

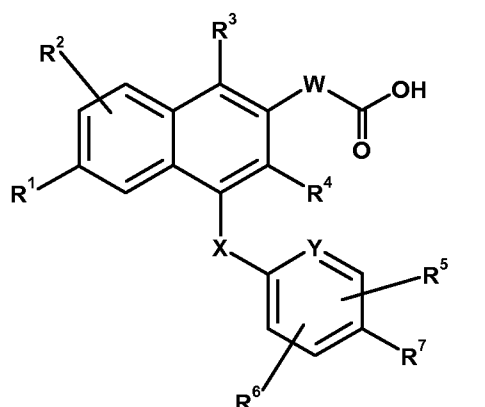
NAPHTHYLACETIC ACIDS

The present invention relates to novel substituted naphthalene-2-yl acetic acids, their manufacture, pharmaceutical compositions containing them and their use as CRTH2 antagonists or partial agonists.

- 5 Prostaglandin D₂ (PGD₂) is the major prostanoid produced by activated mast cells and has been implicated in the pathogenesis of allergic diseases such as allergic asthma and atopic dermatitis. Chemoattractant Receptor-homologous molecule expressed on T-helper type cells (CRTH2) is one of the prostaglandin D₂ receptors and is expressed on the effector cells involved in allergic
- 10 inflammation such as T helper type 2 (Th2) cells, eosinophils, and basophils (Nagata *et al.*, *FEBS Lett* 459: 195-199, 1999). It has been shown to mediate PGD₂-stimulated chemotaxis of Th2 cells, eosinophils, and basophils (Hirai *et al.*, *J Exp Med* 193: 255-261, 2001). Moreover, CRTH2 mediates the respiratory burst and degranulation of eosinophils (Gervais *et al.*, *J Allergy Clin Immunol*
- 15 108: 982-988, 2001), induces the production of proinflammatory cytokines in Th2 cells (Xue *et al.*, *J Immunol* 175: 6531-6536), and enhances the release of histamine from basophils (Yoshimura-Uchiyama *et al.*, *Clin Exp Allergy* 34:1283-1290). Sequence variants of the gene encoding CRTH2, which differentially influence its mRNA stability, are shown to be associated with asthma (Huang *et al.*, *Hum Mol Genet* 13, 2691-2697, 2004). Increased numbers of circulating T
- 20 cells expressing CRTH2 have also been correlated with severity of atopic dermatitis (Cosmi *et al.*, *Eur J Immunol* 30, 2972-2979, 2000). These findings suggest that CRTH2 plays a proinflammatory role in allergic diseases. Therefore, antagonists of CRTH2 are believed to be useful for treating disorders such as
- 25 asthma, allergic inflammation, COPD, allergic rhinitis, and atopic dermatitis.

The invention is concerned with the compounds of formula I:

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and pharmaceutically acceptable salts and esters thereof, wherein W, X, Y, R¹, R², R³, R⁴, R⁵, R⁶, and R⁷ are defined in the detailed description and claims. In

5 addition, the present invention relates to methods of manufacturing and using the compounds of formula I as well as pharmaceutical compositions containing such compounds. The compounds of formula I are antagonists or partial agonists at the CRTH2 receptor and may be useful in treating diseases and disorders associated with that receptor such as asthma.

10

Unless otherwise indicated, the following specific terms and phrases used in the description and claims are defined as follows:

The term “moiety” refers to an atom or group of chemically bonded atoms that is attached to another atom or molecule by one or more chemical bonds thereby

15 forming part of a molecule. For example, the variables R¹-R⁷ of formula I refer to moieties that are attached to the core structure of formula I by a covalent bond.

In reference to a particular moiety with one or more hydrogen atoms, the term “substituted” refers to the fact that at least one of the hydrogen atoms of that moiety is replaced by another substituent or moiety. For example, the term

20 “lower alkyl substituted by halogen” refers to the fact that one or more hydrogen atoms of a lower alkyl (as defined below) is replaced by one or more halogen atoms (e.g., trifluoromethyl, difluoromethyl, fluoromethyl, chloromethyl, etc.).

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The term "optionally substituted" refers to the fact that one or more hydrogen atoms of a moiety (with one or more hydrogen atoms) can be, but does not necessarily have to be, substituted with another substituent.

The term "alkyl" refers to an aliphatic straight-chain or branched-chain saturated hydrocarbon moiety having 1 to 20 carbon atoms. In particular embodiments the alkyl has 1 to 10 carbon atoms.

The term "lower alkyl" refers to an alkyl moiety having 1 to 7 carbon atoms. In particular embodiments the lower alkyl has 1 to 4 carbon atoms and in other particular embodiments the lower alkyl has 1 to 3 carbon atoms. Examples of lower alkyls include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl.

The term "lower cycloalkyl" refers to a saturated or partly unsaturated non-aromatic hydrocarbon ring moiety having 3 to 7 carbon atoms bonded together to form a ring structure. Examples of cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "lower alkoxy" refers to the moiety -O-R, wherein R is lower alkyl as defined previously. Examples of lower alkoxy moieties include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy.

The term "lower alkoxy carbonyl" refers to the moiety -C(O)-O-R, wherein R is lower alkyl as defined previously. Examples of lower alkoxy carbonyl moieties include methoxycarbonyl and ethoxycarbonyl.

The term "heteroatom" refers to nitrogen, oxygen, or sulfur.

The term "lower heterocycloalkyl" refers to a saturated or partly unsaturated non-aromatic ring moiety having 3 to 7 ring atoms bonded together to form a ring structure wherein one, two or three of the ring atoms is a heteroatom while the remaining ring atoms are carbon atoms. Examples of lower heterocycloalkyls include piperidinyl, piperazinyl, pyrrolidinyl, and morpholinyl.

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The term "lower alkylamino" refers to the moiety -N(R), wherein R is lower alkyl as defined previously. An example of a lower alkylamino is methylamino.

The term "lower dialkylamino" refers to the moiety -N(R)(R'), wherein R and R' are lower alkyl as defined previously. An example of a lower dialkylamino is
5 dimethylamino.

The term "lower alkylsulfonyl" refers to the moiety -S(O)₂-R, wherein R is lower alkyl as defined previously. Examples of lower alkylsulfonyls include methylsulfonyl and ethylsulfonyl.

The term "halogen" refers to a moiety of fluoro, chloro, bromo or iodo.

10 Unless otherwise indicated, the term "hydrogen" or "hydro" refers to the moiety of a hydrogen atom (-H) and not H₂.

Unless otherwise indicated, the term "a compound of the formula" or "a compound of formula" or "compounds of the formula" or "compounds of formula" refers to any compound selected from the genus of compounds as defined by the
15 formula (including any pharmaceutically acceptable salt or ester of any such compound if not otherwise noted).

The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. Salts may be formed with inorganic
20 acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, preferably hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, salicylic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic
25 acid, *p*-toluenesulfonic acid, *N*-acetylcystein and the like. In addition, salts may be prepared by the addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of

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primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, *N*-ethylpiperidine, piperidine, polyamine resins
5 and the like.

The compounds of the present invention can be present in the form of pharmaceutically acceptable salts. The compounds of the present invention can also be present in the form of pharmaceutically acceptable esters (i.e., the methyl and ethyl esters of the acids of formula I to be used as prodrugs). The
10 compounds of the present invention can also be solvated, i.e. hydrated. The solvation can be effected in the course of the manufacturing process or can take place i.e. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration).

Compounds that have the same molecular formula but differ in the nature or
15 sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Diastereomers are stereoisomers with opposite configuration at one or more chiral centers which are not enantiomers. Stereoisomers bearing one or more asymmetric centers that are non-
20 superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center or centers and is described by the R- and S-sequencing rules of Cahn, Ingold and Prelog, or
25 by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

30 The term "a therapeutically effective amount" of a compound means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of

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disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art. The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such

5 dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 0.1 mg to about 5,000 mg,

10 1 mg to about 1,000 mg, or 1 mg to 100 mg may be appropriate, although the lower and upper limits may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion.

The term "pharmaceutically acceptable carrier" is intended to include any and all

15 material compatible with pharmaceutical administration including solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and other materials and compounds compatible with pharmaceutical administration. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions

20 of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases; thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other

25 protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose,

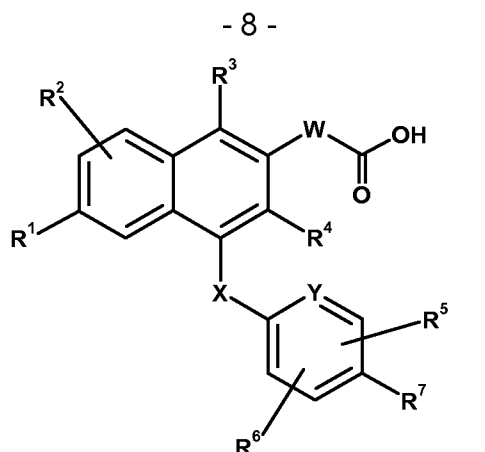
30 and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s)

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which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention or a combination of any of the compounds of this invention or a pharmaceutically acceptable salt or ester thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form of solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

In detail, the present invention relates to the compounds of formula I:



and pharmaceutically acceptable salts and esters thereof, wherein:

W is CH_2 , $\text{CH}_2\text{-CH}_2$, $\text{C(H)(CH}_3\text{)}$, $\text{CH}_2\text{-C(H)(CH}_3\text{)}$, or $\text{C(H)(CH}_3\text{)-CH}_2$;

X is selected from the group consisting of:

- 5 (1) O, (2) N(H), (3) N(CH₃), (4) S, (5) S(O), and (6) S(O)₂;

Y is carbon or nitrogen;

R¹ is selected from the group consisting of:

- (1) hydrogen, (2) halogen, (3) methyl optionally substituted by fluoro, (4) lower alkoxy optionally substituted by fluoro, (5) cyano, and (6) lower alkylsulfonyl;
- 10

R² is hydrogen, fluoro, chloro, lower alkyl, or lower alkoxy;

R³ is hydrogen, fluoro, chloro, bromo, or methyl;

R⁴ is selected from the group consisting of:

- (1) hydrogen, (2) halogen, (3) lower alkyl optionally substituted by fluoro, (4) lower cycloalkyl, and (5) ethenyl;
- 15

R⁵ and R⁶, independently of each other, are selected from the group consisting of:

- (1) hydrogen, (2) halogen, (3) lower alkyl, (4) cyano, and (5) lower cycloalkyl;

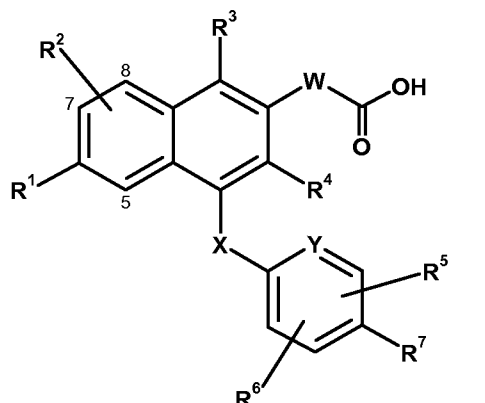
- 20 R⁷ is cyano or S(O)₂-R⁸, wherein R⁸ is selected from the group consisting of:

- (1) lower alkyl, (2) lower cycloalkyl, (3) phenyl optionally substituted by (a) halogen, (b) lower alkyl optionally substituted by fluoro, or (c) lower alkoxy, (4) lower alkylamino, (5) lower dialkylamino, (6) lower heterocycloalkyl optionally substituted by halogen, lower alkyl, or lower alkoxy, and (7) 2-oxa-6-aza-spiro[3.3]hept-6-yl.
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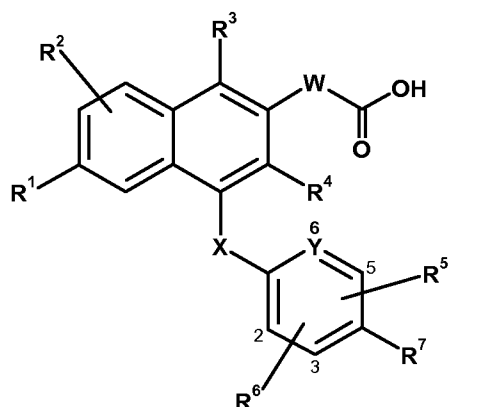
Unless indicated otherwise, the R^2 moiety in formula I (or in any subgeneric formula of formula I) is bonded to a carbon atom on the naphthalene core structure at position 5, 7, or 8 in place of a hydrogen atom that would otherwise be bonded to that carbon atom (absent being substituted by R^2) where such

5 positions are indicated as follows:



In one particular embodiment the present invention is directed to the compounds of formula I or a subgeneric formula of formula I (and the pharmaceutically acceptable salts and esters thereof), wherein R^2 is bonded to the naphthalene core structure at position 5 or 7 (where such positions are as previously indicated).

Unless indicated otherwise, the R^5 and R^6 moieties (independently of each other) are bonded to one of the ring carbon atoms on the ring containing Y in formula I (or in any subgeneric formula of formula I) at positions 2, 3, 5, or 6 in place of a hydrogen atom that would otherwise be bonded to that carbon atom (absent being substituted by R^5 or R^6) where such positions are indicated as follows, with the proviso that that R^5 and R^6 are not simultaneously bonded to the same carbon atom and are not bonded to Y when Y is nitrogen:



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Thus, unless indicated otherwise, in reference to formula I or a subgenus of formula I, the terms "Y is carbon or nitrogen" or "Y is carbon" or "Y is nitrogen" indicates that when Y is carbon it is either bonded to a hydrogen atom, R⁵, or R⁶; and when Y is nitrogen it is not bonded to a hydrogen atom, R⁵, or R⁶.

- 5 In one particular embodiment, the present invention is directed to the compounds of formula I or a subgeneric formula of formula I (and the pharmaceutically acceptable salts and esters thereof), wherein at least one of R⁵ or R⁶ is bonded to a carbon atom on the ring containing Y at position 2 (where position 2 is as previously indicated).
- 10 In another particular embodiment, the present invention is directed to the compounds of formula I or a subgeneric formula of formula I (and the pharmaceutically acceptable salts and esters thereof), wherein at least one of R⁵ or R⁶ is bonded to a carbon atom on the ring containing Y at position 2 or 6 when Y is carbon (where positions 2 and 6 are as previously indicated).
- 15 In another embodiment, the present invention is directed to the compounds of formula I or a subgeneric formula of formula I (and the pharmaceutically acceptable salts and esters thereof), wherein R⁵ and R⁶ are bonded to carbon atoms on the ring containing Y at positions 2 and 6 when Y is carbon (where positions 2 and 6 are as previously indicated).
- 20 Unless indicated otherwise, the genus of formula I and any subgenera thereof encompass all possible stereoisomers (i.e., (*R*)-enantiomers, (*S*)-enantiomers, diastereomers) as well as racemic and scalemic mixtures thereof.

In one embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein W is

25 C(H)₂.

In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein W is C(H)₂-C(H)₂.

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In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein X is O.

In another particular embodiment, the present invention is directed to the
5 compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein X is N(H).

In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein X is S, S(O) or S(O)₂.

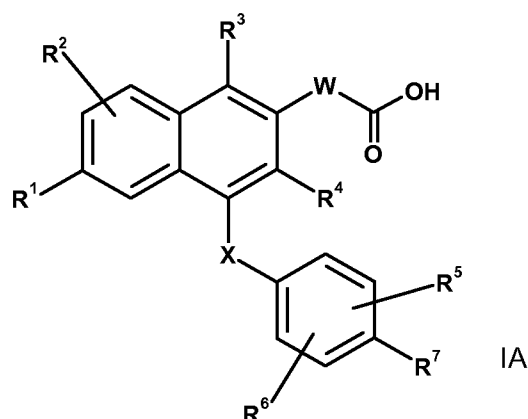
10 In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein X is S.

In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof
15 wherein X is S(O).

In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein X is S(O)₂.

In another particular embodiment, the present invention is directed to the
20 compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein Y is carbon as depicted below in formula IA (a subgenus of formula I):

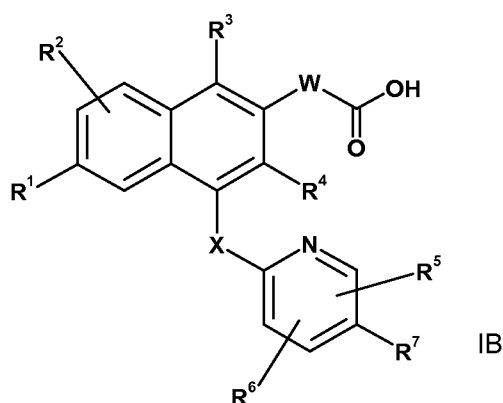
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wherein W, X, and R¹-R⁷ are defined as in formula I.

In another particular embodiment, the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof

5 wherein Y is nitrogen as depicted below in formula IB (a subgenus of formula I):



wherein W, X, and R¹-R⁷ are defined as in formula I.

10 In one embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is hydrogen, fluoro, chloro, bromo, cyano, methyl, trifluoromethyl, methoxy, trifluoromethoxy or methylsulfonyl.

In another embodiment the present invention is directed to the compounds of
 15 formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is halogen, methyl or methoxy.

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In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is halogen.

In another particular embodiment the present invention is directed to the
5 compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is chloro or fluoro.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is chloro.

10 In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is fluoro.

In one embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R² is hydrogen.

15 In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R² is fluoro.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof
20 wherein R² is chloro.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R² is methyl.

In another particular embodiment the present invention is directed to the
25 compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R² is methoxy.

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In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R¹ is Fluoro and R² is Hydrogen.

In another embodiment the present invention is directed to the compounds of
5 formula I or pharmaceutically acceptable salts or esters thereof wherein R³ is hydrogen, fluoro, or methyl.

In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R³ is hydrogen.

10 In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R³ is fluoro.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof
15 wherein R³ is methyl.

In another embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁴ is hydrogen, fluoro, methyl, ethyl, ethenyl or cyclopropyl.

In another embodiment the present invention is directed to the compounds of
20 formula I or pharmaceutically acceptable salts or esters thereof wherein R⁴ is hydrogen, fluoro or methyl.

In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁴ is hydrogen.

25 In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁴ is fluoro.

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In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁴ is methyl.

In another embodiment the present invention is directed to the compounds of
5 formula I or pharmaceutically acceptable salts or esters thereof wherein R⁵ and R⁶, independently of each other, are selected from the group consisting of: (1) hydrogen, (2) halogen, (3) lower alkyl and (4) cyano.

In another embodiment the present invention is directed to the compounds of
10 formula I or pharmaceutically acceptable salts or esters thereof wherein R⁵ and R⁶, independently of each other, are selected from the group consisting of: (1) hydrogen, (2) fluoro, (3) chloro, (4) methyl, (5) ethyl, (6) cyclopropyl and (7) cyano.

In another embodiment the present invention is directed to the compounds of
15 formula I or pharmaceutically acceptable salts or esters thereof wherein R⁵ and R⁶, independently of each other, are selected from the group consisting of: (1) hydrogen, (2) fluoro, (3) chloro, (4) methyl and (5) cyano.

In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein at least one of R⁵ or R⁶ is hydrogen.

20 In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁵ and R⁶ are both hydrogen.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof
25 wherein at least one of R⁵ or R⁶ is hydrogen and the other is fluoro, chloro, or bromo.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein at least one of R⁵ or R⁶ is hydrogen and the other is methyl.

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In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁵ and R⁶ are not both cyano.

In another particular embodiment the present invention is directed to the
5 compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein at least one of R⁵ or R⁶ is hydrogen and the other is cyano.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁵ and R⁶ are both halogen.

10 In another embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁷ is S(O)₂-R⁸ and R⁸ is selected from the group consisting of:

(1) methyl, (2) ethyl, (3) propyl, (4) isopropyl, (5) butyl, (6) *sec*-butyl, (7) *tert*-butyl, (8) cyclopropyl, (9) cyclobutyl, (10) cyclopentyl, (11) cyclohexyl,
15 (12) phenyl optionally substituted by halogen, methyl or methoxy, (13) dimethylamino, (14) diethylamino, (15) pyrrolidin-1-yl, (16) morpholin-4-yl, (17) piperidin-1-yl optionally substituted by halogen, (18) piperazin-1-yl optionally substituted by methyl, and (19) 2-oxa-6-aza-spiro[3.3]hept-6-yl.

In another embodiment the present invention is directed to the compounds of
20 formula I or pharmaceutically acceptable salts or esters thereof wherein R⁷ is S(O)₂-R⁸ and R⁸ is selected from the group consisting of:

(1) methyl, (2) ethyl, (3) propyl, (4) isopropyl, (5) butyl, (6) cyclopropyl, (7) cyclobutyl, (8) cyclopentyl, (9) dimethylamino, (10) diethylamino, (11) pyrrolidin-1-yl, (12) morpholin-4-yl, (13) 4,4-difluoro-piperidin-1-yl, (14) 4-methyl-piperazin-1-yl, and (15) 2-oxa-6-aza-spiro[3.3]hept-6-yl.
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In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R⁷ is S(O)₂-R⁸ and R⁸ is selected from the group consisting of:

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(1) methyl, (2) ethyl, (3) propyl, (4) isopropyl, (5) butyl, (6) cyclopropyl, (7) cyclopentyl, (8) dimethylamino, (9) diethylamino, (10) pyrrolidin-1-yl, (11) morpholin-4-yl, (12) 4,4-difluoro-piperidin-1-yl, (13) 4-methyl-piperazin-1-yl, and (14) 2-oxa-6-aza-spiro[3.3]hept-6-yl.

5 In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R^7 is $S(O)_2-R^8$ and R^8 is selected from the group consisting of:

(1) methyl, (2) ethyl, (3) isopropyl, (4) butyl, (5) dimethylamino, (6) diethylamino, (7) pyrrolidin-1-yl, (8) 4-methyl-piperazin-1-yl, and (9) 2-oxa-
10 6-aza-spiro[3.3]hept-6-yl.

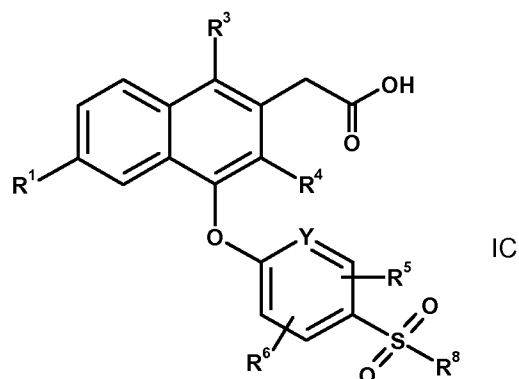
In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R^7 is $S(O)_2-R^8$ and R^8 is selected from the group consisting of:

15 (1) ethyl, (2) propyl, (3) isopropyl, (4) cyclopropyl, (5) butyl, and (6) cyclopentyl.

In a more particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein R^7 is $S(O)_2-R^8$ and R^8 is ethyl.

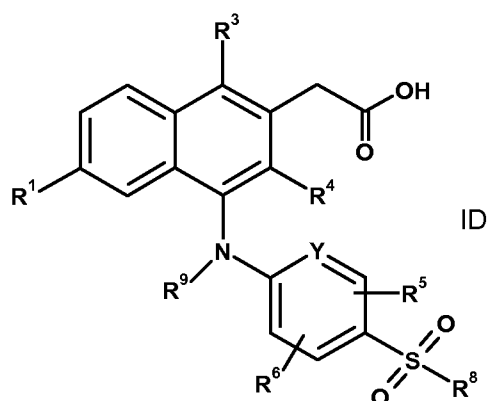
20 In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein W is $C(H)_2$, X is O, R^2 is hydrogen and R^7 is $S(O)_2-R^8$, as depicted below in formula IC (a subgenus of formula I):

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wherein Y, R¹, R³-R⁶ and R⁸ are defined as in formula I.

In another particular embodiment the present invention is directed to the
 5 compounds of formula I or pharmaceutically acceptable salts or esters thereof
 wherein R² is hydrogen and R⁷ is S(O)₂-R⁸, W is C(H)₂, and X is N(R⁹) wherein
 R⁹ is hydrogen or methyl, as depicted below in formula ID (a subgenus of formula
 I):

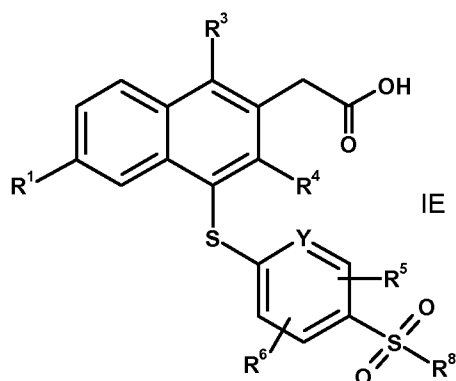


10 wherein Y, R¹, R³-R⁶ and R⁸ are defined as in formula I.

In another particular embodiment the present invention is directed to the
 compounds of formula I or pharmaceutically acceptable salts or esters thereof
 wherein W is C(H)₂, X is S, R² is hydrogen and R⁷ is S(O)₂-R⁸, as depicted below
 in formula IE (a subgenus of formula I):

15

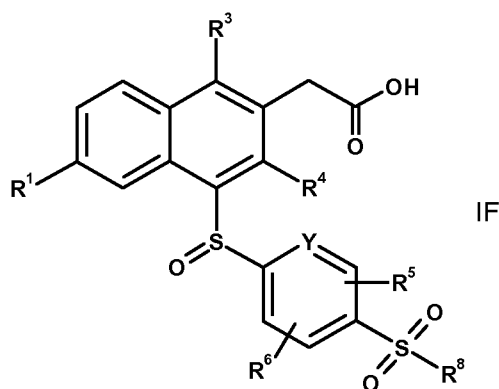
- 19 -



wherein Y, R¹, R³-R⁶ and R⁸ are defined as in formula I.

In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof

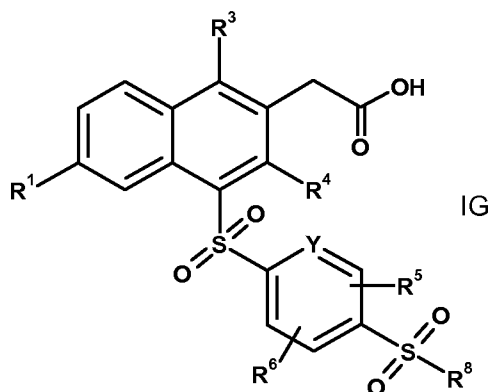
- 5 wherein W is C(H)₂, X is S(O), R² is hydrogen and R⁷ is S(O)₂-R⁸, as depicted below in formula IF (a subgenus of formula I):



wherein Y, R¹, R³-R⁶ and R⁸ are defined as in formula I.

- 10 In another particular embodiment the present invention is directed to the compounds of formula I or pharmaceutically acceptable salts or esters thereof wherein W is C(H)₂, X is S(O)₂, R² is hydrogen and R⁷ is S(O)₂-R⁸, as depicted below in formula IG (a subgenus of formula I):

- 20 -



wherein Y, R¹, R³-R⁶ and R⁸ are defined as in formula I.

In a more specific embodiment, the present invention is directed to a compound of formula I selected from the group consisting of:

- 5 [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid;
- [6-chloro-4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid;
- {6-fluoro-4-[4-(propane-2-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;
- [4-(4-cyclopropanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid;
- 10 [6-fluoro-4-(4-methanesulfonyl-2-methyl-phenoxy)-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(4-methanesulfonyl-3-methyl-phenoxy)-naphthalen-2-yl]-acetic acid;
- [4-(4-ethanesulfonyl-2-methyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid;
- 15 [6-fluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(5-methanesulfonyl-3-methyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid;
- 20 [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid;
- [4-(5-ethanesulfonyl-3-methyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid;
- [4-(3-bromo-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid;
- 25 [4-(3-bromo-5-methanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid;

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- [4-(4-ethanesulfonyl-phenoxy)-6-methoxy-naphthalen-2-yl]-acetic acid;
[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-trifluoromethyl-naphthalen-2-yl]-
acetic acid;
[4-(4-ethanesulfonyl-phenoxy)-6-trifluoromethyl-naphthalen-2-yl]-acetic
5 acid;
[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-trifluoromethoxy-naphthalen-2-yl]-
acetic acid;
[4-(4-ethanesulfonyl-phenoxy)-6-trifluoromethoxy-naphthalen-2-yl]-acetic
acid;
10 [4-(4-ethanesulfonyl-phenoxy)-7-fluoro-naphthalen-2-yl]-acetic acid;
[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-methoxy-naphthalen-2-yl]-acetic
acid;
[4-(4-Ethanesulfonyl-phenoxy)-5-fluoro-naphthalen-2-yl]-acetic acid;
[4-(4-Ethanesulfonyl-phenoxy)-6,7-dimethoxy-naphthalen-2-yl]-acetic acid;
15 [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic
acid;
[6-fluoro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic
acid;
[6-fluoro-4-(4-methanesulfonyl-2-methyl-phenoxy)-3-methyl-naphthalen-2-
20 yl]-acetic acid;
{6-fluoro-3-methyl-4-[4-(propane-2-sulfonyl)-phenoxy]-naphthalen-2-yl}-
acetic acid;
[4-(4-cyclopropanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-
acetic acid;
25 [6-fluoro-4-(4-methanesulfonyl-3-methyl-phenoxy)-3-methyl-naphthalen-2-
yl]-acetic acid;
[6-chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic
acid;
[6-chloro-4-(4-methanesulfonyl-3-methyl-phenoxy)-3-methyl-naphthalen-2-
30 yl]-acetic acid;
[6-chloro-4-(4-methanesulfonyl-2-methyl-phenoxy)-3-methyl-naphthalen-2-
yl]-acetic acid;

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- [4-(4-ethanesulfonyl-2-methyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(3-chloro-4-methanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 5 [6-fluoro-4-(2-fluoro-4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(4-ethanesulfonyl-2-fluoro-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(4-ethanesulfonyl-3-methyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 10 [4-(2,5-difluoro-4-methanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(3-fluoro-4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid;
- 15 [4-(4-ethanesulfonyl-3-fluoro-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(2-cyano-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(3-chloro-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 20 [4-(2-chloro-4-methanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(2-chloro-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 25 {6-fluoro-3-methyl-4-[4-(propane-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;
- {4-[4-(butane-1-sulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid;
- [4-(5-chloro-4-ethanesulfonyl-2-fluoro-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 30 [4-(2-chloro-4-ethanesulfonyl-5-fluoro-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;

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- [4-(4-cyclopentanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- {6-fluoro-4-[4-(4-fluoro-benzenesulfonyl)-phenoxy]-3-methyl-naphthalen-2-yl}-acetic acid;
- 5 [4-(4-benzenesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- {6-fluoro-3-methyl-4-[4-(toluene-4-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;
- {6-fluoro-4-[4-(4-methoxy-benzenesulfonyl)-phenoxy]-3-methyl-naphthalen-2-yl}-acetic acid;
- 10 {4-[4-(4-chloro-benzenesulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid;
- [6-fluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-3-methyl-naphthalen-2-yl]-acetic acid;
- 15 [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(5-methanesulfonyl-3-methyl-pyridin-2-yloxy)-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(5-ethanesulfonyl-3-methyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 20 [4-(3-bromo-5-methanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(4-dimethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- 25 {6-fluoro-3-methyl-4-[4-(pyrrolidine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;
- [4-(4-diethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- {6-fluoro-3-methyl-4-[4-(morpholine-4-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;
- 30 {6-fluoro-3-methyl-4-[4-(4-methyl-piperazine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;

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- {4-[4-(4,4-difluoro-piperidine-1-sulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid;
- {6-fluoro-3-methyl-4-[4-(2-oxa-6-aza-spiro[3.3]heptane-6-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid;
- 5 [4-(4-cyano-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;
- [6-chloro-4-(4-cyano-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid;
- [4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid;
- [4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid;
- [1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic
- 10 acid;
- [1,6-difluoro-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid;
- [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid;
- 15 [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid;
- 3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid;
- [6-fluoro-4-(4-methanesulfonyl-phenylamino)-naphthalen-2-yl]-acetic acid;
- 20 [6-fluoro-4-(4-methanesulfonyl-phenylamino)-3-methyl-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(4-methanesulfonyl-phenylsulfanyl)-naphthalen-2-yl]-acetic acid;
- [6-fluoro-4-(4-methanesulfonyl-benzenesulfinyl)-naphthalen-2-yl]-acetic
- 25 acid;
- [6-fluoro-4-(4-methanesulfonyl-benzenesulfonyl)-naphthalen-2-yl]-acetic acid;
- [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid;
- [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid;
- 30 [6-cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid;
- [6-bromo-4-(4-ethanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid;
- [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid;

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[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid; [3-cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid;

5 [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid; [4-(5-ethanesulfonyl-3-ethyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid;

[4-(3-cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid and

any pharmaceutically acceptable salt or ester thereof.

10

In a more specific embodiment, the present invention is directed to a compound of formula I selected from the group consisting of:

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid

15 [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

[6-Chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid

[6-fluoro-4-(2-fluoro-4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid

20

[4-(4-ethanesulfonyl-3-methyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

[4-(2-cyano-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

25 {4-[4-(butane-1-sulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid

[6-fluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-3-methyl-naphthalen-2-yl]-acetic acid

[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

30

[4-(3-bromo-5-methanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

[4-(4-dimethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

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{6-fluoro-3-methyl-4-[4-(pyrrolidine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-
acetic acid

[4-(4-diethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic
acid

- 5 {6-fluoro-3-methyl-4-[4-(4-methyl-piperazine-1-sulfonyl)-phenoxy]-
naphthalen-2-yl}-acetic acid
{6-fluoro-3-methyl-4-[4-(2-oxa-6-aza-spiro[3.3]heptane-6-sulfonyl)-
phenoxy]-naphthalen-2-yl}-acetic acid.

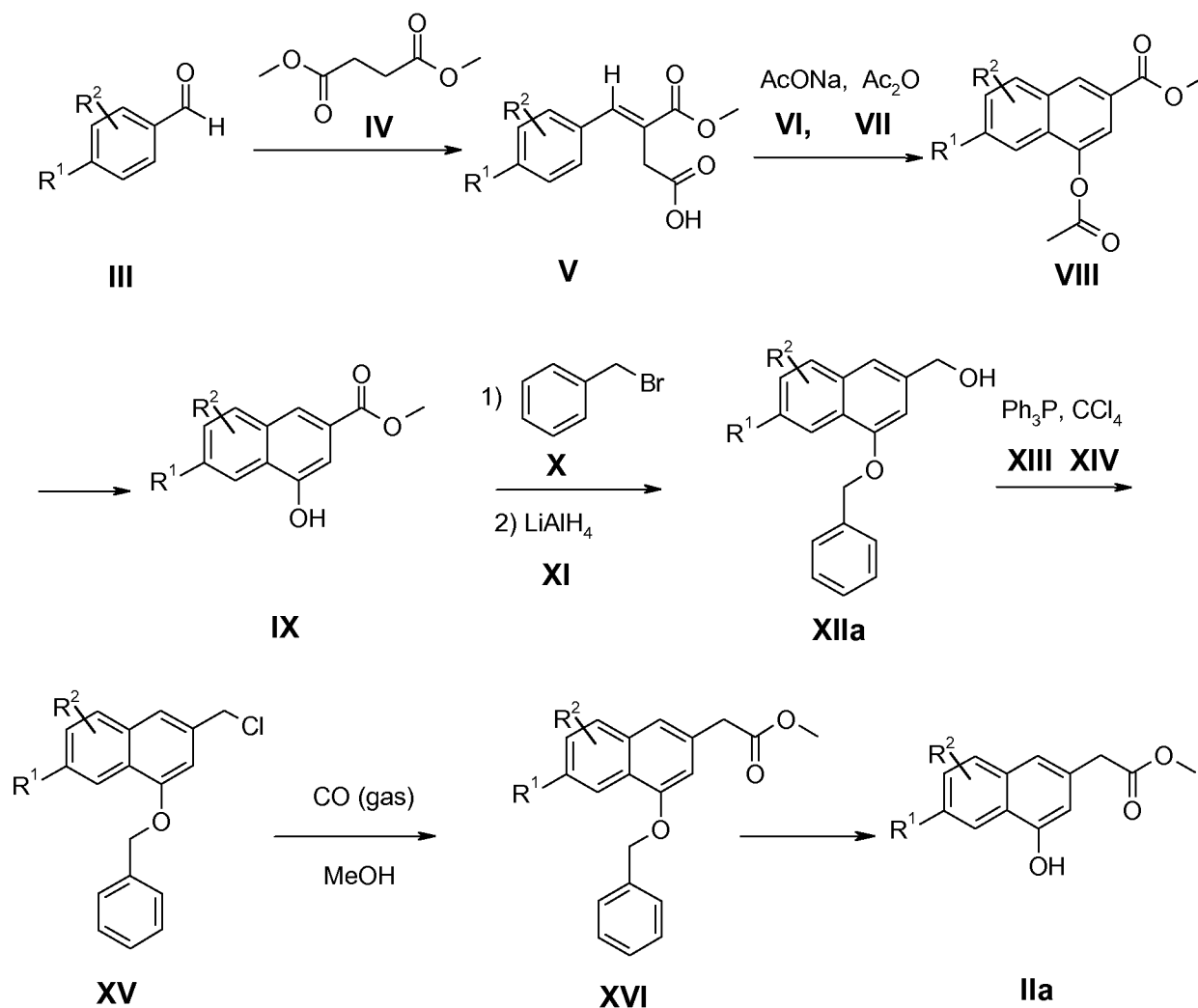
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GENERAL SYNTHESIS OF COMPOUNDS ACCORDING TO THE INVENTION

- The compounds of the present invention can be prepared by any conventional
means. Suitable processes for synthesizing these compounds are provided in the
15 examples. Generally, compounds of formula I can be prepared according to the
schemes illustrated below. Unless otherwise indicated, the variables W, X, Y,
and R¹ to R⁸ are defined in the same manner as defined previously for the genus
of formula I.

Scheme 1

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The key intermediates of formula **IIa** can be prepared according to Scheme 1. In this process, the Stobbe condensation reaction between the benzaldehydes **III** and dimethyl succinate (**IV**) gives the unsaturated acids **V**, which subsequently undergo cyclization in the presence of sodium acetate (**VI**) and acetic anhydride (**VII**) to produce compounds **VIII**. The naphthalene derivatives **VIII** are then converted to the corresponding hydroxyl analogues **IX** by a deacetylation reaction. The treatment of the hydroxyl derivatives **IX** with benzyl bromide (**X**), followed by reduction using lithium aluminum hydride (**XI**), affords the alcohols **XIIa**. Compounds **XIIa** are then converted to the corresponding chloro intermediates **XV** by treatment with triphenylphosphine (**XIII**) and carbon tetrachloride (**XIV**). Conversion of the chlorides **XV** to the methyl esters **XVI** can be accomplished by

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a palladium-catalyzed carbonylation reaction in methanol. Hydrogenolysis of compounds **XVI** affords the intermediates **Ila**.

In the first step outlined in Scheme 1, the unsaturated acids **V** can be prepared by a condensation reaction between the benzaldehydes **III** and dimethyl succinate (**IV**). The reaction can be carried out in the presence of a base such as sodium methoxide, lithium methoxide, sodium *tert*-butoxide, sodium hydride or potassium *tert*-butoxide, in an organic solvent such as methanol, *tert*-butanol, toluene, or mixtures thereof, at a temperature between room temperature and 90 °C for several hours (reference: Dian, Y. L. *et al.*, *Tetrahedron Lett.*, 32 (1991) 5255).

Cyclization of the unsaturated acids **V** to produce the naphthalene derivatives **VIII** can be achieved by treatment of the unsaturated acids **V** with sodium acetate (**VI**) and acetic anhydride (**VII**) at a temperature between room temperature and 140 °C for 0.5 to 12 hours (references: Boger, D. L. *et al.*, *J. Org. Chem.* 61 (1996) 4894-4912; Kim, M. *et al.*, *J. Org. Chem.* 69 (2004) 6945-6948).

