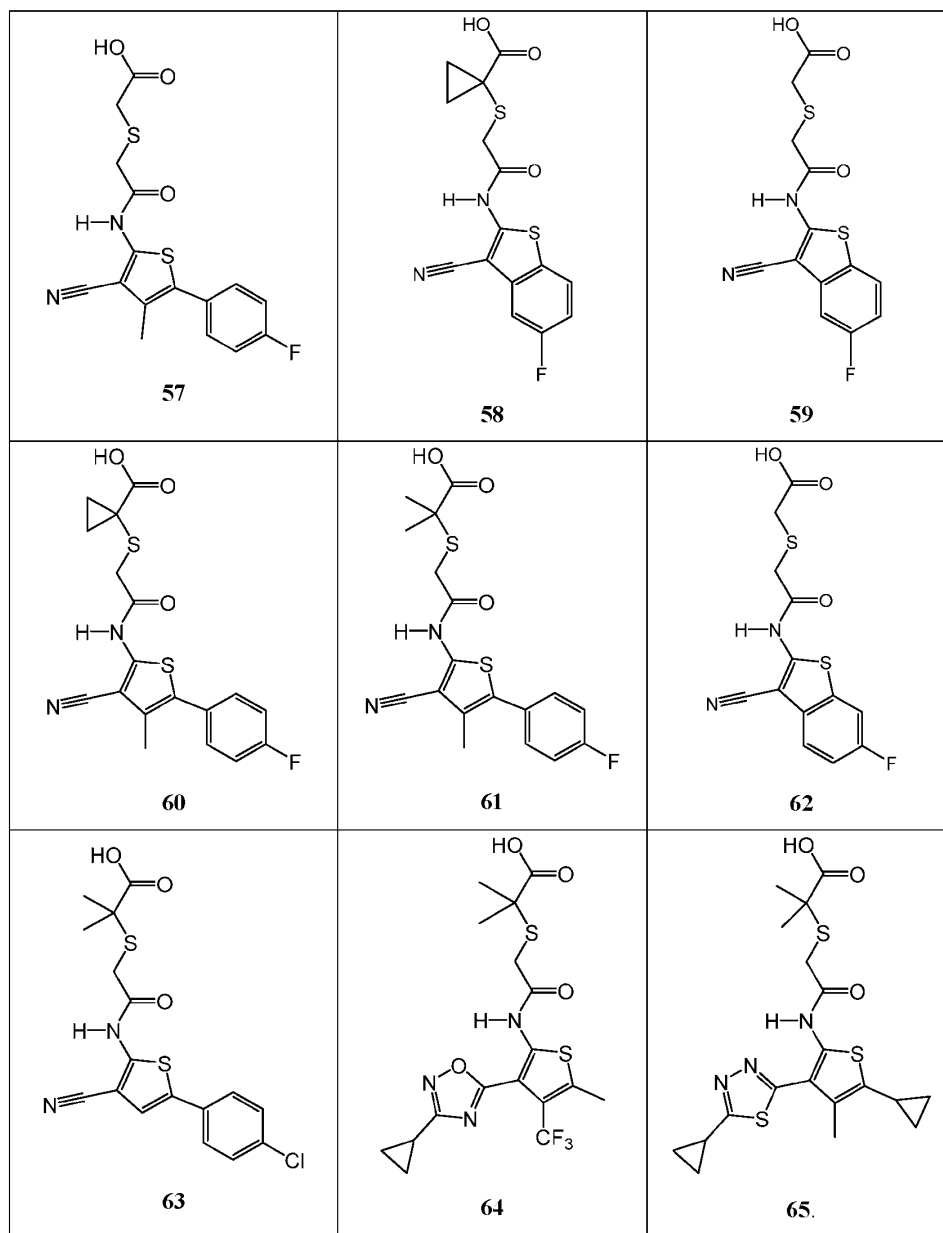
 1	 2	 3
 4	 5	 6
 7	 8	
 9	 10	

9		10
 12	 13	 14
 15	 16	 17
 18	 19	 20
 21	 22	 23





45	46	47
48	49	50
51	52	53
54	55	56



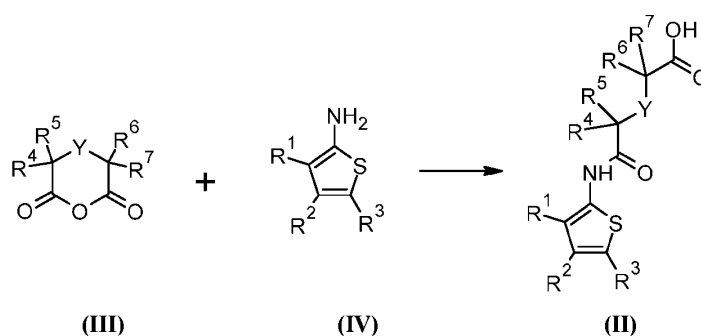
[0118] As described elsewhere herein, one of ordinary skill will understand that the FABP3/4/5/7 compounds provided herein can exist in various well-known closely-related and/or equivalent forms not explicitly described by the chemical structures and formulae. It is intended that the FABP3/4/5/7 inhibitor compounds of structural formulas **I** and **II** of the present disclosure (including the compounds of Tables 2-5, and 9-13, and as described the Examples) includes these closely-related

forms of the compounds defined by the chemical structures and formulae including, but not limited to, pharmaceutically acceptable salts of the compounds, mixture of stereoisomers of the compounds, single stereoisomers of the compounds, tautomeric forms of the compounds, and/or prodrug forms of the compounds.

[0119] Preparation of FABP3/4/5/7 Inhibitor Compounds

[0120] The present disclosure also provides processes for preparing the FABP3/4/5/7 inhibitor compounds disclosed herein, including the compounds of structural formula **I** and **II** (as defined elsewhere herein), which is outlined generally in Scheme A, and described in greater detail below.

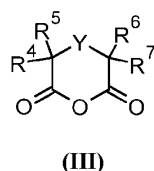
Scheme A



[0121] A mixture of the substituted anhydride compound of structural formula **III**, and the substituted 2-amino-thiophene compound of structural formula **IV**, (1:0.75 molar ratio) is purged with argon then dissolved in a dry solvent. The reaction mixture is then stirred at a temperature from room temperature to the reflux temperature of the chosen solvent. The progress of the reaction can be followed by one or more analytical methods, for example, thin layer chromatography (TLC), gas chromatography, and the like. After the starting material 2-amino-thiophene **IV**, or substituted anhydride, **III**, is deemed to be consumed, the solvent is removed *in vacuo* to afford the desired FABP3/4/5/7 inhibitor of structural formula **II**.

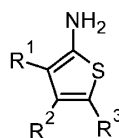
[0122] In at least one embodiment, the process for preparing the disclosed FABP3/4/5/7 inhibitor compounds of structural formula **II**, comprising:

- (a) combining in a solvent a substituted anhydride compound of formula **III**:



wherein Y is a heteroatom selected from -S-, and -O-, or is -CR⁸R⁹-, wherein R⁸ and R⁹ are each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, phenyl, and

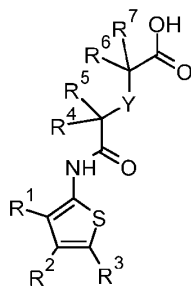
benzyl, or R⁸ and R⁹ together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;
 R⁴, R⁵, R⁶ and R⁷ is each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, phenyl, and benzyl, and/or R⁴ and R⁵ together or R⁶ and R⁷ together form a cyclopropyl ring or a cyclobutyl ring, or R⁵ and R⁶ together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring;
 with a substituted 2-amino-thiophene compound of formula **IV**:



(IV)

wherein, R¹ is selected from hydrogen, cyano, and 5-membered heteroaryl ring; and R² and R³ are each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl, or R² and R³ together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C₁-C₄-alkyl, methoxy, or fluoro;
 and

(b) removing the solvent to obtain a compound having the structural formula **II**:



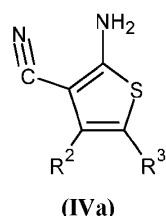
(II)

wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are as defined above.

[0123] In at least one embodiment of the substituted anhydride of formula **III**, the chemical group Y is a sulfur atom. In another embodiment of the anhydride of formula **III**, the chemical group Y is an oxygen atom. In a further embodiment of the anhydride of formula **III**, the chemical group Y is –CR⁵R⁶– wherein R⁵ and R⁶ are each independently chosen from hydrogen, C₁-C₄ linear or branched alkyl. In a still further embodiment when Y is R⁵ and R⁶ are each independently chosen from C₁-C₄ linear alkyl, R⁵ and R⁶ can be taken together to form a spirocyclic ring having from 4 to 7 atoms. In a still further embodiment when Y is sulfur or oxygen R¹ and R⁴ can be taken together to form a

heterocyclic ring having from 4 to 6 carbon atoms. A range of specific anhydride compounds of formula **III** that can be used in the preparation of compound of formula **II** are further described in the Examples.

[0124] In at least one embodiment of the substituted 2-amino-thiophene compounds of formula **IV**, the compound is a compound of structural formula **IVa**:



wherein, the chemical groups at R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl, optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, chloro or fluoro. Such exemplary compounds of structural formula **IVa** include but are not limited to the compounds **4a**, **4b**, **4c**, **4d**, **4e**, and **4f** shown in Table 14 below.

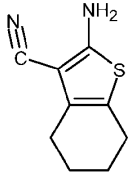
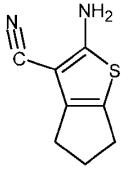
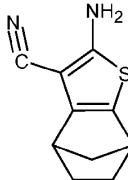
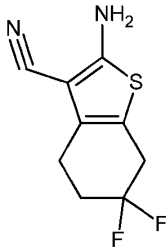
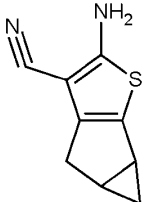
[0125] **TABLE 14**

(4a)	(4b)	(4c)
(4d)	(4e)	(4f)

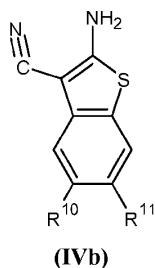
[0126] In at least one embodiment of the substituted 2-amino-thiophene compounds of formula **IVa**, the chemical substituents at positions R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring,. Such exemplary compounds of structural

formula **IVa** include but are not limited to the compounds **4g**, **4h**, **4i**, **4j**, and **4k**, shown in Table 15 below.

[0127] **TABLE 15**

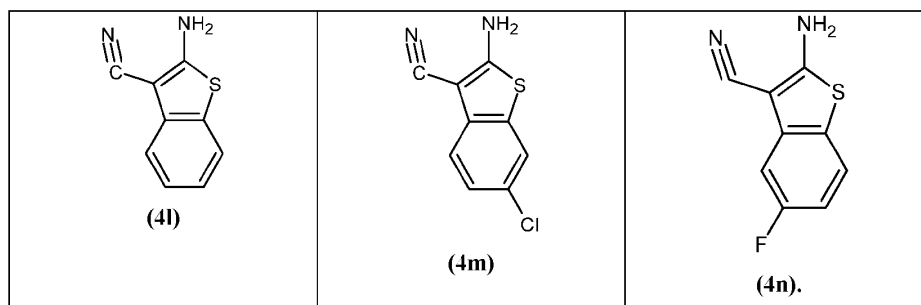
 (4g)	 (4h)	 (4i)
 (4j)	 (4k).	

[0128] In at least one embodiment of the substituted 2-amino-thiophene compounds of formula **IVa**, the chemical substituents at positions R^2 and R^3 together form a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro, as depicted by the compound of structural formula **IVb**:



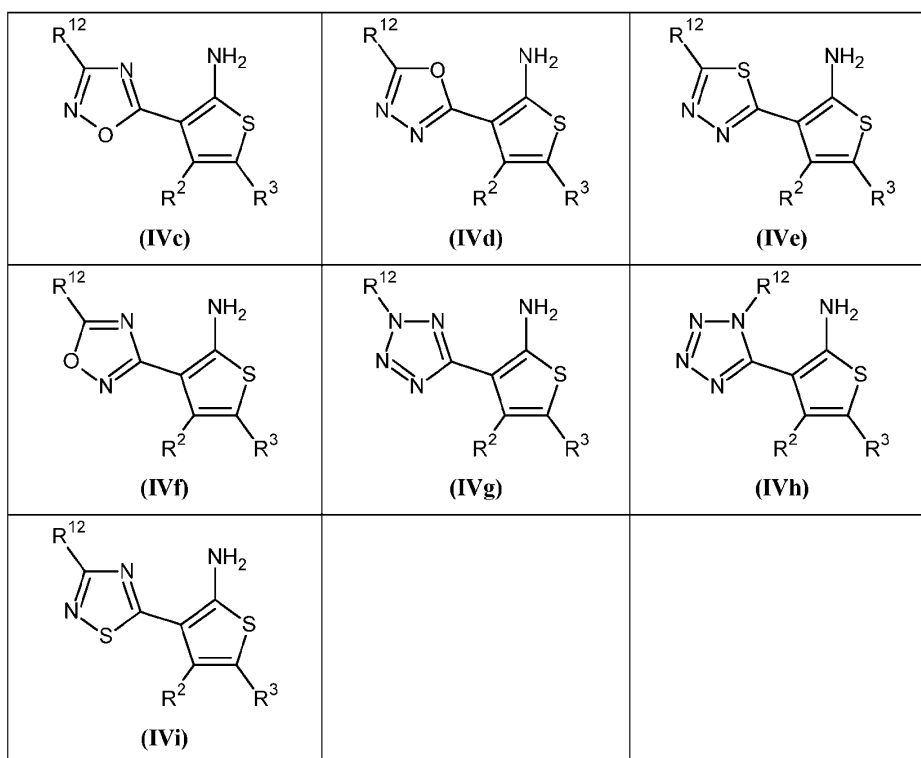
wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl. Such compounds of structural formula **IVb** include but are not limited to the compounds **4l**, **4m**, and **4n** shown in Table 16 below.

[0129] **TABLE 16**



[0130] In at least one embodiment of the substituted 2-amino-thiophene compounds of formula **IV**, the chemical group at R^1 is a 5-membered heteroaryl ring (e.g., 3-substituted 1,2,4-oxadiazol) and the compound is selected from the compounds of structural formula **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, and **IVi** shown in Table 17 below.

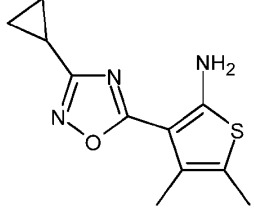
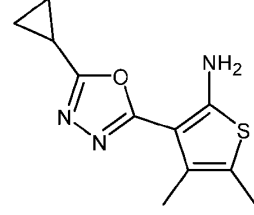
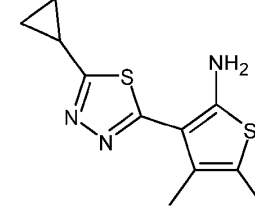
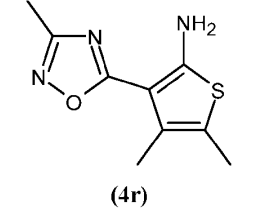
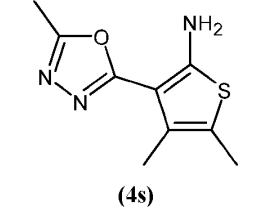
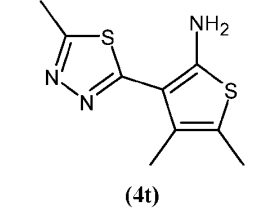
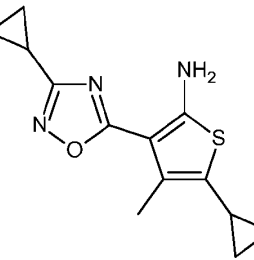
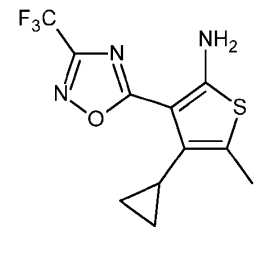
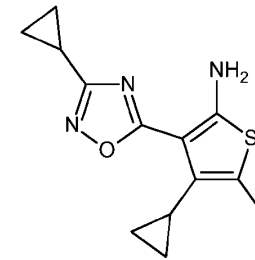
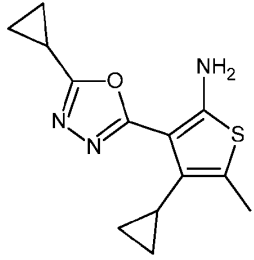
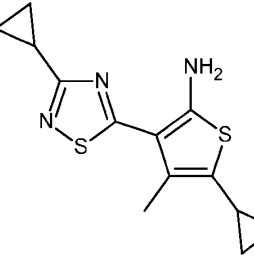
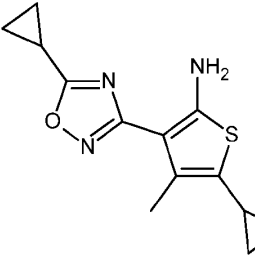
[0131] TABLE 17

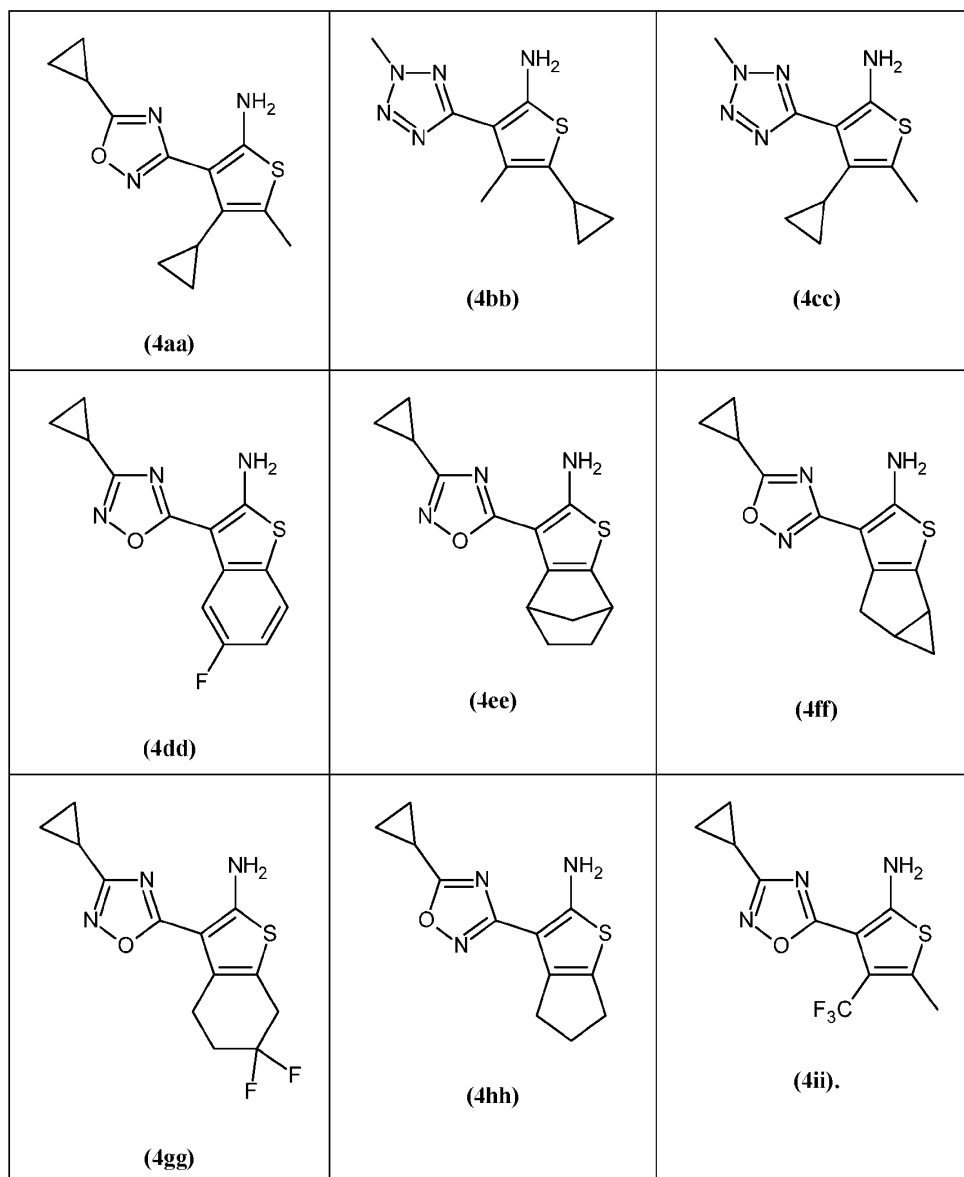


wherein, the chemical groups at R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is

optionally substituted with one or two substituents selected from C₁-C₄-alkyl, methoxy, or fluoro; and the chemical group at R¹² is selected from hydrogen, halogen, C₁-C₄ linear or branched alkyl, cyclopropyl, cyclobutyl, and phenyl. Such compounds of structural formulas **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, **IVh**, and **IVi** include but are not limited to the compounds **4o**, **4p**, **4q**, **4r**, **4s**, **4t**, **4u**, **4v**, **4w**, **4x**, **4y**, **4z**, **4aa**, **4bb**, **4cc**, **4dd**, **4ee**, **4ff**, **4gg**, **4hh**, and **4ii** shown in Table 18 below.

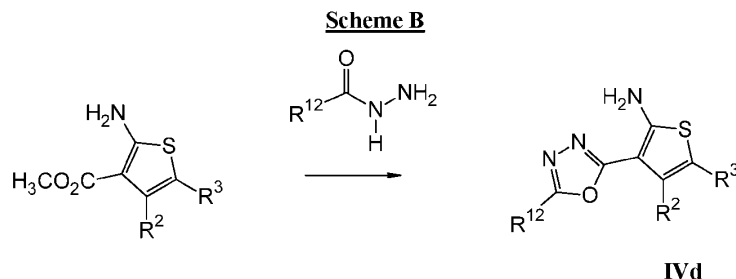
[0132] TABLE 18

 (4o)	 (4p)	 (4q)
 (4r)	 (4s)	 (4t)
 (4u)	 (4v)	 (4w)
 (4x)	 (4y)	 (4z)

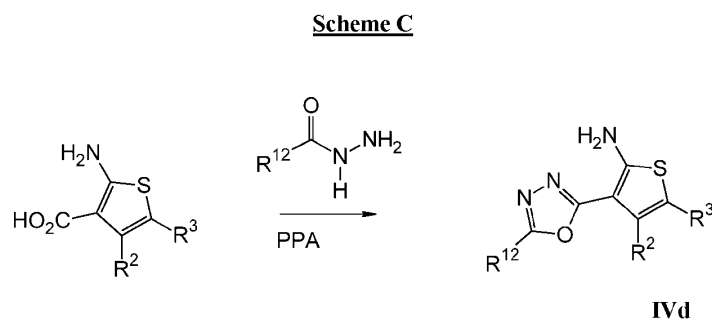


[0133] Methods of synthesis of 2-amino-thiophenes of structural formula **IV** have been reported previously in e.g., US Pat. No. 9,353,102, US Pat. Publ. No. 2015/0175594A1, and PCT Publ. No. WO2014/040938, each of which is hereby incorporated by reference herein. These previously reported methods of synthesis can be used for preparing starting materials useful in the synthetic routes for preparing compounds of structural formula **II** as described herein and in the Examples below. In particular, these starting materials are useful in the preparation of the intermediate compounds of structural formulas **IVa**, **IVb**, **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, or **IVh** shown above.

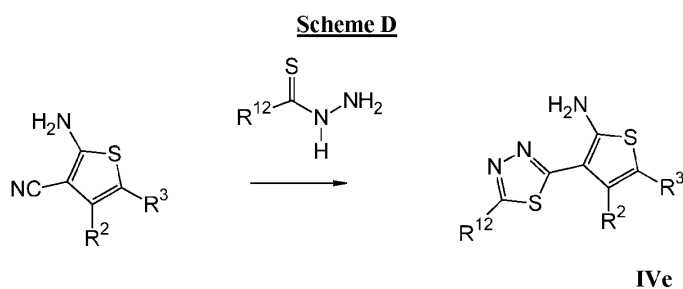
[0134] For example, the compound of structural formula **IVd** may be synthesized using the routes shown in Scheme B below.



[0135] Another route by which the compound of structural formula **IVd** may be synthesized has been described by J. Sarvanan, et al., (Indian Journal of Heterocyclic Chemistry 1998, 7, 285-288) and is shown in Scheme C below.

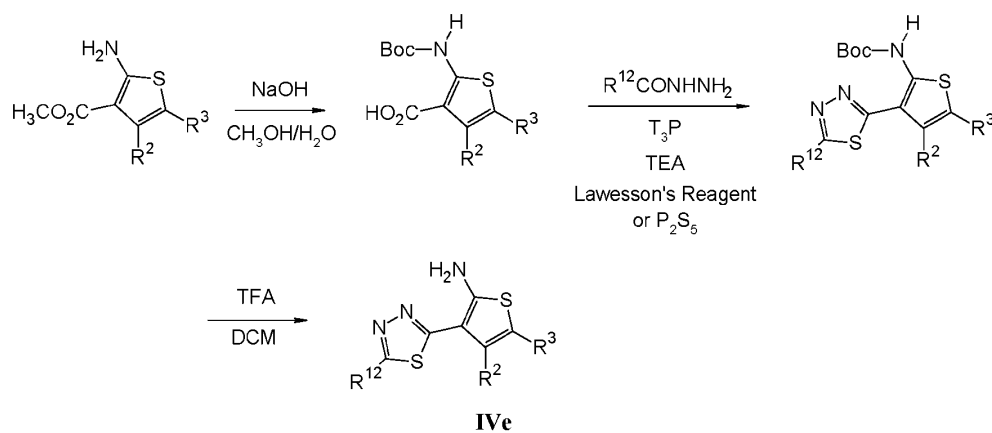


[0136] A route by which a compound of structural formula **IVe** may be synthesized starting with a 2-amino-3-cyano-thiophene has been described R. W. Sabnis et al. (*J. Het. Chem.* 1992, 4, 285-288), and is shown in Scheme D below.



[0137] Another synthetic route by which the compound of structural formula **IVe** may be synthesized has been described J. K. Augustine et al., (*Tetrahedron* 2009, 65, 9989-9996) and is shown in Scheme E below.

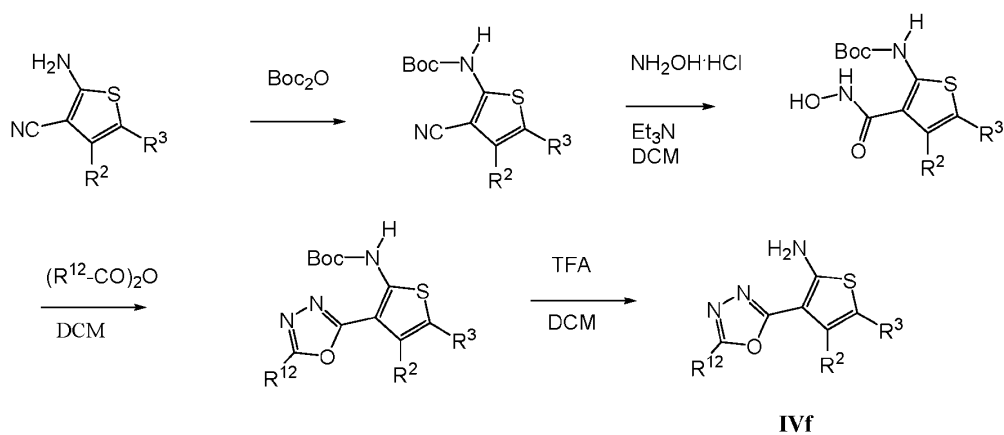
Scheme E



[0138] Another useful method for introduction of the 1,3,4-thiadiazole ring compound of structural formula **IVe** has been reported in V. Polshettiwar et al., *Tetrahedron Lett.*, 2008, 49, 879.

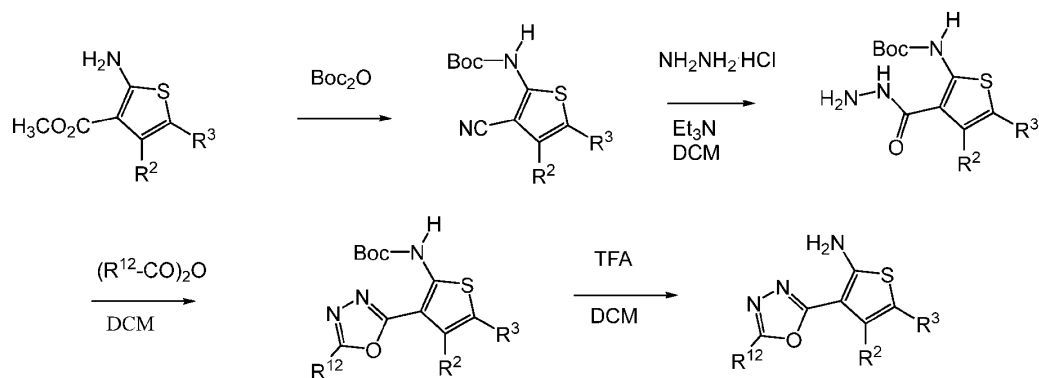
[0139] An exemplary synthetic route by which a compound of structural formula **IVf** may be prepared starting with a 2-amino-3-cyano-thiophene is illustrated in **Scheme F** below.

Scheme F



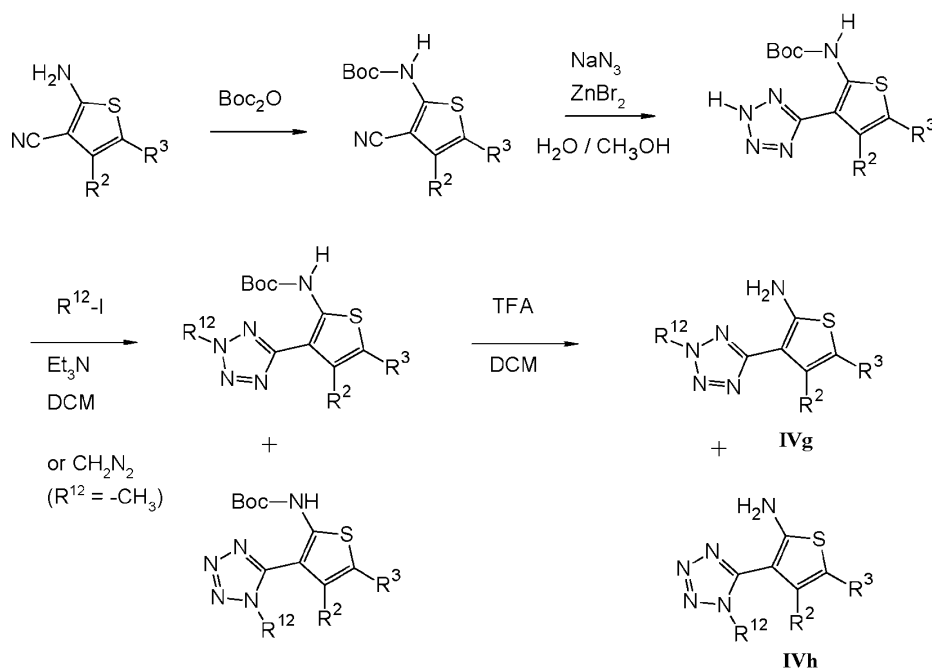
[0140] An alternative synthetic route by which a compound of structural formula **IVf** may be prepared is illustrated in **Scheme G** below.

Scheme G



IVf

[0141] An exemplary synthetic route by which a compound of structural formula **IVg** or formula **IVh** may be prepared starting with a 2-amino-3-cyano-thiophene is illustrated in **Scheme H** below (see also e.g., Z. P. Demko et al., *J. Org. Chem.*, 2001, **66**, 7945-7950).

Scheme H

IVh

[0142] As shown in the above reaction schemes, in some cases, it may be advantageous to protect the 2-amino substituent of the 2-amino-thiophene precursor with a Boc group, using standard methods, before further reactions are carried out.

[0143] A general synthetic route for preparing compounds of structural formula **IVc** is illustrated in the Examples (see e.g., Scheme 21). Further, specific 2-amino-thiophene compounds of formula **VI** that can be used in the preparation of compound of formula **II** are described in the Examples.

[0144] A non-limiting example of the general procedure for preparing the disclosed FABP3/4/5/7 inhibitors. A mixture of the substituted anhydride **III** and the substituted 2-amino-thiophene (1:0.75 molar ratio) is purged with argon then dissolved in dry dichloromethane. The reaction mixture is stirred for 24 h at room temperature. The solvent is removed using a rotary evaporator. The residue is then dissolved in 5mL of ice-cold dichloromethane and transferred to a glass dram vial. The vial is then cooled on dry ice until visible crystals form. The resulting crystals are isolated via vacuum filtration and rinsed with ice cold dichloromethane. The crystals are allowed to air dry via vacuum filtration for 30 minutes. A small sample of isolated crystal is dissolved in acetone and purity is verified with silica thin-layer chromatography using a solvent system of 40% ethyl acetate in hexanes with 0.1% acetic acid. Plates are stained with PMA as a general stain and the formation of the carboxylic acid is verified with bromocresol green stain. Structure of the purified crystals is verified via ¹H NMR. The crystals are transferred to a clean, pre-weighed glass dram vial and yield is calculated. A range of specific synthesis procedures and reagents useful for preparing compounds of structural formula **I** and **II**, including the specific compounds of Table 1 are provided in the Examples below.

[0145] **Uses and Methods of Treatment**

[0146] As noted elsewhere herein, FABP3/4/5/7 inhibitor compounds of structural formula **I** and **II** the present disclosure have been shown to provide potentially therapeutic effects, based on in vitro studies, pre-clinical, or clinical studies in a number of conditions, and diseases. Accordingly, the present disclosure contemplates that the inhibitor compounds of the present disclosure can be used in compositions and methods for treatment of diseases and/or conditions that are known to be affected by FABP3, FABP4, FABP5, and/or FABP7. Generally, methods for treating a subject having a disease or condition affected by FABP3, FABP4, FABP5, and/or FABP7 using a FABP3/4/5/7 inhibitor compound of the present disclosure comprises administering to the subject in need thereof, a therapeutically effective amount of a compound of structural formula **I** and **II**, or a pharmaceutical composition comprising such a compound and one or more pharmaceutically acceptable adjunct ingredients.

[0147] The conditions and diseases known to be affected by one or more of FABP4, FABP5, FABP3 and FABP7 which are contemplated for treatment using the FABP3/4/5/7 inhibitor compounds of structural formula **I** and **II** include, but are not limited to, the following: atherosclerosis, coronary atherosclerosis, arterial fibrosis, pulmonary hypertension, heart failure, obesity, Type-2 diabetes, Type-1-diabetes, gestational diabetes, polycystic ovary syndrome, endometriosis, conditions affected by lipid metabolism and free fatty acid serum levels, metabolic disorders, fatty liver disease, kidney

fibrosis, systemic inflammation, acute inflammation, allergic inflammation, airway inflammation, viral infection (e.g., COVID-19, common cold), skin diseases (e.g., vitiligo, psoriasis, atopic dermatitis, allergic contact dermatitis, mycosis fungoides, alopecia areata, cicatricial alopecia, graft vs. host disease (GvHD), contact dermatitis, chronic eczema, dermatitis herpetiformis, cutaneous lupus, scleroderma, dermatomyositis, vasculitis, pemphigus, epidermolysis bullosa, linear IgA, blistering disease), neurological conditions and diseases (e.g., pain, multiple sclerosis (MS), Parkinson's disease, autoimmune diseases (e.g., experimental autoimmune encephalomyelitis (EAE), asthma, type-1-diabetes, autoimmune lung disease, autoimmune hepatitis, rheumatoid arthritis (RA), spondyloarthritis, vesicular stomatitis virus infection, multiple sclerosis (MS), lupus nephritis, Crohn's disease, ulcerative colitis, and food allergy), ischemic stroke, graft versus host disease (GvHD) and cancer (e.g., breast cancer, prostate cancer, ovarian cancer, skin cancer, gastric cancer, glioma, cholangiocarcinoma, bladder cancer, multiple myeloma, colorectal cancer, hepatocellular cancer, cervical cancer, oral squamous cell carcinoma, and/or non-small cell lung cancer (NSCLC)). Further specific description of various uses and treatment indications for the FABP3/4/5/7 inhibitor compounds of structural formula **I** and **II** are provided below.

[0148] A. Cancer Treatment

[0149] As noted elsewhere herein, inhibition of FABP5 provides a method of inhibiting the metastasis of cancer cells in humans. Triple-Negative Breast Cancer (TNBC) accounts for about 10-20% of all breast cancers. The term "triple-negative breast cancer" refers to the fact that the cancer cells do not produce sufficient estrogen or progesterone receptors or make sufficient amounts of the protein Human Epidermal Growth Factor Receptor 2 (HER-2). Because tumors of TNBC lack definitive prognostic markers and selective targets for therapy, the treatment and management of this disease is a significant clinical problem and warrants an urgent need for a direct approach to inhibiting the biological processes which regulate development and metastasis of tumors. Without wishing to be limited by theory, data disclosed herein indicate that the disclosed FABP inhibitor compounds can provide inhibition of FABP5 and can thereby modulate the level of TNBC.

