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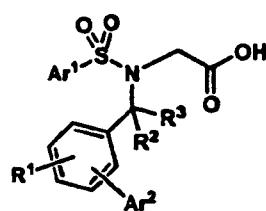
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(54) Title: GLYCINE SULFONAMIDES FOR USE AS INHIBITORS OF DIACYLGLYCEROL LIPASE



(I)

(57) Abstract: The present disclosure is generally directed to compounds of Formula (I) that can inhibit DAGL α and/or β activity, compositions comprising such compounds, and methods for inhibiting DAGL α and/or β activity.

GLYCINE SULFONAMIDES FOR USE AS INHIBITORS OF DIACYLGLYCEROL LIPASE

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional Application Serial Number 61/305,996 filed February 19, 2010.

The present disclosure is generally directed to compounds that can inhibit DAGL α and/or β activity, compositions comprising such compounds, and methods for inhibiting DAGL α and/or β activity.

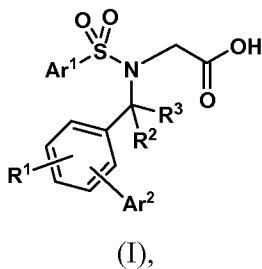
10 Diacylglycerol Lipase enzymes are esterases that hydrolyze diacylglycerol to form the endogenous cannabinoid 2-arachidonyl glycerol (2-AG) (*J Cell Biol* 2003;163:463–8). There are two isoforms of the enzyme, DAGL α and DAGL β . DAGL α is predominantly expressed throughout the CNS with limited expression in the periphery, whereas DAGL β is predominantly expressed in peripheral tissues (*J Cell Biol* 2003;163:463–8). Immunohistochemical studies have demonstrated DAGL α is localized post-synaptically, consistent with its role in generating 2-AG which acts as a retrograde messenger activating presynaptic cannabinoid receptors including CB1 (*J Neurosci* 2007;27(14):3663–3676, PLoS August 2007; 8:e709).

20 Consistent with the proposed role for DAGL α and DAGL β as key enzymes in endocannabinoid synthesis, genetically-modified mice that lack DAGL α expression (BMS, Lexicon) exhibit decreased tissue concentrations of 2-AG. In addition, the DAGL α knockout animals exhibit multiple phenotypes in animal models relevant to human diseases. For example, in models predictive of activity in affective disorders, DAGL α $-\text{}/-$ animals exhibit anxiolytic and antidepressant phenotypes. DAGL α $-\text{}/-$ animals also are resistant to diet-induced obesity, have decreased food intake. These animals also exhibit decreased body weight, body fat, sensitivity to pain, and improved cognitive performance demonstrating broad therapeutic potential for the enzyme.

25 Based on these data and the role of DAGL enzymes in endocannabinoid synthesis, compounds that inhibit DAGL α and/or β activity are predicted to have therapeutic utility in the treatment of schizophrenia, psychosis, bipolar disorder, depression, anxiety, pain, cognitive impairment, diabetes, obesity, hepatic steatosis, dyslipidemias, and other related disease states.

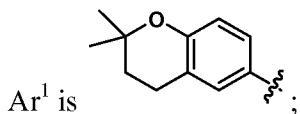
Currently, the only reported inhibitors of DAGL are chemically reactive molecules, that as such, can be expected to have limited utility due to lack of selectivity (*Bioorganic & Medicinal Chemistry Letters* (2008), 18(22), 5838-5841).

In a first aspect the present disclosure provides a compound of Formula (I)



or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is selected from naphthyl and phenyl, wherein the phenyl is substituted with 0, 1, or 2 substituents independently selected from alkyl, halo, haloalkoxy, 10 alkoxy, and cyano; or



Ar² is selected from hydrogen, phenyl, naphthyl, pyrimidinyl, thiazolyl, and quinolinyl, wherein the phenyl, naphthyl, pyrimidinyl, thiazolyl, and quinolinyl are each substituted with 0, 1, or 2 substituents independently selected from alkyl, 15 alkoxy, trifluoromethyl, trifluoromethoxy, cyano, and halo;

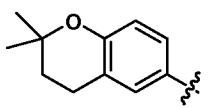
R¹ is selected from hydrogen, cyano, halo, alkyl, alkoxy, and haloalkoxy; and R² and R³ are each lower alkyl; or R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom.

20 In a first embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom.

In a second embodiment of the first aspect the present disclosure provides a 25 compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom and Ar¹ is naphthyl.

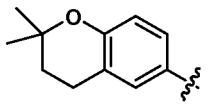
In a third embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom, Ar¹ is naphthyl, 5 R¹ is halo and Ar² is hydrogen.

In a fourth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom and Ar¹ is



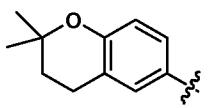
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In a fifth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom, Ar¹ is



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In a sixth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom, Ar¹ is



20

R¹ is hydrogen, and Ar² is phenyl optionally substituted with two halo groups.

In a seventh embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom and Ar¹ is phenyl substituted with 0, 1, or 2 groups selected from alkyl, halo, haloalkoxy, alkoxy, and cyano.

In an eighth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom, Ar¹ is phenyl substituted with 0, 1, or 2 groups selected from alkyl, halo, haloalkoxy, alkoxy, and cyano, R¹ is halo, and Ar² is hydrogen.

In a ninth embodiment of the first aspect the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom, Ar¹ is phenyl substituted with 0, 1, or 2 groups selected from alkyl, halo, haloalkoxy, alkoxy, and cyano, R¹ is hydrogen and Ar² is selected from phenyl, pyrimidinyl, and thiazolyl, wherein the phenyl, pyrimidinyl, and thiazolyl are substituted with 0, 1, or 2 groups independently selected from alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, and halo.

In a second aspect the present disclosure provides a composition comprising a pharmaceutically acceptable amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a third aspect the present disclosure provides a method for treating a disorder associated with DAGL α and/or DAGL β activity, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the third aspect the disorder is selected from schizophrenia, psychosis, bipolar disorder, depression, anxiety, pain, cognitive impairment, diabetes, obesity, hepatic steatosis, and dyslipidemia. In a second embodiment of the third aspect the disorder is selected from schizophrenia, bipolar disorder, depression, anxiety, diabetes, obesity, hepatic steatosis, and dyslipidemia.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it

may be necessary to remove a hydrogen atom in order accommodate a substituent at any given location.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

5 All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used in the present specification, the following terms have the meanings indicated:

10 As used herein, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

In some instances, the number of carbon atoms in any particular group is denoted before the recitation of the group. For example, the term “C₂₋₆ alkenyl” denotes an alkenyl group containing two to six carbon atoms. Where these 15 designations exist they supercede all other definitions contained herein.

The term “alkoxy,” as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term “alkyl,” as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms.

20 The term “cyano,” as used herein, refers to -CN.

The terms “halo” and “halogen,” as used herein, refer to F, Cl, Br, or I.

The term “haloalkoxy,” as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

25 The term “haloalkyl,” as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

Asymmetric centers may exist in the compounds of the present disclosure. These centers are designated by the symbols “R” or “S”, depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures 30 thereof, which possess the ability to inhibit DAGL. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers

followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

5 Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures
10 thereof.

 The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

15 The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ¹³C and ¹⁴C. Isotopically-labeled compounds of the invention can generally
20 be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such
25 compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

 The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure
30 which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended

use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; 5 digluconate, dihydrobromide, dihydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, 10 succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

15 Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as 20 well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'- 25 dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of Formula (I), as well as pharmaceutically acceptable salts thereof, 30 may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of Formula (I) or pharmaceutically acceptable salts thereof,

and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit. When applied to an individual active ingredient, administered alone, the term refers to that 5 ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of Formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being 10 compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The 15 term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended 20 use.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the 25 compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier 30 materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit

dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the 5 optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or 10 prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, 15 nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the 20 carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in- 25 water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a 30 similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and

filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to 5 improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or 10 sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and 15 disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or 20 dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to 25 prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a 30 sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit

form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and 5 polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the 10 release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of Formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles.

15 Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of Formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled 20 with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, 25 polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be 30 presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research* 1986, 3(6), 318.

Pharmaceutical formulations adapted for topical administration may be

formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

5 Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for 10 administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

15 Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the 20 blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately 25 prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for 30 oral administration may include flavoring agents.

The term "patient" includes both human and other mammals.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or

condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

5 This disclosure is intended to encompass compounds having Formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in 10 the art. Some of the abbreviations used are as follows: DMAP for N,N-dimethylaminopyridine; BEMP for 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; TFA for trifluoroacetic acid; DCM for dichloromethane; rt or RT or Rt for retention time or room temperature (context will dictate); MeOH for methanol; DMSO for dimethylsulfoxide; EtOAc for ethyl acetate; 15 MeCN or ACN for acetonitrile; THF for tetrahydrofuran; dba for dibenzylideneacetone; and DMF for N,N-dimethylformamide.

EXAMPLES

The present disclosure will now be described in connection with certain 20 embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain 25 embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

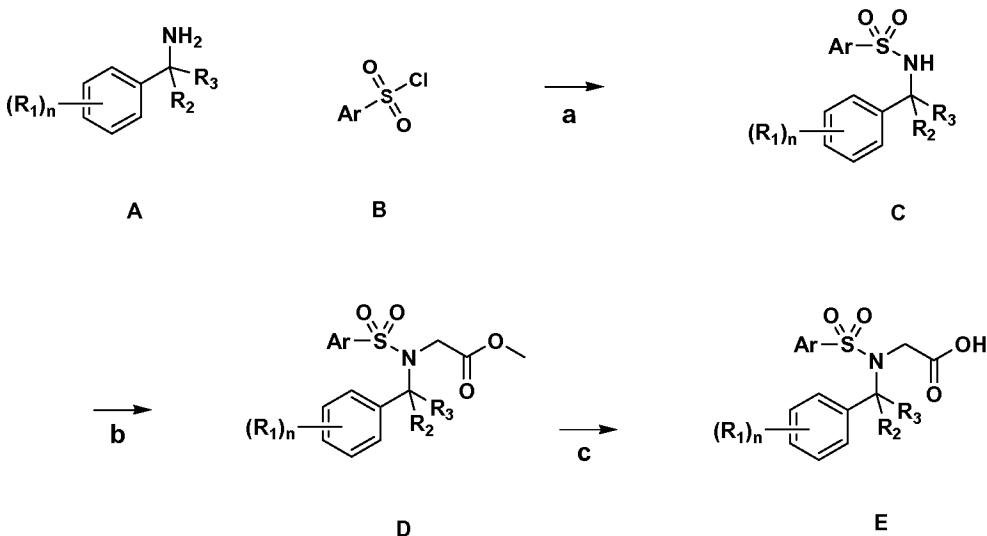
The compounds of the present disclosure may be prepared using the reactions and techniques described in this section as well as other synthetic methods known to those of ordinary skill in the art. The reactions are performed in solvents appropriate 30 to the reagents and materials employed and suitable for the transformation being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvents, reaction temperature, duration of the experiment and workup procedures, are chosen

to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which 5 are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

The compounds of the invention can be made according to methods known in the art including those illustrated in Scheme 1 below. Arylcycloalkyl amine intermediates **A** can be treated with aryl sulfonylchlorides **B** the presence of base and 10 catalytic DMAP to give sulfonamide intermediates of type **C**. Subsequent alkylation with methyl bromoacetate can give sulfonamides esters of type **D**. Examples **E** of the invention can be formed by hydrolysis of the intermediate esters **D** with, for example, sodium hydroxide in methanol.