The acetate derivatives **VIII** can be converted to the corresponding hydroxyl compounds **IX** in the presence of a base such as sodium methoxide, potassium *tert*-butoxide, potassium carbonate or sodium bicarbonate, in a solvent such as methanol, water, or mixtures thereof, at a temperature between room temperature and 80 °C for 10 minutes to several hours (reference: Kim, M. *et al.*, *J. Org. Chem.* 69 (2004) 6945-6948).

Treatment of the hydroxyl compounds **IX** with benzyl bromide (**X**) affords the corresponding benzyl ethers. The reaction can be carried out in the presence of a base such as potassium carbonate, or cesium carbonate, in an inert organic solvent such as acetone, acetonitrile, or *N,N*-dimethylformamide at a temperature between room temperature and 60 °C for several hours.

Reduction of the above benzyl ethers with lithium aluminum hydride (**XI**) affords the alcohols **XIIa**. The reaction can be carried out in an inert organic solvent such as tetrahydrofuran, diethyl ether, toluene, or mixtures thereof, at a temperature

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between room temperature and 80 °C for several hours (reference: Chan W. K, *et al.*, *J. Med. Chem.* 39 (1996) 3756-3768).

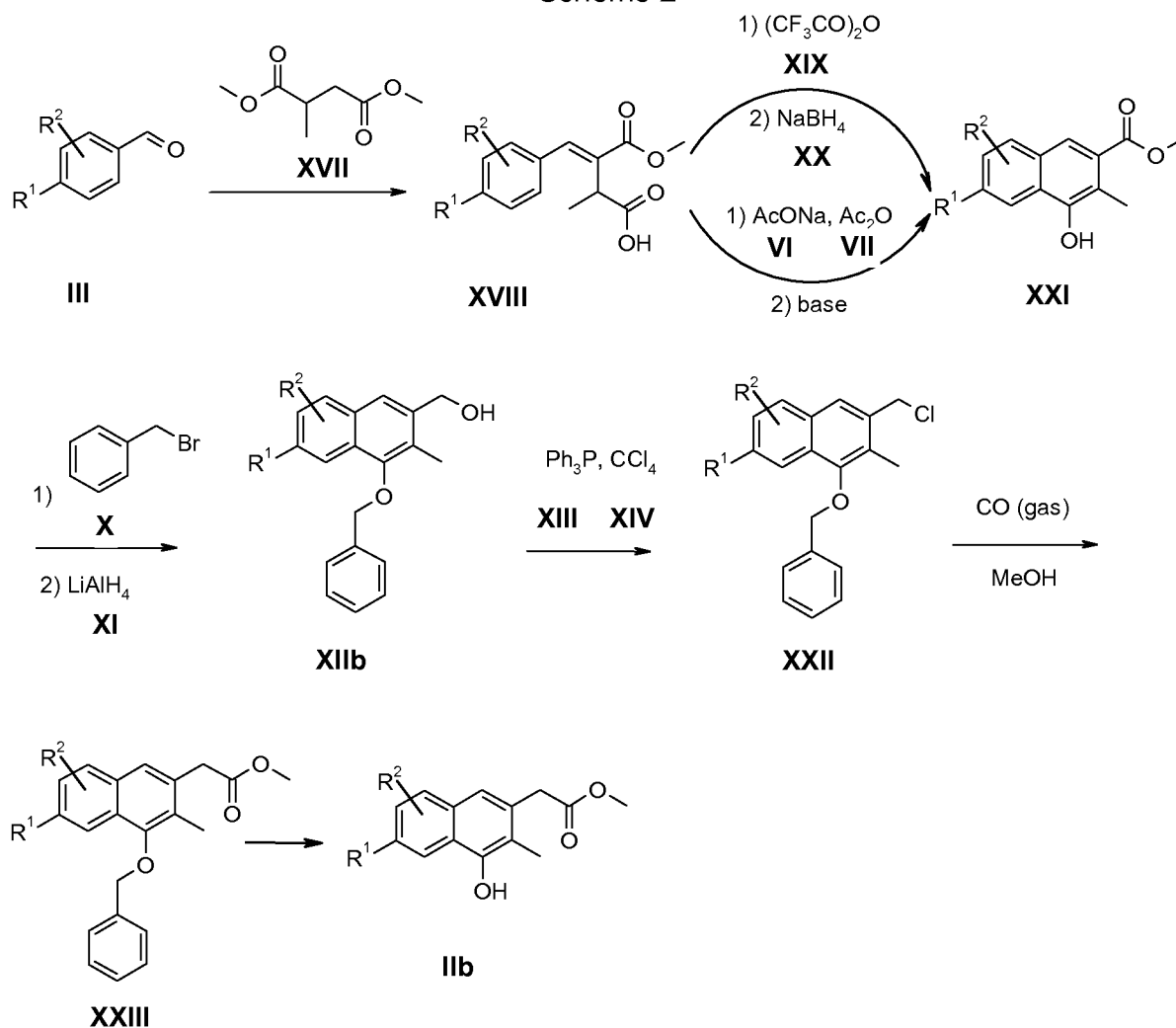
The intermediates **XV** can be prepared by the treatment of the alcohols **XIIa** with triphenylphosphine (**XIII**) and carbon tetrachloride (**XIV**) in an inert organic
5 solvent such as toluene, acetonitrile, dichloromethane, *N,N*-dimethylformamide, or tetrahydrofuran, at a temperature between 0 °C and 120 °C for several hours (reference: Kozhinov, D. V. *et al.*, *J. Org. Chem.* 69 (2004) 1378-1379).

Conversion of the intermediates **XV** to the methyl esters **XVI** can be accomplished by a palladium catalyzed carbonylation reaction under 1
10 atmospheric pressure of carbon monoxide in methanol. The reaction can be carried out in the presence of a palladium catalyst such as bis(triphenylphosphine)dichloropalladium(II) ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$), palladium(II) acetate ($\text{Pd}(\text{OAc})_2$), tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), or tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$), in the presence or absence
15 of a phosphine ligand such as tricyclohexylphosphine, or triphenylphosphine, at a temperature between room temperature and 90 °C for 10 minutes to several hours (reference: Kozhinov, D. V. *et al.*, *J. Org. Chem.* 69 (2004) 1378-1379).

Hydrogenolysis of benzyl ethers **XVI** affords the intermediates **IIa**. The reaction can be carried out in the presence of 10% palladium on carbon under 1
20 atmospheric pressure of hydrogen, in an organic solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours. Note that hydrogenolysis of benzyl ethers **XVI**, in which R^1 is Cl or Br, can afford **IIa**, in which R^1 is reduced to H, when the hydrogenations are carried out in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen
25 for a longer period of reaction time.

- 30 -

Scheme 2



- The key intermediates of formula **IIb** can be prepared according to Scheme 2. In
- 5 this process, the Stobbe condensation reaction between the benzaldehydes **III** and dimethyl 2-methylsuccinate (**XVII**) affords the unsaturated acids **XVIII**. Cyclization of the unsaturated acids **XVIII** using trifluoroacetic anhydride (**XIX**), followed by reduction affords compounds **XXI**. Alternatively, compounds **XXI** can be obtained by treatment of the unsaturated acids **XVIII** with sodium acetate (**VI**)
- 10 and acetic anhydride (**VII**) followed by treatment with a base. Treatment of the hydroxyl derivatives **XXI** with benzyl bromide (**X**), followed by reduction affords the alcohols **XIIb**. The alcohols **XIIb** are then converted to the corresponding chlorides **XXII** by treatment with triphenylphosphine (**XIII**) and carbon tetrachloride (**XIV**). The chlorides **XXII** can be converted to the esters **XXIII** by a

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palladium catalyzed carbonylation reaction in methanol. Hydrogenolysis of compounds **XXIII** affords the intermediates **IIb**.

In the first step outlined in Scheme 2, the unsaturated acids **XVIII** can be prepared by a condensation reaction between the benzaldehydes **III** with
5 dimethyl 2-methyl-succinate (**XVII**). The reaction can be carried out in the presence of a base such as sodium methoxide, lithium methoxide, sodium *tert*-butoxide, sodium hydride, or potassium *tert*-butoxide, in an organic solvent such as methanol, *tert*-butanol, toluene, or mixtures thereof, at a temperature between room temperature and 90 °C for several hours (references: Liu, J. *et al.*, *Org. Lett.*
10 4 (2002) 3521-3524; Bloomer, J. L. *et al.*, *J. Org. Chem.* 58 (1993) 7906-7912).

The naphthalene derivatives **XXI** can be prepared by a cyclization reaction, followed by reduction. Cyclization of the unsaturated acids **XVIII** can be achieved by treatment with trifluoroacetic anhydride (**XIX**) and triethylamine in an inert organic solvent such as tetrahydrofuran, or dichloromethane at room temperature.
15 The subsequent reduction with sodium borohydride (**XX**) can be carried out in an alcoholic solvent such as methanol at a temperature between 0 °C and room temperature (reference: Fuganti, C. *et al.*, *J. Chem. Res. (S)* 1998, 638-639).

Alternatively, the naphthalene derivatives **XXI** can be prepared in a manner analogous to the one described for the intermediates **IX** in Scheme 1. Cyclization
20 of the unsaturated acids **XVIII** can be achieved by treatment with sodium acetate (**VI**) and acetic anhydride (**VII**) at a temperature between room temperature and 140 °C for 0.5 to 12 hours. The generated acetates can be converted to the corresponding hydroxyl compounds **XXI** by treatment with a base such as sodium methoxide, potassium *tert*-butoxide, potassium carbonate, or sodium bicarbonate,
25 in a solvent such as methanol, water or mixtures thereof, at a temperature between room temperature and 80 °C for 10 minutes to several hours (references: Boger, D. L. *et al.*, *J. Org. Chem.* 61 (1996) 4894-4912; Kim, M. *et al.*, *J. Org. Chem.* 69 (2004) 6945-6948).

Treatment of the hydroxyl compounds **XXI** with benzyl bromide (**X**) affords the
30 corresponding benzyl ethers. The reaction can be carried out in the presence of a

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base such as potassium carbonate, or cesium carbonate, in an inert organic solvent such as acetone, acetonitrile, or *N,N*-dimethylformamide at a temperature between room temperature and 60 °C for several hours.

- Reduction of the ester moieties in the above benzyl ethers with lithium aluminum
5 hydride (**XI**) affords the alcohols **XIb**. The reaction can be carried out in an inert organic solvent such as tetrahydrofuran, diethyl ether, toluene or mixtures thereof, at a temperature between room temperature and 80 °C for several hours.

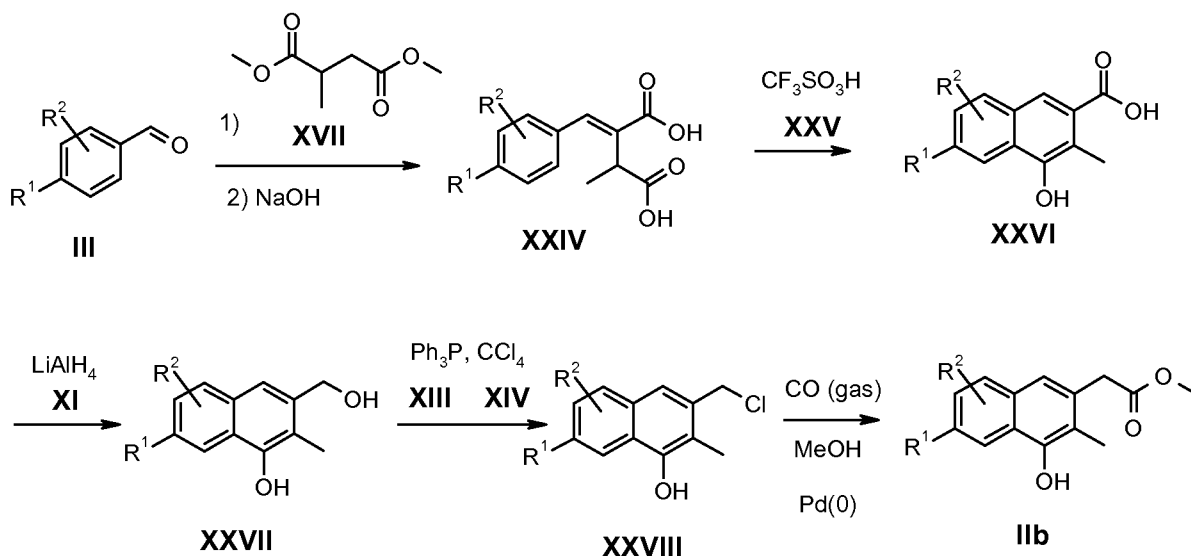
- The reaction of the alcohols **XIb** with triphenylphosphine (**XIII**) and carbon tetrachloride (**XIV**) can be carried out in an inert organic solvent such as
10 tetrahydrofuran, acetonitrile, toluene, *N,N*-dimethylformamide, or dichloromethane, at a temperature between 0 °C and 120 °C for several hours (reference: Kozhinov, D. V. *et al.*, *J. Org. Chem.* 69 (2004) 1378-1379).

- Conversion of the chlorides **XXII** to the methyl esters **XXIII** can be accomplished by a palladium catalyzed carbonylation reaction under 1 atmospheric pressure of
15 carbon monoxide in methanol. The reaction can be carried out in the presence of a palladium catalyst such as bis(triphenylphosphine)dichloropalladium(II) ($\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$), palladium(II) acetate ($\text{Pd}(\text{OAc})_2$), tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), or tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$), in the presence or absence
20 of a phosphine ligand such as tricyclohexylphosphine, or triphenylphosphine at a temperature between room temperature and 90 °C for 10 minutes to several hours (reference: Kozhinov, D. V. *et al.*, *J. Org. Chem.* 69 (2004) 1378-1379).

- Hydrogenolysis of benzyl ethers **XXIII** affords the intermediates **IIb**. The reaction can be carried out in the presence of 10% palladium on carbon under 1
25 atmospheric pressure of hydrogen, in an organic solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours.

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Scheme 3



Alternatively, the hydroxyl intermediates **IIb** can be prepared according to

5 Scheme 3.

In this process, the Stobbe condensation reaction between the benzaldehydes **III** and dimethyl 2-methyl-succinate (**XVII**) followed by hydrolysis affords the unsaturated diacids **XXIV**. Cyclization of the unsaturated diacids **XXIV** followed by reduction affords compounds **XXVII**. Treatment of compounds **XXVII** with

10 triphenylphosphine (**XIII**) and carbon tetrachloride (**XIV**) affords the corresponding chlorides **XXVIII**. The chlorides **XXVIII** can be converted to the methyl esters **IIb** by a palladium catalyzed carbonylation reaction.

In this process, the Stobbe condensation can be carried out in the presence of a base such as sodium hydride, in an organic solvent such as toluene, at room

15 temperature for several hours. The unsaturated diacids **XXIV** can be formed by treatment of the products of condensation with an aqueous inorganic base such as sodium hydroxide, in an organic solvent such as toluene, at a temperature between room temperature and 100 °C for several hours.

Cyclization of the diacids **XXIV** can be achieved by treatment of the diacids with

20 trifluoromethanesulfonic acid (**XXV**), at room temperature for several hours.

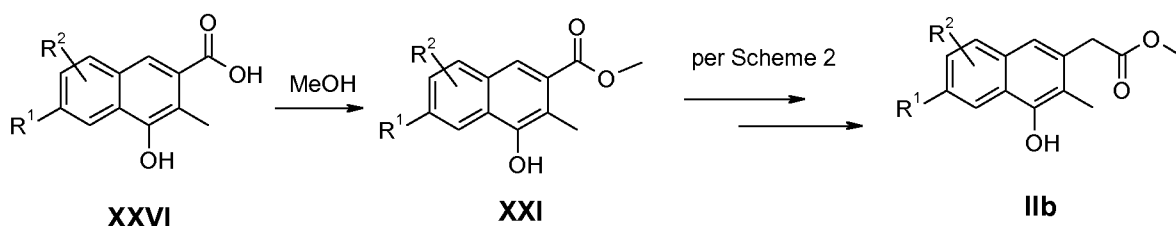
- 34 -

Reduction of the carboxyl moieties in the intermediates **XXVI** with lithium aluminum hydride (**XI**) affords the alcohols **XXVII**. The reaction can be carried out in an inert organic solvent such as tetrahydrofuran, diethyl ether, toluene or mixtures thereof, at a temperature between room temperature and 80 °C for several hours.

The reaction of the alcohols **XXVII** with carbon tetrachloride (**XIV**) in the presence of triphenylphosphine (**XIII**) can be carried out in an inert organic solvent such as tetrahydrofuran, acetonitrile, toluene, *N,N*-dimethylformamide, or dichloromethane, at a temperature between 0 °C and 120 °C for several hours.

10 Conversion of the chlorides **XXVIII** to the intermediates **IIb** can be accomplished by a carbonylation reaction, in a manner analogous to the one described in Scheme 1 for the preparation of the methyl esters **XVI**.

Scheme 4



15

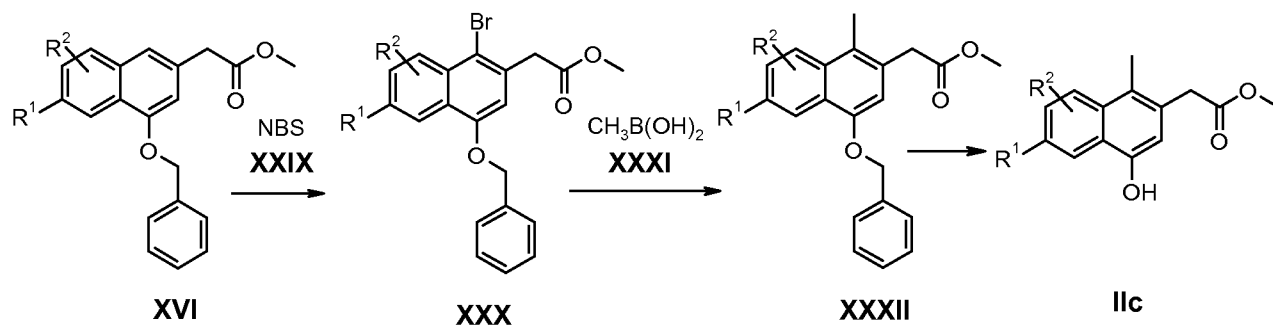
Alternatively, intermediates **IIb** may be prepared according to Scheme 4 starting from the 4-hydroxy-naphthalene carboxylic acid compounds **XXVI** which were described above in Scheme 3. Esterification of **XXVI** forms the naphthalene carboxylic acid methyl ester **XXI**. Conversion of **XXI** to intermediates **IIb** can occur using the methods described in Scheme 2.

Intermediates **XXVI** can be readily converted to the 4-hydroxy-naphthalene carboxylic acid methyl ester intermediates **XXI** in the presence of a catalytic amount of concentrated sulfuric acid and an excess of methanol at temperatures between room temperature and 80 °C for several hours. Alternatively, the esterification reaction can be carried out in the presence of thionyl chloride and an excess of methanol at temperatures between 65 °C and 80 °C for several

25

hours. The obtained compounds **XXI** can be transformed into intermediates **IIb** using the process described above in Scheme 2.

Scheme 5



5

The intermediates of formula **IIc** can be prepared according to Scheme 5. In this process, bromination of the intermediates **XVI**, followed by a Suzuki coupling reaction affords the intermediates **XXXII**. Hydrogenolysis of the intermediates **XXXII** gives the hydroxyl intermediates **IIc**.

- 10 In this process, bromination can be achieved by treatment of the intermediates **XVI** with *N*-bromosuccinimide (NBS, **XXIX**) in an organic solvent such as acetonitrile, dichloromethane, acetone, *N,N*-dimethylformamide, tetrahydrofuran, chloroform, or carbon tetrachloride, at room temperature for 30 minutes to several hours (reference: Hidemitsu U., *et al.*, *J. Chem. Soc., Perkin Trans. 1*,
15 2001, 229).

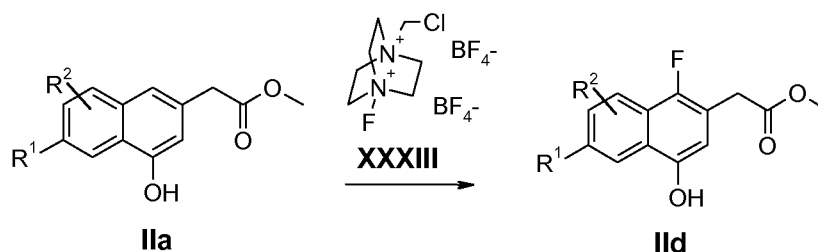
- The Suzuki coupling reaction of the intermediates **XXX** with methylboronic acid (**XXXI**) gives compounds **XXXII**. The reaction can be carried out in the presence of a palladium catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (PdCl₂(dppf)), palladium acetate (Pd(OAc)₂), or tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄), in
20 the presence or absence of a ligand such as tricyclohexylphosphine, triphenylphosphine, or tri-2-tolylphosphine, and a base such as potassium *tert*-butoxide, sodium hydroxide, potassium phosphate, potassium carbonate, or sodium carbonate, in a suitable solvent such as *N,N*-dimethylformamide, dimethyl
25 sulfoxide, toluene, tetrahydrofuran, 1,4-dioxane, water or mixtures thereof, at a

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temperature between 130 °C and 180 °C for 15 to 30 minutes under microwave irradiation. Alternatively, the reactions can be carried out at an elevated temperature such as 130 °C without microwave irradiation for a longer reaction time (reference: Wallace, D. J. *et al.*, *Tetrahedron Lett.* 43 (2002) 6987–6990).

- 5 Hydrogenolysis of benzyl ethers **XXXII** affords the intermediates **IIc**. The reaction can be carried out in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen, in an organic solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours.

Scheme 6



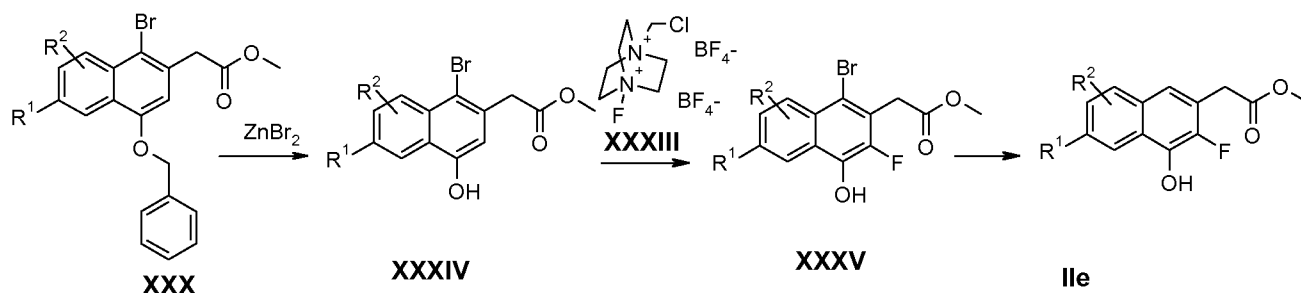
10

The intermediates of formula **IIId** can be prepared according to Scheme 6. In this process, the reaction between compounds **IIa** (prepared as described above in Scheme 1) and Selectfluor® fluorinating reagent (Air Products and Chemicals, Inc.) generically shown as **XXXIII** can be carried out in a suitable solvent such as acetonitrile, methanol, *N,N*-dimethylformamide, trifluoroacetic acid, water or mixtures thereof, at a temperature between 0 °C and 80 °C for several hours (reference: Zupan M. *et al.*, *Bull. Chem. Soc. Jpn.*, 68 (1995) 1655-1660).

15

Scheme 7

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The intermediates **IIe** can be prepared according to Scheme 7. Debenzylation of compounds **XXX** followed by a fluorination reaction affords the intermediates

5 **XXXV**. Hydrogenolysis of compounds **XXXV** gives the intermediates **IIe**.

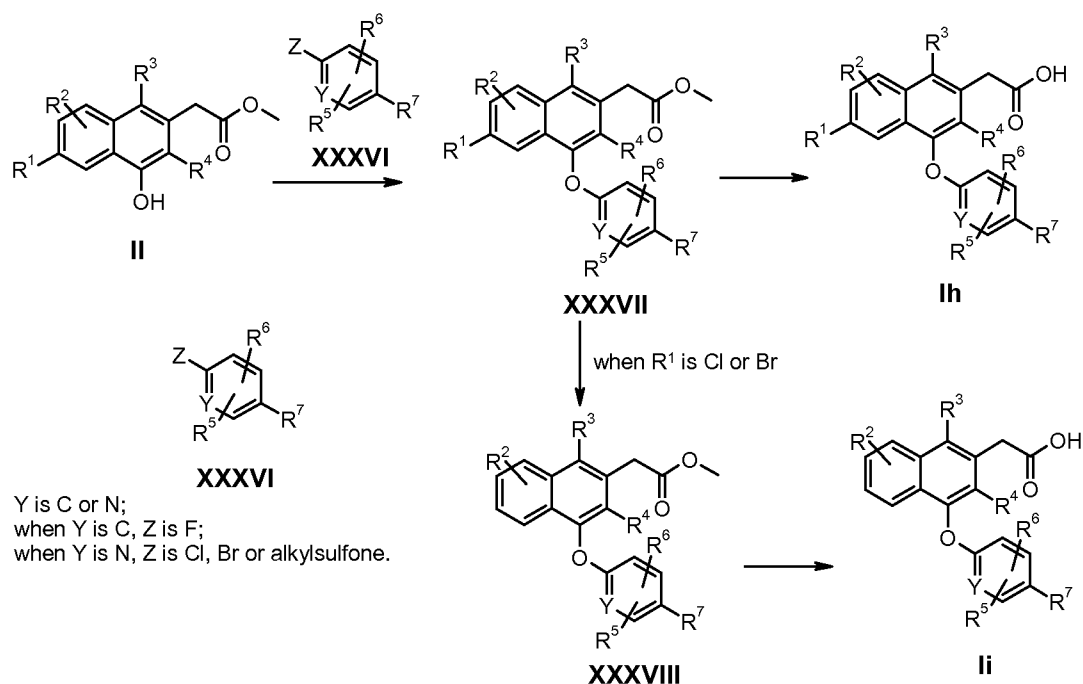
Debenzylation of compounds **XXX** (prepared as described above in Scheme 5) affords the hydroxyl intermediates **XXXIV**. The reaction can be accomplished by treatment of the benzyl ethers **XXX** with zinc bromide in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen, in an organic
 10 solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours (reference: Wu G. *et al.*, *Synthesis* 11 (2003) 1657-1660).

Conversion of compounds **XXXIV** to the fluorinated derivatives **XXXV** can be achieved by using Selectfluor® fluorinating reagent (**XXXIII**) in a suitable solvent such as *N,N*-dimethylformamide, acetonitrile, methanol, trifluoroacetic acid, water
 15 or mixtures thereof, at a temperature between 0 °C and 80 °C for several hours (reference: Zupan M. *et al.*, *Bull. Chem. Soc. Jpn.*, 68 (1995) 1655-1660).

Hydrogenolysis of the bromo-substituted derivatives **XXXV** affords the intermediates **IIe**. The reaction can be carried out in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen, in an organic
 20 solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours.

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Scheme 8



The compounds of interest of formula **Ih** and **li** can be prepared according to Scheme 8. A reaction between the hydroxyl intermediates **II** and the aryl derivatives **XXXVI** followed by ester hydrolysis affords the compounds of interest of formula **Ih**. Hydrogenolysis of the intermediates **XXXVII** when R^1 is Cl or Br, followed by ester hydrolysis affords the compounds of interest of formula **li**.

Conversion of the hydroxyl intermediates **II** (which encompass **Ila**, **Ilb**, **Ilc**, **Ild**, and **Ile** from Schemes 1-7) to the ethers **XXXVII** can be achieved by treating compounds **II** and the aryl derivatives **XXXVI** with a base such as sodium carbonate, potassium carbonate, or cesium carbonate, in a suitable organic solvent such as *N,N*-dimethylformamide, or dimethyl sulfoxide. The reaction can be carried out at a temperature between 100 °C and 150 °C for 30 to 60 minutes under microwave irradiation. Alternatively, the reactions can be carried out at an elevated temperature without microwave irradiation for a longer period of time.

Hydrolysis of the methyl esters **XXXVII** affords the compounds of interest of formula **Ih**. The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or potassium

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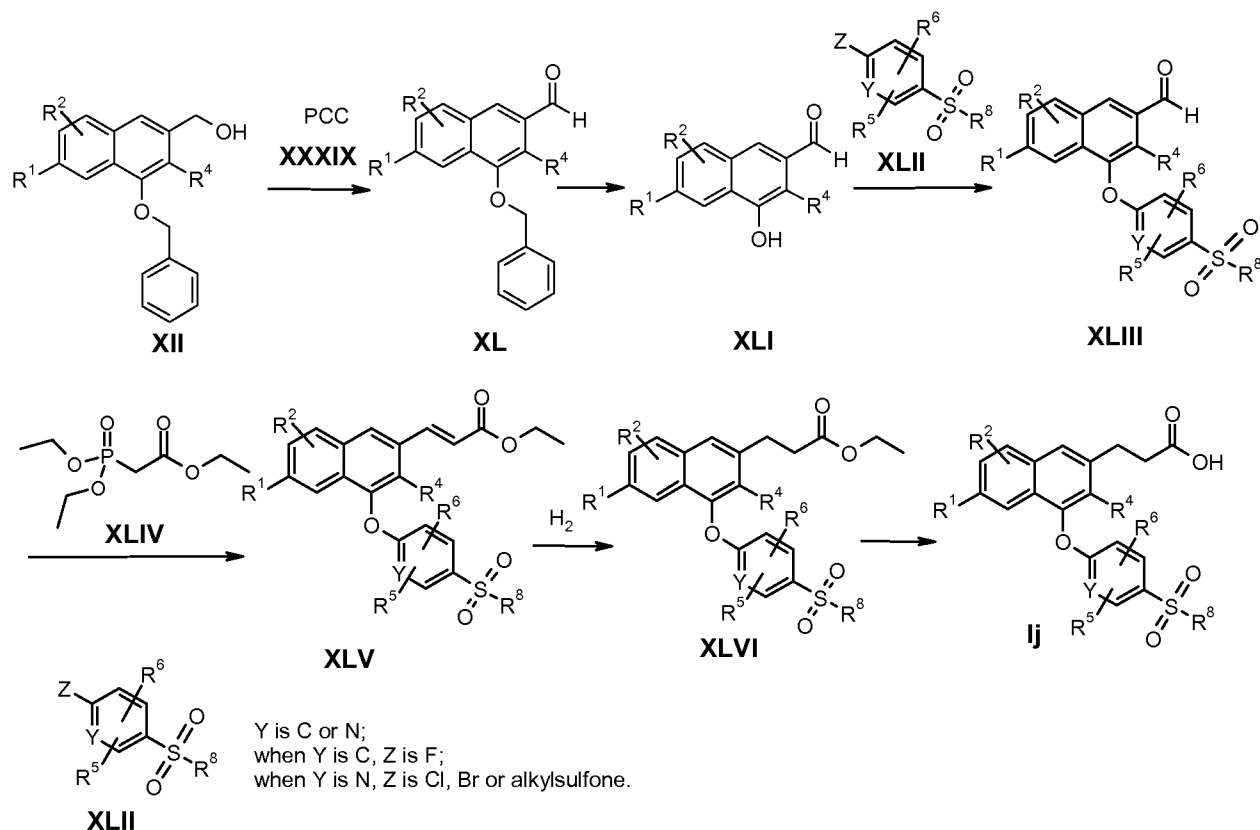
hydroxide in an inert solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for several hours.

Hydrogenolysis of the intermediates **XXXVII** can be carried out in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen, in an
5 organic solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours.

Hydrolysis of the products of the hydrogenolysis reaction affords the compounds of interest of formula **II**. The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or
10 potassium hydroxide in an inert solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for several hours.

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Scheme 9



The compounds of interest of formula **Ij** can be prepared according to Scheme 9.

- 5 Oxidation of the alcohols **XII** (which encompass **XIIa** and **XIIb** from Schemes 1 and 2) affords the aldehydes **XL**. Hydrogenolysis of benzyl ethers **XL** followed by treatment of the resulting naphthols **XLI** with the aryl derivatives **XLII** affords the ether intermediates **XLIII**. The aldehydes **XLIII** are converted to the alkenes **XLV** by the Horner-Wadsworth-Emmons reaction. Hydrogenation of the alkenes **XLV**
- 10 followed by ester hydrolysis affords the compounds of interest of formula **Ij**.

- The intermediates **XII** can be oxidized to the aldehydes **XL** using pyridinium chlorochromate (PCC) (**XXXIX**). The reaction can be carried out in a suitable solvent such as dichloromethane, at a temperature between 0 °C and room temperature for several hours (reference: Thibault, M. E. *et al.*, *J. Org. Chem.* 68
- 15 (2003), 8373-8378). Alternatively, the conversion can also be achieved using manganese oxide, pyridinium dichromate, Dess-Martin periodinane, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), or iron(III) nitrate monohydrate as the oxidizing reagent.

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Debenzylation of compounds **XL** affords the hydroxyl intermediates **XLI**. The reaction can be accomplished in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen, in an organic solvent such as ethyl acetate, methanol, or ethanol, at room temperature for several hours.

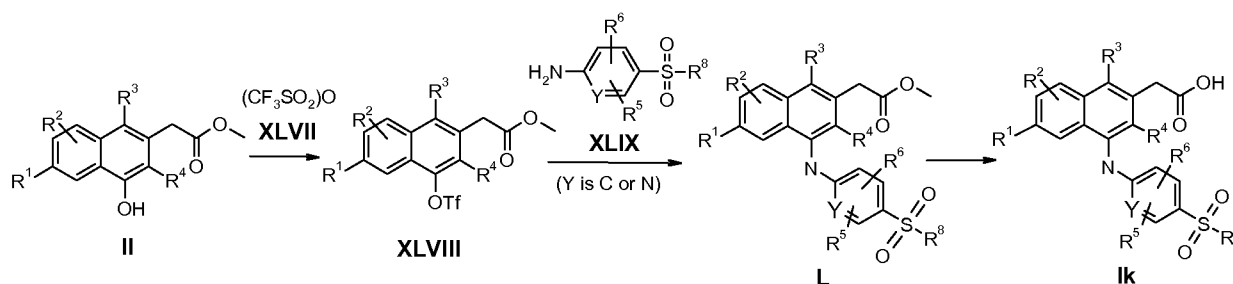
- 5 Conversion of the hydroxyl intermediates **XLI** to the ether compounds **XLIII** can be achieved by treatment of compounds **XLI** and compounds **XLII** with a base such as sodium carbonate, potassium carbonate, or cesium carbonate, in a suitable organic solvent such as *N,N*-dimethylformamide, or dimethyl sulfoxide, at a temperature between 100 °C and 150 °C for 30 to 60 minutes under microwave
10 irradiation. Alternatively, the reaction can be carried out at an elevated temperature without microwave irradiation for a longer period of time.

- The alkenes **XLV** can be prepared by the Horner-Wadsworth-Emmons reaction between the aldehydes **XLIII** and triethyl phosphonoacetate (**XLIV**). The reaction can be carried out in the presence of a base such as sodium hydride, potassium
15 carbonate, cesium carbonate, sodium ethoxide, potassium *tert*-butoxide, *n*-butyllithium, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, potassium hydroxide, or lithium hydroxide, in a suitable solvent such as *N,N*-dimethylformamide, acetonitrile, benzene, dichloromethane, tetrahydrofuran, 1,4-dioxane, diethyl ether, ethanol, water or mixtures thereof, at a temperature
20 between 0 °C and 60 °C for several hours (reference: Chan W. K. *et al.*, *J. Med. Chem.* 39 (1996) 3756-3768).

- Hydrogenation of the alkenes **XLV** affords the intermediates **XLVI**. The reaction can be carried out in the presence of 10% palladium on carbon under 1 atmospheric pressure of hydrogen, in an organic solvent such as ethyl acetate,
25 methanol, or ethanol, at room temperature for several hours.

- Hydrolysis of the methyl esters **XLVI** affords the compounds of interest of formula **Ij**. The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in an organic solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for
30 several hours.

Scheme 10



- 5 The compounds of interest of formula **Ik** can be prepared according to Scheme 10. In this process, the hydroxyl compounds **II** (which encompass **Ila**, **Ilb**, **Ilc**, **Ild**, and **Ile** from Schemes 1-7) are treated with trifluoromethanesulfonic anhydride (**XLVII**) to afford the triflates **XLVIII**. A reaction between the triflates **XLVIII** and the substituted aryl amine compounds **XLIX** followed by a hydrolysis reaction
- 10 affords the compounds of interest of formula **Ik**.

- The hydroxyl compounds **II** can be converted to the triflates **XLVIII** by treatment with trifluoromethanesulfonic anhydride (**XLVII**). The reaction can be carried out in the presence of a base such as pyridine, triethylamine, diisopropylethylamine, *N,N*-dimethyl-4-pyridinamine, 2,6-dimethylpyridine, 2,4,6-trimethylpyridine,
- 15 sodium hydride, or potassium carbonate, in a suitable solvent such as dichloromethane, chloroform or acetonitrile, at a temperature between -78 °C and room temperature for 30 minutes to several hours (reference: Chan W. K. *et al.*, *J. Med. Chem.* 39 (1996) 3756-3768).

- Reaction of the triflates **XLVIII** with the aryl amine compounds **XLIX** can be
- 20 carried out in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium(0) (Pd(PPh₃)₄), palladium acetate (Pd(OAc)₂), or (tris(dibenzylideneacetone) dipalladium(0) (Pd₂(dba)₃) in combination with a phosphine ligand such as tricyclohexylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene,
- 25 or di(*tert*-butyl)(1,1'-biphenyl-2-yl)phosphine, and a base such as cesium carbonate, potassium carbonate, sodium *tert*-butoxide, or potassium phosphate, in a suitable solvent such as *N,N*-dimethylformamide, dimethyl sulfoxide, toluene, or tetrahydrofuran, at a temperature between 130 °C and 180 °C for 15 to 30

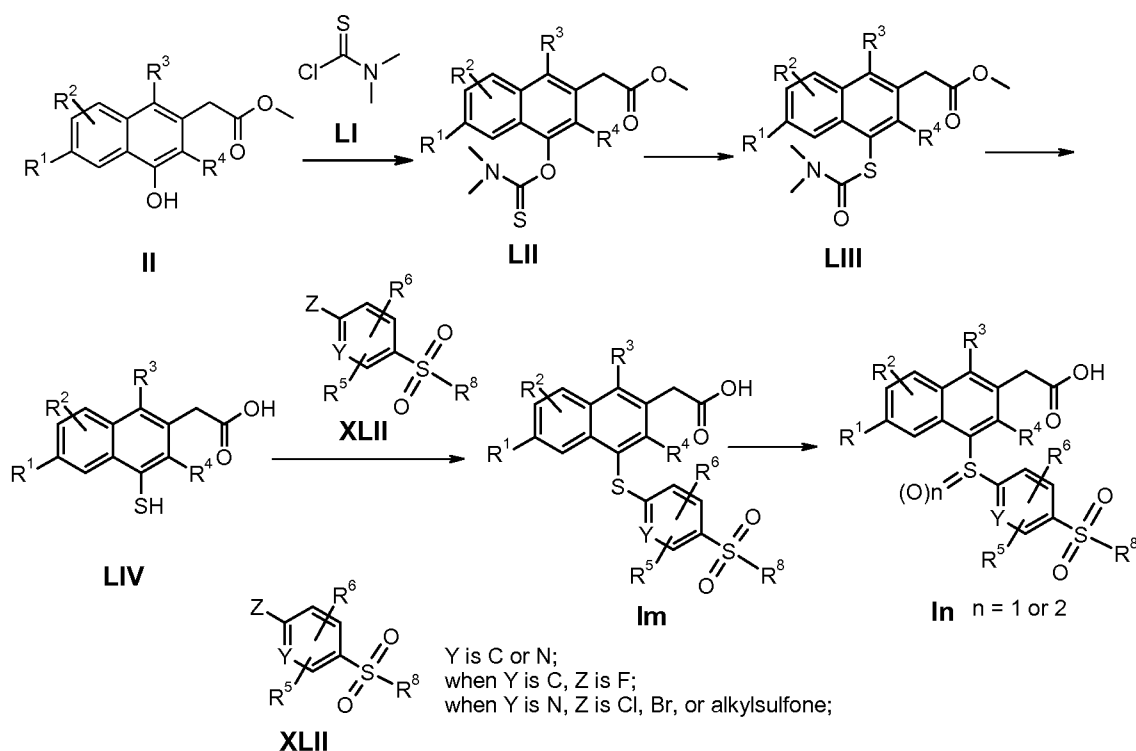
- 43 -

minutes under microwave irradiation. Alternatively, the reaction can be carried out at an elevated temperature such as 130 °C without microwave irradiation for a longer reaction time (reference: Uwe S. *et al.*, *Tetrahedron Lett.* 46 (2005) 7111-7115).