[0150] Accordingly, in at least one embodiment, the FABP3/4/5/7 inhibitor compounds of structural formula **I** and **II** can be used in methods treating cancer in a subject, wherein the methods comprise administering to a subject in need thereof a composition, comprising: (a) an effective amount of one or more of the disclosed FABP3/4/5/7 inhibitors or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients. In at least one embodiment of the method, the subject can be diagnosed with, suffering from, and/or undergoing treatment for one or more cancers selected from breast cancer, prostate cancer, ovarian cancer, skin cancer, gastric cancer, glioma, cholangiocarcinoma, bladder cancer, multiple myeloma, colorectal cancer, hepatocellular cancer, cervical cancer, oral squamous cell carcinoma, and/or non-small cell lung cancer (NSCLC). In one embodiment of the disclosed cancer treatment method relates to breast cancer. In another

embodiment of the disclosed methods relate to preventing the metastasis of TNBC cells in a subject diagnosed with cancer.

[0151] Another still further aspect of the disclosed methods relates to methods treating cancer in a subject, comprising administering to a subject in need a composition, comprising: (a) an effective amount of one or more of the disclosed FABP3/4/5/7 inhibitors or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients. In at least one embodiment of the method of treating cancer, the cancer is chosen from breast cancer, prostate cancer, ovarian cancer, hepatocellular cancer, multiple myeloma, neuroblastoma, lung adenocarcinoma or gastric carcinoma. In one example, the cancer is breast cancer. In a further example the cancer is prostate cancer. In another example the cancer is ovarian cancer. In a yet another example the cancer is hepatocellular cancer. In a still further example, the cancer is multiple myeloma. In another yet example the cancer is neuroblastoma. In a yet still further example, the cancer is lung adenocarcinoma. In a still yet another further example the cancer is gastric carcinoma.

[0152] In at least another embodiment, it is contemplated that the FABP3/4/5/7 inhibitors of the present disclosure can be used in a method of sensitizing cancer cells for treatment with other chemotherapeutic agents. Such agents can include standard chemotherapeutic compounds, such as doxorubicin, gemcitabine, cisplatin, paclitaxel, all-trans retinoic acid (atRA), a PARP inhibitor compound, and an immune checkpoint inhibitor compound, including but not limited to, an antibody that targets PD-1, or PD-L1. Accordingly, in at least one embodiment, the present disclosure provides a method of sensitizing cancer cells for treatment with other chemotherapeutic agents, wherein the method comprises contacting the cancer cells with one or more of the disclosed FABP3/4/5/7 inhibitors and contacting the cells with one or more chemotherapeutic agents. It is contemplated that this method can be carried out where the FABP3/4/5/7 inhibitor is contacted with the cancer cells prior to, or concurrently with, or after contacting the cells with the chemotherapeutic agent.

[0153] In at least one embodiment, the present disclosure also provides the use of a FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutical composition comprising such a compound, for the manufacture of a medicament for treating a cancer in a subject. In at least one embodiment, the cancer treated by the use or medicament is chosen from breast cancer, prostate cancer, ovarian cancer, hepatocellular cancer, multiple myeloma, neuroblastoma, lung adenocarcinoma or gastric carcinoma.

[0154] B. Fatty Acid Control

[0155] One aspect of the disclosed uses and methods relates to methods for inhibiting one or more of FABP3, FABP4, FABP5, and FABP7 in a subject, comprising administering to a subject in need a composition, comprising: (a) an effective amount of one or more of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0156] A further aspect of the disclosed uses and methods relates to methods for controlling the free fatty acid serum levels in a subject, comprising administering to a subject in need a composition, comprising: (a) an effective amount of one or more of the disclosed FABP3/4/5/7 inhibitors of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0157] In at least one embodiment, the present disclosure also provides the use of a FABP3/4/5/7 inhibitor compound of the present disclosure, or a pharmaceutical composition comprising a FABP3/4/5/7 inhibitor compound of structural formula **I** or **II**, for the manufacture of a medicament for treating a disease or condition affected by FABP3/4/5/7 in a subject. In at least one embodiment, the disease or condition relates to control of the free fatty acid serum levels in a subject.

[0158] C. Metabolic Disorders Treatment

[0159] Additionally, FABP4 and FABP5 are members of a family of small, soluble proteins which contribute to the trafficking of fatty acids within the cytosolic compartments of cells. These proteins have no catalytic function but transport hydrophobic fatty acids within the aqueous environment of the cytosol to the various destinations enabling fatty acid oxidation, membrane homeostasis or nuclear signaling. In addition, they are involved in signaling processes which are so far poorly understood. FABP4 is highly expressed in adipose tissue, macrophages, and endothelial cells. FABP5 is also expressed in macrophages, adipocytes and endothelial cells, as well as in skin and several other tissues.

[0160] Without wishing to be limited by theory, in humans, plasma levels of FABP4 are increased in patients with metabolic syndrome and atherosclerosis. In addition, there is evidence for involvement of FABP4 in angiogenesis. More than a quarter of the population suffers from an aggregation of co-morbidities, including obesity, atherosclerosis, insulin resistance, dyslipidemias, coagulopathies, hypertension, and a pro-inflammatory state known as the metabolic syndrome. Patients with metabolic syndrome have high risk of atherosclerosis as well as Type-2 diabetes and other health problems. Like obesity, atherosclerosis has very limited therapeutic options.

[0161] A yet further aspect of the disclosed methods relates to methods for regulating insulin sensitivity in a subject, comprising administering to a subject in need a composition, comprising: (a) an effective amount of one or more of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0162] A yet still further aspect of the disclosed methods relates to methods for treating Type-2 diabetes in a subject, comprising administering to a subject in need thereof a composition, comprising: (a) an effective amount of one or more of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0163] A still yet further aspect of the disclosed methods relates to methods for the glucose plasma level in a subject, comprising administering to a subject in need thereof a composition, comprising: (a) an effective amount of one or more of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0164] A yet still further aspect of the disclosed methods relates to methods for treating atherosclerosis in a subject, comprising administering to a subject in need thereof a composition, comprising: (a) an effective amount of one or more of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0165] A yet further aspect of the disclosed methods relates to methods for treating liver steatosis in a subject, comprising administering to a subject in need thereof a composition, comprising: (a) an effective amount of one or more of the FABP3/4/5/7 inhibitor compounds of structural formula **I** or **II**, or a pharmaceutically acceptable salt thereof; and (b) a pharmaceutically acceptable carrier or other adjunct ingredients.

[0166] In at least one embodiment, the present disclosure also provides the use of a FABP3/4/5/7 inhibitor compound of structural formula **I** or **II**, or a pharmaceutical composition comprising a FABP3/4/5/7 inhibitor compound of the present disclosure, for the manufacture of a medicament for treating a metabolic disorder in a subject.

[0167] D. Modulation of immune cell activity and populations

[0168] As described elsewhere herein, FABPs are involved in the regulation of immune cell activity. Without intending to be limited by mechanism, FABPs are believed to mediate immune cell metabolism, which is critical for the proper functioning of the immune system. More specifically, the activity of FABPs affects the utilization of fatty acids, thereby regulating energy production and the signaling pathways involved in the activation and function of immune cells. For example, FABP5 was found to regulate lipid metabolism and function in T-cells in the tumor microenvironment (TME) by mediating the uptake and oxidation of long-chain FAs in the cells. Further, tumor-infiltrating T lymphocytes (TIL) that express high FABP5 levels usually exhibit an exhausted phenotype and impaired anti-tumor activity due to the limited availability of glucose and high levels of long-chain FAs. Accordingly, inhibition of FABP5 in TILs is expected to activate the anti-tumor activity of the cell. FABP4 is highly expressed in Ly6C⁺MHCII⁺CD36⁺ circulating monocyte/macrophages to facilitate oxidative lipid uptake, foam cell formation, angiogenesis, tissue remodeling and pro-tumor functions. This high expression suggests that inhibition of FABP4 can enhance anti-tumor immune responses in cancer cells and can also block formation of foam cells and chronic inflammation in obesity. Another function of FABP4/5 in immune cells is their role in maintenance of CD8⁺ tissue resident memory T-cells (Trm). Specifically, it was reported elsewhere that skin Trm, that rely on fatty acids as energy source, express high levels of FABP4/5 that are necessary for uptake of fatty

acids into the cells and transport them to the mitochondria for metabolism. The energy produced in this process is required for survival of Trm cells. Targeting Trm cells by inhibition of FABP4/5 is expected to have therapeutic effect in autoimmune diseases. Overall, the role of FABPs in immune cell regulation highlights the importance of lipid metabolism in the regulation of the immune system and imply that targeting FABPs may be a promising strategy for improving immune cell function and treating a wide range of diseases and conditions caused by chronic inflammation and cancer.

[0169] A method for modulating immune cell populations and/or immune cell activity in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structural formula **I** or **II**, or a pharmaceutical composition of such a compound. In at least one embodiment, the subject in need thereof has a disease or disorder caused by, affected by, and/or characterized by immune cell populations and/or immune cell activity, for example, wherein the immune cells are M2 macrophages or tumor associated macrophages (TAMs). In at least one embodiment, the subject in need of a treatment for modulating immune cell populations and/or immune cell activity has been diagnosed with, is suffering from, or is being treated for cancer. In another embodiment, it is contemplated that the subject in need of a treatment for modulating immune cell populations and/or immune cell activity has an autoimmune disease or disorder.

[0170] Pharmaceutical Compositions

[0171] The present disclosure also provides uses and methods in which a FABP4/5 inhibitor compounds, such as a compound of structural formula **I** or **II**, is administered to a subject in the form of a pharmaceutical composition. In such embodiments, the pharmaceutical composition includes a therapeutically effective amount of the FABP3/4/5/7 inhibitor compound (e.g., compound of Table 11), or a pharmaceutically acceptable salt or ester of such a compound and one or more pharmaceutically acceptable carriers. Such pharmaceutical compositions can be prepared using methods well known in the pharmaceutical art (see, e.g., *Remington's Pharmaceutical Sciences*, Mace Publishing Co., Philadelphia, PA 17th Ed. (1985) and *Modern Pharmaceutics*, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.). Methods of preparing pharmaceutical compositions of FABP3/4/5/7 inhibitor compounds are described in the present disclosure, including the Examples disclosed herein.

[0172] In at least one embodiment, the present disclosure provides a pharmaceutical composition comprising: an effective amount of one or more of the disclosed FABP3/4/5/7 inhibitors, such as a compound of structural formula **I** or **II**; and one or more adjunct ingredients, such as a pharmaceutically acceptable carrier. The disclosed compositions can comprise from about 10% to about 95% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors. In another embodiment, the compositions comprise from about 10% to about 80% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors. In a further embodiment the compositions comprise from about 20% to about 50% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors. In a still further

embodiment, the compositions comprise from about 50% to about 90% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors. In a yet another embodiment the compositions comprise from about 70% to about 90% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors. In a yet further embodiment, the compositions comprise from about 80% to about 95% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors. In a still yet further embodiment, the compositions comprise from about 90% to about 95% by weight of one or more of the disclosed FABP3/4/5/7 inhibitors.

[0173] Generally, the pharmaceutical compositions can be prepared by diluting the active ingredient(s) with an excipient and/or enclosing it within a carrier in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the pharmaceutical composition(s) suitable for administering in the methods of the disclosure can be in the dosage form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[0174] The carriers used in the preparation of the pharmaceutical compositions can include excipients such as inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Suitable excipients for use in the pharmaceutical compositions comprising a celastrol derivative of the present disclosure are well known in the art and include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The pharmaceutical compositions can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0175] In the uses and methods of treatment, it is contemplated that the pharmaceutical composition comprising the FABP3/4/5/7 inhibitor compounds, such as a compound of structural formula I, can be administered either as single or multiple doses, and by any of the accepted modes of administration of active ingredients having similar utility. For example, a pharmaceutical composition comprising an celastrol derivative can be administered using a variety of different modes including oral administration, intravenous administration, topical administration, parenteral administration, intraperitoneal administration, intramuscular administration, intrathecal administration, intralesional administration, intracranial administration, intranasal administration, intraocular administration, intracardiac administration, intravitreal administration, intraosseous administration, intracerebral administration, intraarterial administration, intraarticular administration, intradermal administration, transdermal administration, transmucosal administration, sublingual administration, enteral

administration, sublabial administration, insufflation administration, suppository administration, inhaled administration, or subcutaneous administration.

[0176] The pharmaceutical compositions including the FABP3/4/5/7 inhibitor compounds of the present disclosure can be used in a range of therapeutic methods of treatment and a range of dosages are contemplated for administration of a pharmaceutically effective amount. The dosage and frequency (single or multiple doses) of administration of the pharmaceutical composition to a subject can vary depending upon a range of factors, such as, the route of administration; the subject's size, age, sex, health, body mass, and/or diet; the state of the disease being treated; whether the subject is suffering from any other diseases, and any concurrent treatment being received. One of ordinary skill will understand that adjustment of established dosages (e.g., frequency and duration) to obtain the therapeutically effective amount may be required depending on the subject. Typically, the amount of a pharmaceutical composition containing a FABP3/4/5/7 inhibitor compound to be administered to a subject in a therapeutic method of treatment will be determined by a physician, in view of relevant circumstances of the subject being so treated, the chosen route of administration, and of course, the age, the weight, the severity of symptoms, the response of the individual subject to the treatment, and the like.

[0177] Generally, a therapeutically effective amount is the amount sufficient for the administered composition to accomplish a desired therapeutic purpose relative to the absence of the compound. For example, the therapeutically effective amount can be the amount determined to be sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. Methods for determining the dosage providing a therapeutically effective amount of a compound are well-known to those of ordinary skill in the art, and typically are based on analysis of amounts determined in cellular assays and/or animal models. For example, a dosage for administration to humans can be formulated to achieve a concentration that has been observed as therapeutically effective in an animal model. The dosage in the pharmaceutical composition for humans can further be adjusted by monitoring the effectiveness and adjusting upwards or downwards. One of ordinary skill can use methods well known in the art to adjust the dosage in a pharmaceutical composition of the present disclosure to achieve maximal therapeutic efficacy for humans.

[0178] Generally, methods for therapeutic treatment are developed by starting with a pharmaceutical composition containing less than the optimal dose of the FABP3/4/5/7 inhibitor compound. Thereafter, the dosage of the compound is increased incrementally until optimal efficacy is attained. A key factor considered in developing the optimal dose is the ratio between the toxicity and the therapeutic efficacy of the active ingredient. This ratio, referred to as the compound's therapeutic index, is typically described as the ratio of the active ingredient's LD₅₀ (the amount of compound lethal in 50% of the population) to its ED₅₀ (the amount of compound effective in 50% of the population). Typically, a higher therapeutic index for a compound is preferred. Therapeutic index data can be obtained from cell culture assays and/or animal model studies and then used to determine

a safe range of dosages of the active ingredient in a pharmaceutical composition for administration to humans. Ideally the dosage determined provides the active ingredient at its ED₅₀ level in the subject with little or no toxicity.

[0179] Solid form preparations of pharmaceutical compositions can include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances that can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

[0180] In powders, generally the carrier is a finely divided solid that is in an admixture with the finely divided active component, e.g., a disclosed FABP3/4/5/7 inhibitor. In tablets, the active ingredient is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The solid form preparation of a pharmaceutical composition of the present disclosure can comprise from about 0.5% to about 10% by weight of a binding agent. Non-limiting examples of binding agents suitable for use in the disclosed compositions are chosen from polyethylene glycol 1500, polyethylene glycol 2000, polyethylene glycol 3000, polyethylene glycol 4000, polyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, methylcellulose, ethylcellulose, hydroxymethyl cellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, polyoxyethylene, copolymers of polyoxyethylene-polyoxypropylene and mixtures thereof. In one embodiment the binding agent is methylcellulose, ethylcellulose, hydroxymethyl cellulose, or hydroxyethylcellulose. In one non-limiting example the binding agent is ethylcellulose.

[0181] In some embodiments, the solid compositions can comprise from about 0.5% to about 10% by weight of a carrier. Non-limiting examples of solid carriers include: starch such as tapioca starch, corn starch, potato starch, gelatin, dextrin, inulin, cyclodextrin, oxidized starch, starch ester, starch ether, crosslinked starch, alpha starch, octenyl-succinate ester, and processed starch obtained by treating a starch by an acid, heat, or enzyme, or an emulsifier such as gum arabic, modified starch, pectin, xanthan gum, gum ghatti, gum tragacanth, fenugreek gum, mesquite gum, mono-glycerides and di-glycerides of long chain fatty acids, sucrose monoesters, sorbitan esters, polyethoxylated glycerols, stearic acid, palmitic acid, mono-glycerides, di-glycerides, propylene glycol esters, lecithin, lactylated mono- and di-glycerides, propylene glycol monoesters, polyglycerol esters, diacetylated tartaric acid esters of mono- and di-glycerides, citric acid esters of monoglycerides, stearyl-2-lactylates, polysorbates, succinylated monoglycerides, acetylated monoglycerides, ethoxylated monoglycerides, quillaia, whey protein isolate, casein, soy protein, vegetable protein, pullulan, sodium alginate, guar gum, locust bean gum, tragacanth gum, tamarind gum, carrageenan, furcellaran, Gellan gum, psyllium, curdlan, konjac mannan, agar, and cellulose derivatives, and combinations thereof, or a sugar alcohol that can optionally have humectant properties such as ethylene glycol, glycerol, erythritol, threitol, arabitol, xylitol, ribitol, mannitol, sorbitol, galactitol, fructitol, iditol, sucrose, fructose, isomalt, maltitol, lactitol, sorbitol, dextrose or inositol, and combinations thereof.

[0182] The disclosed compositions can comprise from about 25 mg to about 1200 mg of one or more of the disclosed FABP3/4/5/7 inhibitor. In one aspect the disclosed single dose compositions of a disclosed FABP3/4/5/7 inhibitor can comprise any amount from about 25 mg to about 500 mg.

[0183] In a further aspect the disclosed single dose compositions of a disclosed FABP3/4/5/7 inhibitor can comprise any amount from about 100 mg to about 500 mg. In a yet further aspect, the disclosed single dose compositions of a disclosed FABP3/4/5/7 inhibitor can comprise any amount from about 500 mg to about 1000 mg.

[0184] The single dose compositions can comprise any amount of FABP3/4/5/7 inhibitor from about 25 mg to about 250 mg. For example, the disclosed compositions can comprise 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 101 mg, 102 mg, 103 mg, 104 mg, 105 mg, 106 mg, 107 mg, 108 mg, 109 mg, 120 mg, 121 mg, 122 mg, 123 mg, 124 mg, 125 mg, 126 mg, 127 mg, 128 mg, 129 mg, 130 mg, 131 mg, 132 mg, 133 mg, 134 mg, 135 mg, 136 mg, 137 mg, 138 mg, 139 mg, 140 mg, 141 mg, 142 mg, 143 mg, 144 mg, 145 mg, 146 mg, 147 mg, 148 mg, 149 mg, 150 mg, 151 mg, 152 mg, 153 mg, 154 mg, 155 mg, 156 mg, 157 mg, 158 mg, 159 mg, 160 mg, 161 mg, 162 mg, 163 mg, 164 mg, 165 mg, 166 mg, 167 mg, 168 mg, 169 mg, 170 mg, 171 mg, 172 mg, 173 mg, 174 mg, 175 mg, 176 mg, 177 mg, 178 mg, 179 mg, 180 mg, 181 mg, 182 mg, 183 mg, 184 mg, 185 mg, 186 mg, 187 mg, 188 mg, 189 mg, 190 mg, 191 mg, 192 mg, 193 mg, 194 mg, 195 mg, 196 mg, 197 mg, 198 mg, 199 mg, 200 mg, 201 mg, 202 mg, 203 mg, 204 mg, 205 mg, 206 mg, 207 mg, 208 mg, 209 mg, 210 mg, 211 mg, 212 mg, 213 mg, 214 mg, 215 mg, 216 mg, 217 mg, 218 mg, 219 mg, 220 mg, 221 mg, 222 mg, 223 mg, 224 mg, 225 mg, 226 mg, 227 mg, 228 mg, 229 mg, 230 mg, 231 mg, 232 mg, 233 mg, 234 mg, 235 mg, 236 mg, 237 mg, 238 mg, 239 mg, 240 mg, 241 mg, 242 mg, 243 mg, 244 mg, 245 mg, 246 mg, 247 mg, 248 mg, 249 mg, or 250 mg of one or more of the disclosed FABP3/4/5/7 inhibitors.

[0185] Liquid forms of the pharmaceutical compositions can include, for example, solutions suitable for oral or parenteral administration, suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, buffered water, saline, PBS, ethanol, or propylene glycol are examples of liquid compositions suitable for parenteral administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, detergents, and the like. In

at least one embodiment, the disclosed liquid compositions can comprise from about 5% to about 25% by weight of a liquid carrier.

[0186] For liquid embodiments of the present compositions, the targeted cells, for example, cancer cells or tumor cells can be contacted with an aqueous solution comprising from about 0.5 µg/mL to about 250 µg/mL. In one embodiment the compositions can comprise from about 1 µg/mL to about 100 µg/mL. In another embodiment the compositions can comprise from about 10 µg/mL to about 100 µg/mL. In a further embodiment the compositions can comprise from about 5 µg/mL to about 20 µg/mL. In a yet further embodiment, the compositions can comprise from about 1 µg/mL to about 50 µg/mL. In a yet another embodiment the compositions can comprise from about 1 µg/mL to about 10 µg/mL. In a still further embodiment, the compositions can comprise from about 15 µg/mL to about 50 µg/mL. In still another embodiment the compositions can comprise from about 20 µg/mL to about 200 µg/mL.

[0187] The disclosed compositions can provide a single dose of a disclosed FABP3/4/5/7 inhibitor based upon the body mass of the subject being treated. Therefore, a single dose of a disclosed FABP3/4/5/7 inhibitor can range from about 0.35 mg/kg to about 20 mg/kg of the subject's body mass. In one embodiment, the amount of a disclosed FABP3/4/5/7 inhibitor in a single dose is from about 1 mg/kg to about 8 mg/kg of the subject's body mass. In another embodiment, the amount of a disclosed FABP3/4/5/7 inhibitor in a single dose is from about 2 mg/kg to about 5 mg/kg of the subject's body mass. In a further embodiment, the amount of a disclosed FABP3/4/5/7 inhibitor in a single dose is from about 1.5 mg/kg to about 4 mg/kg of the subject's body mass. In a yet further embodiment, the amount of a disclosed FABP3/4/5/7 inhibitor in a single dose is from about 4 mg/kg to about 10 mg/kg of the subject's body mass. In a still further embodiment, the amount of a disclosed FABP3/4/5/7 inhibitor in a single dose is from about 5 mg/kg to about 8 mg/kg of the subject's body mass.

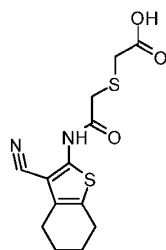
[0188] For example, the dose can comprise any amount from about 0.5 mg/kg to about 10 mg/kg on the body mass of the subject being treated. For example, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4.0 mg/kg, 4.1 mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, or 50 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8 mg/kg, 5.9 mg/kg, 6.0 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7.0 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8.0 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 90 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, or 10.0 mg/kg of body mass.

EXAMPLES

[0189] Various features and embodiments of the disclosure are illustrated in the following representative examples, which are intended to be illustrative, and not limiting. Those skilled in the art will readily appreciate that the specific examples are only illustrative of the invention as described more fully in the claims which follow thereafter. Every embodiment and feature described in the application should be understood to be interchangeable and combinable with every embodiment contained within.

[0190] The following examples illustrate methods of synthesis for compounds of Formula 1:

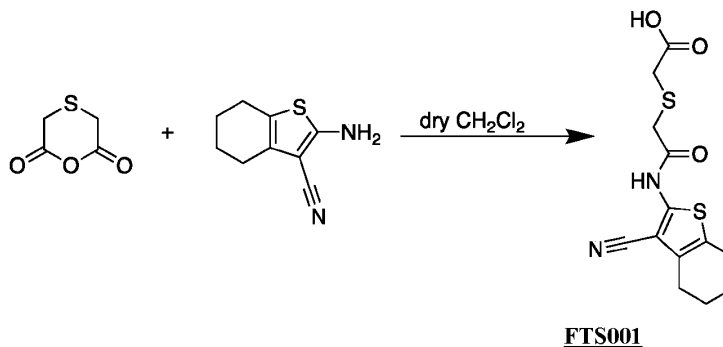
Example 1: Preparation of 2-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-oxoethyl)thio)acetic acid (compound **FTS001**)



FTS001 (CAS 41922-19-1)

[0191] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS001** via the synthetic method of Scheme 1 as shown below.

Scheme 1



FTS001

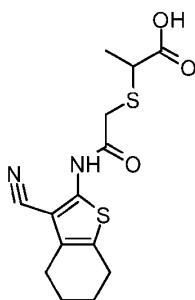
[0192] *Materials and methods*

[0193] 1,4-oxathiane-2,6-dione (0.552mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (0.552mmol) were charged into a 50mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary

evaporation to yield 2-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)acetic acid (137mg, 80%).

[0194] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.75 ppm (4H, t, J= 6.0 Hz), 2.59 ppm (2H, m, J=6.0Hz), 3.41 ppm (2H,s), 3.55 ppm (2H,s) 11.68 (1H, s), 12.66 (1H, s).

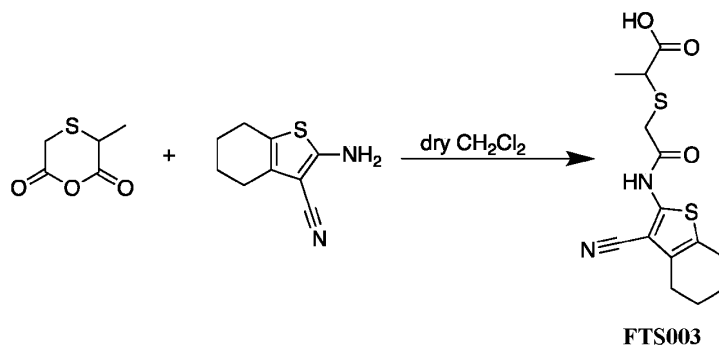
[0195] **Example 2:** Preparation of 2-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS003**)



FTS003

[0196] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS003** via the synthetic method of Scheme 2 as shown below.

Scheme 2



FTS003

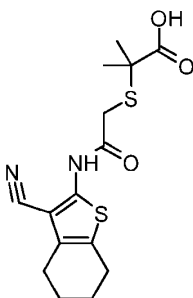
[0197] **Materials and methods**

[0198] 3,3-dimethyl-1,4-oxathiane-2,6-dione (2.13mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (1.58mmol, 0.75eq.) were charged into a 100mL round bottom flask. The flask was purged with argon and 50mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 2-((2-((3-cyano-4,5,6,7-

tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a white powder (355mg, 66.4%).

[0199] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.43 (s, 4H), 1.75 (m, 4H), 2.59 (m, 4H), 3.70 (s, 2H), 11.71 (s, 1H), 12.66 (s, 1H). ¹³C NMR (125MHz): 175.3, 167.7, 146.7, 131.2, 128, 114.5, 93.2, 47.43, 33.59, 25.95, 23.95, 23.77, 23.05, 22.16.

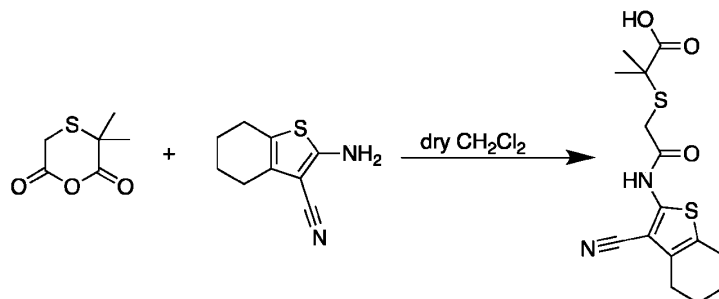
[0200] **Example 3:** Preparation of 2-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS005**)



FTS005

[0201] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS005** via the synthetic method of Scheme 3 as shown below.

Scheme 3



FTS005

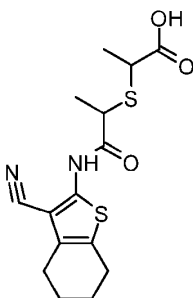
[0202] **Materials and methods**

[0203] 3,3-dimethyl-1,4-oxathiane-2,6-dione (2.13mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (1.58mmol, 0.75eq.) were charged into a 100mL round bottom flask. The flask was purged with argon and 50mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 2-((2-((3-cyano-4,5,6,7-

tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a white powder (355mg, 66.4%).

[0204] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.43 (s, 4H), 1.75 (m, 4H), 2.59 (m, 4H), 3.70 (s, 2H), 11.71 (s, 1H), 12.66 (s, 1H). ¹³C NMR (125MHz): 175.3, 167.7, 146.7, 131.2, 128, 114.5, 93.2, 47.43, 33.59, 25.95, 23.95, 23.77, 23.05, 22.16.

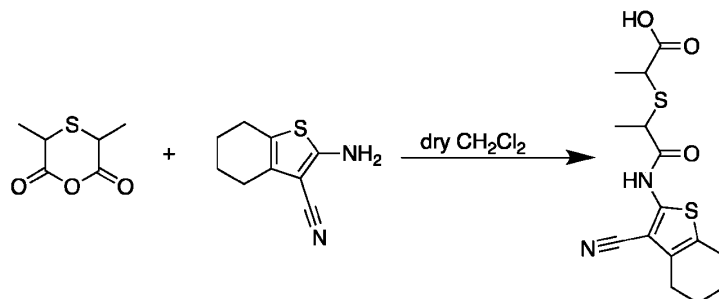
[0205] **Example 4:** Preparation of 2-((1-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-1-oxopropan-2-yl)thio)propanoic acid (compound **FTS007**)



FTS007

[0206] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS007** via the synthetic method of Scheme 4 as shown below.

Scheme 4



FTS007

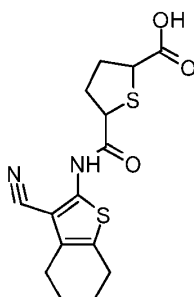
[0207] *Materials and methods*

[0208] 3,5-dimethyl-1,4-oxathiane-2,6-dione (0.357mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (0.226mmol, 0.75eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂.

Residual solvent is removed via rotary evaporation to yield 2-((1-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-1-oxopropan-2-yl)thio)propanoic acid (26mg, 34%).

[0209] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ : 1.33 (d, 3H, *J*=7.13MHz), 1.43 (d, 3H, *J*=6.99 MHz), 1.75 (s, 4H), 2.36-2.63 (m, 4H), 3.56 (q, 1H, *J*=7.12 MHz), 4.05 (q, 1H, *J*=6.97 MHz), 11.74 (s, 1H), 12.65 (s, 1H)

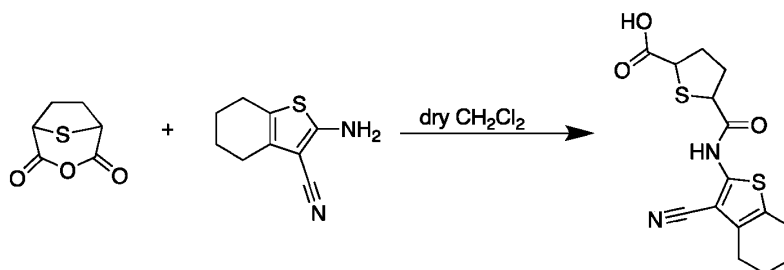
[0210] **Example 5:** Preparation of 5-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)tetrahydrothiophene-2-carboxylic acid (compound **FTS009**)



FTS009

[0211] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS009** via the synthetic method of Scheme 5 as shown below.

Scheme 5



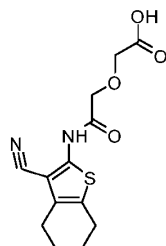
FTS009

[0212] **Materials and methods**

[0213] 3-oxa-8-thiabicyclo[3.2.1]octane-2,4-dione (0.312mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (0.219mmol, 0.75eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 5-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)tetrahydrothiophene-2-carboxylic acid (20mg, 27.2%).

[0214] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.75 (s, 4H), 2.05 (m, 2H), 2.38 (m, 2H), 2.58 (m, 2H), 4.04 (t, 1H), 4.30 (t, 1H), 11.70 (s, 1H), 12.67 (s, 1H)

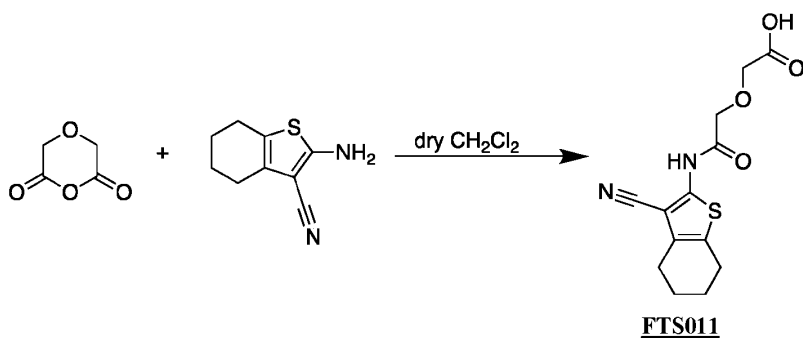
[0215] **Example 6:** Preparation of 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)acetic acid (compound **FTS011**)



FTS011 (CAS 74195-03-8)

[0216] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS011** via the synthetic method of Scheme 6 as shown below.

Scheme 6

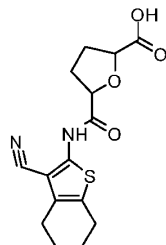


[0217] **Materials and methods**

[0218] 1,4-dioxane-2,6-dione (0.968mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (0.907mmol) were charged into a 50mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)acetic acid (152mg, 57%).

[0219] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.72 ppm (2H, dt, J=5.7 Hz), 1.76 (2H, dt, J=5.7 Hz), 2.60 ppm (4H, m, J=5.7 Hz), 4.19 (2H, s), 4.35 (2H, s), 11.41 ppm (1H, s), 12.81 ppm (1H, s).

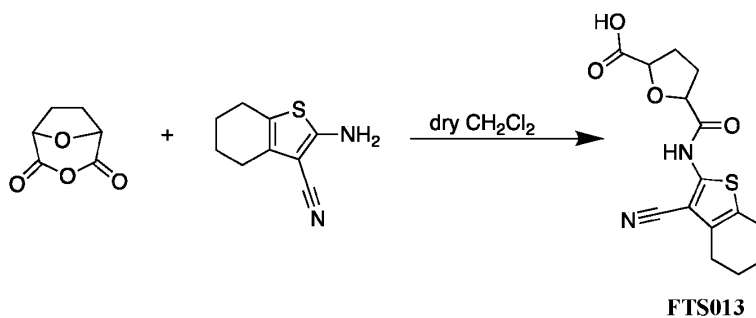
[0220] **Example 7:** Preparation of 5-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)tetrahydrofuran-2-carboxylic acid (compound **FTS013**)



FTS013 (CAS 2191241-83-3)

[0221] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS013** via the synthetic method of Scheme 7 as shown below.

Scheme 7

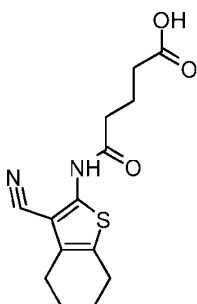


[0222] **Materials and methods**

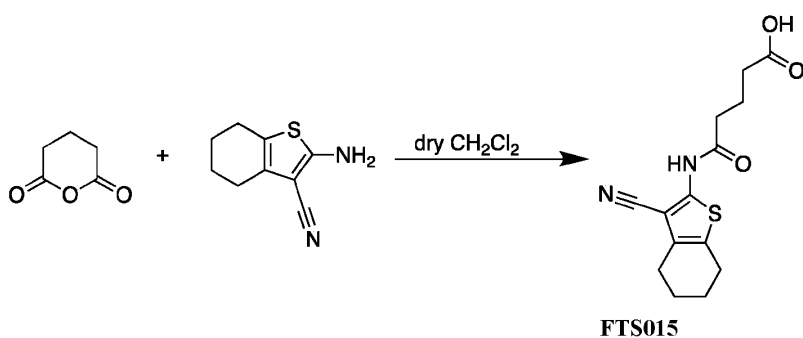
[0223] 3,8-dioxabicyclo[3.2.1]octane-2,4-dione (0.191mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (0.176mmol, 0.75eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 5-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)tetrahydrofuran-2-carboxylic acid (30mg, 53.2%).

