

ANILINE DERIVATIVES, THEIR PREPARATION AND THEIR THERAPEUTIC APPLICATION

The present invention relates to aniline derivatives, to their preparation and to their
5 therapeutic application.

Prostanoids comprise prostaglandins (PGs) and thromboxanes (TxS) and their receptors fall into five different classes (DP, EP, FP, IP and TP) based on their sensitivity to the five naturally occurring prostanoids, PGD₂, PGE₂, PGF_{2a}, PGI₂ and TxA₂.

10 EP receptors (for which the endogenous ligand is PGE₂) have been subdivided into four types termed EP₁, EP₂, EP₃ and EP₄. These four types of EP receptors have been cloned and are distinct at both molecular and pharmacological level. EP₂ agonists have been shown to be effective in the treatment of a number of conditions, including (but not limited to) dysmenorrhoea, pre-term labour, glaucoma, ocular hypertension, immune
15 disorders, osteoporosis, asthma, allergy, bone disease, fracture repair, male sexual dysfunction, female sexual dysfunction, periodontal disease, gastric ulcer, and renal disease.

EP₂ agonists have also been described in the treatment of inflammatory and immune disorders such as psoriasis, dermatitis, rheumatoid arthritis, multiple sclerosis, scleroderma, transplant rejection, allergy, systemic lupus erythematosus, vasculitis, type
20 1 diabetes mellitus, and inflammatory lung diseases such as chronic obstructive pulmonary disease, asthma, acute respiratory distress syndrome and cystic fibrosis.

In addition, EP₂ agonists have also been described in the treatment of fibrosis, including, but not limited to, scleroderma and systemic sclerosis, post-operative fibrosis following trabulectomy, liver repair and regeneration following cirrhosis, hepatitis, toxicity, cancer
25 or renal fibrosis. EP₂ agonists can also be used in the prevention of fibroblast to myofibroblast conversion to treat asthma and other fibrotic lung diseases. EP₂ agonists may also be used to maintain ductus arteriosus patency in infants with congenital heart disease.

30

Glaucoma is a disease of the eye. It is a multifactorial, progressive optic neuropathy with

a characteristic loss of retinal ganglion cells that form the optic nerve. It is the second leading cause of blindness in the world. Prevalence models estimate that 8.4 millions individuals suffered from glaucoma-induced bilateral blindness in 2010, rising to 11.1 million in 2020. Glaucoma is asymptomatic in the early stages, which is why 50% of patients affected are undiagnosed. It then results in peripheral visual field loss and if untreated, can lead to irreversible blindness.

Primary glaucoma is a congenital glaucoma and secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or enlarged cataract.

10

Primary Chronic Open-angle glaucoma is generally associated with increased pressure in the eye caused by trabecular blockage. Not all people with primary open-angle glaucoma show an elevated intra-ocular pressure, but decreasing the eye pressure has been shown to stop progression even in these cases. Primary open-angle glaucoma is characterized by progressive visual field loss and optic nerves changes.

15

In Primary Chronic or acute Closed-angle glaucoma, the iridocorneal angle is completely closed because of forward displacement of the final roll and root of the iris against the cornea. This can lead to acute crises characterized by sudden ocular pain, seeing halos around lights, red eye, very high intraocular pressure, nausea and vomiting, and sudden decreased vision. Acute angle closure is an ocular emergency.

20

The diagnosis of glaucoma is generally made by intra-ocular pressure measurements, visual field tests and by looking for changes in the optic nerve.

25

The different treatments of glaucoma aim to reduce intra-ocular pressure.

Several treatments are currently available: for example, beta-adrenergic antagonists, carbonic anhydrase inhibitors or topical prodrugs of prostaglandin FP receptor agonists (FP-agonists), like latanaprost, travoprost and bimatoprost. Applied *in vivo*, the marketed

30

topical prodrugs release their active drug (FP-agonist), which mainly increase uveoscleral outflow.

The marketed drugs nevertheless have important side effects; for example, latanoprost induces a gradual change in the eye colour of the patient by increasing the amount of brown pigment in the coloured part of the eye known as the iris. This pigmentation is irreversible and usually appears within 8 months of treatment. Latanoprost further induces an eye irritation (a feeling of burning, grittiness, itching, stinging or the sensation of a foreign body in the eye), a gradual change to eyelashes of the treated eye and the fine hairs around the treated eye, irritation or disruption to the surface of the eye, eyelid inflammation (blepharitis) and eye pain amongst others.

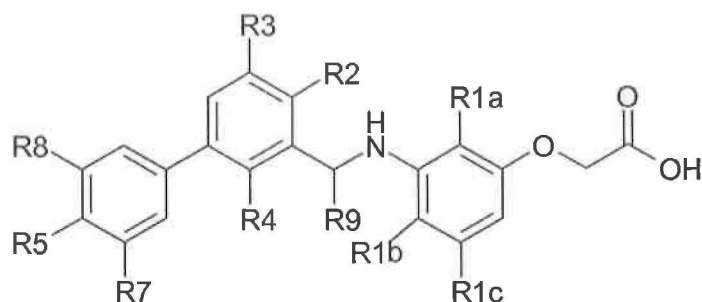
Therefore, there is a need for new treatments that reduce intraocular pressure in order to treat and/or prevent ocular diseases involving EP2 receptors, such as glaucoma, for example.

The invention relates to EP2 agonists and their prodrugs, to their preparation and to their therapeutic applications.

Fig. 1 shows the effect of topical administration of compound II(d) on intraocular pressure (IOP) in laser-induced glaucomatous monkeys.

The present invention provides compounds of formula (I) as described in the present specification or one of its prodrugs.

Compounds of formula (I) are drugs, in which:



(I)

R1a represents H, an halogen, a (C₁-C₆)alkyl or a CN;

5 R1b represents H, an halogen or a (C₁-C₆)alkyl;

R1c represents H or a(C₁-C₆)alkyl;

R2 represents H, an halogen, an OH, an O-(C₁-C₆)alkyl or (C₁-C₆)alkyl;

R3 represents H, an halogen, a (C₁-C₆)alkyl, an OH, an O-(C₁-C₆)alkyl, a CONH₂ or CN;

R4 represents H, an halogen or a (C₁-C₆)alkyl;

10 R5 represents H or F;

R7 represents H or F;

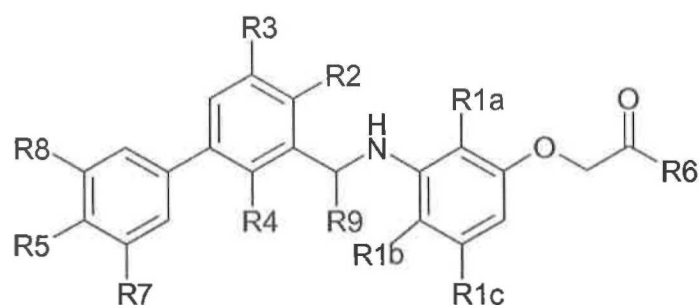
R8 represents H or F;

R9 represents H or (C₁-C₆)alkyl, or one of its enantiomers..

The compounds of formula (I) may contain one or more asymmetric carbon atoms. They
 15 may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including the racemic mixtures, form part of the invention.

The compounds of formula (I) may be present as well under tautomer forms and are part
 20 of the invention

Compounds of formula (II) are prodrugs of compounds of formula (I), in which:



(II)

- R1a represents H, an halogen, a (C₁-C₆)alkyl or a CN;
- 5 R1b represents H, an halogen or a (C₁-C₆)alkyl;
- R1c represents H or a (C₁-C₆)alkyl;
- R2 represents H, an halogen, an OH, an O-(C₁-C₆)alkyl or (C₁-C₆)alkyl;
- R3 represents H, an halogen, a (C₁-C₆)alkyl, an OH, an O-(C₁-C₆)alkyl, a CONH₂ or a CN;
- 10 R4 represents H, an halogen or a (C₁-C₆)alkyl;
- R5 represents H or F;
- R6 represents an O-(C₁-C₆)alkyl, an O-(C₁-C₆)alkyl-heterocycloalkyl, a NH₂, a NH-(C₁-C₆)alkyl, an O-(C₁-C₆)alkyl optionally substituted by one to three hydroxyl groups, O-(C₁-C₆)alkyl-O-CO(C₁-C₆)alkyl);
- 15 R7 represents H or F;
- R8 represents H or F;
- R9 represents H or a (C₁-C₆)alkyl, or one of its enantiomers..

The compounds of formula (II) may contain one or more asymmetric carbon atoms. They may therefore exist in the form of enantiomers or diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including the racemic mixtures, form part of the invention.