- 5 Hydrolysis of the methyl esters **L** affords the compounds of interest of formula **Ik**. The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in an organic solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for several hours.

10

Scheme 11



- The compounds of interest of formula **Im** and **In** can be prepared according to Scheme 11. Treatment of intermediates **II** (which encompass **Ila**, **Ilb**, **Ilc**, **Ild**, and **Ile** from Schemes 1-7) with dimethylthiocarbamoyl chloride (**LI**) affords the dimethylthiocarbamoyloxy compounds **LII**. Newman-Kwart rearrangement of the dimethylthiocarbamoyloxy compounds **LII** affords the intermediates **LIII**. Hydrolysis of compounds **LIII** followed by treatment with the aryl derivatives **XLII**

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affords the sulfanyl compounds **Im**. Oxidation of **Im** gives the sulfinyl or sulfonyl compounds **In**.

Conversion of the intermediates **II** to the dimethylthiocarbamoyloxy compounds **LII** can be achieved by treatment of the intermediates **II** with

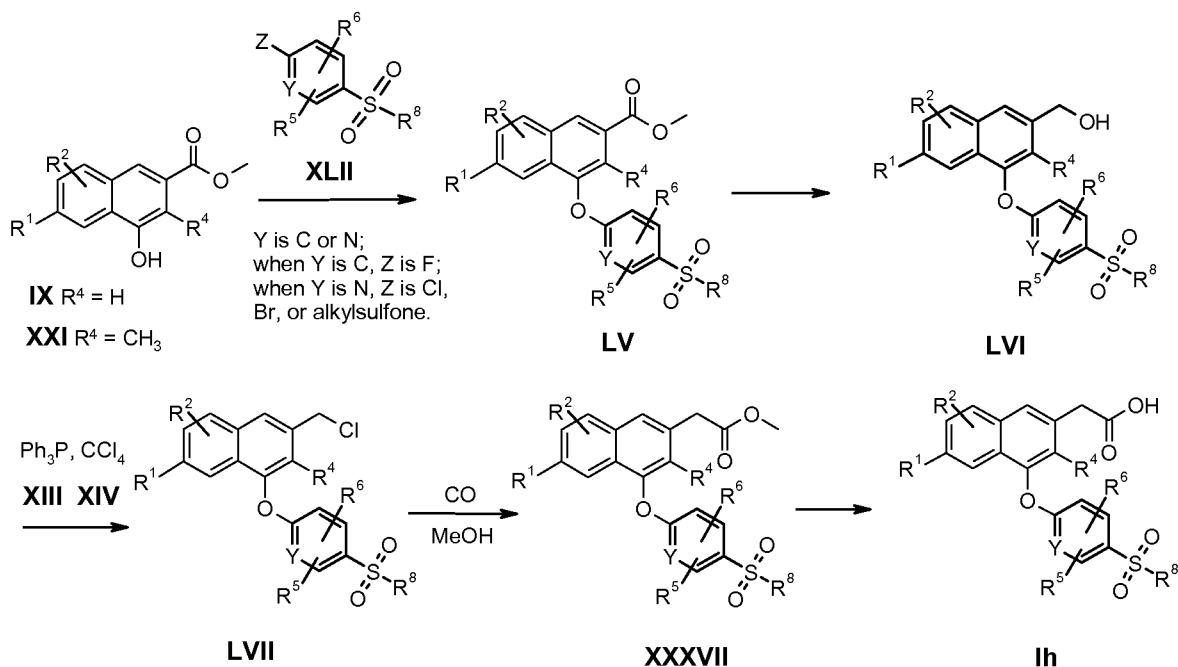
- 5 dimethylthiocarbamoyl chloride (**LI**) in the presence of a base such as potassium carbonate, potassium hydroxide, triethylamine, or sodium hydride, in a suitable solvent such as *N,N*-dimethylformamide, tetrahydrofuran, acetone, water or mixtures thereof, at a temperature between room temperature and 100 °C for several hours.
- 10 The Newman-Kwart rearrangement of the dimethylthiocarbamoyloxy compounds **LII** can be achieved by heating in the presence or absence of an organic solvent such as *N*-methylpyrrolidone, tetradecane, diphenyl ether, or 1,1-dioxethanol, at a temperature between 150 °C and 300 °C for 10 minutes to several hours (reference: Moseley, J. D. *et al.*, *Tetrahedron* 62 (2006) 4685-4689).
- 15 Hydrolysis of compounds **LIII** can afford compounds **LIV**. The reaction can be carried out in the presence of a base such as potassium hydroxide, sodium hydroxide, or sodium methoxide, in a suitable solvent such as methanol, ethanol, water, or mixtures thereof at a temperature between 60 °C and 100 °C for 30 minutes to several hours.
- 20 The sulfonyl compounds **Im** can be prepared by the reaction of compounds **LIV** with the aryl derivatives **XLII**. The reaction can be carried out in the presence of a base such as sodium carbonate, potassium carbonate, or cesium carbonate, in a suitable solvent such as dimethyl sulfoxide, or *N,N*-dimethylformamide, at a temperature between 100 °C and 150 °C for about 30 to 60 minutes under
- 25 microwave irradiation. Alternatively, the reaction can be also carried out at an elevated temperature without microwave irradiation for a longer period of time.

Oxidation of the sulfanyl compounds **Im** to the sulfinyl or sulfonyl analogues **In** can be achieved using an oxidant such as *m*-chloroperoxybenzoic acid (*m*-CPBA), or hydrogen peroxide in an inert solvent such as dichloromethane or 1,2-

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dichloroethane (or an aqueous solution if hydrogen peroxide is used), at a temperature between 0 °C and room temperature for several hours.

Scheme 12



5

Compounds of interest of formula **Ih** can alternatively be prepared according to Scheme 12. A substitution reaction between the hydroxyl compounds **IX** or **XXI** (prepared as described in Scheme 1 or Scheme 2) and the aryl derivatives **XLII** followed by reduction gives the alcohols **LVI**. The alcohols **LVI** are then transformed to the corresponding chlorides **LVII** by treatment with carbon tetrachloride (**XIV**) and triphenylphosphine (**XIII**). Conversion of the chlorides **LVII** to the methyl esters **XXXVII** can be accomplished by a palladium catalyzed carbonylation reaction in methanol. Ester hydrolysis of the methyl esters **XXXVII** affords the compounds of interest of formula **Ih**.

Conversion of the hydroxyl intermediates **IX** or **XXI** to the ether derivatives **LV** can be achieved by treatment of compounds **IX** or **XXI** and compounds **XLII** with a base such as sodium carbonate, potassium carbonate, or cesium carbonate, in a suitable organic solvent such as *N,N*-dimethylformamide, or dimethyl sulfoxide, at a temperature between 100 °C and 150 °C for 30 to 60 minutes under

20

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microwave irradiation. Alternatively, the reaction can be carried out at an elevated temperature without microwave irradiation for a longer period of time.

The alcohols **LVI** can be formed by treatment of the methyl esters **LV** with diisobutylaluminum hydride in an organic solvent such as toluene, at a
5 temperature between -78 °C and room temperature for several hours.

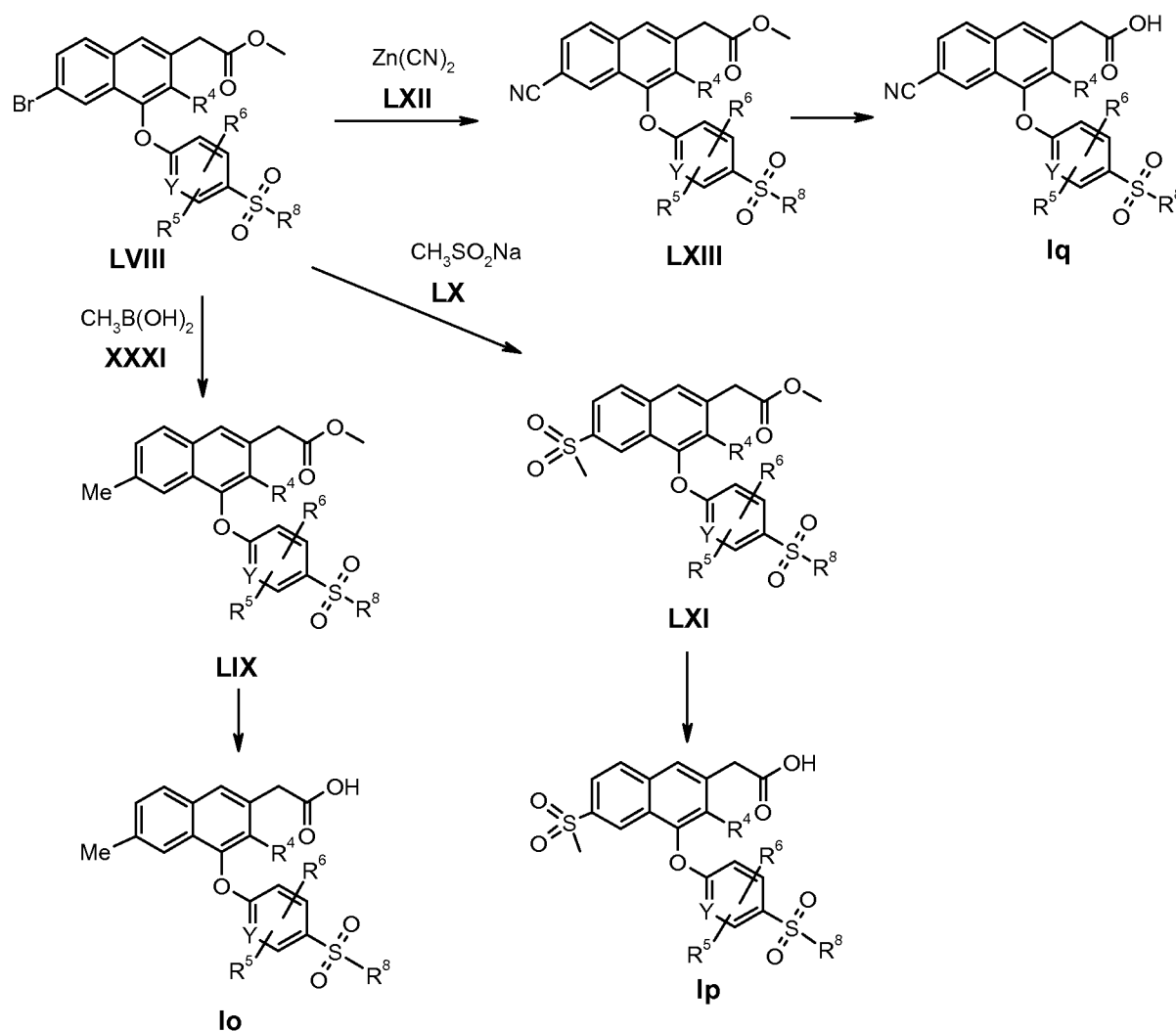
The chlorides **LVII** can be prepared by the treatment of the alcohols **LVI** with carbon tetrachloride (**XIV**) and triphenylphosphine (**XIII**) in an inert organic solvent such as toluene, acetonitrile, dichloromethane, *N,N*-dimethylformamide, or tetrahydrofuran, at a temperature between 0 °C and 120 °C for several hours.

10 Conversion of the chlorides **LVII** to the methyl esters **XXXVII** can be accomplished by a palladium catalyzed carbonylation reaction under an atmosphere of carbon monoxide in methanol, using a method analogous to the one described in Scheme 1 for the preparation of the methyl esters **XVI**.

As described above in Scheme 8, hydrolysis of the methyl esters **XXXVII** affords
15 the compounds of interest of formula **Ih**. The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for several hours.

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Scheme 13



- Compounds of interest **lo**, **lp**, and **lq** can be prepared according to Scheme 13
- 5 starting from the bromo-substituted naphthylacetic acid methyl esters **LVIII**. A Suzuki coupling reaction between the bromo derivatives **LVIII** and methylboronic acid (**XXXI**) followed by an ester hydrolysis affords the compounds of interest of formula **lo**. A copper (I) iodide catalyzed reaction of the bromo derivatives **LVIII** with methanesulfinic acid sodium salt (**LX**) followed by an ester hydrolysis affords the compounds of interest of formula **lp**.
- 10

Conversion of the bromo derivatives **LVIII** to the cyano derivatives **LXIII** followed by an ester hydrolysis affords the compounds of interest of formula **lq**.

The Suzuki coupling reactions of the bromo derivatives **LVIII** with methylboronic acid (**XXXI**) affords the methyl derivatives **LIX**. The reaction can be carried out in

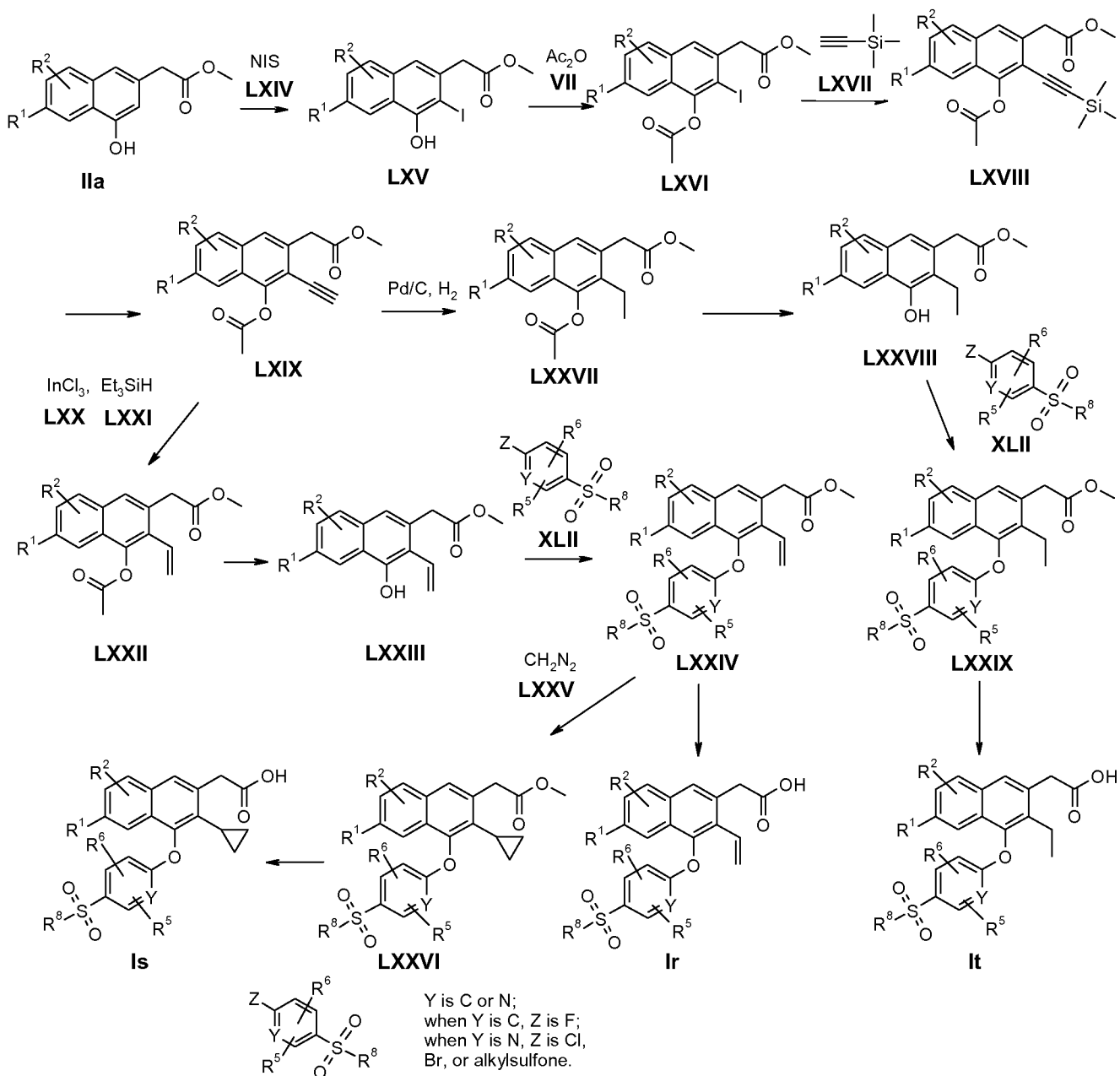
- 48 -

- the presence of a palladium catalyst such as tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), or [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($\text{PdCl}_2(\text{dppf})$), and a base such as potassium *tert*-butoxide, potassium phosphate, or sodium carbonate, in
- 5 an inert solvent such as *N,N*-dimethylformamide, dimethyl sulfoxide, toluene, tetrahydrofuran, water or mixtures thereof, at a temperature between 130 °C and 180 °C for 15 to 30 minutes under microwave irradiation. Alternatively, the reactions can be carried out at a heated temperature such as 130 °C without microwave irradiation for a longer reaction time.
- 10 The sulfonyl compounds **LXI** can be formed via a copper (I) iodide catalyzed reaction of the bromo derivative **LVIII** with methanesulfinic acid sodium salt (**LX**). The reaction can be carried out in the presence of catalysts copper(I) iodide and L-proline in a polar solvent such as *N,N*-dimethylformamide, dimethyl sulfoxide, or 1,4-dioxane at 150 °C for 30 minutes under microwave irradiation. Alternatively,
- 15 the reaction can be carried out at a heated temperature such as 110 °C without microwave irradiation for a longer reaction time.

- Conversion of the bromo derivatives **LVIII** to the cyano derivatives **LXIII** can be achieved by treatment of the bromo derivatives with zinc cyanide (**LXII**) in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0)
- 20 ($\text{Pd}(\text{PPh}_3)_4$), in an inert organic solvent such as *N,N*-dimethylacetamide, at a heated temperature such as 150 °C for several hours.

Hydrolysis of the methyl esters **LIX**, **LXI** or **LXIII** in a manner analogous to the one described above for the preparation of **Ih** affords the compounds of interest of formula **Io**, **Ip** and **Iq**, respectively.

Scheme 14



The compounds of interest of formula **Ir**, **Is** and **It** can be prepared according to Scheme 14. In this process, iodination of the intermediates **Ila** followed by acylation affords the iodo derivatives **LXVI**. The acetylene derivatives **LXIX** can be formed by a Sonogashira coupling reaction between the iodo derivatives **LXVI** and trimethylsilylacetylene (**LXVII**), followed by a potassium fluoride-mediated trimethylsilanyl removal. Reduction of the acetylene derivatives **LXIX** to the olefins **LXXII** followed by treatment of the olefins **LXXII** with a base affords the

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corresponding hydroxyl compounds **LXXIII**. The ether intermediates **LXXIV** can be obtained by treatment of the hydroxyl intermediates **LXXIII** with the aryl derivatives **XLII**. Hydrolysis of the ether intermediates **LXXIV** affords the final compounds **Ir**. The cyclopropyl derivatives **Is** can be formed by treating the intermediates **LXXIV** with diazomethane (**LXXV**) followed by a hydrolysis reaction. Hydrogenation of the acetylene derivatives **LXIX**, followed by treatment with a base affords the hydroxyl intermediates **LXXVIII**. The ethyl derivatives **It** can be obtained by a reaction between the hydroxyl intermediates **LXXVIII** and the aryl derivatives **XLII** followed by a hydrolysis reaction.

- 5
- 10 In the first step, iodination can be achieved by treatment of the intermediates **Ila** with *N*-iodosuccinimide (NIS, **LXIV**) in an organic solvent such as chloroform, acetonitrile, dichloromethane, acetone, *N,N*-dimethylformamide, tetrahydrofuran, or carbon tetrachloride, at a temperature between 0 °C and room temperature for 30 minutes to several hours.
- 15 The acetates **LXVI** can be formed by a reaction of the intermediates **LXV** with acetic anhydride (**VII**). The reaction can be carried out in the presence of a base such as 4-dimethylaminopyridine, in an organic solvent such as pyridine, at room temperature for several hours.

- The intermediates **LXVIII** can be generated by a coupling reaction between the iodo derivatives **LXVI** and trimethylsilylacetylene (**LXVII**) in the presence of a palladium catalyst such as bis(triphenylphosphine)dichloropalladium(II), or tetrakis(triphenylphosphine) palladium(0), and a copper(I) catalyst such as copper(I) iodide. The reaction can be carried out in the presence of a base such as triethylamine, or diisopropylethylamine in an inert solvent such as tetrahydrofuran, *N,N*-dimethylformamide or toluene at 150 °C for about 6 minutes under microwave irradiation (Baldwin, K. P. *et al.*, *Synlett* 11 (1993) 853).
- 20
- 25

- Removal of the trimethylsilyl group of the compounds **LXVIII** to give the acetylenes **LXIX** can be achieved by treating with potassium fluoride or tetrabutylammonium fluoride in a suitable solvent such as water, tetrahydrofuran, dimethyl sulfoxide, *N,N*-dimethylformamide, methanol, or mixtures thereof, at
- 30

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room temperature for several hours. Alternatively, a base such as potassium carbonate or potassium hydroxide can be used for the trimethylsilyl group removal. The reaction can be carried out in a suitable solvent such as methanol, tetrahydrofuran, water or the mixtures thereof at room temperature for several
5 hours.

Reduction of the acetylene derivatives **LXIX** affords the olefins **LXXII**. The reduction can be achieved by treatment of the acetylene derivatives **LXIX** with indium trichloride (**LXX**) and triethylsilane (**LXXI**) in the presence of triethylborane in an inert organic solvent such as acetonitrile, tetrahydrofuran, hexane, or
10 mixtures thereof, at a temperature between -15 °C and room temperature for several hours (Hayashi, N.; *et al.*, *Org. Lett.* 6(2004) 4981-4983). Alternatively, diphenylsilane can be used as the hydride source (Hayashi, N.; *et al.*, *Org. Lett.* 7 (2005) 3093-3096).

Compounds **LXXII** can be converted to the corresponding hydroxyl compounds
15 **LXXIII** by treatment with a base such as sodium methoxide, potassium *tert*-butoxide, potassium carbonate, or sodium bicarbonate, in a solvent such as methanol, water or mixtures thereof, at a temperature between room temperature and 80 °C for 10 minutes to several hours (references: Boger, D. L. *et al.*, *J. Org. Chem.* 61 (1996) 4894-4912; Kim, M. *et al.*, *J. Org. Chem.* 69 (2004) 6945-6948).

20 Conversion of the hydroxyl intermediates **LXXIII** to the ethers **LXXIV** can be achieved by treating the hydroxyl intermediates **LXXIII** and the aryl derivatives **XLII** with a base such as sodium carbonate, potassium carbonate, or cesium carbonate, in the presence of potassium iodide, in a suitable organic solvent such as *N,N*-dimethylformamide, acetone, dimethyl sulfoxide or mixtures thereof. The
25 reaction can be carried out at a temperature between 100 °C and 150 °C for 30 to 60 minutes under microwave irradiation. Alternatively, the reactions can be carried out at an elevated temperature without microwave irradiation for a longer period of time.

Hydrolysis of the methyl ester moieties of the olefins **LXXIV** affords the final
30 compounds **Ir**.

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The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for several hours.

5

Transformation of the olefins **LXXIV** to the corresponding cyclopropyl derivatives **LXXVI** can be done by treatment of compounds **LXXIV** with diazomethane (**LXXV**) in the presence of a palladium catalyst such as

10 palladium(II)acetylacetonate, palladium acetate, or palladium dichloride bis(benzonitrile), in a solvent such as dichloromethane, diethyl ether, tetrahydrofuran, or mixtures thereof, at a temperature between 0 °C and room temperature for several hours (reference: Staas, D. D. *et al. Bioorg. Med. Chem.* 14 (2006) 6900).

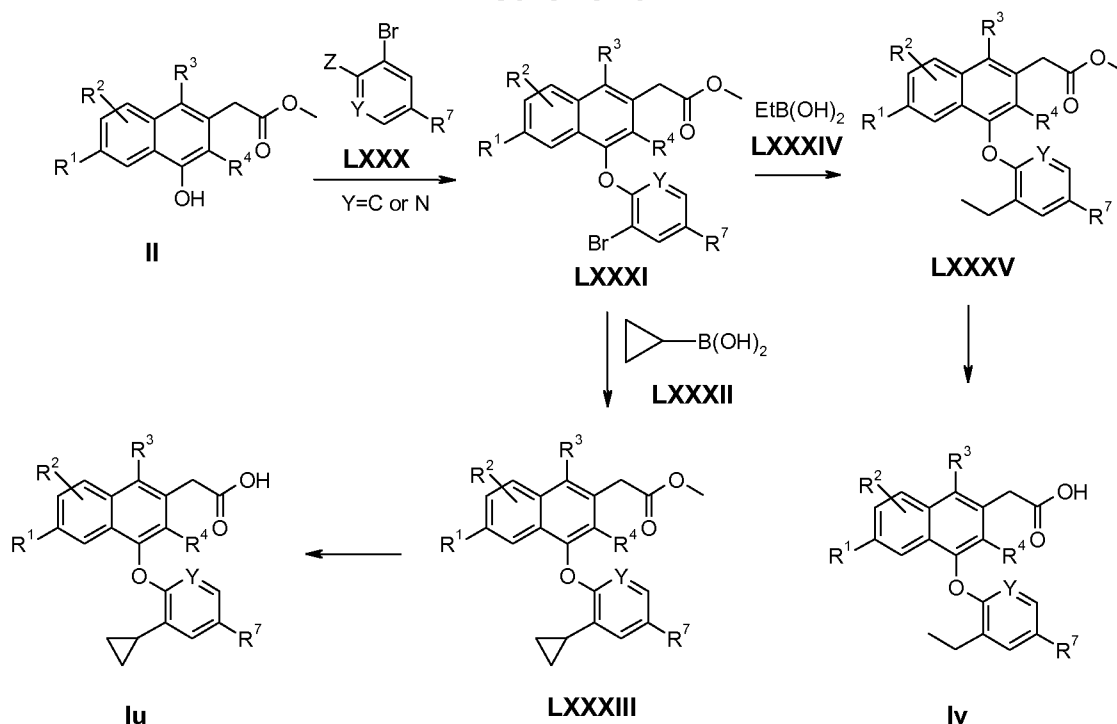
15 Further hydrolysis of the generated ether derivatives **LXXVI** in a manner analogous to the one described for the ether derivatives **LXXIV** affords the final compounds **Is**.

Hydrogenation of the acetylene derivatives **LXIX** can be carried out in the presence of 10% palladium on carbon under 40 psi of hydrogen, in an organic solvent such as ethyl acetate, methanol, or ethanol, at room temperature for
20 several hours.

In a manner analogous to the one described above for the transformation of the acetates **LXXII** to the ether derivatives **LXXIV**, compounds **LXXVII** can be converted to the corresponding ethers **LXXIX**. Hydrolysis of the generated ether derivatives **LXXIX** in a manner analogous to the one described for the ether
25 derivatives **LXXIV** affords the final compounds **It**.

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Scheme 15



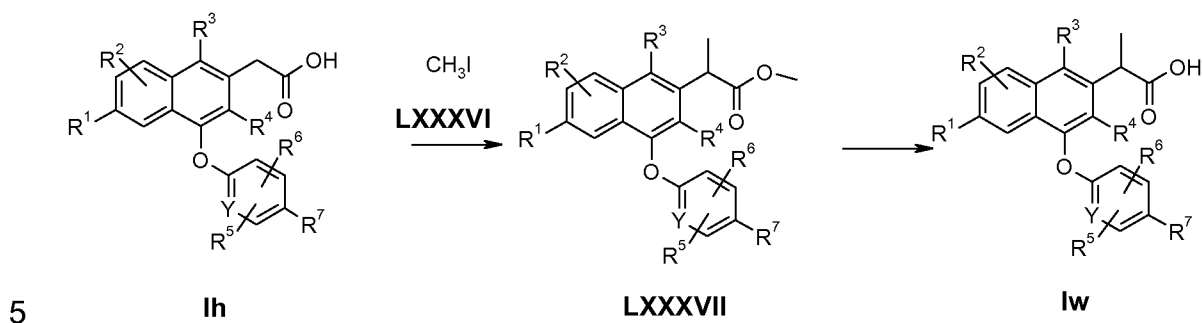
- 5 The compounds of interest of formula **Iu** and **Iv** can be prepared according to Scheme 15. In this process, the bromo derivatives **LXXXI** can be generated by a reaction between the hydroxyl intermediates **II** (which encompass **Ila**, **Ilb**, **Ilc**, **Ild**, and **Ile** from Schemes 1-7) and the aryl derivatives **LXXX**. A Suzuki coupling reaction between the bromo derivatives and cyclopropyl boronic acid (**LXXXII**)
- 10 followed by a hydrolysis reaction affords the final compounds **Iu**. A Suzuki coupling reaction between the bromo derivatives and ethyl boronic acid (**LXXXIV**) followed by a hydrolysis reaction affords the final compounds **Iv**.

- In a manner analogous to the one described in Scheme 8 for the preparation of the intermediates **XXXVII**, the ethers **LXXXI** can be generated by a reaction
- 15 between the hydroxyl intermediates **II** and the aryl derivatives **LXXX**.

- The bromo group of the generated ethers **LXXXI** can be converted to ethyl or cyclopropyl by a Suzuki coupling reaction between compounds **LXXXI** and ethyl boronic acid (**LXXXIV**), or cyclopropyl boronic acid (**LXXXII**), in a manner analogous to the one described in Scheme 13 for the preparation of the methyl
- 20 intermediates **LIX**. In a method analogous to the hydrolysis step described in

Scheme 8, hydrolysis of compounds **LXXXIII** and compounds **LXXXIV** affords the final compounds of interest **lu** and **lv**, respectively.

Scheme 16



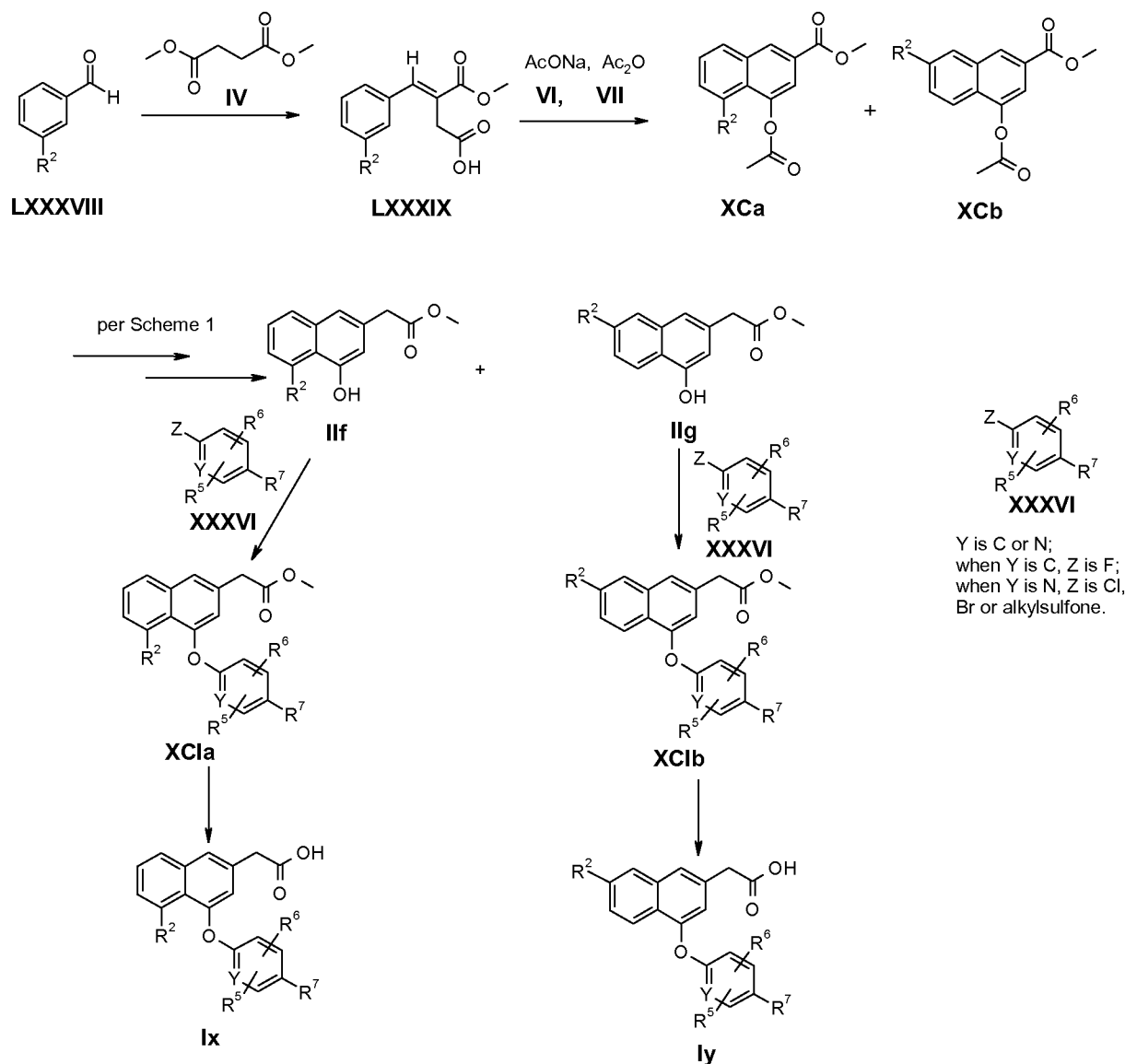
The compounds of interest of formula **lw** can be prepared according to Scheme 16. In this process, treatment of compounds **lh** with iodomethane (**LXXXVI**) followed by hydrolysis affords the final compounds **lw**.

In the first step of this process, the intermediates **LXXXVII** can be formed by treatment of compounds **lh** with iodomethane (**LXXXVI**) in the presence of a base such as sodium hydride, in an inert organic solvent such as *N,N*-dimethylformamide, at a temperature between -30 °C and -15 °C for several hours.

In a manner analogous to the hydrolysis step described in Scheme 8, hydrolysis of the intermediates **LXXXVII** affords the final compounds **lw**.

- 55 -

Scheme 17



- The compounds of interest of formula **IX** and **IY** can be prepared according to
- 5 Scheme 17. In this process, the Stobbe condensation reaction between the *meta*-substituted-benzaldehydes **LXXXVIII** and dimethyl succinate (**IV**) gives the unsaturated acids **LXXXIX**, which subsequently undergo cyclization in the presence of sodium acetate (**VI**) and acetic anhydride (**VII**) to produce the mixture of compounds **XCa** and **XCb**. Using the method described in Scheme 1, the
 - 10 mixtures of the naphthalene derivatives **XCa** and **XCb** are then converted to the mixture of the corresponding intermediates **IIIf** and **IIg**, which are separated by column chromatography to afford the intermediates **IIIf** and **IIg**. A reaction

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between the hydroxyl intermediates **II_f** and the aryl derivatives **XXXVI** followed by ester hydrolysis affords the compounds of interest of formula **I_x**. A reaction between the hydroxyl intermediates **II_g** and the aryl derivatives **XXXVI** followed by ester hydrolysis affords the compounds of interest of formula **I_y**.

- 5 In the first step outlined in Scheme 17, the unsaturated acids **LXXXIX** can be prepared by a condensation reaction between the *meta*-substituted-benzaldehydes **LXXXVIII** and dimethyl succinate (**IV**). The reaction can be carried out in the presence of a base such as sodium methoxide, lithium methoxide, sodium *tert*-butoxide, sodium hydride or potassium *tert*-butoxide, in
10 an organic solvent such as methanol, *tert*-butanol, toluene, or mixtures thereof, at a temperature between room temperature and 90 °C for several hours (reference: Dian, Y. L. *et al.*, *Tetrahedron Lett.*, 32 (1991) 5255).

- Cyclization of the unsaturated acids **LXXXIX** to produce the mixture of naphthalene derivatives **XC_a** and **XC_b** can be achieved by treatment of the
15 unsaturated acids **LXXXIX** with sodium acetate (**VI**) and acetic anhydride (**VII**) at a temperature between room temperature and 140 °C for 0.5 to 12 hours (references: Boger, D. L. *et al.*, *J. Org. Chem.* 61 (1996) 4894-4912; Kim, M. *et al.*, *J. Org. Chem.* 69 (2004) 6945-6948). Using the process described above in scheme 1, the mixture of naphthalene derivatives **XC_a** and **XC_b** can be
20 transformed into the mixture of the hydroxyl intermediates **II_f** and **II_g**, which are separated by column chromatography to afford the intermediates **II_f** and **II_g**.

- Conversion of the hydroxyl intermediates **II_f** to the ethers **XC_{1a}** can be achieved by treating compounds **II_f** and the aryl derivatives **XXXVI** with a base such as sodium carbonate, potassium carbonate, or cesium carbonate, in a suitable
25 organic solvent such as *N,N*-dimethylformamide, or dimethyl sulfoxide. The reaction can be carried out at a temperature between 100 °C and 150 °C for 30 to 60 minutes under microwave irradiation.

Alternatively, the reactions can be carried out at an elevated temperature without microwave irradiation for a longer period of time.

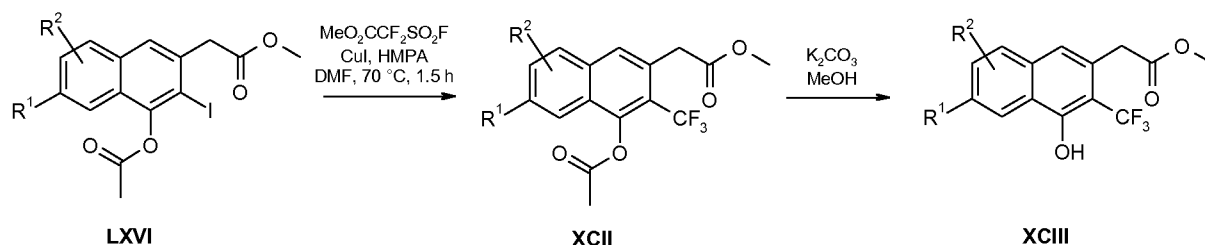
- 57 -

Hydrolysis of the methyl esters **XCla** affords the compounds of interest of formula **lx**. The reaction can be carried out in the presence of an aqueous inorganic base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in an inert solvent such as 1,4-dioxane or tetrahydrofuran at room temperature for several hours.

Conversion of the hydroxyl intermediates **IIg** to the compounds of interest of formula **ly** can be accomplished in a manner analogous to the one described above for the preparation of the compounds of interest of formula **lx**.

Scheme 18

10



Compounds of the invention when R^4 represents trifluoromethyl can be prepared using the intermediates **XCIII** which can be prepared as described in Scheme 18.

15 Treatment of the intermediate iodides of formula **LXVI** (prepared as described above in Scheme 14) with methyl 2,2-difluoro-2-(fluorosulfonyl)acetate under copper(I) iodide catalysis gives the intermediates of formula **XCII**. The acetyl protecting groups in **XCII** can then be removed to give the phenols of formula **XCIII** which correspond to the starting materials in Schemes 8, 10, 11, when R^4

20 represents trifluoromethyl, and can be used to prepare compounds of interest of formula **li**, **lk**, **lm**, and **ln** (when R^4 represents trifluoromethyl), using the reactions described in these schemes.