[0224] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.65-2.76 ppm, (6H, m), 3.0- 3.14 ppm (6H, m), 3.34 ppm (2H, t, J=4.98 Hz), 5.41-5.47 ppm (2H, dt, J=8.45 Hz), 12.25 ppm (1H, s), 14.40 ppm (1H, s).

[0225] **Example 8:** Preparation of 5-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-5-oxopentanoic acid (compound **FTS015**)

**FTS015 (CAS 313230-00-1)**

[0226] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS015** via the synthetic method of Scheme 8 as shown below.

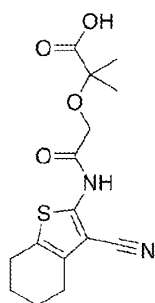
Scheme 8**FTS015**

[0227] *Materials and methods*

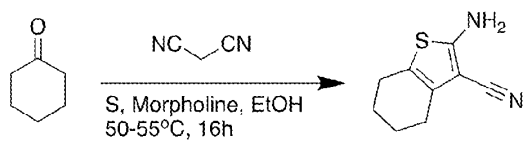
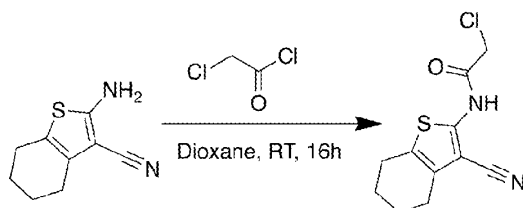
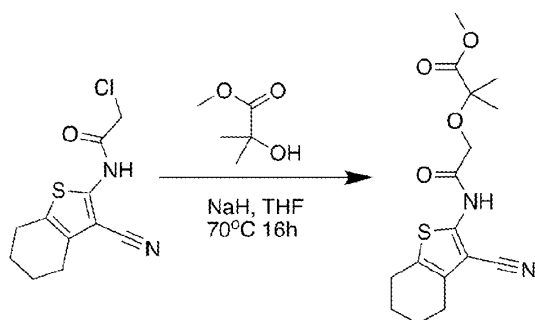
[0228] Dihydro-2H-pyran-2,6(3H)-dione (1.07mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (0.75mmol, 0.75 eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 5-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-5-oxopentanoic acid (83mg, 37.8%).

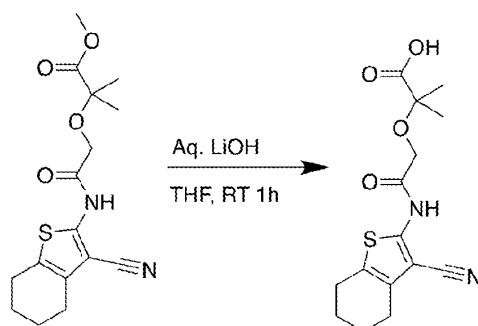
[0229] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.68-1.82 ppm (6H, m), 2.22-2.28 (4H, dt, J= 5.8 Hz), 2.58 ppm (4H, t, J=4.45 Hz), 11.53 ppm (1H, s), 12.38 ppm (1H, s).

[0230] **Example 9:** Preparation of 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)-2-methylpropanoic acid (compound **FTS027**)

**FTS027**

[0231] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS027** via the four step synthetic method of Scheme 9 as shown below.

Scheme 9Step 1Step 2Step 3Step 4

**FTS027****[0232] Materials and methods**

[0233] Step 1 - synthesis of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile: In a 250 mL single necked dried round bottom flask under nitrogen atmosphere cyclohexanone (5.0 g, 50.9 mmol) was dissolved in dioxane (100 mL) and malononitrile (3.37 g, 50.9 mmol), sulfur (1.633 g, 50.9 mmol) was added and heated to 50 °C and morpholine (4.44 g, 50.9 mmol) was added and stirred for 16h at same temperature. Progress of the reaction was monitored by LCMS & TLC. On completion of the reaction, RM was concentrated on rotary evaporator and the obtained residue was diluted with water (80 mL) and extracted with Ethyl acetate (2 X 50 mL). The combined organic layers were washed with Brine solution, and dried over sodium sulfate and concentrated to get crude compound. Crude product was purified by column chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 10 % EtOAc in Pet ether) to get pure 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile as a pale yellow crystalline solid.

[0234] NMR analysis confirmed preparation of the desired step 1 intermediate compound. ¹H NMR: 400 MHz DMSO-*d*₆ δ: 6.94 (s, 2H), 2.42-2.39 (m, 2H), 2.35-2.32 (m, 2H), 1.73-1.68 (m, 4H).

[0235] Step 2 - synthesis of 2-chloro-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)acetamide: To a stirred solution of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (2.0 g, 11.22 mmol) in Dioxane (25 mL) and 2-chloroacetyl chloride (1.521 g, 13.46 mmol) was added in a 100 mL single necked dried round bottom flask under nitrogen atmosphere and stirred at RT for 16h. Progress of the reaction was monitored by TLC. (20% EtOAc in hexane, 0.7 rf) On completion of the reaction, hexane was added to the RM and stirred for 10mins, obtained solid was filtered through Buchner funnel and washed with hexane to get pure 2-chloro-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)acetamide.

[0236] NMR analysis confirmed preparation of the desired step 2 intermediate compound. ¹H NMR: 400 MHz DMSO-*d*₆ δ: 11.91 (s, 1H), 4.46 (s, 2H), 2.61-2.51 (m, 2H), 2.51-2.50 (m, 2H), 1.77-1.75 (m, 4H).

[0237] Step 3 - synthesis of methyl 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)-2-methylpropanoate: To a stirred solution of methyl 2-hydroxy-2-methylpropanoate

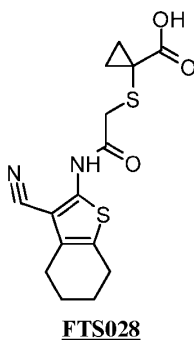
(0.464 g, 3.93 mmol) in THF (25 mL) and methyl 2-hydroxy-2-methylpropanoate (0.464 g, 3.93 mmol), 2-chloro-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)acetamide (0.500 g, 1.963 mmol) was added in a 100 mL single necked dried round bottom flask under nitrogen atmosphere and heated to 70 °C for 16h. Progress of the reaction was monitored by TLC. (20% EtOAc in hexane, 0.4 rf). On completion of the reaction, RM was diluted with water (80 mL) and extracted with Ethyl acetate (2 X 100 mL). The combined organic layers were washed with brine solution, dried over sodium sulfate and concentrated to afford crude compound. Crude product was purified by column chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 15 % EtOAc in Pet ether) to get pure methyl 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)-2-methylpropanoate as an orange solid.

[0238] NMR analysis confirmed preparation of the desired step 3 intermediate compound. ¹H NMR: 400 MHz DMSO-*d*₆ δ : 10.96 (s, 1H), 4.25 (s, 2H), 3.68 (s, 3H), 2.61-2.60 (m, 2H), 2.51-2.50 (m, 2H), 1.76 (s, 4H), 1.42 (s, 6H).

[0239] Step 4 Synthesis of 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)-2-methylpropanoic acid: In a 100 mL single necked dried round bottom flask under nitrogen atmosphere methyl 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)-2-methylpropanoate (0.180 g, 0.535 mmol) was dissolved in THF (5 mL). Water (3 mL) and lithium hydroxide hydrate (0.067 g, 1.605 mmol) were added and stirred at RT for 1hr. Progress of the reaction was monitored by TLC (05% MeOH in DCM). On completion of the reaction. The reaction mixture was diluted with water (5 mL) and washed with ethyl acetate (25 mL). The aqueous layer was acidified with citric acid and extracted with 10% MeOH in DCM (3X20), Organic layers dried over sodium sulphate and concentrated on rotary evaporator to get pure 2-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethoxy)-2-methylpropanoic acid as an off white solid.

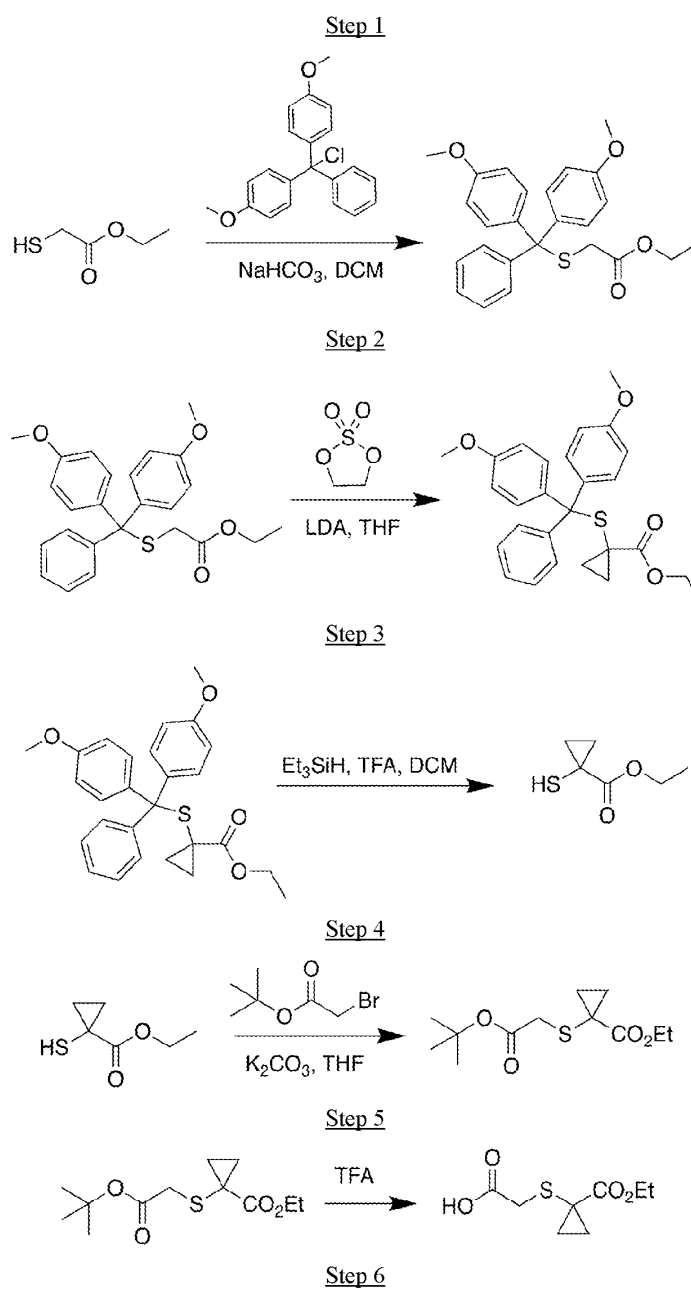
[0240] NMR analysis confirmed preparation of the desired product compound. ¹H NMR: 400 MHz DMSO-*d*₆ δ : 12.95 (s, 1H), 11.17 (s, 1H), 4.23 (s, 2H), 2.70-2.51 (m, 4H), 1.76 (s, 4H), 1.40 (s, 6H).

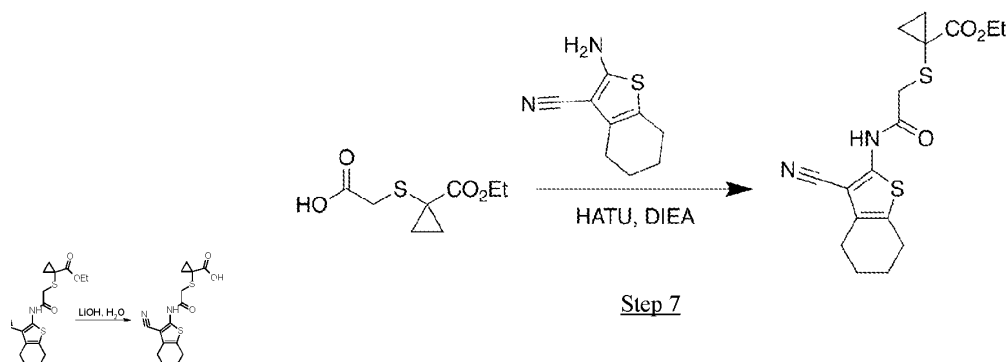
[0241] Example 10: Preparation of 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylic acid (compound **FTS028**)



[0242] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS028** via the seven step synthetic method of Scheme 10 as shown below.

Scheme 10



**FTS028****[0243] Materials and methods**

[0244] Step 1 – Synthesis of ethyl 2-((bis(4-methoxyphenyl)(phenyl)methyl)thio)acetate: To a solution of ethyl 2-sulfanylacetate (10.0 g, 83.22 mmol, 1.0 eq) in DCM (120 mL) was added NaHCO_3 (8.3 g, 99.86 mmol, 1.2 eq). The mixture was stirred at 25°C for 20 min. 1-[chloro-(4-methoxyphenyl)-phenyl-methyl]-4-methoxy-benzene (28.20 g, 83.22 mmol, 1 eq) was added, the mixture was stirred at 25°C for 3 h. The reaction mixture was quenched by addition of H_2O (120 mL), and extracted with DCM (120 mL x 2). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated, and purified by flash chromatography on silica gel (ethyl acetate in petroleum ether = 0 to 10%) to give ethyl 2-((bis(4-methoxyphenyl)(phenyl)methyl)thio)acetate (10.0 g, 23.67 mmol, 58.8% yield) as an off-white oil.

[0245] NMR analysis confirmed preparation of the desired intermediate compound. ^1H NMR (400 MHz, CDCl_3) δ = 7.34 (d, J = 8.0 Hz, 2H), 7.26-7.16 (m, 6H), 7.15-7.14 (m, 1H), 6.76-6.73 (m, 4H), 4.00-3.95 (m, 2H), 3.72 (s, 6H), 2.90 (s, 2H), 1.31 (t, J = 6.8 Hz, 3H).

[0246] Step 2 - Synthesis of ethyl 1-

((bis(4methoxyphenyl)(phenyl)methyl)thio)cyclopropanecarboxylate: To a solution of ethyl 2-[[bis(4-methoxyphenyl)-phenyl-methyl]sulfanylacetate (10.0 g, 23.67 mmol, 1.0 eq) in THF (100 mL) was added dropwise LDA (2 M, 29.58 mL, 2.5 eq) at -60°C. After stirring at -60°C for 1.5 h, 1,3,2-dioxathiolane 2,2-dioxide (4.41 g, 35.50 mmol, 1.5 eq) in THF (17 mL) was added dropwise at -60°C, followed by adding DMPU (4.55 g, 35.50 mmol, 4.29 mL, 1.5 eq) dropwise at -60°C. The mixture was stirred at 25°C for 16 h. After cooling to -60°C, saturated NH_4Cl (200 mL) was added. The

mixture was extracted with EtOAc (400 mL). The organic layer was washed with brine (400 mL), dried over Na₂SO₄, filtered, concentrated, purified by flash chromatography on silica gel (ethyl acetate in petroleum ether = 0 to 10%) to give ethyl 1-((bis(4-methoxyphenyl)

(phenyl)methyl)thio)cyclopropanecarboxylate (7.6 g, 16.94 mmol, 73.6% yield) as a yellow oil.

[0247] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, CDCl₃) δ = 7.36 (d, *J* = 7.2 Hz, 2H), 7.26-7.20 (m, 3H), 7.19-7.17 (m, 4H), 6.72 (d, *J* = 9.2 Hz, 4H), 3.73 (s, 3H), 3.60 (m, 2H), 1.29 (m, 2H), 1.09 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

[0248] Step 3 - Synthesis of ethyl 1-mercaptocyclopropanecarboxylate: To a solution of ethyl 1-[bis(4-methoxyphenyl)-phenyl-methyl]sulfanylcyclopropanecarboxylate (3.0 g, 6.69 mmol, 1.0 eq) in DCM (30 mL), was added triethylsilane (933.2 mg, 8.03 mmol, 1.28 mL, 1.2 eq) at 0°C. After addition, TFA (762.5 mg, 6.69 mmol, 495.16 uL, 1.0 eq) was added, the mixture was stirred at 25°C for 16h. The resulting solution was used in the next step directly.

[0249] Step 4 - Synthesis of ethyl 1-((2-(tert-butoxy)-2-oxoethyl)thio)cyclopropanecarboxylate: To the solution above was added THF (300 mL), K₂CO₃ (4.4 g, 32.49 mmol, 5.0 eq) and tert-butyl 2-bromoacetate (1.3 g, 6.50 mmol, 960.12 uL, 1.0 eq) at 0°C. The mixture was stirred at 25°C for 16h, filtered and concentrated to give ethyl 1-((2-(tert-butoxy)-2-oxoethyl)thio)cyclopropanecarboxylate (1.6 g, 6.49 mmol, crude) as a brown oil, which was used into the next step without further purification.

[0250] Step 5 - Synthesis of 2-((1-(ethoxycarbonyl)cyclopropyl)thio)acetic acid: To a solution of ethyl 1-(2-tert-butoxy-2-oxo-ethyl)sulfanylcyclopropanecarboxylate (1.6 g, 6.49 mmol, 1.0 eq) in DCM (10 mL) was added TFA (15.4 g, 135.06 mmol, 10 mL, 20.8 eq). The mixture was stirred at 25°C for 1 h, filtered and concentrated to give 2-((1-(ethoxycarbonyl)cyclopropyl)thio)acetic acid (1.3 g, 6.51 mmol, crude) as a yellow oil, which was used into the next step without further purification.

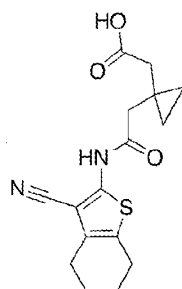
[0251] Step 6-Synthesis of ethyl 2-(1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropyl)-2-oxoacetate: To a solution of 2-(1-ethoxycarbonylcyclopropyl)sulfanylacetic acid (1.15 g, 5.61 mmol, 5.0 eq) in DMF (2.0 mL) was added DIEA (1.16 g, 8.98 mmol, 1.56 mL, 8.0 eq). After stirring at 25°C for 10 min, HATU (639.9 mg, 1.68 mmol, 1.5 eq) and 2-amino-4,5,6,7-tetrahydrobenzothiothiophene-3-carbonitrile (200 mg, 1.12 mmol, 1.0 eq) were added. The mixture was stirred at 50°C for 16 h. The reaction mixture was quenched by addition of H₂O (20 mL) and extracted with DCM (20 mL). The organic layer was washed with brine (25 mL x 3), dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography on silica gel (Ethyl acetate in Petroleum ether = 0 to 10%) to yield ethyl 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylate (405.0 mg, 1.11 mmol, 99.0% yield) as a yellow solid, which was used into the next step directly.

[0252] LCMS analysis confirmed preparation of the desired intermediate compound. LCMS R_t = 0.454 min in 0.8 min chromatography, 5-95AB. ESI calcd. For C₁₇H₂₀N₂O₃S₂Na [M+Na]⁺ 387.1, found 387.0.

[0253] Step 7-Synthesis of 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylic acid (FTS028): To a solution of ethyl 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylate (400 mg, 1.10 mmol, 1.0 eq) in a mixed solvent of MeOH (5 mL) and H₂O (1 mL) was added LiOH.H₂O (230.2 mg, 5.49 mmol, 5.0 eq). The mixture was stirred at 25°C for 16 h, filtered, concentrated and purified by prep-HPLC (column: Phenomenex luna C18 150*25 mm* 10 µm; mobile phase: [water(FA)-ACN]; B%: 35%-65%, 8 min) to give 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylic acid (78.5 mg, 233.33 µmol, 21.2% yield) as a white solid.

[0254] NMR, LCMS, and HPLC analyses confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-d₆) δ = 3.66 (s, 2H), 2.68-2.53 (m, 4H), 1.75-1.72 (m, 4H), 1.46-1.43 (m, 2H), 1.19-1.12 (m, 2H). LCMS R_t = 1.455 min in 3 min chromatography, 5-95 AB, ESI calcd. For C₁₅H₁₆N₂O₃S₂Na [M+Na]⁺ 359.1, found 358.9. HPLC 98.8% purity, R_t = 2.967 min in 6.0 min chromatography, 10-80AB_6min.

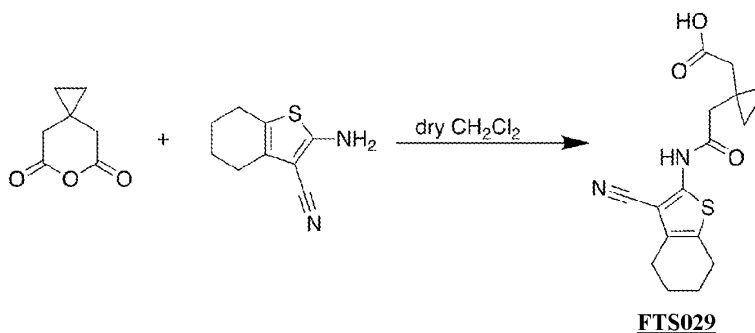
[0255] **Example 11:** Preparation of 2-(1-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)cyclopropyl)acetic acid (compound FTS029)



FTS029

[0256] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound FTS029 via the synthetic method of Scheme 11 as shown below.

Scheme 11



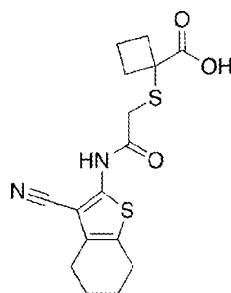
FTS029

[0257] Materials and methods

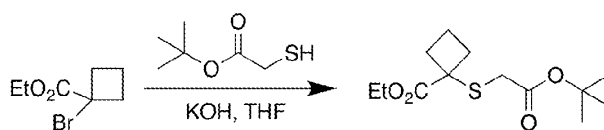
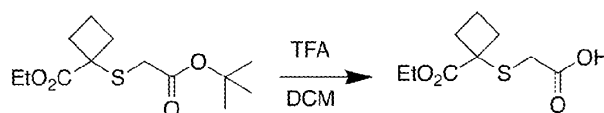
[0258] 6-oxaspiro[2.5]octane-5,7-dione (0.638 mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (0.488 mmol, 0.75 eq.) were charged into a 50 mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 2-(1-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)cyclopropyl)acetic acid) as an amorphous white powder (23 mg, 14.8%).

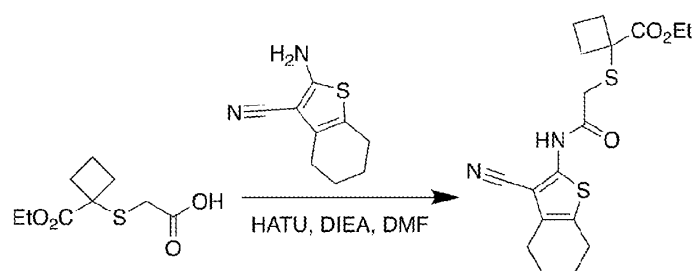
[0259] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (500 MHz, DMSO-d₆) δ = 12.13 (bs, 1H), 11.41 (s, 1H), 2.73 (s, 2H), 2.44 (m, 2H), 2.34 (m, 2H), 2.27 (s, 2H), 1.77-1.65 (m, 4H), 0.53 (d, 2H), 0.43 (d, 2H)

[0260] Example 12: Preparation of 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylic acid (compound **FTS030**)

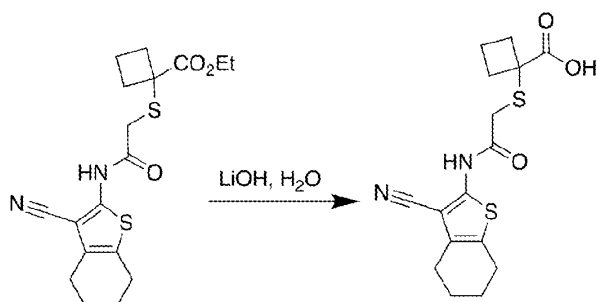
**FTS030**

[0261] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS030** via the four step synthetic method of Scheme 12 as shown below.

Scheme 12**Step 1****Step 2****Step 3**



Step 4



FTS030

[0262] Materials and methods

[0263] Step 1 - Synthesis of ethyl 1-((2-(tert-butoxy)-2-oxoethyl)thio)cyclobutanecarboxylate: To a solution of ethyl 1-bromocyclobutanecarboxylate (2.0 g, 9.66 mmol, 1.56 mL, 1.0 eq) in THF (10 mL) was added tert-butyl 2-sulfanylacacetate (1.43 g, 9.66 mmol, 1.0 eq) and KOH (541.9 mg, 9.66 mmol, 1.0 eq). The mixture was stirred at 25°C for 2h. The reaction mixture was quenched by saturated NH₄Cl (20 mL), and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated to give ethyl 1-((2-(tert-butoxy)-2-oxoethyl)thio)cyclobutanecarboxylate (2.6 g, 9.48 mmol, quant.) as an off-white liquid, which was used into the next step without further purification.

[0264] Step 2 - 2-((1-(ethoxycarbonyl)cyclobutyl)thio)acetic acid: To a solution of ethyl 1-(2-tert-butoxy-2-oxo-ethyl)sulfanyl cyclobutanecarboxylate (1.0 g, 3.64 mmol, 1.0 eq) in DCM (15 mL) was added TFA (5.9 g, 51.94 mmol, 3.85 mL, 14.2 eq). The mixture was stirred at 25°C for 16 h. The reaction mixture was concentrated to give 2-((1-(ethoxycarbonyl) cyclobutyl)thio)acetic acid (0.79 g, 4.58 mmol, quant.) as an off- white liquid, which was used into the next step without further purification.

[0265] Step 3 - Ethyl 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylate: To a solution of 2-(1-ethoxycarbonylcyclobutyl)sulfanylacetic acid (0.75 g, 3.44 mmol, 1.0 eq) in DMF (1 mL) was added DIEA (2.22 g, 17.18 mmol, 2.99 mL, 5.0 eq). After stirring at 25°C for 0.5 h, HATU (1.96 g, 5.15 mmol, 1.5 eq) and 2-amino-4,5,6,7-tetrahydrobenzothioiophene-3-carbonitrile (612.5 mg, 3.44 mmol, 1.0 eq) were added. The mixture was

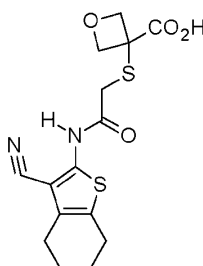
stirred at 50°C for 16 h. The reaction mixture was quenched by addition H₂O (20 mL) and extracted with DCM (20 mL). The organic layer was washed with brine (25 mL x 3), dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography on silica gel (Ethyl acetate in Petroleum ether = 0 to 10%) to give ethyl 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutene carboxylate (0.8 g, 2.11 mmol, 61.5% yield) as a yellow solid, which was used into next step directly.

[0266] LCMS analysis confirmed preparation of the desired intermediate compound. LCMS R_t = 0.475 min in 0.8 min chromatography, 5-95AB, ESI calcd. For C₁₈H₂₂N₂O₃S₂ [M+H]⁺ 379.1, found 379.1.

[0267] Step 4 - Synthesis of 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylic acid: To a solution of ethyl 1-[2-((3-cyano-4,5,6,7-tetrahydrobenzothiothiophen-2-yl)amino)-2-oxo-ethyl]sulfanyl cyclobutanecarboxylate (800.0 mg, 2.11 mmol, 1.0 eq) in a mixed solvent of MeOH (10 mL) and H₂O (2 mL) was added LiOH.H₂O (443.4 mg, 10.57 mmol, 5.0 eq). The mixture was stirred at 50°C for 2 h, filtered, concentrated and purified by prep-HPLC (column: Phenomenex luna C18 150 x 25mm x 10µm; mobile phase: [water(FA)-ACN]:B%: 40%-70%,10min) to give 1-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylic acid (63.6 mg, 181.48 µmol, 8.5% yield) as a yellow solid.

[0268] NMR, LCMS, and HPLC analyses confirmed preparation of the desired product compound. ¹H NMR (400 MHz, CDCl₃) δ = 9.98 (s, 1H), 3.56 (s, 2H), 2.80-2.70 (m, 2H), 2.65-2.54 (m, 4H), 2.32-2.14 (m, 3H), 2.04-1.92 (m, 1H), 1.87-1.77 (m, 4H). LCMS R_t = 1.548 min in 3 min chromatography, 5-95 AB, ESI calcd. For C₁₆H₁₈N₂O₃S₂Na [M+Na]⁺ 373.1, found 373.0. HPLC 97.6% purity, R_t = 3.008 min in 6.0 min chromatography, 10-80AB_6min.

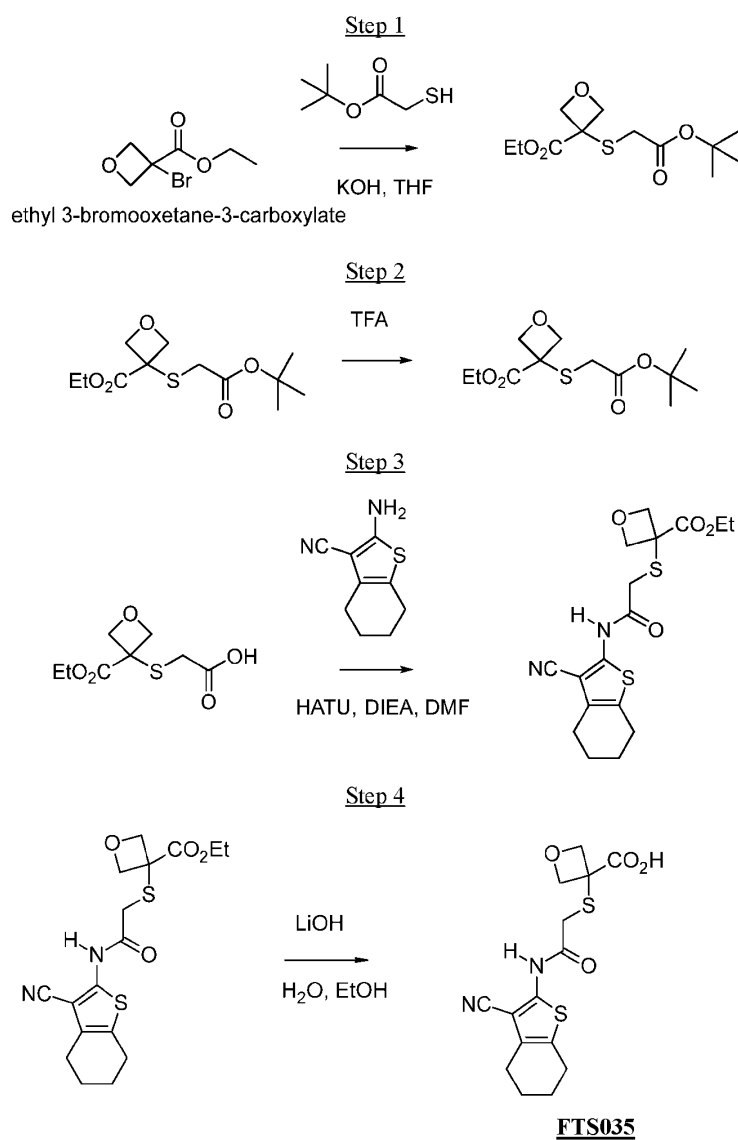
[0269] **Example 13**: Preparation of 3-((2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)oxetane-3-carboxylic acid (**FTS035**).



FTS035

[0270] This example illustrates a preparation of the FAB3/4/5/7 inhibitor compound **FTS035** via the four-step synthetic method of Scheme 13 as shown below.

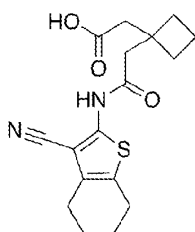
Scheme 13



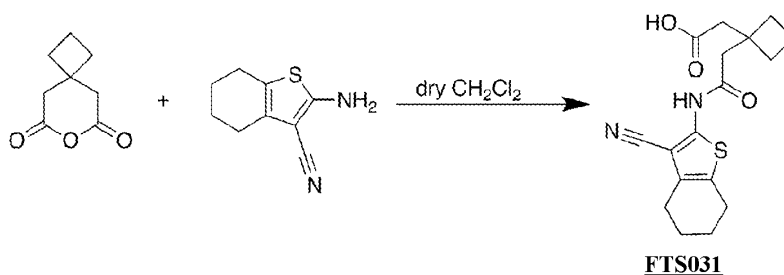
[0271] Materials and methods

[0272] The same general synthetic process described in Example 12 for the preparation of **FTS030** is used to prepare **FTS035** except the starting compound, ethyl 1-bromocyclobutanecarboxylate is substituted with the starting compound, ethyl 3-bromooxetane-3-carboxylate as shown in Scheme 13.

[0273] Example 14: Preparation of 2-(1-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-oxoethyl)cyclobutyl)acetic acid (compound **FTS031**)

**FTS031**

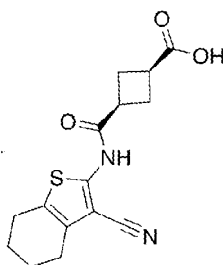
[0274] This example illustrates a preparation of the FAB3/4/5/7 inhibitor compound **FTS031** via the synthetic method of Scheme 14 as shown below.

Scheme 14**FTS031**

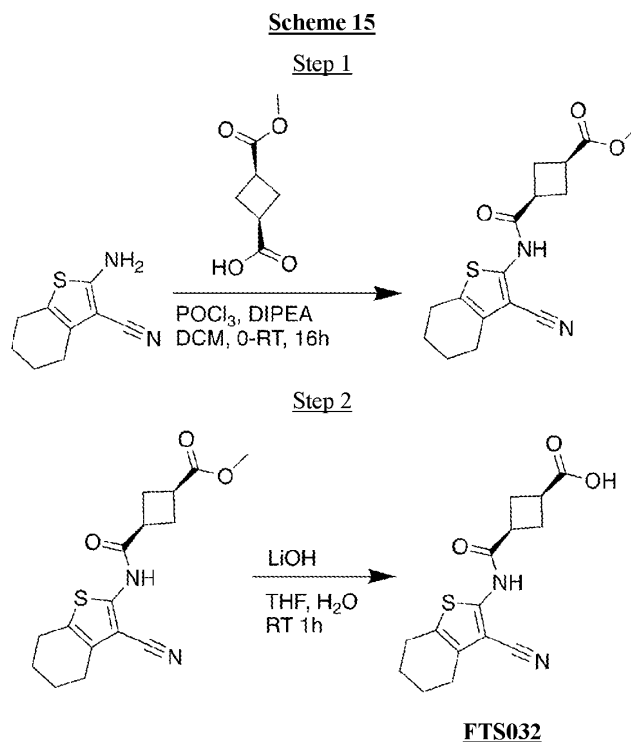
[0275] *Materials and methods*

[0276] 7-oxaspiro[3.5]nonane-6,8-dione (0.275 mmol) and 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (0.236 mmol, 0.75 eq.) are charged into a 50 mL round bottom flask. The flask is purged with argon and 10 mL dry dichloromethane is added. The mixture is allowed to stir overnight under positive pressure of argon. Solvent is removed via rotary evaporation. The crude mixture is purified via preparatory TLC in 2.5:1 hexanes:EtOAc +0.1% acetic acid to yield 2-(1-(2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)cyclobutyl)acetic acid (15 mg, 19.1%).

[0277] **Example 15:** Preparation of (1s,3s)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid (compound **FTS032**)

**FTS032**

[0278] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS032** via the two step synthetic method of Scheme 15 as shown below.



[0279] **Materials and methods**

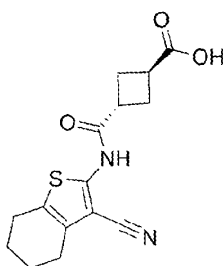
[0280] Step 1 - Synthesis of methyl (1s,3s)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate: In a 100 mL two necked dried round bottom flask under nitrogen atmosphere 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (200 mg, 1.122 mmol) was dissolved in DCM (40 mL). To this reaction mixture, (1s,3s)-3-(methoxycarbonyl)cyclobutane-1-carboxylic acid (266 mg, 1.683 mmol) and DIPEA (1.176 mL, 6.73 mmol) were added at 25 °C under nitrogen atmosphere. Then reaction mixture was cooled to 0 °C and POCl₃ (0.314 mL, 3.37 mmol) was added dropwise and stirred at 25 °C for 16 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20 % EtOAc in pet-ether, 0.3 *rf*). After completion of reaction, reaction mixture was quenched with NaHCO₃ solution (100mL). Reaction mixture was extracted with DCM (3 x 100 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) to get crude. Crude was purified by column chromatography (Isolera) by using Ethyl acetate and Pet ether as an eluting solvent system (product eluted at 18 % Ethyl acetate in pet ether) to get pure methyl (1s,3s)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate as a yellow solid.

[0281] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.46 (s, 1H), 3.61 (s, 3H), 3.39 (dd, J = 9.60, 18.00 Hz, 1H), 3.17 (t, J = 8.80 Hz, 1H), 2.68 (s, 4H), 2.36 (t, J = 8.80 Hz, 4H), 1.75 (s, 4H).