The compounds of formula (II) may be present as well under tautomer forms and are part

of the invention

In the context of the present invention, the following terms have to be understood as:

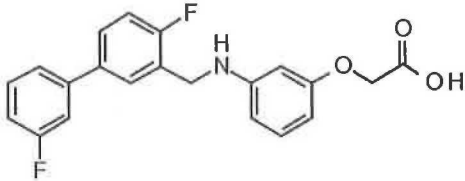
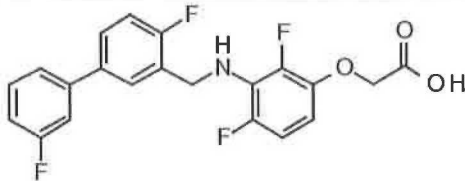
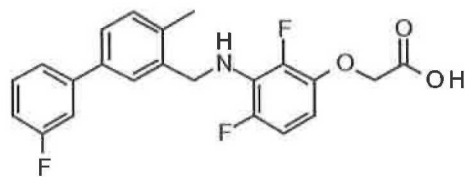
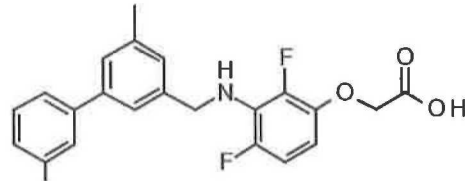
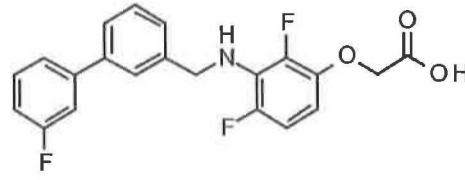
- enantiomers: Organic compounds that contain a chiral carbon usually have two non-superimposable structures.
 - halogen: a fluorine, a chlorine, a bromine or an iodine atom;
 - (C₁-C₆)alkyl : a linear or branched saturated hydrocarbon group. Examples include, but are not limited to the groups methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, etc. If a branched (C₁-C₆)alkyl is substituted, the substitution can occur, for example, on terminal hydrocarbon groups;
 - heterocycloalkyl: a 5 to 8 membered saturated ring, comprising at least one of the following heteroatoms: O, N or S. The heterocycloalkyl can be linked to the rest of the molecule *via* a carbon or a heteroatom. If the heterocycloalkyl is substituted, substitution can occur on a carbon atom or on a heteroatom. Examples of heterocycloalkyl include morpholine;
 - a prodrug: a compound that, on administration, must undergo conversion by chemical or metabolic processes before becoming an active pharmacological agent. Once administered, the prodrug is converted *in vivo* into a therapeutically active compound (drug). This conversion can take place in one or more steps. A prodrug is usually not a therapeutically active compound itself and will usually not elicit *in vitro* the biological response of the corresponding therapeutically active compound. For example, esters and amides can act as prodrugs of their corresponding carboxylic acids where the ester or amide bond can be hydrolysed either chemically or metabolically to provide the free carboxylic acid.
- A major aim of prodrug design is to improve the safety and pharmacokinetic behaviour of active carboxylic acids. A carboxylic acid group, being ionized in the physiological pH range, contributes significantly to reduce the lipophilicity of compounds containing this moiety. As a result, a large number of pharmacologically active carboxylic acids display unfavorable pharmacokinetic properties such as low bioavailability, a problem of particular concern for compounds that contain other moieties of high polarity.

In the eye, the EP2 receptor has been identified in the plexiform and nerve fiber layers of the human retina and in the cornea, conjunctiva, sclera, and lens.

In addition, an EP2 receptor agonist may have an opportunity to enhance long term
5 treatment outcomes following glaucoma filtration surgery. Scar formation is a major
source of failure for glaucoma filtration surgery. Limiting fibrotic response is important
for limiting scar formation and tissue fibrosis.

Among the compounds of formula (I) and (II) that are subject matter of the invention,
10 mention may be made in particular of the compounds in table 1:

Table 1:

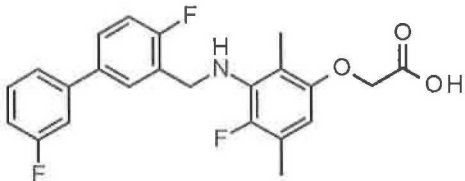
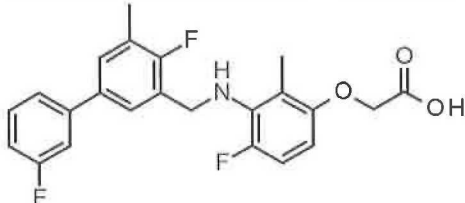
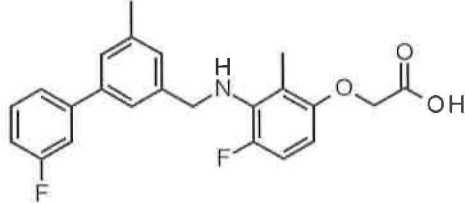
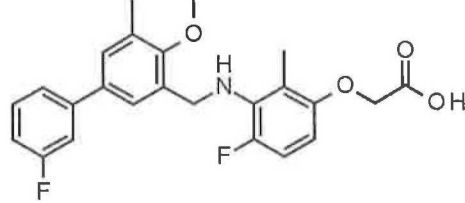
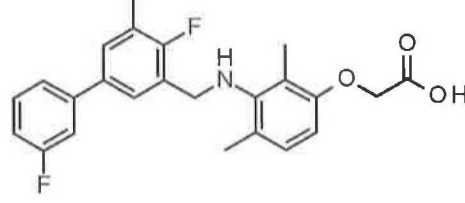
Compound number	Structure	Name
I(a)		2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
I(b)		2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
I(c)		2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methylphenyl]methylamino]phenoxy]acetic acid
I(d)		2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methylphenyl]methylamino]phenoxy]acetic acid
I(e)		2-[2,4-difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid

Compound number	Structure	Name
I(f)		2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetic acid
I(g)		2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methylphenoxy]methylamino]phenoxy]acetic acid
I(h)		2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methylphenoxy]methylamino]phenoxy]acetic acid
I(i)		2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methylphenoxy]acetic acid
I(j)		2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethylphenoxy]acetic acid
I(k)		2-[4-chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid

Compound number	Structure	Name
I(l)		2-[3-[[2-chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenoxy]acetic acid
I(m)		2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methylphenoxy]acetic acid
I(n)		2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
I(o)		2-[2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
I(p)		2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetic acid
I(q)		2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxyphenyl]methylamino]phenoxy]acetic acid

Compound number	Structure	Name
I(r)		2-[2,4-dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
I(s)		2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenoxy]acetic acid
I(t)		2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methylphenyl]methylamino]phenoxy]acetic acid
I(u)		2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methylphenyl]methylamino]phenoxy]acetic acid
I(v)		2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethylphenyl]methylamino]phenoxy]acetic acid

Compound number	Structure	Name
I(w)		2-[3-[[5-(3,4-difluorophenyl)-2-fluoro-phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid
I(x)		2-[3-[[3-cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid
I(y)		2-[2,4-difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid
I(z)		2-[3-[[3-carbamoyl-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid
I(aa)		2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid
I(ab)		2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenoxy]acetic acid

Compound number	Structure	Name
I(ac)		2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenoxy]acetic acid
I(ad)		2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid
I(ae)		2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid
I(af)		2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid
I(ag)		2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid

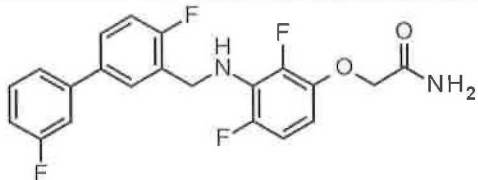
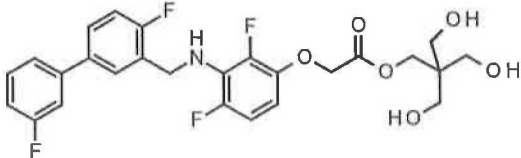
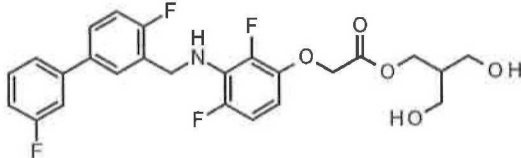
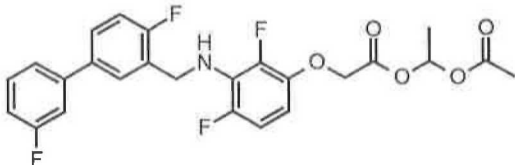
Compound number	Structure	Name
I(ah)		2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl-phenoxy]acetic acid
I(ai)		2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid
I(aj)		2-[3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid
I(ak)		2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid
I(al)		2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid
I(am)		2-[3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid

Compound number	Structure	Name
I(an)		2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
I(ao)		2-[3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid
I(ap)		2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid
I(aq)		2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid
I(ar)		2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid

Compound number	Structure	Name
I(as)		2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy]acetic acid
I(at)		2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethylphenyl]methylamino]-2-methylphenoxy]acetic acid
I(au)		2-[3-[(2,3-dimethyl-5-phenylphenyl)methylamino]-2,4-difluorophenoxy]acetic acid
I(av)		2-[4-fluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methylphenyl]methylamino]-2-methylphenoxy]acetic acid
I(aw)		2-[3-[[3-fluoro-5-(3-fluorophenyl)-2-methylphenyl]methylamino]-2,4-dimethylphenoxy]acetic acid

Compound number	Structure	Name
II(a)		ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(b)		ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetate
II(c)		methyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(d)		isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(e)		isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methylphenyl]methylamino]phenoxy]acetate

Compound number	Structure	Name
II(f)		isopropyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)]-5-methyl-phenyl]methylamino]phenoxy]acetate
II(g)		isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)]phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(h)		ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)]-3-methyl-phenyl]methylamino]phenoxy]acetate
II(i)		isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)]phenyl]methylamino]-2-methyl-phenoxy]acetate
II(j)		2-hydroxyethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)]phenyl]methylamino]phenoxy]acetate
II(k)		2-morpholinoethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)]phenyl]methylamino]phenoxy]acetate