The conversion of the intermediates of formula **LXVI** to intermediates of formula **XCII** can be effected using any conventional means. For example, the

25 intermediates of formula **LXVI** may be treated with the commercially available reagent methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of copper(I) iodide and in the additional presence of hexamethylphosphoramide in an inert

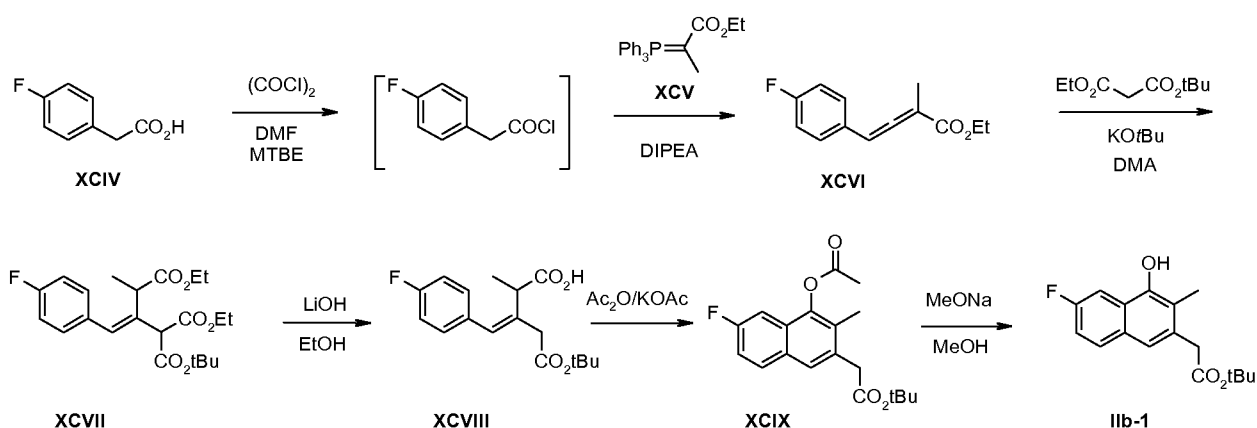
- 58 -

solvent such as *N,N*-dimethylformamide at a temperature about 70 °C for several hours to give the corresponding trifluoromethyl derivatives of formula **XCII** (reference: Briner, K. *et al.* WO 2007028132).

- The acetate derivatives **XCII** can be converted to the corresponding hydroxyl compounds **XCIII** in the presence of a base such as sodium methoxide, potassium *tert*-butoxide, potassium carbonate or sodium bicarbonate, in a solvent such as methanol, water, or mixtures thereof, at a temperature between room temperature and 80 °C for 10 minutes to several hours (reference: Kim, M. *et al.*, *J. Org. Chem.* 69 (2004) 6945-6948).

10

Scheme 19



- The key intermediate **IIb-1** (which can be used as a replacement for intermediate **II** in scheme 8 to make the compounds of formula **Ih** and **Ii**) can be prepared as described in Scheme 19. Treatment of (4-fluoro-phenyl)-acetic acid (**XCIV**) with oxalyl chloride generates the corresponding acid chloride *in situ*, which is not isolated, but treated with the Wittig-type reagent **XCV** in the presence of a base to produce the allene derivative **XCVI**. A conjugate addition reaction of the allene with malonic acid *tert*-butyl ester ethyl ester produces the tri-ester derivative **XCVII**, which upon hydrolysis and subsequent decarboxylation generates the acid derivative **XCVIII**. Acetic anhydride-promoted cyclization of **XCVIII** furnishes

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the naphthalene derivative **XCIX**, which upon hydrolysis of the acetyl group produces the key intermediate **Iib-1**.

The conversion of (4-fluorophenyl)-acetic acid to its corresponding acid chloride derivatives can be accomplished by methods known in the art. For example, the
5 reaction can be carried out with oxalyl chloride and a catalytic amount of *N,N*-dimethylformamide (DMF), in an ether solvent, at room temperature. Subsequent treatment of the in situ generated acid chloride with a base such as *N,N*-diisopropylethylamine will lead to the generation of the corresponding ketene, which upon treatment with a Wittig type reagent such as **XCIV** in an ether solvent
10 at a temperature between 0-10 °C produces the allene derivative **XCVI**.

The conjugate addition reaction between the allene derivative **XCVI** and malonic acid *tert*-butyl ester ethyl ester to produce the tri-ester derivative **XCVII** is conducted in the presence of a base such as potassium *tert*-butoxide, in a solvent such as *N,N*-dimethyl acetamide at room temperature.

15 The ester hydrolysis of the two ethyl esters in **XCVII** can be accomplished using methods known in the art. For example, the reaction can be conducted using an aqueous base such as lithium hydroxide, in the presence of a solvent such as ethanol, at room temperature overnight. The subsequent decarboxylation reaction can then be carried out by heating the solution of the resulting diacid at
20 reflux for several hours, to produce **XCVIII**.

The cyclization of the unsaturated acid derivative **XCVIII** to the naphthalene **XCIX** is accomplished as previously described (similar to Scheme 2), in the presence of acetic anhydride and potassium acetate or sodium acetate, at a temperature of about 85 °C, for several hours.

25 The acetate derivative **XCIX** then undergoes a hydrolysis, upon treatment with a base such as sodium methoxide, in a solvent such as methanol, at room temperature, to produce the desired key intermediate **Iib-1**.

EXAMPLES

- 60 -

Although certain exemplary embodiments are depicted and described herein, the compounds of the present invention can be prepared using appropriate starting materials according to the methods described generally herein and/or by methods available to one of ordinary skill in the art.

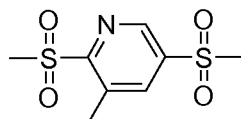
- 5 Intermediates and final compounds were purified by either flash chromatography and/or preparative HPLC (high performance liquid chromatography). Flash chromatography was performed using (1) the Biotage SP1™ system and the Quad 12/25 Cartridge module from Biotage AB) or (2) the ISCO CombiFlash® chromatography instrument (from Teledyne Isco, Inc.); unless otherwise noted.
- 10 The silica gel brand and pore size utilized were: (1) KP-SIL™ 60 Å, particle size: 40-60 micron (from Biotage AB); (2) Silica Gel CAS registry No: 63231-67-4, particle size: 47-60 micron; or (3) ZCX from Qingdao Haiyang Chemical Co., Ltd, pore size: 200-300 mesh or 300-400 mesh. Preparative HPLC was performed on a reversed phase column using an Xbridge™ Prep C₁₈ (5 µm, OBD™ 30 × 100
- 15 mm) column (from Waters Corporation), or a SunFire™ Prep C₁₈ (5 µm, OBD™ 30 × 100 mm) column (from Waters Corporation).

- Mass spectrometry (MS) was performed using a Waters® Alliance® 2795-ZQ™2000 (from Waters Corporation). Mass spectra data generally only indicates the parent ions unless otherwise stated. MS data is provided for a particular
- 20 intermediate or compound where indicated.

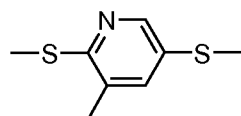
Nuclear magnetic resonance spectroscopy (NMR) was performed using a Bruker Avance™ 400 MHz Digital NMR Spectrometer (for the ¹H NMR spectrum acquired at 400 MHz) (from Bruker BioSpin AG Ltd.). NMR data is provided for a particular intermediate or compound where indicated.

- 25 The microwave assisted reactions were carried out in a Biotage Initiator™ Sixty (from Biotage AB).

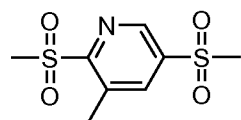
All reactions involving air-sensitive reagents were performed under an inert atmosphere. Reagents were used as received from commercial suppliers unless otherwise noted.

PART I: PREPARATION OF PREFERRED INTERMEDIATES**Preparation of 2,5-bis-methanesulfonyl-3-methyl-pyridine**

5

3-Methyl-2,5-bis-methylsulfanyl-pyridine

To a cooled (ice-water bath) solution of 5-bromo-2-fluoro-3-methyl-pyridine (1.0 g, 5.3 mmol) in anhydrous *N,N*-dimethylformamide (50 mL) was added sodium methanethiolate (775 mg, 11.1 mmol) portion-wise under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 15 minutes, then at 100 °C overnight. The reaction mixture was cooled to room temperature, poured into water, and extracted with diethyl ether (50 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to afford 3-methyl-2,5-bis-methylsulfanyl-pyridine, which was used in the next step without purification (reference: Testaferri, L. *et al.*, *Tetrahedron* 41 (1985) 1373-1384).

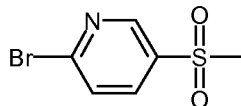
2,5-Bis-methanesulfonyl-3-methyl-pyridine

To a cooled (ice-water bath) solution of 3-methyl-2,5-bis-methylsulfanyl-pyridine in dichloromethane (50 mL) was added *m*-chloroperoxybenzoic acid (5.3 g, 80% purity, 24.6 mmol). After being stirred at room temperature for 2 hours, the mixture was treated with a saturated aqueous solution of sodium sulfite (20 mL), and stirred for 15 minutes. The organic layer was separated, washed with a saturated aqueous solution of sodium carbonate and brine, then dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from ethyl acetate to give 2,5-bis-methanesulfonyl-3-methyl-pyridine (1.2 g, 91 % yield for two steps) as a white solid (reference: Testaferri, L. *et al.*, *Tetrahedron* 41

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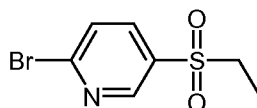
(1985) 1373-1384). ^1H NMR (400 MHz, CD_3OD) δ ppm 9.00 (d, $J = 1.6$ Hz, 1 H), 8.52 (d, $J = 1.6$ Hz, 1 H), 3.48 (s, 3 H), 3.41 (s, 3 H), 2.72 (s, 3 H).

Preparation of 2-bromo-5-methanesulfonyl-pyridine



- 5 Starting with 2-bromo-5-fluoro-pyridine, sodium methanethiolate and *m*-chloroperoxybenzoic acid, using a method analogous to the one described for 2,5-bis-methanesulfonyl-3-methyl-pyridine, 2-bromo-5-methanesulfonyl-pyridine was obtained as a white solid.

Preparation of 2-bromo-5-ethanesulfonyl-pyridine

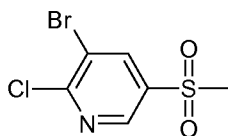


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- To a solution of 2,5-dibromopyridine (2 g, 8.4 mmol) in diethyl ether (50 mL) was added *n*-butyl lithium (1.6 M in hexanes, 9.24 mmol) dropwise at -78°C under a nitrogen atmosphere. After the mixture was stirred at this temperature for 1 hour, diethyldisulfide (1.15 mL, 9.24 mmol) was added slowly at -78°C , and the
- 15 mixture was stirred at this temperature for 1 hour and at 0°C for an additional 1 hour. The reaction mixture was then quenched with 1 N hydrochloric acid (20 mL). The aqueous layer was separated and extracted with diethyl ether (20 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL). To the solution,
- 20 *m*-chloroperoxybenzoic acid (4.3 g, 80% purity, 16.8 mmol) was added portion-wise at 0°C . After being stirred at room temperature for 2 hours, the mixture was treated with a saturated aqueous solution of sodium sulfite (20 mL), and stirred for 15 minutes. The organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate (20 mL), then dried over sodium sulfate,
- 25 and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 30% ethyl acetate in petroleum ether) to give 2-bromo-5-ethanesulfonyl-pyridine (400 mg, 19%) as a white solid (reference: Li J. *et al.*, *Bioorg. Med. Chem.* 13 (2005) 1805-1809).

Preparation of 3-bromo-2-chloro-5-methanesulfonyl-pyridine

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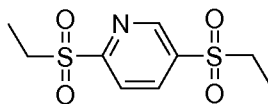


A stirred solution of sodium sulfite (4.80 g, 38.1 mmol) and sodium bicarbonate (6.10 g, 72.6 mmol) in water (100 mL) was cooled to 15 °C, and 5-bromo-6-chloropyridine-3-sulfonyl chloride (10.00 g, 34.4 mmol) was added. After being stirred at 15 °C for 3 hours and then at room temperature overnight under a nitrogen atmosphere, the mixture was heated to 40 °C, and a solution of 2-chloroacetic acid (3.80 g, 40.2 mmol) and sodium hydroxide (1.90 g, 47.5 mmol) in water (20 mL) was added. The resulting mixture was stirred at reflux for 48 hours and then cooled to room temperature. The precipitated product was collected by filtration, washed with water (50 mL) and purified by column chromatography (gradient elution with 15-20% ethyl acetate in petroleum ether) to afford 3-bromo-2-chloro-5-methanesulfonyl-pyridine (1.80 g, 6.65 mmol) as a white solid.

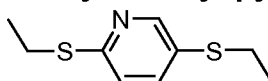
A solution of 2-chloroacetic acid (1.90 g, 20.1 mmol) and sodium hydroxide (0.80 g, 20.0 mmol) in water (10 mL) was added to the filtrate. The mixture was heated at reflux overnight, and then evaporated to remove most of the water (about 100 mL). The residue was cooled to room temperature, and then extracted with dichloromethane (80 mL × 3). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient elution with 15-20% ethyl acetate in petroleum ether) to afford another batch of 3-bromo-2-chloro-5-methanesulfonyl-pyridine (1.30 g, 4.8 mmol, yield of two batches 35.5 %) as a white solid (reference: US 5424481).

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Preparation of 2,5-bis-ethanesulfonyl-pyridine



2,5-bis-ethylsulfanyl-pyridine

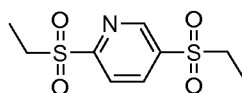


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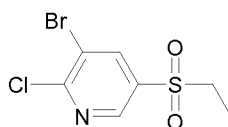
To a solution of sodium hydroxide (16.0 g, 400 mmol) in dimethyl sulfoxide (200 mL), was added ethanethiol (49.6 g, 798 mmol) followed by 2,5-dibromopyridine (23.7 g, 100 mmol) between -5 °C and 0 °C under a nitrogen atmosphere. After being heated at 180 °C for 5 hours, the reaction mixture was cooled to room temperature, poured into water (340 mL) and extracted with diethyl ether (400 mL × 2). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue (21.0 g) was directly used in the next step without further purification (reference: Testaferri, L. *et al.*, *Tetrahedron* 41 (1985) 1373-1384).

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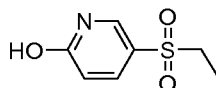
2,5-bis-ethanesulfonyl-pyridine

To a solution of the crude 2,5-bis-ethylsulfanyl-pyridine (prepared above) in 6 N hydrochloric acid (100 mL) was added an aqueous solution of sodium hypochlorite (8.0 %, 500 mL) at 0 °C. The resulting precipitate was collected by filtration, washed with water, dried *in vacuo* and then recrystallized from diethyl ether to afford 2,5-bis-ethanesulfonyl-pyridine (18.0 g, 70 %) as a white solid (reference: US 4371537).

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Preparation of 3-bromo-2-chloro-5-ethanesulfonyl-pyridine

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5-ethanesulfonyl-pyridin-2-ol

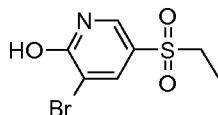
A solution of potassium hydroxide (11.0 g, 196 mmol, 50 %) in water was added to a suspension of 2,5-bis-ethanesulfonyl-pyridine (12.0 g, 45.6 mmol, prepared using the method described above) in water and tetrahydrofuran (100 mL, 1:1, v/v). After being heated at reflux for 1 hour, the mixture was acidified with 0.5 N hydrochloric acid to pH 3 and concentrated *in vacuo* to remove the solvent. The residue was triturated with boiling ethanol (150 mL) and filtered. The filtrates were

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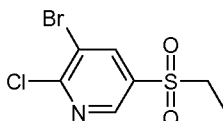
concentrated *in vacuo* to afford the crude product which was used in the next step without further purification.

3-bromo-5-ethanesulfonyl-pyridin-2-ol



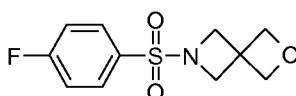
- 5 To a solution crude of 5-ethanesulfonyl-pyridin-2-ol prepared above, and sodium acetate (3.74 g, 45.6 mmol) in acetic acid (50 mL) was added a solution of bromine (7.3 g, 46.0 mmol) in acetic acid (10 mL) dropwise over a period of 1 hour. After being stirred at room temperature overnight, additional bromine (7.3 g, 46.0 mmol) in acetic acid (10 mL) was added dropwise to the reaction mixture over a period of 1 hour. After being stirred overnight, the reaction mixture was warmed to 30 °C and stirred for 2 hours. The mixture was concentrated *in vacuo* to remove the solvent. The residue was triturated with water (100 mL). The solid was collected by filtration, washed with a dilute solution of sodium thiosulfate and
- 10 dried *in vacuo* to afford 3-bromo-5-ethanesulfonyl-pyridin-2-ol (9.1 g, 75 %, two steps) as a white solid (reference: Bargar, T. M. *et al.*, *J. Heterocyclic Chem.* 22 (1985) 1583-1592).

3-bromo-2-chloro-5-ethanesulfonyl-pyridine



- 20 A suspension of 3-bromo-5-ethanesulfonyl-pyridin-2-ol (6.0 g, 22.5 mmol) in phosphorus oxychloride (30 mL) was heated at reflux for 4 hours under a nitrogen atmosphere. After removal of the excess of phosphorus oxychloride *in vacuo*, the white solid residue was triturated with cooled water (200 mL). The mixture was stirred for 1 hour.
- 25 The solid was collected by filtration, and dried *in vacuo* to afford 3-bromo-2-chloro-5-ethanesulfonyl-pyridine (5.5 g, 85.7 %) as a white solid (reference: Bargar, T. M. *et al.*, *J. Heterocyclic Chem.* 22 (1985) 1583-1592).

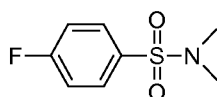
Preparation of 2-(4-fluorobenzenesulfonyl)-2-aza-spiro[3.3]heptane



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To a cooled (ice-water bath) solution of 4-fluoro-benzenesulfonamide (320 mg, 1.83 mmol) in *N,N*-dimethylformamide (5 mL), was added sodium hydride (150 mg, 60% dispersion, 3.75 mmol) portion-wise. After the mixture was stirred at 0 °C for 10 minutes, a solution of 3,3-bis-bromomethyl-oxetane (440 mg, 1.8 mmol) in *N,N*-dimethylformamide (3 mL) was added. The resulting mixture was stirred at room temperature overnight, then neutralized with 1 N hydrochloric acid, and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 20% ethyl acetate in petroleum ether) to afford 2-(4-fluoro-benzenesulfonyl)-2-aza-spiro[3.3]heptane (120 mg, 26%) as a white solid (reference: Blizzard T. A. *et al.*, *Bioorg. Med. Chem. Lett.* 14 (2004) 3861–3864), MS calcd, for C₁₂H₁₄FNO₂S 255, obsd. (ESI⁺) [(M+H)⁺] 256.

Preparation of 4-fluoro-*N,N*-dimethyl-benzenesulfonamide



A solution of 4-fluorobenzenesulfonyl chloride (1.95 g, 10 mmol) and dimethylamine hydrochloric acid salt (978 mg, 12 mmol) in tetrahydrofuran (10 mL) was added to a solution of 4-dimethylaminopyridine (3.05 g, 25 mmol) in tetrahydrofuran (10 mL) dropwise at room temperature. The resulting mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified by flash column (elution with 20% ethyl acetate in petroleum ether) to afford 4-fluoro-*N,N*-dimethyl-benzenesulfonamide (1.02 g, 50%) as a white solid.

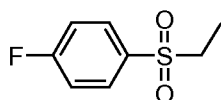
The following sulfonamides were prepared in an analogous manner as described for 4-fluoro-*N,N*-dimethyl-benzenesulfonamide by the reaction of 4-fluorobenzenesulfonyl chloride with commercially available amines.

Starting benzenesulfonyl chloride	Starting amine	Sulfonamide
4-fluoro-benzenesulfonyl chloride	pyrrolidine	1-(4-fluoro-benzenesulfonyl)-pyrrolidine
4-fluoro-benzenesulfonyl chloride	diethylamine	<i>N,N</i> -diethyl-4-fluoro-benzenesulfonamide

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4-fluoro-benzenesulfonyl chloride	morpholine	4-(4-fluoro-benzenesulfonyl)-morpholine
4-fluoro-benzenesulfonyl chloride	1-methyl-piperazine	1-(4-fluoro-benzenesulfonyl)-4-methyl-piperazine
4-fluoro-benzenesulfonyl chloride	4,4-difluoro-piperidine	4,4-difluoro-1-(4-fluoro-benzenesulfonyl)-piperidine

Preparation of 1-ethanesulfonyl-4-fluoro-benzene



To a solution of sodium hydrogen phosphate (14.2 g, 0.1 mol) and sodium sulfite
 5 (25.2 g, 0.2 mol) in water (200 mL) was added 4-fluoro-benzenesulfonyl chloride (19.5 g, 0.1 mol). After the mixture was stirred at 60 °C overnight, a solution of bromoethane (32.7 g, 0.3 mol) in acetone (20 mL) was added dropwise, followed by the addition of tetrabutylammonium iodide (3.7 g, 0.01 mol) in one portion. The resulting reaction mixture was stirred at room temperature for 5 days, then diluted
 10 with water (50 mL), and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (elution with 20% ethyl acetate in petroleum ether) to afford 1-ethanesulfonyl-4-fluoro-benzene (11.9 g, 63%) as a yellow oil (reference: Arnold, Leggy A. A., *et al.*, *Org. Lett.*, 6 (2004), 3005-3007).
 15

The following sulfone-substituted fluoro-benzenes were prepared in an analogous manner as described for 1-ethanesulfonyl-4-fluoro-benzene starting with commercially available alkyl halides and substituted benzenesulfonyl chlorides.

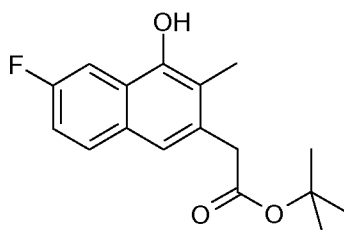
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Starting benzenesulfonyl chloride	Starting alkyl halide	Sulfone substituted fluoro-benzene
4-fluoro-benzenesulfonyl chloride	bromoethane	1-ethanesulfonyl-4-fluoro-benzene
4-fluoro-benzenesulfonyl chloride	<i>n</i> -propyl iodide	1-fluoro-4-(propane-1-sulfonyl)-benzene
4-fluoro-benzenesulfonyl chloride	2-bromo-propane	1-fluoro-4-(propane-2-sulfonyl)-benzene
4-fluoro-benzenesulfonyl chloride	cyclopropyl bromide	1-cyclopropanesulfonyl-4-fluoro-benzene

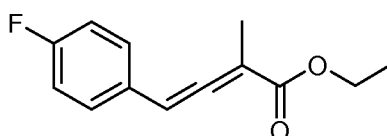
Starting benzenesulfonyl chloride	Starting alkyl halide	Sulfone substituted fluoro-benzene
4-fluoro-benzenesulfonyl chloride	1-bromo-butane	1-(butane-1-sulfonyl)-4-fluoro-benzene
4-fluoro-benzenesulfonyl chloride	bromo-cyclopentane	1-cyclopentanesulfonyl-4-fluoro-benzene
4-fluoro-3-methyl-benzenesulfonyl chloride	methyl iodide	1-fluoro-4-methanesulfonyl-2-methyl-benzene
4-fluoro-3-methyl-benzenesulfonyl chloride	bromoethane	4-ethanesulfonyl-1-fluoro-2-methyl-benzene
4-fluoro-2-methyl-benzenesulfonyl chloride	methyl iodide	4-fluoro-1-methanesulfonyl-2-methyl-benzene
4-fluoro-2-methyl-benzenesulfonyl chloride	bromoethane	1-ethanesulfonyl-4-fluoro-2-methyl-benzene
3-chloro-4-fluoro-benzenesulfonyl chloride	methyl iodide	2-chloro-1-fluoro-4-methanesulfonyl-benzene
3-chloro-4-fluoro-benzenesulfonyl chloride	bromoethane	2-chloro-4-ethanesulfonyl-1-fluoro-benzene
3,4-difluoro-benzenesulfonyl chloride	methyl iodide	1,2-difluoro-4-methanesulfonyl-benzene
3,4-difluoro-benzenesulfonyl chloride	bromoethane	4-ethanesulfonyl-1,2-difluoro-benzene
3-cyano-4-fluoro-benzenesulfonyl chloride	bromoethane	5-ethanesulfonyl-2-fluoro-benzonitrile
2-chloro-4-fluoro-benzenesulfonyl chloride	methyl iodide	2-chloro-4-fluoro-1-methanesulfonyl-benzene
2-chloro-4-fluoro-benzenesulfonyl chloride	bromoethane	2-chloro-1-ethanesulfonyl-4-fluoro-benzene
2,4-difluoro-benzenesulfonyl chloride	methyl iodide	2,4-difluoro-1-methanesulfonyl-benzene
2,4-difluoro-benzenesulfonyl chloride	bromoethane	1-ethanesulfonyl-2,4-difluoro-benzene
2,4,5-trifluoro-benzenesulfonyl chloride	methyl iodide	1,2,4-trifluoro-5-methanesulfonyl-benzene
2-chloro-4,5-difluoro-benzenesulfonyl chloride	bromoethane	1-chloro-2-ethanesulfonyl-4,5-difluoro-benzene
5-chloro-2,4-difluoro-benzenesulfonyl chloride	bromoethane	1-chloro-5-ethanesulfonyl-2,4-difluoro-benzene

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**Preparation of (6-fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-
acetic acid tert-butyl ester**



5 **4-(4-Fluoro-phenyl)-2-methyl-buta-2,3-dienoic acid ethyl ester**

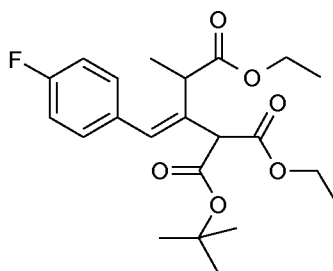


To a solution of (4-fluoro-phenyl)-acetic acid (22.33 g, 144.9 mmol) in 100 mL of methyl *tert*-butyl ether and 250 μ L of DMF was added 13.02 mL (146.3 mmol) of
 10 oxalyl chloride at room temperature dropwise over 30 minutes. The resulting mixture was stirred at room temperature for an additional 20 minutes (HPLC indicated completed reaction), and then the entire solution was added dropwise over 1 hour to a solution of *N,N*-diisopropylethylamine (50.48 mL, 289.8 mmol) and ethyl 2-(triphenylphosphoranylidene)propionate (50.0 g, 138.0 mmol) in 100
 15 mL of methyl *tert*-butyl ether, while maintaining the internal temperature between 0-15 °C. After the addition was complete, the reaction mixture was stirred for an additional 10 minutes at 0-10 °C, when HPLC indicated a completed reaction. The reaction mixture was then diluted with 100 mL of heptane, and stirred for 30 minutes at 0-10 °C. The resulting solid was filtered and washed with 2x 100 mL
 20 of 1:1 methyl *tert*-butyl ether:heptane. The filtrate and the washings were combined and washed with 100 mL of water, 100 mL of 1M citric acid, 2x100 mL of water, then concentrated azeotropically at 25 °C/60 mmHg to a total volume of ~40 mL. The residue was diluted with 60 mL of methyl *tert*-butyl ether. This solution was then directly used for the next step.

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**2-Ethoxycarbonyl-3-[1-(4-fluoro-phenyl)-meth-(E)-ylidene]-
4-methyl-pentanedioic acid 1-*tert*-butyl ester 5-ethyl ester**

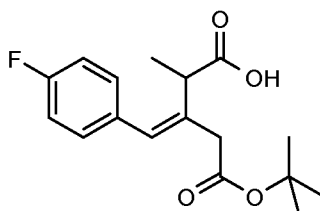
- 70 -



Malonic acid *tert*-butyl ester ethyl ester (30.08 g, 151.8 mmol) was added to a solution of potassium *tert*-butoxide (16.30 g, 138.0 mmol) in 200 mL of *N,N*-dimethyl acetamide, while the reaction temperature was maintained at ~25 °C.

- 5 To the resulting mixture was then added the solution of 4-(4-fluoro-phenyl)-2-methyl-buta-2,3-dienoic acid ethyl ester prepared above, at such a rate that the reaction temperature was maintained between 20-28 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 20 minutes, when HPLC indicated completed reaction. The mixture was then treated with
- 10 100 mL of 1M citric acid and 150 mL of ice-water, and then extracted with 400 mL of methyl *tert*-butyl ether. The organic extract was separated and washed with 2x200 mL of water, and then concentrated to produce 56.36 g of a yellow oil, which was used in the next step without further purification.

15 **3-[1-(4-Fluoro-phenyl)-meth-(Z)-ylidene]-2-methyl-pentanedioic acid 5-*tert*-butyl ester**

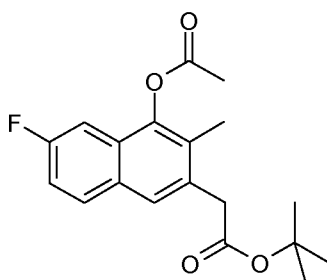


- The malonate ester derivative prepared above (56.36 g, 138 mmol) was dissolved in 280 mL of absolute ethanol. Lithium hydroxide (1M solution, 414.0 mL, 414.0 mmol) was added slowly over 15 minutes, and the resulting reaction mixture was stirred at room temperature overnight. The solution was then heated at reflux for 3 hours (HPLC analysis indicated completed decarboxylation). At this time, the solution was concentrated at 30 °C/30 mmHg to remove ~350 mL of solvent. The residue was cooled to 10 °C, and treated with concentrated
- 20
- 25 hydrochloric acid (32.0 mL, 389.7 mmol) dropwise, in order to adjust the pH to

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2.75. The reaction mixture was then extracted with methyl *tert*-butyl ether (400 mL). The organic phase was separated and washed with 200 mL of water, then treated with 17.00 mL of 1M sodium carbonate in 150 mL of water, washed with an additional 200 mL of water, and then concentrated azeotropically at 30 °C/80 mmHg to produce an oil. Methyl *tert*-butyl ether (200 mL) was added, and the residue was concentrated azeotropically at 30 °C/80 mmHg to produce 38.3 g of a yellow oil, which was used in the next step without further purification.

(4-Acetoxy-6-fluoro-3-methyl-naphthalen-2-yl)-acetic acid *tert*-butyl ester



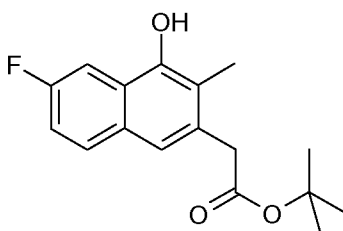
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The above prepared 3-[1-(4-fluoro-phenyl)-meth-(Z)-ylidene]-2-methyl-pentanedioic acid 5-*tert*-butyl ester (38.3 g, 124.2 mmol) was dissolved in acetic anhydride (96.00 mL, 995.3 mmol). To this solution was added potassium acetate (18.66 g, 186.3 mmol), and the reaction mixture was stirred at 85±2 °C for 10 hours, when HPLC analysis showed completed reaction. The reaction mixture was then cooled to room temperature and diluted with 96 mL of heptane. To this solution, 270 mL of water was added over 1 hour, while maintaining the internal temperature at ~ 23 °C. The mixture was then cooled to 0-5 °C, and stirred for 2 hours. The solid formed was filtered, and then washed with water (2x40 mL), heptane (2x40 mL), and then dried under vacuum to furnish 28.5 g of a yellow solid, which was used in the next step without further purification.

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(6-Fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid *tert*-butyl ester

(IIb-1)



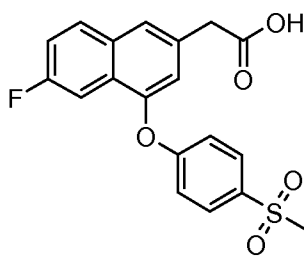
- 72 -

To a mixture of the above prepared (4-acetoxy-6-fluoro-3-methyl-naphthalen-2-yl)-acetic acid *tert*-butyl ester (28.4 g, 85.44 mmol) in 140 mL of methanol was added sodium methoxide (25% solution in methanol, 23.44 mL, 102.5 mmol) rapidly dropwise. The resulting reaction mixture was stirred at room temperature for 20 minutes, when HPLC analysis indicated a completed reaction. The mixture was cooled to 0 °C, and then acidified to pH 2 with 1N hydrochloric acid solution (111.1 mL, 111.1 mmol). The mixture was then stirred at 0-5 °C for an additional 30 minutes. The resulting solid was filtered, and washed with water (2x40 mL), then dried under vacuum overnight (40 °C), to produce 23.7 g of a light yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 9.09 (s, 1 H), 7.76-7.86 (m, 2 H), 7.26-7.35 (m, 2 H), 3.71 (s, 2 H), 2.23 (s, 3 H), 1.41 (s, 9 H).

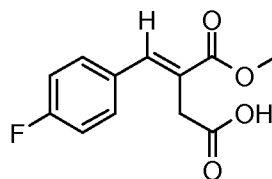
PART II: PREPARATION OF SPECIFIC COMPOUNDS

EXAMPLE 1-1

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid



2-(4-fluoro-benzylidene)-succinic acid 1-methyl ester

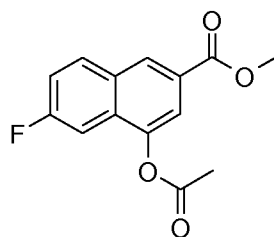


To a refluxing mixture of potassium *tert*-butoxide (27 g, 242 mmol) and *tert*-butanol (150 mL) was added a solution of 4-fluoro-benzaldehyde (20 g, 161 mmol) and dimethyl succinate (28 g, 193.2 mmol) in *tert*-butanol (100 mL) dropwise. After being heated at reflux for 3 hours, the mixture was concentrated *in vacuo* to remove *tert*-butanol. The residue was dissolved in 1 N hydrochloric acid (180 mL). The resulting aqueous solution was extracted with ethyl acetate

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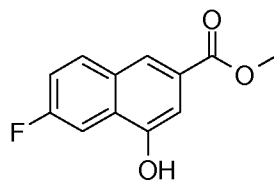
(100 mL × 3). The combined organic layers were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 30% ethyl acetate in petroleum ether) to afford 2-(4-fluoro-benzylidene)-succinic acid 1-methyl ester (25.5 g, 66%) as a light yellow solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.84 (s, 1 H), 7.41 - 7.46 (m, 2 H), 7.13 - 7.20 (m, 2 H), 3.81 (s, 3 H), 3.49 (s, 2 H).

4-acetoxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester



To a solution of 2-(4-fluoro-benzylidene)-succinic acid 1-methyl ester (2 g, 8.4 mmol) in acetic anhydride (10 mL) was added sodium acetate (0.83 g, 10.1 mmol). After being heated at reflux for 6 hours, the mixture was concentrated *in vacuo*. The residue was dissolved in 1 N hydrochloric acid (20 mL). The aqueous solution was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (10-20% ethyl acetate in petroleum ether) to afford 4-acetoxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester (1.1 g, 50%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.52 (s, 1 H), 8.00 (dd, *J* = 9.09, 5.56 Hz, 1 H), 7.89 (s, 1 H), 7.50 (dd, *J* = 9.85, 2.53 Hz, 1 H), 7.37 (td, *J* = 8.59, 2.53 Hz, 1 H), 3.99 (s, 3 H), 2.49 (s, 3 H).

6-fluoro-4-hydroxy-naphthalene-2-carboxylic acid methyl ester

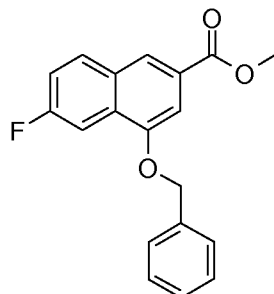


To a solution of 4-acetoxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester (1 g, 3.8 mmol) in methanol (20 mL) was added sodium methoxide (309 mg, 5.7 mmol). After being stirred at room temperature for 1 hour, the reaction mixture was acidified with 1 N hydrochloric acid to pH 3. The resulting precipitate was collected by filtration and dissolved in ethyl acetate. The organic solution was

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dried over sodium sulfate, and concentrated *in vacuo* to afford 900 mg of crude 6-fluoro-4-hydroxy-naphthalene-2-carboxylic acid methyl ester as a pale yellow solid, which was used in the next step without further purification.

4-benzyloxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester

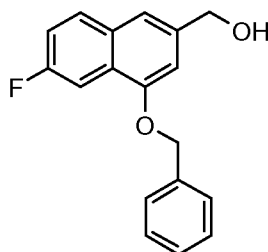


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To a mixture of 6-fluoro-4-hydroxy-naphthalene-2-carboxylic acid methyl ester (4.6 g, 21 mmol), potassium carbonate (5.8 g, 42 mmol) and acetone (100 mL) was added benzyl bromide (5.47 g, 32 mmol). After being stirred vigorously at reflux for 4 hours under a nitrogen atmosphere, the resulting mixture was cooled to room temperature, and filtered. The organic solution was concentrated *in vacuo* to give 4-benzyloxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester (5.85 g, 90%) as a white solid.

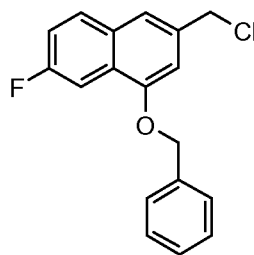
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(4-benzyloxy-6-fluoro-naphthalen-2-yl)-methanol

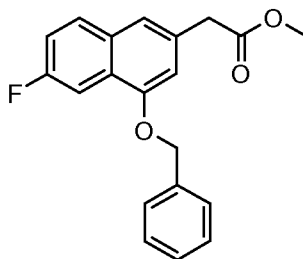


To the slurry of lithium aluminum hydride (1.4 g, 36.9 mmol) in tetrahydrofuran (30 mL) was added a solution of 4-benzyloxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester (5.8 g, 18.7 mmol) in tetrahydrofuran (30 mL) at 0 °C under a nitrogen atmosphere. After being heated at 60 °C for 1 hour under a nitrogen atmosphere, the resulting mixture was cooled to 0 °C and 1 N hydrochloric acid was added to quench the reaction. The aqueous layer was extracted with diethyl ether (50 mL x 4). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give (4-benzyloxy-6-fluoro-naphthalen-2-yl)-methanol (4.9 g, 93%) as a white solid.

20

1-benzyloxy-3-chloromethyl-7-fluoro-naphthalene

To a solution of triphenylphosphine (2.8 g, 10.6 mmol) in anhydrous
5 tetrahydrofuran (16 mL) was added carbon tetrachloride (5 mL). After the mixture
was stirred at room temperature for 10 minutes, (4-benzyloxy-6-fluoro-
naphthalen-2-yl)-methanol (1.5 g, 5.3 mmol) was added as a solid under a
nitrogen atmosphere. After being stirred at reflux for 2 hours, the resulting mixture
was cooled to room temperature, diluted with water, and extracted with ethyl
10 acetate (100 mL). The organic layer was washed with water (50 mL × 2). The
combined aqueous layers were extracted with ethyl acetate (100 mL). The
combined organic layers were dried over sodium sulfate and concentrated *in*
vacuo. The residue was purified by column chromatography (elution with 5%
ethyl acetate in petroleum ether) to afford 1-benzyloxy-3-chloromethyl-7-fluoro-
15 naphthalene (1.4 g, 87.5 %) as a white solid.

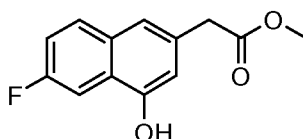
(4-benzyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester

To a flask containing 1-benzyloxy-3-chloromethyl-7-fluoro-naphthalene (5.4 g, 18
mmol), bis(triphenylphosphine)dichloropalladium(II) (630 mg, 0.9 mmol) and
20 potassium carbonate (2.6 g, 18.9 mmol), which was evacuated and then filled
with carbon monoxide (balloon), methanol (25 mL) and tetrahydrofuran (50 mL)
were added by means of a syringe. After being stirred at room temperature under
a carbon monoxide atmosphere overnight, the resulting mixture was diluted with
water (100 mL), and extracted with ethyl acetate (100 mL). The organic layer was

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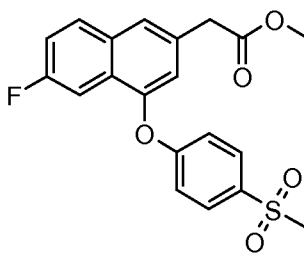
washed with water (50 mL × 2). The combined aqueous layers were extracted with ethyl acetate (150 mL), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 20% ethyl acetate in petroleum ether) to afford (4-benzyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (5.3 g, 91%) as a white solid.