[0282] Step 2 - Synthesis of (1*s*,3*s*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid: In a 100 mL single necked dried round bottom flask under nitrogen atmosphere, methyl(1*s*,3*s*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate (150 mg, 0.471 mmol) were dissolved in THF (10 mL), and water (5 mL). To this reaction mixture Lithium hydroxide monohydrate (59.4 mg, 1.413 mmol) was added at 25 °C under nitrogen atmosphere. Reaction mixture was stirred at 25 °C for 1h under nitrogen atmosphere. Progress of reaction was monitored by TLC (10% MeOH in DCM, 0.2 *rf*). After completion of reaction, reaction mixture was concentrated over rotary evaporator under reduced pressure (bath temperature 45 °C). Reaction mixture was extracted with ethyl acetate (30 mL). Then acidify the Aqueous layer by using Citric acid (PH=5-6). Reaction mixture was extracted with 10% MeOH in DCM (3x50 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) and lyophilized to get pure (1*s*,3*s*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid as a white solid.

[0283] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.11(s, 1H), 11.50 (s, 1H), 3.52 (t, J = 7.60 Hz, 1H), 3.05-3.01 (m, 1H), 2.68 (t, J = 1.60 Hz, 2H), 2.51 (t, J = 1.60 Hz, 2H), 2.42-2.34 (m, 4H), 1.75 (s, 4H).

[0284] **Example 16:** Preparation of (1*r*,3*r*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid (compound **FTS033**)

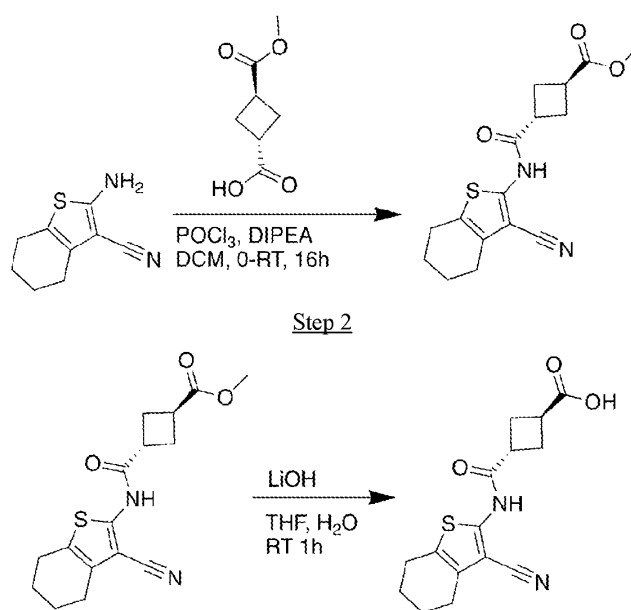


FTS033

[0285] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS033** via the two-step synthetic method of Scheme 16 as shown below.

Scheme 16

Step 1

**FTS033****[0286] Materials and methods**

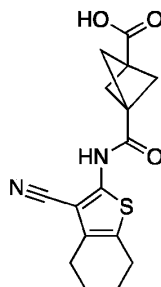
[0287] Step 1 - Synthesis of methyl (1r,3r)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate: In a 100 mL two necked dried round bottom flask under nitrogen 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (400 mg, 2.244 mmol) was dissolved in DCM (15 mL). To this reaction mixture, (1r,3r)-3-(methoxycarbonyl)cyclobutane-1-carboxylic acid (426 mg, 2.69 mmol) and DIPEA (2.352 mL, 13.46 mmol) were added at 25 °C under nitrogen atmosphere. Then reaction mixture was cooled to 0 °C and POCl₃ (0.629 mL, 6.73 mmol) was added dropwise and stirred at 25 °C for 16 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20 % EtOAc in pet ether, 0.6 *rf*). After completion of reaction, reaction mixture was quenched with NaHCO₃ solution (100 mL). Reaction mixture was extracted with DCM (3 x 100 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (bath temperature 45 °C) to get crude product. Crude product was purified by column chromatography (Isolera) by using ethyl acetate and pet ether as an eluting solvent system (product eluted at 15 % Ethyl acetate in pet ether) to get pure methyl (1r,3r)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate as a yellow solid.

[0288] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ= 11.50 (s, 1H), 4.09-4.03 (m, 1H), 3.76 (dt, *J* = 4.80, Hz, 1H), 3.74 (s, 3H), 3.73 (t, *J* = 4.80 Hz, 1H), 3.16-3.13 (m, 1H), 2.68 (t, *J* = 2.00 Hz, 2H), 2.51-2.43 (m, 4H), 1.75 (s, 4H).

[0289] Step 2 - Synthesis of (1*r*,3*r*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid: In a 50 mL single necked dried round bottom flask under nitrogen atmosphere, methyl(1*r*,3*r*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate (48 mg, 0.151 mmol) was dissolved in THF (2 mL) and water (1 mL). To this reaction mixture LiOH monohydrate (19 mg, 0.452 mmol) was added at 25 °C under nitrogen atmosphere. Reaction mixture was stirred at 25 °C for 1h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20% EtOAc in pet ether, 0.1 *r**f*). After completion of reaction, reaction mixture was concentrated over rotary evaporator under reduced pressure (bath temperature 45 °C). Reaction mixture was extracted with ethyl acetate (30 mL). Then acidify the combined aqueous layers with citric acid (2gm, PH=1-2). Reaction mixture was extracted with 10% MeOH in DCM (3x30 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (bath temperature 45 °C) and lyophilized to get pure (1*r*,3*r*)-3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)cyclo-butane-1-carboxylic acid as a white solid.

[0290] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ= 12.21 (s, 1H), 11.53 (s, 1H), 3.52 (t, J = 7.60 Hz, 1H), 3.05-3.01 (m, 1H), 2.68 (t, J = 1.60 Hz, 2H), 2.51 (t, J = 1.60 Hz, 2H), 2.42-2.34 (m, 4H), 1.75 (s, 4H).

[0291] **Example 17:** Preparation of 3-((3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid (compound **FTS034**)

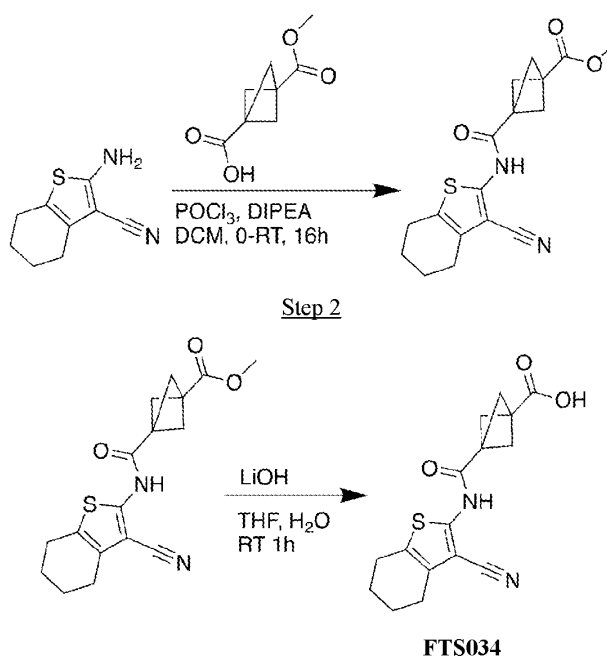


FTS034

[0292] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS034** via the two-step synthetic method of Scheme 17 as shown below.

Scheme 17

Step 1



[0293] Materials and methods

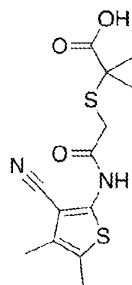
[0294] Step 1 - Synthesis of methyl 3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate: In a 100 mL two necked dried round bottom flask under nitrogen 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile (200 mg, 1.122 mmol) was dissolved in CH₂Cl₂ (10 mL). To this reaction mixture, 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (229 mg, 1.346 mmol) and DIPEA (1.176 mL, 6.73 mmol) were added at 25 °C under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and POCl₃ (0.315 mL, 3.37 mmol) was added dropwise and stirred at 25 °C for 16 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20 % EtOAc in pet-ether, 0.6 *rf*). After completion of reaction, reaction mixture was quenched with NaHCO₃ solution (100 mL). Reaction mixture was extracted with 10% MeOH in DCM (3 x 50 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (bath temperature 45 °C) to get crude product. Crude product was purified by column chromatography (Isolera) by using Ethyl acetate and Pet ether as an eluting solvent system (product eluted at 10 % Ethyl acetate in pet ether) to get pure methyl 3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl) bicyclo[1.1.1]pentane-1-carboxylate as a white solid.

[0295] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ= 11.30 (s, 1H), 3.74 (s, 3H), 2.76 (s, 2H), 2.68 (s, 2H), 2.40 (s, 2H), 2.35 (d, J = 6.40 Hz, 2H), 2.25 (s, 2H), 1.78 (d, J = 14.40 Hz, 4H).

[0296] Step 2 - Synthesis of 3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid: In a 25 mL single necked dried round bottom flask under nitrogen atmosphere, methyl 3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (100 mg, 0.303 mmol) were dissolved in THF (3.00 mL), water (3 mL), and MeOH (1 mL). To this reaction mixture, LiOH (21.74 mg, 0.908 mmol) was added at 25 °C under nitrogen atmosphere. Reaction mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (10% MeOH in DCM 0.4 *r_f*). After completion of reaction, reaction mixture was concentrated over rotary evaporator under reduced pressure (bath temperature 45 °C). Reaction mixture was washed with ethyl acetate (10 mL), Aqueous layer was acidified by using 1.5N HCl solution (PH=1-2) and extracted with 10% MeOH in DCM (3*20 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) and lyophilized to get pure 3-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid as a white solid.

[0297] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ= 12.43 (bs, 1H), 11.27 (bs, 1H), 2.6 (dd, J = 5.60, 12.80 Hz, 4H), 2.29 (s, 6H), 1.75 (t, J = 2.40 Hz, 4H).

[0298] **Example 18:** Preparation of 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylic acid (compound **FTS036**)

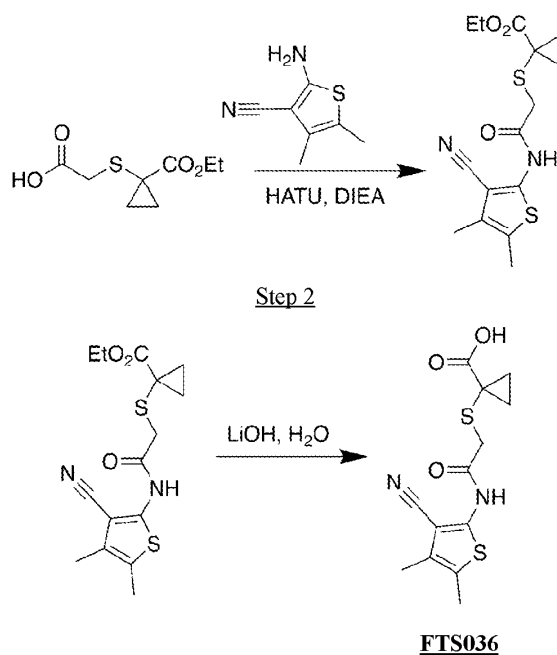


FTS036

[0299] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS036** via the two-step synthetic method of Scheme 18 as shown below.

Scheme 18

Step 1



[0300] Materials and methods

[0301] Step 1 - Synthesis of ethyl 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylate: To a solution of 2-(1-ethoxycarbonylcyclopropyl)sulfanylacetic acid (1.0 g, 4.93 mmol, 5.0 eq) in DMF (2 mL) was added DIEA (891.5 mg, 6.90 mmol, 1.20 mL, 7.0 eq). After stirring at 25°C for 10 min, HATU (562.0 mg, 1.48 mmol, 1.5 eq), 2-amino-4,5-dimethylthiophene-3-carbonitrile (150 mg, 985.44 µmol, 1.0 eq) were added. The mixture was stirred at 50°C for 16 h. The reaction mixture was quenched by addition H₂O (20 mL) and extracted with DCM (20 mL). The organic layer was washed with brine (25 mL x 3), dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography on silica gel (Ethyl acetate in Petroleum ether = 0 to 10%) to give Ethyl 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylate (290.0 mg, 103.68 µmol, 10.5% yield) as a yellow solid, which was used into the next step directly.

[0302] LCMS analysis confirmed preparation of the desired intermediate compound. LCMS R_t = 0.438 min in 0.8 min chromatography, 5-95AB, ESI calcd. For C₁₅H₁₈N₂O₃S₂Na [M+Na]⁺ 361.1, found 361.0.

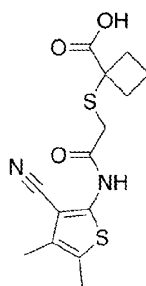
[0303] Step 2-Synthesis of 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclopropanecarboxylic acid (FTS036): To a solution of ethyl 1-[[2-[(3-cyano-4,5-dimethyl-2-thienyl)amino]-2-oxo-ethyl]sulfanyl]cyclopropanecarboxylate (290 mg, 856.86 µmol, 1.0 eq) in a mixed solvent of MeOH (5 mL) and H₂O (1 mL) was added LiOH.H₂O (179.8 mg, 4.28 mmol, 5.0 eq). The mixture was stirred at 25°C for 16 h, filtered, concentrated and purified by prep-

HPLC (column: Phenomenex luna C18 150x25mmx10um; mobile phase: [water(FA)-ACN];B%: 40%-70%,10min) to give desired compound (14.4 mg, 46.39 μmol , 5.4% yield) as a yellow solid.

[0304] NMR, LCMS, and HPLC analyses confirmed preparation of the desired product compound.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 3.70-3.62 (s, 2H), 2.23 (s, 3H), 2.10 (s, 3H), 1.48-1.42 (m, 2H), 1.19-1.11 (m, 2H). LCMS R_t = 1.300 min in 3 min chromatography, 5-95 AB, ESI calcd. For $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3\text{S}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 333.0, found 332.9. HPLC 98.8% purity, R_t = 2.568 min in 6.0 min chromatography, 10-80AB_6min.

[0305] **Example 19:** Preparation of 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylic acid (compound **FTS037**)

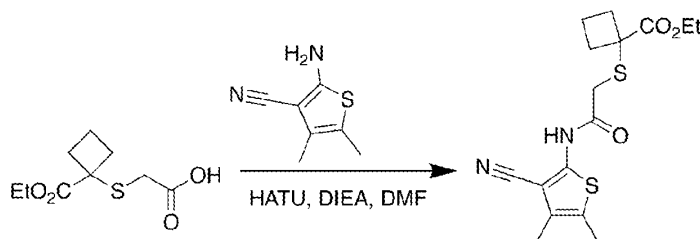


FTS037

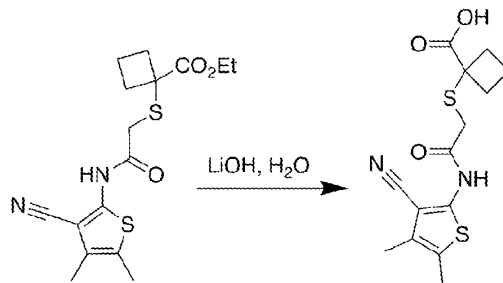
[0306] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS037** via the two-step synthetic method of Scheme 19 as shown below.

Scheme 19

Step 1



Step 2



FTS037**[0307] Materials and methods**

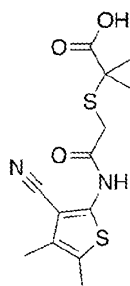
[0308] Step 1 - Synthesis of ethyl 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylate: To a solution of 2-(1-ethoxycarbonylcyclobutyl)sulfanylacetic acid (358.4 mg, 1.64 mmol, 5.0 eq) in DMF (1 mL) was added DIEA (212.26 mg, 1.64 mmol, 286.07 μ L, 5.0 eq), HATU (187.35 mg, 492.72 μ mol, 1.5 eq) and 2-amino-4,5-dimethyl-thiophene-3-carbonitrile (50.0 mg, 328.4 μ mol, 1.0 eq). The mixture was stirred at 50°C for 16 h. The reaction mixture was quenched by addition H₂O (20 mL) and extracted with DCM (20 mL). The organic layer was washed with brine (25 mL x 3), dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography on silica gel (Ethyl acetate in Petroleum ether = 0 to 16%) to give ethyl 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylate (70.0 mg, 198.6 μ mol, 60.4% yield) as a yellow solid, which was used into the next step directly.

[0309] LCMS analysis confirmed preparation of the desired intermediate compound. LCMS R_t = 0.445 min in 0.8 min chromatography, 5-95AB, ESI calcd. For C₁₆H₂₁N₂O₃S₂ [M+H]⁺ 353.1, found 352.9.

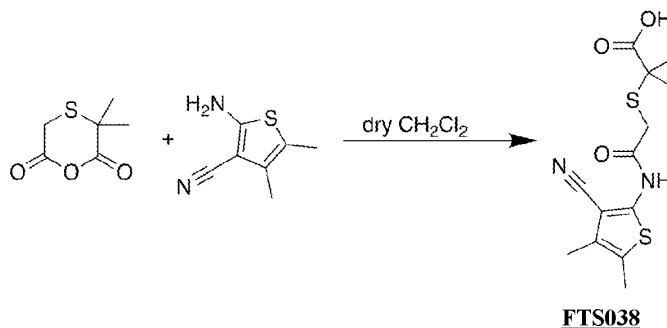
[0310] Step 2-Synthesis of 1-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)cyclobutanecarboxylic acid (FTS037): To a solution of ethyl 1-[2-[(3-cyano-4,5-dimethyl-2-thienyl)amino]-2-oxo-ethyl]sulfanylcyclobutanecarboxylate (70.0 mg, 198.6 μ mol, 1.0 eq) in a mixed solvent of MeOH (1 mL) and H₂O (0.2 mL) was added LiOH.H₂O (41.6 mg, 992.9 μ mol, 5.0 eq). The mixture was stirred at 50°C for 2 hr, filtered, concentrated and purified by prep-HPLC (column: Phenomenex luna C18 150x25mmx10 μ m; mobile phase: [water(FA)-ACN]; B%: 28%-58%, 10min) to give desired compound (25.3 mg, 77.99 μ mol, 39.2% yield) as a yellow solid.

[0311] NMR, LCMS, and HPLC analyses confirmed preparation of the desired product compound. ¹H NMR (400 MHz, CDCl₃) δ = 9.95 (s, 1H), 3.55 (s, 2H), 2.79-2.72 (m, 2H), 2.81-2.71 (m, 1H), 2.33-2.27 (m, 1H), 2.26 (s, 3H), 2.22 (m, 1H), 2.20-2.17 (m, 1H), 2.16 (s, 3H), 2.02-1.95 (m, 1H). LCMS R_t = 1.406 min in 3 min chromatography, 5-95 AB, ESI calcd. For C₁₄H₁₆N₂O₃S₂Na [M+Na]⁺ 347.1, found 347.0. HPLC 99.4% purity, R_t = 2.640 min in 6.0 min chromatography, 10-80AB_6min.

[0312] Example 20: Preparation of 2-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS038**)

**FTS038**

[0313] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS038** via the synthetic method of Scheme 20 as shown below.

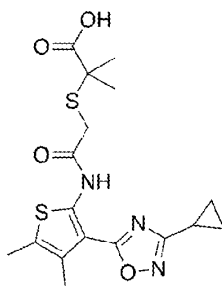
Scheme 20**FTS038**

[0314] *Materials and methods*

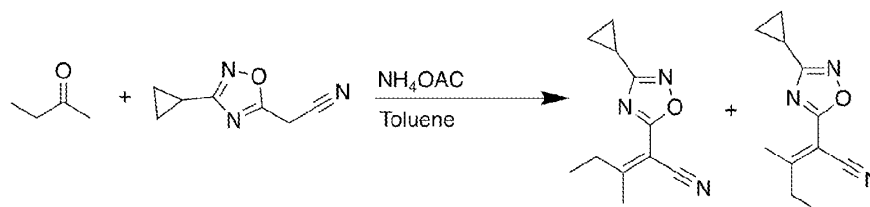
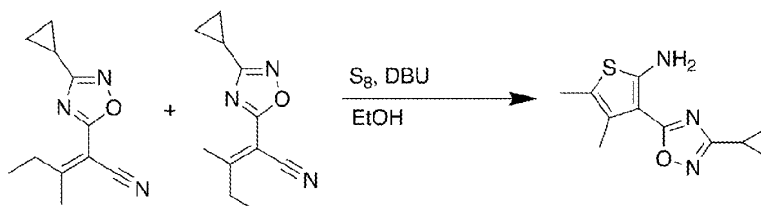
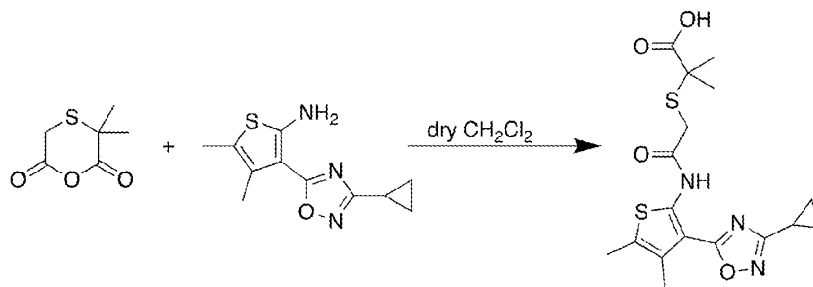
[0315] 3,3-dimethyl-1,4-oxathiane-2,6-dione (0.281 mmol) and 2-amino-4,5-dimethylthiophene-3-carbonitrile (0.213 mmol, 0.75 eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 15mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. The crude mixture is purified by dissolving impurities in ethyl acetate and acetone. The resultant white powder is filtered and washed with more ethyl acetate to yield 2-((2-((3-cyano-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a light yellow powder.

[0316] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (500MHz), DMSO-d₆ δ: 12.65 (s, 1H), 11.66 (s, 1H), 4.15, 3.69 (s, 2H), 2.25 (s, 3H), 2.10 (s, 3H), 1.42 (s, 6H)

[0317] **Example 21:** Preparation of 2-((2-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS039**)

**FTS039**

[0318] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS039** via the three-step synthetic method of Scheme 21 as shown below.

Scheme 21Step 1Step 2Step 3**FTS039****[0319] Materials and methods**

[0320] Step 1: 2-butanone (0.680 mmol), 2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)acetonitrile (1.36 mmol, 2 eq.) and ammonium acetate (1.36 mmol, 2 eq.) were charged into a 100mL 2-neck round

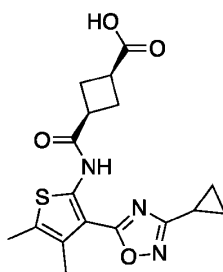
bottom flask. The flask was purged with argon and 10mL dry toluene is added. The reaction mixture is heated to reflux for 18h. The reaction is cooled and poured onto 30mL 10% aq. NaHCO_3 and 30mL EtOAc. The aqueous layer is separated and extracted once more with 30mL EtOAc. The organic layers are combined, washed with brine and dried over anhydrous sodium sulfate. Excess solvent is removed via rotary evaporation. The crude mixture is purified via silica column in 90% hexanes in ethyl acetate to yield a mixture of (Z)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3-methylpent-2-enitrile and (E)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3-methylpent-2-enitrile.

[0321] **Step 2:** A mixture of (Z)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3-methylpent-2-enitrile and (E)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-3-methylpent-2-enitrile (1.12 mmol), DBU (2.8 mmol, 2.5eq.) and elemental sulfur (1.12 mmol, 1eq.) were charged into a 100mL 2-neck round bottom flask. The flask was purged with argon and 20mL dry EtOH. The reaction mixture was heated to 65°C under reflux for 2 hours. The reaction mixture is cooled, then poured onto 30mL 10% aq. NaHCO_3 and 30mL EtOAc. The aqueous layer is separated and extracted once more with 30mL EtOAc. The organic layers are combined, washed with brine and dried over anhydrous sodium sulfate. Excess solvent is removed via rotary evaporation. The crude mixture is purified via silica column in 90% hexanes in ethyl acetate to yield 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine as a pale yellow powder (42mg, 15.9%).

[0322] **Step 3:** 3,3-dimethyl-1,4-oxathiane-2,6-dione (0.227 mmol) and 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine (0.170, 0.75 eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 15mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. The crude mixture was purified via preparatory TLC in 2.5 hexanes in ethyl acetate + 0.1% acetic acid to recover 2-((2-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a light yellow powder (5 mg, 7.4%).

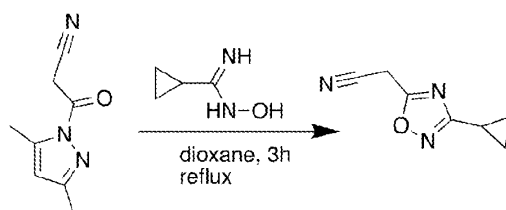
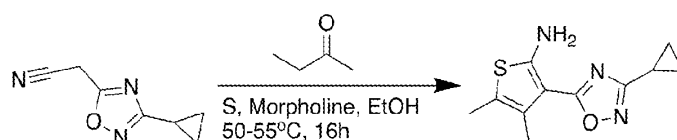
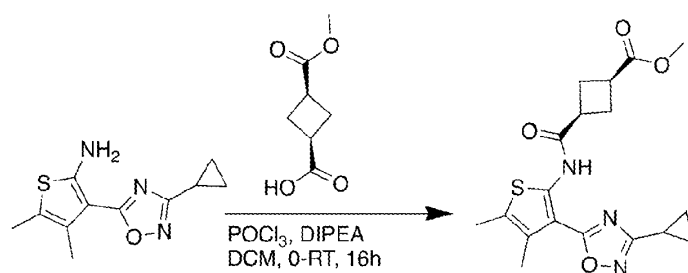
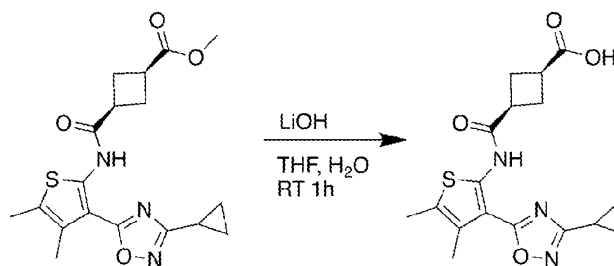
[0323] NMR analysis confirmed preparation of the desired product compound. ^1H NMR (500 MHz, DMSO-d_6) δ = 12.67 (bs), 3.64 (s, 2H), 1.83 (m, 3H), 1.73 (m, 3H), 1.52 (m, 1H), 1.24 (m, 2H), 0.83 (m, 2H)

[0324] **Example 22:** Preparation of (1s,3s)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid (compound FTS040)



FTS040

[0325] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS040** via the four-step synthetic method of Scheme 22 as shown below.

Scheme 22Step 1Step 2Step 3Step 4**FTS040****[0326] Materials and methods**

[0327] Step 1- Synthesis of 2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)acetonitrile: To a stirred solution of 3-(3,5-dimethyl-1H-pyrazol-1-yl)-3-oxopropanenitrile (0.5 g, 3.06 mmol) in Dioxane (25 mL) and N-hydroxy cyclopropane carboximidamide (0.368 g, 3.68 mmol) was added in a single necked dried

round bottom flask under nitrogen atmosphere and heated to 105 °C for 3h. Progress of the reaction was monitored by TLC. (10%EtOAc in pet ether, 0.5 *rf*). On completion of the reaction, RM was concentrated on rotary vaporator under reduced pressure to get crude 2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl) acetonitrile as an orange liquid. TLC (10% EtOAc in Pet-ether) R_f = 0.5. LCMS Method C, 1.44 min 19.12% found [M-H] 148.1.

[0328] Step 2- Synthesis of 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine:

To a stirred solution of 2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)acetonitrile (1 g crude) in Ethanol (30 mL) and butan-2-one (0.218 g, 3.06 mmol), sulfur (0.097 g, 3.06 mmol) was added in a single necked dried round bottom flask under nitrogen atmosphere and heated to 50 °C and morpholine (0.263 mL, 3.06 mmol) was added at 50 °C and stirred at 50 °C for 16h. Progress of the reaction was monitored by TLC. (10%EtOAc in pet ether, 0.7 *rf*). On completion of the reaction, RM was concentrated on rotavapour under reduced pressure and the obtained residue was diluted with water (80 mL) and extracted with Ethyl acetate (2 X 50mL). Organic layer washed with Brine solution and dried over sodium sulfate and concentrated to get crude compound. Crude product was purified by column chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 10 % EtOAc in Pet ether) to get 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine as an off-white solid.

[0329] NMR analysis confirmed preparation of the desired intermediate compound. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 7.41 (s, 2H), 2.19 (s, 3H), 2.14-2.09 (m, 4H), 2.14-2.09 (m, 4H).

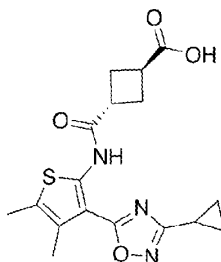
[0330] Step 3- Synthesis of methyl (1s,3s)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate: To a stirred solution of 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine (200 mg, 0.850 mmol) was dissolved in DCM (40 mL, (1s,3s)-3-(methoxycarbonyl)cyclobutane-1-carboxylic acid (202 mg, 1.275 mmol) and DIPEA (0.891 mL, 5.10 mmol) were added in two necked dried round bottom flask under nitrogen at 25 °C. Reaction mixture was cooled to 0 °C and POCl₃ (0.238 mL, 2.55 mmol) was added dropwise at 0 °C and stirred at 25 °C for 16 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20 % EtOAc in pet ether, 0.5 *rf*). After completion of reaction, reaction mixture was quenched with NaHCO₃ solution (100 mL). Reaction mixture was extracted with DCM (3 x 100 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) to get crude product. Crude product was purified by column chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 10 % EtOAc in Pet ether) to get pure methyl (1s,3s)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate as a Brown solid.

[0331] NMR analysis confirmed preparation of the desired intermediate compound. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 11.12 (s, 1H), 3.62 (s, 3H), 3.42-3.35 (m, 1H), 3.28-3.21 (m, 1H), 2.51 (s, 5H), 2.37-2.27 (m, 5H), 2.26-2.22 (m, 1H), 1.22-1.16 (m, 2H), 1.13-1.04 (m, 2H).

[0332] Step 4- Synthesis of (1*s*,3*s*)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid: To a stirred solution of methyl (1*s*,3*s*)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate (0.120 g, 0.320 mmol) was dissolved in THF (6 mL), water (5 mL) and lithium hydroxide monohydrate (0.040 g, 0.959 mmol) was added in single necked dried round bottom flask and stirred at RT for 1hr. Progress of the reaction was monitored by TLC. TLC complies. On completion of the reaction, Rm was diluted with water (5 mL) and extracted with ethyl acetate (15 mL) and Aqueous layer was acidified with citric acid and extracted with 10% MeOH/DCM. Organic layer dried over sodium sulfate and concentrated on rotavapour under reduced pressure to obtain pure (1*s*,3*s*)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid (0.080 g, 0.221 mmol, 69.1 % yield) as a white solid.

[0333] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.24 (s, 1H), 11.13 (s, 1H), 3.37 (s, 1H), 3.35-3.10 (m, 1H), 2.51-2.47 (m, 4H), 2.46-2.41 (m, 6H), 2.21 (s, 1H), 1.17-1.14 (m, 2H), 1.06-1.03 (m, 2H).

[0334] **Example 23:** Preparation of (1*r*,3*r*)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid (compound **FTS041**)

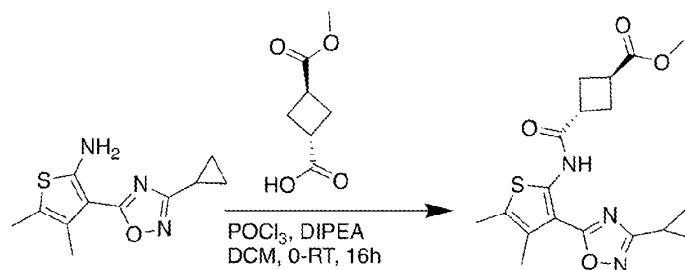


FTS041

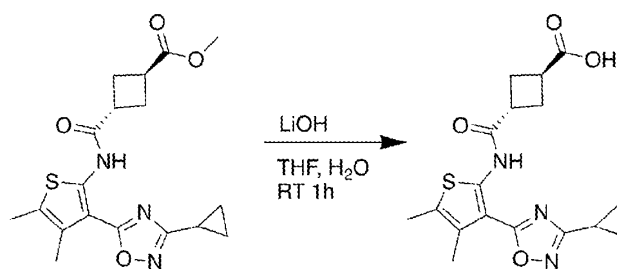
[0335] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS041** via the two-step synthetic method of Scheme 23 as shown below.

Scheme 23

Step 1



Step 2

**FTS041****[0336] Materials and methods**

[0337] Step 1 - Synthesis of methyl (1r,3r)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate: In a 50 mL two necked dried round bottom flask under nitrogen 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine (0.170 g, 0.722 mmol) was dissolved in DCM (10 mL). To this reaction mixture, (1r,3r)-3-(methoxycarbonyl) cyclobutane-1-carboxylic acid (0.137 g, 0.867 mmol) and DIPEA (0.560 g, 4.33 mmol) were added at 25 °C under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and POCl₃ (0.332 g, 2.167 mmol) was added dropwise and stirred at 25 °C for 16 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20 % EtOAc in pet ether, 0.6 *rf*). After completion of reaction, reaction mixture was quenched with NaHCO₃ solution (50 mL). Reaction mixture was extracted with DCM (3 x 50 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) to get crude product. Crude product was purified by column chromatography (Isolera) by using Ethyl acetate and Pet ether as an eluting solvent system (product eluted at 15 % Ethyl acetate in pet ether) to get pure methyl (1r,3r)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate (0.060 g, 0.160 mmol, 22.12 % yield).

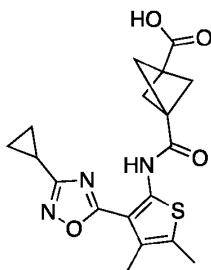
[0338] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.13 (s, 1H), 3.66 (s, 3H), 3.40-3.50 (m, 1H), 3.12-3.25 (m, 1H), 2.52-2.50 (m, 4H), 2.30-2.29 (m, 7H), 1.16-1.14 (m, 2H), 1.05-1.03 (m, 2H).

[0339] Step 2 - Synthesis of (1r,3r)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid: In a 25 mL single necked dried round bottom flask under nitrogen atmosphere methyl (1r,3r)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylate (0.050 g, 0.133 mmol) was dissolved in THF (3 mL), water (2 mL) and lithium hydroxide (9.57 mg, 0.400 mmol) was added and stirred at RT for 1 hr. Progress of the reaction was monitored by TLC (5% MeOH in DCM). On completion of the reaction, Rm was diluted with water (5 mL) and extracted with ethyl acetate (15 mL) and Aqueous layer was acidified with citric acid and extracted with 10% MeOH/DCM. Organic layer dried over sodium sulfate and concentrated on rotavapor under reduced pressure to obtain pure

(1r,3r)-3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)cyclobutane-1-carboxylic acid as a white solid.

[0340] NMR analysis confirmed preparation of the desired product compound. ^1H NMR (400 MHz, DMSO- d_6) δ = 11.06 (s, 1H), 3.44-3.40 (m, 1H), 3.08 (s, 1H), 2.49 (s, 4H), 2.34-2.33 (m, 6H), 2.30-2.22 (m, 1H), 1.17-1.15 (m, 2H), 1.05-1.03 (m, 2H).

[0341] **Example 24:** Preparation of 3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)-bicyclo[1.1.1]pentane-1-carboxylic acid (compound **FTS042**)

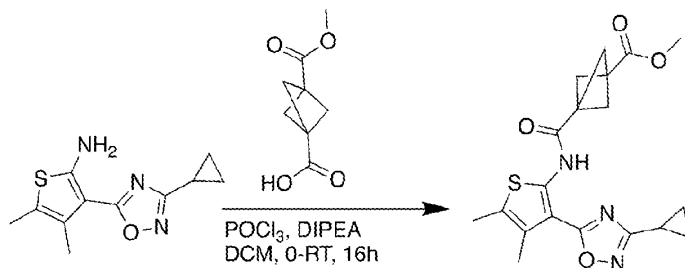


FTS042

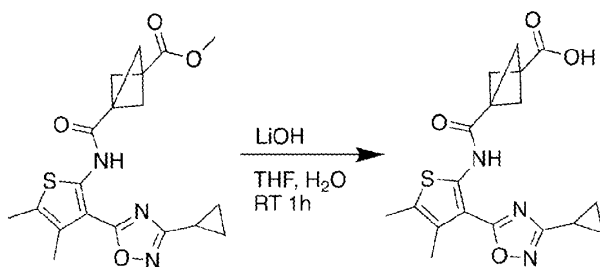
[0342] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS042** via the synthetic method of Scheme 24 as shown below.