Compound number	Structure	Name
II(l)		2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetamide
II(m)		2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]-N-ethylacetamide
II(n)		[3-hydroxy-2,2-bis(hydroxymethyl)propyl] 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(o)		[3-hydroxy-2-(hydroxymethyl)propyl] 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(p)		1-acetoxyethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate

Compound number	Structure	Name
II(q)		isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxyphenyl]methylamino]phenoxy]acetate
II(r)		isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetate
II(s)		ethyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(t)		ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methylphenyl]methylamino]phenoxy]acetate
II(u)		ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(v)		ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetate

Compound number	Structure	Name
II(w)		ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methylphenyl]methylamino]phenoxy]acetate
II(x)		ethyl 2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methylphenoxy]acetate
II(y)		ethyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methylphenoxy]acetate
II(z)		ethyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(aa)		ethyl 2-[2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(ab)		ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxyphenyl]methylamino]phenoxy]acetate

Compound number	Structure	Name
II(ac)		ethyl 2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetate
II(ad)		ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methylphenyl]methylamino]phenoxy]acetate
II(ae)		isopropyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methylphenyl]methylamino]phenoxy]acetate
II(af)		isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenoxy]acetate
II(ag)		isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenoxy]acetate
II(ah)		isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methylphenyl]methylamino]-2-methyl-phenoxy]acetate

Compound number	Structure	Name
II(ai)		isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
II(aj)		isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
II(ak)		isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(al)		isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl-phenoxy]acetate
II(am)		isopropyl 2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate

Compound number	Structure	Name
II(an)		isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methylphenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(ao)		isopropyl 2-[3-[[5-(3-fluorophenyl)-2,3-dimethylphenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(ap)		isopropyl 2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methylphenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(aq)		isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methylphenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(ar)		isopropyl 2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate
II(as)		isopropyl 2-[3-[[3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]-2,4-dimethyl-phenoxy]acetate

Compound number	Structure	Name
II(at)		isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methoxyphenyl]methylamino]-2,4-dimethylphenoxy]acetate
II(au)		isopropyl 2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethylphenyl]methylamino]-2,4-difluorophenoxy]acetate
II(av)		isopropyl 2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethylphenyl]methylamino]-2,4-difluorophenoxy]acetate
II(aw)		isopropyl 2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy]acetate
II(ax)		isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethylphenyl]methylamino]-2-methylphenoxy]acetate

Compound number	Structure	Name
II(ay)		isopropyl 2-[3-[(2,3-dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate
II(az)		isopropyl 2-[4-fluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
II(ba)		isopropyl 2-[3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
II(bb)		isopropyl 2-[3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate

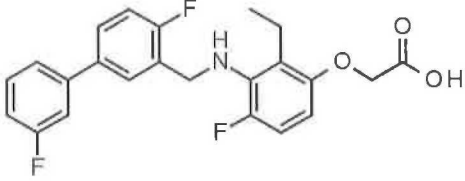
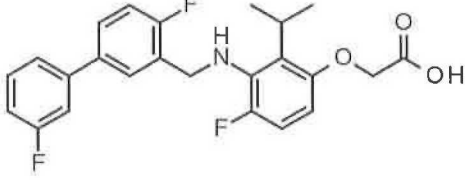
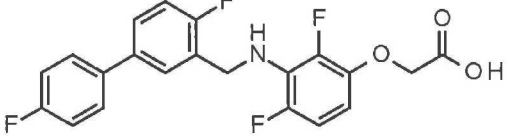
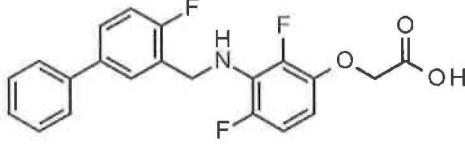
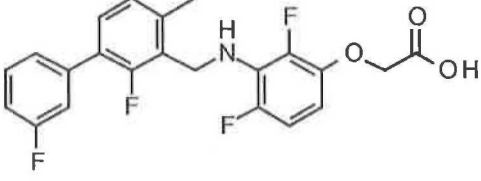
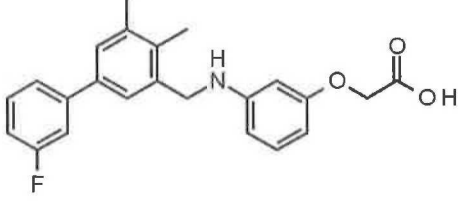
(IUPAC chemical names have been attributed by the SymyxDraw program, version 3.2)

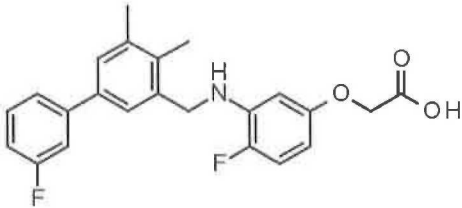
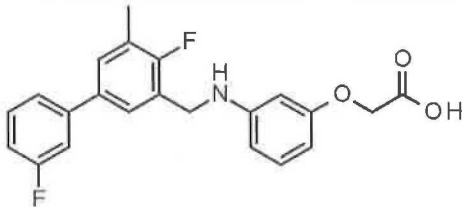
In another aspect of the present invention, the invention comprises compounds of formula
 5 (I) as described above with the proviso that compounds of formula (I) are not
 compounds of table 2:

Table 2:

Formula	Chemical name
	2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid
	2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
	2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-phenyl]methylamino]phenoxy]acetic acid

Formula	Chemical name
	2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-2,5-dimethyl-phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[5-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-6-hydroxy-phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-6-methoxy-phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-isopropyl-phenyl]methylamino]phenoxy]acetic acid
	2-[3-[[3-ethyl-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid

Formula	Chemical name
	2-[2-ethyl-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
	2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-isopropyl-phenoxy]acetic acid
	2-[2,4-difluoro-3-[[2-fluoro-5-(4-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[(2-fluoro-5-phenyl)phenyl]methylamino]phenoxy]acetic acid
	2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-6-methylphenyl]methylamino]phenoxy]acetic acid
	2-[3-[[5-(3-fluorophenyl)-2,3-dimethylphenyl]methylamino]phenoxy]acetic acid

Formula	Chemical name
	2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenoxy]acetic acid
	2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetic acid

In another aspect, the invention comprises compounds of formula (I) as described above, where when R1a, R1b, R1c, R2, R3 and/or R9 represent a (C₁-C₆)alkyl, this (C₁-C₆)alkyl is a methyl, or one of its enantiomers.

5

In another aspect, the invention comprises compounds of formula (I) as described above, where halogen is fluorine or chlorine, or one of its enantiomers.

In another aspect, the invention comprises compounds of formula (I) as described above, where both R1a and R1b are fluorine, or one of its enantiomers.

10

In another aspect, the invention comprises compounds of formula (I) as described above, where two of R2, R3 and R4 are H, or one of its enantiomers.

In another aspect, the invention comprises compounds of formula (I) as described above, where one of R2, R3 and R4 is H, or one of its enantiomers.

15

In another aspect, the invention comprises compounds of formula (I) as described above, where R5 and R8 are hydrogen, or one of its enantiomers.

20

In another aspect, the invention comprises compounds of formula (I), or one of its prodrugs, as described above, where

R1a and R1b represent, independently from each other, H or an halogen,

R1c is H,

5 R2 represents H, an halogen or a (C₁-C₆)alkyl,

R3 represents H an halogen, an OH, or a (C₁-C₆)alkyl,

R4 represents H, an halogen, an OH or a (C₁-C₆)alkyl,

R5, R8 and R9 are H and,

R7 is F,

10 or one of its enantiomers.

In another aspect, the invention comprises compounds of formula (I), or one of its prodrugs, as described above, where

R1a and R1b represent, independently from each other, H or an halogen,

15 R1c is H,

R2 represents H, an halogen or a (C₁-C₆)alkyl,

R3 represents H, an halogen, an OH or a (C₁-C₆)alkyl,

R4 represents H, an halogen, or a (C₁-C₆)alkyl,

R5, R8 and R9 are H and,

20 R7 is F

or one of its enantiomers.

In another aspect, the invention comprises compounds of formula (I), or one of its prodrugs, as described above, where

25 R1a represents H, an halogen or a (C₁-C₆)alkyl,

R1b represents, H, an halogen or a (C₁-C₆)alkyl,

R1c is H or a (C₁-C₆)alkyl,

R2 represents H, an halogen, an OH, an O-(C₁-C₆)alkyl or a (C₁-C₆)alkyl,

R3 represents H, an halogen, an OH, a (C₁-C₆)alkyl, an O-(C₁-C₆)alkyl, a CONH₂ or a

30 CN,

R4 represents H, an halogen or a (C₁-C₆)alkyl,

R5 represents H or **F**
 R8 and R9 are H and,
 R7 is F
 or one of its enantiomers.

5

In another aspect, the invention comprises compounds of formula (II) as described above, where R1a and R1b represent, independently from each other, methyl and/or fluorine, or one of its enantiomers.

- 10 In another aspect, the invention comprises compounds of formula (II) as described above, where R1c, R5 and R8 represent H, or one of its enantiomers.

- In another aspect, the invention comprises compounds of formula (II) as described above where R2 and R4 represent, independently from each other, H and/or fluorine, or one of
 15 its enantiomers.

In another aspect, the invention comprises compounds of formula (II) as described above, where R6 is O-isopropyl, or one of its enantiomers.