(6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester



To a solution of (4-benzyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (876 mg, 2.7 mmol) in methanol (20 mL) was added 10% palladium on carbon (132 mg). The resulting mixture was stirred vigorously under a hydrogen atmosphere (balloon) overnight and then filtered. The filtrate was concentrated *in vacuo* to give (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (601 mg, 95%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 - 7.76 (m, 2 H), 7.30 (s, 1 H), 7.22 - 7.26 (m, 1 H), 6.82 (s, 1 H), 3.74 (s, 3 H), 3.72 (s, 2 H).

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester

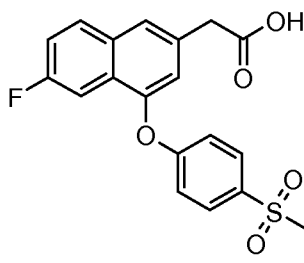


A sealed tube containing (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (49 mg, 0.21 mmol), 1-ethanesulfonyl-4-fluoro-benzene (87 mg, 0.427 mmol), and potassium carbonate (73 mg, 0.53 mmol) was evacuated and filled with nitrogen. Anhydrous *N,N*-dimethylformamide (2 mL) was added. After being stirred at 100 °C overnight, the mixture was cooled to room temperature, then diluted with water (10 mL), and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (10 mL × 3), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column

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chromatography (elution with 30% ethyl acetate in petroleum ether) to give [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester (67.6 mg, 80%) as a white solid.

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid



5

5 N lithium hydroxide (6 mL) was added to a solution of [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester (64 mg, 0.16 mmol) in tetrahydrofuran (4 mL). After being stirred at room temperature overnight, the resulting mixture was acidified to pH 3 with 5 N hydrochloric acid, and then extracted with ethyl acetate (10 mL × 2). The organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was precipitated from ethyl ester/ petroleum ether (1:10) to give [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid (25 mg) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.84 - 7.90 (m, 3 H), 7.65 (s, 1 H), 7.57 (dd, *J* = 9.85, 2.53 Hz, 1 H), 7.33 (td, *J* = 8.65, 2.65 Hz, 1 H), 7.09 - 7.14 (m, 3 H), 3.80 (s, 2 H), 3.13 (q, *J* = 7.33 Hz, 2 H), 1.30 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₀H₁₇FO₅S 388, obsd. (ESI⁺) [(M+H)⁺] 389.

20

EXAMPLES 1-2 to 1-23

The following examples **1-2** to **1-23** were prepared in an analogous manner to example **1-1** starting with 4-fluoro-benzaldehyde, 4-chloro-benzaldehyde, 4-methoxy-benzaldehyde, 4-trifluoromethyl-benzaldehyde, 4-trifluoromethoxy-benzenaldehyde, 3,4-dimethoxy-benzaldehyde, and 3-fluoro-benzaldehyde, to derive (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester, (6-chloro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester, (4-hydroxy-6-methoxy-naphthalen-2-yl)-acetic acid methyl ester, (4-hydroxy-6-trifluoromethyl-naphthalen-2-yl)-acetic acid methyl ester, (4-hydroxy-6-trifluoromethoxy-

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- naphthalen-2-yl)-acetic acid methyl ester, (4-hydroxy-6,7-dimethoxy-naphthalen-2-yl)-acetic acid methyl ester, and derive (5-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester and (7-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (Note: Starting with 3-fluoro-benzaldehyde, both of (5-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester and (7-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester can be obtained. See Scheme 17) respectively, which were then further treated with the appropriate commercially available or prepared sulfonylaryl derivatives in accordance with the procedure described for example 1-1.

10

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺])	Structure
1-2	[6-fluoro-4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid	7.82 - 7.89 (m, 1 H), 7.86 (d, <i>J</i> = 8.84 Hz, 2 H), 7.61 (s, 1 H), 7.53 (dd, <i>J</i> = 9.98, 2.40 Hz, 1 H), 7.26 - 7.32 (m, 1 H), 7.07 (d, <i>J</i> = 9.09 Hz, 2 H), 7.10 (s, 1 H), 3.76 (s, 2 H), 3.03 (s, 3 H)	375	
1-3*	[6-chloro-4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid	7.90 - 7.96 (m, 4 H), 7.72 (s, 1 H), 7.52 (dd, <i>J</i> = 8.84, 2.02 Hz, 1 H), 7.18 - 7.22 (m, 3 H), 3.79 (s, 2 H), 3.12 (s, 3 H)	391	
1-4	{6-fluoro-4-[4-(propane-2-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	7.83 - 7.92 (m, 3 H), 7.67 (s, 1 H), 7.60 (dd, <i>J</i> = 9.85, 2.53 Hz, 1 H), 7.35 (td, <i>J</i> = 8.65, 2.65 Hz, 1 H), 7.13 (s, 3 H), 3.82 (s, 2 H), 3.17 - 3.25 (m, 1 H), 1.34 (d, <i>J</i> = 7.07 Hz, 6 H)	403	

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Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
1-5	[4-(4-cyclopropanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid	7.86 - 7.92 (m, 3 H), 7.65 - 7.69 (m, 1 H), 7.61 (dd, <i>J</i> = 9.98, 2.65 Hz, 1 H), 7.35 (td, <i>J</i> = 8.59, 2.53 Hz, 1 H), 7.10 - 7.16 (m, 3 H), 3.79 (br. s, 2 H), 2.45 - 2.53 (m, 1 H), 1.37 (dd, <i>J</i> = 4.80, 1.77 Hz, 2 H), 1.07 (dd, <i>J</i> = 7.96, 1.89 Hz, 2 H)	401	
1-6	[6-fluoro-4-(4-methanesulfonyl-2-methyl-phenoxy)-naphthalen-2-yl]-acetic acid	7.91 (br. s, 1 H), 7.88 (t, 1 H), 7.68 (dd, <i>J</i> = 8.46, 1.89 Hz, 1 H), 7.60 - 7.64 (m, 2 H), 7.35 (td, <i>J</i> = 8.72, 2.53 Hz, 1 H), 6.98 (s, 1 H), 6.82 (d, <i>J</i> = 8.59 Hz, 1 H), 3.79 (s, 2 H), 3.09 (s, 3 H), 2.50 (s, 3 H)	389	
1-7	[6-fluoro-4-(4-methanesulfonyl-3-methyl-phenoxy)-naphthalen-2-yl]-acetic acid	7.99 (d, <i>J</i> = 8.59 Hz, 1 H), 7.87 (dd, <i>J</i> = 9.09, 5.31 Hz, 1 H), 7.64 (s, 1 H), 7.58 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 7.33 (td, <i>J</i> = 8.65, 2.40 Hz, 1 H), 7.12 (s, 1 H), 6.95 (d, <i>J</i> = 2.27 Hz, 1 H), 6.89 (dd, <i>J</i> = 8.72, 2.40 Hz, 1 H), 3.80 (s, 2 H), 3.09 (s, 3 H), 2.66 (s, 3 H)	389	
1-8	[4-(4-ethanesulfonyl-2-methyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid	7.98 (dd, <i>J</i> = 8.97, 5.43 Hz, 1 H), 7.88 (d, <i>J</i> = 1.52 Hz, 1 H), 7.68 (s, 1 H), 7.65 (dd, <i>J</i> = 8.46, 2.15 Hz, 1 H), 7.57 (dd, <i>J</i> = 10.23, 2.65 Hz, 1 H), 7.37 (td, <i>J</i> = 8.78, 2.65 Hz, 1 H), 7.05 (s, 1 H), 6.87 (d, <i>J</i> = 8.59 Hz, 1 H), 3.75 (s, 2 H), 3.21 (q, <i>J</i> = 7.49 Hz, 2 H), 2.50 (s, 3 H), 1.23 (t, <i>J</i> = 7.45 Hz, 3 H)	403	
1-9**	[6-fluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid	8.56 (d, <i>J</i> = 2.53 Hz, 1 H), 8.38 (dd, <i>J</i> = 8.59, 2.53 Hz, 1 H), 8.09 (dd, <i>J</i> = 8.84, 5.56 Hz, 1 H), 7.82 (s, 1 H), 7.44 - 7.51 (m, 2 H), 7.42 (s, 1 H), 7.38 (s, 1 H), 3.76 (s, 2 H), 3.28 (s, 3 H)	376	

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
1-10**	[6-fluoro-4-(5-methanesulfonyl-3-methyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid	12.45 (s, 1 H), 8.31 (br. s, 2 H), 8.08 (br. s, 1 H), 7.81 (s, 1 H), 7.42 - 7.51 (m, 2 H), 7.34 (s, 1 H), 3.77 (s, 2 H), 3.26 (s, 3 H), 2.56 (s, 3 H)	390	
1-11**	[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid	8.53 (d, <i>J</i> = 2.02 Hz, 1 H), 8.34 (dd, <i>J</i> = 8.72, 2.40 Hz, 1 H), 8.10 (dd, <i>J</i> = 8.97, 5.68 Hz, 1 H), 7.83 (s, 1 H), 7.35 - 7.55 (m, 4 H), 3.78 (s, 2 H), 3.35 - 3.40 (m, 2 H), 1.14 (t, <i>J</i> = 7.45 Hz, 3 H)	390	
1-12*	[4-(5-ethanesulfonyl-3-methyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid	8.27 (s, 1 H), 8.17 (s, 1 H), 7.97 (dd, <i>J</i> = 8.08, 6.06 Hz, 1 H), 7.75 (s, 1 H), 7.30 - 7.38 (m, 3 H), 3.79 (s, 2 H), 3.24 (t, 2 H), 2.60 (s, 3 H), 1.25 (t, <i>J</i> = 6.95 Hz, 3 H)	404	
1-13*	[4-(3-bromo-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid	8.60 (d, <i>J</i> = 2.27 Hz, 1 H), 8.42 (d, <i>J</i> = 2.27 Hz, 1 H), 7.99 (dd, <i>J</i> = 8.97, 5.18 Hz, 1 H), 7.79 (s, 1 H), 7.32 - 7.43 (m, 3 H), 3.81 (s, 2 H), 3.26 - 3.29 (m, 2 H), 1.26 (t, <i>J</i> = 7.33 Hz, 3 H)	468	
1-14*	[4-(3-bromo-5-methanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid	8.65 (d, <i>J</i> = 2.27 Hz, 1 H), 8.46 (d, <i>J</i> = 2.02 Hz, 1 H), 7.99 (dd, <i>J</i> = 9.73, 5.43 Hz, 1 H), 7.79 (s, 1 H), 7.32 - 7.40 (m, 3 H), 3.81 (s, 2 H), 3.20 (s, 3 H)	454	
1-15	[4-(4-Ethanesulfonyl-phenoxy)-6-methoxy-naphthalen-2-yl]-acetic acid	7.87 (d, <i>J</i> = 8.59 Hz, 2 H), 7.79 (d, <i>J</i> = 8.84 Hz, 1 H), 7.60 (s, 1 H), 7.19 - 7.24 (m, 2 H), 7.14 (d, <i>J</i> = 8.59 Hz, 2 H), 7.10 (d, <i>J</i> = 1.26 Hz, 1 H), 3.84 (s, 3 H), 3.79 (s, 2 H), 3.14 (q, <i>J</i> = 7.49 Hz, 2 H), 1.32 (t, <i>J</i> = 7.45 Hz, 3 H)	401	

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
1-16*	[4-(5-Ethanesulfonylpyridin-2-yloxy)-6-trifluoromethyl-naphthalen-2-yl]-acetic acid	8.55 (d, <i>J</i> = 2.53 Hz, 1 H), 8.34 (dd, <i>J</i> = 8.59, 2.27 Hz, 1 H), 8.10 - 8.15 (m, 2 H), 7.86 (s, 1 H), 7.73 (d, <i>J</i> = 9.09 Hz, 1 H), 7.46 (s, 1 H), 7.40 (d, <i>J</i> = 8.84 Hz, 1 H), 3.86 (s, 2 H), 3.27 (dd, 2 H) 1.26 (t, <i>J</i> = 7.33 Hz, 3 H)	440	
1-17*	[4-(4-Ethanesulfonylphenoxy)-6-trifluoromethyl-naphthalen-2-yl]-acetic acid	8.30 (s, 1 H) 8.13 (d, <i>J</i> = 8.59 Hz, 1 H) 7.93 (d, <i>J</i> = 8.84 Hz, 2 H) 7.80 (s, 1 H) 7.76 (dd, <i>J</i> = 8.34, 1.26 Hz, 1 H) 7.23 - 7.31 (m, 3 H) 3.84 (s, 2 H) 3.22 (q, <i>J</i> = 7.33 Hz, 2 H) 1.24 (t, <i>J</i> = 7.33 Hz, 3 H)	439	
1-18*	[4-(5-Ethanesulfonylpyridin-2-yloxy)-6-trifluoromethoxy-naphthalen-2-yl]-acetic acid	8.55 (d, <i>J</i> = 2.27 Hz, 1 H), 8.32 (dd, <i>J</i> = 8.84, 2.53 Hz, 1 H), 8.06 (d, <i>J</i> = 8.84 Hz, 1 H), 7.82 (s, 1 H), 7.62 (s, 1 H), 7.46 (d, <i>J</i> = 1.52 Hz, 1 H), 7.42 (s, 1 H), 7.36 (d, <i>J</i> = 8.59 Hz, 1 H), 3.84 (s, 2 H), 3.26 (q, <i>J</i> = 7.33 Hz, 2 H), 1.25 (t, <i>J</i> = 7.33 Hz, 3 H)	456	
1-19*	[4-(4-Ethanesulfonylphenoxy)-6-trifluoromethoxy-naphthalen-2-yl]-acetic acid	8.05 (d, <i>J</i> = 9.09 Hz, 1 H), 7.91 (d, <i>J</i> = 8.84 Hz, 2 H), 7.77 (s, 2 H), 7.46 (d, <i>J</i> = 8.84 Hz, 1 H), 7.27 (s, 1 H), 7.25 (d, <i>J</i> = 8.84 Hz, 2 H), 3.81 (s, 2 H), 3.20 (q, <i>J</i> = 7.33 Hz, 2 H), 1.25 (d, <i>J</i> = 7.33 Hz, 3 H)	455	
1-20*	[4-(4-Ethanesulfonylphenoxy)-7-fluoro-naphthalen-2-yl]-acetic acid	8.02 (dd, <i>J</i> = 9.09, 5.56 Hz, 1 H), 7.90 (d, <i>J</i> = 8.84 Hz, 2 H), 7.69 (s, 1 H), 7.62 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 7.32 (td, <i>J</i> = 8.78, 2.40 Hz, 1 H), 7.22 (d, <i>J</i> = 8.59 Hz, 2 H), 7.15 (s, 1 H), 3.80 (s, 2 H), 3.22 (q, <i>J</i> = 7.41 Hz, 2 H), 1.25 (t, <i>J</i> = 7.45 Hz, 3 H)	389	
1-21*	[4-(5-Ethanesulfonylpyridin-2-yloxy)-6-methoxy-naphthalen-2-yl]-acetic acid	8.60 (d, <i>J</i> = 2.80 Hz, 1 H), 8.30 (dd, <i>J</i> = 8.84, 2.40 Hz, 1 H), 7.85 (d, <i>J</i> = 9.20 Hz, 1 H), 7.69 (s, 1 H), 7.28-7.25 (m, 2 H), 7.21 (dd, <i>J</i> = 9.20, 2.40 Hz, 1 H), 7.10 (d, <i>J</i> = 2.40 Hz, 1 H), 3.80 (s, 5 H), 3.20 (q, <i>J</i> = 7.45 Hz, 2 H), 1.28 (t, <i>J</i> = 7.45 Hz, 3 H)	402	

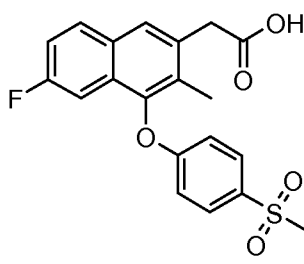
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Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
1-22*	[4-(4-Ethanesulfonyl-phenoxy)-5-fluoro-naphthalen-2-yl]-acetic acid	7.87 (d, <i>J</i> = 8.84 Hz, 2 H), 7.81 (s, 1 H), 7.77 (d, <i>J</i> = 8.84 Hz, 1 H), 7.50 (td, 1 H), 7.30 (s, 1 H), 7.14 (dd, 1 H), 7.08 (d, <i>J</i> = 8.84 Hz, 2 H), 3.81 (s, 2 H), 3.20 (q, <i>J</i> = 7.45 Hz, 2 H), 1.26 (t, <i>J</i> = 7.45 Hz, 3 H)	389	
1-23*	[4-(4-Ethanesulfonyl-phenoxy)-6,7-dimethoxy-naphthalen-2-yl]-acetic acid	7.89 (d, <i>J</i> = 8.84 Hz, 2 H), 7.59 (s, 1 H), 7.34 (s, 1 H), 7.22-7.19 (m, 3 H), 7.04 (s, 1 H), 3.99 (s, 3 H), 3.83 (s, 3 H), 3.75 (s, 2 H), 3.23 (q, <i>J</i> = 7.45 Hz, 2 H), 1.25 (t, <i>J</i> = 7.45 Hz, 3 H)	431	

*CD₃OD was used as the solvent; **DMSO-*d*₆ was used as the solvent.

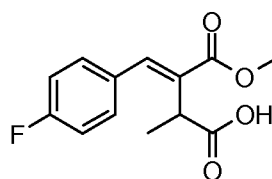
EXAMPLE 2-1

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid



5

2-(4-fluoro-benzylidene)-3-methyl-succinic acid 1-methyl ester



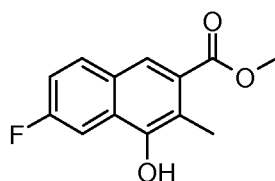
After careful addition of absolute methanol (0.1 mL) to a suspension of sodium hydride (60% in mineral oil, 20 g, 0.5 mol) in anhydrous toluene (200 mL), a solution of 4-fluoro-benzaldehyde (31 g, 0.25 mol) and 2-methyl-succinic acid dimethyl ester (60 g, 0.38 mol) in anhydrous toluene (100 mL) was added at room temperature under a stream of nitrogen. The resulting mixture was stirred at room temperature for 30 minutes and then quenched by the slow addition of water (20 mL). The mixture was acidified by the addition of concentrated hydrochloric acid, and extracted with ethyl acetate (200 mL × 3). The combined

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organic layers were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 30% ethyl acetate in petroleum ether) to afford 2-(4-fluoro-benzylidene)-3-methyl-succinic acid 1-methyl ester (20 g, 33%) as a white solid. ¹H NMR (400 MHz, acetone-*d*₆) δ ppm

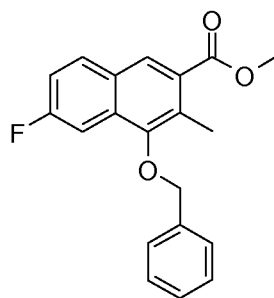
5 7.77 (s, 1 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 3.82 (q, 7.2 Hz, 1 H), 1.40 (d, *J* = 6.8 Hz, 3 H).

6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid methyl ester

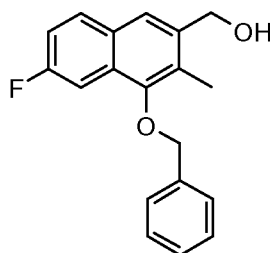


- 10 To a solution of 2-(4-fluoro-benzylidene)-3-methyl-succinic acid 1-methyl ester (1 g, 4 mmol) in anhydrous tetrahydrofuran (10 mL), trifluoroacetic anhydride (3.3 g, 15.7 mmol) was added in one portion followed by the addition of triethylamine (3.3 mL, 24 mmol) dropwise. After being stirred at room temperature for 4 hours, the mixture was acidified to pH 3 with 5% aqueous hydrochloric acid and
- 15 extracted with ethyl acetate (30 mL). The organic layer was concentrated *in vacuo*. The residue was dissolved in methanol (15 mL). The resulting solution was cooled to 0 °C, then treated with sodium borohydride (380 mg, 10 mmol), and stirred for 1 hour. The reaction mixture was diluted with ethyl acetate (20 mL) and 5% aqueous hydrochloric acid (20 mL). The aqueous phase was separated
- 20 and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 10% ethyl acetate in hexanes) to afford 6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid methyl ester (740 mg, 80%) as a pale solid.
- 25 Alternatively, 6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid methyl ester was obtained by treating 2-(4-fluoro-benzylidene)-3-methyl-succinic acid 1-methyl ester with acetic anhydride and sodium acetate followed by sodium methoxide, in a manner analogous to the one described above for the preparation of 6-fluoro-4-hydroxy-naphthalene-2-carboxylic acid methyl ester.

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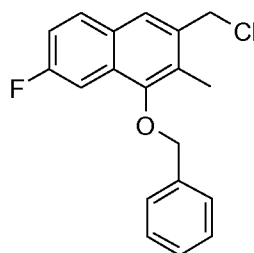
4-benzyloxy-6-fluoro-3-methyl-naphthalene-2-carboxylic acid methyl ester

To a mixture of 6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid methyl ester (8.0 g, 34.2 mmol) and potassium carbonate (9.45 g, 68.4 mmol) was added benzyl bromide (4.5 mL, 37.6 mmol) in acetone (100 mL). The resulting mixture was vigorously stirred at reflux for 10 hours under a nitrogen atmosphere. The mixture was cooled and filtered. The combined organic solution was concentrated *in vacuo* to give 4-benzyloxy-6-fluoro-3-methyl-naphthalene-2-carboxylic acid methyl ester (10.4 g, 94%) as a white solid.

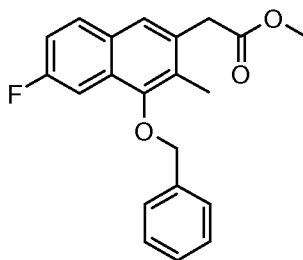
(4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-methanol

To the slurry of lithium aluminum hydride (1.8 g, 47.5 mmol) in tetrahydrofuran (50 mL) was added a solution of 4-benzyloxy-6-fluoro-3-methyl-naphthalene-2-carboxylic acid methyl ester (10 g, 30.8 mmol) in tetrahydrofuran (50 mL) at 0 °C under a nitrogen atmosphere. After being heated at 60 °C for 2 hours, the resulting mixture was cooled to 0 °C and treated with 1 N hydrochloric acid to quench the reaction. The aqueous layer was extracted with diethyl ether (100 mL x 5). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give (4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-methanol (8.4 g, 92%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.84 (dd, *J* = 5.6, 9.2 Hz, 1 H), 7.70 (dd, *J* = 2.4, 10.0 Hz, 1 H), 7.69 (s, 1 H), 7.40 - 7.50 (m, 5 H), 7.24 (td, *J* = 2.4, 8.4 Hz, 1 H), 4.99 (s, 2 H), 4.87 (s, 2 H), 2.47 (s, 3 H).

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1-benzyloxy-3-chloromethyl-7-fluoro-2-methyl-naphthalene

To a solution of triphenylphosphine (7.1 g, 27.2 mmol) in anhydrous tetrahydrofuran (32 mL) was added carbon tetrachloride (10 mL). The mixture was stirred for 10 minutes and 4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-methanol (4 g, 13.6 mmol) was introduced as a solid under a nitrogen atmosphere. After being stirred at reflux for 2 hours, the resulting mixture was diluted with water, extracted with ethyl acetate (150 mL) and washed with water (50 mL × 2). The combined aqueous layers were then extracted with ethyl acetate (150 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (5% ethyl acetate in petroleum ether) to afford 1-benzyloxy-3-chloromethyl-7-fluoro-2-methyl-naphthalene (3.5 g, 83%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.83 (dd, *J* = 5.6, 9.3 Hz, 1 H), 7.71 (d, *J* = 2.4 Hz, 1 H), 7.68 (s, 1 H), 7.40 - 7.58 (m, 5 H), 7.25 (td, *J* = 2.4, 8.8 Hz, 1 H), 5.01 (s, 2 H), 4.79 (s, 2 H), 2.54 (s, 3 H); MS calcd. for C₁₉H₁₆ClFO 314, obsd. (ESI⁺) [(M+H)⁺] 315.

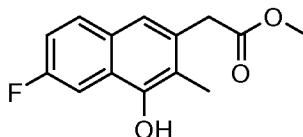
(4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-acetic acid methyl ester

A flask containing 1-benzyloxy-3-chloromethyl-7-fluoro-2-methyl-naphthalene (3.3 g, 10.4 mmol), bis(triphenylphosphine)dichloropalladium(II) (360 mg, 0.5 mmol) and potassium carbonate (1.52 g, 11.0 mmol) was evacuated and then filled with carbon monoxide (balloon). Methanol (18 mL) and tetrahydrofuran (35 mL) were added by means of a syringe. After being stirred at room temperature under a

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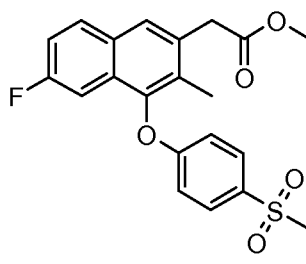
carbon monoxide atmosphere overnight, the resulting mixture was diluted with water (50 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL × 2). The combined aqueous layers were extracted with ethyl acetate (150 mL) and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford (4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (3.4 g, 96%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.80 (dd, *J* = 5.2, 8.4 Hz, 1 H), 7.70 (d, *J* = 10.4 Hz, 1 H), 7.40 - 7.59 (m, 6 H), 7.25 (td, *J* = 2.0, 8.8 Hz, 1 H), 5.00 (s, 2 H), 3.84 (s, 2 H), 3.75 (s, 3 H), 2.42 (s, 3 H); MS calcd. for C₂₁H₁₉FO₃ 338, obsd. (ESI⁺) [(M+H)⁺] 339.

(6-fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester



To a solution of (4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (3.4 g, 10.0 mmol) in methanol (50 mL) was added 10% palladium on carbon (0.5 g). The resulting mixture was vigorously stirred under a hydrogen (balloon) atmosphere overnight. The filtrate was concentrated *in vacuo* to give (6-fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (2.44 g, 98 %) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 - 7.74 (m, 2 H), 7.34 (s, 1 H), 7.21 (td, *J* = 2.4, 8.4 Hz, 1 H), 5.16 (s, 1 H), 3.82 (s, 2 H), 3.74 (s, 3 H), 2.35 (s, 3 H); MS calcd. for C₁₄H₁₃FO₃ 248, obsd. (ESI⁺) [(M+H)⁺] 249.

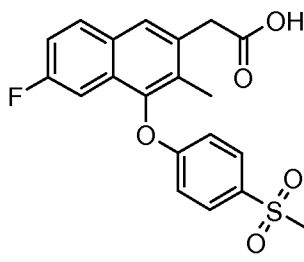
[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester



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- A sealed tube containing 6-fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (100 mg, 0.4 mmol), 1-ethanesulfonyl-4-fluoro-benzene (152 mg, 0.8 mmol), and potassium carbonate (111 mg, 0.8 mmol) was evacuated and filled with nitrogen. Anhydrous *N,N*-dimethylformamide (2 mL) was added. After
- 5 being stirred at 100 °C overnight, the mixture was cooled to room temperature, then diluted with water (10 mL), and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine (10 mL × 3), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate in petroleum ether) to give [4-(4-
- 10 ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (160 mg, 96%). MS cald. for C₂₂H₂₁FO₅S 416, obsd. (ESI⁺) [(M+H)⁺] 417.

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid



- 15 Starting with [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (150 mg, 0.36 mmol), using a method analogous to the one described for example 1-1, final step, [4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid (116 mg, 80%) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.82 (d, *J* = 8.84 Hz, 2 H), 7.80 - 7.86 (m,
- 20 1 H), 7.70 (s, 1 H), 7.34 (dd, *J* = 9.98, 2.40 Hz, 1 H), 6.92 (d, *J* = 8.84 Hz, 2 H), 3.90 (s, 2 H), 3.11 (q, *J* = 7.33 Hz, 2 H), 2.25 (s, 3 H), 1.30 (t, *J* = 7.45 Hz, 3 H); MS cald. for C₂₁H₁₉FO₅S 402, obsd. (ESI⁺) [(M+H)⁺] 403.

EXAMPLES 2-2 to 2-45

- 25 The following examples 2-2 to 2-45 were prepared in an analogous manner to example 2-1 starting with 4-fluoro-benzaldehyde or 4-chloro-benzaldehyde to derive (6-fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester or (6-chloro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester,

respectively, which were then further treated with the appropriate commercially available or prepared aryl derivatives in accordance with the procedure described for example **2-1**.

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
2-2	[6-fluoro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.82 - 7.88 (m, 1 H), 7.86 (d, <i>J</i> = 9.09 Hz, 2 H), 7.70 (s, 1 H), 7.33 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 7.25 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 6.92 (d, <i>J</i> = 8.84 Hz, 2 H), 3.89 (s, 2 H), 3.06 (s, 3 H), 2.25 (s, 3 H)	389	
2-3	[6-fluoro-4-(4-methanesulfonyl-2-methyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.88 (d, <i>J</i> = 2.27 Hz, 1 H), 7.84 (dd, <i>J</i> = 9.73, 5.43 Hz, 1 H), 7.70 (s, 1 H), 7.52 (dd, <i>J</i> = 8.21, 2.40 Hz, 1 H), 7.23 - 7.26 (m, 1 H), 6.26 (d, <i>J</i> = 8.84 Hz, 1 H), 3.90 (s, 2 H), 3.05 (s, 3 H), 2.63 (s, 3 H), 2.22 (s, 3 H)	403	
2-4	{6-fluoro-3-methyl-4-[4-(propane-2-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	7.84 (dd, <i>J</i> = 8.97, 5.43 Hz, 1 H), 7.79 (d, <i>J</i> = 8.84 Hz, 2 H), 7.70 (s, 1 H), 7.35 (dd, <i>J</i> = 10.11, 2.27 Hz, 1 H), 6.90 - 6.94 (m, 2 H), 3.90 (s, 2 H), 3.14 - 3.22 (m, 1 H), 2.24 (s, 3 H), 1.31 (d, <i>J</i> = 6.82 Hz, 6 H)	417	
2-5	[4-(4-cyclopropanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	7.81 (d, <i>J</i> = 9.09 Hz, 2 H), 7.79 - 7.86 (m, 1 H), 7.70 (s, 1 H), 7.35 (dd, <i>J</i> = 9.98, 2.40 Hz, 1 H), 6.91 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 2.43 - 2.50 (m, 1 H), 2.25 (s, 3 H), 1.31 - 1.36 (m, 2 H), 1.04 (m, 1 H)	415	
2-6	[6-fluoro-4-(4-methanesulfonyl-3-methyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.92 (d, <i>J</i> = 8.84 Hz, 1 H), 7.84 (dd, <i>J</i> = 8.97, 5.68 Hz, 1 H), 7.69 (s, 1 H), 7.34 (dd, <i>J</i> = 10.23, 2.40 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 6.80 (d, <i>J</i> = 2.02 Hz, 1 H), 6.64 (dd, <i>J</i> = 8.72, 2.40 Hz, 1 H), 3.90 (s, 2 H), 3.07 (s, 3 H), 2.64 (s, 3 H), 2.25 (s, 3 H)	403	

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
2-7	[6-Chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.86 (d, <i>J</i> = 8.84 Hz, 2 H), 7.79 (d, <i>J</i> = 8.59 Hz, 1 H), 7.72 (s, 1 H), 7.69 (s, 1 H), 7.42 (d, <i>J</i> = 7.07 Hz, 1 H), 6.93 (d, <i>J</i> = 8.59 Hz, 2 H), 3.90 (s, 2 H), 3.07 (s, 3 H), 2.24 (s, 3 H)	405	
2-8*	[6-chloro-4-(4-methanesulfonyl-3-methyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.91 (d, <i>J</i> = 8.84 Hz, 1 H), 7.86 (d, <i>J</i> = 8.84 Hz, 1 H), 7.72 (s, 1 H), 7.62 (d, <i>J</i> = 1.52 Hz, 1 H), 7.39 (dd, <i>J</i> = 8.59, 2.02 Hz, 1 H), 6.91 (d, <i>J</i> = 2.27 Hz, 1 H), 6.77 - 6.82 (m, 1 H), 3.74 (s, 2 H), 3.11 (s, 3 H), 2.62 (s, 3 H), 2.26 (s, 3 H)	419	
2-9	[6-chloro-4-(4-methanesulfonyl-2-methyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.89 (s, 1 H), 7.79 (d, <i>J</i> = 8.34 Hz, 1 H), 7.69 (s, 1 H), 7.65 (s, 1 H), 7.53 (br. s, 1 H), 7.43 (dd, 1 H), 6.25 (d, <i>J</i> = 8.59 Hz, 1 H), 3.90 (s, 2 H), 3.05 (s, 3 H), 2.64 (s, 3 H), 2.21 (s, 3 H)	419	
2-10	[4-(4-ethanesulfonyl-2-methyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	7.85 (br. s, 2 H), 7.70 (s, 1 H), 7.48 (d, <i>J</i> = 8.08 Hz, 1 H), 7.24 (br. s, 2 H), 6.25 (d, <i>J</i> = 8.08 Hz, 1 H), 3.90 (s, 2 H), 3.11 (q, <i>J</i> = 7.49 Hz, 2 H), 2.62 (s, 3 H), 2.22 (s, 3 H), 1.29 (t, <i>J</i> = 6.82 Hz, 3 H)	417	
2-11	[4-(3-chloro-4-methanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	(d, <i>J</i> = 8.84 Hz, 1 H), 7.86 (dd, <i>J</i> = 8.72, 5.43 Hz, 1 H), 7.72 (s, 1 H), 7.29 (br. s, 1 H), 7.24 - 7.26 (m, 1 H), 6.99 (d, <i>J</i> = 1.77 Hz, 1 H), 6.80 (dd, <i>J</i> = 9.09, 2.02 Hz, 2 H), 3.91 (s, 2 H), 3.26 (s, 3 H), 2.26 (s, 3 H)	423	
2-12	[6-fluoro-4-(2-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.85 (t, <i>J</i> = 8.34 Hz, 2 H), 7.72 (s, 1 H), 7.49 (d, <i>J</i> = 8.34 Hz, 1 H), 7.35 (d, <i>J</i> = 9.85 Hz, 1 H), 7.29 (br. s, 1 H), 6.45 (t, <i>J</i> = 8.21 Hz, 1 H), 3.91 (s, 2 H), 3.07 (s, 3 H), 2.28 (s, 3 H),	407	

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
2-13	[4-(4-ethanesulfonyl-2-fluorophenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	7.86 (dd, <i>J</i> = 8.97, 5.43 Hz, 1 H), 7.80 (dd, <i>J</i> = 9.73, 2.15 Hz, 1 H), 7.72 (s, 1 H), 7.45 (dd, <i>J</i> = 8.59, 1.26 Hz, 1 H), 7.36 (dd, <i>J</i> = 9.85, 2.27 Hz, 1 H), 7.29 (br. s, 1 H), 6.45 (t, 1 H), 3.91 (s, 2 H), 3.13 (q, <i>J</i> = 7.41 Hz, 2 H), 2.27 (s, 3 H), 1.31 (t, <i>J</i> = 7.33 Hz, 3 H)	421	
2-14	[4-(4-ethanesulfonyl-3-methylphenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	7.88 (d, <i>J</i> = 8.84 Hz, 1 H), 7.84 (dd, <i>J</i> = 8.97, 5.18 Hz, 1 H), 7.70 (s, 1 H), 7.35 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 7.24 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 6.80 (d, <i>J</i> = 2.27 Hz, 1 H), 6.65 (dd, <i>J</i> = 8.72, 2.40 Hz, 1 H), 3.90 (s, 2 H), 3.14 (q, <i>J</i> = 7.49 Hz, 2 H), 2.62 (s, 3 H), 2.25 (s, 3 H), 1.29 (t, <i>J</i> = 7.45 Hz, 3 H)	417	
2-15	[4-(2,5-difluoro-4-methanesulfonylphenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	7.86 (ddd, <i>J</i> = 9.73, 5.43, 5.05 Hz, 2 H), 7.74 (s, 1 H), 7.31 (ddd, <i>J</i> = 9.35, 7.07, 2.53 Hz, 2 H), 6.17 (dd, <i>J</i> = 10.36, 6.32 Hz, 1 H), 3.91 (s, 2 H), 3.20 (s, 3 H), 2.29 (s, 3 H)	425	
2-16	[6-fluoro-4-(3-fluoro-4-methanesulfonylphenoxy)-3-methylnaphthalen-2-yl]-acetic acid	7.83 - 7.90 (m, 2 H), 7.72 (s, 1 H), 7.30 (br. s, 1 H), 7.25 (br. s, 1 H), 6.75 (dd, <i>J</i> = 8.97, 1.89 Hz, 1 H), 6.62 (dd, <i>J</i> = 11.49, 2.15 Hz, 1 H), 3.91 (s, 2 H), 3.21 (s, 3 H), 2.26 (s, 3 H)	407	
2-17	[4-(4-ethanesulfonyl-3-fluorophenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	7.85 (ddd, <i>J</i> = 8.65, 4.23, 4.04 Hz, 2 H), 7.71 (s, 1 H), 7.31 (br. s, 1 H), 7.25 (br. s, 1 H), 6.75 (dd, <i>J</i> = 8.72, 2.15 Hz, 1 H), 6.61 (dd, <i>J</i> = 11.12, 2.27 Hz, 1 H), 3.90 (s, 2 H), 3.29 (q, <i>J</i> = 7.49 Hz, 2 H), 2.25 (s, 3 H), 1.33 (t, <i>J</i> = 7.45 Hz, 3 H)	421	

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
2-18	[4-(2-cyano-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	8.29 (d, <i>J</i> = 2.27 Hz, 1 H), 7.85 (dd, <i>J</i> = 8.97, 2.15 Hz, 2 H), 7.88 (dd, 1 H), 7.74 (s, 1 H), 7.31 (br. s, 2 H), 6.49 (d, <i>J</i> = 8.84 Hz, 1 H), 3.91 (s, 2 H), 3.15 (q, <i>J</i> = 7.41 Hz, 2 H), 2.26 (s, 3 H), 1.33 (t, <i>J</i> = 7.45 Hz, 3 H)	428	
2-19	[4-(3-chloro-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	8.02 (d, <i>J</i> = 8.84 Hz, 1 H), 7.85 (dd, <i>J</i> = 8.97, 5.43 Hz, 1 H), 7.71 (s, 1 H), 7.31 (br. s, 1 H), 7.25 (br. s, 1 H), 6.98 (d, <i>J</i> = 2.27 Hz, 1 H), 6.79 (dd, <i>J</i> = 8.84, 2.27 Hz, 1 H), 3.90 (s, 2 H), 3.41 (q, <i>J</i> = 7.58 Hz, 2 H), 2.25 (s, 3 H), 1.30 (t, <i>J</i> = 7.45 Hz, 3 H)	437	
2-20	[4-(2-chloro-4-methanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	8.12 (d, <i>J</i> = 2.27 Hz, 1 H), 7.86 (dd, <i>J</i> = 8.84, 5.31 Hz, 1 H), 7.73 (s, 1 H), 7.59 (dd, <i>J</i> = 8.72, 2.40 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.25 (br. s, 1 H), 6.41 (d, <i>J</i> = 8.84 Hz, 1 H), 3.91 (s, 2 H), 3.07 (s, 3 H), 2.26 (s, 3 H)	423	
2-21	[4-(2-chloro-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	8.08 (d, <i>J</i> = 2.27 Hz, 1 H), 7.86 (dd, <i>J</i> = 9.09, 5.31 Hz, 1 H), 7.72 (s, 1 H), 7.55 (dd, <i>J</i> = 8.72, 2.15 Hz, 1 H), 7.30 (br. s, 1 H), 7.25 (br. s, 1 H), 6.41 (d, <i>J</i> = 8.84 Hz, 1 H), 3.91 (s, 2 H), 3.13 (q, <i>J</i> = 7.58 Hz, 2 H), 2.26 (s, 3 H), 1.32 (t, <i>J</i> = 7.45 Hz, 3 H)	437	
2-22	{6-fluoro-3-methyl-4-[4-(propane-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	7.85 (t, 1 H), 7.81 (d, <i>J</i> = 8.84 Hz, 2 H), 7.70 (s, 1 H), 7.34 (dd, <i>J</i> = 10.11, 2.53 Hz, 1 H), 7.25 (dd, 1 H), 6.92 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 3.03 - 3.09 (m, 2 H), 2.25 (s, 3 H), 1.71 - 1.81 (m, 2 H), 1.02 (t, <i>J</i> = 7.45 Hz, 3 H)	417	
2-23	{4-[4-(butane-1-sulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid	7.83 - 7.87 (m, 1 H), 7.81 (d, <i>J</i> = 8.84 Hz, 2 H), 7.70 (s, 1 H), 7.34 (dd, <i>J</i> = 10.23, 2.40 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 6.92 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 3.04 - 3.11 (m, 2 H), 2.25 (s, 3 H), 1.68 - 1.76 (m, 2 H), 1.36 - 1.46 (m, 2 H)	431	