15

Scheme 1



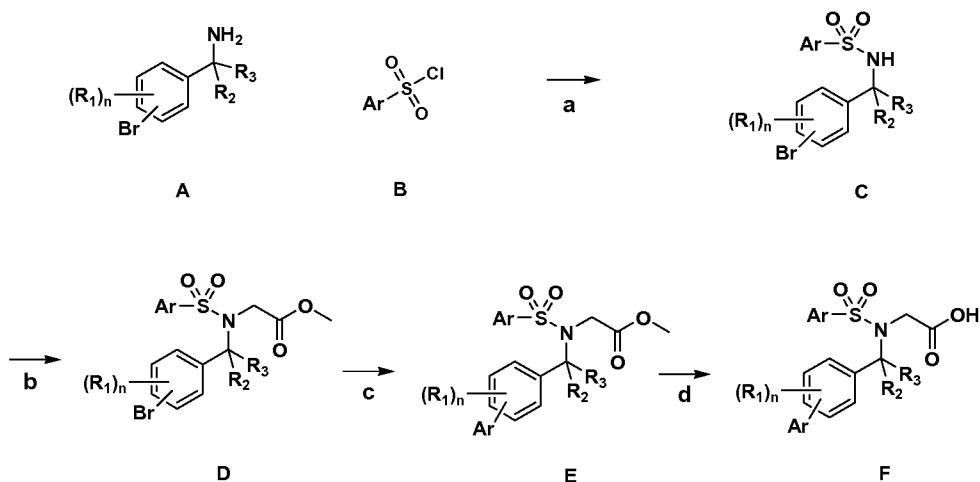
Reagents and conditions: a) Hunig's base, cat. DMAP, DCM, rt, overnight b) methyl bromoacetate, BEMP-resin, acetonitrile, 80 °C, overnight c) NaOH, MeOH, rt.

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Additional methodology that can provide examples of the invention is depicted in Scheme 2. The methodology to generate the bromo intermediates **D**, is as described above. These compounds can be coupled to aryl boronic acids under, for

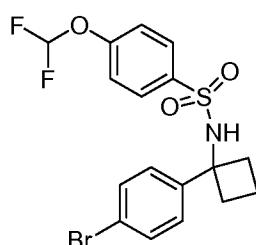
example, Suzuki coupling conditions, to give intermediate esters of type E. Subsequent treatment with, for example, NaOH in methanol, can generate additional examples F of the invention. Alternatively, intermediate esters of type D can be hydrolyzed using methods known in the art, and the product acids can then be 5 coupled using for example, Suzuki coupling conditions, to give further examples F of the invention.

Scheme 2.



10 Reagents and conditions: a), Hunig's base, cat. DMAP, DCM, rt, overnight b) methyl bromoacetate, BEMP-resin, acetonitrile, 80 °C, overnight. Ar boronic acid, Pd₂(dba)₃, dicyclohexyl(2',3',6'-triisopropylbiphenyl-2-yl)phosphine, 100°C, 3h. d) NaOH, MeOH, rt.

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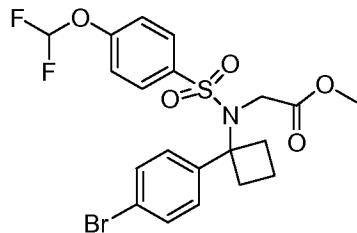


Intermediate A

N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)benzenesulfonamide

To a solution of 1-(4-bromophenyl)cyclobutanamine, HCl (845 mg, 3.22 mmol) in DMF (1.0 mL), was added diisopropylethylamine (1.69 mL, 9.66 mmol) 20 and 4-(difluoromethoxy)benzene-1-sulfonyl chloride (0.529 mL, 3.22 mmol). The

reaction mixture was then stirred at r.t., overnight. This mixture was then used, as is, in the following experiment.



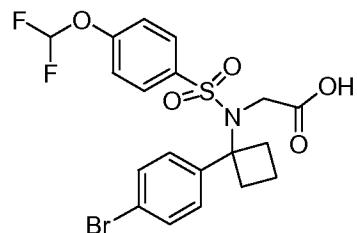
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Intermediate B

methyl 2-(N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetate

To the crude reaction mixture from the preparation of N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)benzenesulfonamide, methyl bromoacetate (0.612 mL, 6.44 mmol) and BEMP (1325 mg, 4.83 mmol) were added and the resultant mixture was heated at 80 °C overnight. The solution was then diluted with EtOAc and washed sequentially with HCl (1N) and brine and then dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was fractionated using silica gel, (3:1 Hex/EtOAc; 90g silica column). Homogeneous fractions were combined and concentrated under vacuum. The product was obtained as a light yellow-colored oil 1.15 g (71 %).

EXAMPLES



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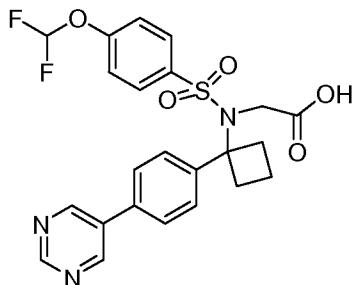
Example 1

2-(N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

Methyl 2-(N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido) acetate was dissolved in THF (5 mL) and

MeOH (5mL) and NaOH (1N, 3 mL) was added. The mixture was heated at 90 °C for 20 min. The solution was then allowed to cool, and was then acidified and the product extracted into EtOAc. The organic solution was washed with dilute HCl (0.1N) and dried over Na₂SO₄, filtered and the filtrate concentrated under vacuum to give the title compound as a light yellow-colored, semi-solid, 1.05 g. ESI-MS *m/z* 491 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.63 (d, *J*=10.68 Hz, 1H), 1.84 (dd, *J*=9.31, 1.68 Hz, 1H), 2.57 - 2.72 (m, 2H), 2.76 - 2.92 (m, 2H), 4.09 (s, 2H), 6.57 (t, *J*=75 Hz (C-F), 1H), 7.02 (m, *J*=8.85 Hz, 2H), 7.27 - 7.31 (m, 2H), 7.41 - 7.46 (m, 2H), 7.47 (m, 2 H).

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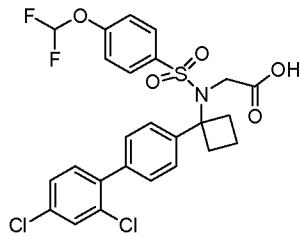
Example 2

2-(4-(difluoromethoxy)-N-(1-(4-(pyrimidin-5-yl)phenyl)cyclobutyl)phenylsulfonamido) acetic acid

15 To a solution of 2-(N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid (20 mg, 0.041 mmol) in n-butanol (2 mL) was added pyrimidin-5-ylboronic acid (7.58 mg, 0.061 mmol), followed by potassium phosphate (17.32 mg, 0.082 mmol) and Pd₂dba₃ (2.345 mg, 4.08 μmol) and dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (3.89 mg, 8.16 μmol). The 20 mixture was degassed and flushed with argon and then shook at 100 °C for 3h. The resultant mixture was filtered and the filtrate purified using Shimadzu prep HPLC employing an ACN/water and 0.1 % TFA buffer with a Xterra column, 30 mm x 100 mm, Gradient over 15 min; Starting conc: 10 %B; Ending conc: 100 %B. The solvent was removed in vacuo to give 3.3 mg (16% yield, 95 % pure) of the title compound 25 as a light gray solid. ESI-MS *m/z* 490 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.67 (q, *J*=10.07 Hz, 1H), 1.78 - 1.92 (m, 1H), 2.63 (t, *J*=8.70 Hz, 2H), 2.86 (d, *J*=2.44 Hz, 2H), 4.21 (s, 3H), 6.58 (t, *J*=75.00 Hz, 1H), 7.09

(d, $J=8.55$ Hz, 2H), 7.54 (d, $J=8.24$ Hz, 2H), 7.67 (dd, $J=14.80, 8.70$ Hz, 4H), 9.10 (s, 2H), 9.31 (s, 1 H).

Using these methods with appropriate reagents the following intermediates
5 and examples were prepared.

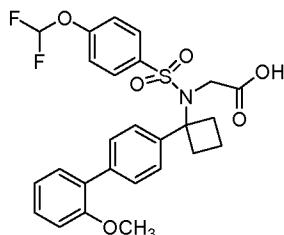


Example 3

2-(*N*-(1-(2',4'-dichlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid

10 ESI-MS m/z 557 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.69 (d, $J=10.68$ Hz, 1H), 1.83 - 1.92 (m, 1H), 2.67 (t, $J=8.70$ Hz, 2H), 2.79 - 2.91 (m, 2H), 4.13 (s, 2H), 6.54 (t, $J=75.00$ Hz, 1H), 7.06 (d, $J=8.55$ Hz, 2H), 7.22 - 7.31 (m, 1H), 7.37 (d, $J=8.24$ Hz, 3H), 7.47 - 7.58 (m, 5 H).

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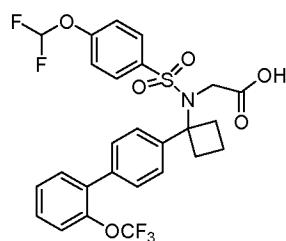


Example 4

2-(4-(difluoromethoxy)-*N*-(1-(2'-methoxybiphenyl-4-yl)cyclobutyl)phenylsulfonamido) acetic acid

20 ESI-MS m/z 518 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.65 - 1.76 (m, 1H), 1.87 (d, $J=10.68$ Hz, 1H), 2.60 - 2.73 (m, 2H), 2.78 - 2.90 (m, 2H), 3.89 (s, 3H), 4.13 (s, 2H), 6.43 (t, $J=75.00$ Hz, 1H), 6.99 (d, $J=8.85$ Hz, 2H), 7.05 (d, $J=8.24$ Hz, 1H), 7.09 (t, $J=7.48$ Hz, 1H), 7.32 (d, $J=7.32$ Hz, 1H), 7.35 - 7.40 (m, 1H), 7.42 (d, $J=8.55$ Hz, 2H), 7.44 - 7.48 (m, 4 H).