Scheme 24

Step 1



Step 2



FTS042

[0343] Materials and methods

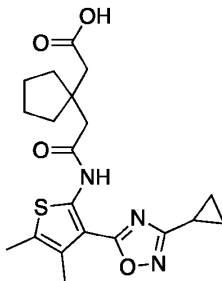
[0344] Step 1 - Synthesis of methyl 3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate: In a 100 mL two necked dried round bottom flask under nitrogen 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine (500 mg, 2.125 mmol) was dissolved in DCM (15 mL). To this reaction mixture, 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (542 mg, 3.19 mmol) and DIPEA (1.856 mL, 10.62 mmol) were added at 25 °C under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and POCl₃ (0.596 mL, 6.37 mmol) was added dropwise and stirred at 25 °C for 16 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20 % EtOAc in pet-ether, 0.4 rf). **[0345]** After completion of reaction, reaction mixture was quenched with NaHCO₃ solution (250 mL). Reaction mixture was extracted with DCM (3 x 200 mL). Combined organic layers were dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) to get crude product. Crude product was purified by column chromatography (Isolera) by using EtOAc and Pet-ether as an eluting solvent system (product eluted at 15 % EtOAc in Pet-ether) to get pure methyl 3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate as pale yellow solid.

[0346] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.29 (s, 1H), 3.67 (s, 3H), 2.46 (s, 6H), 2.30 (s, 6H), 2.28 (t, J = Hz, 1H), 1.14 (d, J = 8.00 Hz, 2H), 1.12 (d, J = 6.00 Hz, 2H).

[0347] Step 2 - Synthesis of 3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid: In a 50 mL single necked dried round bottom flask under nitrogen atmosphere, methyl 3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (250 mg, 0.645 mmol) were dissolved in water (5 mL), THF (5 mL), and MeOH (1 mL). To this reaction mixture Lithium hydroxide monohydrate (81 mg, 1.936 mmol) was added at 25 °C under nitrogen atmosphere. Reaction mixture was stirred at 25 °C for 1 h under nitrogen atmosphere. Progress of reaction was monitored by TLC (20% EtOAc in petether, 0.2 rf). After completion of reaction, reaction mixture was concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C). Reaction mixture was washed with ethyl acetate (10 mL). Then acidify the Aqueous layer by using Citric acid (PH=5-6). Reaction mixture was extracted with 10% MeOH in DCM (3x20 mL). Combined organic layers were dried over sodium sulphate, concentrated over rotary evaporator under reduced pressure (Bath Temperature 45 °C) and lyophilised to get pure 3-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)carbamoyl)-bicyclo[1.1.1]pentane-1-carboxylic acid as a white solid.

[0348] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.73 (s, 1H), 11.30 (s, 1H), 2.35 (s, 3H), 2.22 (s, 1H), 2.13 (s, 6H), 1.93 (s, 3H), 1.21-1.17 (m, 2H), 1.10-1.06 (m, 2H).

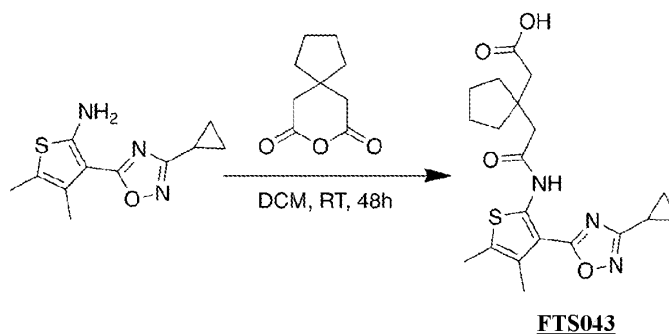
[0349] **Example 25:** Preparation of 2-(1-(2-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)cyclopentyl)acetic acid (compound **FTS043**)



FTS043

[0350] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS043** via the synthetic method of Scheme 25 as shown below.

Scheme 25



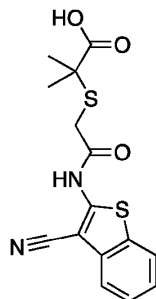
FTS043

[0351] **Materials and methods**

[0352] To a stirred solution of 3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-amine (0.100 g, 0.425 mmol) was dissolved in DCM (10 mL) and 8-oxaspiro[4.5]decane-7,9-dione (0.086 g, 0.510 mmol) was added in single necked dried round bottom flask under nitrogen atmosphere and stirred at RT for 48h. Progress of the reaction was monitored by TLC (20% EtOAc in hexane, 0.3 rf). TLC shows completion of the reaction. Reaction mixture was concentrated under reduced pressure to get crude compound. Crude product was purified by column chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 15 % EtOAc in Pet ether) product peaks were pooled together and concentrated to get pure 2-(1-(2-((3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,5-dimethylthiophen-2-yl)amino)-2-oxoethyl)cyclopentyl)acetic acid as a white solid.

[0353] NMR analysis confirmed preparation of the desired product compound. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.05 (s, 1H), 11.16 (s, 1H), 2.69 (s, 2H), 2.38 (s, 2H), 2.29 (d, *J* = 7.20 Hz, 6H), 2.26-2.21 (m, 1H), 1.67-1.58 (m, 8H), 1.15-1.12 (m, 4H).

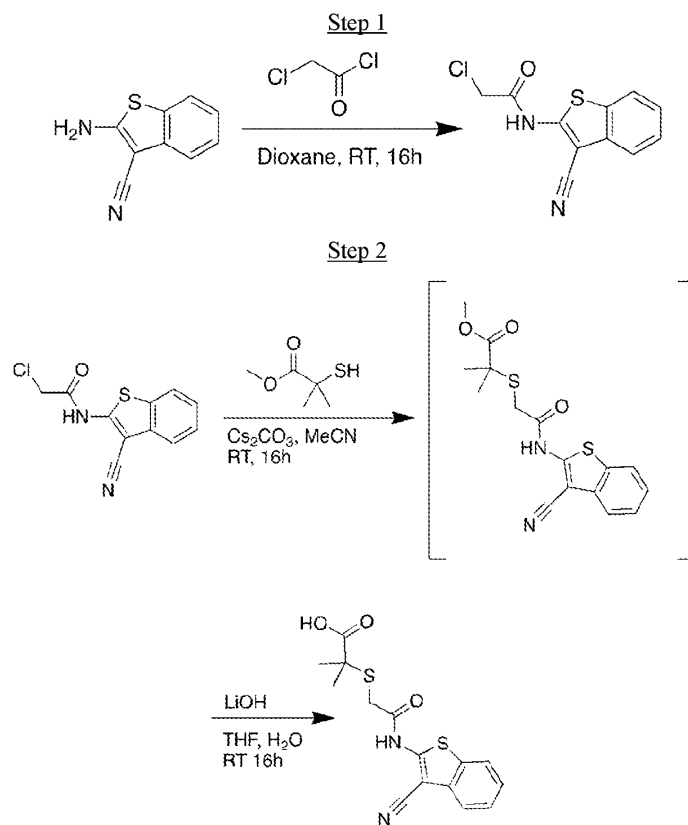
[0354] **Example 26:** Preparation of 2-((2-((3-cyanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS044**)



FTS044

[0355] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS044** via the two-step synthetic method of Scheme 26 as shown below.

Scheme 26



FTS044

[0356] *Materials and methods*

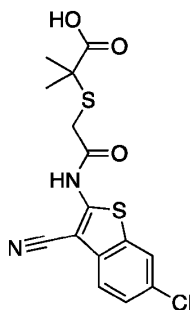
[0357] Step 1 -Synthesis of 2-chloro-N-(3-cyanobenzo[b]thiophen-2-yl)acetamide: In a single necked dried round bottom flask under nitrogen atmosphere, 2-aminobenzo[b]thio-phene-3-carbonitrile (0.200 g, 1.148 mmol) was dissolved in dioxane (10 mL) and 2-chloroacetyl chloride (0.130 g, 1.148 mmol) was added at RT and stirred for 16h at same temperature. Completion of the reaction was monitored by TLC. To the reaction mixture, hexane(10 mL) was added and stirred for 10 mins. Solid was observed in the reaction mixture and the solid was filtered through Buchner funnel and washed with hexane. The solid dried under reduced pressure to obtain pure 2-chloro-N-(3-cyanobenzo[b]thiophen-2-yl)acetamide as an off-white solid.

[0358] NMR analysis confirmed preparation of the desired intermediate compound. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.43 (s, 1H), 8.04 (d, *J* = 8.00 Hz, 1H), 7.71 (d, *J* = 8.00 Hz, 1H), 7.56-7.51 (m, 1H), 7.45-7.41 (m, 1H), 4.58 (s, 2H).

[0359] Step 2 -Synthesis of 2-((2-((3-cyanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid: To a stirred solution of 2-chloro-N-(3-cyanobenzo[b]thiophen-2-yl)acetamide (0.220 g, 0.878 mmol), in a 50 mL single necked dried round bottom flask under nitrogen atmosphere, methyl 2-mercapto-2-methylpropanoate (0.141 g, 1.053 mmol) and cesium carbonate (0.572 g, 1.755 mmol) were added and stirred at RT for 16h. Completion of the reaction was monitored by TLC(20% EtOAc in Pet-ether). Then, to this reaction mixture THF (5 mL), water (5.00 mL) and lithium hydroxide (0.017 g, 0.717 mmol) were added and stirred at RT for 16 hr. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with water (5 mL) and washed with ethyl acetate (15 mL) and Aqueous layer was acidified with citric acid (pH~4) and extracted with 10% MeOH/DCM. Organic layer dried over sodium sulfate and concentrated on rotary vaporator under reduced pressure to obtain pure 2-((2-((3-cyanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as an Off-white solid.

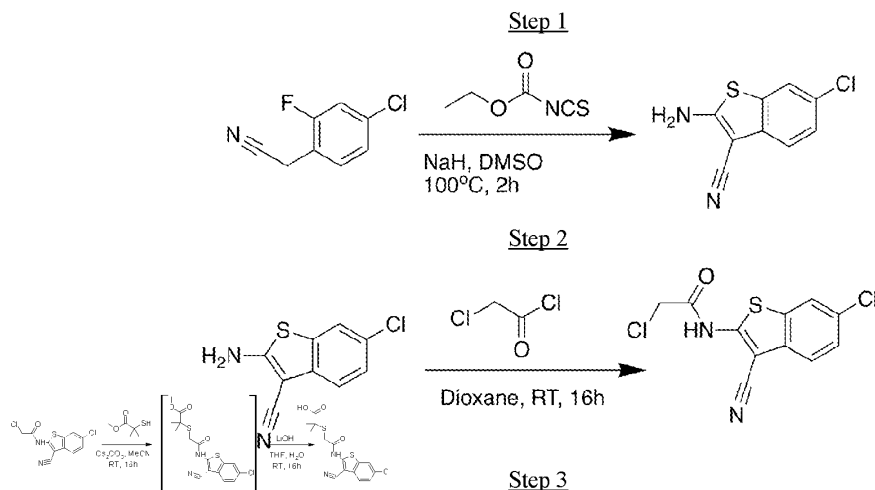
[0360] NMR analysis confirmed preparation of the desired product compound. ^1H NMR (400 MHz, DMSO-*d*₆) δ = 12.69 (s, 1H), 12.20 (s, 1H), 8.00 (d, *J* = 8.00 Hz, 1H), 7.69 (d, *J* = 8.00 Hz, 1H), 7.52 (t, *J* = 7.20 Hz, 1H), 7.41 (t, *J* = 7.20 Hz, 1H), 3.83 (s, 2H), 1.46 (s, 6H).

[0361] **Example 27:** Preparation of 2-((2-((6-chloro-3-cyanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS045**)



FTS045

[0362] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS045** via the three-step synthetic method of Scheme 27 as shown below.

Scheme 27**FTS045****[0363] Materials and methods**

[0364] Step 1-Synthesis of 2-amino-6-chlorobenzo[b]thiophene-3-carbonitrile: To a solution of 2-(4-chloro-2-fluorophenyl)acetonitrile (2.0 g, 11.79 mmol) in DMSO (30.0 mL) was added sodium hydride (0.660 g, 16.51 mmol) portion wise under N₂ at RT (slightly exothermic). After 30 min, the reaction mixture was cooled to 15 °C with cold water bath and O-ethyl carbonisothiocyanatide (1.530 mL, 12.97 mmol) was added drop wise. After 1 h, the reaction mixture was heated at 100 °C for 2h. The progress of reaction was monitored by TLC (30% EtOAc in pet ether) and LC-MS. After completion of reaction, the reaction mixture was quenched with water, and obtained solid. The solid was filtered and washed with water and dried under vacuum to yield titled compound as crude yellow solid. Crude product was purified by column chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 30 % EtOAc in Petether) to get 3-amino-6-chlorobenzo[b]thiophene-2-carbonitrile as solid.

[0365] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.96 (br s, 2H), 7.83 (d, J = 2.00 Hz, 1H), 7.32 (dd, J = 2.00, 8.40 Hz, 1H), 7.26 (d, J = 8.40 Hz, 1H).

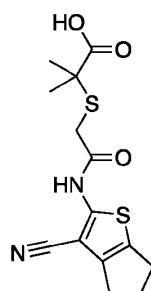
[0366] Step 2-Synthesis of 2-chloro-N-(6-chloro-3-cyanobenzo[b]thiophen-2-yl)acetamide: To a solution of 2-amino-6-chlorobenzo[b]thiophene-3-carbonitrile (350 mg, 1.677 mmol) in dioxane (10.0 mL) was added 2-chloroacetyl chloride (379 mg, 3.35 mmol) at room temperature. The resulting mixture was stirred at RT for 16h. The progress of reaction was monitored by TLC (30% EtOAc in pet ether) and LCMS. After completion of reaction was diluted with hexane. Obtained solid was filtered and washed with hexane and dried under vacuum to yield titled compound 2-chloro-N-(6-chloro-3-cyanobenzo[b]thiophen-2-yl)acetamide (400 mg, 1.019 mmol, 60.8 % yield) as a white solid.

[0367] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.53 (s, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 8.80 Hz, 1H), 7.55 (dd, J = 2.00, 8.80 Hz, 1H), 4.59 (s, 2H).

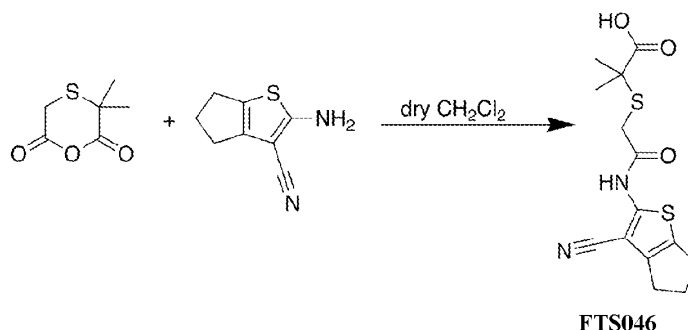
[0368] Step 3-Synthesis of 2-((2-((6-chloro-3-cyanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid: To a solution of 2-chloro-N-(6-chloro-3-cyanobenzo[b]thiophen-2-yl)acetamide (250 mg, 0.877 mmol) and cesium carbonate (428 mg, 1.315 mmol) in ACN (15.0 mL) was added methyl 2-mercapto-2-methylpropanoate (176 mg, 1.315 mmol). The resulting mixture was stirred at RT for 16h. Progress of reaction was monitored by TLC and LCMS which showed formation of intermediate 7. To the same reaction mass was added THF (10.0 mL) followed by lithium hydroxide monohydrate (184 mg, 4.38 mmol) in water (3.0 mL). The resulting mixture was continued to be stirred at RT for 16h. The reaction was monitored by TLC (30% EtOAc in pet ether + 0.5 mL acetic acid) and LC-MS. After completion of reaction, reaction mixture was quenched with water. Reaction mixture was extracted with ethyl acetate (2 x 30 mL). Separated aqueous layer was acidified with aq. 6N HCl and extracted with ethyl acetate (3 x 30 mL). Combined organic layers was washed with brine, dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure to get crude product. Crude product was purified by column chromatography (Isolera) by using DCM and methanol as an eluting solvent system (product eluted at 3-5% MeOH in DCM) to get pure 2-((2-((6-chloro-3-cyanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (28.6mg, 0.877 mmol, 8.84 % yield) as a white solid.

[0369] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.70 (br s, 1H), 12.31 (br s, 1H), 8.18 (s, 1H), 7.67 (d, J = 8.40 Hz, 1H), 7.54 (d, J = 8.40 Hz, 1H), 3.82 (s, 2H), 1.46 (s, 6H).

[0370] **Example 28:** Preparation of 2-((2-((3-cyano-5,6-dihydro-4*H*-cyclopenta[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS046**)

**FTS046**

[0371] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS046** via the synthetic method of Scheme 28 as shown below.

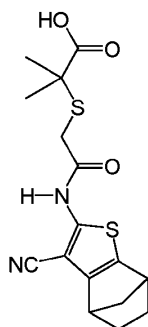
Scheme 28**FTS046**

[0372] **Materials and methods**

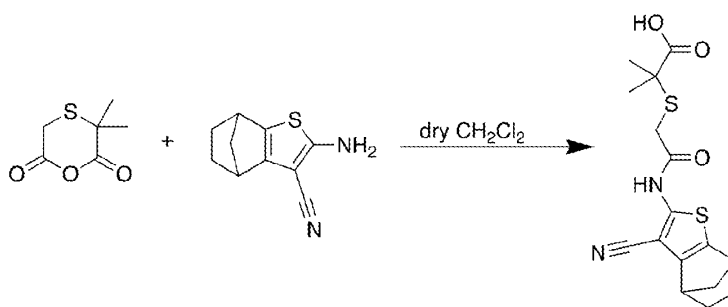
[0373] 3,3-dimethyl-1,4-oxathiane-2,6-dione (0.911 mmol) and 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carbonitrile (0.684 mmol, 0.75 eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 15mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 2-((2-((3-cyano-5,6-dihydro-4H-cyclopenta[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a grey powder (95mg, 42.8%).

[0374] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400MHz), DMSO-d₆ δ: 1.43 (s, 6H), 2.36 (quintet, 2H), 2.72 (t, 2H), 2.82 (t, 2H), 3.70 (s, 2H), 11.71 (s, 1H), 12.66 (s, 1H).

[0375] **Example 29:** Preparation of 2-((2-((3-cyano-4,5,6,7-tetrahydro-4,7-methanobenzo[b]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS047**)

**FTS047**

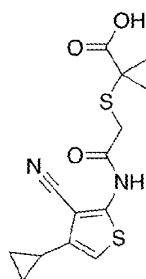
[0376] This example illustrates a preparation of the FAB3/4/5/7 inhibitor compound **FTS047** via the synthetic method of Scheme 29 as shown below.

Scheme 29**FTS047**

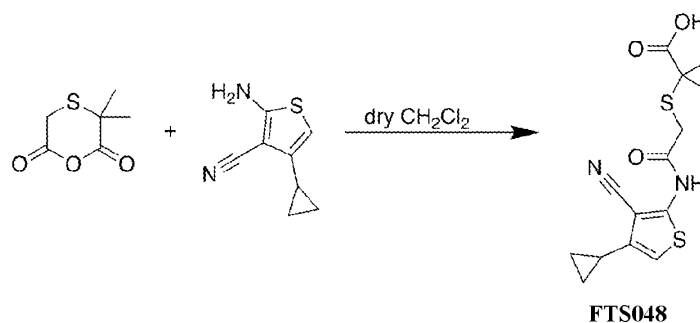
[0377] *Materials and methods*

[0378] 3,3-dimethyl-1,4-oxathiane-2,6-dione (0.697 mmol) and 2-amino-4,5,6,7-tetrahydro-4,7-methanobenzo[*b*]thiophene-3-carbonitrile (0.523 mmol, 0.75eq.) was charged into a 50 mL round bottom flask. The flask was purged with argon and 20mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. The reaction mixture was extracted with saturated NaHCO₃. Concentrated HCl was added to the aqueous layer and then extracted with CH₂Cl₂, washed with brine, and dried over anhydrous sodium sulfate. Excess solvent was removed via rotary evaporation to yield 2-((2-((3-cyano-4,5,6,7-tetrahydro-4,7-methanobenzo[*b*]thiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a white powder (19 mg, 10.4%).

[0379] **Example 30:** Preparation of 2-((2-((3-cyano-4-cyclopropylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS048**)

**FTS048**

[0380] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS048** via the synthetic method of Scheme 30 as shown below.

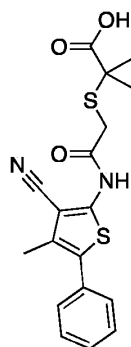
Scheme 30**FTS048**

[0381] *Materials and methods*

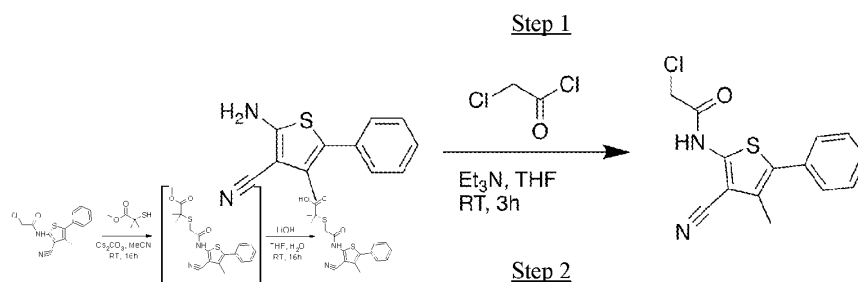
[0382] 3,3-dimethyl-1,4-oxathiane-2,6-dione (0.787 mmol) and 2-amino-4-cyclopropylthiophene-3-carbonitrile (0.590 mmol, 0.75 eq.) were charged into a 50mL round bottom flask. The flask was purged with argon and 15mL dry dichloromethane was added. The mixture was allowed to stir overnight under positive pressure of argon. White powder forms under rapid cooling recrystallization and is isolated via vacuum filtration and washed with cold CH₂Cl₂. Residual solvent is removed via rotary evaporation to yield 2-((2-((3-cyano-4-cyclopropylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid as a white powder (45mg, 23.4%).

[0383] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (500MHz, DMSO-d₆ δ: 0.66 (dd, 2H), 0.917 (dd, 2H), 1.437 (s, 6H), 1.84 (m, 1H), 3.72 (s, 2H), 6.65 (s, 1H), 11.76 (s, 1H), 12.67 (s, 1H).

[0384] **Example 31:** Preparation of 2-((2-((3-cyano-4-methyl-5-phenylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (compound **FTS049**)

**FTS049**

[0385] This example illustrates the preparation of the FAB3/4/5/7 inhibitor compound **FTS049** via the synthetic method of Scheme 31 as shown below.

Scheme 31**FTS049**

[0386] **Materials and methods**

[0387] **Step 1-Synthesis of 2-amino-4-methyl-5-phenylthiophene-3-carbonitrile:** To a solution of 2-amino-4-methyl-5-phenylthiophene-3-carbonitrile (500 mg, 2.333 mmol) in THF (15 mL) was added Et₃N (826 mg, 8.17 mmol) followed by 2-chloroacetyl chloride (659 mg, 5.83 mmol) at 0 °C. The resulting mixture was stirred at RT for 2h. Progress of reaction was monitored by TLC (10% EtOAc in pet ether) and LCMS. After completion of reaction, reaction mixture was quenched with water. Reaction mixture was extracted with ethyl acetate (3 x 20 mL). Combined organic layers were separated and washed with brine, dried over sodium sulphate and concentrated in rotary-evaporator under reduced pressure to get crude. Crude product was purified by column

chromatography (Isolera) by using EtOAc and pet ether as an eluting solvent system (product eluted at 5-10 % EtOAc in Petether) to get pure 2-chloro-N-(3-cyano-4-methyl-5-phenylthiophen-2-yl)acetamide (290mg, 0.997 mmol, 43% yield) as a brown solid.

[0388] NMR analysis confirmed preparation of the desired intermediate compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.16 (s, 1H), 7.39-7.51 (m, 5H), 4.52 (s, 2H), 2.30 (s, 3H).

[0389] Step 2-Synthesis of 2-((2-((3-cyano-4-methyl-5-phenylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid: To a solution of 2-chloro-N-(3-cyano-4-methyl-5-phenylthiophen-2-yl)acetamide (350 mg, 1.204 mmol) and cesium carbonate (588 mg, 1.806 mmol) in ACN (15.0 mL) was added methyl 2-mercapto-2-methylpropanoate (242 mg, 1.806 mmol). The resulting mixture was stirred at RT for 16h. Reaction was monitored by TLC and LCMS which showed formation of intermediate 5. To the same reaction mixture was added THF (10.0 mL) followed by lithium hydroxide monohydrate (253 mg, 6.02 mmol) in water (3.0 mL). The resulting mixture was continued to be stirred at RT for 16h. Progress of reaction was monitored by TLC [30% (10 mL) EA in pet ether + 0.5 mL acetic acid] and LCMS. After completion of reaction, reaction mixture was quenched with water. Reaction mixture was extracted with ethyl acetate (2 x 30 mL). Separated aq. layer was acidified with aq. 6N HCl, extracted with ethyl acetate (3 x 30 mL). Combined organic layers was washed with brine, dried over sodium sulphate and concentrated over rotary evaporator under reduced pressure to get crude product. Crude product was purified by column chromatography (Isolera) by using DCM and methanol as an eluting solvent system (product eluted at 3-5% MeOH in DCM) to get pure 2-((2-((3-cyano-4-methyl-5-phenylthiophen-2-yl)amino)-2-oxoethyl)thio)-2-methylpropanoic acid (48.10mg, 0.128 mmol, 10.67 % yield) as a white solid.

[0390] NMR analysis confirmed preparation of the desired product compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 12.67 (br s, 1H), 11.97 (br s, 1H), 7.44-7.51 (m, 4H), 7.38-7.42 (m, 1H), 3.76 (s, 2H), 2.29 (s, 3H), 1.44 (s, 6H).

[0391] **Example 32: Screening of FABP3/4/5/7 Inhibitor Compounds**

[0392] This example illustrates a two-step fluorescence binding assay study used to determine the binding affinity of the various inhibitor compounds disclosed herein with the various FABPs: FABP3, FABP4, FABP5 and FABP7. Further secondary screening studies were carried out for compounds with high binding affinities toward the FABPs and based on their ability to activate the nuclear receptors PPAR α , PPAR γ , or PPAR δ .

[0393] **Materials and methods**

[0394] **A. Binding assays**

[0395] Binding assays for FABP3, FABP4, FABP5 and FABP7 were carried out by fluorescence titrations. His-tagged FABPs were bacterially expressed in *E. coli*, purified using Ni Sepharose beads, and the equilibrium dissociation constants (K_d) that characterize their interactions with different inhibitor compounds were measured by fluorescence competition assays. The method entails two

steps as described in e.g., Lin, Q. et al., “Ligand selectivity of the peroxisome proliferator-activated receptor alpha,” *Biochemistry* 38, 185-190, doi:10.1021/bi9816094 bi9816094 [pii] (1999). In the first step, K_d for the association of the protein with the fluorescent fatty acid probe ANS was measured. Protein (2 μM) was titrated with ANS from a concentrated solution in DMSO. Ligand binding was monitored by following the increase in the fluorescence of the ligand upon binding to the protein, and K_d for the association of ANS with the each FABP was computed from titration curves as described in e.g., Norris, A. W. & Li, E., “Fluorometric titration of the CRABPs,” *Methods Mol Biol* 89, 123-139 (1998)). In the second step, K_ds for binding of non-fluorescent ligands were measured by monitoring their ability to displace ANS in the binding pocket of the protein. Each FABP was precomplexed with ANS at 1:1 molar ratio and titrated with the different compounds whose binding was reflected by a decrease in probe fluorescence. K_ds were extracted from the EC₅₀ of the competition curve and the measured K_d for ANS.

[0396] B. Transcriptional activation assays

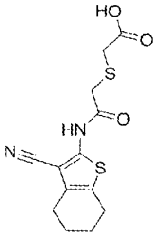
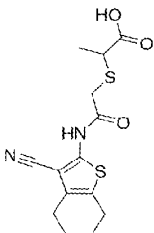
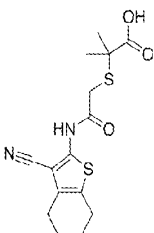
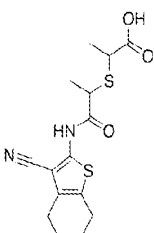
[0397] COS-7 were cultured in 6-well plates and co-transfected with either a luciferase reporter driven by 3 copies of a PPRE and expression vector for either PPARδ, PPARα or PPARγ together with a vector harboring cDNA for β-galactosidase, serving as a transfection control. To test whether FABP4 or FABP5 mediate activation of their cognate receptors PPARγ and PPARδ, respectively, cells were also co-transfected with a plasmid harboring sequence of either FABP4 or FABP5. 18 h post-transfection, cells were placed in a serum-free medium and treated with agonist/compound. 18 h later, cells were lysed, luciferase activity was assayed (Promega, WI, USA) and corrected for transfection efficiency by the activity of β-galactosidase.

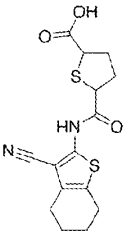
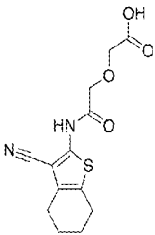
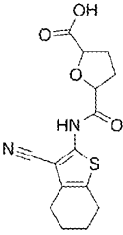
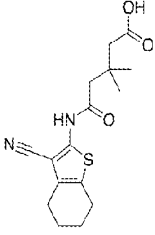
[0398] *Results*

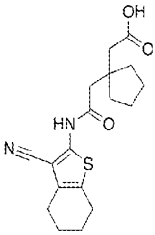
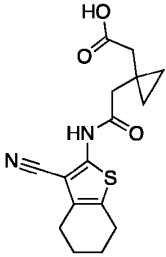
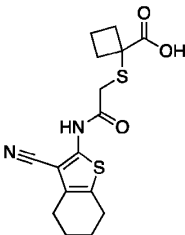
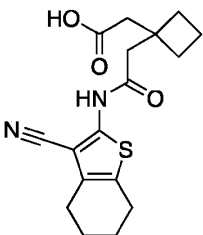
[0399] Results of the binding assays of FABP5, FABP4, FABP3 and FABP7 with the disclosed compounds **FTS001, FTS003, FTS005, FTS007, FTS009, FTS011, FTS013, FTS017, FTS019, FTS026, FTS029, FTS030, FTS031, FTS032, FTS033, FTS034, FTS037, FTS039, FTS040, FTS041, FTS042, FTS043, FTS044, FTS045, FTS046, FTS048 and FTS049**, are summarized in Table 19 below. None of these tested compounds activated PPARα, PPARγ, or PPARδ.

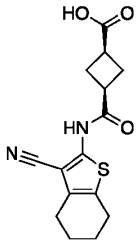
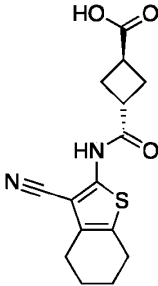
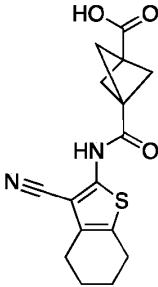
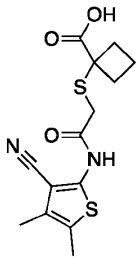
[0400] **TABLE 19**

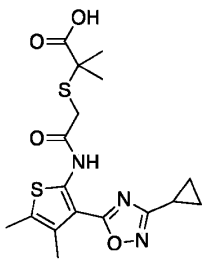
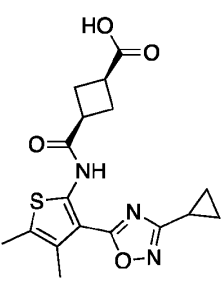
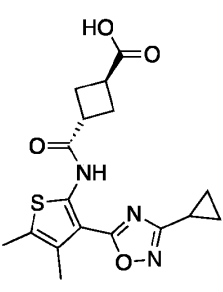
Compound	K _d (FABP5) (nM)	K _d (FABP4) (nM)	K _d (FABP3) (nM)	K _d (FABP7) (nM)	Inhibitor specificity
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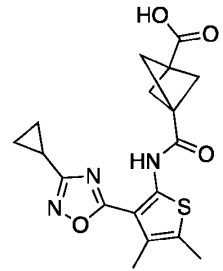
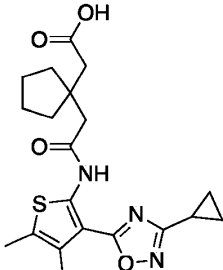
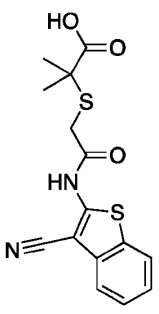
 FTS001	247	267	780	220	FABP4/5/7
 FTS003 (compound 2)	72	194	2541	> 1000	FABP4/5
 FTS005 (compound 1)	65	170	3053	>1000	FABP4/5
 FTS007 (compound 3)	38	310	>1000	>1000	FABP5

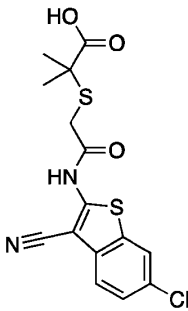
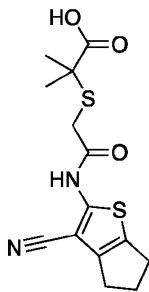
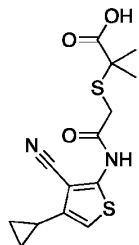
 FTS009 (compound 4)	17	58	407	>1000	FABP4/5
 FTS011	79	135	>1000	>1000	FABP4/5
 FTS013	52	145	229	>1000	FABP3/4/5
 FTS017	70	189	190	644	FABP3/4/5

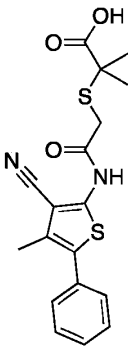
 FTS019	74	121	155	695	FABP3/4/5
 FTS029 (compound 10)	113	127	280	602	FABP3/4/5
 FTS030 (compound 7)	58	159	247	797	FABP3/4/5
 FTS031 (compound 8)	28	158	>1000	>1000	FABP5

 FTS032 (compound 12)	113	165	200	718	FABP3/4/5
 FTS033 (compound 13)	230	321	343	>1000	FABP3/4/5
 FTS034 (compound 14)	213	267	418	>1000	FABP4/5
	136	174	177	773	FABP3/4/5

FTS037 (compound 17)					
 FTS039 (compound 19)	6	4	5	6	FABP3/4/5/7
 FTS040 (compound 20)	19	36	113	141	FABP4/5
 FTS041 (compound 21)	17	36	94	185	FABP4/5

 FTS042 (compound 22)	28	72	69	37	FABP3/4/5/7
 FTS043 (compound 23)	44	36	63	>1000	FABP3/4/5
 FTS044 (compound 24)	85	71	93	>1000	FABP3/4/5

 FTS045 (compound 25)	74	121	156	407	FABP3/4/5/7
 FTS046 (compound 26)	112	247	153	193	FABP3/4/5/7
 FTS048 (compound 28)	174	247	125	218	FABP3/4/5/7

 FTS049 (compound 29)	14	34	119	>1000	FABP4/5
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[0401] **Example 33: Biological Studies of FABP3/4/5/7 Inhibitor Compounds FTS005, FTS030, FTS031, FTS037, and FTS039**

[0402] This example illustrates studies of the biological function of the FABP3/4/5/7 inhibitor compounds **FTS005, FTS030, FTS031, FTS037, and FTS039** in cancer models and in models of metabolic diseases.

[0403] ***Materials and methods***

[0404] ***A. Cells***

[0405] COS-7, MDA-MB-231, NPG, HepG2, 3T3-L1, were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (Invitrogen Life Sciences, Carlsbad, CA). 4T1, 4T01, NR67, MDA-MB-157, MB-549 and OVCAR8 cells were cultured in L-Glutamine containing RPMI medium supplemented with 10% fetal calf serum (Invitrogen Life Sciences, Carlsbad, CA).

[0406] ***B. Transcriptional activation assays***

[0407] Transcriptional activation assays were carried out utilizing COS7 cells as described above.

[0408] ***C. Real-Time PCR***

[0409] Cells were treated with a compound for 6 h. then lysed and RNA was extracted using Trizol, according to the manufacturer's instructions. cDNA was generated using GeneAmp RNA PCR (Applied Biosystems). qPCR was carried out using TaqMan chemistry and Assays-on-Demand probes (Applied Biosystems). 18s (4352930) rRNA was used for normalization. Relative expression was calculated as 2^{-DDCT} .