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Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺])	Structure
		0.91 (t, <i>J</i> = 7.33 Hz, 3 H)		
2-24	[4-(5-chloro-4-ethanesulfonyl-2-fluorophenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	8.03 (d, <i>J</i> = 10.36 Hz, 1 H), 7.87 (dd, <i>J</i> = 8.84, 5.31 Hz, 1 H), 7.74 (s, 1 H), 7.28 - 7.36 (m, 2 H), 6.43 (d, <i>J</i> = 7.07 Hz, 1 H), 3.91 (s, 2 H), 3.39 (q, <i>J</i> = 7.33 Hz, 2 H), 2.28 (s, 3 H), 1.32 (t, <i>J</i> = 7.45 Hz, 3 H)	455	
2-25	[4-(2-chloro-4-ethanesulfonyl-5-fluorophenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	8.10 (d, <i>J</i> = 6.82 Hz, 1 H), 7.87 (dd, <i>J</i> = 9.47, 5.68 Hz, 1 H), 7.74 (s, 1 H), 7.28 - 7.32 (m, 2 H), 6.09 - 6.16 (m, 1 H), 3.91 (s, 2 H), 3.27 (q, <i>J</i> = 7.41 Hz, 2 H), 2.27 (s, 3 H), 1.34 (t, <i>J</i> = 7.45 Hz, 3 H)	455	
2-26	[4-(4-cyclopentanesulfonylphenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	7.83 - 7.87 (m, 1 H), 7.81 (d, <i>J</i> = 8.84 Hz, 2 H), 7.70 (s, 1 H), 7.35 (dd, <i>J</i> = 10.11, 2.27 Hz, 1 H), 7.24 (dd, <i>J</i> = 10.11, 2.27 Hz, 1 H), 6.91 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 2.21 - 2.26 (m, 3 H), 2.01 - 2.11 (m, 2 H), 1.85 - 1.95 (m, 2 H), 1.73 - 1.81 (m, 2 H), 1.56 - 1.67 (m, 2 H)	443	
2-27	{6-fluoro-4-[4-(4-fluorobenzenesulfonyl)phenoxy]-3-methylnaphthalen-2-yl}-acetic acid	7.92 - 7.98 (m, 2 H), 7.80 - 7.87 (m, 3 H), 7.69 (s, 1 H), 7.28 - 7.32 (m, 1 H), 7.14 - 7.25 (m, 3 H), 6.87 (d, <i>J</i> = 8.84 Hz, 2 H), 3.89 (s, 2 H), 2.22 (s, 3 H)	469	
2-28	[4-(4-benzenesulfonylphenoxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	7.94 (d, <i>J</i> = 7.07 Hz, 1 H), 7.80 - 7.89 (m, 3 H), 7.68 (s, 1 H), 7.49 - 7.59 (m, 3 H), 7.29 - 7.32 (m, 1 H), 7.20 - 7.26 (m, 1 H), 6.86 (d, <i>J</i> = 8.84 Hz, 2 H), 3.89 (s, 2 H), 2.22 (s, 3 H)	451	
2-29	{6-fluoro-3-methyl-4-[4-(toluene-4-sulfonyl)phenoxy]naphthalen-2-yl}-acetic acid	7.82 (t, <i>J</i> = 8.21 Hz, 5 H), 7.68 (s, 1 H), 7.30 (d, <i>J</i> = 8.08 Hz, 2 H), 7.26 (br. s, 2 H), 6.84 (d, <i>J</i> = 8.84 Hz, 2 H), 3.89 (s, 2 H), 2.41 (s, 3 H), 2.22 (s, 3 H)	465	

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Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
2-30	{6-fluoro-4-[4-(4-methoxybenzenesulfonyl)-phenoxy]-3-methylnaphthalen-2-yl}-acetic acid	7.78 - 7.91 (m, 5 H), 7.70 (s, 1 H), 7.30 - 7.34 (m, 1 H), 7.21 - 7.27 (m, 1 H), 6.98 (d, <i>J</i> = 8.84 Hz, 2 H), 6.85 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 3.86 (s, 3 H), 2.23 (s, 3 H)	481	
2-31	{4-[4-(4-chlorobenzenesulfonyl)-phenoxy]-6-fluoro-3-methylnaphthalen-2-yl}-acetic acid	7.82 - 7.89 (m, 5 H), 7.70 (s, 1 H), 7.50 (d, <i>J</i> = 8.84 Hz, 2 H), 7.32 (m, 1 H), 7.24 (m, 1 H), 6.88 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 2.23 (s, 3 H)	485	
2-32**	[6-fluoro-4-(5-methanesulfonylpyridin-2-yloxy)-3-methylnaphthalen-2-yl]-acetic acid	12.50 (s, 1 H), 8.52 (d, <i>J</i> = 2.53 Hz, 1 H), 8.39 (dd, <i>J</i> = 8.59, 2.53 Hz, 1 H), 8.03 (dd, <i>J</i> = 9.09, 5.56 Hz, 1 H), 7.82 (s, 1 H), 7.38 - 7.46 (m, 2 H), 7.30 (dd, <i>J</i> = 10.36, 2.27 Hz, 1 H), 3.84 (s, 2 H), 3.29 (s, 3 H), 2.14 (s, 3 H)	390	
2-33**	[4-(5-ethanesulfonylpyridin-2-yloxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	8.48 (br. s, 1 H), 8.34 (d, <i>J</i> = 8.34 Hz, 1 H), 8.02 (ddd, <i>J</i> = 6.63, 3.79, 3.47 Hz, 1 H), 7.81 (s, 1 H), 7.43 (br. s, 2 H), 7.31 (d, <i>J</i> = 10.11 Hz, 1 H), 3.84 (s, 2 H), 3.36 (br. s, 2 H), 2.14 (s, 3 H), 1.13 (t, <i>J</i> = 6.95 Hz, 3 H)	404	
2-34**	[6-fluoro-4-(5-methanesulfonyl-3-methylpyridin-2-yloxy)-3-methylnaphthalen-2-yl]-acetic acid	8.29 (dd, <i>J</i> = 10.86, 2.02 Hz, 2 H), 8.01 (dd, <i>J</i> = 8.97, 5.68 Hz, 1 H), 7.79 (s, 1 H), 7.39 (td, <i>J</i> = 8.84, 2.53 Hz, 1 H), 7.28 (dd, <i>J</i> = 10.48, 2.65 Hz, 1 H), 3.83 (s, 2 H), 3.25 (s, 3 H), 2.60 (s, 3 H), 2.11 (s, 3 H)	404	
2-35**	[4-(5-ethanesulfonyl-3-methylpyridin-2-yloxy)-6-fluoro-3-methylnaphthalen-2-yl]-acetic acid	8.24 (d, <i>J</i> = 9.35 Hz, 5 H), 8.22 - 8.27 (m, 5 H), 8.01 (dd, <i>J</i> = 9.09, 5.81 Hz, 5 H), 7.79 (s, 5 H), 7.40 (td, <i>J</i> = 8.84, 2.53 Hz, 5 H), 7.31 (dd, <i>J</i> = 10.48, 2.40 Hz, 5 H), 3.83 (s, 2 H), 3.31 (t, 2 H), 2.59 (s, 3 H), 2.10 (s, 3 H), 1.12 (t, <i>J</i> = 7.45 Hz, 3 H)	418	

Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺]	Structure
2-36*	[4-(3-bromo-5-methanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	8.67 (d, <i>J</i> = 2.02 Hz, 1 H), 8.41 (d, <i>J</i> = 2.27 Hz, 1 H), 7.94 (dd, <i>J</i> = 8.97, 5.43 Hz, 1 H), 7.77 (s, 1 H), 7.28 (td, <i>J</i> = 8.84, 2.27 Hz, 1 H), 7.20 (dd, <i>J</i> = 10.23, 2.40 Hz, 1 H), 3.88 (s, 2 H), 3.20 (s, 3 H), 2.22 (s, 3 H)	468	
2-37	[4-(4-dimethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	7.84 (dd, <i>J</i> = 8.84, 5.56 Hz, 1 H), 7.70 (br. s, 3 H), 7.36 (dd, <i>J</i> = 10.23, 2.40 Hz, 1 H), 7.25 (dd, <i>J</i> = 10.23, 2.40 Hz, 1 H), 6.90 (d, <i>J</i> = 8.84 Hz, 2 H), 3.90 (s, 2 H), 2.72 (s, 6 H), 2.25 (s, 3 H)	418	
2-38**	{6-fluoro-3-methyl-4-[4-(pyrrolidine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	12.51 (s, 1 H), 8.05 (dd, <i>J</i> = 9.09, 5.56 Hz, 1 H), 7.85 (s, 1 H), 7.77 (d, <i>J</i> = 9.09 Hz, 2 H), 7.43 (td, <i>J</i> = 8.84, 2.53 Hz, 1 H), 7.31 (dd, <i>J</i> = 10.61, 2.53 Hz, 1 H), 3.86 (s, 2 H), 3.11 (br. s, 4 H), 2.17 (s, 3 H), 1.64 (ddd, <i>J</i> = 6.38, 3.66, 3.35 Hz, 4 H)	444	
2-39**	[4-(4-diethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	12.51 (s, 1 H), 8.05 (dd, <i>J</i> = 8.97, 5.68 Hz, 1 H), 7.84 (s, 1 H), 7.74 (d, <i>J</i> = 9.09 Hz, 2 H), 7.43 (td, <i>J</i> = 8.84, 2.53 Hz, 1 H), 7.30 (dd, <i>J</i> = 10.36, 2.53 Hz, 1 H), 6.94 (d, <i>J</i> = 9.09 Hz, 2 H), 3.86 (s, 2 H), 3.13 (q, <i>J</i> = 7.07 Hz, 4 H), 2.17 (s, 3 H), 1.02 (t, <i>J</i> = 7.07 Hz, 6 H)	446	
2-40**	{6-fluoro-3-methyl-4-[4-(morpholine-4-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	12.53 (br. s, 1 H), 8.06 (dd, <i>J</i> = 8.97, 5.68 Hz, 1 H), 7.85 (s, 1 H), 7.70 (d, <i>J</i> = 8.84 Hz, 2 H), 7.44 (td, <i>J</i> = 8.84, 2.78 Hz, 1 H), 7.33 (dd, <i>J</i> = 10.23, 2.65 Hz, 1 H), 7.00 (d, <i>J</i> = 8.59 Hz, 2 H), 3.87 (s, 2 H), 3.59 - 3.65 (m, 4 H), 2.84 (t, 4 H), 2.18 (s, 3 H)	460	
2-41**	{6-fluoro-3-methyl-4-[4-(4-methyl-piperazine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	12.53 (br. s, 1 H), 8.07 (dd, <i>J</i> = 9.09, 5.56 Hz, 1 H), 7.87 (s, 1 H), 7.76 (d, <i>J</i> = 8.84 Hz, 2 H), 7.45 (td, <i>J</i> = 8.84, 2.53 Hz, 1 H), 7.31 (dd, <i>J</i> = 10.23, 2.40 Hz, 1 H), 7.04 (d, <i>J</i> = 9.09 Hz, 2 H), 3.86 (s, 2 H), 3.44 (br. s, 8 H), 2.77 (s, 3 H), 2.18 (s, 3 H)	473	

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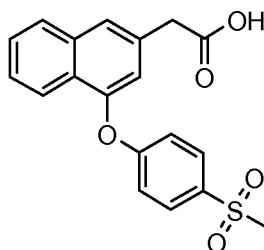
Example No.	Systematic Name	¹ H NMR (400 MHz, CDCl ₃) δ ppm	MS (ESI ⁺ , [(M+H) ⁺])	Structure
2-42**	{4-[4-(4,4-difluoro-piperidine-1-sulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid	12.53 (s, 1 H), 8.05 (dd, <i>J</i> = 9.09, 5.56 Hz, 1 H), 7.85 (s, 1 H), 7.75 (d, <i>J</i> = 8.84 Hz, 2 H), 7.43 (td, <i>J</i> = 8.72, 2.53 Hz, 1 H), 7.32 (dd, <i>J</i> = 10.36, 2.53 Hz, 1 H), 7.00 (d, <i>J</i> = 8.84 Hz, 2 H), 3.86 (s, 2 H), 3.04 - 3.11 (m, 4 H), 2.18 (s, 3 H), 1.98 - 2.10 (m, 4 H)	494	
2-43	{6-fluoro-3-methyl-4-[4-(2-oxa-6-aza-spiro[3.3]heptan-6-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid	7.85 (dd, <i>J</i> = 8.97, 5.43 Hz, 1 H), 7.75 (d, <i>J</i> = 8.84 Hz, 2 H), 7.70 (s, 1 H), 7.33 (dd, <i>J</i> = 9.98, 2.15 Hz, 1 H), 6.93 (d, <i>J</i> = 8.84 Hz, 2 H), 4.64 (s, 4 H), 3.95 (s, 4 H), 3.90 (s, 2 H), 2.25 (s, 3 H)	472	
2-44	[4-(4-cyano-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid	7.83 (dd, <i>J</i> = 9.09, 5.56 Hz, 1 H), 7.69 (s, 1 H), 7.58 (d, <i>J</i> = 8.84 Hz, 2 H), 7.32 (dd, <i>J</i> = 10.11, 2.27 Hz, 1 H), 7.24 (dd, <i>J</i> = 10.11, 2.27 Hz, 1 H), 6.86 (d, <i>J</i> = 8.84 Hz, 2 H), 3.89 (s, 2 H), 2.24 (s, 3 H)	336	
2-45	[6-chloro-4-(4-cyano-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid	7.78 (d, <i>J</i> = 8.84 Hz, 1 H), 7.70 (d, <i>J</i> = 1.77 Hz, 1 H), 7.67 (s, 1 H), 7.58 (d, <i>J</i> = 8.84 Hz, 2 H), 7.42 (dd, <i>J</i> = 8.84, 2.02 Hz, 1 H), 6.85 (d, <i>J</i> = 8.84 Hz, 2 H), 3.89 (s, 2 H), 2.23 (s, 3 H)	352	

* CD₃OD was used as the solvent for ¹H NMR; ** DMSO-*d*₆ was used as the solvent for ¹H NMR.

EXAMPLE 3-1

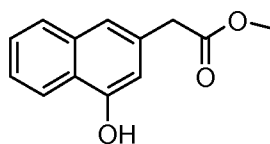
5

[4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid



(4-Hydroxy-naphthalen-2-yl)-acetic acid methyl ester

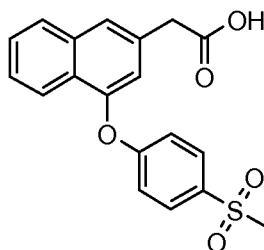
- 96 -



To a solution of (4-benzyloxy-6-chloro-naphthalen-2-yl)-acetic acid methyl ester (340 mg, 1.0 mmol, prepared using a method analogous to the one described above for the preparation of 4-benzyloxy-6-fluoro-naphthalene-2-carboxylic acid methyl ester, 1st-7th step for example **1-1**) in methanol was added 10% palladium on carbon (10 mg). The resulting mixture was vigorously stirred at room temperature overnight under a hydrogen atmosphere (balloon) and then filtered. The filtrate was concentrated *in vacuo* to give (4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (200 mg, 92.6%) as a white solid.

10

[4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid



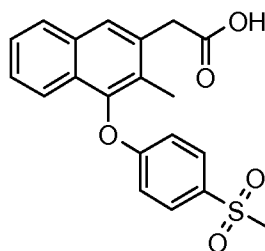
Starting with (4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (108 mg, 0.5 mmol) and 1-fluoro-4-methanesulfonyl-benzene (174 mg, 1.0 mmol), using a method analogous to the one described for example **1-1**, the final two steps), 4-(4-methanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid (65.8 mg, 37%) was obtained as a white solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.89 - 7.94 (m, 4 H), 7.71 (s, 1 H), 7.54 (dt, *J* = 8.08, 4.04 Hz, 1 H), 7.48 (s, 2 H), 7.14 - 7.19 (m, 3 H), 3.80 (s, 2 H), 3.11 (s, 3 H); MS calcd. for C₁₉H₁₆O₅S 356, obsd. (ESI⁺) [(M+H)⁺]

20 357.

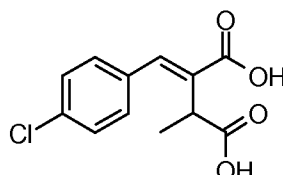
EXAMPLE 3-2

[4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid

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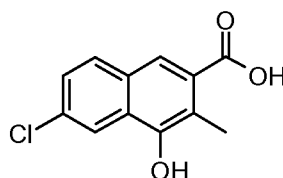


2-(4-Chloro-benzylidene)-3-methyl-succinic acid



After careful addition of absolute methanol (0.1 mL) to a suspension of sodium
 5 hydride (60% in mineral oil, 16 g, 0.40 mol) in anhydrous toluene (200 mL), a
 solution of 4-chloro-benzaldehyde (28 g, 0.20 mol) and 2-methyl-succinic acid
 dimethyl ester (48 g, 0.30 mol) in anhydrous toluene (100 mL) was added
 dropwise at room temperature under a stream of nitrogen. After being stirred at
 room temperature for 2 hours, the resulting mixture was diluted by adding 2 N
 10 sodium hydroxide (200 mL) dropwise, then heated to 80 °C, and stirred at the
 same temperature for 2 hours. After being cooled to room temperature naturally,
 the aqueous layer was separated, washed with ethyl acetate (100 mL × 3), then
 acidified with 2 N hydrochloric acid to pH 2, and extracted with ethyl acetate (150
 mL × 3). The combined organic layers were dried over sodium sulfate, and
 15 concentrated *in vacuo*. The residue was precipitated from ethyl acetate/petroleum
 ether (10:1) to give 2-(4-chloro-benzylidene)-3-methyl-succinic acid (13.4 g, 26%)
 as a yellow solid.

6-Chloro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid

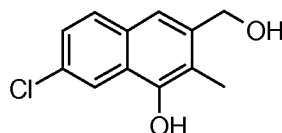


20 To a flask containing trifluoromethanesulfonic acid (40 mL), 2-(4-chloro-
 benzylidene)-3-methyl-succinic acid (14.0 g) was added in portions. After being
 stirred at room temperature for 18 hours, the resulting mixture was poured onto
 ice-water, and stirred for 15 minutes. The formed precipitate was collected by

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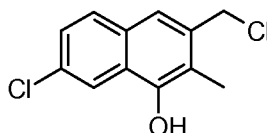
filtration, and dissolved in ethyl acetate (150 mL). The solution was dried over sodium sulfate, and concentrated *in vacuo*. The residue was precipitated from ethyl acetate/petroleum ether (1:10) to afford 6-chloro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid (12.7 g, 97.6%) as a pink solid.

5

7-Chloro-3-hydroxymethyl-2-methyl-naphthalen-1-ol

To a slurry of lithium aluminum hydride (4.1 g) in tetrahydrofuran (80 mL) was added a solution of 6-chloro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid (12.7 g, 54 mmol) in tetrahydrofuran (80 mL) at 0 °C under a nitrogen atmosphere. After being heated at 60 °C for 5 hours, the resulting mixture was cooled to 0 °C and treated with 1 N hydrochloric acid to quench the reaction. The aqueous layer was extracted with ethyl acetate (100 mL x 4). The combined organic layers were washed with brine (200 mL x 2), dried over sodium sulfate and concentrated *in vacuo* to give 7-chloro-3-hydroxymethyl-2-methyl-naphthalen-1-ol (8.5 g, 71%) as a white solid.

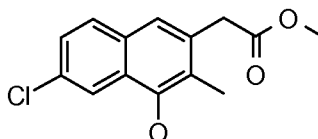
15

7-Chloro-3-chloromethyl-2-methyl-naphthalen-1-ol

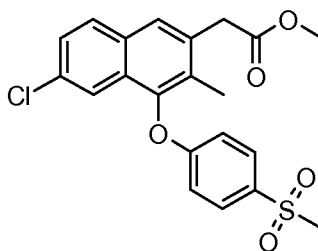
To a solution of triphenylphosphine (20 g, 75.6 mmol) in anhydrous tetrahydrofuran (165 mL) was added carbon tetrachloride (50 mL). After the mixture was stirred at room temperature for 20 minutes, 7-chloro-3-hydroxymethyl-2-methyl-naphthalen-1-ol (8.4 g, 37.8 mmol) was added as a solid under a nitrogen atmosphere. After being stirred at reflux for 2 hours, the resulting mixture was cooled to room temperature, and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 5% ethyl acetate in petroleum ether) to afford 7-chloro-3-chloromethyl-2-methyl-naphthalen-1-ol (8.7 g, 96%) as a white solid.

25

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(6-Chloro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester

To a flask containing 7-chloro-3-chloromethyl-2-methyl-naphthalen-1-ol (8.64 g, 36 mmol), bis(triphenylphosphine)dichloropalladium(II) (1.26 g, 1.8 mmol) and potassium carbonate (5.2 g, 37.8 mmol), which was evacuated and then filled with carbon monoxide (balloon), methanol (30 mL) and tetrahydrofuran (60 mL) were added by means of a syringe. After being stirred at room temperature under a carbon monoxide atmosphere overnight, the resulting mixture was diluted with water (100 mL), and extracted with ethyl acetate (100 mL). The organic layer was washed with water (50 mL × 2). The combined aqueous layers were extracted with ethyl acetate (150 mL), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (elution with 20% ethyl acetate in petroleum ether) to afford (6-chloro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (7.0 g, 74 %) as an orange solid.

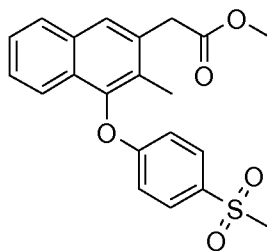
[6-Chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid methyl ester

Starting with (6-chloro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (132 mg, 0.5 mmol) and 1-fluoro-4-methanesulfonyl-benzene (174 mg, 1.0 mmol), using a method analogous to the one described for the methyl ester of example 1-1, [6-chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (70 mg, 33%) was obtained as a yellow oil.

25

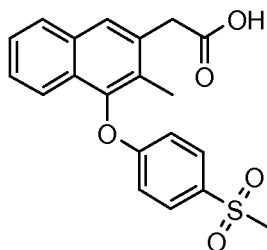
- 100 -

[4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid methyl ester



To a solution of [6-chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (110 mg, 0.26 mmol) in methanol (3 mL) was added 10% palladium on carbon (10 mg). The resulting mixture was vigorously stirred at room temperature overnight under a hydrogen atmosphere (balloon) and then filtered. The filtrate was concentrated *in vacuo* to give [4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (68 mg, 67%) as a colorless oil which was directly used in the next step without further purification.

[4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid



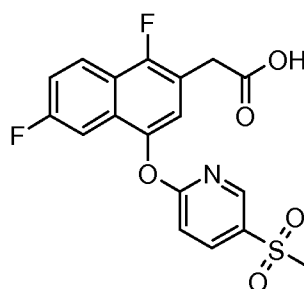
Starting with [6-chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (68 mg), using a method analogous to the one described for example **1-1**, final step, [4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid (24 mg, 37%) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.84 (d, J = 8.84 Hz, 3 H), 7.70 - 7.75 (m, 2 H), 7.45 (ddd, J = 23.43, 7.26, 6.69 Hz, 2 H), 6.94 (d, J = 8.84 Hz, 2 H), 3.92 (s, 2 H), 3.04 (s, 3 H), 2.26 (s, 3 H); MS calcd. for $\text{C}_{20}\text{H}_{18}\text{O}_5\text{S}$ 370, obsd. (ESI^+) $[(\text{M}+\text{H})^+]$ 371.

20

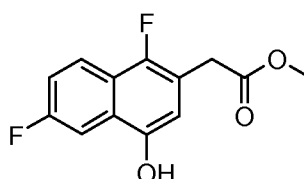
EXAMPLE 4-1

[1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid

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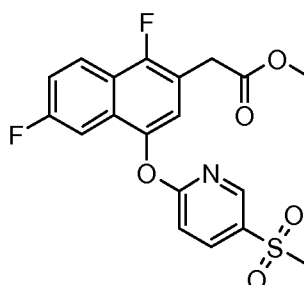
(1,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester



- 5 To a solution of (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (100 mg, 0.277 mmol) in acetonitrile (3 mL) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (255 mg, 0.72 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight, and diluted with water, then extracted with ethyl acetate (20 mL × 3). The combined
10 organic layers were washed with brine (20 mL × 3), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% ethyl acetate in petroleum ether) to give (1,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (60 mg, 86%) as a yellow solid. MS calcd. for C₁₃H₁₀F₂O₃ 252, obsd. (ESI⁺) [(M+H)⁺] 253.

15

[1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester

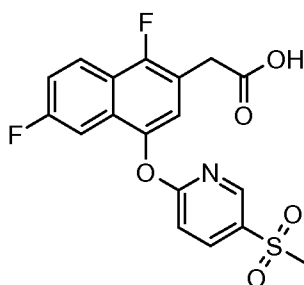


- A mixture of (1,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (50
20 mg, 0.198 mmol), 2-bromo-5-methanesulfonyl-pyridin (52 mg, 0.22 mmol),

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potassium carbonate (60 mg, 0.434 mmol) and *N,N*-dimethylformamide (2.0 mL) was heated at 70 °C for 3 hours. The resulting mixture was cooled to room temperature, acidified with 1 N hydrochloric acid to pH 3, and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over sodium sulfate, and concentrated *in vacuo* to afford [1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (70 mg, 87%) as a white solid which was used in the next step without further purification.

[1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid

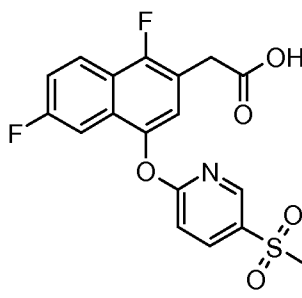


Starting with [1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (70 mg, 0.172 mmol), using a method analogous to the one described for example 1-1, final step, [1,6-difluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid (10 mg, 15%) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.56 (d, *J* = 2.53 Hz, 1 H), 8.39 (dd, *J* = 8.84, 2.53 Hz, 1 H), 8.19 (dd, *J* = 9.35, 5.31 Hz, 1 H), 7.60 (td, *J* = 8.97, 2.53 Hz, 1 H), 7.49 - 7.54 (m, 1 H), 7.43 - 7.48 (m, 2 H), 3.82 (s, 2 H), 3.28 (s, 3 H); MS calcd. for C₁₈H₁₃F₂NO₅S 393, obsd. (ESI⁺) [(M+H)⁺] 394.

EXAMPLE 4-2

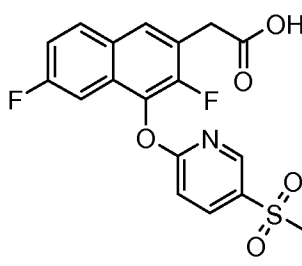
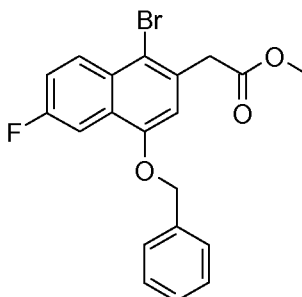
[1,6-difluoro-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid

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Starting with (1,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (50 mg, 0.198 mmol) and 2-bromo-5-ethanesulfonyl-pyridine (52 mg, 0.208 mmol), using a method analogous to the one described for example **4-1**, [1,6-difluoro-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid (10 mg, 12%) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 8.52 (d, 1 H), 8.34 (dd, 1 H), 8.19 (dd, 1 H), 7.42 - 7.76 (m, 4 H), 3.78 - 3.86 (m, 2 H), 3.37 - 3.40 (m, 2 H), 1.12 (t, 3 H); MS calcd. for $\text{C}_{19}\text{H}_{15}\text{F}_2\text{NO}_5\text{S}$ 407, obsd. (ESI^+) $[(\text{M}+\text{H})^+]$ 408.

10

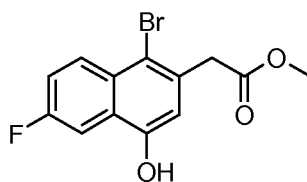
EXAMPLE 5-1**[4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid**15 **(4-benzyloxy-1-bromo-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester**

To a stirred solution of (4-benzyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (350 mg, 1.08 mmol) in acetonitrile (10 mL) was added *N*-

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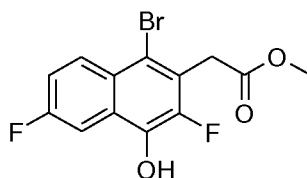
bromosuccinimide (385 mg, 2.16 mmol). After being stirred at room temperature for 1 hour, the resulting mixture was diluted with water (20 mL), and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with water (15 mL) and brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (gradient elution with 0-20% ethyl acetate in hexanes) to afford (4-benzyloxy-1-bromo-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (400 mg, 92%) as a white solid.

(1-bromo-6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester



To a solution of (4-benzyloxy-1-bromo-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (400 mg, 0.992 mmol) in ethyl acetate (10 mL) was added zinc bromide (670 mg, 2.978 mmol) and 10% palladium on carbon (40 mg) under a hydrogen atmosphere (balloon). After being stirred at room temperature for 1 hour, the resulting mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC (gradient elution with 50-80% 0.1% trifluoroacetic acid in water in acetonitrile, 8 minutes) to afford (1-bromo-6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (200 mg, 64.4%) as a white solid.

(1-bromo-3,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester

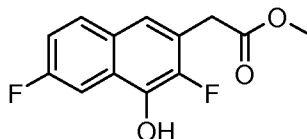


To a solution of (1-bromo-6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (135 mg, 0.433 mmol) in acetonitrile (4 mL) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (230 mg, 0.650 mmol) at 0 °C. The resulting mixture was stirred at room temperature overnight, then diluted with water (10 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over sodium

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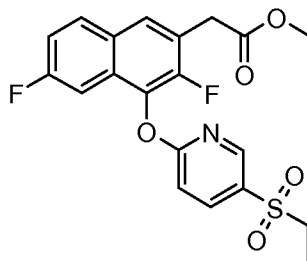
sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% ethyl acetate in petroleum ether) to give (1-bromo-3,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (60 mg, 42%) as a yellow solid. MS calcd. for C₁₃H₉BrF₂O₃ 330, obsd. (ESI⁺) [(M+H)⁺] 331.

5 **(3,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester**



To a solution of (1-bromo-3,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (50 mg, 0.152 mmol) in methanol was added 10% palladium on carbon (10 mg). After being stirred at room temperature under a hydrogen
10 atmosphere overnight, the resulting mixture was filtered. The filtrate was concentrated *in vacuo* to afford (3,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (25 mg, 65%) as a white solid.

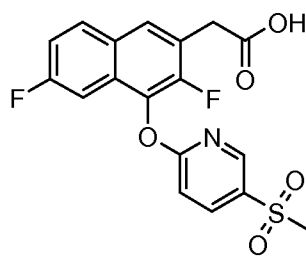
15 **[4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid methyl ester**



Starting with (3,6-difluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (25 mg, 0.099 mmol) and 2-bromo-5-ethanesulfonyl-pyridine (28 mg, 0.112 mmol), using a method analogous to the one described for the methyl ester of example
20 **1-1**, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid methyl ester (20 mg, 48%) was obtained as a white solid, which was used in the next step without further purification.

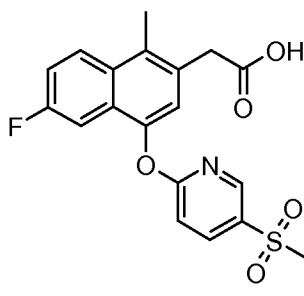
25 **[4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid**

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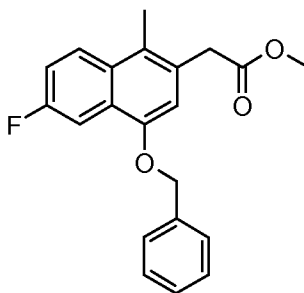


Starting with [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid methyl ester (20 mg, 0.475 mmol), using a method analogous to the one described for example **1-1**, final step, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3,6-difluoro-naphthalen-2-yl]-acetic acid (1.9 mg) was obtained as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.51 (d, *J* = 2.02 Hz, 1 H), 8.37 (dd, *J* = 8.72, 2.65 Hz, 1 H), 8.09 (dd, *J* = 9.09, 5.56 Hz, 1 H), 7.92 (d, *J* = 6.82 Hz, 1 H), 7.55 (d, *J* = 8.59 Hz, 1 H), 7.51 (dd, *J* = 10.23, 2.65 Hz, 1 H), 7.42 - 7.48 (m, 1 H), 3.74 (s, 2 H), 3.37 (t, 2 H), 1.14 (t, *J* = 7.33 Hz, 3 H); MS calcd. for C₁₉H₁₅F₂NO₅S 407, obsd. (ESI⁺) [(M+H)⁺] 408.

EXAMPLE 6-1**[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid**

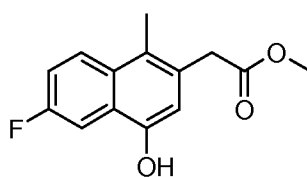
15

(4-benzyloxy-6-fluoro-1-methyl-naphthalen-2-yl)-acetic acid methyl ester

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To a solution of (4-benzyloxy-1-bromo-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (100 mg, 0.248 mmol, prepared using an analogous procedure to the first step of example **5-1**), methylboronic acid (19.3 mg, 0.322 mmol), potassium phosphate (184 mg, 0.868 mmol) and tricyclohexylphosphine (69.4 mg, 0.248 mmol) in toluene (4.0 mL) and water (2 drops) was added palladium acetate (3 mg, 0.0124 mmol) under a nitrogen atmosphere. After being heated under microwave conditions (150 °C, 30 minutes), the mixture was cooled to room temperature, then diluted with water (10 mL), and extracted with ethyl acetate (15 mL × 2). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to afford (4-benzyloxy-6-fluoro-1-methyl-naphthalen-2-yl)-acetic acid methyl ester (50 mg, 59.5%) as a light yellow solid.

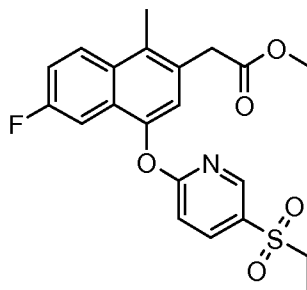
(6-fluoro-4-hydroxy-1-methyl-naphthalen-2-yl)-acetic acid methyl ester



15

To a solution of (4-benzyloxy-6-fluoro-1-methyl-naphthalen-2-yl)-acetic acid methyl ester (50 mg) in methanol was added 10% palladium on carbon (10 mg). After being stirred at room temperature under a hydrogen atmosphere overnight, the resulting mixture was filtered. The filtrate was concentrated *in vacuo* to afford (6-fluoro-4-hydroxy-1-methyl-naphthalen-2-yl)-acetic acid methyl ester (30 mg) as a white solid.

[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid methyl ester

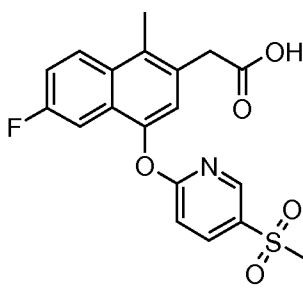


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Starting with (6-fluoro-4-hydroxy-1-methyl-naphthalen-2-yl)-acetic acid methyl ester (18 mg, 0.073 mmol) and 2-bromo-5-ethanesulfonyl-pyridine (27 mg, 0.109 mmol), using a method analogous to the one described for the methyl ester of example 1-1, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid methyl ester (22.7 mg, 75%) was obtained as a light yellow solid.

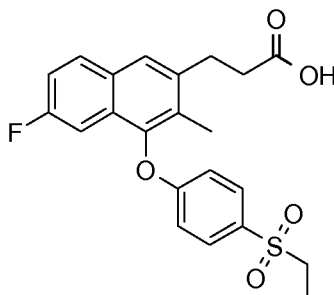
[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid



Starting with [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid methyl ester (22.7 mg, 0.054 mmol), using a method analogous to the one described for example 1-1, final step, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-1-methyl-naphthalen-2-yl]-acetic acid was obtained (10 mg) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.54 (d, *J* = 2.53 Hz, 1 H), 8.20 - 8.30 (m, 2 H), 7.35 - 7.45 (m, 2 H), 7.28 (t, *J* = 4.42 Hz, 2 H), 3.88 (s, 2 H), 3.26 (q, *J* = 7.33 Hz, 2 H), 2.67 (s, 3 H), 1.25 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₀H₁₈FNO₅S 403, obsd. (ESI⁺) [(M+H)⁺] 404.

EXAMPLE 7-1

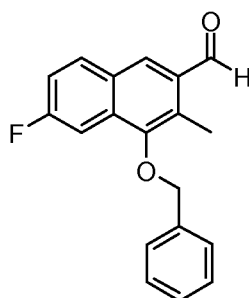
3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid



20

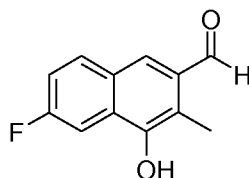
4-benzyloxy-6-fluoro-3-methyl-naphthalene-2-carbaldehyde

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To a solution of (4-benzyloxy-6-fluoro-3-methyl-naphthalen-2-yl)-methanol (180 mg, 0.6 mmol) in dichloromethane (10 mL) was added pyridinium chlorochromate (260 mg, 1.2 mmol) in portions. After being stirred at room temperature for 3 hours, the resulting dark mixture was diluted with diethyl ether, and stirred at room temperature for 10 minutes. The mixture was filtered through a short silica gel column. The filtrate was concentrated *in vacuo* to give 4-benzyloxy-6-fluoro-3-methyl-naphthalene-2-carbaldehyde (165 mg, 93%) as a white solid, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.31 (s, 1 H), 8.16 (s, 1 H), 8.00 (dd, *J* = 8.84, 5.56 Hz, 1 H), 7.73 (dd, *J* = 10.48, 2.40 Hz, 1 H), 7.55 (d, *J* = 6.82 Hz, 2 H), 7.39 - 7.49 (m, 2 H), 7.32 (td, *J* = 8.65, 2.65 Hz, 1 H), 4.99 (s, 2 H), 2.75 (s, 3 H).

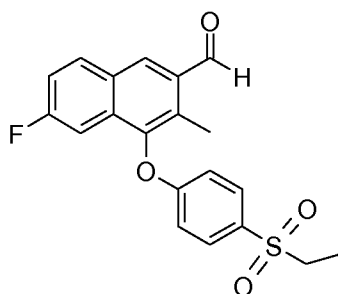
6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carbaldehyde



To a solution of 4-benzyloxy-6-fluoro-3-methyl-naphthalene-2-carbaldehyde (165 mg, 0.56 mmol) in ethyl acetate (5 mL) was added 10% palladium on carbon (7 mg). The resulting mixture was stirred vigorously under a hydrogen atmosphere (balloon) for 4 hours, and then filtered. The filtrate was concentrated *in vacuo* to give 6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carbaldehyde (115 mg, 99 %) as a yellow solid which was directly used in the next step without further purification.