- 20 In another aspect, the invention comprises compounds of formula (II) as described above, where
 R1a and R1b represent, independently from each other, H or an halogen,
 R1c is H,
 R2 represents H, an halogen or a (C₁-C₆)alkyl,
 25 R3 represents H, an halogen, an OH, or a (C₁-C₆)alkyl,
 R4 represents H, an halogen, an OH, or a (C₁-C₆)alkyl,
 R5, R8 and R9 are H,
 R7 is F and
 R6 is an O-(C₁-C₆)alkyl, an O-ethyl-morpholine, an O-CH(CH₃)-OCOCH₃, an O-CH₂-
 30 CH₂-OH, an O-CH-(CH₂OH)₂, an O-CH₂-CH-(CH₂OH)₂ or an O-CH₂-C-(CH₂OH)₃,
 or one of its enantiomers.

In another aspect, the invention comprises compounds of formula (II) as described above, where

R1a and R1b represent, independently from each other, H or an halogen,

R1c is H,

5 R2 represents H, an halogen or a (C₁-C₆)alkyl,

R3 represents H, an halogen, an OH, or a (C₁-C₆)alkyl,

R4 represents H, an halogen or a (C₁-C₆)alkyl,

R5, R8 and R9 are H,

R7 is F and

10 R6 is an O-(C₁-C₆)alkyl, an O-ethyl-morpholine, an O-CH(CH₃)-OCOCH₃, an O-CH₂-CH₂-OH, an O-CH-(CH₂OH)₂, an O-CH₂-CH-(CH₂OH)₂ or an O-CH₂-C-(CH₂OH)₃, or one of its enantiomers.

In another aspect, the invention comprises compounds of formula (II) as described above,

15 where

R1a represents H, an halogen or a (C₁-C₆)alkyl,

R1b represents H, an halogen or a (C₁-C₆)alkyl,

R1c is H or a (C₁-C₆)alkyl,

R2 represents H, an halogen, an OH, an O-(C₁-C₆)alkyl or a (C₁-C₆)alkyl,

20 R3 represents H, an halogen, an OH, a (C₁-C₆)alkyl, an O-(C₁-C₆)alkyl, a CONH₂ or a CN,

R4 represents H, an halogen or a (C₁-C₆)alkyl,

R5 represents H or F

R8 and R9 are H,

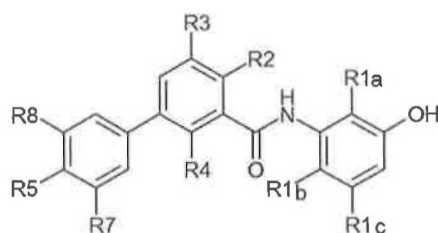
25 R7 is F, and

R6 represents O-(C₁-C₆)alkyl, O-(C₁-C₆)alkyl-heterocycloalkyl, NH₂, NH-(C₁-C₆)alkyl, O-(C₁-C₆)alkyl optionally substituted by one to three hydroxyl groups, O-(C₁-C₆)alkyl-O-CO(C₁-C₆)alkyl,

or one of its enantiomers.

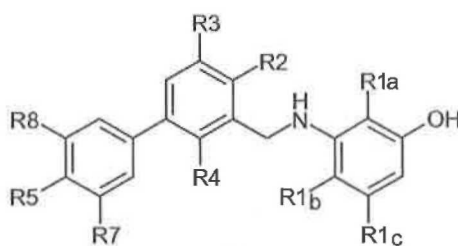
30

In another aspect, the invention comprises a process for preparing a compound of formula (I) or one of its prodrugs, characterized in that a compound of formula (XI):



XI

5 is reduced to give a compound of formula (IX),:

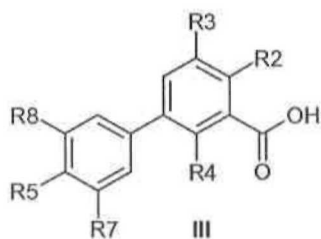


IX

which is reacted with $\text{BrCH}_2\text{COR}_6$ to give a compound of formula (II),
in which R1a, R1b, R1c, R2, R3, R4, R5, R7, R8 and R6 are as defined above .

10

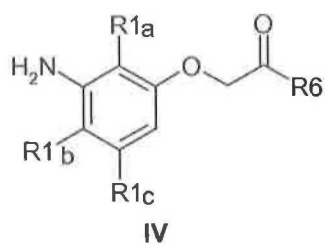
In another aspect, the invention comprises a compound of formula (III):



III

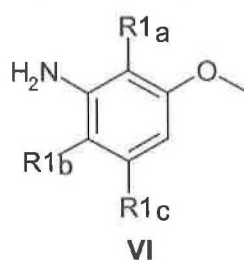
in which R2, R3, R4, R5, R7 and R8 are as defined above, or one of its enantiomers.

15 In another aspect, the invention comprises a compound of formula (IV):



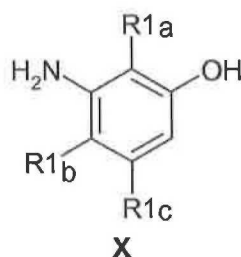
in which R1a, R1b, R1c and R6 are as defined above, or one of its enantiomers.

In another aspect, the invention comprises a compound of formula (VI):



in which R1a, R1b and R1c are as defined above, or one of its enantiomers.

In another aspect, the invention comprises a compound of formula (X):



in which R1a, R1b and R1c are as defined above, or one of its enantiomers.

In another aspect, the invention comprises a medicament, characterized in that it comprises a compound of formula (I) or one of its prodrugs as defined above.

In another aspect, the invention comprises a pharmaceutical composition, characterized in that it comprises a compound of formula (I) or one of its prodrugs as defined above, and also at least one pharmaceutically acceptable excipient.

In another aspect, the invention comprises a use of a compound of formula (I) or one of its prodrugs as defined above, for preparing a medicament intended for the treatment of glaucoma.

- 5 In another aspect, the invention comprises a compound of formula (I) or one of its prodrugs as defined above, as EP2 agonist.

- In another aspect, the invention comprises a method of treatment of glaucoma, which comprises administering to a patient an effective dose of a compound of formula (I) or
10 one of its prodrugs as defined above.

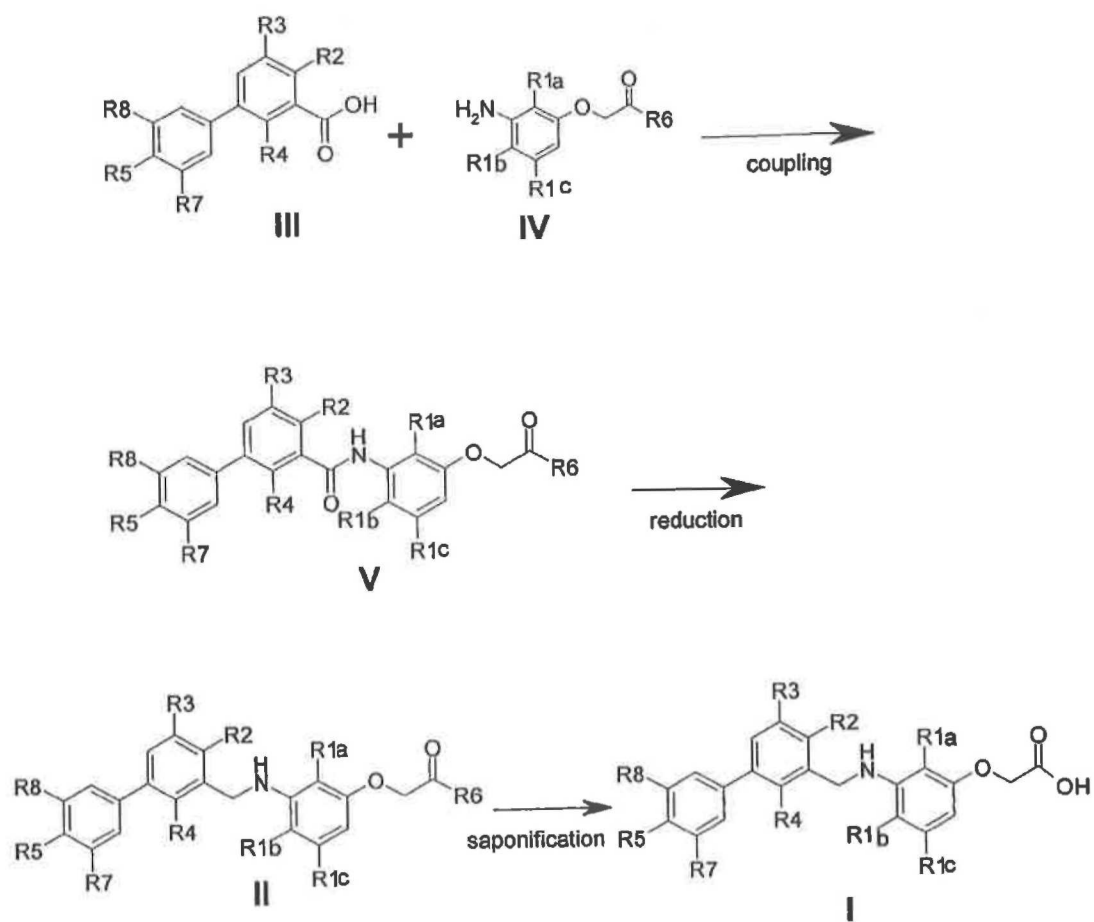
In another aspect, the invention comprises a compound of formula (I) or one of its prodrugs as defined above, as a medicament.