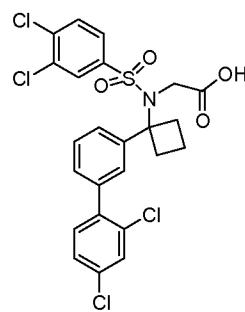
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Example 5

2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethoxy)biphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid

5 ESI-MS m/z 572 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.66 - 1.75 (m, 1H), 1.84 - 1.92 (m, 1H), 2.58 - 2.72 (m, 2H), 2.87 (dt, J =11.67, 9.88 Hz, 2H), 4.13 (s, 2H), 6.51 (t, J =75.00 Hz, 1H), 7.04 (d, J =8.85 Hz, 2H), 7.38 - 7.45 (m, 6H), 7.51 - 7.55 (m, 4 H)



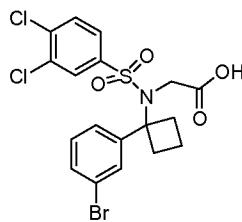
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Example 6

2-(3,4-dichloro-N-(1-(2',4'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

15 ESI-MS m/z 560 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.65 - 1.73 (m, 1H), 1.88 (d, J =10.68 Hz, 1H), 2.66 (t, J =8.85 Hz, 2H), 2.82 - 2.92 (m, 2H), 4.18 (s, 2H), 7.19 (d, J =8.24 Hz, 1H), 7.33 - 7.42 (m, 5H), 7.46 (d, J =1.22 Hz, 1H), 7.47 - 7.53 (m, 3 H).

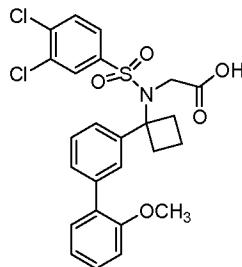
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*Example 7*

2-(N-(1-(3-bromophenyl)cyclobutyl)-3,4-dichlorophenylsulfonamido)acetic acid

ESI-MS *m/z* 494 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm

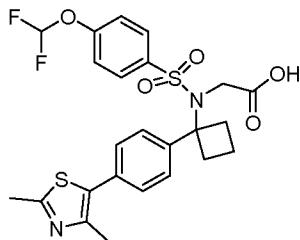
5 1.60 - 1.70 (m, 1H), 1.82 - 1.91 (m, 1H), 2.57 (t, *J*=8.39 Hz, 2H), 2.77 - 2.88 (m, 2H),
4.24 (s, 2H), 7.19 (t, *J*=7.78 Hz, 1H), 7.33 - 7.38 (m, 1H), 7.38 - 7.47 (m, 5 H)

*Example 8*

10 *2-(3,4-dichloro-N-(1-(2'-methoxybiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid*

ESI-MS *m/z* 521 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm

1.64 - 1.74 (m, 1H), 1.83 - 1.91 (m, 1H), 2.68 (t, *J*=8.70 Hz, 2H), 2.81 - 2.90 (m, 2H),
3.83 (s, 3H), 4.16 (s, 2H), 6.97 - 7.11 (m, 2H), 7.22 (d, *J*=7.32 Hz, 1H), 7.24 - 7.31
15 (m, 1H), 7.31 - 7.40 (m, 4H), 7.44 - 7.49 (m, 2H), 7.64 (s, 1 H)

*Example 9*

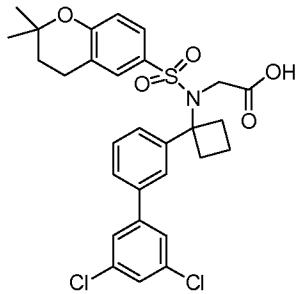
2-(4-(difluoromethoxy)-N-(1-(4-(2,4-dimethylthiazol-5-yl)phenyl)cyclobutyl)

phenylsulfonamido)acetic acid

ESI-MS *m/z* 523 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm

1.60 (dt, *J*=10.61, 7.97 Hz, 1H), 1.82 (dd, *J*=9.31, 1.68 Hz, 1H), 2.52 - 2.58 (m, 2H), 2.76 - 2.84 (m, 2H), 2.92 (s, 3H), 2.99 (s, 3H), 4.16 (s, 2H), 6.61 (t, *J*=75.00 Hz, 1H), 7.07 (m, 2H), 7.36 (m, 4H), 7.54 (m, 2H), 8.05 (s, 1 H)

5

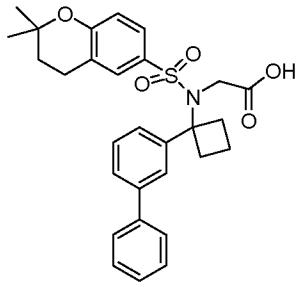


Example 10

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid

10 ESI-MS *m/z* 575 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
1.26 (s, 6H), 1.67 (t, *J*=6.71 Hz, 3H), 1.85 - 1.94 (m, 1H), 2.53 (t, *J*=6.56 Hz, 2H), 2.67 (t, *J*=8.85 Hz, 2H), 2.83 - 2.92 (m, 2H), 4.14 (s, 2H), 6.68 (d, *J*=8.85 Hz, 1H), 6.89 (d, *J*=1.83 Hz, 1H), 7.23 - 7.27 (m, 3H), 7.36 (t, *J*=1.83 Hz, 1H), 7.43 - 7.48 (m, 2H), 7.49 (s, 1H), 7.60 (dd, *J*=5.49, 2.44 Hz, 1 H).

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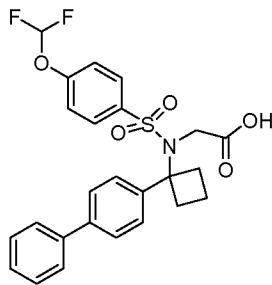


Example 11

2-(N-(1-(biphenyl-3-yl)cyclobutyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid

ESI-MS *m/z* 506 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm

20 1.24 (s, 6H), 1.63 (t, *J*=6.71 Hz, 2H), 1.65 - 1.74 (m, 1H), 1.84 - 1.92 (m, 1H), 2.49 (t, *J*=6.71 Hz, 2H), 2.71 (t, *J*=8.39 Hz, 2H), 2.82 - 2.92 (m, 2H), 4.09 (s, 2H), 6.66 (d, *J*=8.55 Hz, 1H), 6.83 (d, *J*=2.14 Hz, 1H), 7.24 (dd, *J*=8.55, 2.14 Hz, 1H), 7.37 (td, *J*=6.10, 2.44 Hz, 1H), 7.40 - 7.48 (m, 5H), 7.48 - 7.55 (m, 2H), 7.58 (s, 1 H).

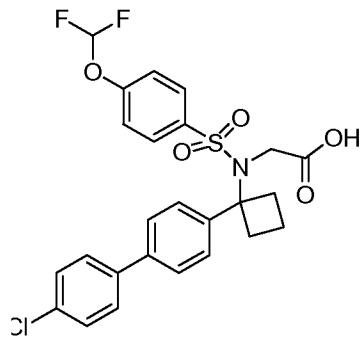


Example 12

2-(N-(1-(biphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

5 ESI-MS m/z 488 (MH^+), ^1H NMR (600 MHz, DMSO-CDCl_3) δ ppm 1.49 - 1.63 (m, 1H), 1.77 (q, $J=9.37$ Hz, 1H), 2.50 - 2.58 (m, 2H), 2.87 (q, $J=10.16$ Hz, 2H), 4.11 (s, 2H), 7.07 (d, $J=8.79$ Hz, 1H), 7.16 (t, $J = 78$ Hz, 1H) 7.40 (t, $J=7.03$ Hz, 1H), 7.44 - 7.53 (m, 4H), 7.57 (t, $J=8.50$ Hz, 4H), 7.64 (d, $J=7.62$ Hz, 2H), 7.68 - 7.76 (m, 1 H).

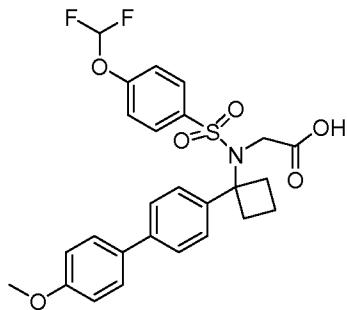
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Example 13

2-(N-(1-(4'-chlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

15 ESI-MS m/z 523 (MH^+), ^1H NMR (600 MHz, DMSO-CDCl_3) δ ppm 1.50 - 1.61 (m, 1H), 1.77 (q, $J=9.37$ Hz, 1H), 2.52 - 2.58 (m, 2H) 2.82 - 2.90 (m, 2 H)) 4.10 (s, 2H), 7.08 (m, 1H), 7.19 (t, $J = 78$ Hz, 1H), 7.47 - 7.55 (m, 4H), 7.58 (t, $J=9.08$ Hz, 4H), 7.66 (d, $J=8.79$ Hz, 2H), 7.71 (d, $J=8.20$ Hz, 1 H).

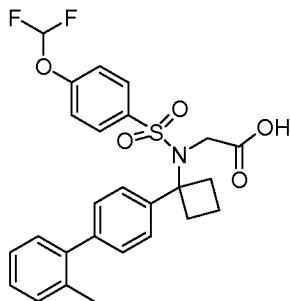


Example 14

2-(4-(difluoromethoxy)-N-(1-(4'-methoxybiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid

5 ESI-MS m/z 518 (MH^+), ^1H NMR (600 MHz, CDCl_3) δ ppm 1.51 - 1.60 (m, 1H), 1.75 (t, $J=9.08$ Hz, 1H), 2.49 - 2.56 (m, 2H), 2.82 - 2.89 (m, 2H), 3.82 - 3.88 (m, 3H), 4.08 (s, 2H), 7.05 (d, $J=10.55$ Hz, 3H), 7.17 (t, $H = 72$ Hz, 1H), 7.45 (d, $J=8.20$ Hz, 2H), 7.53 (d, $J=8.20$ Hz, 2H), 7.56 - 7.62 (m, 4H), 7.62 - 7.70 (m, 1H).

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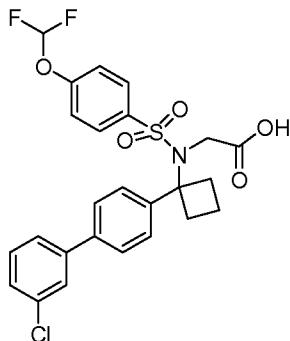


Example 15

2-(4-(difluoromethoxy)-N-(1-(2'-methylbiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid

15 ESI-MS m/z 502 (MH^+), ^1H NMR (600 MHz, CDCl_3) δ ppm 1.52 - 1.63 (m, 1H), 1.78 (d, $J=9.37$ Hz, 1H), 2.29 (s, 3H) 2.58 - 2.67 (m, 2H), 2.90 (q, $J=10.16$ Hz, 2H), 4.09 (s, 2H), 7.12 (d, $J=8.20$ Hz, 2H), 7.17 - 7.25 (m, 3H), 7.25 - 7.35 (m, 3H), 7.41 (d, $J=7.62$ Hz, 1H), 7.56 (d, $J=7.62$ Hz, 2H), 7.62 (d, $J=8.20$ Hz, 2H).