[0410] ***D. Proliferation assays***

[0411] 2000 cells were plated in each well of 96-well plate. The next day cells were treated with compounds and incubated in Incucyte for 4 days. Images taken every 4 hours for the duration of the

time were analyzed to calculate percentage of confluency in response to the treatments. Growth inhibition was calculated as 1 - (percentage of viable cells out of untreated cells).

[0412] E. Lipid uptake assays

[0413] 1) HepG2 cells: 5000 cells were plated in 96-well plate. The next day cells were treated with tested compounds for 4 hours and then treated with 1 mM oleic acid for additional 24 hours. Cells were then stained with Nile Red and Dapi and lipid content was quantified using Cytation5 (Agilent).

[0414] 2) 3T3-L1: Mouse 3T3-L1 cells were differentiate in culture according to ATCC protocol to become mature adipocytes. At day 6 of the differentiation, compound treatment started. Cells were stained by Nile Red on day and color intensity in each cell was measured relative to Dapi staining.

[0415] F. Xenograft experiments

[0416] Seven-week-old NSG females were injected subcutaneously into the right flank with 5×10^6 MB-231 cells 1:1 with Matrigel. Treatments started the day after cells injections 5 days a week. Mice were orally treated by gavage with either vehicle (sesame oil), or either 20 mg/kg, or 40 mg/kg **FTS005** dissolved in vehicle. Tumor size was assessed twice per week using a digital caliper. Tumor volumes were determined by measuring the length (l) and the width (w) of the tumor and calculating the volume ($V = lw^2/2$). Mice were scarified 24 days after injection. Statistical significance between the control and treated mice in both experiments was evaluated using a Student's t -test. Mouse experiments were conducted after approval by the institutional animal care and use committee at Case Western Reserve University.

[0417] G. TNBC syngeneic mouse model

[0418] Seven-week-old BALB/c females were injected subcutaneously into the mammary fat pad with 1×10^5 4T1 cells 1:1 with Matrigel. Treatments started the day after cells injections 5 days a week. Mice were orally treated by gavage with either vehicle (sesame oil), or 40 mg/kg **FTS005** dissolved in vehicle. Tumor size was assessed twice per week using a digital caliper. Tumor volumes were determined by measuring the length (l) and the width (w) of the tumor and calculating the volume ($V = lw^2/2$). Mice were scarified 32 days after injection. Statistical significance between the control and treated mice in both experiments was evaluated using a Student's t -test. Mouse experiments were conducted after approval by the institutional animal care and use committee at Case Western Reserve University.

[0419] H. Isolation of primary T-cells

[0420] T cells were harvested from splenocytes of control BALB/c mice bearing the 4T1 tumors or those treated with FABP3/4/5/7 inhibitor.

[0421] I. Metabolomics analysis of tumor samples

[0422] 50 mg of tumor samples was lysed in 500 μ L of PBS and protein concentration was measured. Samples were subjected to LC/MS/MS using C18 (Gemini 5 μ M, 2 x 150 mm, Phenomnex) column. Mobile phases for: 1) detection of TCA metabolites were: A) water + 5 mM AmAc and B) methanol + 5mM AmAc and 0.3 mL/min flow rate; 2) detection of glycolysis, fatty

acids, and arachidonic acid oxidation metabolites were: A) water + 0.1% acetic acid and B) methanol/CAN (1/1) + 0.1% acetic acid and 0.3 mL/min flow rate.

[0423] Results

[0424] A. Compounds FTS005, FTS030, FTS031, FTS037, and FTS039 do not activate transcription by PPARs

[0425] To eliminate the possibility that the thiophene compounds **FTS005**, **FTS030**, **FTS031**, **FTS037**, and **FTS039** are ligands of the nuclear receptor PPAR α , PPAR γ , or PPAR δ , that activate transcription by these transcription factors, transcriptional activation assays were conducted utilizing COS7 cells. For comparison the known specific PPAR α , PPAR γ , or PPAR δ agonist compounds, Wy-14643 (**FIG. 1A**), rosiglitazone (**FIG. 1B**), and GW0742 (**FIG. 1C**) (5 mM for all), respectively, were also assayed. As shown by the plots of data in **FIG. 1A**, **FIG. 1B**, and **FIG. 1C**, unlike these known agonist compounds which induced activation of their respective receptors, none of the tested compounds **FTS005**, **FTS030**, **FTS031**, **FTS037**, and **FTS039** activated transcription.

[0426] B. Compound FTS005 suppresses growth of TNBC cells that express FABP5 more effectively than the commercially available inhibitor SBF-I26

[0427] The TNBC lines MB-231 and BT-549 were used to calculate the efficacy of compound **FTS005** in inhibiting proliferation of the cancer cells. Cells were treated with serial dilution of the compound and proliferation was measured in Incucyte by calculating percentage of confluency every 4 hours over 4 days. As shown in **FIG. 2A**, **FTS005** inhibited proliferation of the 2 human TNBC lines MB-231 and BT-549 very effectively with calculated IC₅₀ of 0.145 mM, and IC₅₀ of 0.25 mM, respectively.

[0428] To verify the inhibitory effect of **FTS005** on TNBC cells is mediated through FABP5 MB-231 line stably expressing FABP5 shRNA were utilized. As shown in **FIG. 2B**, **FTS005** only inhibited proliferation of the WT MB-231 and BT-549 lines that express FABP5 but did not affect proliferation of the F5_KD MB-231 cell line in which levels of FABP5 are low.

[0429] The efficiency of **FTS005** in inhibiting proliferation of MB-231 cells was also compared to the known FABP5/7 inhibitor compound, SBF-I26. As shown in **FIG. 2C**, the data clearly show that treatment of MB-231 cells with the thiophene compound suppress proliferation of the TNBC cells 10 to 20-fold more effectively than the SBF-I26.

[0430] Additionally, the effect of **FTS005** was also tested on proliferation of the mouse mammary carcinoma lines 67NR, 4T07, and 4T1 that serve as a model for human TNBC. Lines 4T07 and 4T1 originated from NR67 with 4T1 being the most metastatic and aggressive of them all. Expression levels of FABP5 were measured in all lines and compared to the human line MB-231. Levels of FABP5 were found to be positively correlated with the aggressiveness of the cells with MB-231 having the highest levels then 4T1 and 4T07. As shown in **FIG. 3A**, FABP5 was not detected in 67NR cells. As expected, treatment of the mouse carcinoma cells with **FTS005** inhibit their proliferation but less efficiently than MB-231 cells (see results in **FIG. 3B** and **FIG. 3C**), indicating

the effect of the inhibitor is dependent of expression levels of FABP5. 67NR cells were not affected by **FTS005** at all (**FIG. 3C**).

[0431] C. Compounds **FTS005**, **FTS040**, **FTS041**, **FTS042**, **FTS043**, **FTS044**, **FTS045**, and **FTS049** suppress growth of human ovarian cancer cells OVCAR8

[0432] The ovarian cancer cell line OVCAR8 was used to calculate the efficacy of compounds **FTS005**, **FTS040**, **FTS041**, **FTS042**, **FTS043**, **FTS044**, **FTS045**, and **FTS049** in inhibiting proliferation of the ovarian cancer cells. Cells were treated with serial dilution of the compounds and proliferation was measured in Incucyte by calculating percentage of confluency every 4 hours over 4 days. As shown in **FIG. 4A**, all compounds inhibited proliferation of the cancer line very effectively. Calculated IC_{50} shown in **FIG. 4B**, indicating similar efficacy among all compounds ranging between 0.602 μ M (FTS044) to 1.1 μ M (FTS042).

[0433] D. Compound **FTS005** suppresses growth of neuroblastoma (NB) cells and increases sensitivity to all-trans retinoic acid (atRA) in combination treatments.

[0434] When available in the cell, FABP5 was shown to bind atRA, deliver it to PPAR δ and activate the nuclear receptor. Activation of PPAR β by atRA shifts the signaling of this vitamin from its cognate receptor RAR that is known to have anti-carcinogenic activities in multiple cancers to the pro-carcinogenic PPAR δ . Hence, inhibition of FABP5 is expected to sensitize cancer cells to atRA by shifting their signaling back to RAR. Accordingly, NB, human NPG cells were used to test the effect of FABP5 inhibitors on cells' proliferation in combination with atRA. Cells were treated with **FTS005** in the presence or absence of atRA.

[0435] As shown in **FIG. 5A**, treatment of the cells with **FTS005** significantly inhibited proliferation of the cells, a trend that was enhanced when the compounds were combined with atRA. Additionally, combination treatment of **FTS005** together with atRA significantly improved the sensitivity of the cells to atRA (see results in **FIG. 5B** and **FIG. 5C**).

[0436] E. Compound **FTS005** suppresses tumor growth and restrains infiltration of macrophages into TNBC tumors in an *in vivo* xenograft model

[0437] TNBC xenograft model was used to test the efficacy of **FTS005** in suppressing growth on tumors *in vivo*. 5×10^5 MB-231 cells were subcutaneously injected into the right flank of NSG mice. Mice were treated with **FTS005** (20 mg/kg. or 40 mg/kg) or a vehicle by gavage 5 times a week and tumor growth was monitored. As shown in **FIG. 6A**, **FTS005** significantly inhibited growth of MB-231 tumors as determined by tumor volume and tumor weight (**FIGS. 6A** and **6B**). Molecular analysis of the tumors indicated that levels of proliferation marker Ki67 were markedly reduced in tumors of mice treated with **FTS005** (**FIGS. 6C** and **6D**). Similarly, levels of the angiogenesis marker that is also a known PPAR δ target genes VEGFA was significantly lower in treated tumors (**FIGS. 6C**, **6E**, and **6G**). Amazingly, staining of the macrophage marker F4/80 in the tumors indicates total number of tumor-associated macrophages (TAM) in the treated tumors is markedly reduced compared to

untreated control (**FIGS. 6C**, and **6F**). This indicated inhibition of FABP5 affects the immune cell population in the tumor microenvironment. Levels of the genes ACSL1 and PLIN2 that are involved in FA metabolism and lipid accumulation and are also known PPAR δ targets were measured by QPCR and their levels were found to be significantly reduced in treated tumors (**FIG. 6G**).

[0438] F. Compound **FTS005** suppresses growth of TNBC tumors *in vivo* in syngeneic mouse model

[0439] 4T1 cells were utilized in TNBC syngeneic model to test the efficacy of **FTS005** in suppressing growth on tumors *in vivo* in an immunocompetent model. 1×10^5 4T1 cells were injected into the mammary fat pad of BALB/c mice. Mice were treated with **FTS005** (40 mg/kg) or a vehicle by gavage 5 times a week and tumor growth was monitored.

[0440] As shown in **FIG. 7A**, **FTS005** significantly inhibited growth of 4T1 tumors as determined by tumor volume and tumor weight (see **FIG. 7A** and **FIG. 7B**). Expression levels of the angiogenesis marker that is also a known PPAR δ target genes VEGFA were measured by QPCR and were found to be significantly lower in treated tumors (**FIG. 7C**). Similarly, levels of the genes ACSL1 and PLIN2 that are involved in FA metabolism and lipid accumulation and are also known PPAR δ targets were significantly reduced in treated tumors (**FIG. 7C**). Immunohistochemical staining of the tumors indicated that protein levels of proliferation marker Ki67 and those of VEGFA were markedly reduced in tumors of mice treated with **FTS005** (see **FIG. 7D**, **FIG. 7E**, and **FIG. 7F**, respectively).

[0441] G. Compound **FTS005** reprograms fatty acid metabolism in the tumor microenvironment (TME)

[0442] 4T1 tumor samples that were either treated with **FTS005** or untreated were analyzed for amounts of different fatty acids-related metabolites. More specifically, using LC/MS/MS analyses, metabolites of TCA cycle, glycolysis, long-chain fatty acids, arachidonic acid oxidation, and ATP/ADP were measured and quantified based on protein concentration in each sample. As can be seen in **FIG 8**, the metabolites profiles measured in tumors treated with **FTS005** significantly changed following the treatment. Amount of long-chain fatty acids (**FIG. 8A**) measured in treated tumors was significantly lower than in untreated tumors and similarly, lower levels of TCA cycle metabolites were detected (**FIG. 8B**). Concomitantly, the amount of glycolysis metabolites increased following treatment (**FIG. 8D**) indicating **FTS005** treatment triggers reprogramming of fatty acids metabolism in the tumors and a shift in energy use from fatty acids to glycolysis. Markedly higher amounts of ADP were measured in treated tumors and while no difference was observed in levels of ATP, the significantly higher levels of ADP resulted in lower ATP/ADP ratio (**FIG. 8C**) which is a known marker for low proliferation rate and cell death.

[0443] H. Compound **FTS005** modulates the immune cell population in tumor microenvironment (TME)

[0444] Sample from tumor arose on the immunocompetent BALB/c mice injected with 4T1 cells were used to further study the effect of **FTS005** treatment on immune cells in the TME. To evaluate the effect of **FTS005** on tumor infiltrating macrophages (TAMs), tumors were stained with the TAM

markers F4/80 and CD68, and the specific M2 marker CD163 (**FIG. 9A, FIG. 9B, and FIG. 9C**). While levels of total macrophages were not found to be regulated by **FTS005** treatment, as indicated by staining for F4/80 and CD68 (**FIG. 9A, FIG. 9B, FIG. 9D, and FIG. 9E**), levels of the M2 marker CD163 was significantly lower in the treated tumors (**FIG. 9C, and FIG. 9F**). The data suggests that the FABP5 inhibitor **FTS005** restrains the immune-suppressive M2 macrophages in the tumors, hence triggering self-immune response against tumor cells.

[0445] To evaluate effects of **FTS005** on tumor infiltrating T-cells, tumor samples were stained with the T-cells markers CD3, CD4 and CD8. Remarkably, levels of CD3, CD4 and CD8 in the treated tumors were significantly higher than in untreated control (**FIG. 10A, and FIG. 10B**). The number of CD4 and CD8 T-cells were also measured by flow cytometry among cells isolated from spleens collected from the mice. Although no significant difference was observed in frequency of either CD4 or CD8 in splenocytes collected from treated vs. untreated mice (**FIG. 10C**), the amount of activated $\text{TNF}\alpha^+$ CD8 T-cells was significantly higher in splenocytes collected from treated mice (**FIG. 10D**). The 4T1 cells utilized in this experiment stably express Luc2 and therefore, to stimulate an immune response by the harvested splenocytes, harvested cells were treated with Luc2 peptides in the growth media for 2 weeks and cell number was measured. As shown in **FIG. 10E**, the number of T-cells harvested from **FTS005**-treated spleens was markedly higher than those harvested from untreated mice, indicating treated T-cells proliferated more in response to the Luc2 antigen exposure. To test the cytotoxic activity of the T-cells, the splenic T cells were co-cultured overnight with 4T1Luc2-CFSE high (target, Balb/c origin) and F420Luc2-CFSE low (control, B6 origin) (Target:Effector=1:5). Next day, the live CFSE+ cells were counted by flow cytometry and the percentage of lysed cells was calculated. As shown in **FIG. 10F**, the number of lysed cells was markedly higher after incubation with T-cells harvested from treated mice. Hence, the data suggests that treatment with FABP3/4/5/7 inhibitor **FTS005** stimulates formation of memory T-cells.

[0446] To evaluate the effect of **FTS005** on multiple immune cells and onco-immune functions. RNA samples extracted from untreated and treated tumors were used to for comprehensive profiling of the immune response by utilizing nCounter PanCancer Immune Profiling Panel. As shown in **FIG. 11**, treatment of tumor-bearing mice with **FTS005** resulted in change in immune cells' profile in the tumors. Based on this analysis, higher number of CD45 cells, macrophages, B-cells, dendritic cells, cytotoxic cells, T-cells, CD8 T-cells, NK cells and NK CD56dim cells was found in treated tumors indicating a more immune-active TME. Taken together, the data collected from mice treated with **FTS005** suggests that inhibition of FABP3/4/5/7 modulates immune cells in the TME in two ways: 1) suppressing the immune-suppressive M2 tumor associated macrophages and, 2) stimulating tumor infiltrating lymphocytes (TILs) into the tumors including activated CD4 and CD8, NK cells, cytotoxic and dendritic cells, all are known to activate the immune-repressed tumors and turning them into "hot" tumors that can be recognized by the immune system.

[0447] F. **FTS005** inhibits uptake of lipids into hepatocytes in *in vitro* model for liver steatosis

[0448] HepG2 cells were used to test effect of **FTS005** on uptake of lipid into hepatic cells in an *in vitro* liver steatosis model. Cells were treated with oleic acid (OA) (1 mM) in the presence or absence of the aniline compounds or the known FABP4 inhibitor BMS-309403 (BMS) and lipid accumulation in the cells was quantified using Nile Red. Uptake of lipid into hepatic cells treated with FTS005 was markedly inhibited (**FIG. 12A**). Inhibition of lipid uptake was more efficient by **FTS005** compared with BMS. For comparison, lipids accumulated in the cells following treatment with 5 μ M **FTS005** was comparable to that established after treatment with 25 μ M BMS (**FIG. 12A**), indicating the thiophene compound is more efficient than BMS.

[0449] G. **FTS005** inhibits uptake of lipids into mature adipocytes

[0450] Mouse 3T3-L1 cells were differentiated in culture to become mature adipocytes. Compounds **FTS005** or the known FABP4 inhibitor BMS in varying concentrations were added to the cells starting at day 6 of the differentiation. On day 12, the lipid droplets were stained by Nile Red and quantified (**FIG. 12B**). Uptake of lipid into hepatic cells treated with FTS005 was markedly inhibited (**FIG. 12A**). Inhibition of lipid uptake was more efficient by **FTS005** compared with BMS. For comparison, lipids accumulated in the cells following treatment with 10 μ M **FTS005** was comparable to that established after treatment with 30 μ M BMS (**FIG. 12B**), indicating the thiophene compound is more efficient than BMS.

[0451] **Example 34:** Biological studies of FABP3/4/5/7 inhibitor compound effects on immune cell populations

[0452] This example illustrates studies of the biological effect of the FABP inhibitor compound **FTS005** on immune cell populations in cancer models.

[0453] *Materials and methods*

[0454] A. Isolation and differentiation of Mouse bone marrow-derived macrophages (BMDMs)

[0455] BMDMs were isolated from C57BL6 mice. Briefly, bone marrow was flushed with RPMI media and cell lysis was done using AKL buffer. Harvested cells were plated in growth media (DMEM, 10% HI FBS, 1% pen/strep, 25 ng/mL M-CSF) for 7 days (M ϕ macrophages). To promote macrophages differentiation in culture, M ϕ cells were treated with either LPS (10 pM) and INF γ (20 ng/mL) to promote differentiation into M1 macrophages, or IL-4 (20 ng/mL) and IL-13 (20 ng/mL) to promote differentiation into M2 macrophages. Cells were incubated with the cytokines for 3 days in the presence or absence of FABP3/4/5/7 inhibitors then lysed and immunostained for further analysis.

[0456] B. Fluorescence-activated cell sorting (FACS)

[0457] Macrophages were fixed then stained. Viable cells were identified using LIVE/DEAD™ Fixable Aqua Dead Cell Stain Kit according to the manufacture's protocol. To measure frequency of macrophages, cells were stained with the markers F4/80 (total macrophages), CD11b (total macrophages), MHC-II (M1 macrophages), CD36 (M2 macrophages), and CD206 (M2

macrophages). To evaluate T-cells' frequency the following markers were used: CD4, CD8, CD25 and FoxP3 (Treg), and TNFa (activated T-cells). Data was analyzed using FlowJo software.

[0458] C. Quantification of IL-10 and IL-12

[0459] Levels of the cytokines interleukin-10 (IL-10) and interleukin-12 p70 (IL-12) that were secreted from macrophages were measured in the media of treated cells using ELISA assay kits and according to manufacturer's protocol.

[0460] *Results*

[0461] A. FABP3/4/5/7 inhibitor treatment of macrophages during differentiation supports M1 phenotype while suppressing M2 phenotype

[0462] Bone marrow-derived macrophages (BMDM) were isolated from mice and differentiated in culture. Cells treated with M-CSF for 7 days were established as naïve macrophages (M ϕ). Naïve macrophages were then treated with either LPS and IFN γ to promote differentiation into M1 macrophages, or with IL-4 and IL-13 to promote differentiation into M2 macrophages. This was done in the absence or presence of FABP3/4/5/7 inhibitors. High frequency of the marker MHC-II (**FIG. 13A**) and high levels of IL-12 (**FIG. 13B**) were used to verify M1 polarization of macrophages. High frequency of the markers CD36 (**FIG. 13C**) and CD206 (**FIG. 13D**), and high levels of IL-10 (**FIG. 13E**) were used to verify M2 polarization of macrophages. Expression levels of CD206 in macrophages that were differentiated into M2 status in the presence of one of FABP inhibitors **FTS005**, or the commercially available inhibitor BMS480404 were significantly lower than the M2 control (**FIG. 13F**). Similarly, levels of IL-10 that is well known to be secreted by M2 macrophages in the cells differentiated in the presence of FABP3/4/5/7 inhibitors, were markedly decrease (**FIG. 13G**) while levels of IL-12, known to be secreted by M1 macrophages, were significantly elevated (**FIG. 13H**). Thus, the data indicate that FABP3/4/5/7 inhibitors can be utilized to block differentiation of macrophages from naïve to M2 state as indicated in by both cell surface markers and secreted cytokines. To test the effect of FABP3/4/5/7 inhibitors on differentiation of macrophages from M1 to M2 status, cells were initially differentiated into M1 macrophages then into M2 macrophages in the presence of FABP3/4/5/7 inhibitors. Frequency of CD206+ macrophage population (**FIG. 13I**) as well as expression levels of CD206 (**FIG. 13J**) in differentiated cells were significantly decrease in the presence of FABP3/4/5/7 inhibitors and levels of IL-12 was markedly increased (**FIG. 13K**). Taken together, the data suggest that FABP3/4/5/7 inhibitors can be utilized to modulate M1 and M2 macrophage cells population.

[0463] While the foregoing disclosure of the present invention has been described in some detail by way of example and illustration for purposes of clarity and understanding, this disclosure including the examples, descriptions, and embodiments described herein are for illustrative purposes, are intended to be exemplary, and should not be construed as limiting the present disclosure. It will be clear to one skilled in the art that various modifications or changes to the examples, descriptions, and

embodiments described herein can be made and are to be included within the spirit and purview of this disclosure and the appended claims. Further, one of skill in the art will recognize a number of equivalent methods and procedure to those described herein. All such equivalents are to be understood to be within the scope of the present disclosure and are covered by the appended claims.

[0464] Additional embodiments of the invention are set forth in the following claims.

[0465] The disclosures of all publications, patent applications, patents, or other documents mentioned herein are expressly incorporated by reference in their entirety for all purposes to the same extent as if each such individual publication, patent, patent application or other document were individually specifically indicated to be incorporated by reference herein in its entirety for all purposes and were set forth in its entirety herein. In case of conflict, the present specification, including specified terms, will control.

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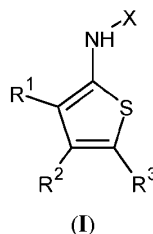
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28. Zhang Y, Li Q, Rao E, Sun Y, Grossmann ME, Morris RJ, Cleary MP, Li B: **Epidermal Fatty Acid binding protein promotes skin inflammation induced by high-fat diet.** Immunity 2015, **42**:953-964.
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CLAIMS

What is claimed is:

1. A compound of structural formula I or a pharmaceutically acceptable salt thereof.

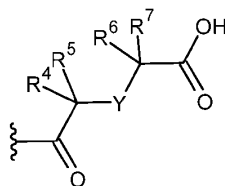


wherein,

R^1 is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro;

X is a moiety of formula:



wherein,

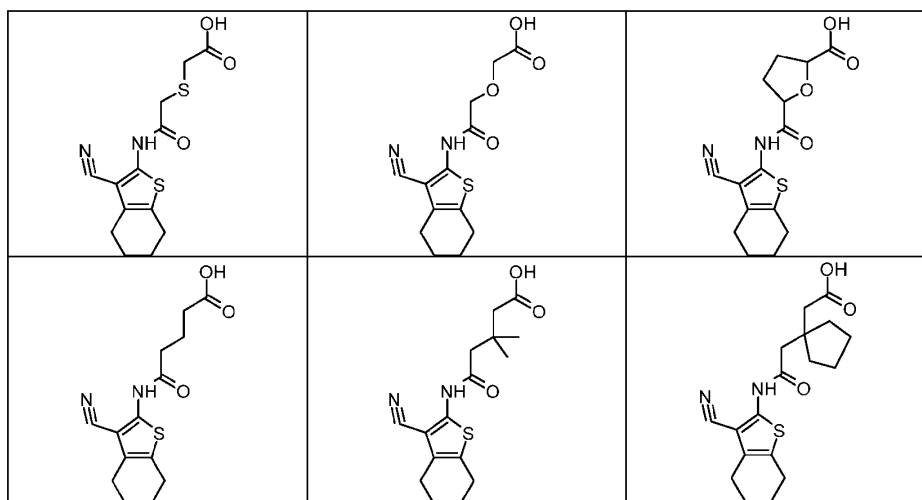
Y is a heteroatom selected from $-S-$, and $-O-$, or is $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

R^4 , R^5 , R^6 and R^7 is each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, and/or

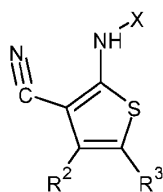
R^4 and R^5 together or R^6 and R^7 together form a cyclopropyl ring or a cyclobutyl ring, or

R^5 and R^6 together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring;

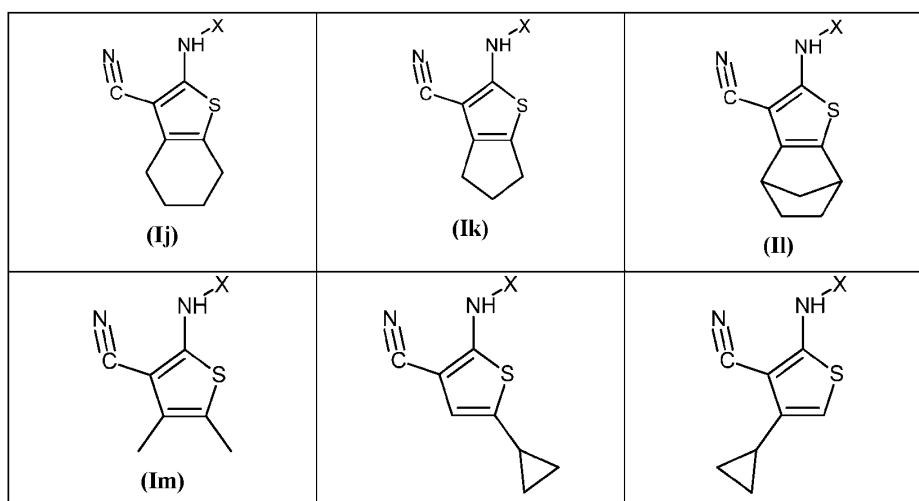
with the proviso that the compound of structural formula I excludes the following compounds:

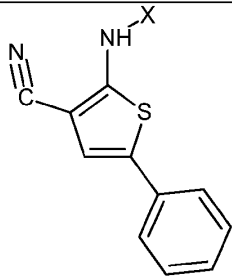
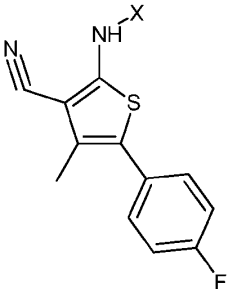
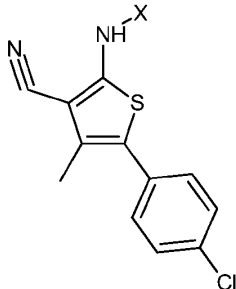
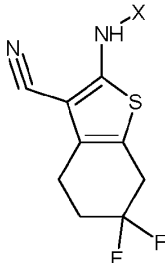
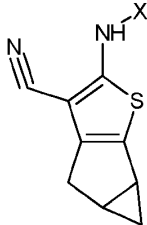


- The compound of claim 1, wherein R¹ is cyano.
- The compound of claim 1, wherein the compound has a structural formula **Ia**:

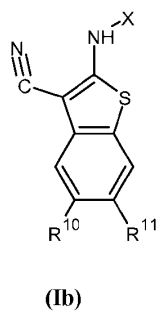
**(Ia).**

- The compound according to claim 3, wherein the compound has a structural formula selected from **Ij**, **Ik**, **Il**, **Im**, **In**, **Io**, **Ip**, **Ir**, **Is**, and **It**:



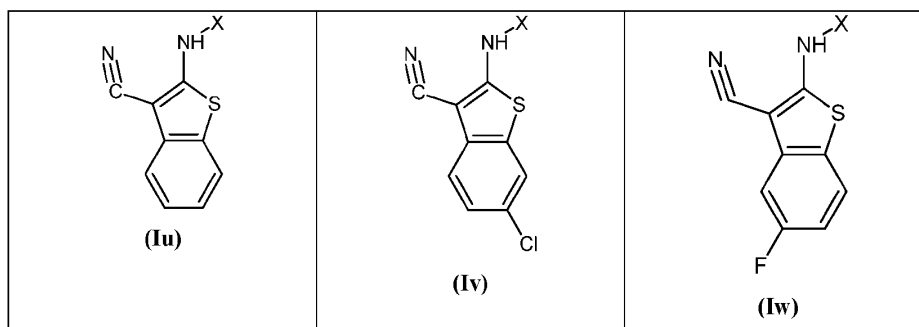
	(In)	(Io)
 (Ip)	 (Iq)	 (Ir)
 (Is)	 (It)	

5. The compound of claim 1, wherein the compound has a structural formula selected from **Ib**

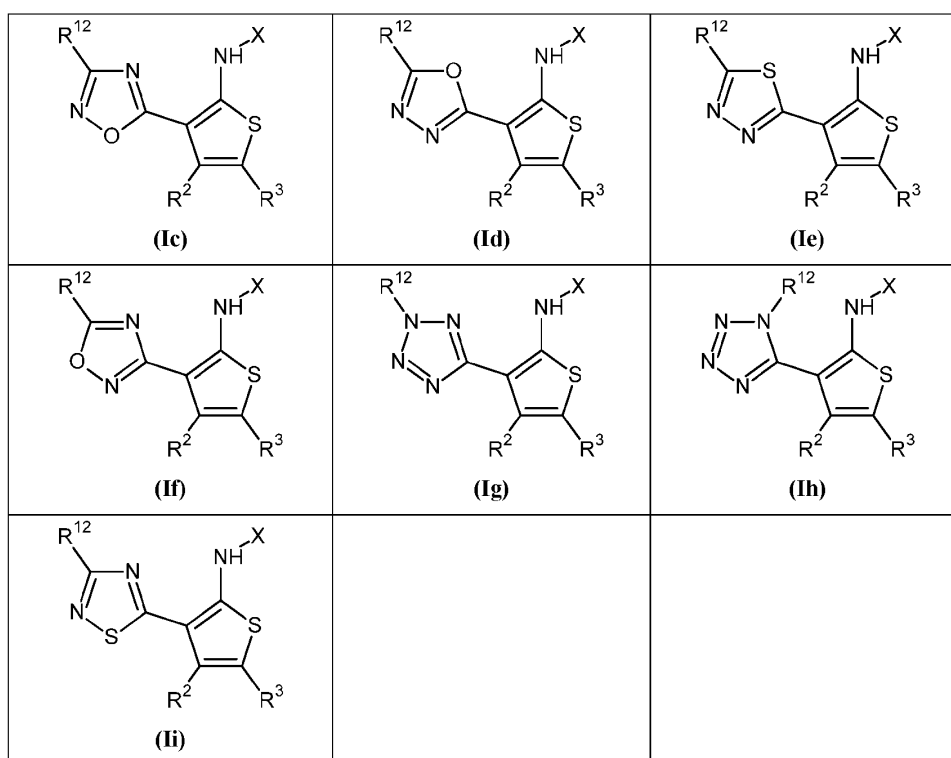


wherein R¹⁰ and R¹¹ are each independently selected from hydrogen, halogen, C₁-C₄ linear or branched alkyl, cyclopropyl, and cyclobutyl.

6. The compound according to claim 5, wherein the compound has a structural formula selected from **Iu**, **Iv**, and **Iw**:

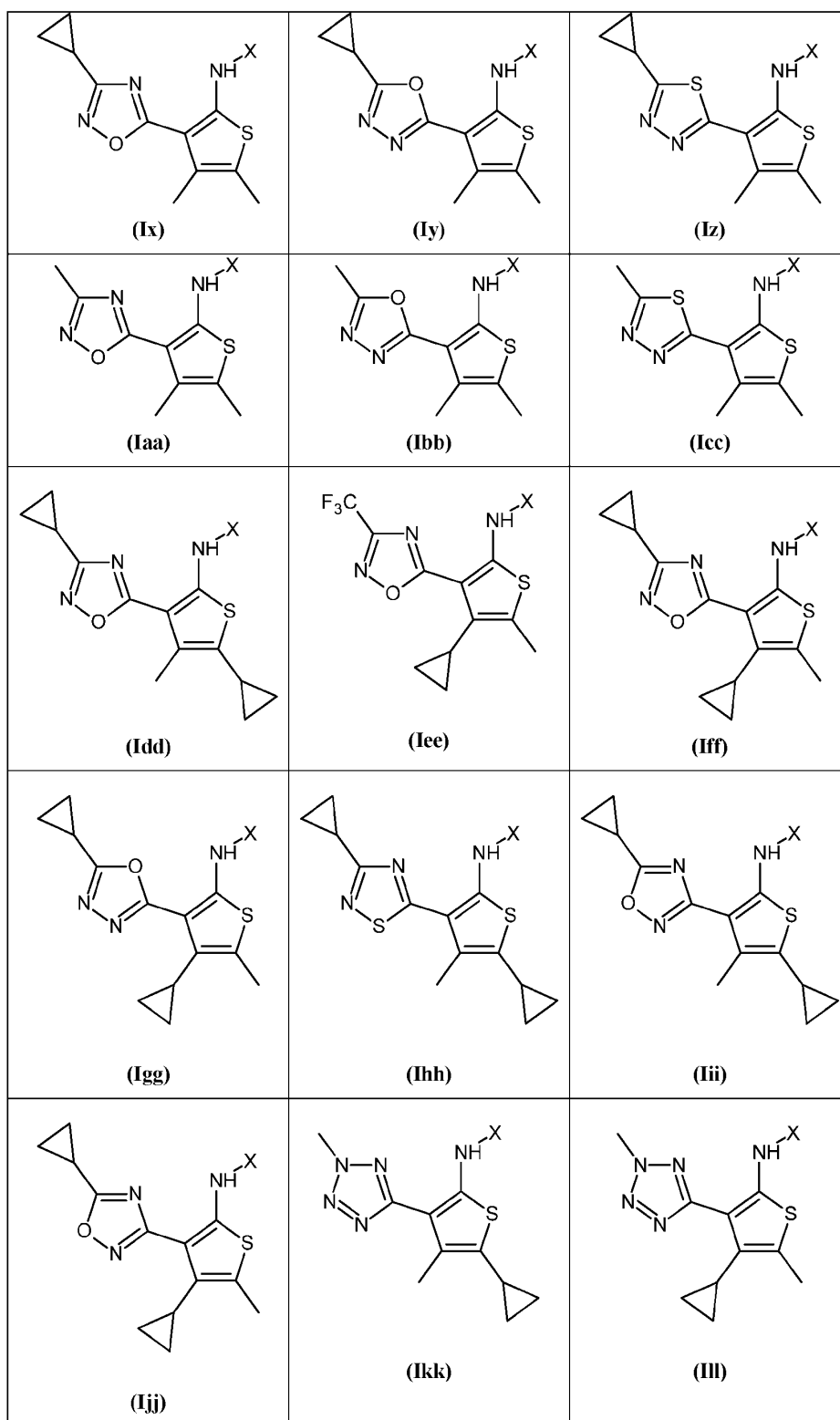


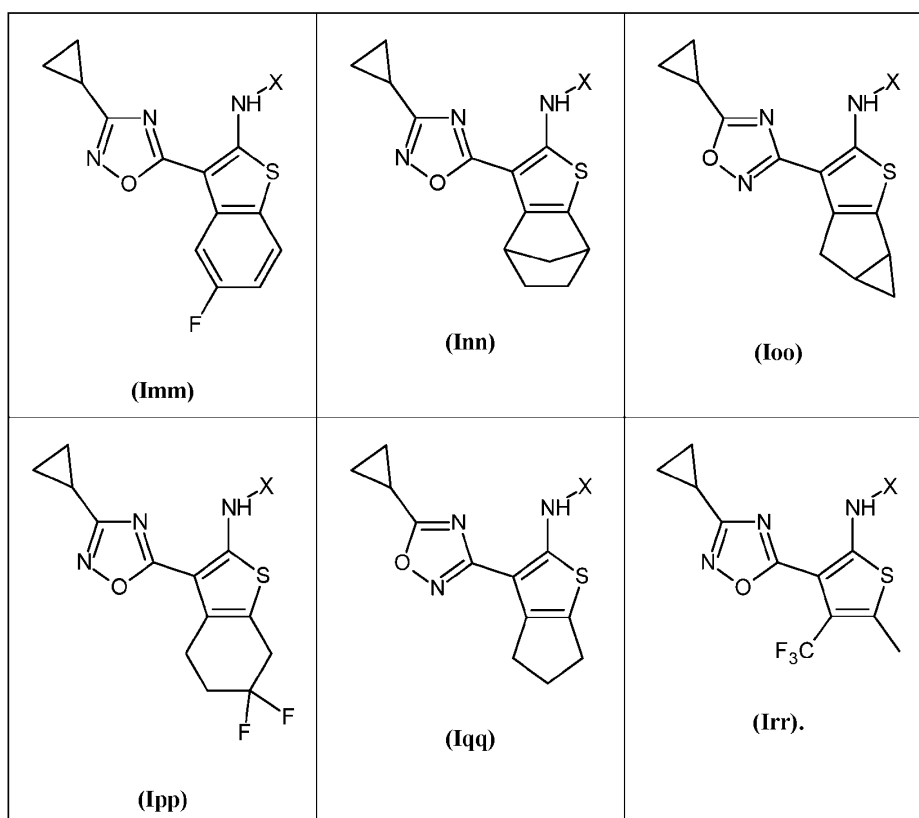
7. The compound of claim 1, wherein R^1 is a 5-membered heteroaryl ring, and R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl.
8. The compound of claim 1, wherein the compound has a structural formula selected from formulas **Ic**, **Id**, **Ie**, **If**, **Ig**, **Ih**, and **Ii**:



wherein R^{12} is selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl.