- 15 In another aspect, the invention comprises a combination of a compound of formula (I) or one of its prodrugs, as defined above, with beta-blockers, prostaglandins, sympathomimetic collyres, inhibitors of carbonic anhydrase, or parasympathomimetic collyres.
- 20 In accordance with the invention the compounds of general formula (I) and (II) can be prepared by the following processes.

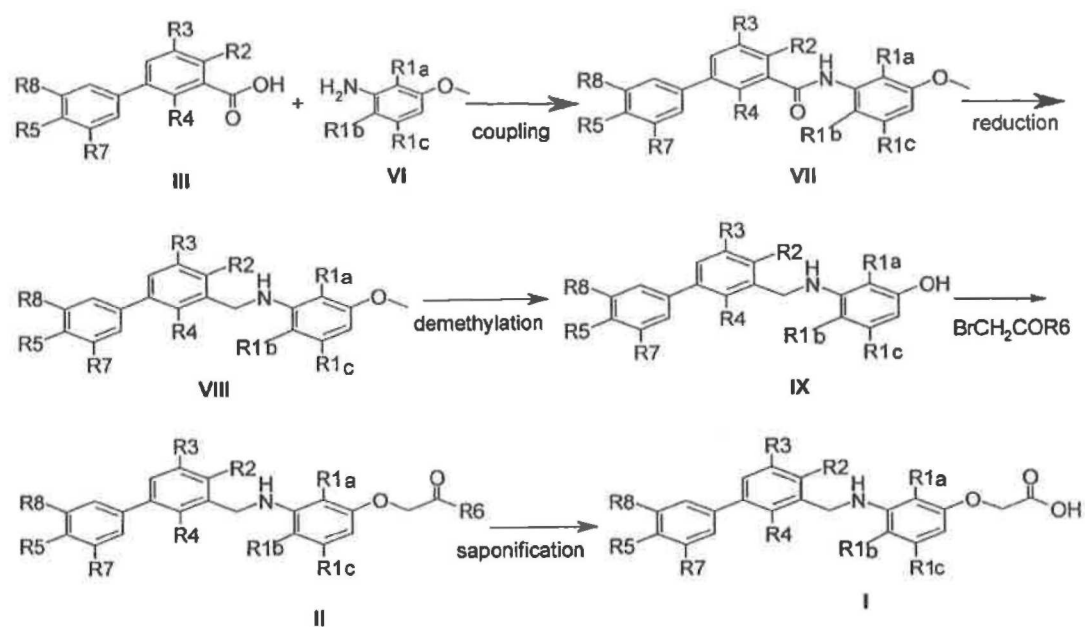
- Acids of formula (I) according to the invention can be prepared by the route outlined in schemes 1 to 5, where R1a, R1b, R1c, R2, R3, R4, R5, R6, R7, R8 and R9 are as defined
25 above. In a particular aspect, R6 is $-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$.

Scheme 1:

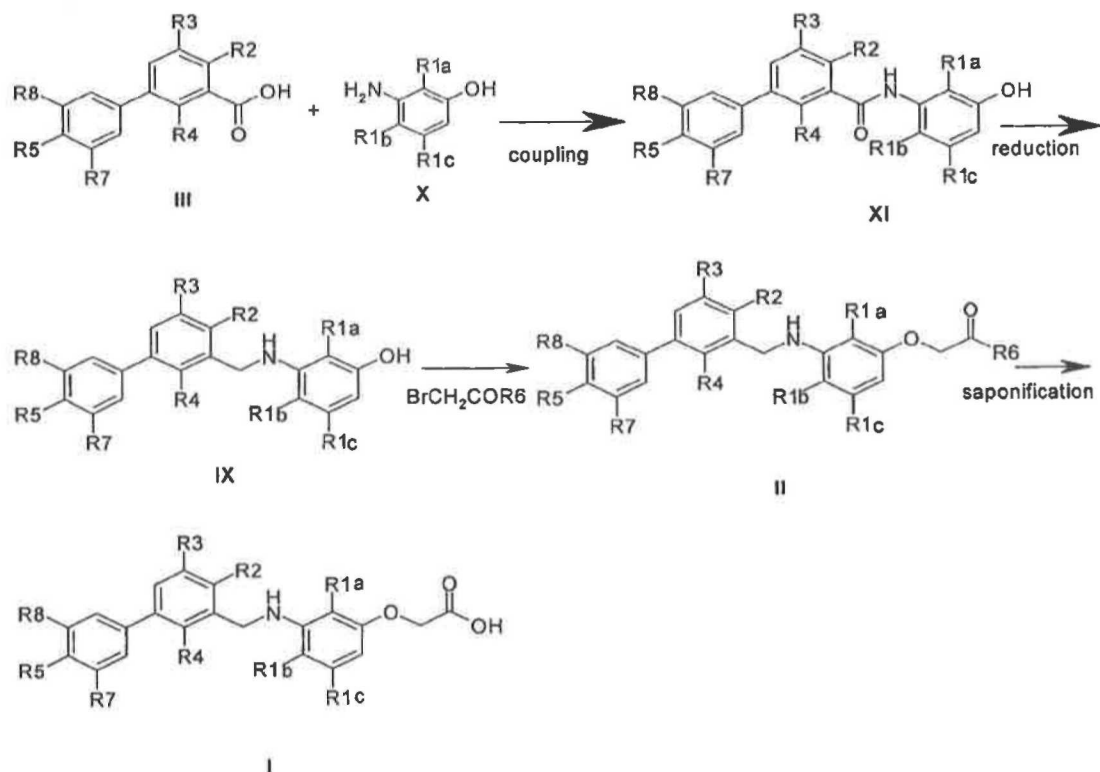
Scheme 1:



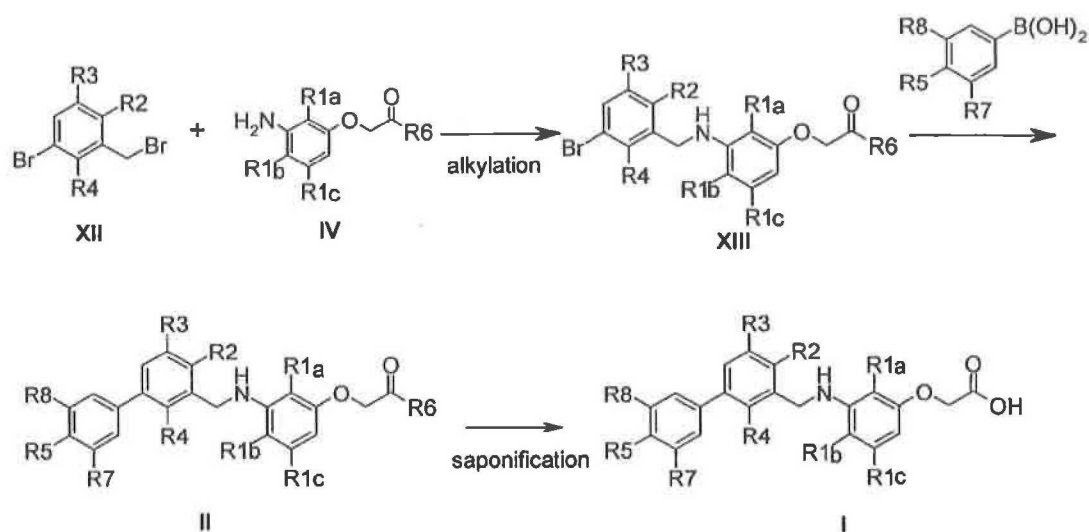
Scheme 2:



5 Scheme 3:

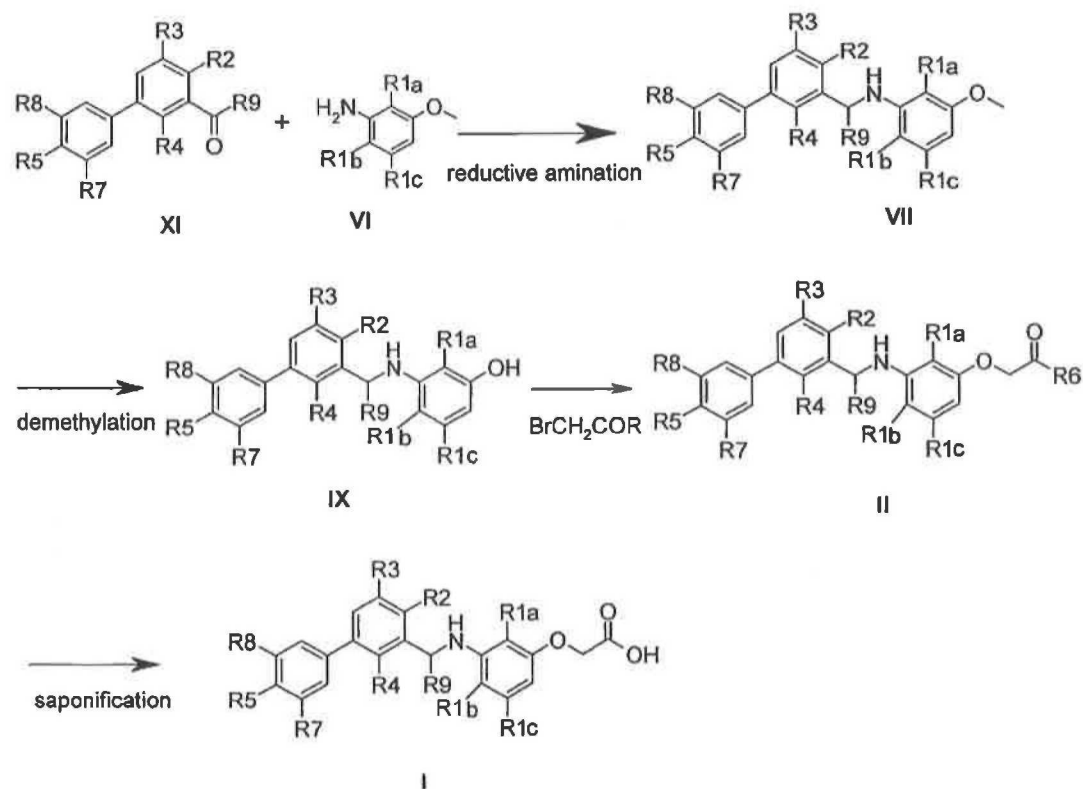


Scheme 4:



5

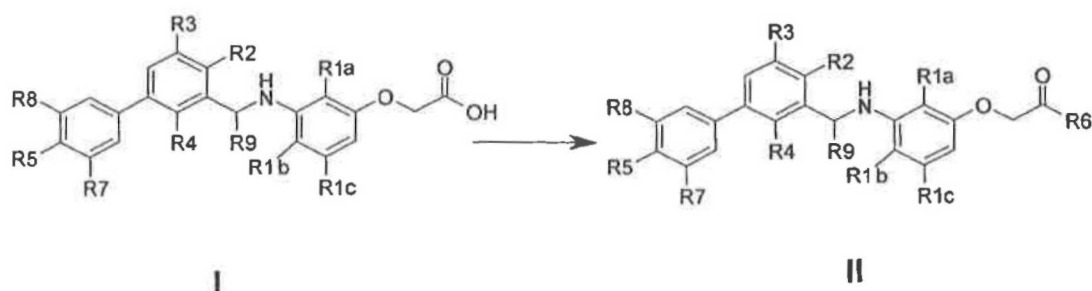
Scheme 5:



Prodrugs of formula (II) according to the present invention can also be synthesized according to scheme 6, where acids of formula (I) are converted into the corresponding esters or amides of formula (II) by standard methods known to those skilled in the art.

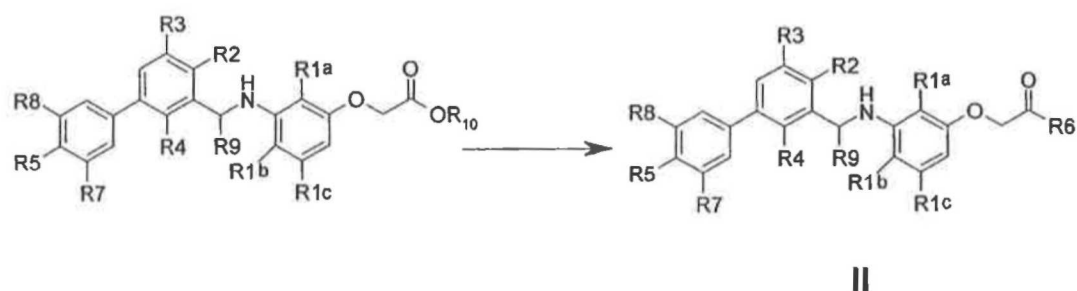
5

Scheme 6:



Prodrugs of formula (II) according to the present invention can also be synthesized according to scheme 7, where esters with R₁₀ being a (C₁-C₆)alkyl, are converted into the corresponding esters or amides of formula (II) by standard methods known to those skilled in the art.

Scheme 7:



EXAMPLES

20

The following non-limiting preparations and examples illustrate the preparation of the compounds of the invention.

¹H Nuclear Magnetic Resonance (NMR) spectra were in all cases consistent with the proposed structures. We used a Fourier 300 MHz and 400 MHz Bruker. Characteristic chemical shifts δ are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bb, broad band. The mass spectra (m/z) (Agilent MSD) were recorded using electrospray ionisation (ESI). The following abbreviations have been used for common solvents:

(Boc)₂O, di-tert-butyl dicarbonate,
CDCl₃, deuteriochloroform,
10 DCM, dichloromethane,
DMA, N,N-dimethyl acetamide,
DMAP, 4-dimethylaminopyridine,
DMF, dimethylformamide,
DMSO-d₆, deuterodimethylsulphoxide,
15 Dppf, 1,1'-bis(diphenylphosphino)ferrocene,
EDC, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide,
EtOAc, ethyl acetate,
EtOH, ethanol,
HATU, peptide coupling reagent (CAS nb. 148893-10-1)
20 HOBt, 1-hydroxybenzotriazole,
iPrOH, 2-propanol,
MeOD, deuterated methanol,
MeOH, methanol,
MTBE, methyl tertiary-butyl ether,
25 NBS, N-bromosuccinimide,
n-BuLi, n-butyllithium,
petroleum ether, that fraction of petroleum that boils between 60 and 80°C
PMDTA, N, N, N', N', N'' pentamethyldiethylenetriamine,
sBuLi, sec-butyllithium,
30 tBuOH, tert-butylalcohol
t-BuOK, Potassium tert-butoxide

TEA, triethylamine,

TFA, trifluoroacetic acid,

THF, tetrahydrofuran,

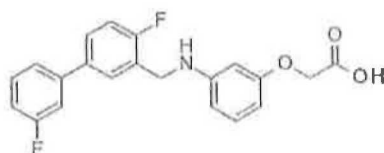
5 TLC, thin layer chromatography,

TIPSCl, triisopropylsilylchloride,

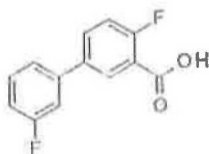
Where thin layer chromatography (TLC) has been used it refers to silica gel 60 F254 plates, R_f is the distance travelled by a compound divided by the distance travelled by the solvent front on a TLC plate.

Example 1 – Compound I(a) synthesized according to scheme 2

2-[3-[[2-Fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(a))



2-Fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a))



20 To a mixture of 5-bromo-2-fluorobenzoic acid (3g, 13.2 mmol, 1.0 eq) and 3-fluorophenyl boronic acid (2.1 g, 15.1 mmol, 1.1 eq) in water (15 mL), EtOH (15 mL) and DMF (60 mL) was added Na_2CO_3 (5.81 g, 54.8 mmol, 4.1 eq) and $\text{Pd}(\text{PPh}_3)_4$ (1.58 g, 1.37 mmol, 0.1 eq). The reaction mixture was heated at 100°C under nitrogen for 4h, then
25 cooled to room temperature. The resulting mixture was poured into water and extracted

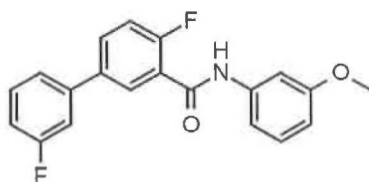
with ethyl acetate. The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a white powder (3 g, 97 %).

LC-MS: m/z 235.1 $[\text{M}+\text{H}]^+$, 257.0 $[\text{M}+\text{Na}]^+$

5

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.10 (dd, $J = 6.9, 2.5$ Hz, 1H), 7.96 (ddd, $J = 8.5, 4.5, 2.6$ Hz, 1H), 7.59 – 7.48 (m, 3H), 7.42 (dd, $J = 10.6, 8.7$ Hz, 1H), 7.22 (m, 1H).

10 *2-Fluoro-5-(3-fluorophenyl)-N-(3-methoxyphenyl)benzamide*

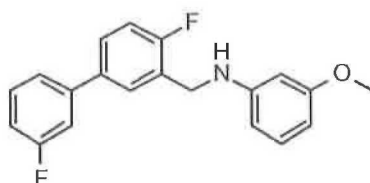


A mixture of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (500 mg, 2.10 mmol, 1.0 eq) in SOCl_2 (5 mL) was heated at 65°C under N_2 for 1h. The solution was then evaporated *in vacuo* and the remaining residue dissolved in CH_2Cl_2 and added dropwise to a mixture of 3-methoxyaniline (220 mg, 1.9 mmol, 0.9 eq) and K_2CO_3 (1.4 g, 10.1 mmol, 5.0 eq) in THF (10 mL) at 0°C . The reaction was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with water and the solution extracted with EtOAc. The combined organic extracts were washed with aqueous Na_2CO_3 and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a colourless oil (580 mg, 96 %).

20

LC-MS: m/z 340.2 $[\text{M}+\text{H}]^+$

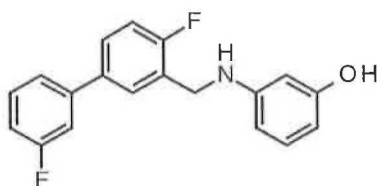
N-[[2-Fluoro-5-(3-fluorophenyl)phenyl]methyl]-3-methoxy-aniline



To a solution of 2-fluoro-5-(3-fluorophenyl)-N-(3-methoxyphenyl)benzamide (605 mg, 1.80 mmol, 1.0 eq) in THF (3 mL) was added dropwise a solution of BH_3 (1 M in THF, 5.3 mL, 5.3 mmol, 2.9 eq) at 0°C . The reaction was heated at reflux overnight, then
5 cooled to room temperature and quenched by addition of methanol and water. The reaction was diluted with EtOAc and water and the aqueous layer extracted further with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography (petroleum ether: EtOAc, 10:1) to give the title compound as a colourless oil (512 mg,
10 88 %).