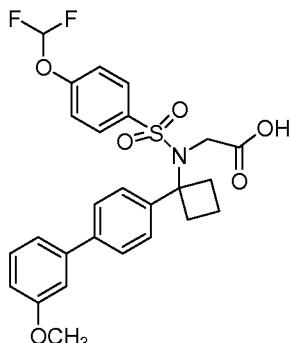
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Example 16

2-(N-(1-(3'-chlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

5 ESI-MS *m/z* 523 (MH^+), ^1H NMR (600 MHz, DMSO-CDCl_3) δ ppm 1.49 - 1.61 (m, 1H), 1.76 (d, $J=9.37$ Hz, 1H), 2.54 - 2.61 (m, 2H), 2.84 - 2.93 (m, 2H), 4.09 (s, 2H), 7.07 (d, $J=8.79$ Hz, 1H), 7.19 (t, $J=72$ Hz, 1H) 7.44 (d, $J=7.62$ Hz, 1H), 7.47 - 7.55 (m, 3H), 7.59 (t, $J=9.08$ Hz, 4H), 7.66 (br. s., 2H), 7.70 - 7.78 (m, 1 H).

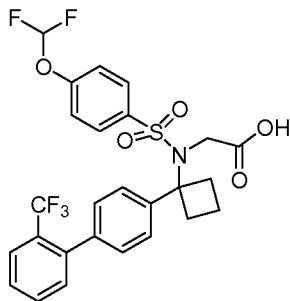


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Example 17

2-(4-(difluoromethoxy)-N-(1-(3'-methoxybiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid

15 ESI-MS *m/z* 518 (MH^+), ^1H NMR (600 MHz, DMSO-CDCl_3) δ ppm 1.52 - 1.61 (m, 1H), 1.77 (q, $J=9.37$ Hz, 1H), 2.57 - 2.67 (m, 2H), 2.87 (q, $J=10.55$ Hz, 2H), 3.84 - 3.92 (m, 3H), 4.10 (s, 2H), 6.97 (d, $J=5.86$ Hz, 1H), 7.02 - 7.11 (m, 2H), 7.16 (br. s., 1H), 7.18 - 7.23 (m, 1H), 7.36 - 7.46 (m, 1H), 7.47 - 7.52 (m, 2H), 7.57 (dd, $J=18.46$, 8.50 Hz, 4H), 7.64 (d, $J=8.20$ Hz, 1 H).

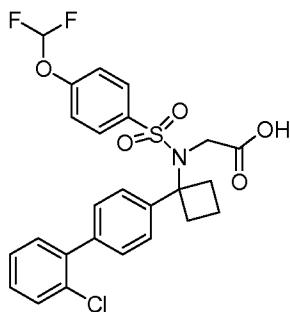


Example 18

2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethyl)biphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid

5 ESI-MS m/z 556 (MH^+), ^1H NMR (600 MHz, CDCl_3) δ ppm 1.50 - 1.62 (m, 1H), 1.77 (t, $J=9.08$ Hz, 1H), 2.58 - 2.66 (m, 2H), 2.84 - 2.94 (m, 2H), 4.06 (s, 2H), 7.14 (d, $J=8.79$ Hz, 2H), 7.22 (d, $J=7.62$ Hz, 2H), 7.35 - 7.46 (m, 2H), 7.58 (d, $J=7.62$ Hz, 2H), 7.61 - 7.69 (m, 3H), 7.73 (t, $J=7.62$ Hz, 1H), 7.84 (d, $J=7.62$ Hz, 1 H).

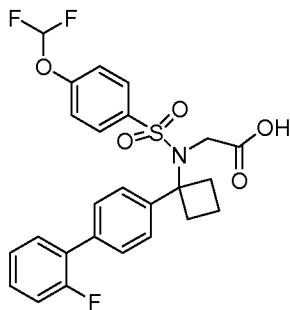
10



Example 19

2-(N-(1-(2'-chlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

15 ESI-MS m/z 523 (MH^+), ^1H NMR (600 MHz, CDCl_3) δ ppm 1.52 - 1.65 (m, 1H), 1.79 (q, $J=8.98$ Hz, 1H), 2.56 (br. s., 3H), 2.58 - 2.66 (m, 1H), 2.85 - 2.93 (m, 2H), 4.09 (s, 2H), 7.11 (d, $J=8.20$ Hz, 2H), 7.23 (s, 1H), 7.33 (d, $J=8.20$ Hz, 2H), 7.37 - 7.48 (m, 3H), 7.49 - 7.61 (m, 5 H).

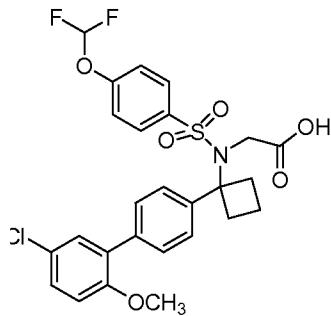


Example 20

2-(4-(difluoromethoxy)-N-(1-(2'-fluorobiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid

5 ESI-MS m/z 506 (MH^+), ^1H NMR (600 MHz, CDCl_3) δ ppm 1.53 - 1.62 (m, 1H), 1.78 (q, $J=9.37$ Hz, 1H), 2.57 - 2.69 (m, 2H), 2.89 (q, $J=10.16$ Hz, 2H), 4.11 (s, 2H), 7.08 (d, $J=8.79$ Hz, 1H), 7.19 (t, $J=60$ Hz, 1H) 7.32 (d, $J=8.20$ Hz, 2H), 7.38 - 7.48 (m, 3H), 7.51 (t, $J=7.32$ Hz, 1H), 7.57 (dd, $J=15.53, 8.50$ Hz, 4H), 7.62 - 7.70 (m, 1 H).

10

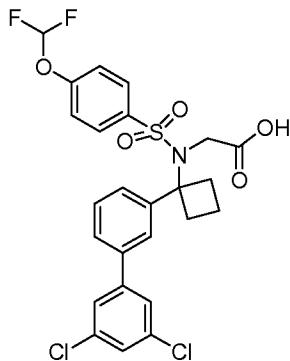


Example 21

2-(N-(1-(5'-chloro-2'-methoxybiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid

15 ESI-MS m/z 553 (MH^+), ^1H NMR (600 MHz, CDCl_3) δ ppm 1.51 - 1.63 (m, 1H), 1.78 (d, $J=9.37$, 1H), 2.58 - 2.65 (m, 1H), 2.88 (q, $J=9.96$ Hz, 2H), 3.85 (s, 3H), 4.08 (s, 2H), 7.09 (d, $J=8.79$ Hz, 2H), 7.15 (d, $J=8.79$ Hz, 1H), 7.26 - 7.34 (m, 1H), 7.35 - 7.42 (m, 3H), 7.52 (d, $J=8.79$ Hz, 3H), 7.55 (s, 1H), 7.56 - 7.62 (m, 1 H).

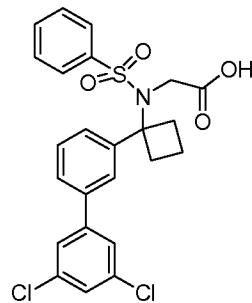
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Example 22

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

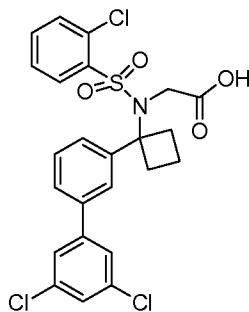
5 ESI-MS m/z 557 (MH^+), ^1H NMR (400 MHz, MeOD) δ ppm 1.58 - 1.69 (m, 1H), 1.78 - 1.88 (m, 1H), 2.56 - 2.65 (m, 2H), 2.97 - 3.08 (m, 2H), 4.18 (s, 2H), 6.69 (t, J =75.00 Hz, 1H), 6.90 - 6.99 (m, 2H), 7.38 - 7.44 (m, 5H), 7.44 - 7.49 (m, 2H), 7.59 (t, J =1.76 Hz, 1H), 7.64 (dd, J =7.65, 1.38 Hz, 1 H).



Example 23

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

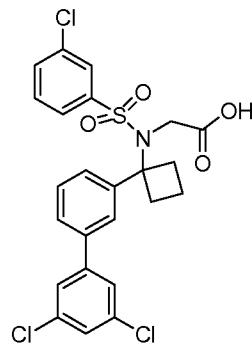
10 ESI-MS m/z 491 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.62 - 1.70 (m, J =10.60, 10.60, 7.78, 2.75 Hz, 1H), 1.82 - 1.90 (m, 1H), 2.59 - 2.67 (m, 2H), 2.85 - 2.94 (m, 2H), 4.17 (s, 2H), 7.27 (d, J =2.14 Hz, 2H), 7.31 - 7.38 (m, 3H), 7.39 - 7.50 (m, 4H) 7.52 - 7.59 (m, 3 H).



Example 24

2-(2-chloro-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

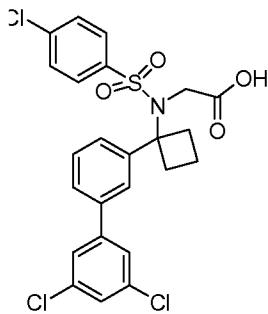
5 ESI-MS m/z 525 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.51 - 1.58 (m, 1H), 1.73 - 1.80 (m, 1H), 2.53 - 2.60 (m, 2H), 2.91 - 2.98 (m, 2H), 4.47 (s, 2H), 7.15 - 7.22 (m, 1H), 7.29 - 7.38 (m, 7H), 7.49 - 7.55 (m, 2H), 7.83 (dd, J =8.09, 1.37 Hz, 1 H).



Example 25

2-(3-chloro-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

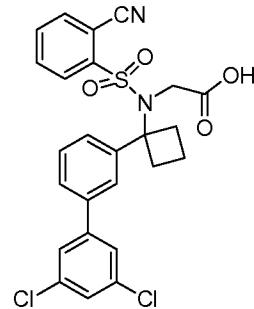
10 ESI-MS m/z 525 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.64 - 1.72 (m, 1H), 1.89 (m, 1H), 2.63 - 2.69 (m, 2H), 2.84 - 2.92 (m, 2H), 4.25 (s, 2H), 7.23 - 7.28 (m, 2H), 7.28 - 7.31 (m, 2H), 7.34-7.38 (m, 2H), 7.39 - 7.47 (m, 3H), 7.48 - 7.50 (m, 1H), 7.53 - 7.56 (m, 1 H).



Example 26

2-(4-chloro-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

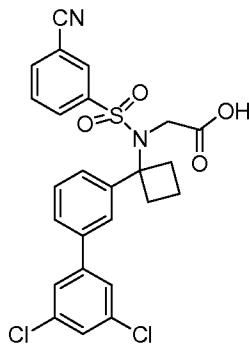
5 ESI-MS m/z 525 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
 1.63 - 1.71 (m, 1H), 1.87 (m, 1H), 2.60 - 2.66 (m, 2H), 2.83 - 2.91 (m, 2H), 4.22 (s, 2H), 7.23 - 7.27 (m, 2H), 7.27 - 7.30 (m, 2H), 7.38 (t, $J=1.83$ Hz, 1H), 7.40 - 7.46 (m, 4H), 7.47 - 7.49 (m, 1H), 7.54 - 7.59 (m, 1 H).