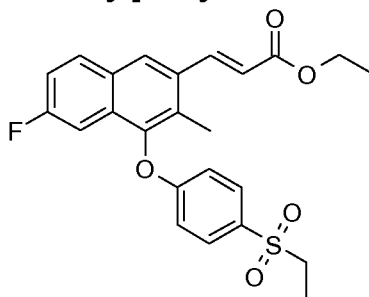
4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalene-2-carbaldehyde

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Starting with 6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carbaldehyde (115 mg, 0.6 mmol) and 1-ethanesulfonyl-4-fluoro-benzene (226 mg, 1.2 mmol), using a method analogous to the one described for the methyl ester of example **1-1**, 4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalene-2-carbaldehyde (120 mg, 57%) was obtained as a yellow solid which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.35 (s, 1 H), 8.32 (s, 1 H), 8.07 (dd, *J* = 8.97, 5.68 Hz, 1 H), 7.84 (d, *J* = 9.09 Hz, 2 H), 7.33 - 7.45 (m, 2 H), 6.94 (d, *J* = 8.84 Hz, 2 H), 3.12 (q, *J* = 7.41 Hz, 2 H), 2.59 (s, 3 H), 1.31 (t, *J* = 7.45 Hz, 3 H).

3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acrylic acid ethyl ester

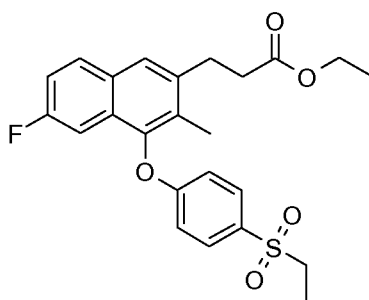


To a suspension of sodium hydride (15 mg, 0.37 mmol, 60% in mineral oil) in anhydrous tetrahydrofuran (1 mL) was added triethyl phosphonoacetate (83 mg, 0.37 mmol) in anhydrous tetrahydrofuran (2 mL) dropwise at 0 °C. After the mixture was warmed naturally to room temperature and stirred at room temperature for 30 minutes, a solution of 4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalene-2-carbaldehyde (120 mg, 0.33 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. The resulting mixture was diluted with water (10 mL), and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*.

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The residue was purified by column chromatography (20% ethyl acetate in petroleum ether) to afford 3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acrylic acid ethyl ester (80 mg, 56%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.02 - 8.08 (m, 2 H), 7.90 (dd, *J* = 9.22, 5.43 Hz, 1 H), 7.83 (d, *J* = 8.84 Hz, 2 H), 7.34 (dd, *J* = 10.23, 2.15 Hz, 1 H), 7.28 - 7.31 (m, 1 H), 6.94 (d, *J* = 8.59 Hz, 2 H), 6.53 (d, *J* = 15.66 Hz, 1 H), 4.32 (q, *J* = 7.07 Hz, 2 H), 3.11 (q, *J* = 7.58 Hz, 2 H), 1.38 (t, *J* = 7.20 Hz, 3 H), 1.30 (t, *J* = 7.45 Hz, 3 H).

3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid ethyl ester



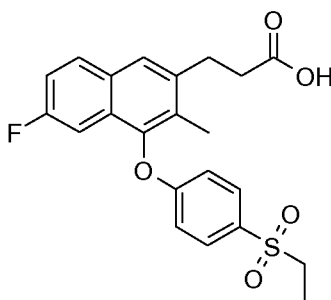
10

To a solution of 3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acrylic acid ethyl ester (40 mg, 0.09 mmol) in ethyl acetate (3 mL) was added 10% palladium on carbon (4 mg). The resulting mixture was stirred vigorously under a hydrogen (balloon) atmosphere overnight, and then filtered. The filtrate was concentrated *in vacuo* to give 3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid ethyl ester (30 mg, 75 %) as a yellow solid, which was used for the next step without any further purification.

15

3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid

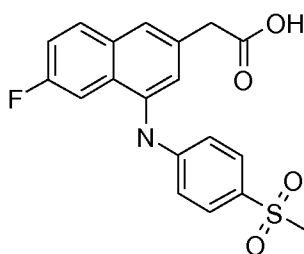
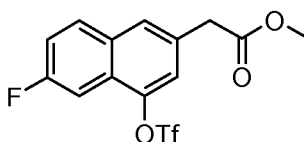
20



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Starting with 3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid ethyl ester (30 mg, 0.068 mmol), using a method analogous to the one described for example **1-1**, final step, 3-[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid (19 mg, 68%) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.78 - 7.85 (m, 3 H), 7.63 (s, 1 H), 7.32 (dd, *J* = 10.11, 2.27 Hz, 1 H), 7.24 (dd, 1 H), 6.91 (d, *J* = 8.84 Hz, 2 H), 3.08 - 3.19 (m, 4 H), 2.80 (t, *J* = 7.83 Hz, 2 H), 2.27 (s, 3 H), 1.30 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₂H₂₁FO₅S 416, obsd. (ESI⁺) [(M+H)⁺] 417.

10

EXAMPLE 8-1**[6-fluoro-4-(4-methanesulfonyl-phenylamino)-naphthalen-2-yl]-acetic acid****(6-fluoro-4-trifluoromethanesulfonyloxy-naphthalen-2-yl)-acetic acid methyl ester**

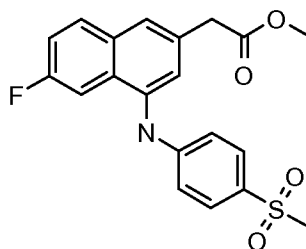
15

To a mixture of (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (350 mg, 1.5 mmol) and trifluoromethanesulfonic anhydride (506 mg, 1.8 mmol) in dichloromethane (20 mL), which was cooled to 0 °C in an ice bath, pyridine (0.6 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 hours and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL). The resulting solution was washed with water, 1 N aqueous hydrochloric acid, water, and brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (0-30% ethyl acetate in hexanes) to afford (6-fluoro-4-trifluoromethanesulfonyloxy-naphthalen-2-yl)-acetic acid methyl ester (450 mg, 82%) as a light yellow solid.

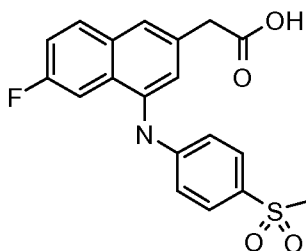
25

[6-fluoro-4-(4-methanesulfonyl-phenylamino)-

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naphthalen-2-yl]-acetic acid methyl ester

To a solution of (6-fluoro-4-trifluoromethanesulfonyloxy-naphthalen-2-yl)-acetic acid methyl ester (115 mg, 0.31 mmol) and 4-methanesulfonyl-phenylamine (59 mg, 0.35 mmol) in *N,N*-dimethylformamide (3 mL), was added (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (39 mg, 0.063 mmol), tris(dibenzylideneacetone)dipalladium(0) (14 mg, 0.016 mmol), and cesium carbonate (102 mg, 0.31 mmol). After being heated under microwave conditions (160 °C, 15 minutes), the resulting mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL × 3). The organic layer was washed with brine, then dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (gradient elution with 0-50% ethyl acetate in hexanes) to afford [6-fluoro-4-(4-methanesulfonyl-phenylamino)-naphthalen-2-yl]-acetic acid methyl ester (84.0 mg, 69% yield) as a yellow solid.

[6-fluoro-4-(4-methanesulfonyl-phenylamino)-naphthalen-2-yl]-acetic acid

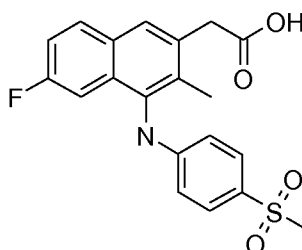
Starting with [6-fluoro-4-(4-methanesulfonyl-phenylamino)-naphthalen-2-yl]-acetic acid methyl ester (30 mg), using a method analogous to the one described for example **1-1**, final step, [6-fluoro-4-(4-methanesulfonyl-phenylamino)-naphthalen-2-yl]-acetic acid (17 mg) was obtained as a white solid. ¹H NMR (400 MHz, CD₃OD) δ ppm (dd, *J* = 9.09, 5.56 Hz, 1 H), 7.67 - 7.72 (m, 2 H), 7.66 (br. s., 1 H), 7.61 (dd, *J* = 10.99, 2.65 Hz, 1 H), 7.49 (s, 1 H), 7.30 - 7.36 (m, 1 H), 6.95 - 7.00

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(m, 2 H), 3.77 (s, 2 H), 3.06 (s, 3 H); MS cald. for $C_{19}H_{16}FNO_4S$ 373, obsd. (ESI⁺) [(M+H)⁺] 374.

EXAMPLE 8-2

5 **[6-fluoro-4-(4-methanesulfonyl-phenylamino)-3-methyl-naphthalen-2-yl]-acetic acid**

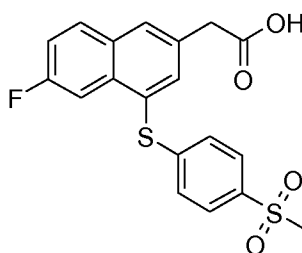


Starting with 6-fluoro-4-hydroxy-3-methyl-naphthalene-2-carboxylic acid methyl ester (36 mg), using a method analogous to the one described for example 8-1, 10 [6-fluoro-4-(4-methanesulfonyl-phenylamino)-3-methyl-naphthalen-2-yl]-acetic acid (20 mg) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.85 (dd, *J* = 8.97, 5.68 Hz, 1 H), 7.76 (s, 1 H), 7.70 (d, *J* = 8.84 Hz, 2 H), 7.47 (dd, *J* = 10.36, 2.27 Hz, 1 H), 6.56 (s, 2 H), 5.97 (s, 1 H), 3.92 (s, 2 H), 3.02 (s, 3 H), 2.36 (s, 3 H); MS cald. for $C_{20}H_{18}FNO_4S$ 387, obsd. (ESI⁺) [(M+H)⁺] 388.

15

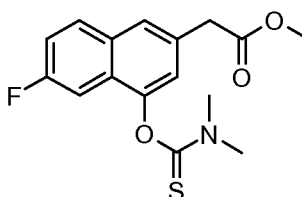
EXAMPLE 9-1

[6-fluoro-4-(4-methanesulfonyl-phenylsulfanyl)-naphthalen-2-yl]-acetic acid



(4-dimethylthiocarbamoyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester

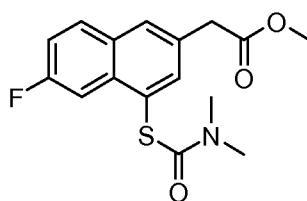
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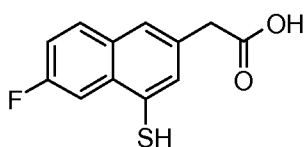
- A mixture of (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (500 mg, 2.14 mmol), finely ground potassium carbonate (591 mg, 4.28 mmol), and *N,N*-dimethylformamide (10 mL) was stirred at room temperature for 20 minutes. Dimethylthiocarbamoyl chloride (290 mg, 2.35 mmol) was added in one portion.
- 5 After being stirred for 2 hours, the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with water (15 mL) and brine (20 mL), then dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (gradient elution with 0-30% ethyl acetate in hexanes) to afford
- 10 (4-dimethylthiocarbamoyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (491 mg, 71.5%) as a yellow oil.

(4-dimethylcarbamoylsulfanyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester



- 15 Neat (4-dimethylthiocarbamoyloxy-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (100 mg, 0.31 mmol) was heated at 240 °C for 1 hour with rigorous exclusion of air. The resulting brown oil was then purified by flash column chromatography (gradient elution with 20-30% ethyl ester in hexanes) to afford
- 20 (4-dimethylcarbamoylsulfanyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (40 mg, 40%) as a yellow oil.

(6-fluoro-4-mercapto-naphthalen-2-yl)-acetic acid

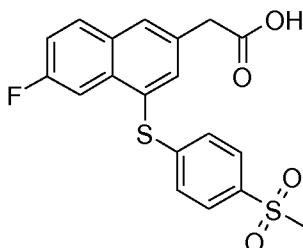


- 25 A solution of (4-dimethylcarbamoylsulfanyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (40 mg, 0.13 mmol) and potassium hydroxide (72 mg, 1.3 mmol) in methanol (10 mL) was heated at reflux for 3 hours. The resulting mixture was

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cooled to room temperature, diluted with water (10 mL), acidified with 2 N hydrochloric acid, and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with water and brine, then dried over sodium sulfate and concentrated *in vacuo* to afford crude (6-fluoro-4-mercapto-naphthalen-2-yl)-acetic acid (30 mg) as a yellow solid.

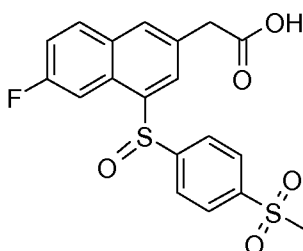
[6-fluoro-4-(4-methanesulfonyl-phenylsulfanyl)-naphthalen-2-yl]-acetic acid



To a solution of (6-fluoro-4-mercapto-naphthalen-2-yl)-acetic acid (30 mg, 0.127 mmol) in *N,N*-dimethylformamide (2 mL), was added 1-fluoro-4-methanesulfonyl-benzene (43.4 mg, 0.25 mmol) and potassium carbonate (35 mg, 0.25 mmol) under a nitrogen atmosphere. After being heated under microwave conditions (100 °C, 30 minutes), the resulting mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (0-20% methanol in dichloromethane) to afford [6-fluoro-4-(4-methanesulfonyl-phenylsulfanyl)-naphthalen-2-yl]-acetic acid (37.0 mg, 74.6%) as an off-white powder. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.86 - 7.93 (m, 4 H), 7.69 - 7.74 (m, 2 H), 7.34 (td, *J* = 8.53, 2.65 Hz, 1 H), 7.08 - 7.15 (m, 2 H), 3.85 (s, 2 H), 3.01 (s, 3 H); MS calcd. for C₁₉H₁₅FO₄S₂ 390, obsd. (ESI⁺) [(M+H)⁺] 391.

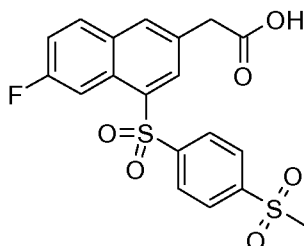
EXAMPLE 10-1

[6-fluoro-4-(4-methanesulfonyl-benzenesulfinyl)-naphthalen-2-yl]-acetic acid



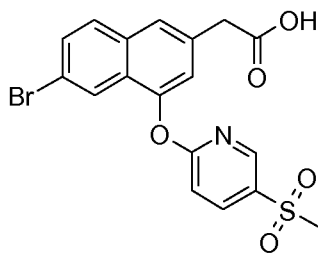
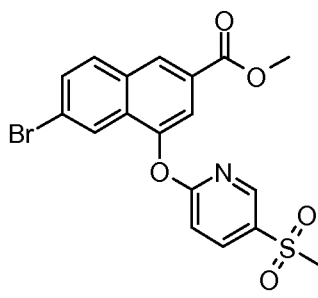
- 117 -

To a solution of 6-fluoro-4-(4-methanesulfonyl-phenylsulfanyl)-naphthalen-2-yl]-acetic acid (25 mg, 0.064 mmol) in dichloromethane was added *m*-chloroperoxybenzoic acid (12.1 mg, 0.07 mmol, 80% purity) at 0 °C. After being stirred at room temperature for 2 hours, the resulting mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (gradient elution with 30-50% 0.1% trifluoroacetic acid in water in acetonitrile, 8 minutes) to afford [6-fluoro-4-(4-methanesulfonyl-benzenesulfonyl)-naphthalen-2-yl]-acetic acid (12.0 mg, 46%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.59 (br. s, 1 H), 8.21 (d, *J* = 1.26 Hz, 1 H), 8.09 - 8.15 (m, 2 H), 8.07 (s, 1 H), 8.03 (s, 4 H), 7.55 (td, *J* = 8.84, 2.53 Hz, 1 H), 3.89 (s, 2 H), 3.21 (s, 3 H); MS calcd. For C₁₉H₁₅FO₅S₂ 406, obsd. (ESI⁺) [(M+H)⁺] 407.

EXAMPLE 11-1**[6-fluoro-4-(4-methanesulfonyl-benzenesulfonyl)-naphthalen-2-yl]-acetic acid**

To a solution of 6-fluoro-4-(4-methanesulfonyl-phenylsulfanyl)-naphthalen-2-yl]-acetic acid (25 mg, 0.064 mmol) in dichloromethane was added *m*-chloroperoxybenzoic acid (41.4 mg, 0.192 mmol, 80% solution in water) at 0 °C. After being stirred at reflux for 3 hours, the resulting mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC (gradient elution with 30-50% 0.1% trifluoroacetic acid in water in acetonitrile, 8 minutes) to afford [6-fluoro-4-(4-methanesulfonyl-benzenesulfonyl)-naphthalen-2-yl]-acetic acid (18 mg, 66.7%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.65 (s, 1 H), 8.58 (d, *J* = 1.52 Hz, 1 H), 8.24 - 8.31 (m, 3 H), 8.11 - 8.23 (m, 4 H), 7.61 (dd, *J* = 10.23, 7.45 Hz, 1 H), 3.97 (s, 2 H), 3.26 (s, 3 H); MS calcd. for C₁₉H₁₅FO₆S₂ 422, obsd. (ESI⁺) [(M+H)⁺] 423.

EXAMPLE 12-1

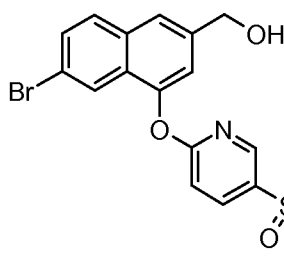
[6-Bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid**6-Bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-
naphthalene-2-carboxylic acid methyl ester**

5

A mixture of 6-bromo-4-hydroxy-naphthalene-2-carboxylic acid methyl ester (423 mg, 1.5 mmol), potassium carbonate (414 mg, 3 mmol), 2,5-bis-ethanesulfonyl-pyridine (420 mg, 1.6 mmol) and *N,N*-dimethylformamide (4 mL) was vigorously stirred and heated at 100 °C overnight under an argon atmosphere, then cooled to room temperature, and diluted with ethyl acetate (10 mL). The resulting mixture was washed with water (10 mL x 3). The combined aqueous layers were extracted with ethyl acetate (10 mL). The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (silica gel, 100-200 mesh, 30% ethyl acetate in petroleum ether) to give 6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalene-2-carboxylic acid methyl ester (280 mg, 41%, crude yield) as a yellow solid.

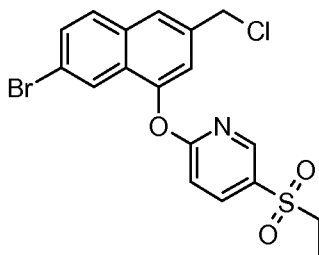
[6-Bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-methanol

- 119 -



To a solution of 6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalene-2-carboxylic acid methyl ester (280 mg, 0.63 mmol) in tetrahydrofuran (5 mL) was added a solution of diisobutylaluminium hydride (1 M in toluene, 1.3 mL, 1.3 mmol) dropwise at -78 °C under a nitrogen atmosphere. The resulting mixture was warmed to room temperature and stirred at room temperature (the total stirring time between -78 °C and room temperature was 3 hours). The reaction mixture was treated with an aqueous solution of potassium sodium tartrate tetrahydrate at 0 °C, warmed to room temperature, and stirred at room temperature for 30 min. The resulting mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (silica gel, 100-200 mesh, 30% ethyl acetate in petroleum ether) to give [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-methanol (263 mg, 99%) as a colorless oil.

2-(7-Bromo-3-chloromethyl-naphthalen-1-yloxy)-5-ethanesulfonyl-pyridine



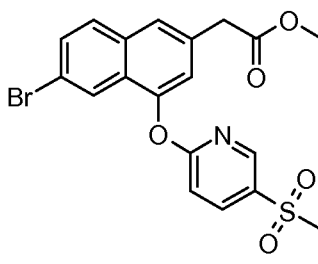
After a solution of triphenylphosphine (330 mg, 1.26 mmol) and carbon tetrachloride (2 mL) in anhydrous tetrahydrofuran (6 mL) was stirred at room temperature for 10 minutes under a nitrogen atmosphere, [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-methanol (265 mg, 0.63 mmol) was introduced as a solid. The resulting mixture was heated at reflux for 4 hours, cooled to room temperature, then diluted with water (10 mL), and extracted with ethyl acetate (30 mL x 2). The combined organic layers were dried over sodium

- 120 -

sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography (silica gel, 100-200 mesh, 5% ethyl acetate in petroleum ether) to afford 2-(7-bromo-3-chloromethyl-naphthalen-1-yloxy)-5-ethanesulfonyl-pyridine (210 mg, 76 %) as a yellow oil.

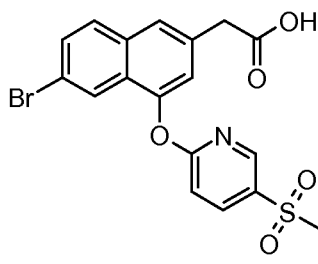
5

[6-Bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester



To a flask containing 2-(7-bromo-3-chloromethyl-naphthalen-1-yloxy)-5-ethanesulfonyl-pyridine (210 mg, 0.46 mmol),
10 bis(triphenylphosphine)dichloropalladium(II) (16 mg, 0.023 mmol) and potassium carbonate (67 mg, 0.48 mmol), which was evacuated and then filled with carbon monoxide (balloon), were added methanol (2 mL) and tetrahydrofuran (4 mL) by means of a syringe. After being stirred at room temperature under a carbon
15 monoxide atmosphere for 3 hours, the reaction mixture was diluted with water (5 mL), and extracted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL × 2). The combined aqueous layers were extracted with ethyl acetate (20 mL), and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography
20 (silica gel, 100-200 mesh, 20% ethyl acetate in petroleum ether) to afford [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (245 mg, 99 %) as a yellow solid.

[6-Bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid

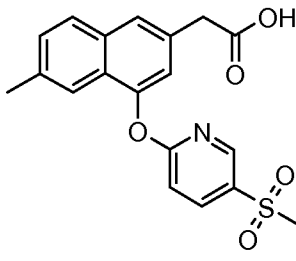


- 121 -

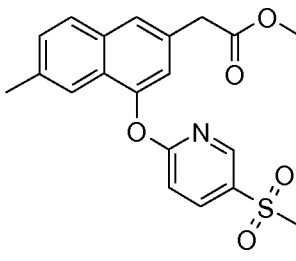
Starting with [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (23 mg, 0.05 mmol), using a method analogous to the one described for example **1-1**, final step, [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid (10.2 mg, 45%) was obtained as a white solid.

- 5 ^1H NMR (400 MHz, CDCl_3) δ ppm 8.63 (d, $J = 2.53$ Hz, 1 H), 8.23 (dd, $J = 8.84$, 2.53 Hz, 1 H), 8.03 (d, $J = 1.26$ Hz, 1 H), 7.77 (d, $J = 8.84$ Hz, 1 H), 7.69 (s, 1 H), 7.62 (dd, $J = 8.72$, 1.89 Hz, 1 H), 7.31 (d, $J = 1.01$ Hz, 1 H), 7.23 (d, $J = 8.84$ Hz, 1 H), 3.85 (s, 2 H), 3.17 (q, $J = 7.33$ Hz, 2 H), 1.35 (t, $J = 7.45$ Hz, 3 H); MS calcd. for $\text{C}_{19}\text{H}_{16}\text{BrNO}_5\text{S}$ 449, obsd. (ESI^+) $[(\text{M}+\text{H})^+]$ 450.

10

EXAMPLE 13-1**[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid****[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid methyl ester**

15

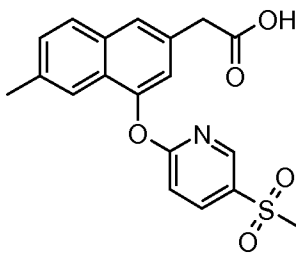


- A mixture of [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (30 mg, 0.07 mmol, methyl ester of example **12-1**), methylboronic acid (7 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (8 mg, 0.007 mmol), potassium phosphate (45 mg, 0.21 mmol) and toluene (0.5 mL) was stirred at 115 °C overnight under an argon atmosphere. The resulting mixture was diluted with water (5 mL), and then extracted with ethyl acetate (20 mL $\times$ 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by
- 20

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preparative TLC (20% ethyl acetate in petroleum ether) to give [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid methyl ester (20 mg) as a colorless oil.

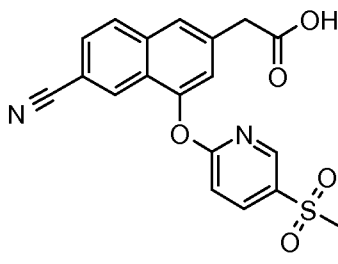
5 **[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid**



Starting with [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid methyl ester (20 mg, 0.05 mmol), using a method analogous to the one described for example 1-1, final step, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid (4.5 mg, 17%, two steps) was obtained as a white powder. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.66 (d, *J* = 2.53 Hz, 1 H), 8.18 (dd, *J* = 8.72, 2.40 Hz, 1 H), 7.79 (d, *J* = 8.34 Hz, 1 H), 7.68 (s, 1 H), 7.59 (s, 1 H), 7.38 (d, *J* = 8.34 Hz, 1 H), 7.24 (s, 1 H), 7.15 (d, *J* = 8.59 Hz, 1 H), 3.84 (s, 2 H), 3.16 (q, *J* = 7.16 Hz, 2 H), 2.47 (s, 3 H), 1.34 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₀H₁₉NO₅S 385, obsd. (ESI⁺) [(M+H)⁺] 386.

EXAMPLE 14-1

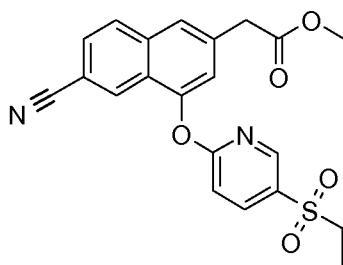
[6-Cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid



20

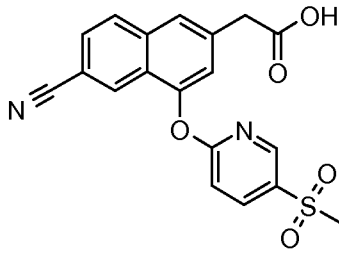
[6-Cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester

- 123 -



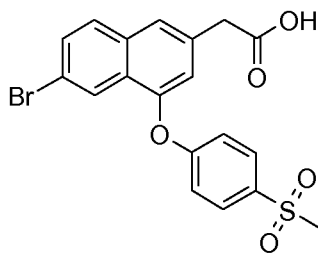
A mixture of [6-bromo-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (29 mg, 0.07 mmol, methyl ester of example **12-1**), zinc cyanide (10 mg, 0.084 mmol), tetrakis(triphenylphosphine)palladium(0) (18 mg, 0.014 mmol) and *N,N*-dimethylacetamide (0.2 mL) was stirred at 150 °C for 24 hours under an argon atmosphere. The reaction mixture was diluted with water (5 mL), and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative TLC (30% ethyl acetate in petroleum ether) to give [6-cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (17 mg) as a white solid.

[6-Cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid



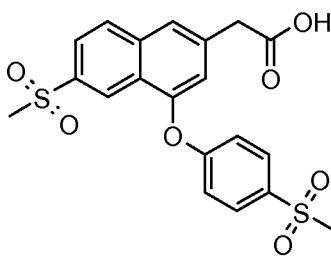
Starting with [6-cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid methyl ester (17 mg, 0.04 mmol), using a method analogous to the one described for example **1-1**, final step, [6-cyano-4-(5-ethanesulfonyl-pyridin-2-yloxy)-naphthalen-2-yl]-acetic acid (1.1 mg) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.61 (d, *J* = 2.27 Hz, 1 H), 8.25 - 8.30 (m, 2 H), 7.99 (d, *J* = 8.59 Hz, 1 H), 7.78 (s, 1 H), 7.68 (dd, *J* = 8.59, 1.26 Hz, 1 H), 7.42 (d, *J* = 1.01 Hz, 5 H), 7.31 (d, *J* = 8.84 Hz, 5 H), 3.90 (s, 2 H), 3.19 (q, *J* = 7.24 Hz, 2 H), 1.37 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₀H₁₆N₂O₅S 396, obsd. (ESI⁺) [(M+H)⁺] 397.

EXAMPLE 15-1

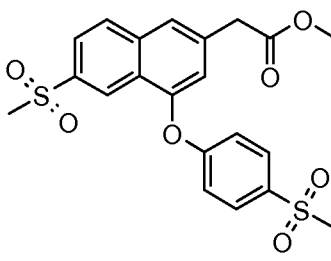
[6-Bromo-4-(4-ethanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid

Starting with 6-bromo-4-hydroxy-naphthalene-2-carboxylic acid methyl ester and 1-ethanesulfonyl-4-fluoro-benzene, using a method analogous to the one described for example **14-1**, [6-bromo-4-(4-ethanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid (10.4 mg, 63%) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.18 (s, 1 H), 7.89 (d, $J = 8.84$ Hz, 2 H), 7.76 (d, $J = 8.59$ Hz, 1 H), 7.57 - 7.68 (m, 2 H), 7.10 - 7.17 (m, 3 H), 3.80 (s, 2 H), 3.15 (q, $J = 7.58$ Hz, 2 H), 1.33 (t, $J = 7.45$ Hz, 3 H); MS calcd. for $\text{C}_{20}\text{H}_{17}\text{BrO}_5\text{S}$ 448, obsd. (ESI^+)

10 $[(\text{M}+\text{H})^+]$ 449.

EXAMPLE 16-1**[4-(4-Ethanesulfonyl-phenoxy)-6-methanesulfonyl-naphthalen-2-yl]-acetic acid**

15

[4-(4-Ethanesulfonyl-phenoxy)-6-methanesulfonyl-naphthalen-2-yl]-acetic acid methyl ester

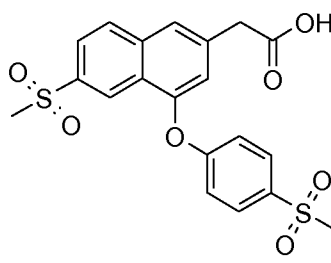
A mixture of [6-bromo-4-(4-ethanesulfonyl-phenoxy)-naphthalen-2-yl]-acetic acid methyl ester (32 mg, 0.07 mmol, methyl ester of example **15-1**), sodium

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methanesulfinate (10 mg, 0.09 mmol), L-proline (4 mg, 0.028 mmol), copper(I) iodide (3 mg, 0.014 mmol) and dimethyl sulfoxide (0.3 mL) was stirred at 115 °C overnight under an argon atmosphere. The resulting mixture was diluted with water (5 mL), and extracted with ethyl acetate (20 mL × 2). The combined organic

5 layers were washed with brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by preparative TLC (30% ethyl acetate in petroleum ether) to give [4-(4-ethanesulfonyl-phenoxy)-6-methanesulfonyl-naphthalen-2-yl]-acetic acid methyl ester (11 mg) as a yellow solid.

10 **[4-(4-Ethanesulfonyl-phenoxy)-6-methanesulfonyl-naphthalen-2-yl]-acetic acid**



Starting with [4-(4-ethanesulfonyl-phenoxy)-6-methanesulfonyl-naphthalen-2-yl]-acetic acid methyl ester (11 mg, 0.024 mmol), using a method analogous to the

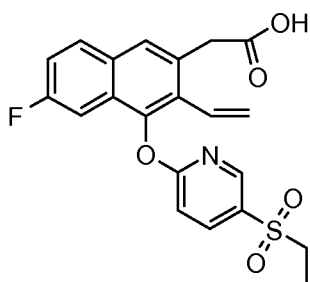
15 one described for example **1-1**, final step, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-methyl-naphthalen-2-yl]-acetic acid (8 mg, 26%, two steps) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.80 (s, 1 H), 8.05 - 8.09 (m, 1 H), 7.99 - 8.04 (m, 1 H), 7.94 (d, *J* = 8.59 Hz, 2 H), 7.72 (s, 1 H), 7.23 (d, *J* = 8.59 Hz, 2 H), 7.14 (s, 1 H), 3.85 (s, 2 H), 3.17 (q, *J* = 7.58 Hz, 2 H), 3.13 (s, 3 H), 1.34 (t,

20 *J* = 7.45 Hz, 3 H); MS calcd. for C₂₁H₂₀O₇S₂ 448, obsd. (ESI⁺) [(M+H)⁺] 449.

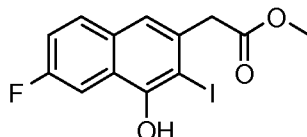
EXAMPLE 17-1

[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid

- 126 -

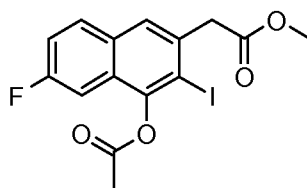


(6-Fluoro-4-hydroxy-3-iodo-naphthalen-2-yl)-acetic acid methyl ester



To a solution of (6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester
 5 (600 mg, 2.56 mmol, the product of 8th step for example **1-1**) in chloroform (260 mL) was added *N*-iodosuccinimide (577 mg, 2.56 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred at room temperature for 2 hours. The resulting mixture was diluted with 10% aqueous solution of sodium bisulfate (100 mL). The organic layer was separated, washed with brine (100 mL), dried
 10 over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column (elution with 15% ethyl acetate in petroleum ether) to afford (6-fluoro-4-hydroxy-3-iodo-naphthalen-2-yl)-acetic acid methyl ester (500 mg, 54%) as a white solid.

(4-Acetoxy-6-fluoro-3-iodo-naphthalen-2-yl)-acetic acid methyl ester



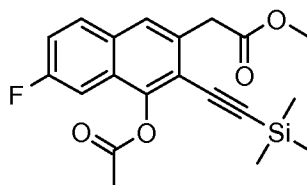
To a stirred solution of (6-fluoro-4-hydroxy-3-iodo-naphthalen-2-yl)-acetic acid methyl ester (500 mg, 1.4 mmol) and 4-dimethylaminopyridine (34 mg, 0.28 mmol) in pyridine (3 mL) was added acetic anhydride (160 µL, 1.7 mmol). After
 20 being stirred at room temperature overnight, the resulting mixture was diluted with 10% hydrochloric acid (20 mL), and extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine (30 mL × 2), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash

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column (elution with 20% ethyl acetate in petroleum ether) to afford (4-acetoxy-6-fluoro-3-iodo-naphthalen-2-yl)-acetic acid methyl ester (300 mg, 53%) as a white solid.

5

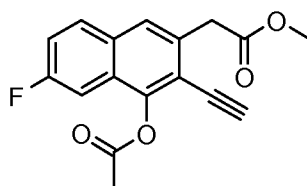
(4-Acetoxy-6-fluoro-3-trimethylsilanylethynyl-naphthalen-2-yl)-acetic acid methyl ester



To a solution of (4-acetoxy-6-fluoro-3-iodo-naphthalen-2-yl)-acetic acid methyl ester (300 mg, 0.75 mmol) and triethylamine (3 mL) in *N,N*-dimethylformamide (3 mL), was added bis(triphenylphosphine)dichloropalladium(II) (53 mg, 0.075 mmol), copper iodide (42 mg, 0.229 mmol) and trimethylsilylacetylene (108 mg, 1.12 mmol) under an argon atmosphere. After being heated at 150 °C for 6 minutes with microwave irradiation, the resulting mixture was cooled, diluted with ethyl acetate (20 mL), and washed with brine (15 mL × 2). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column (elution with 10% ethyl acetate in petroleum ether) to afford (4-acetoxy-6-fluoro-3-trimethylsilanylethynyl-naphthalen-2-yl)-acetic acid methyl ester (208 mg, 75%) as a light yellow solid.

20

(4-Acetoxy-3-ethynyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester



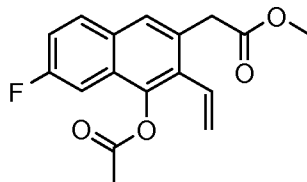
To a solution of (4-acetoxy-6-fluoro-3-trimethylsilanylethynyl-naphthalen-2-yl)-acetic acid methyl ester (200 mg, 0.538 mmol) in *N,N*-dimethylformamide and water (6 mL, v/v=150:1), was added potassium fluoride (156 mg, 2.7 mmol). The resulting mixture was stirred at room temperature for 4 hours, then poured into water (10 mL), and extracted with ethyl acetate (10 mL × 3). The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated

25

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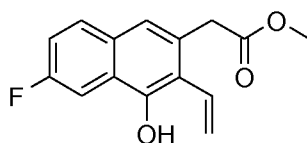
in vacuo. The residue was purified by flash column (elution with 10% ethyl acetate in petroleum ether) to afford (4-acetoxy-3-ethynyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (153 mg, 95%) as a light yellow solid.

5 **(4-Acetoxy-6-fluoro-3-vinyl-naphthalen-2-yl)-acetic acid methyl ester**



A round-bottom flask (5 mL) charged with indium trichloride (88 mg, 0.40 mmol) was heated at 100 °C under reduced pressure for 1h, and filled with nitrogen. A solution of triethylsilane (46 mg, 0.4 mmol) in acetonitrile (4 mL), which was
10 cooled to 0 °C, was added by means of syringe. After the mixture was stirred at 0 °C for 5 minutes, (4-acetoxy-3-ethynyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (60 mg, 0.20 mmol) and a solution of triethylborane (1M solution in tetrahydrofuran, 20 µL, 0.02 mmol) were added. The resulting mixture was stirred
15 at 0 °C for 3 hours, then poured into water (10 mL), and extracted with ethyl acetate (10 mL × 3). The organic layers were combined, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column (elution with 10% ethyl acetate in petroleum ether) to afford (4-acetoxy-6-fluoro-3-vinyl-naphthalen-2-yl)-acetic acid methyl ester (38 mg, 62.9%) as a pale solid.

20 **(6-Fluoro-4-hydroxy-3-vinyl-naphthalen-2-yl)-acetic acid methyl ester**

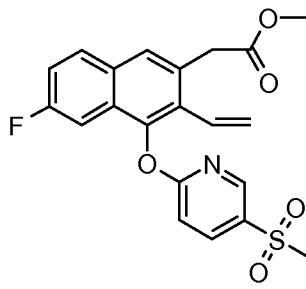


A mixture of (4-acetoxy-6-fluoro-3-vinyl-naphthalen-2-yl)-acetic acid methyl ester (38 mg, 0.126 mmol), sodium methoxide (10.1 mg, 0.189 mmol), and methanol (4 mL) was stirred at room temperature for 2 hours. After the reaction mixture was
25 acidified with concentrated hydrochloric acid to pH 5, a precipitate formed, which was collected by filtration, and dissolved in ethyl acetate (20 mL). The organic solution was dried over sodium sulfate, and concentrated *in vacuo* to afford the

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crude product (6-fluoro-4-hydroxy-3-vinyl-naphthalen-2-yl)-acetic acid methyl ester (32 mg, 97.7%) as a light yellow solid.

[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid methyl ester

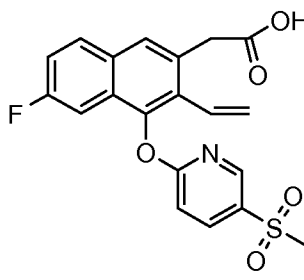


5

A mixture of (6-fluoro-4-hydroxy-3-vinyl-naphthalen-2-yl)-acetic acid methyl ester (22 mg, 0.084 mmol), 2,5-bis-ethanesulfonyl-pyridine (33 mg, 0.126 mmol), potassium iodide (5 mg), and cesium carbonate (68 mg, 0.21 mmol), *N,N*-dimethylformamide (0.5 mL) and acetone (1.5 mL) was heated at 100 °C for 30 minutes with microwave irradiation. The mixture was then concentrated *in vacuo*. The residue was purified by flash column (gradient elution with 0-50% ethyl acetate in petroleum ether) to afford [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid methyl ester (13 mg, 36.1%) as a yellow solid.