LC-MS: m/z 326.1 $[\text{M}+\text{H}]^+$

3-[[2-Fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol



15

To a solution of N-[[2-fluoro-5-(3-fluorophenyl)phenyl]methyl]-3-methoxy-aniline (512 mg, 1.60 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at -70°C was added BBr_3 (0.6 mL, 65.3 mmol, 40.8 eq). The reaction was warmed to room temperature and stirred for 1 h. The reaction was then cooled to 0°C and quenched by addition of water. The pH of the solution was
20 adjusted to pH 7 with aqueous Na_2CO_3 , then extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a colourless oil (460 mg, 94 %).

LC-MS: m/z 312.1 $[\text{M}+\text{H}]^+$

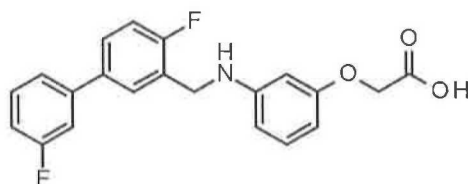
Ethyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(s))

To a mixture of 3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol (300 mg, 0.96 mmol, 1.0 eq.) and t-BuOK (216 mg, 1.90 mmol, 2.0 eq) in DMF (3 mL) was added dropwise ethyl bromoacetate (193 mg, 128uL, 1.20 mmol, 1.2 eq) at 0°C. The resulting mixture was stirred for 1h at room temperature. The reaction was quenched with water and neutralized with 1 M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by chromatography (petroleum ether: EtOAc, 4:1) to give the title compound as a colourless oil (200 mg, 52 %).

LC-MS: m/z 398.1 [M+H]⁺

¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.39 (m, 1H), 7.35 – 7.28 (m, 2H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.16 – 7.07 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.86 – 6.79 (m, 2H), 6.76 (dd, *J* = 7.9, 2.4 Hz, 1H), 6.36 (m, 1H), 4.72 (s, 2H), 4.42 (d, *J* = 6.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 2H).

2-[3-[[2-Fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (compound I(a))



To a stirred solution of ethyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (317.0 mg, 0.83 mmol, 1.0 eq) in a mixture of THF (6 mL) and H₂O (6 mL) was added LiOH.H₂O (134 mg, 3.19 mmol, 4.0 eq). The reaction was stirred at room

temperature for 1h, then diluted with water (30 mL) and the solution neutralized by addition of 1M HCl. The mixture was extracted with EtOAc, the combined organic extracts were washed with brine, dried (Na₂CO₃), filtered and evaporated *in vacuo*. The residue obtained was triturated with petroleum ether and EtOAc (2:1) and the solid that
5 formed collected by filtration, washed with petroleum ether: EtOAc (2:1) and dried to give the title compound I(a) as an off-white solid (200 mg, 68 %).

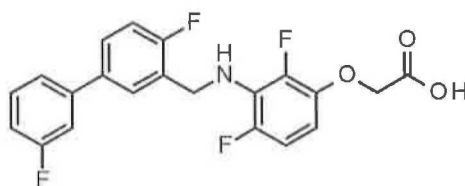
LC-MS : m/z 370.1 [M+H]⁺

10 ¹H NMR (400MHz, DMSO-d₆) δ 7.77 - 7.60 (m, 1H), 7.57 - 7.47 (m, 1H), 7.44 - 7.35 (m, 1H), 7.35 - 7.29 (m, 2H), 7.27 - 7.14 (m, 1H), 7.11 - 7.01 (m, 1H), 6.85 (s, 1H), 6.22 - 6.11 (m, 2H), 6.11 - 6.03 (m, 1H), 6.02 - 5.87 (m, 1H), 4.42 (s, 2H), 4.22 (d, *J*=3.3 Hz, 2H)

15

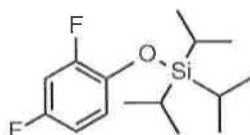
Example 2– Compound I(b) synthesized according to scheme 1

2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(b))



20

(2,4-Difluorophenoxy)-triisopropyl-silane



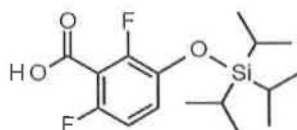
To a stirred solution of 2,4-difluorophenol (69.3 g, 0.53 mol, 1.0 eq) and imidazole (43.5
25 g, 0.64 mol, 1.2 eq) in DMF (300 mL) at 0 °C under N₂ was added TIPSCl (108 g, 0.56

mol, 1.05 eq) dropwise. After the addition was complete, the reaction mixture was allowed to warm to 25 °C and stirred for 1h. The reaction was then poured into water and extracted with a mixture of EtOAc and petroleum ether (10:1). The combined organic extracts were washed with water and brine, dried and evaporated *in vacuo*. The crude
5 residue was purified by column chromatography (petroleum ether) to give the title compound as a colourless oil (170 g, 86 %).

¹H NMR (400 MHz, CDCl₃) δ 6.90 (td, *J* = 9.2, 5.6 Hz, 1H), 6.87 – 6.80 (m, 1H), 6.76 – 6.69 (m, 1H), 1.35 – 1.21 (m, 3H), 1.11 (d, *J* = 7.3 Hz, 18H)

10

2,6-Difluoro-3-triisopropylsilyloxy-benzoic acid

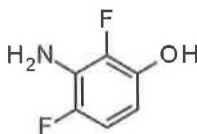


To a solution of ((2,4-difluorophenoxy)-triisopropyl-silane (50 g, 0.175 mol, 1.0 eq) in dry THF (500 mL) under N₂ at -60°C was added a solution of *s*-BuLi (147.7 mL, 1.3 M
15 in THF, 0.192 mol, 1.1 eq) over a period of 1h. The reaction mixture was stirred at -60°C for 2h and then CO₂ (gas) was bubbled into the mixture. After 1h, the reaction mixture was quenched with saturated NH₄Cl and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography (MeOH: DCM, 0:1 to 1:20) to give the
20 title compound as a yellow oil (23.3 g, 37%).

LC-MS: *m/z* 329.1 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 9.34 (s, 1H), 6.65 (ddd, *J* = 11.0, 9.0, 2.2 Hz, 1H), 6.07
25 (td, *J* = 9.2, 5.1 Hz, 1H), 5.04 (s, 2H)

3-Amino-2,4-difluoro-phenol (intermediate X(a))



To a solution of 2,6-difluoro-3-triisopropylsilyloxy-benzoic acid (18.4 g, 0.056 mol, 1.0 eq) in DCM (180 mL) and DMF (3 drops) at 0°C was added (COCl)₂ (21.19g, 0.167 mmol, 3.0 eq) dropwise. The mixture was warmed to room temperature and stirred for 1h.

5 The reaction mixture was evaporated *in vacuo* and the residue obtained dissolved in acetone (100 mL). The resultant solution was added dropwise to a cooled solution of NaN₃ (14.5g, 0.223 mol, 4.0 eq) in acetone (160 mL) and water (100 mL) at 0°C. The reaction was stirred for 1h at 0°C. Further water was then added (200 mL) and the reaction heated at 70 °C overnight. The acetone was removed under reduced pressure and

10 the aqueous layer extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained dissolved in EtOH (94 mL) and water (30 mL). Concentrated H₂SO₄ (30 mL) was added and the reaction heated at 110 °C overnight. The ethanol was removed under reduced pressure and the aqueous layer extracted with EtOAc. The combined organic

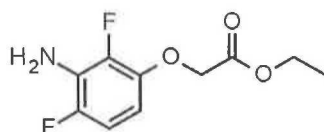
15 extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 20:1 to 6:1) to give the title compound as a white solid (4.0 g, 50 %).

LC-MS: m/z 146.1 [M+H]⁺

20

¹H NMR (400 MHz, DMSO-d₆) δ 9.34 (s, 1H), 6.65 (ddd, *J* = 11.0, 9.0, 2.2 Hz, 1H), 6.07 (ddd, *J* = 9.2, 9.0, 5.1 Hz, 1H), 5.04 (s, 2H)

Ethyl 2-(3-amino-2,4-difluorophenoxy)acetate (intermediate IV(a))



25

To a stirred solution of 3-amino-2,4-difluorophenol (intermediate X(a)) (713 mg, 4.9 mmol, 1.0 eq) in DMF (30 mL) was added Na₂CO₃ (1.56g, 14.7 mmol, 3.0 eq). The

resulting mixture was stirred for 40 min at room temperature. Ethyl bromoacetate (1 g, 5.90 mmol 1.2 eq) was added and the reaction stirred overnight. The reaction was diluted with water then extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by chromatography (petroleum ether: EtOAc, 25:1) to give the title compound (intermediate IV(a)) as an oil (850 mg, 71 %).