Example 27

2-(2-cyano-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

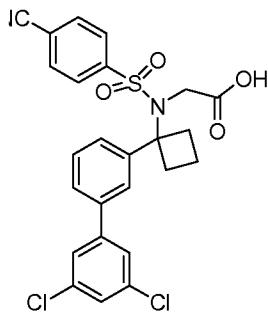
10 ESI-MS m/z 516 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
 15 1.60 (m, 1H), 1.78 - 1.84 (m, 1H), 2.60 - 2.65 (m, 2H), 2.90 (m, 2H), 4.66 (s, 2H), 7.30 - 7.35 (m, 4H), 7.37 (t, $J=1.83$ Hz, 1H), 7.39 - 7.48 (m, 2H), 7.55-7.58 (m, 1H), 7.59-7.63 (m, 2H), 7.65 (dd, $J=7.32, 1.22$ Hz, 1 H).



Example 28

2-(3-cyano-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

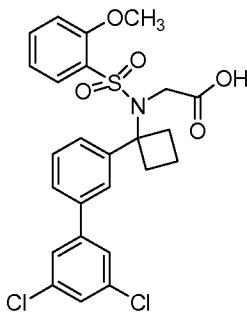
5 ESI-MS *m/z* 516 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.63 - 1.72 (m, 1H), 1.84 - 1.94 (m, 1H), 2.61 - 2.72 (m, 2H), 2.83 - 2.91 (m, 2H), 4.31 (s, 2H), 7.26 - 7.29 (m, 1H), 7.32 - 7.40 (m, 2H), 7.40 - 7.52 (m, 5H), 7.55 (d, *J*=7.93 Hz, 1H), 7.62 - 7.71 (m, 1H), 7.76-7.80 (m, 1H).



Example 29

2-(4-cyano-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid

15 ESI-MS *m/z* 516 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.67 (dd, *J*=7.78, 2.90 Hz, 1H), 1.83 - 1.90 (m, 1H), 2.58 - 2.68 (m, 2H), 2.80 - 2.89 (m, 2H), 4.29 (s, 2H), 7.30 (d, *J*=1.83 Hz, 2H), 7.38 - 7.42 (m, 2H), 7.45 (d, *J*=7.93 Hz, 1H), 7.52 - 7.56 (m, 2H), 7.58 (m, 2H), 7.63 (m, 2 H).

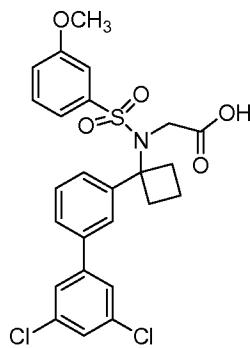


Example 30

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-2-methoxyphenylsulfonamido)acetic acid

5 ESI-MS m/z 521 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
 1.50 - 1.60 (m, 1H), 1.70 - 1.82 (m, 1H), 2.54 - 2.63 (m, 2H), 2.81 - 2.90 (m, 2H),
 3.83 (s, 3H), 4.43 (s, 2H), 6.80 (d, $J=8.54$ Hz, 1H), 6.83 (t, $J=7.63$ Hz, 1H), 7.28 -
 7.31 (m, 4H), 7.32 - 7.35 (m, 1H), 7.36 (t, $J=1.83$ Hz, 1H), 7.48 - 7.53 (m, 2H), 7.60
 (dd, $J=7.93$, 1.53 Hz, 1 H).

10

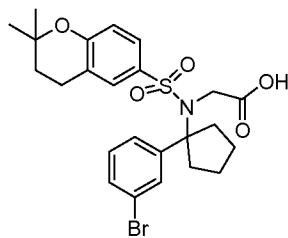


Example 31

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-3-methoxyphenylsulfonamido)acetic acid

15 ESI-MS m/z 521 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
 1.62 - 1.69 (m, 1H), 1.86 (q, $J=9.36$ Hz, 1H), 2.63 (t, $J=8.85$ Hz, 2H), 2.89 (dd,
 $J=10.22$, 2.59 Hz, 2H), 3.72 (s, 3H), 4.20 (s, 2H), 6.96 (dd, $J=7.78$, 1.98 Hz, 1H),
 7.02 - 7.04 (m, 1H), 7.17 (d, $J=8.54$ Hz, 1H), 7.25 (t, $J=7.93$ Hz, 1H), 7.37 (t, $J=1.83$
 Hz, 1H), 7.39 - 7.43 (m, 2H), 7.48 (s, 2H), 7.57 (d, $J=6.41$ Hz, 1 H).

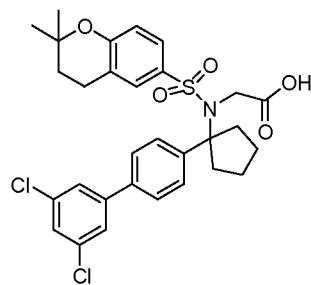
20



Example 32

2-(N-(1-(3-bromophenyl)cyclopentyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid

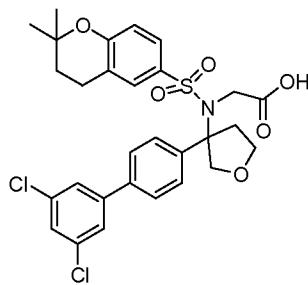
5 ESI-MS m/z 523 (MH^+), ^1H NMR (500 MHz, MeOD) δ ppm 1.27 - 1.35 (m, 2H), 1.36 (s, 6H), 1.66 - 1.76 (m, 2H), 1.85 (t, $J=6.71$ Hz, 2H), 2.36 - 2.53 (m, 4H), 2.70 (t, $J=6.71$ Hz, 2H), 4.13 (s, 2H), 6.66 (d, $J=8.85$ Hz, 1H), 6.91 (d, $J=2.14$ Hz, 1H), 7.26 - 7.38 (m, 5 H).



Example 33

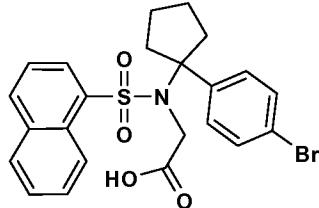
2-(N-(1-(3',5'-dichlorobiphenyl-4-yl)cyclopentyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid

10 ESI-MS m/z 589 (MH^+), ^1H NMR (500 MHz, MeOD) δ ppm 1.28 (s, 6H), 1.69 (t, $J=6.71$ Hz, 2H), 2.35-2.42 (m, 2H), 2.50 - 2.65 (m, 4H), 2.74 - 2.80 (m, 2H), 2.88 (t, $J=6.87$ Hz, 2H), 4.33 (s, 2H), 6.61 (d, $J=8.85$ Hz, 1H), 7.08 (d, $J=2.14$ Hz, 1H), 7.29 (dd, $J=8.55$, 2.44 Hz, 1H), 7.45 (m, 4H), 7.59 (d, $J=3.05$ Hz, 1H), 7.61 (m, 2 H).

*Example 34*

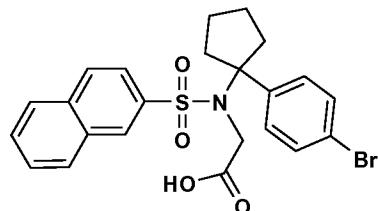
2-(N-(3-(3',5'-dichlorobiphenyl-4-yl)tetrahydrofuran-3-yl)-2,2-dimethylchroman-6-sulfonamido)acetic acid

5 ESI-MS m/z 591 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.39 (s, 6H), 1.87 (t, $J=6.71$ Hz, 2H), 2.31 - 2.45 (m, 2H), 2.82 - 2.90 (m, 1H), 2.90 - 2.97 (m, 1H), 3.51 - 3.63 (m, 1H), 4.02 - 4.07 (m, 1H), 4.35 (q, $J=18.31$ Hz, 2H), 4.46 (d, $J=9.46$ Hz, 1H), 4.64 (d, $J=9.46$ Hz, 1H), 6.53 (d, $J=8.55$ Hz, 1H), 6.91 (d, $J=8.55$ Hz, 1H), 7.00 (s, 1H), 7.16 (dd, $J=8.70$, 1.98 Hz, 1H), 7.32 - 7.39 (m, 2H), 10 7.41 (d, $J=1.83$ Hz, 2H), 7.62 - 7.72 (m, 2H).

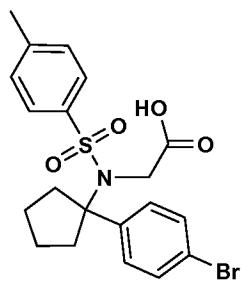
*Example 35*

2-(N-(1-(4-bromophenyl)cyclopentyl)naphthalene-1-sulfonamido)acetic acid

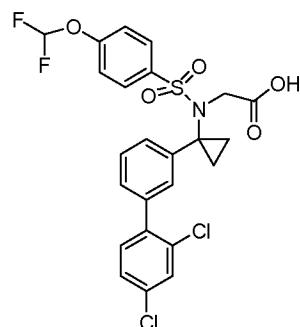
15

*Example 36*

2-(N-(1-(4-bromophenyl)cyclopentyl)naphthalene-2-sulfonamido)acetic acid

*Example 37*

2-(N-(1-(4-bromophenyl)cyclopentyl)-4-methylphenylsulfonamido)acetic acid



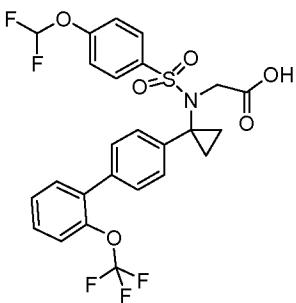
5

Example 38

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid

ESI-MS *m/z* 543 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm

10 1.29 (br. s., 2H), 1.68 (br. s., 2H), 4.36 (s, 2H), 6.56 (t, *J*=75.00 Hz, 1H), 7.10 (m, *J*=8.85 Hz, 2H), 7.19 - 7.24 (m, 3H), 7.24 - 7.31 (m, 1H), 7.31 - 7.36 (m, 2H), 7.52 (d, *J*=1.83 Hz, 1H), 7.76 (m, *J*=8.85 Hz, 2 H).



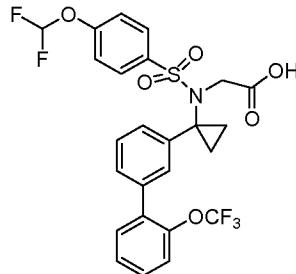
15

Example 39

2-(4-(difluoromethoxy)-N-(1-(2-(trifluoromethoxy)biphenyl-4-yl)cyclopropyl)phenylsulfonamido)acetic acid

ESI-MS *m/z* 558 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.31 (br. s., 2H), 1.71 (br. s., 2H), 4.39 (s, 2H), 6.56 (t, *J*=75.00 Hz (C-F), 1H), 7.13 (m, *J*=8.55 Hz, 2H), 7.21 (d, *J*=7.93 Hz, 2H), 7.35 (d, *J*=8.24 Hz, 2H), 7.37 - 7.42 (m, 4H), 7.77 (m, 2 H), 9.88 (br. s., 1H).