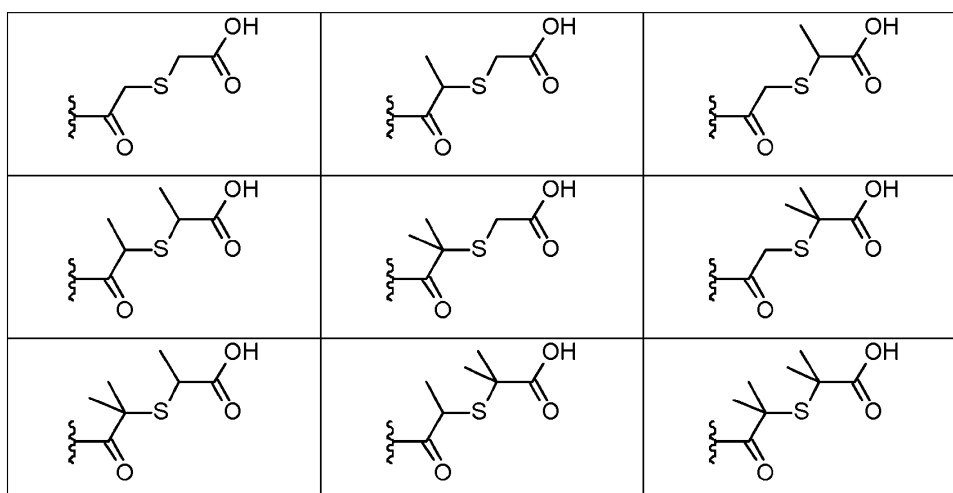
9. The compound of claim 8, wherein the compound has a structural formula selected from **Ix**, **Iy**, **Iz**, **Iaa**, **Ibb**, **Icc**, **Ida**, **Iee**, **Iff**, **Igg**, **Ihh**, **Iii**, **Ijj**, **Ikk**, **Ill**, **Imm**, **Inn**, **Ioo**, **Ipp**, **Iqq**, and **Irr**:

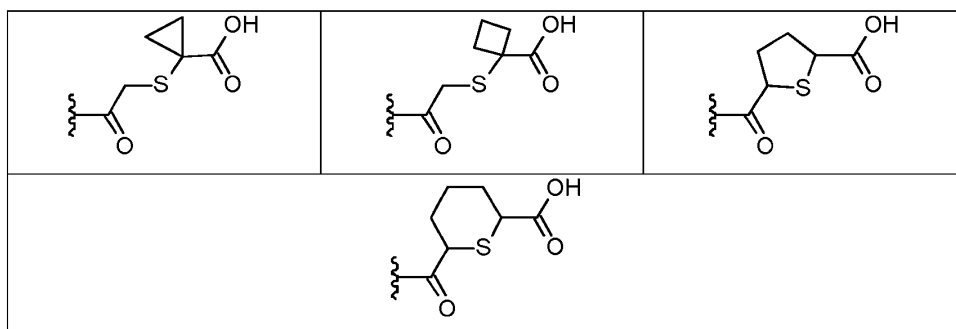




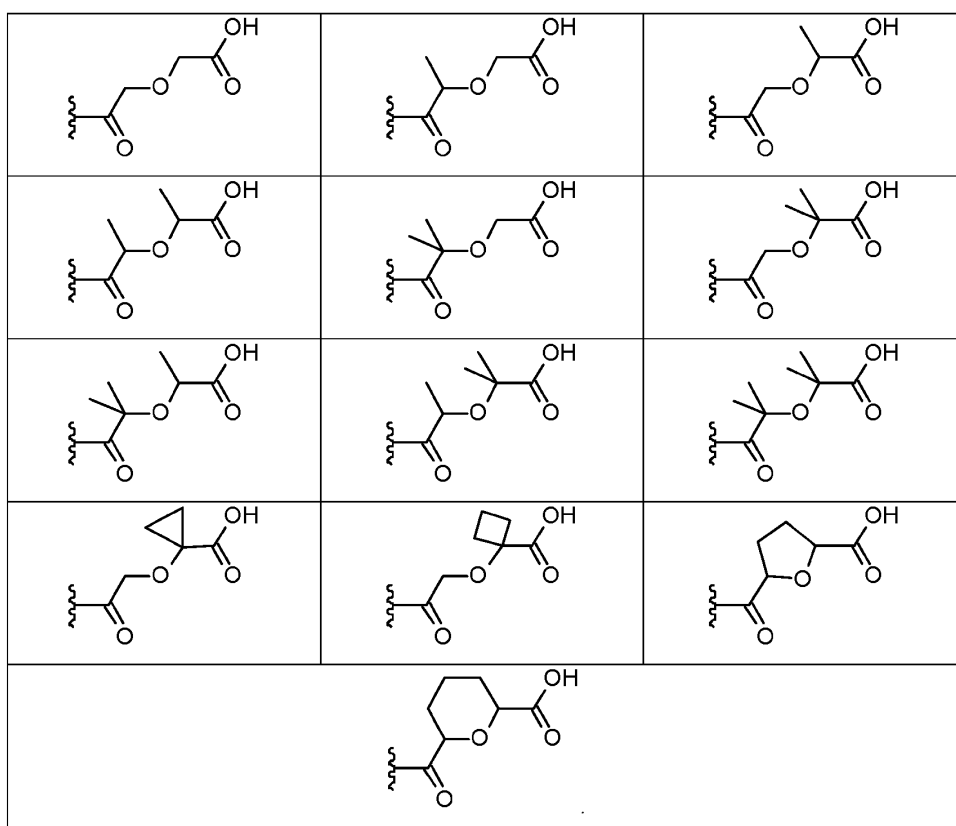
10. The compound of any one of claims 1-9, wherein Y is selected from -S- or -O- and R⁴, R⁵, R⁶ and R⁷ are each independently hydrogen or C₁-C₄ linear or branched alkyl.

11. The compound of any one of claims 1-9, wherein the X moiety is selected from:

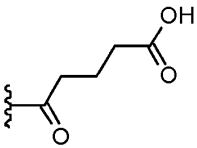
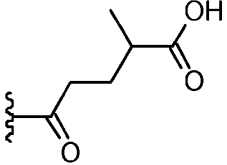
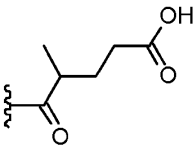
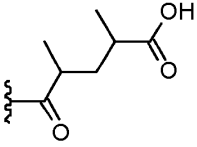
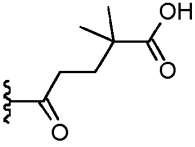
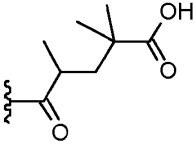
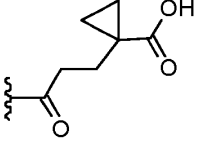
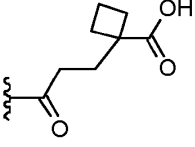
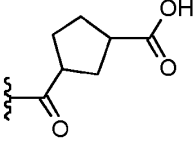
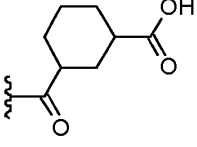
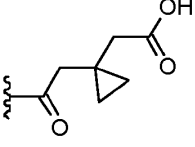
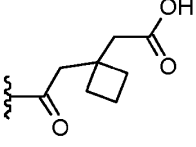
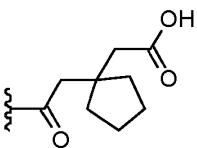
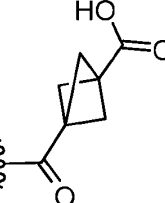
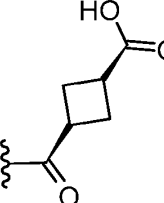
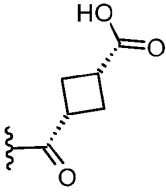




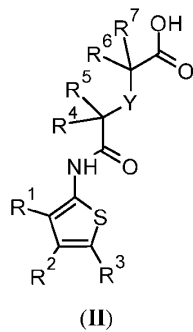
12. The compound of any one of claims 1-9, wherein the X moiety is selected from:



13. The compound of any one of claims 1-9, wherein the X moiety is selected from:

14. A compound of structural formula **II** or a pharmaceutically acceptable salt thereof,



wherein,

R^1 is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro;

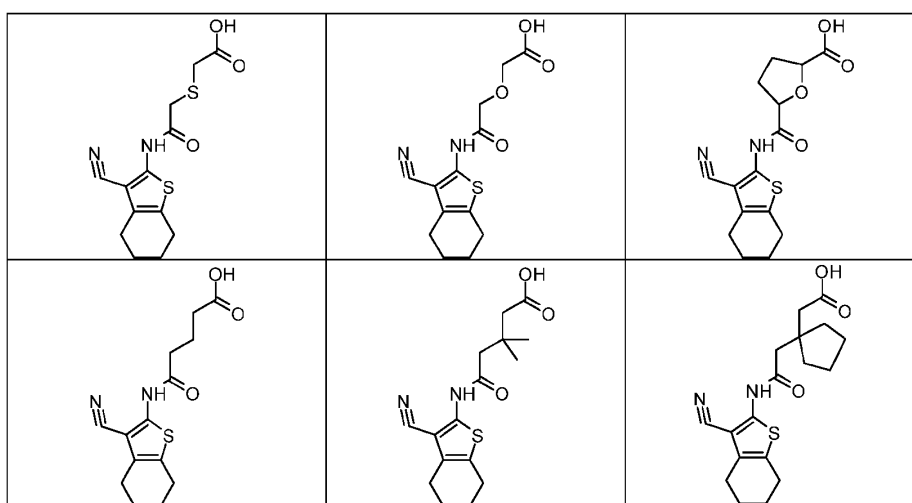
Y is a heteroatom selected from -S-, and -O-, or is $-CR^8R^9$ -, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

R^4 , R^5 , R^6 and R^7 is each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, and/or

R^4 and R^5 together or R^6 and R^7 together form a cyclopropyl ring or a cyclobutyl ring, or

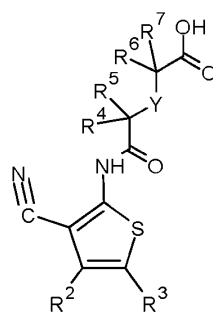
R^5 and R^6 together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring;

with the proviso that the compound of structural formula **II** excludes the following compounds:



15. The compound of claim 13, wherein R^1 is cyano.

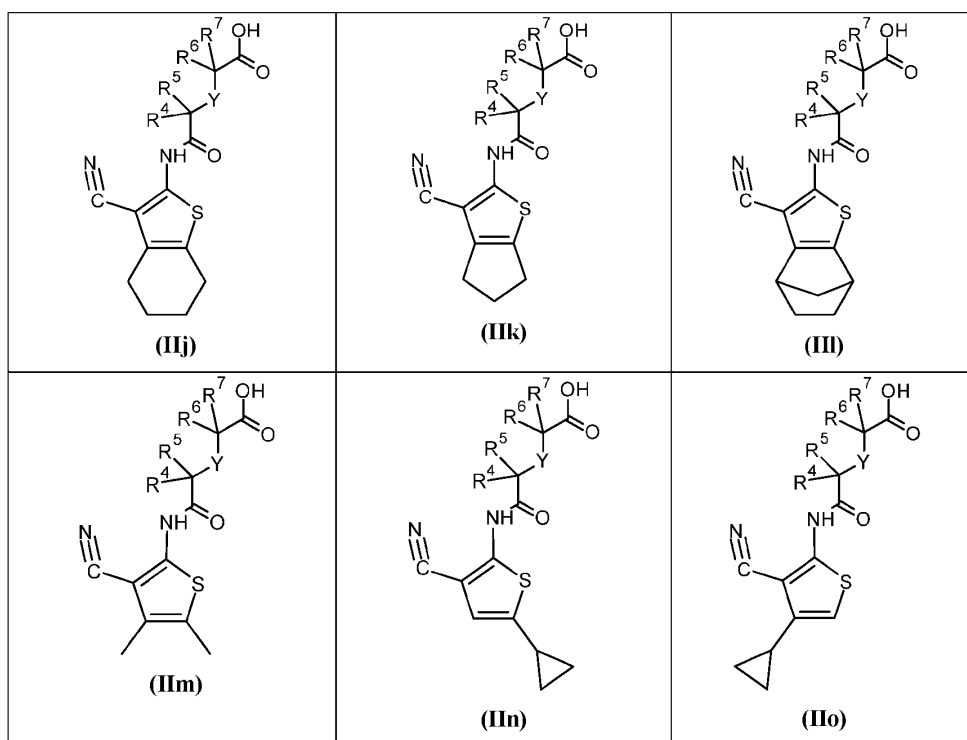
16. The compound of claim 13, wherein the compound has a structural formula **IIa**:

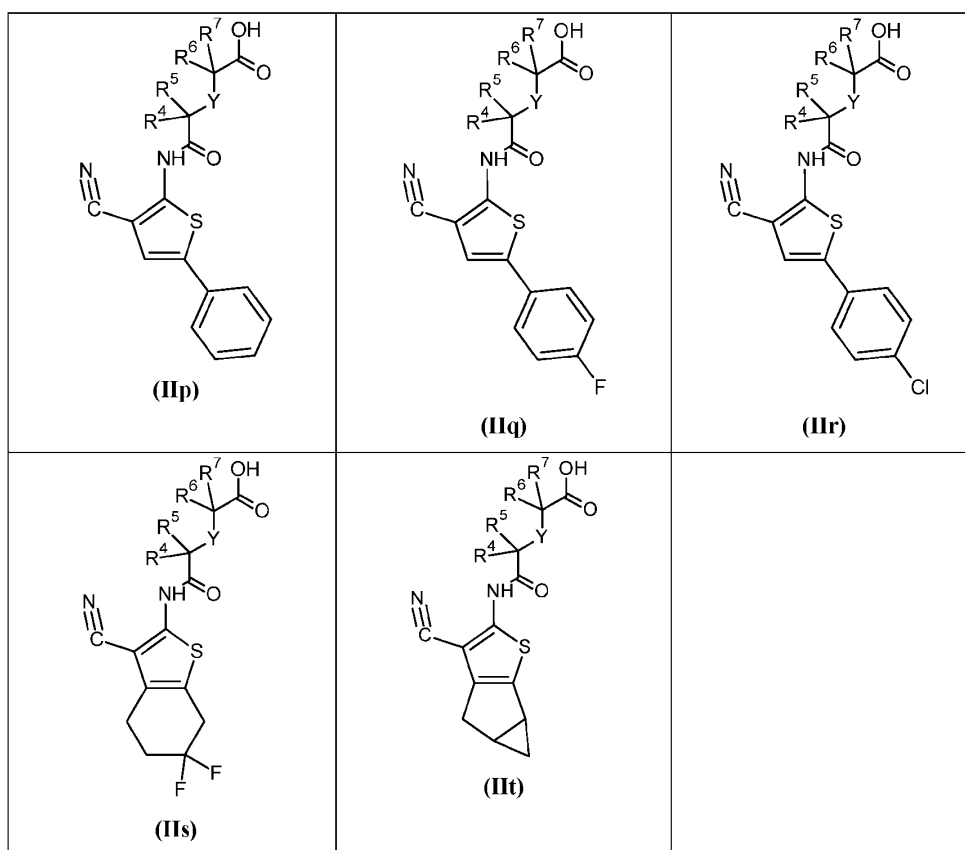


(IIa)

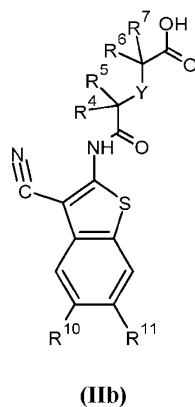
wherein the chemical groups R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II**.

17. The compound of claim 16, wherein the compound has a structural formula selected from **IIj**, **IIk**, **IIl**, **IIm**, **IIo**, **IIp**, **IIq**, **IIr**, **IIs**, and **IIt**:



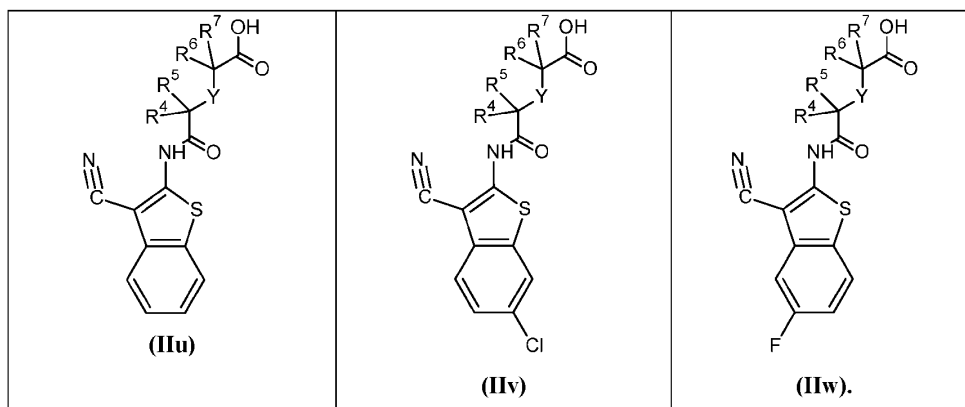


18. The compound of claim 13, wherein the compound has a structural formula **IIb**:

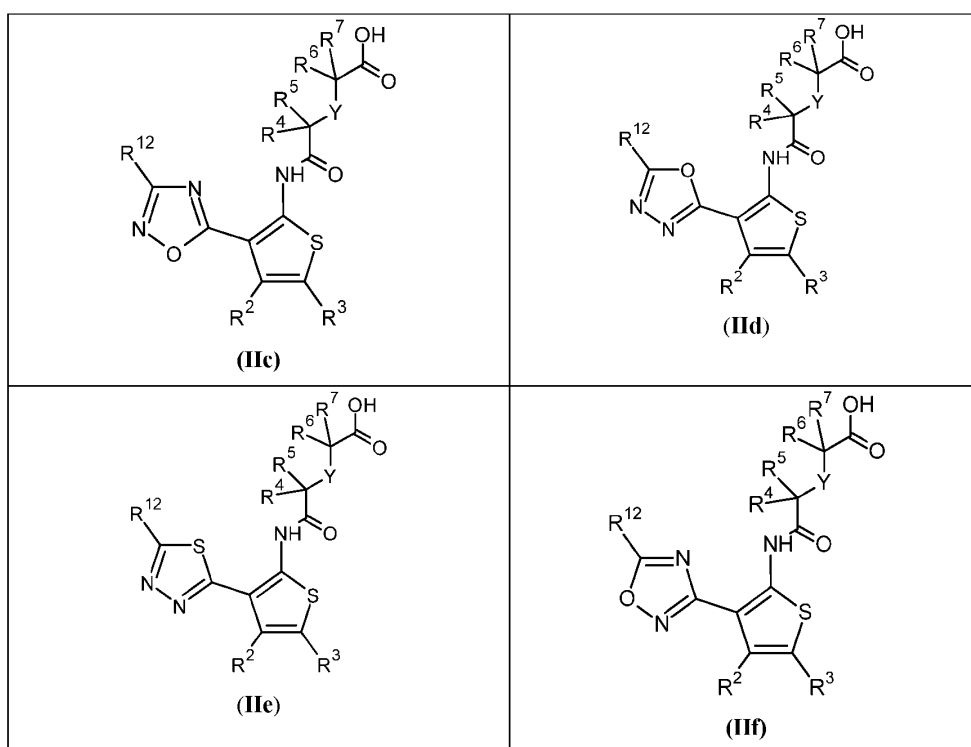


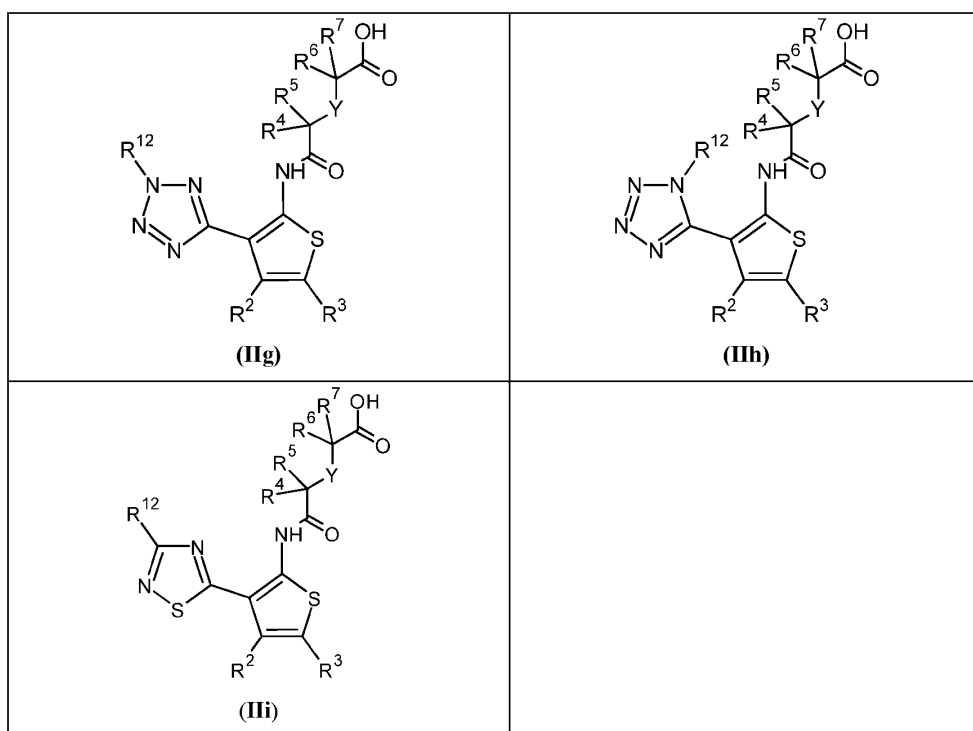
wherein the chemical groups R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II**, and R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl.

19. The compound of claim 18, wherein the compound has a structural formula selected from **IIu**, **IIv**, and **IIw**



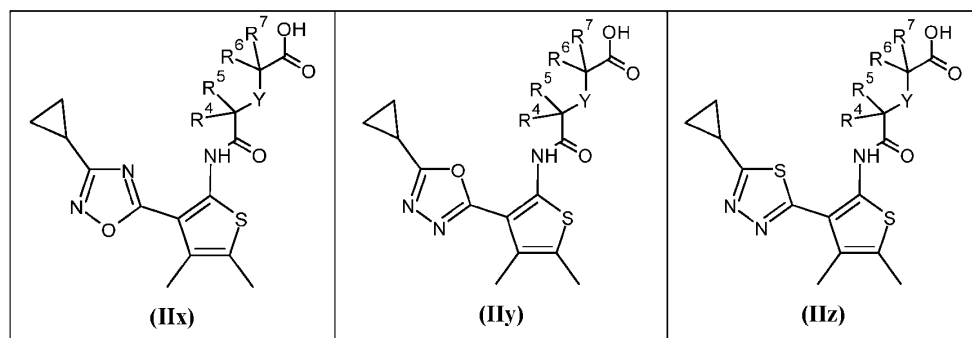
20. The compound of claim 13, wherein the compound has a structural formula selected from formulas **IIc**, **IId**, **IIf**, **IIg**, **IIh**, and **IIi**:

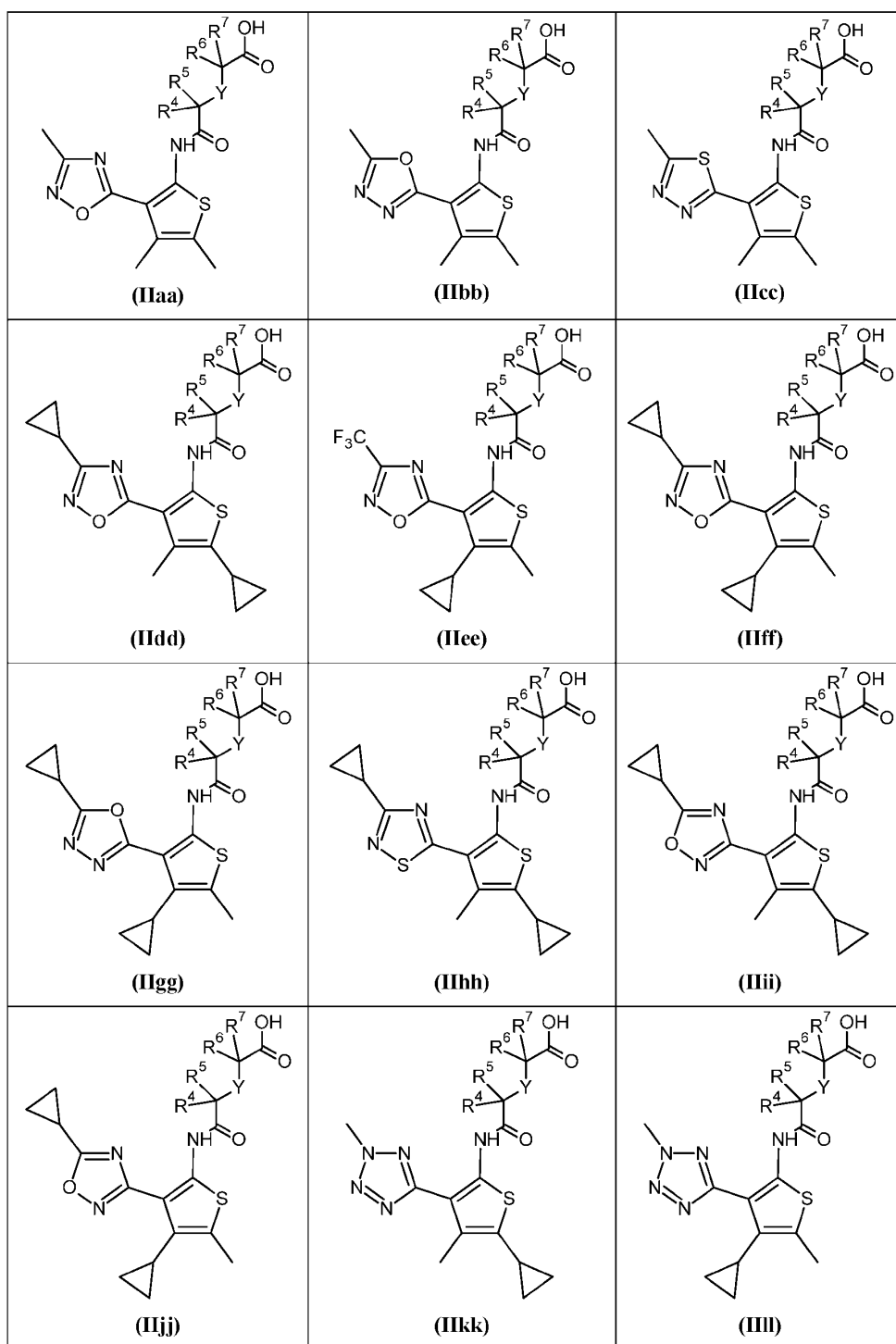


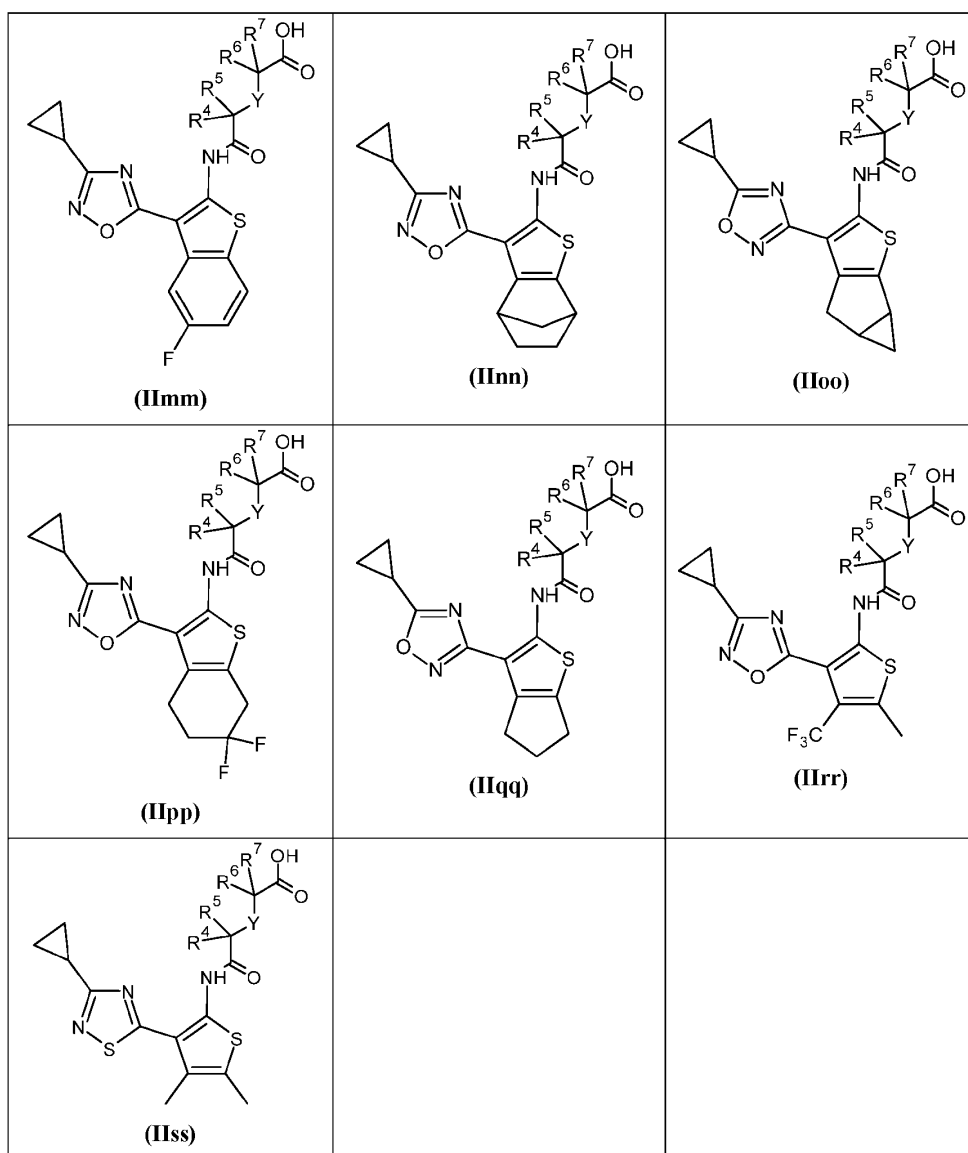


wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for the compound of structural formula **II**, and R^{12} is a hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, or phenyl.