15

[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid



Starting with [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid methyl ester (8.6 mg, 0.02 mmol), using a method analogous to the one described for example **1-1**, final step, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid (1.4 mg) was obtained as an off-white viscous oil. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51 (d, *J* = 2.53 Hz, 1 H), 8.29

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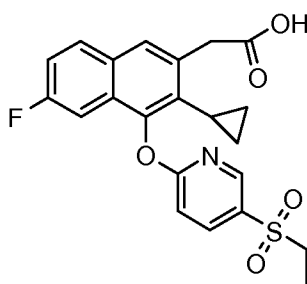
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(dd, $J = 8.84, 2.53$ Hz, 1 H), 7.95 - 8.01 (m, 1 H), 7.83 (s, 1 H), 7.31 - 7.39 (m, 2 H), 7.25 (d, $J = 8.84$ Hz, 1 H), 6.68 (dd, $J = 17.94, 11.62$ Hz, 1 H), 5.47 - 5.58 (m, 2 H), 3.91 (s, 2 H), 3.27 (q, $J = 7.33$ Hz, 2 H), 1.26 (t, $J = 7.45$ Hz, 3 H); MS calcd. for $C_{21}H_{18}FNO_5S$ 415, obsd. (ESI⁺) [(M+H)⁺] 416.

5

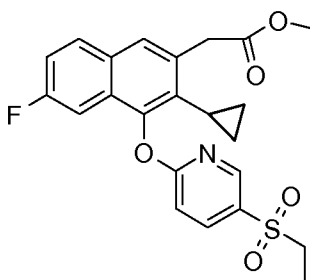
EXAMPLE 18-1

[3-Cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-
6-fluoro-naphthalen-2-yl]-acetic acid



10

[3-Cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-
6-fluoro-naphthalen-2-yl]-acetic acid methyl ester

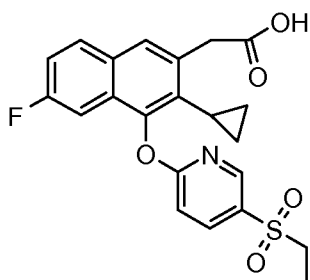


To a cooled solution of [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-vinyl-naphthalen-2-yl]-acetic acid methyl ester (6.0 mg, 0.014 mmol, methyl ester of example **17-1**) in tetrahydrofuran, was added a solution of diazomethane (0.1 M, 5 mL) in diethyl ether at 0 °C under an argon atmosphere, followed by palladium acetate (1 mg) in two portions. After being stirred at 0 °C for 2 hours, the reaction mixture was treated with acetic acid (0.2 mL) to quench the reaction, and then filtered. The filtrate was concentrated *in vacuo* to afford the crude product of [3-cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester as a yellow oil.

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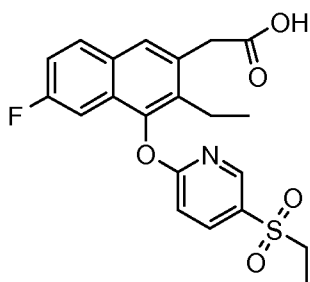
**[3-Cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-
6-fluoro-naphthalen-2-yl]-acetic acid**



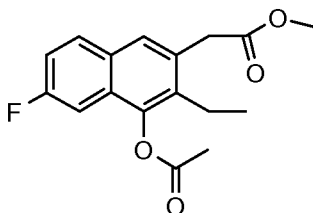
Starting with [3-cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester, using a method analogous to the one described for example **1-1**, final step, [3-cyclopropyl-4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-naphthalen-2-yl]-acetic acid (3.3 mg, 66%, two steps) was obtained as a white powder. ^1H NMR (400 MHz, CD_3OD) δ ppm 9.31 (d, $J = 2.53$ Hz, 1 H), 9.15 (dd, $J = 8.84, 2.53$ Hz, 1 H), 8.85 (dd, $J = 9.60, 5.56$ Hz, 1 H), 8.62 (s, 1 H), 8.19 - 8.29 (m, 3 H), 4.80 (s, 2 H), 4.17 (q, $J = 7.33$ Hz, 2 H), 2.25 - 2.34 (m, 1 H), 1.94 (t, $J = 7.33$ Hz, 3 H), 1.55 - 1.64 (m, 2 H), 1.37 - 1.52 (m, 2 H); MS cald. for $\text{C}_{22}\text{H}_{20}\text{FNO}_5\text{S}$ 429, obsd. (ESI^+) $[(\text{M}+\text{H})^+]$ 430.

EXAMPLE 19-1

4-(5-Ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid



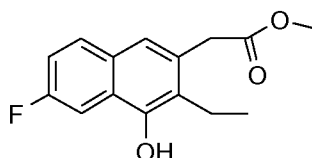
(4-Acetoxy-3-ethyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester



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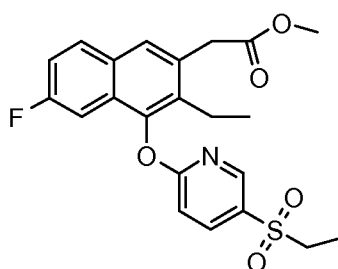
To a solution of (4-acetoxy-3-ethynyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (50 mg) in methanol was added 10% palladium on carbon (10 mg). The resulting mixture was hydrogenated under 40 psi of hydrogen for 2 hours and filtered. The filtrate was concentrated *in vacuo* to afford (4-acetoxy-3-ethyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (50 mg) as a colorless oil.

(3-Ethyl-6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester



A mixture of (4-acetoxy-3-ethyl-6-fluoro-naphthalen-2-yl)-acetic acid methyl ester (50 mg, 0.164 mmol), sodium methoxide (13 mg, 0.247 mmol), and methanol (4 mL) was stirred at room temperature for 2 hours. After the reaction mixture was acidified with concentrated hydrochloric acid to pH 5, a precipitate formed, which was then collected by filtration, and dissolved in ethyl acetate (20 mL). The organic solution was dried over sodium sulfate, and concentrated *in vacuo* to afford the crude product of (3-ethyl-6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (42 mg, 97.7%) as a light yellow solid.

[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester



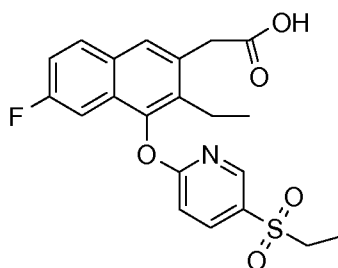
20

Starting with (3-ethyl-6-fluoro-4-hydroxy-naphthalen-2-yl)-acetic acid methyl ester (15 mg, 0.057 mmol) and 2,5-bis-ethanesulfonyl-pyridine (30 mg, 0.115 mmol), using a method analogous to the described for the methyl ester of example **17-1**), [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester (15 mg, 61.1%) was obtained as a light yellow solid.

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[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid

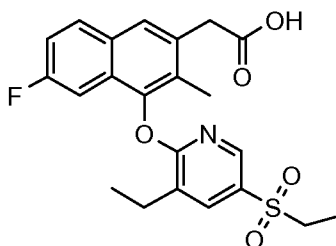


Starting with [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid methyl ester (15 mg), using a method analogous to the one described for example 1-1, final step, [4-(5-ethanesulfonyl-pyridin-2-yloxy)-3-ethyl-6-fluoro-naphthalen-2-yl]-acetic acid (6.0 mg) was obtained as a white semisolid. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51 (d, *J* = 2.53 Hz, 1 H), 8.31 (dd, *J* = 8.84, 2.53 Hz, 1 H), 7.93 (dd, *J* = 9.09, 5.56 Hz, 1 H), 7.79 (s, 1 H), 7.24 - 7.32 (m, 2 H), 7.19 (dd, *J* = 10.23, 2.40 Hz, 1 H), 3.89 (s, 2 H), 3.26 (q, *J* = 7.49 Hz, 2 H), 2.71 (q, *J* = 7.58 Hz, 2 H), 1.25 (t, *J* = 7.45 Hz, 3 H), 1.11 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₁H₂₀FNO₅S 417, obsd. (ESI⁺) [(M+H)⁺] 418.

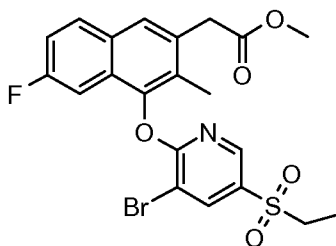
EXAMPLE 20-1

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[4-(5-Ethanesulfonyl-3-ethyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid



[4-(3-Bromo-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester

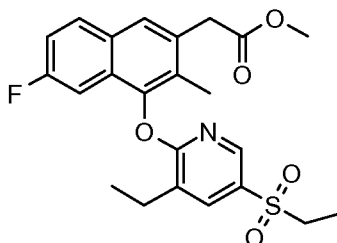


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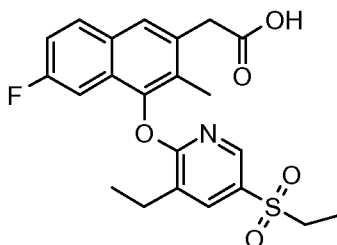
Starting with 6-fluoro-4-hydroxy-3-methyl-naphthalen-2-yl)-acetic acid methyl ester (124 mg, 0.50 mmol) and 3-bromo-2-chloro-5-ethanesulfonyl-pyridine (157 mg, 0.55 mmol), using a method analogous to the one described for the methyl ester of example **2-1**, [4-(3-bromo-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (183 mg, 73.9%) was obtained as a white solid.

**[4-(5-Ethanesulfonyl-3-ethyl-pyridin-2-yloxy)-
6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester**



10 A mixture of [4-(3-bromo-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (42 mg, 0.085 mmol), ethylboronic acid (15 mg, 0.20 mmol), bis(triphenylphosphine)dichloropalladium(II) (7.0 mg, 0.01 mmol), potassium phosphate (64 mg, 0.30 mmol), triphenylphosphine (15.2 mg, 0.05 mmol) and toluene (1 mL) was stirred at 100 °C overnight under an argon
15 atmosphere. The resulting mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (20% ethyl acetate in petroleum ether) to afford [4-(5-ethanesulfonyl-3-ethyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (18 mg, 47.6%) as a white solid.

**[4-(5-Ethanesulfonyl-3-ethyl-pyridin-2-yloxy)-
6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid**



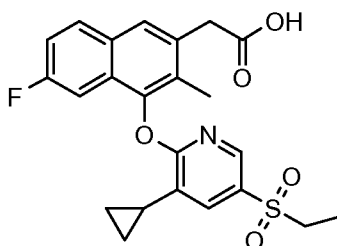
Starting with [4-(5-ethanesulfonyl-3-ethyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (18 mg), using a method analogous to the one described for example **1-1**, final step, [4-(5-ethanesulfonyl-3-ethyl-pyridin-
25 2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid (2.9 mg) was obtained as

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a white powder. ^1H NMR (400 MHz, CDCl_3) δ ppm 8.34 (d, $J = 2.53$ Hz, 1 H), 8.08 (d, $J = 2.53$ Hz, 1 H), 7.85 (dd, $J = 8.97, 5.43$ Hz, 1 H), 7.72 (s, 1 H), 7.17 - 7.28 (m, 2 H), 3.92 (s, 2 H), 3.15 (q, $J = 7.41$ Hz, 2 H), 3.04 (q, $J = 7.58$ Hz, 2 H), 2.20 - 2.24 (m, 3 H), 1.50 (t, $J = 7.45$ Hz, 3 H), 1.34 (t, $J = 7.45$ Hz, 3 H); MS calcd. for $\text{C}_{22}\text{H}_{22}\text{FNO}_5\text{S}$ 431, obsd. (ESI^+) $[(\text{M}+\text{H})^+]$ 432.

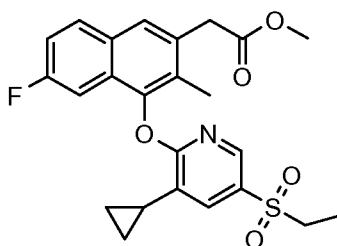
EXAMPLE 21-1

[4-(3-Cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid



10

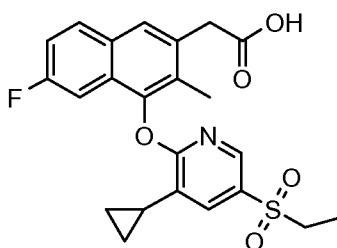
[4-(3-Cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester



Starting with 4-(3-bromo-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (49 mg, 0.10 mmol), and cyclopropylboronic acid (17 mg, 0.20 mmol), using a method analogous to the one described for the methyl ester of example **20-1**, [4-(3-cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (25 mg, 54.7%) as a white solid.

20

[4-(3-Cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid



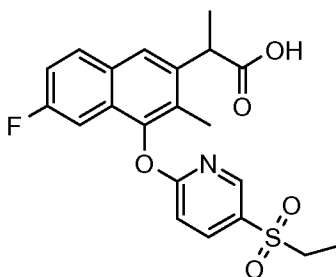
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Starting with [4-(3-cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid methyl ester (25 mg), using a method analogous to the one described for example **1-1**, final step, [4-(3-cyclopropyl-5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid (2.4 mg) was obtained as a white powder.

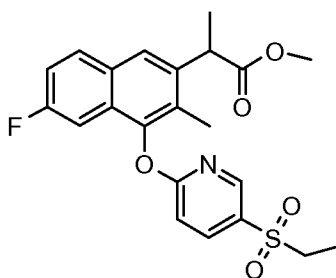
¹H NMR (400 MHz, CDCl₃) δ ppm 8.28 (d, *J* = 2.53 Hz, 1 H), 7.85 (dd, *J* = 8.97, 5.43 Hz, 1 H), 7.77 (d, *J* = 2.02 Hz, 1 H), 7.72 (s, 1 H), 7.21 - 7.28 (m, 2 H), 3.92 (s, 2 H), 3.13 (q, *J* = 7.33 Hz, 2 H), 2.42 - 2.52 (m, 1 H), 2.25 (s, 3 H), 1.32 (t, *J* = 7.33 Hz, 3 H), 1.22 - 1.26 (m, 2 H), 0.91 - 1.04 (m, 2 H); MS calcd. for C₂₃H₂₂FNO₅S 443, obsd. (ESI⁺) [(M+H)⁺] 444.

EXAMPLE 22-1

2-[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid



2-[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid methyl ester

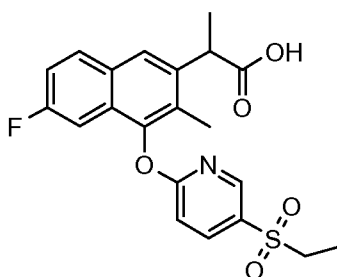


To a solution of [4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid (226.5 mg, 0.56 mmol, example **2-33**) in anhydrous *N,N*-dimethylformamide (10mL), which was cooled to -30 °C, was added sodium hydride (50 mg, 1.12 mol, 60% in mineral oil). The mixture was stirred at -30 °C for 30 minutes, then treated with a solution of iodomethane (76 μL) in *N,N*-

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dimethylformamide (2 mL) dropwise at the same temperature. The mixture was allowed to warm to 0 °C and stirred at the same temperature for 2 hours. The resulting mixture was diluted with ethyl acetate (230 mL), washed with a saturated aqueous solution of ammonium chloride (10 mL × 2), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column to afford 2-[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid methyl ester (220 mg, 85.1%) as a white solid.

2-[4-(5-Ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid



10

Starting with 2-[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid methyl ester (220 mg, 0.510 mmol), using a method analogous to the one described for example **1-1**, final step, 2-[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-propionic acid (205 mg, 96.4%) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.51 (d, *J* = 2.27 Hz, 1 H), 8.31 (dd, *J* = 6.06, 2.78 Hz, 1 H), 7.92 - 7.97 (m, *J* = 5.31, 3.54 Hz, 1 H), 7.81 (s, 1 H), 7.23 - 7.32 (m, 3 H), 4.14 (d, *J* = 7.33 Hz, 1 H), 3.26 (q, *J* = 7.33 Hz, 2 H), 2.29 (s, 3 H), 1.61 (d, *J* = 7.07 Hz, 3 H), 1.26 (t, *J* = 7.45 Hz, 3 H); MS calcd. for C₂₁H₂₀FNO₅S 417, obsd. (ESI⁺) [(M+H)⁺] 418.

20

ACTIVITY AND USE OF THE COMPOUNDS

The compounds of formula I possess valuable pharmacological properties. It has been found that said compounds are antagonists or partial agonists at the CRTH2 receptor and may be useful in treating diseases and disorders associated with that receptor such as asthma. The activity of the present compounds as CRTH2 receptor antagonists or partial agonists is demonstrated by the following biological assays.

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Human CRTH2 Receptor Binding Assay

A whole cell receptor binding assay using [³H]ramatroban as the competing radioactive ligand was employed to evaluate the compound binding activity to human CRTH2. The radioactive ligand [³H]ramatroban was synthesized according to Sugimoto *et. al.* (*Eur. J. Pharmacol.* 524, 30 - 37, 2005) to a specific activity of 42 Ci/mmol.

A cell line stably expressing human CRTH2 was established by transfecting CHO-K1 cells with two mammalian expression vectors that harbored human CRTH2 and G-alpha16 cDNAs, respectively, using FuGene[®] 6 transfection reagent (from Roche). Stable clones expressing CRTH2 were selected by staining each clone with BM16 (BD Pharmingen[™] from BD Biosciences, a division of Becton, Dickinson and Company), which is a rat monoclonal antibody to human CRTH2. The cells were maintained as monolayer cultures in Ham's F-12 medium containing 10% fetal bovine serum, 100 units/mL penicillin, 100 µg/mL streptomycin, 2 mM glutamine, 0.5 mg/mL G418 (geneticin) for CRTH2, and 0.2 mg/mL hygromycin-B (for G-alpha 16). For whole cell receptor binding assay, the monolayer cells were rinsed once with PBS (phosphate buffered saline), dissociated using ethylenediaminetetraacetate (Versene[™] EDTA from Lonza Inc.), and suspended in PBS containing 10 mM MgCl₂ and 0.06% BSA (bovine serum albumin) at 1.5 x 10⁶ cells/mL.

The binding reactions (0.2 mL) were performed in 96-well plates at room temperature in PBS containing 1.5 x 10⁵ cells, 10 mM MgCl₂, 0.06% BSA, 20 nM [³H]ramatroban, and test compound at various concentrations. After 1 hour of binding reactions, the cells were harvested on GF[™]/B filter microplates (microtiter plates with embedded glass fiber from PerkinElmer, Inc.) and washed 5 times with PBS using a Filtermate[™] Harvester (a cell harvester that harvests and washes cells from microplates from PerkinElmer, Inc.). The radioactivities bound to the cells were determined using a microplate scintillation counter (TopCount[®] NXT, from PerkinElmer, Inc.) after adding 50 µL of Microscint[™] 20 scintillation fluid (from PerkinElmer, Inc.) to each well of the filter plates. The radioactivity from non-specific binding was determined by replacing compound with 10 µM of 15(R)-15-methyl PGD₂ (from Cayman Chemical Company) in the

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reaction mixtures. The radioactivity bound to the cells in the absence of compound (total binding) was determined by replacing compound with 0.25% of DMSO (dimethyl sulfoxide) in the reaction mixture. Specific binding data were obtained by subtracting the radioactivity of non-specific binding from each binding data.

- The IC_{50} value is defined as the concentration of the tested compound that is required for 50% inhibition of total specific binding. In order to calculate the IC_{50} value, the percent inhibition data were determined for 7 concentrations for each compound. The percent inhibition for a compound at each concentration was calculated according to the following formula, $[1-(\text{specific binding in the presence of compound})/(\text{total specific binding})] \times 100$. The IC_{50} value was then obtained by fitting the percent inhibition data to a sigmoidal dose-response (4 parameter logistic) model in the XLfit[®] software Excel add-in program [from ID Business Solutions Ltd., model 205, where $F(x) = (A+(B-A)/(1+((C/x)^D)))$].
- Compounds of the foregoing examples were tested using the above Human CRTH2 Receptor Binding Assay. The results of the assay showed that all of the compounds tested have binding activity exhibiting IC_{50} values ranging from less than 0.0010 μM to 0.3785 μM as shown below:

Example No.	Human CRTH2 Binding IC_{50} (μM)
Example 1-1	0.0023
Example 1-2	0.0031
Example 1-3	0.0085
Example 1-4	0.0067
Example 1-5	0.0093
Example 1-6	0.0071
Example 1-7	0.0035
Example 1-8	0.0033
Example 1-9	0.0037
Example 1-10	0.0033

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Example No.	Human CRTH2 Binding IC ₅₀ (μM)
Example 1-11	0.0056
Example 1-12	0.0025
Example 1-13	0.0023
Example 1-14	0.0191
Example 1-15	0.0053
Example 1-16	0.0191
Example 1-17	0.0105
Example 1-18	0.0026
Example 1-19	0.0026
Example 1-20	0.0181
Example 1-21	0.0047
Example 1-22	0.0054
Example 1-23	0.09729
Example 2-1	0.0032
Example 2-2	0.0023
Example 2-3	0.0075
Example 2-4	0.0028
Example 2-5	0.0035
Example 2-6	0.0027
Example 2-7	0.0022
Example 2-8	0.0045
Example 2-9	0.0027
Example 2-10	0.0073
Example 2-11	0.0030
Example 2-12	0.0018
Example 2-13	0.0024
Example 2-14	0.0016
Example 2-15	0.0026

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Example No.	Human CRTH2 Binding IC ₅₀ (μM)
Example 2-16	0.0034
Example 2-17	0.0037
Example 2-18	0.0017
Example 2-19	0.0124
Example 2-20	0.0025
Example 2-21	0.0024
Example 2-22	0.0024
Example 2-23	0.0021
Example 2-24	0.0082
Example 2-25	0.0024
Example 2-26	0.0023
Example 2-27	0.0029
Example 2-28	0.0050
Example 2-29	0.0028
Example 2-30	0.0027
Example 2-31	0.0036
Example 2-32	0.0009
Example 2-33	0.0027
Example 2-34	0.0031
Example 2-35	0.0029
Example 2-36	0.00002
Example 2-37	0.0019
Example 2-38	0.0022
Example 2-39	0.0020
Example 2-40	0.0063
Example 2-41	0.0017
Example 2-42	0.0029
Example 2-43	0.0018

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Example No.	Human CRTH2 Binding IC₅₀ (μM)
Example 2-44	0.0100
Example 2-45	0.1344
Example 3-1	0.0129
Example 3-2	0.0047
Example 4-1	0.0079
Example 4-2	0.0213
Example 5-1	0.0031
Example 6-1	0.0321
Example 7-1	0.1302
Example 8-1	0.0033
Example 8-2	0.0026
Example 9-1	0.0075
Example 10-1	0.0103
Example 11-1	0.0077
Example 12-1	0.0053
Example 13-1	0.0737
Example 14-1	0.0033
Example 15-1	0.0054
Example 16-1	0.0915
Example 17-1	0.01245
Example 18-1	0.0067
Example 19-1	0.0175
Example 20-1	0.0029
Example 21-1	0.0028
Example 22-1	0.3785

Calcium Flux Assay Using Fluorometric Imaging Plate Reader

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Cell Culture Conditions:

- CHO-K1 cells previously transfected with G-alpha 16 were subsequently transfected with the human CRTH2 receptor and the neomycin resistance gene.
- 5 Following selection in 800 µg/mL G418 (geneticin), individual clones were assayed for their receptor expression based on staining with an anti human CRTH2 IgG, followed by assaying for their response to 13,14-dihydro-15-keto Prostaglandin D₂ (DK-PDG₂) (ligand) in the Ca²⁺ Flux assay. Positive clones were then cloned by limiting dilution cloning. The transfected cells were cultured in
- 10 Ham's F-12 medium supplemented with 10% fetal bovine serum, 2 mM glutamine , 100 U/mL penicillin/100 µg/mL streptomycin, 200 µg/mL hygromycin B, and 800 µg/mL G418 (geneticin). Cells were harvested with trypsin-EDTA (trypsin-ethylenediaminetetraacetic acid) and counted using ViaCount[®] reagent (from Guava Technologies, Inc. which contains two DNA-binding dyes that
- 15 enable the reagent user to distinguish between viable and non-viable cells). The cell suspension volume was adjusted to 2.5 x10⁵ cells /mL with complete growth media. Aliquots of 50 µL were dispensed into BD Falcon™ 384 well black/clear microplates (from BD Biosciences, a division of Becton, Dickinson and Company) and the microplates were placed in a 37 °C CO₂ incubator overnight. The
- 20 following day, the microplates were used in the assay.

Dye Loading and Assay:

- Loading Buffer containing dye (from the FLIPR[®] Calcium 3 Assay Kit from
- 25 Molecular Devices, a division of MDS Analytical Technologies and MDS Inc.) was prepared by dissolving the contents of one bottle into 200 mL Hank's Balanced Salt Solution containing 20 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) and 2.5 mM probenecid. Growth media was removed from the cell plates and 25 µL of Hank's Balanced Salt Solution (HBSS)
- 30 containing 20 mM HEPES, 0.05% BSA and 2.5 mM probenecid was added to each well followed by 25 µL of diluted dye using a Multidrop dispenser. The plates were then incubated for 1 hour at 37 °C.

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During the incubation, test compound plates were prepared by adding 90 μ L of HBSS/20 mM HEPES/0.005% BSA buffer to the 2 μ L of serial diluted compounds.

To prepare serial diluted compounds, 20 mM stocks of compounds were dissolved in 100% DMSO. The compound dilution plate was set up as follows:

- 5 well # 1 received 5 μ L of compound plus 10 μ L of DMSO. Wells 2-10 received 10 μ L of DMSO. 5 μ L was mixed and transferred from well #1 into well #2. 1:3 serial dilutions were continued out 10 steps. 2 μ L of diluted compound was transferred into duplicate wells of a 384 well "assay plate" and then 90 μ L of buffer was added.

10

After incubation, both the cell and "assay plate" plates were brought to the fluorometric imaging plate reader (FLIPR[®]) and 20 μ L of the diluted compounds were transferred to the cell plates by the FLIPR[®]. Plates were then incubated for 1 hour at room temperature. After the 1 hour incubation, plates were returned to

- 15 the FLIPR[®] and 20 μ L of 4.5X concentrated ligand was added to the cell plates. During the assay, fluorescence readings were taken simultaneously from all 384 wells of the cell plate every 1.5 seconds. Five readings were taken to establish a stable baseline, then 20 μ L of sample was rapidly (30 μ L/sec) and simultaneously added to each well of the cell plate. The fluorescence was continuously
- 20 monitored before, during and after sample addition for a total elapsed time of 100 seconds. Responses (increase in peak fluorescence) in each well following agonist addition were determined. The initial fluorescence reading from each well, prior to ligand stimulation, was used as a zero baseline value for the data from that well. The responses were expressed as % inhibition of the buffer control. The
- 25 IC₅₀ value, defined as the concentration of a compound that was required for 50% inhibition of the buffer control, was calculated by fitting the percent inhibition data for 10 concentrations to a sigmoidal dose-response (4 parameter logistic) model using Genedata Screener[®] Condoseo software program [from Genedata AG, model 205, where $F(x) = (A + (B - A) / (1 + ((C/x)^D)))$].

30

Specific representative compounds tested in the binding assay were tested using the above FLIPR[®] assay (examples 1-1 to 2-5, 2-7 to 2-18, 2-20, 2-23 to 2-26, 2-28 to 2-35, 2-37 to 11-1, 15-1 and 16-1). The results of the FLIPR[®] assay

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showed that, with the exception of examples 1-1 and 7-1 (which exhibited IC₅₀ values of 5 and 4.198 µM respectively), these compounds exhibited IC₅₀ values ranging from less than 0.0001 µM to 1.4078 µM.

5 **DK-PGD₂-induced IL-13 production assay in Th2 cells**

Inhibition of 13,14-dihydro-15-keto Prostaglandin D₂ (DK-PGD₂)-induced IL-13 production in T helper type 2 (Th2) cells was applied to evaluate compound cellular potency.

10

Cultures of Th2 cells were established from blood of healthy human volunteers according to the following procedure. Peripheral blood mononuclear cells (PBMC) were first isolated from 50 mL of fresh blood by Ficoll-Hypaque density gradient centrifugation, followed by CD4⁺ cell purification using a CD4⁺ T Cell Isolation Kit
15 II (from Miltenyi Biotec Inc.). The CD4⁺ T cells were then differentiated to Th2 cells by culturing the cells in X-VIVO 15[®] medium (from Cambrex BioScience Walkersville Inc.) containing 10% human AB serum (serum of blood type AB from Invitrogen Corporation), 50 U/mL of recombinant human interleukin-2 (rhIL-2) (from PeproTech Inc.) and 100 ng/mL of recombinant human interleukin-4 (rhIL-
20 4) (from PeproTech Inc.) for 7 days. The Th2 cells were isolated using a CD294 (CRTH2) MicroBead Kit (from Miltenyi Biotec Inc.) and amplified in X-VIVO 15[®] medium containing 10% human AB serum and 50 U/mL of rhIL-2 for 2 to 5 weeks. In general, 70% to 80% of the Th2 cells used in the assay are CRTH2-positive when analyzed by fluorescence-activated cell sorting using the BM16 antibody
25 (as previously described) conjugated to phycoerythrin (PE).

To determine cellular inhibitory potency, compounds at various concentrations were incubated with 2.5 x 10⁴ Th2 cells and 500 nM DK-PGD₂ for 4 hrs at 37 °C in 200 µL of X-VIVO 15[®] medium containing 10% human AB serum. IL-13
30 production to the medium was detected by ELISA (enzyme-linked immunosorbent assay) using an "Instant ELISA™" kit (from Bender MedSystems Inc.) according to the procedure suggested by the vendor. The spontaneous production of IL-13 by Th2 cells was determined in the absence of DK-PGD₂

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stimulation and the value was subtracted from that in the presence of each compound for percent inhibition and IC₅₀ calculations.

The percent inhibition of interleukin 13 (IL-13) production for a compound at
5 various concentrations was calculated according to the following formula, $[1 - (\text{IL-13 production in the presence of compound}) / (\text{IL-13 production in the presence of 0.15\% DMSO})] \times 100$. The IC₅₀ value, defined as the concentration of a compound that is required for 50% inhibition of IL-13 production, was calculated by fitting the percent inhibition data for 7 concentrations to a sigmoidal dose-response (4
10 parameter logistic) model in the XLfit[®] software Excel add-in program [ID Business Solutions Ltd., model 205, where $F(x) = (A + (B - A) / (1 + ((C/x)^D)))$].

Representative compounds tested in the binding assay were tested using the foregoing DK-PGD₂-induced IL-13 production assay (examples 1-2 to 1-13, 2-1 to
15 2-8, 2-10 to 2-30, 2-32 to 5-1, 8-1, and 9-1 to 11-1). The results of the DK-PGD₂-induced IL-13 production assay showed that these compounds exhibited activity in inhibiting IL-13 production, with IC₅₀ values ranging from 0.0007 μM to 1.7419 μM.

20 Thus, the compounds of the present invention are useful since the compounds tested show some activity in at least one of the above three assays (i.e., binding at the CRTH2 receptor), and therefore may be useful as antagonists or partial agonists in treating diseases and disorders associated with this receptor such as
25 asthma.

In one embodiment, the present invention relates to a method for the treatment and/or prevention of diseases and disorders which are associated with the modulation of CRTH2 receptors, which method comprises administering a therapeutically effective amount of a compound of formula I to a human being or
30 animal. A method for the treatment and/or prevention of an inflammatory or allergic disease or disorder is preferred. Such diseases or disorders may include (but are not limited to) asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, allergic inflammation, and atopic dermatitis.

The present invention is also directed to the administration of a therapeutically effective amount of a compound of formula I in combination or association with other drugs or active agents for the treatment of inflammatory or allergic diseases and disorders. In one embodiment, the present invention relates to a method for the treatment and/or prevention of such diseases or disorders comprising administering to a human or animal simultaneously, sequentially, or separately, a therapeutically effective amount of a compound of formula I and another drug or active agent (such as another anti-inflammatory or anti-allergic drug or agent).

These other drugs or active agents may have the same, similar, or a completely different mode of action. Suitable other drugs or active agents may include, but are not limited to: Beta2-adrenergic agonists such as albuterol or salmeterol; corticosteroids such as dexamethasone or fluticasone; antihistamines such as loratidine; leukotriene antagonists such as montelukast or zafirlukast; anti-IgE antibody therapies such as omalizumab; anti-infectives such as fusidic acid (particularly for the treatment of atopic dermatitis); anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis); immunosuppressants such as tacrolimus and pimecrolimus; other antagonists of PGD2 acting at other receptors such as DP antagonists; inhibitors of phosphodiesterase type 4 such as cilomilast; drugs that modulate cytokine production such as inhibitors of TNF-alpha converting enzyme (TACE); drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors; PPAR-gamma agonists such as rosiglitazone; and 5-lipoxygenase inhibitors such as zileuton.

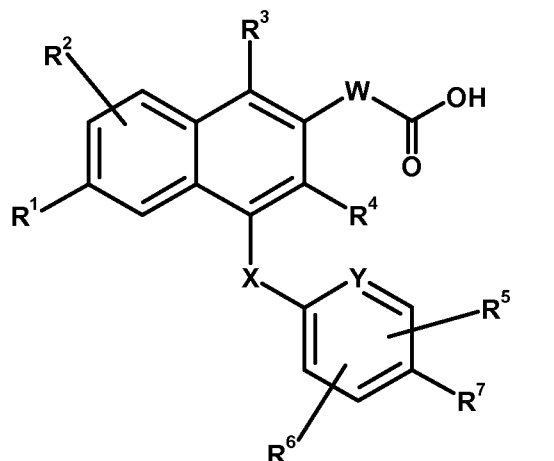
25

Unless stated to the contrary, all compounds in the examples were prepared and characterized as described. All patents and publications cited herein are hereby incorporated by reference in their entirety.

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CLAIMS

1. A compound of formula I:



5

or a pharmaceutically acceptable salt or ester thereof, wherein:

W is C(H)₂, C(H)₂-C(H)₂, C(H)(CH₃), CH₂-C(H)(CH₃), or C(H)(CH₃)-CH₂;

10 X is selected from the group consisting of:

- (1) O,
- (2) N(H),
- (3) N(CH₃),
- (4) S,
- (5) S(O), and
- (6) S(O)₂;

15

Y is carbon or nitrogen;

20 R¹ is selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) methyl optionally substituted by fluoro,
- (4) lower alkoxy optionally substituted by fluoro,
- (5) cyano, and

25

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(6) lower alkylsulfonyl;

R^2 is hydrogen, fluoro, chloro, lower alkyl, or lower alkoxy;

5 R^3 is hydrogen, fluoro, chloro, bromo, or methyl;

R^4 is selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- 10 (3) lower alkyl optionally substituted by fluoro,
- (4) lower cycloalkyl, and
- (5) ethenyl;

15 R^5 and R^6 , independently of each other, are selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) lower alkyl,
- (4) cyano, and
- 20 (5) lower cycloalkyl;

R^7 is cyano or $S(O)_2-R^8$, wherein R^8 is selected from the group consisting of:

- (1) lower alkyl,
- (2) lower cycloalkyl,
- 25 (3) phenyl optionally substituted by (a) halogen, (b) lower alkyl optionally substituted by fluoro, or (c) lower alkoxy,
- (4) lower alkylamino,
- (5) lower dialkylamino,
- (6) lower heterocycloalkyl optionally substituted by halogen, lower alkyl, or
- 30 lower alkoxycarbonyl, and
- (7) 2-oxa-6-aza-spiro[3.3]hept-6-yl.

2. A compound of claim 1 wherein W is $C(H)_2$.

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3. A compound according to any one of claim 1 or 2 wherein X is O.
4. A compound according to any one of claim 1 or 2 wherein X is N(H).
- 5 5. A compound according to any one of claim 1 or 2 wherein X is S, S(O), or S(O)₂.
6. A compound of claim 1 wherein W is C(H)₂, X is O, Y is carbon, and R⁷ is
10 S(O)₂-R⁸.
7. A compound of claim 1 wherein W is C(H)₂, X is O, Y is nitrogen, and R⁷ is S(O)₂-R⁸.
- 15 8. A compound according to any one of claims 1 to 7 wherein R² is hydrogen.
9. A compound according to any one of claims 1 to 8 wherein R¹ is halogen.
10. A compound according to any one of claims 1 to 7 wherein R¹ is fluoro and
20 R² is hydrogen.
11. A compound according to any one of claims 1 to 10 wherein R³ is hydrogen, fluoro, or methyl, preferably R³ is hydrogen.
- 25 12. A compound of according to any one of claims 1 to 11, wherein R⁴ is hydrogen, fluoro, or methyl, preferably R⁴ is methyl.
13. A compound according to any one of claims 1 to 12 wherein R⁵ and R⁶, independently of each other, are selected from the group consisting of: (1)
30 hydrogen, (2) fluoro, (3) chloro, (4) methyl, and (5) cyano.
14. A compound according to any one of claims 1 to 13 wherein at least one of R⁵ or R⁶ is hydrogen.

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15. A compound according to any one of claims 1 to 14 wherein R^5 and R^6 are both hydrogen.
16. A compound according to any one of claims 1 to 15 wherein R^7 is $S(O)_2-R^8$ and R^8 is selected from the group consisting of:
- (1) methyl,
 - (2) ethyl,
 - (3) propyl,
 - (4) isopropyl,
 - 10 (5) butyl,
 - (6) cyclopropyl,
 - (7) cyclobutyl,
 - (8) cyclopentyl,
 - (9) dimethylamino,
 - 15 (10) diethylamino,
 - (11) pyrrolidin-1-yl,
 - (12) morpholin-4-yl,
 - (13) 4,4-difluoro-piperidin-1-yl,
 - (14) 4-methyl-piperazin-1-yl, and
 - 20 (15) 2-oxa-6-aza-spiro[3.3]hept-6-yl.
17. A compound according to any one of claims 1 to 15 wherein R^7 is $S(O)_2-R^8$ and R^8 is selected from the group consisting of:
- (1) methyl, (2) ethyl, (3) isopropyl, (4) butyl, (5) dimethylamino, (6) diethylamino, (7) pyrrolidin-1-yl, (8) 4-methyl-piperazin-1-yl, and (9) 2-oxa-
 - 25 6-aza-spiro[3.3]hept-6-yl.
18. A compound according to any one of claims 1 to 15 wherein R^7 is $S(O)_2-R^8$ and R^8 is selected from the group consisting of:
- (1) ethyl,
 - (2) propyl,
 - 30 (3) isopropyl,
 - (4) cyclopropyl,
 - (5) butyl, and

(6) cyclopentyl.

19. A compound according to any one of claims 1 to 15 wherein R^7 is $S(O)_2-R^8$ and R^8 is ethyl.

5

20. A compound of claim 1 selected from the group consisting of:

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-naphthalen-2-yl]-acetic acid

[4-(4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

10 [6-Chloro-4-(4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid

[6-fluoro-4-(2-fluoro-4-methanesulfonyl-phenoxy)-3-methyl-naphthalen-2-yl]-acetic acid

15 [4-(4-ethanesulfonyl-3-methyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

[4-(2-cyano-4-ethanesulfonyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

{4-[4-(butane-1-sulfonyl)-phenoxy]-6-fluoro-3-methyl-naphthalen-2-yl}-acetic acid

20 [6-fluoro-4-(5-methanesulfonyl-pyridin-2-yloxy)-3-methyl-naphthalen-2-yl]-acetic acid

[4-(5-ethanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

25 [4-(3-bromo-5-methanesulfonyl-pyridin-2-yloxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

[4-(4-dimethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

{6-fluoro-3-methyl-4-[4-(pyrrolidine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid

30 [4-(4-diethylsulfamoyl-phenoxy)-6-fluoro-3-methyl-naphthalen-2-yl]-acetic acid

{6-fluoro-3-methyl-4-[4-(4-methyl-piperazine-1-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid

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{6-fluoro-3-methyl-4-[4-(2-oxa-6-aza-spiro[3.3]heptane-6-sulfonyl)-phenoxy]-naphthalen-2-yl}-acetic acid.

21. A pharmaceutically acceptable salt of a compound of claim 20.
- 5
22. A pharmaceutically acceptable ester of a compound of claim 20.
23. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 20 and a pharmaceutically
- 10 acceptable carrier.
24. The use of a compound according to any one of claims 1 to 20 for the preparation of a medicament for the treatment or prophylaxis of asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, allergic inflammation,
- 15 and atopic dermatitis.
25. The invention as hereinbefore defined, particularly with reference to the new compounds, intermediates, medicaments, uses and processes.