5

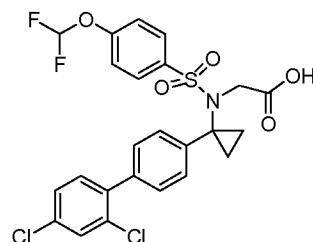


Example 40

2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethoxy)biphenyl-3-yl)cyclopropyl)phenylsulfonamido)acetic acid

10 ESI-MS *m/z* 558 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.28 (br. s., 5H), 1.70 (br. s., 2H), 4.35 (s, 2H), 6.52 (t, *J*=75.00 Hz, 1H), 7.07 (m, *J*=8.85 Hz, 2H), 7.17 - 7.22 (m, 1H), 7.25 (s, 1H), 7.32 (d, *J*=4.88 Hz, 2H), 7.35 - 7.45 (m, 54H) 7.75 (m, *J*=8.85 Hz, 2 H).

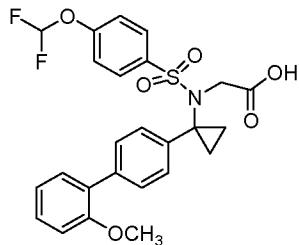
15



Example 41

2-(N-(1-(2',4'-dichlorobiphenyl-4-yl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

ESI-MS *m/z* 543 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 20 1.31 (br. s., 2H), 1.69 (br. s., 2H), 4.38 (s, 2H), 6.58 (t, *J*= 75.00 Hz, 1H), 7.14 (m, *J*=8.55 Hz, 2H), 7.23 (dd, *J*=8.09, 5.04 Hz, 3H), 7.29 - 7.35 (m, 3H), 7.52 (d, *J*=1.53 Hz, 1H), 7.78 (m, *J*=8.85 Hz, 2 H).

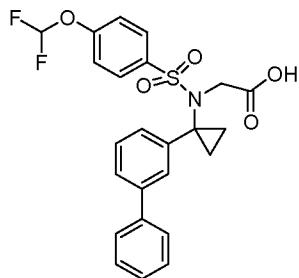


Example 42

2-(4-(difluoromethoxy)-N-(1-(2'-methoxybiphenyl-4-yl)cyclopropyl)phenylsulfonamido)acetic acid

5 ESI-MS m/z 504 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.30 (br. s., 2H), 1.66 (br. s., 2H), 3.85 (s, 3H), 4.39 (s, 2H), 6.53 (t, $J=75.00$ Hz, 1H), 6.93 - 7.09 (m, 2H), 7.11 (d, $J=8.55$ Hz, 2H), 7.19 (m, $J=8.24$ Hz, 2H), 7.25 - 7.32 (m, 1H), 7.36 (t, $J=7.78$ Hz, 1H), 7.42 (m, 2H), 7.74 (d, $J=8.85$ Hz, 2H), 9.16 (br. s., 1 H).

10

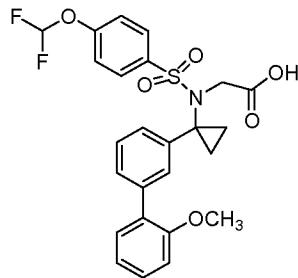


Example 43

2-(N-(1-(biphenyl-3-yl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

15 ESI-MS m/z 474 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.31 (br. s., 2H), 1.71 (s, 2H), 4.38 (s, 2H), 6.44 (t, $J=75.00$ Hz, 1H), 7.04 (m, $J=8.85$ Hz, 2H), 7.15 (d, $J=7.63$ Hz, 1H), 7.34 (d, $J=2.14$ Hz, 2H), 7.39 (t, $J=7.17$ Hz, 1H), 7.42 - 7.52 (m, 5H), 7.75 (m, $J=8.85$ Hz, 2 H).

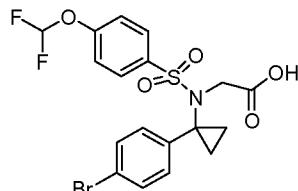
20



Example 44

2-(4-(difluoromethoxy)-N-(1-(2'-methoxybiphenyl-3-yl)cyclopropyl)phenylsulfonamido)acetic acid

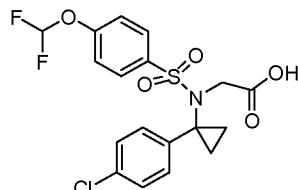
5 ESI-MS m/z 504 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
 1.29 (br. s., 2H), 1.67 (br. s., 2H), 3.84 (s, 3H), 4.35 (s, 2H), 6.49 (t, $J=75$ Hz (C-F),
 1H), 6.99 - 7.09 (m, 4H), 7.11 (d, $J=7.93$ Hz, 1H), 7.22 - 7.28 (m, 2H), 7.37 (q,
 $J=7.93$ Hz, 3H), 7.73 (d, $J=8.85$ Hz, 2 H).



Example 45

2-(N-(1-(4-bromophenyl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

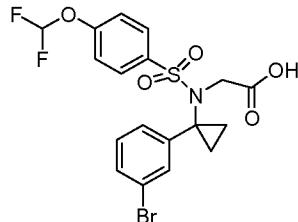
15 ESI-MS m/z 477 (MH^+), ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm
 1.21 (br. s, 2H), 1.60 (br. s, 2H), 4.32 (s, 2H), 6.61 (t, $J=75$ Hz (C-F), 1H), 7.09 (d,
 $J=8.24$ Hz, 2H), 7.16 (m, $J=8.55$ Hz, 2H), 7.39 (m, $J=8.55$ Hz, 2H), 7.78 (d, $J=8.85$
 Hz, 2 H).



Example 46

2-(N-(1-(4-chlorophenyl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

ESI-MS *m/z* 432 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.18 (s, 2H), 1.58 (s, 2H), 4.28 (s, 2H), 7.09 (dd, *J*=16.33, 8.70 Hz, 4H), 7.17 (d, *J*=8.55 Hz, 2H), 7.71 (d, *J*=8.85 Hz, 2H), 9.59 (br. s., 1 H).



5

Example 47

2-(N-(1-(3-bromophenyl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid

ESI-MS *m/z* 477 (MH⁺), ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 10 1.24 (m, 2H), 1.70 (m, 2H), 4.33 (s, 2H), 6.61 (t, *J*=75.00 Hz, 1H), 7.07 - 7.19 (m, 5H), 7.33 (d, *J*=7.02 Hz, 1H), 7.76 (d, *J*=8.85 Hz, 2 H).

BIOLOGICAL METHODS

Plates

15 Black non-binding surface Corning plates (3655) were spotted with 0.9 μ L of compound in twenty point 1:3 dilutions. The same volume of dimethyl sulfoxide (DMSO) was added to column 23 of the plate. In column 24, 0.9 μ L of 2-(N-(4-cyclohexylphenyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid was manually added as a blank to normalize the data.

20

Enzyme

A membrane prep from a stable HEK cell line expressing LG586 was prepared by the Cell Resource Group at BMS in Hopewell, NJ. The protein concentration of the membrane prep was 1.28 μ g/ μ L. These stocks were kept at -25 80°C in 1 mL aliquots. For the assay, membrane was thawed to room temperature and then added to the assay buffer, 100mM HEPES in MQ water at pH 7.5. The concentration of the LG586 enzyme in the assay is 0.005 μ g/mL.

Substrate

The substrate used in this assay was purchased from Sigma (N9876) p-nitrophenyl butyrate (PNP). The substrate is received in the liquid form and must be diluted with DMSO. Stocks were kept in -20°C at 1M concentrations. The final 5 concentration of the substrate is 250μM.

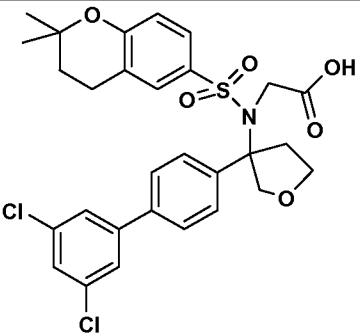
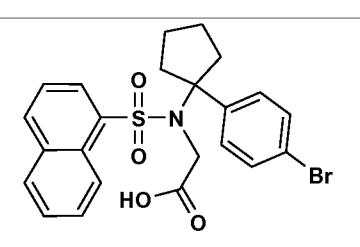
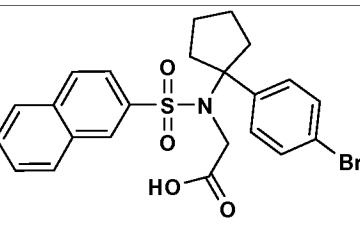
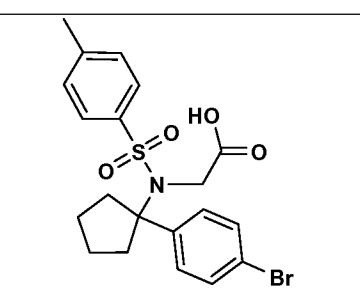
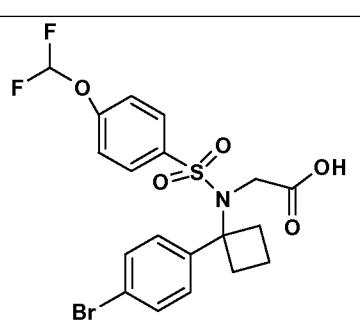
Assay

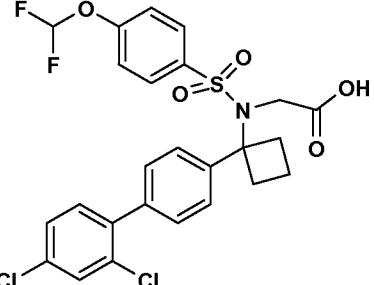
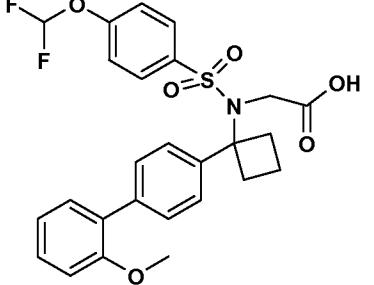
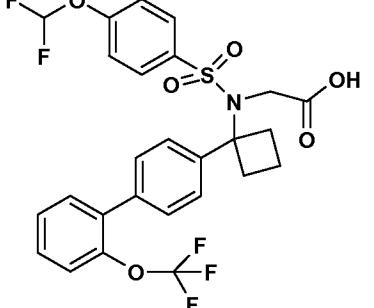
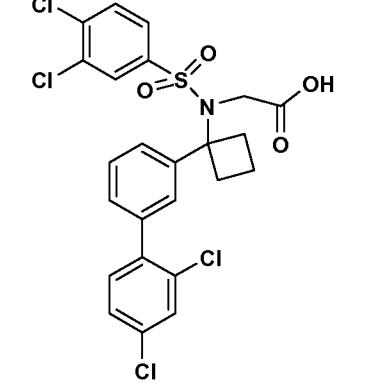
Enzyme was added to the plates 80μL/well using a Multi-drop Combi (Thermo). The plates were incubated with the compound for 10 minutes at room 10 temperature. Then 9μL of substrate was added to each well and the plates were immediately read on the Viewlux Imager (Perkin Elmer) in absorbance mode with the excitation filter of 405nm and emission filter of 564/250nm. The read was kinetic, plates were read once every 30 seconds for 5 minutes and then slopes were calculated for each well and the data was reduced with in-house software.