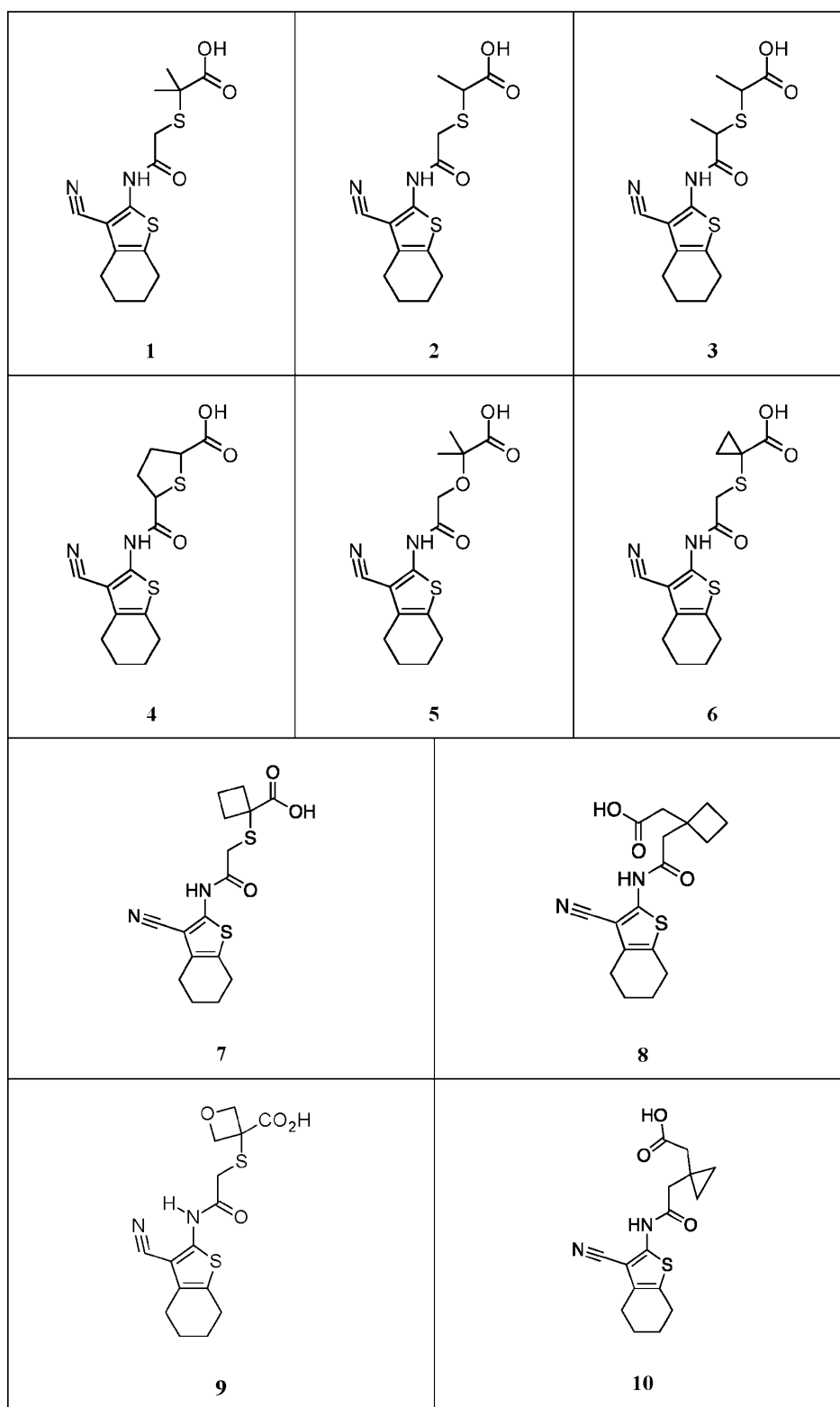
21. The compound of claim 20, wherein the compound has a structural formula selected from **IIx**, **IIy**, **IIz**, **IIaa**, **IIbb**, **IIcc**, **IIdd**, **IIee**, **IIff**, **IIgg**, **IIhh**, **IIii**, **IIjj**, **IIkk**, **IIll**, **IImm**, **IInn**, **IIoo**, **IIpp**, **IIqq**, **IIrr**, and **IIss**:

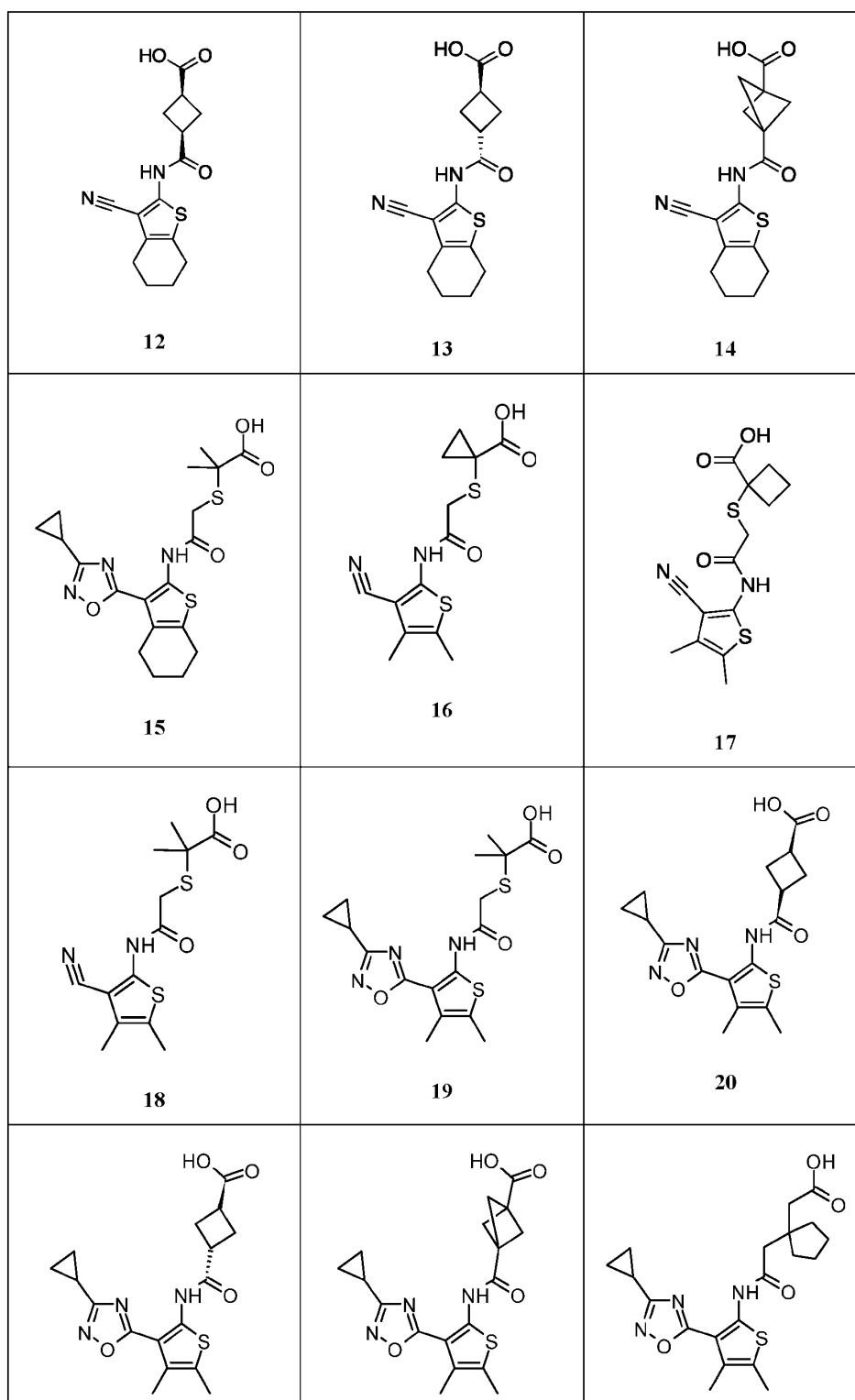


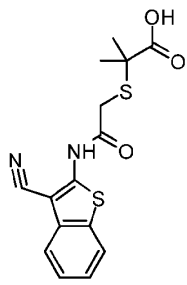
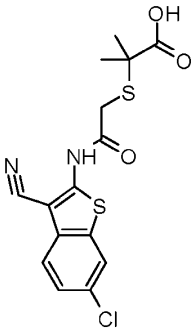
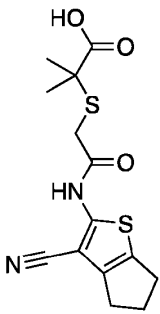
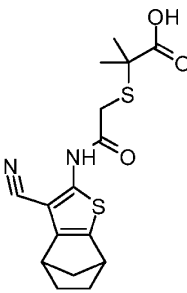
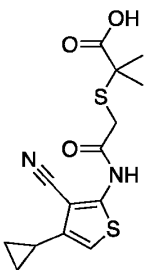
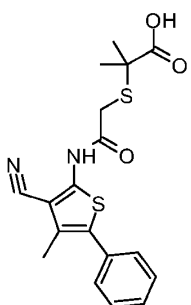
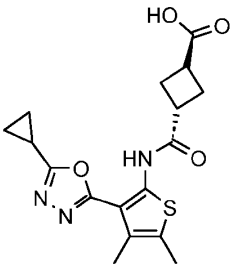
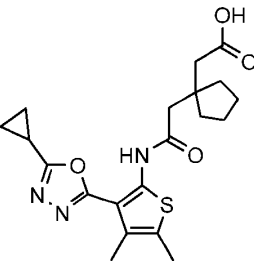
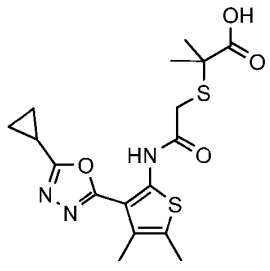


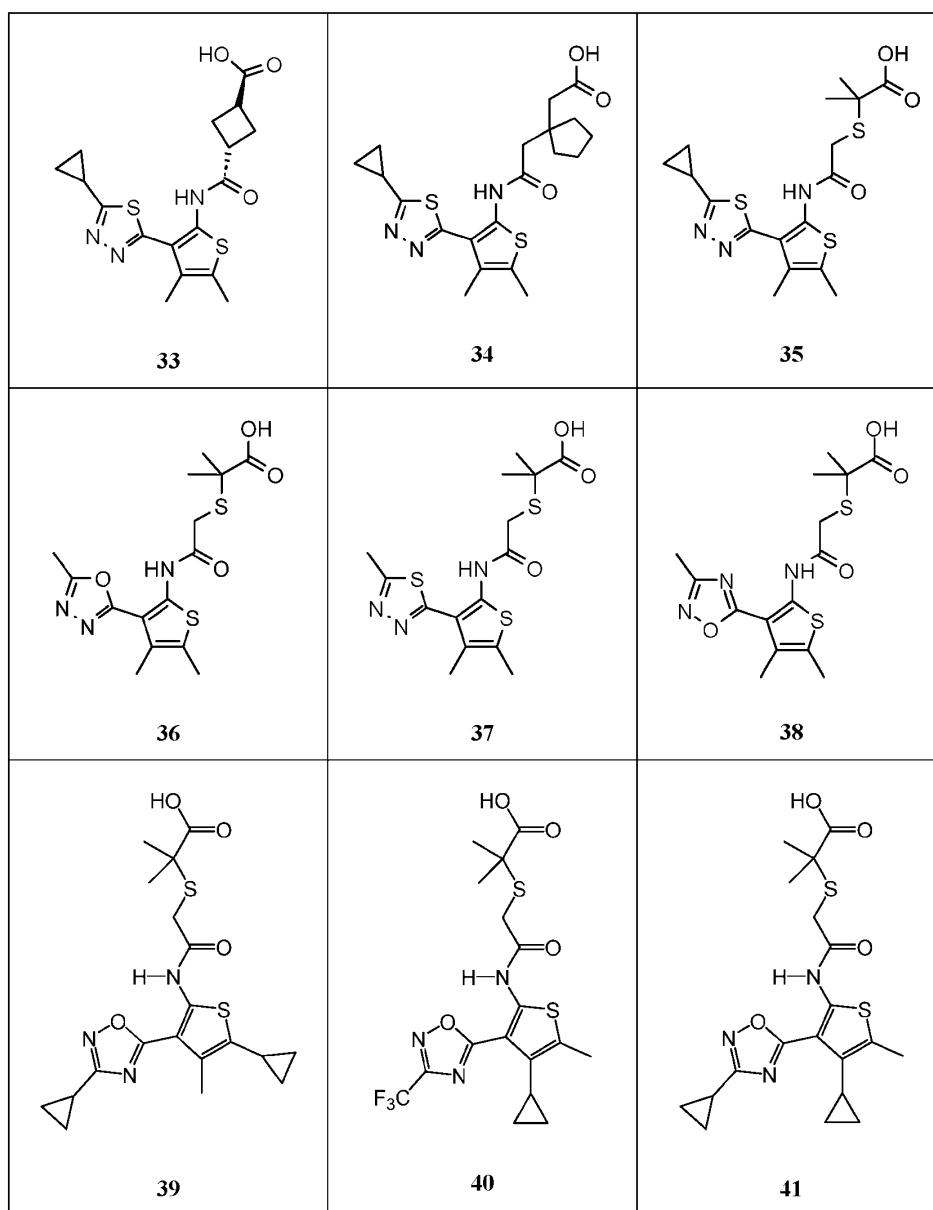


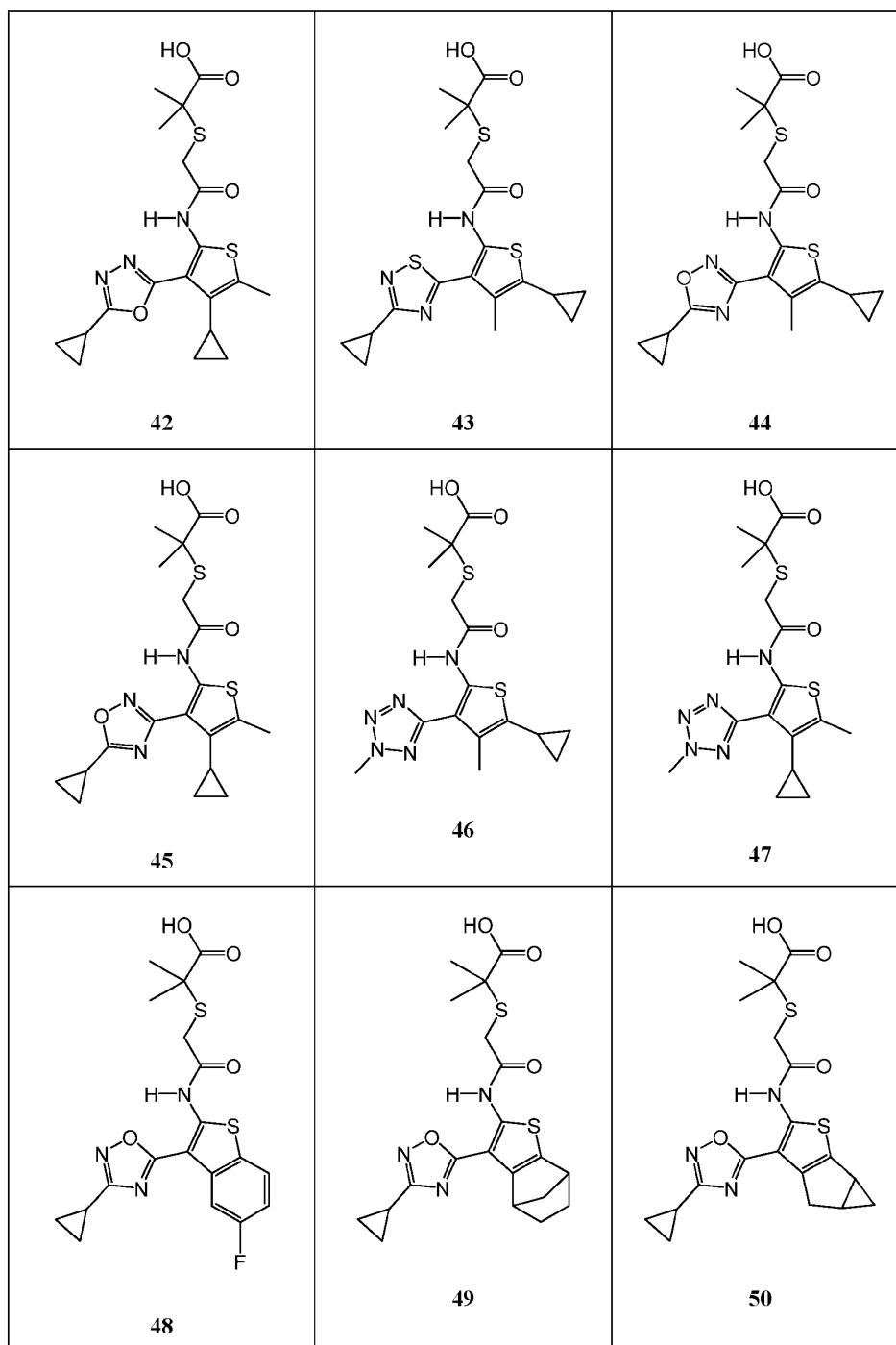
22. The compound of any one of claims 1-21, wherein the compound is selected from compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, and 65:

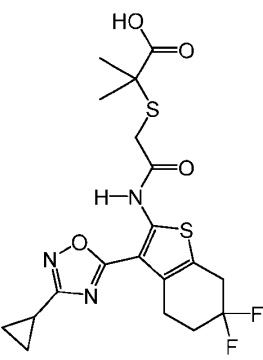
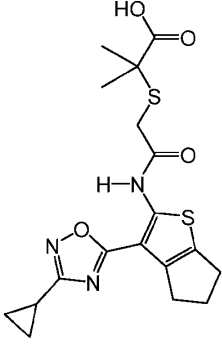
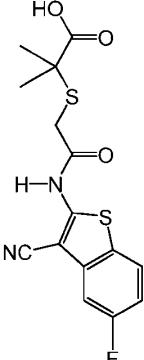
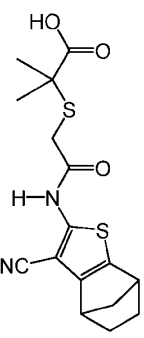
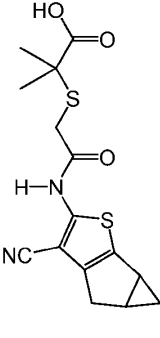
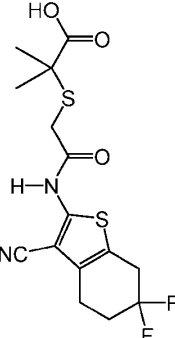
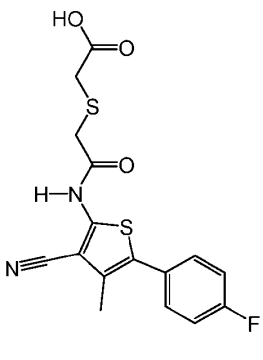
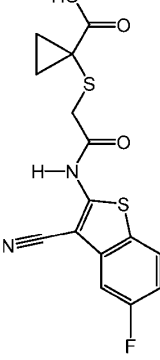
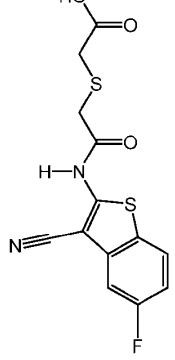


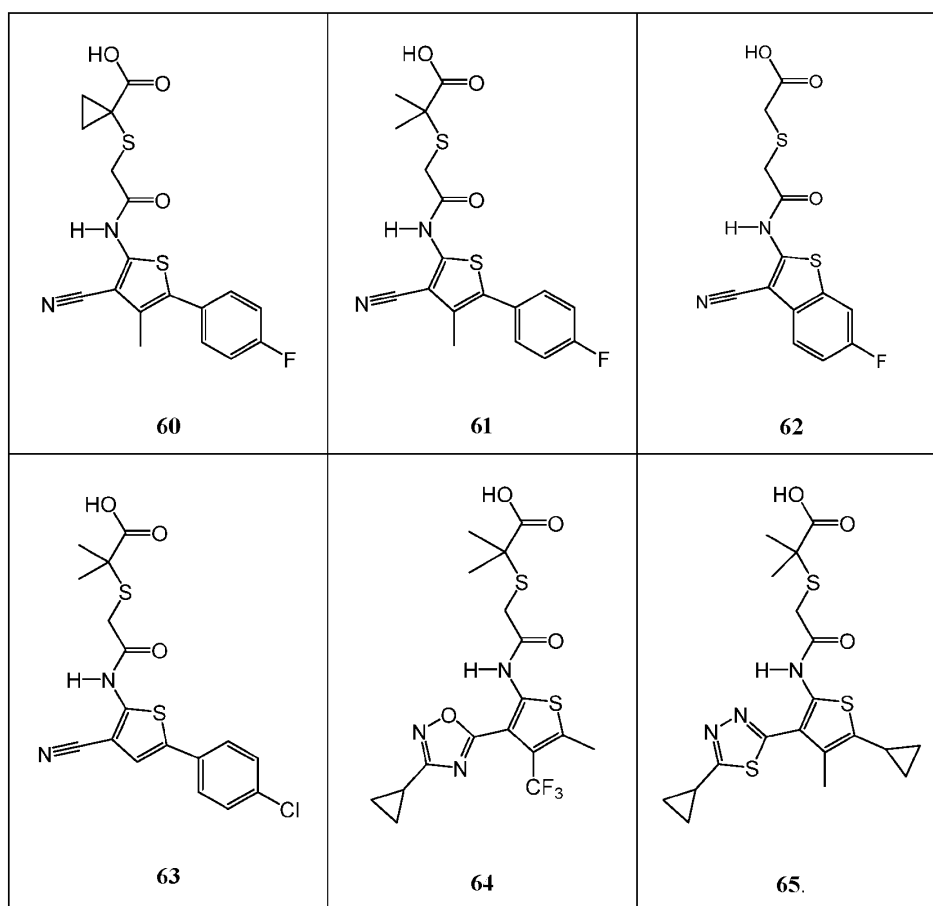


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 54	 55	 56
 57	 58	 59

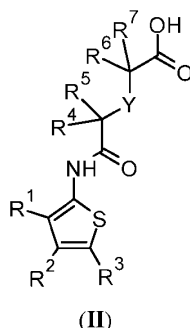


23. A pharmaceutical composition, comprising a compound of any one of claims 1-22 and one or more adjunct ingredients.
24. A method for treating a subject having a disease or condition affected by FABP3/4/5/7, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-22, or a pharmaceutical composition of claim 23.
25. The method of claim 24, wherein disease or condition affected by FABP3/4/5/7 is selected from atherosclerosis, coronary atherosclerosis, arterial fibrosis, pulmonary hypertension, heart failure, obesity, Type-2 diabetes, Type-1-diabetes, gestational diabetes, polycystic ovary syndrome, endometriosis, conditions affected by lipid metabolism and free fatty acid serum levels, metabolic disorders, fatty liver disease, kidney fibrosis, systemic inflammation, acute inflammation, allergic inflammation, airway inflammation, viral infection (e.g., COVID-19, common cold), skin diseases (e.g., vitiligo, psoriasis, atopic dermatitis, allergic contact dermatitis, mycosis fungoides, alopecia areata, cicatricial alopecia, graft vs. host disease (GvHD), contact dermatitis, chronic eczema, dermatitis herpetiformis, cutaneous lupus, scleroderma, dermatomyositis, vasculitis, pemphigus,

epidermolysis bullosa, linear IgA, blistering disease), neurological conditions and diseases (e.g., pain, multiple sclerosis (MS), Parkinson's disease, autoimmune diseases (e.g., experimental autoimmune encephalomyelitis (EAE), asthma, type-1-diabetes, autoimmune lung disease, autoimmune hepatitis, rheumatoid arthritis (RA), spondyloarthropathy, vesicular stomatitis virus infection, multiple sclerosis (MS), lupus nephritis, Crohn's disease, ulcerative colitis, and food allergy), ischemic stroke, graft versus host disease (GvHD) and cancer (e.g., breast cancer, prostate cancer, ovarian cancer, skin cancer, gastric cancer, glioma, cholangiocarcinoma, bladder cancer, multiple myeloma, colorectal cancer, hepatocellular cancer, cervical cancer, oral squamous cell carcinoma, and/or non-small cell lung cancer (NSCLC)).

26. A method for controlling the free fatty acid serum levels in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-22, or a pharmaceutical composition of claim 23.
27. The method of claim 26, wherein the subject has a disease or condition caused by, affected by, and/or characterized by a lack of control of the free fatty acid serum levels in the subject,
28. A method for treating a subject having cancer or diagnosed with cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any claims 1-22, or a pharmaceutical composition of claim 23.
29. The method of claim 28, wherein the cancer is selected from breast cancer, prostate cancer, ovarian cancer, hepatocellular cancer, multiple myeloma, neuroblastoma, lung adenocarcinoma or gastric carcinoma.
30. The method of any one of claims 28-29, wherein the cancer is characterized by metastasis of TNBC cells.
31. A method for sensitizing cancer cells for an additional treatment in a subject having cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-22, or a pharmaceutical composition of claim 23.
32. The method of claim 31, wherein the additional treatment comprises administration of a chemotherapeutic agent; optionally, wherein the chemotherapeutic agent is selected from doxorubicin, gemcitabine, cisplatin, paclitaxel, a PARP inhibitor compound, all-trans retinoic acid (atRA), and an immune checkpoint inhibitor, such as an anti-PD-1 or anti-PD-L1 antibody.
33. A method for treating a subject diagnosed with metabolic syndrome and/or atherosclerosis, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-22, or a pharmaceutical composition of claim 23.

34. The method of claim 33, wherein the subject is diagnosed with Type-2 diabetes.
35. A method for modulating immune cell populations and/or immune cell activity in a subject in need thereof, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of claims 1-22, or a pharmaceutical composition of claim 23.
36. The method of claim 35, wherein the subject has a disease or disorder caused by, affected by, and/or characterized by immune cell populations and/or immune cell activity.
37. The method of claim 36, wherein the immune cells are M2 macrophages.
38. The method of claim 36, wherein the disease or disorder is cancer.
39. The method of claim 38, wherein the immune cells are tumor associated macrophages (TAMs).
40. The method of claim 36, wherein the disease or disorder is an autoimmune disease or disorder.
41. Use of a compound of any one of claims 1-22, or a pharmaceutical composition of claim 23 for the manufacture of a medicament for treating a subject according to any one of claims 24-40.
42. A process for preparing a compound of structural formula **II**



wherein,

R^1 is selected from hydrogen, cyano, and 5-membered heteroaryl ring;

R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, trifluoromethyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro;

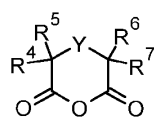
Y is a heteroatom selected from $-S-$, and $-O-$, or is $-CR^8R^9-$, wherein R^8 and R^9 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, or R^8 and R^9 together form a cyclopropyl, cyclobutyl, cyclopentyl, or oxetanyl ring;

R^4 , R^5 , R^6 and R^7 is each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, phenyl, and benzyl, and/or

R^4 and R^5 together or R^6 and R^7 together form a cyclopropyl ring or a cyclobutyl ring, or R^5 and R^6 together form a 5- to 6-membered carbocyclic or heterocyclic ring with Y as a member of the ring;

the method comprising:

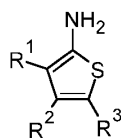
(a) combining in a solvent a substituted anhydride compound of formula **III**:



(III)

wherein Y, R^4 , R^5 , R^6 and R^7 are as defined above;

with a substituted 2-amino-thiophene compound of formula **IV**:

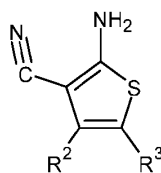


(IV)

wherein, R^1 , R^2 and R^3 are as defined above; and

(b) removing the solvent to obtain a compound having the structural formula **II**.

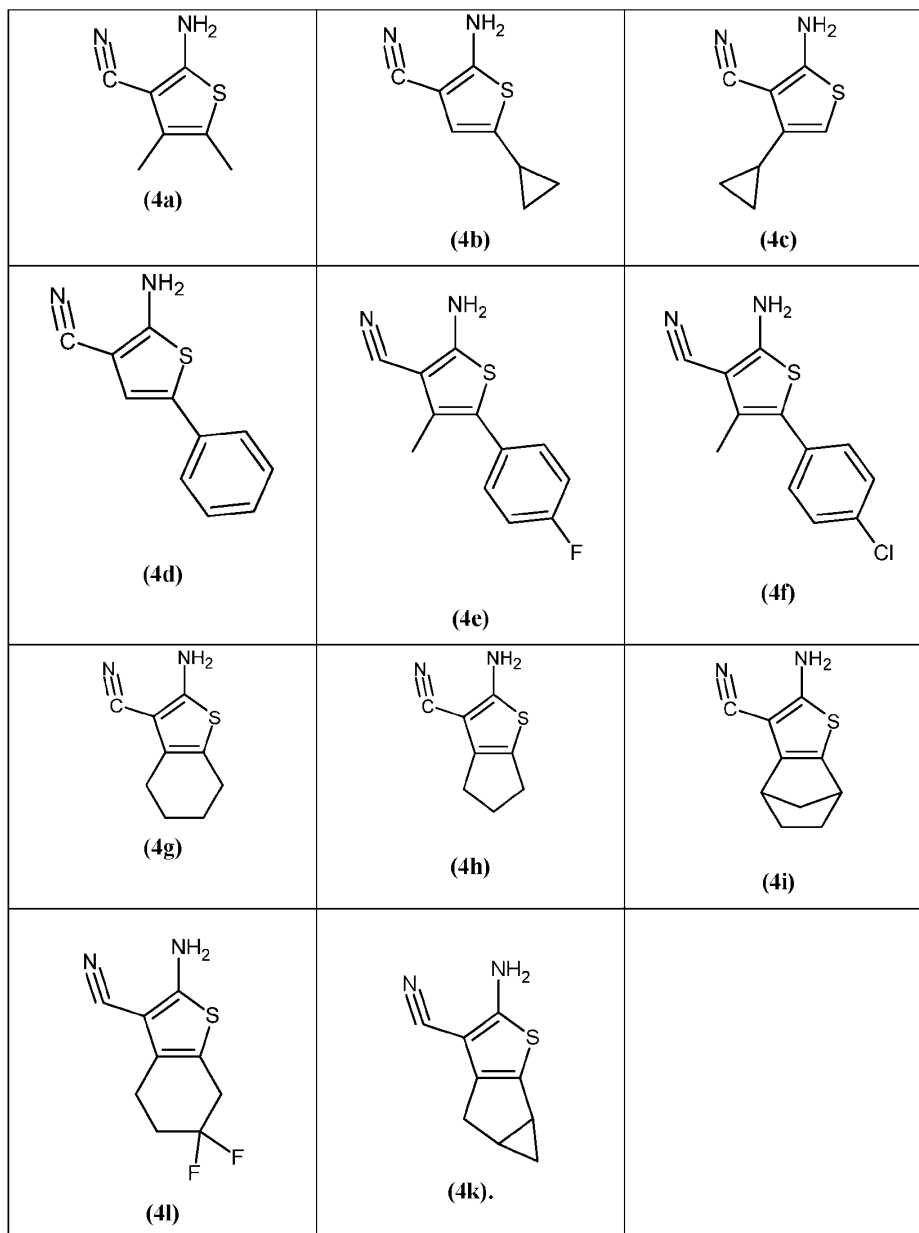
43. The process of claim 42, wherein the compound is the compound of structural formula **(IVa)**



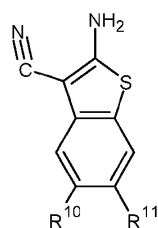
(IVa)

wherein, the chemical groups at R^2 and R^3 are each independently selected from hydrogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl, or R^2 and R^3 together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C_1 - C_4 -alkyl, methoxy, or fluoro.

44. The process of claim 43, wherein the compound is selected from compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4h**, **4i**, **4j**, and **4k**:



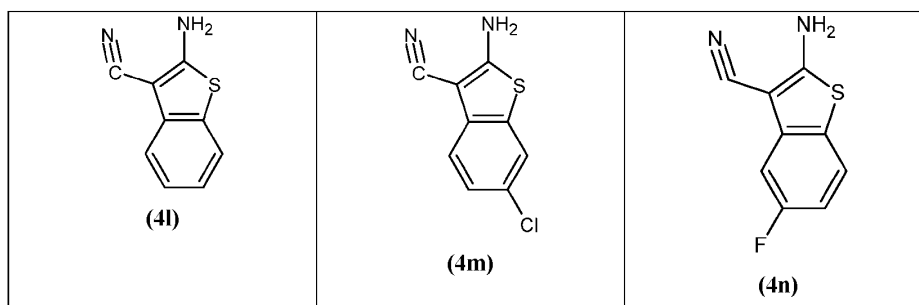
45. The process of claim 42, wherein the compound is the compound of structural formula **IVb**:



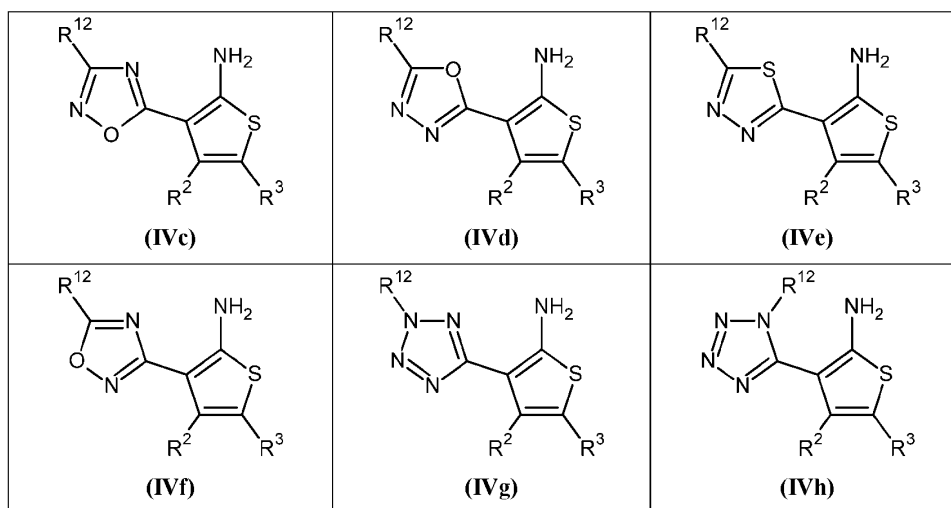
(IVb)

wherein R^{10} and R^{11} are each independently selected from hydrogen, halogen, C_1 - C_4 linear or branched alkyl, cyclopropyl, and cyclobutyl.

46. The process of claim 45, wherein the compound is selected from compounds **4l**, **4m**, and **4n**:



47. The process of claim 42, wherein the compound is selected from the compounds of structural formula **IVc**, **IVd**, **IVe**, **IVf**, **IVg**, and **IVh**:



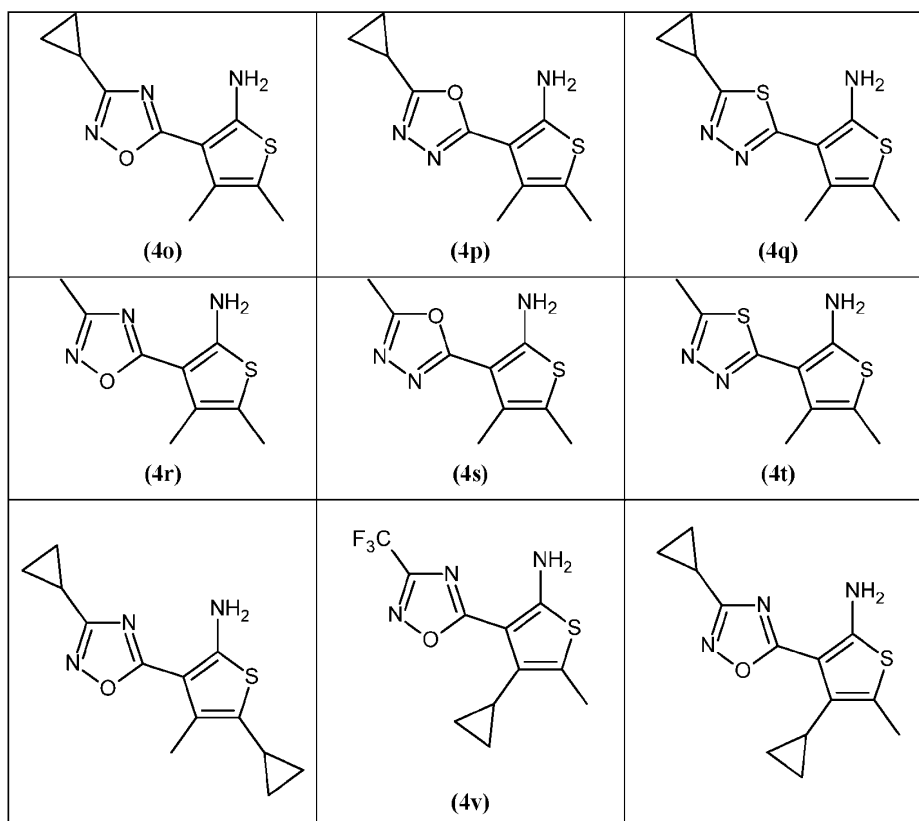


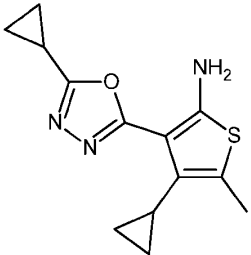
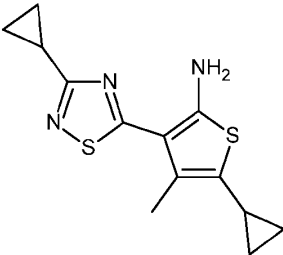
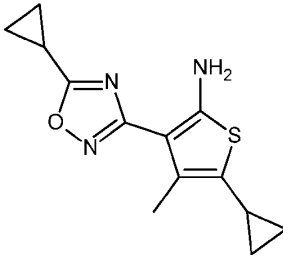
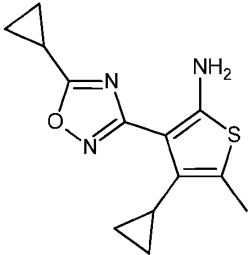
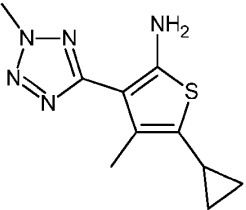
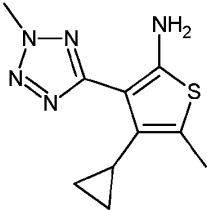
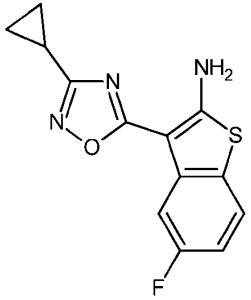
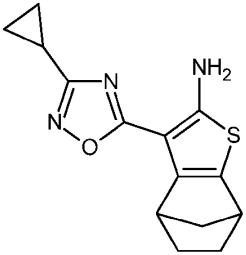
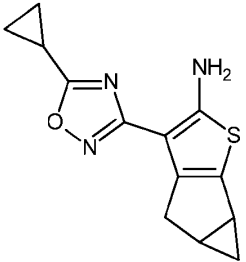
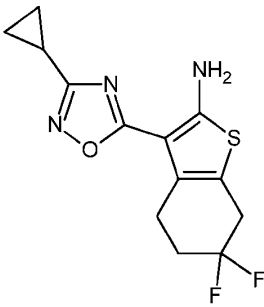
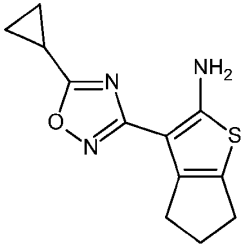
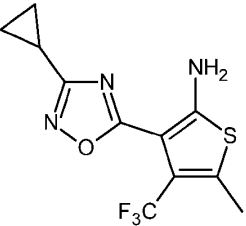
wherein,

the chemical groups at R² and R³ are each independently selected from hydrogen, C₁-C₄ linear or branched alkyl, cyclopropyl, cyclobutyl, phenyl, and benzyl, or R² and R³ together form a 5- to 8-membered monocyclic, bicyclic, or spirocyclic carbocycle or heterocycle ring, or a 5- to 8-membered aryl or heteroaryl ring, wherein the carbocycle, heterocycle, aryl, or heteroaryl ring is optionally substituted with one or two substituents selected from C₁-C₄-alkyl, methoxy, or fluoro; and

the chemical group at R¹² is selected from hydrogen, halogen, C₁-C₄ linear or branched alkyl, cyclopropyl, cyclobutyl, and phenyl.

48. The process of claim 47, wherein the compound is selected from compounds **4o**, **4p**, **4q**, **4r**, **4s**, **4t**, **4u**, **4v**, **4w**, **4x**, **4y**, **4z**, **4aa**, **4bb**, **4cc**, **4dd**, **4ee**, **4ff**, **4gg**, **4hh**, and **4ii**:



(4u)  (4x)	 (4y)	(4w)  (4z)
 (4aa)	 (4bb)	 (4cc)
 (4dd)	 (4ee)	 (4ff)
 (4hh)	 (4ii)	 (4ii).

(4gg)		
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