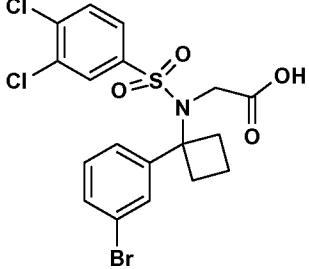
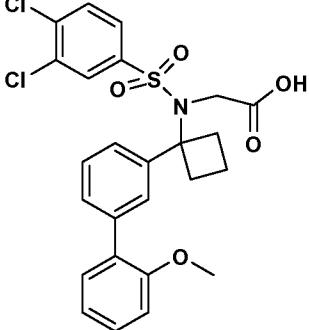
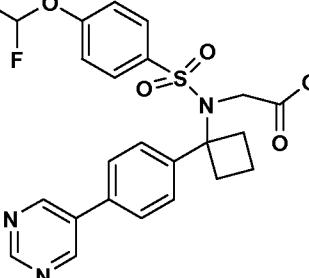
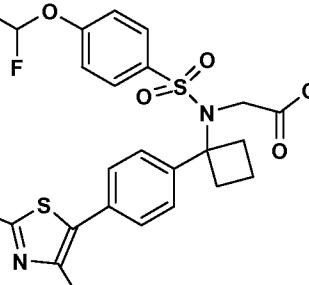
15

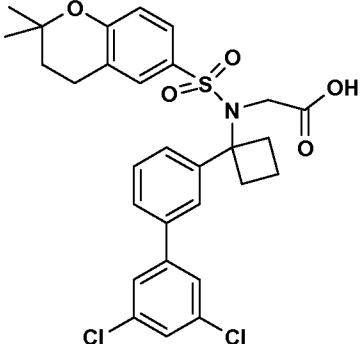
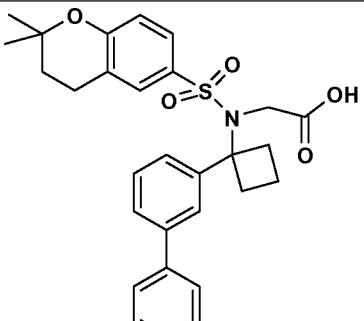
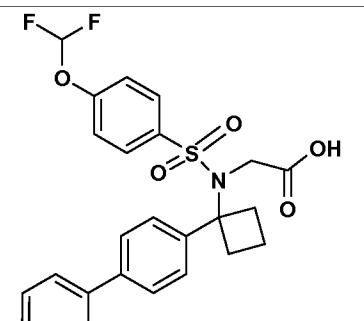
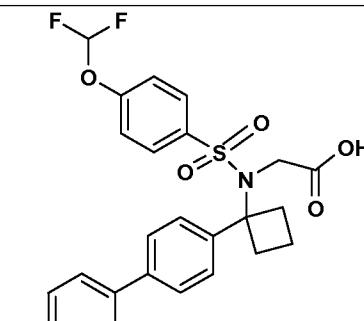
Table 1

Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μM)
32		A	
33		A	0.001

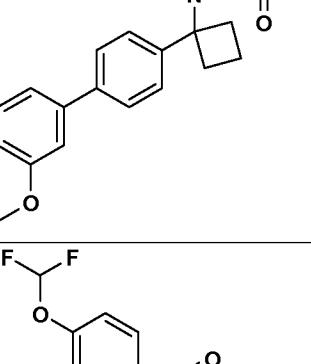
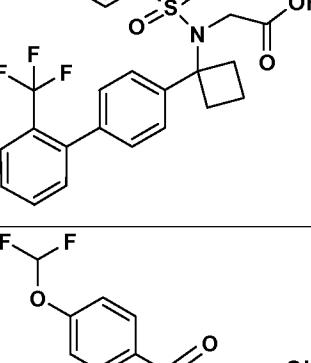
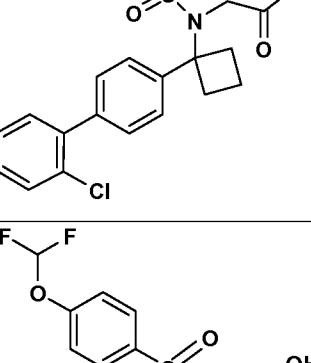
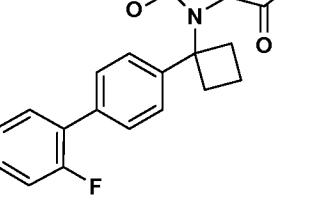
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
34		A	
35			
36			
37			
1		B	

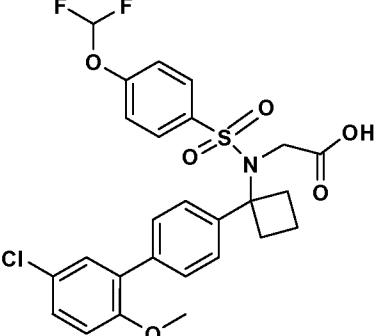
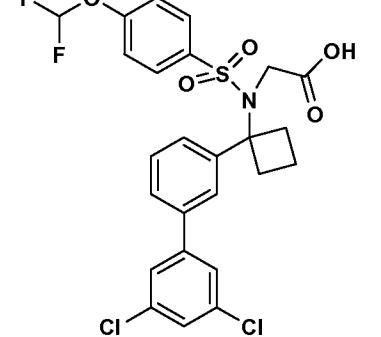
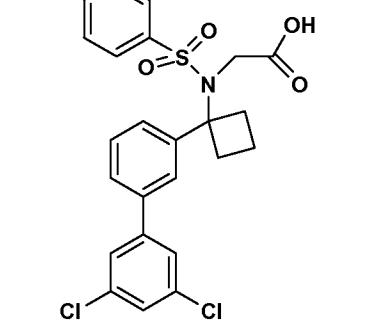
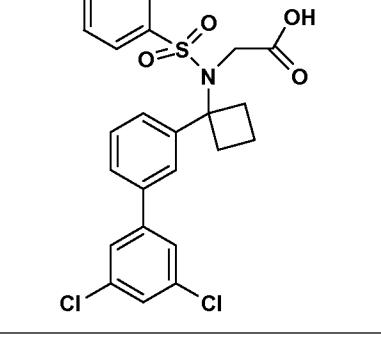
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
3		A	
4		A	
5		A	
6		A	

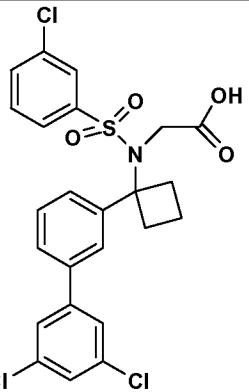
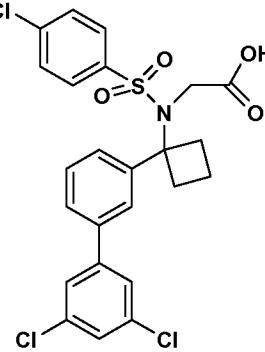
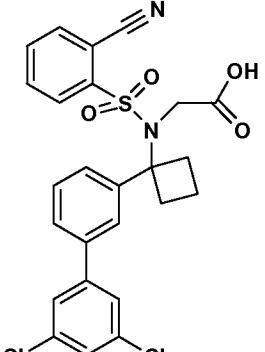
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
7		B	
8		B	
2		C	
9		C	

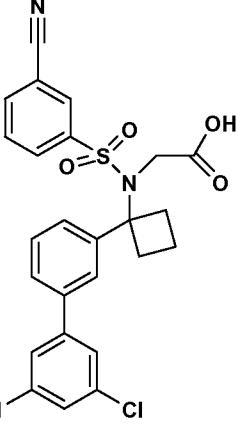
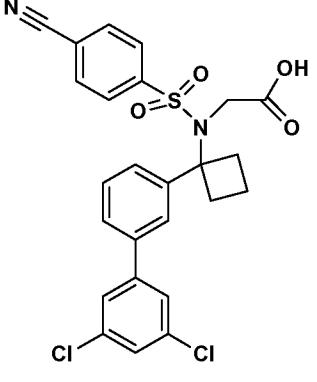
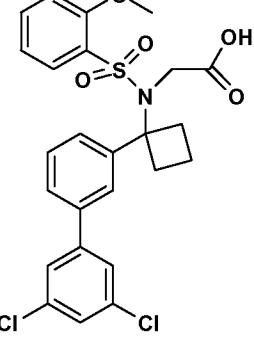
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
10		A	
11		B	0.200
12		A	
13		A	

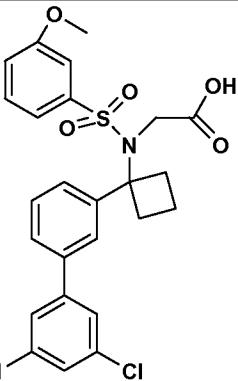
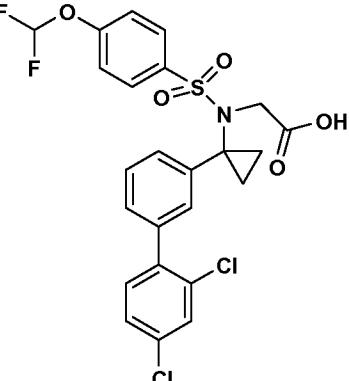
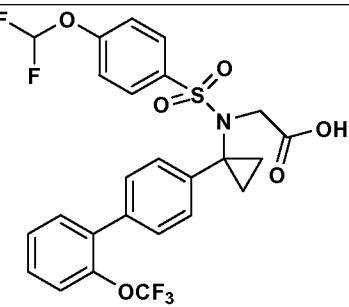
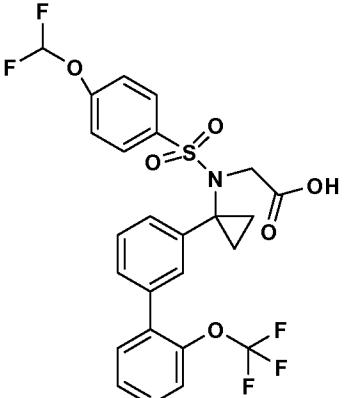
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
14		A	
15		A	
16		A	

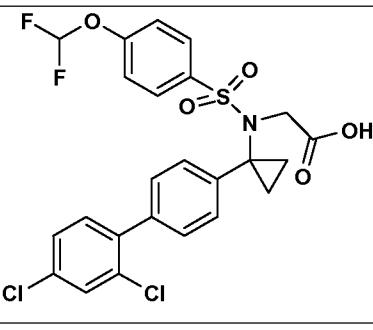
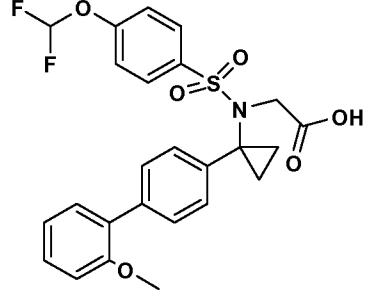
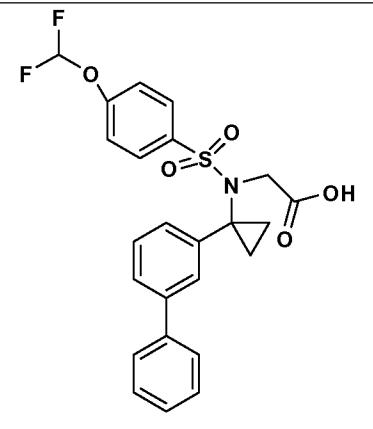
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
17		A	
18		A	
19		A	
20		A	

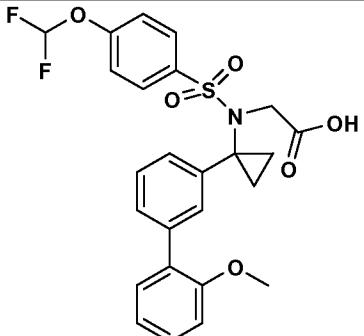
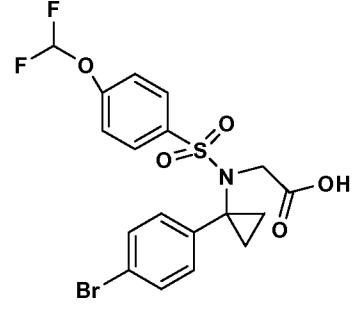
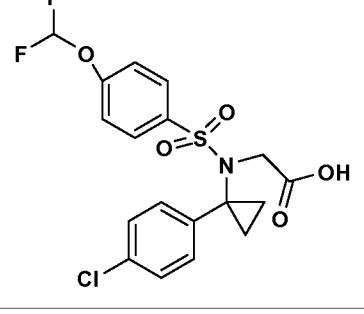
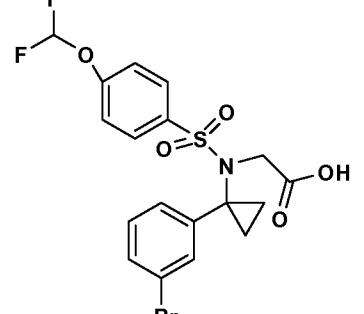
Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
21		A	
22		A	
23		B	
24		B	

Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
25		A	
26		A	0.004
27		C	3.093

Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
28		B	
29		A	
30		C	

Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
31		B	0.109
38		A	
39		A	
40		A	

Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
41		B	
42		B	
43		B	

Example Number	Structure	Data Range*	LE_LG586PNP_D R (IC50, μ M)
44		C	
45		C	
46		C	
47		C	7.495

* A = 0.001-0.100 μ M

B = 0.101-1.003 μ M

C = \geq 1.004 μ M

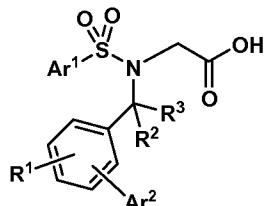
It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not 5 restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

What is claimed is:

1. A compound of Formula (I)

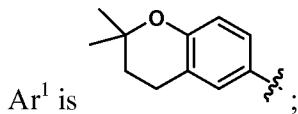
5



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ar¹ is selected from naphthyl and phenyl, wherein the phenyl is substituted with 0, 1, or 2 substituents independently selected from alkyl, halo, haloalkoxy, alkoxy, and cyano; or



Ar² is selected from hydrogen, phenyl, naphthyl, pyrimidinyl, thiazolyl, and quinolinyl, wherein the phenyl, naphthyl, pyrimidinyl, thiazolyl, and quinolinyl are each substituted with 0, 1, or 2 substituents independently selected from alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, and halo;

R¹ is selected from hydrogen, cyano, halo, alkyl, alkoxy, and haloalkoxy; and R² and R³ are each lower alkyl; or R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom.

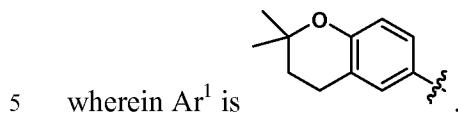
2. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R² and R³, together with the carbon atom to which they are attached, form a 3- to 5-membered carbocyclic ring optionally containing an oxygen atom.

25

3. A compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein Ar¹ is naphthyl.

4. A compound of Claim 3, or a pharmaceutically acceptable salt thereof, wherein R¹ is halo and Ar² is hydrogen.

5. A compound of Claim 2, or a pharmaceutically acceptable salt thereof,



6. A compound of Claim 5, or a pharmaceutically acceptable salt thereof, wherein R¹ is halo and Ar² is hydrogen.

10 7. A compound of Claim 5, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen and Ar² is phenyl optionally substituted with two halo groups.

15 8. A compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein Ar¹ is phenyl substituted with 0, 1, or 2 groups selected from alkyl, halo, haloalkoxy, alkoxy, and cyano.

9. A compound of Claim 8, or a pharmaceutically acceptable salt thereof, wherein R¹ is halo and Ar² is hydrogen.

20 10. A compound of Claim 8, or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen and Ar² is selected from phenyl, pyrimidinyl, and thiazolyl, wherein the phenyl, pyrimidinyl, and thiazolyl are substituted with 0, 1, or 2 groups independently selected from alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, and halo.

25 11. A compound selected from:
2-(N-(1-(4-bromophenyl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;
30 2-(4-(difluoromethoxy)-N-(1-(4-(pyrimidin-5-yl)phenyl)cyclobutyl)phenylsulfonamido) acetic acid;

2-(N-(1-(2',4'-dichlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-methoxybiphenyl-4-yl)cyclobutyl)phenylsulfonamido) acetic acid;

5 2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethoxy)biphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(3,4-dichloro-N-(1-(2',4'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

10 2-(N-(1-(3-bromophenyl)cyclobutyl)-3,4-dichlorophenylsulfonamido)acetic acid;

2-(3,4-dichloro-N-(1-(2'-methoxybiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(4-(2,4-dimethylthiazol-5-yl)phenyl)cyclobutyl)phenylsulfonamido)acetic acid;

15 2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid;

2-(N-(1-(biphenyl-3-yl)cyclobutyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid;

2-(N-(1-(biphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

20 2-(N-(1-(4'-chlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(4'-methoxybiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid;

25 2-(4-(difluoromethoxy)-N-(1-(2'-methylbiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(N-(1-(3'-chlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

30 2-(4-(difluoromethoxy)-N-(1-(3'-methoxybiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethyl)biphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(N-(1-(2'-chlorobiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-fluorobiphenyl-4-yl)cyclobutyl)phenylsulfonamido)acetic acid;

5 2-(N-(1-(5'-chloro-2'-methoxybiphenyl-4-yl)cyclobutyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid;

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

10 2-(2-chloro-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(3-chloro-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(4-chloro-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

15 2-(2-cyano-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(3-cyano-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

2-(4-cyano-N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)phenylsulfonamido)acetic acid;

20 2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-2-methoxyphenylsulfonamido)acetic acid;

2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclobutyl)-3-methoxyphenylsulfonamido)acetic acid;

25 2-(N-(1-(4-bromophenyl)cyclopentyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid;

2-(N-(1-(3',5'-dichlorobiphenyl-4-yl)cyclopentyl)-2,2-dimethylchroman-6-sulfonamido)acetic acid;

2-(N-(3-(3',5'-dichlorobiphenyl-4-yl)tetrahydrofuran-3-yl)-2,2-dimethylchroman-6-sulfonamido)acetic acid;

30 2-(N-(1-(3',5'-dichlorobiphenyl-3-yl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido) acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethoxy)biphenyl-4-yl)cyclopropyl)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-(trifluoromethoxy)biphenyl-3-yl)cyclopropyl)phenylsulfonamido)acetic acid;

5 2-(N-(1-(2',4'-dichlorobiphenyl-4-yl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-methoxybiphenyl-4-yl)cyclopropyl)phenylsulfonamido)acetic acid;

10 2-(N-(1-(biphenyl-3-yl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

2-(4-(difluoromethoxy)-N-(1-(2'-methoxybiphenyl-3-yl)cyclopropyl)phenylsulfonamido)acetic acid;

2-(N-(1-(4-bromophenyl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

15 2-(N-(1-(4-chlorophenyl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

2-(N-(1-(3-bromophenyl)cyclopropyl)-4-(difluoromethoxy)phenylsulfonamido)acetic acid;

2-(N-(1-(4-bromophenyl)cyclopentyl)naphthalene-1-sulfonamido)acetic acid;

20 2-(N-(1-(4-bromophenyl)cyclopentyl)-4-methylphenylsulfonamido)acetic acid; and

2-(N-(1-(4-bromophenyl)cyclopentyl)naphthalene-2-sulfonamido)acetic acid; or a pharmaceutically acceptable salt thereof.

25 12. A composition comprising a pharmaceutically acceptable amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

30 13. A method for treating a disorder associated with DAGL α and/or DAGL β activity, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

14. The method of Claim 13 wherein the disorder is selected from schizophrenia, psychosis, bipolar disorder, depression, anxiety, pain, cognitive impairment, diabetes, obesity, hepatic steatosis, and dyslipidemia.
- 5 15. The method of Claim 14 wherein the disorder is selected from schizophrenia, bipolar disorder, depression, anxiety, diabetes, obesity, hepatic steatosis, and dyslipidemia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/024726

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07D239/26	C07D277/28	C07D311/70	C07D407/12
	A61K31/505	A61K31/426	A61P25/18	A61P25/24
	A61P3/10	A61P3/06		A61P3/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HOOVER H S ET AL: "Selectivity of inhibitors of endocannabinoid biosynthesis evaluated by activity-based protein profiling", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 18, no. 22, 15 November 2008 (2008-11-15), pages 5838-5841, XP025627150, ISSN: 0960-894X, DOI: DOI:10.1016/J.BMCL.2008.06.091 [retrieved on 2008-07-02] cited in the application the whole document figure 1</p> <p>-----</p> <p>-/-</p>	1-15

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2011	08/04/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Papathoma, Sofia

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/024726

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 160 248 A1 (PFIZER [US]; PFIZER LTD [GB]) 5 December 2001 (2001-12-05) the whole document in particular paragraphs 32, 49, 51, claims 19 and 22 and examples 1-5 -----	1-15
A	US 2009/264400 A1 (OBERBOERSCH STEFAN [DE] ET AL) 22 October 2009 (2009-10-22) Compound with the Registry Number 1191240-46-6; page 89, paragraph 525 - paragraph 526 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/024726

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