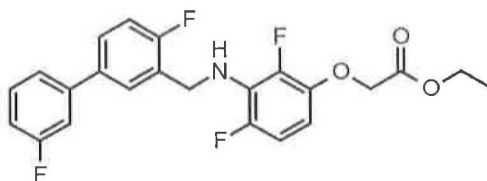
2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)benzoyl]amino]phenoxy]acetate



2-Fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (330 mg, 1.4 mmol, 1.1 eq) was suspended in SOCl₂ (10 mL) and heated to reflux for 3 h. The solution was then concentrated *in vacuo* and the residue was dissolved in dry DCM (10 mL). Ethyl 2-(3-amino-2,4-difluoro-phenoxy)acetate (300 mg, 1.3 mmol, 1 eq) and TEA (260 mg, 2.6 mmol, 2 eq) were added and the mixture stirred at room temperature for 3h. Water was added and the mixture extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by chromatography (Hexane: ethyl acetate, 10:1 to 5:1) to give the title compound as a white solid (290 mg, 50 %).

LC-MS: m/z 470.1 [M+Na]⁺

Ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(a))



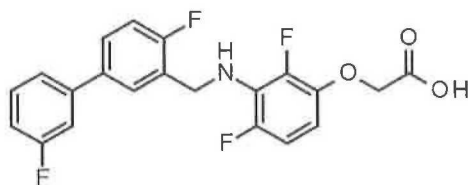
Ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)benzoyl]amino]phenoxy]acetate

(250 mg, 0.56 mmol, 1.0 eq) was dissolved in dry THF (10 mL) and cooled to 0°C. A solution of BH₃ (1 M in THF, 2.8 mL, 2.8 mmol, 5.0 eq) was added dropwise. The solution was then heated at 60°C for 2h. The reaction was quenched by addition of methanol and evaporated *in vacuo*. The residue was purified by column chromatography (DCM:MeOH, 50:1 to 20:1) to give the title compound as a colourless oil (100 mg, 41 %).

LC-MS : m/z 434.0 [M+H]⁺

¹H NMR (300MHz, DMSO-d₆) δ 7.73 (dd, *J*=7.2, 2.4 Hz, 1H), 7.65 - 7.56 (m, 1H), 7.54 - 7.44 (m, 1H), 7.42 - 7.35 (m, 2H), 7.24 (dd, *J*=9.9, 8.5 Hz, 1H), 7.22 - 7.13 (m, 1H), 6.80 (ddd, *J*=11.7, 9.3, 2.2 Hz, 1H), 6.35 (dt, *J*=9.1, 4.6 Hz, 1H), 5.88 (s, 1H), 4.74 (s, 2H), 4.52 (d, *J*=7.2 Hz, 2H), 4.11 (q, *J*=7.1 Hz, 2H), 1.15 (t, *J*=7.1 Hz, 3H)

2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(b))



Ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenoxy] acetate (100 mg, 0.2 mmol, 1.0 eq) was dissolved in a mixture of THF (15 mL) and H₂O (10 mL). LiOH.2H₂O (55 mg, 0.8 mmol, 4.0 eq) was added and the solution heated at 60°C overnight. The THF was removed under reduced pressure and the aqueous phase extracted with EtOAc. The organic extract was discarded and the aqueous layer acidified with 1M HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound (I(b)) as a white solid (80 mg, 99 %).

LC-MS : m/z 406.0 [M+H]⁺

¹H NMR (300MHz, DMSO-d₆) δ 13.02 (br. s., 1H, COOH), 7.74 (dd, *J*=7.2, 2.4 Hz, 1H), 7.64 - 7.55 (m, 1H), 7.54 - 7.44 (m, 1H), 7.43 - 7.34 (m, 2H), 7.24 (dd, *J*=8.5, 9.9 Hz, 1H), 7.22 - 7.13 (m, 1H), 6.80 (ddd, *J*=2.2, 9.3, 11.7 Hz, 1H), 6.32 (td, *J*=9.1, 4.6 Hz, 1H),
5 5.93 - 5.76 (m, 1H), 4.63 (s, 2H), 4.52 (d, *J*=7.0 Hz, 2H)

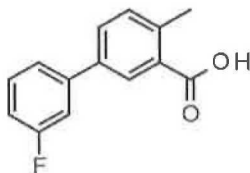
Example 3 – Compound I(c) synthesized according to scheme 3

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid (I(c))

10



5-(3-Fluorophenyl)-2-methyl-benzoic acid (intermediate III(b))



15 To a solution of 5-bromo-2-methyl-benzoic acid (1 g, 5.12 mmol, 1.0 eq) and (3-fluorophenyl)boronic acid (720 mg, 4.65 mmol, 1.1 eq) in a mixture of EtOH (5 mL), DMF (20 mL) and H₂O (5 mL) were added Na₂CO₃ (1.98g, 18.68 mmol, 4 eq) and Pd(PPh₃)₄ (270 mg, 0.23 mmol, 0.05 eq). The mixture was heated at 100°C under N₂ for 4h and the reaction quenched by addition of 1M HCl. The aqueous phase was extracted
20 with EtOAc and the combined organic extracts washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by chromatography (petroleum ether:EtOAc, 20:1 to 1:1) to give the title compound as a white solid (780 mg, 68 %).

LC-MS: m/z 229.0 [M-H]⁻

25

¹H NMR (400 MHz, DMSO-d₆) δ 13.01 (br s, 1H), 8.08 (d, *J* = 1.9 Hz, 1H), 7.78 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.16 (m, 1H), 2.55 (s, 3H).

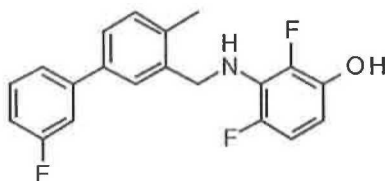
5 *N*-(2,6-Difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)-2-methyl-benzamide



To a solution of 5-(3-fluorophenyl)-2-methyl-benzoic acid (310 mg, 2.07 mmol, 1.0 eq) in CH₂Cl₂ (30 mL) at 0°C was added (COCl)₂ (0.52 mL, 6.0 mmol, 3.0 eq) and DMF (2-3 drops). The reaction was stirred at 0°C for 2 h, and then the solvent was removed *in vacuo*. The residue was taken up in THF (30 mL) and added to a suspension of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (195.4 mg, 2.07 mmol, 1.0 eq) and NaHCO₃ (339.1 mg, 6.2 mmol, 3.0 eq) in THF (70 mL) at 0°C. The reaction was stirred for 3h at 0°C then quenched by addition of water and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue was purified by chromatography (DCM:MeOH, 1:0 to 20:1) to give the title compound as a solid (230 mg, 48 %).

LC-MS: *m/z* 358.1 [M+H]⁺ 380.1 [M+Na]⁺

20 *N*-(2,6-Difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenyl)-2-methyl-benzamide



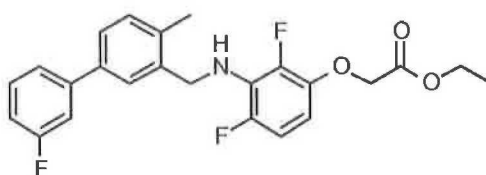
To a solution of *N*-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)-2-methyl-benzamide (150 mg, 0.42 mmol, 1.0 eq) in THF (5 mL) was added dropwise a solution of BH₃ (1 M in THF, 3 mL, 3 mmol, 7 eq). The reaction was heated at 55°C under N₂ for 2h,

and then quenched by the addition of 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give compound the title compound as a solid (124 mg, 86 %).

5

LC-MS: m/z 344.1 [M+H]⁺

Ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetate (II(t))



10

To a stirred solution of 2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methyl amino]phenol (124 mg, 0.361 mmol, 1.0 eq) and Cs₂CO₃ (176.5 mg, 0.542 mmol, 1.5 eq) in 2-Butanone (10 mL) was added ethyl bromoacetate (72.4 mg, 0.433 mmol, 1.2 eq) and the reaction stirred 30 min. The reaction was filtered and the filtrate evaporated *in vacuo*. The residue obtained was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as an oil/gum (100 mg, 65 %).

15

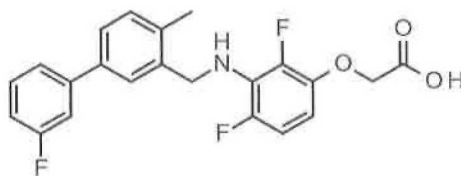
LC-MS: m/z 452.2 [M+Na]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 7.54 (s, 1H), 7.51 – 7.43 (m, 2H), 7.41 – 7.34 (m, 2H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.15 (br t, *J* = 8.6 Hz, 1H), 6.42 (br s, 1H), 6.24 – 6.17 (m, 1H), 6.16 – 6.07 (m, 1H), 4.81 (s, 2H), 4.35 (d, *J* = 5.8 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

20

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid (I(c))

25



To a stirred solution of ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetate (100 mg, 0.23 mmol, 1.0 eq) in THF (8 mL) was added NaOH (1M aqueous solution, 3 mL, 3 mmol, 13.0 eq) at room temperature. The reaction was stirred at room temperature for 2h. The THF was evaporated *in vacuo* and the aqueous layer acidified to pH 3 by addition of 1M HCl. The resultant precipitate was collected by filtration and dried *in vacuo* to give the title compound (I(c)) as a white solid (85 mg, 91 %).

10 LC-MS : m/z 401.9 [M+H]⁺

¹H NMR (300MHz, DMSO-d₆) δ (13.03, br. s., 1H, COOH), 7.59 (s, 1H), 7.54 - 7.32 (m, 4H), 7.24 (d, *J*=7.8 Hz, 1H), 7.15 (td, *J*=8.4, 1.7 Hz, 1H), 6.80 (ddd, *J*=11.6, 9.4, 2.1 Hz, 1H), 6.31 (td, *J*=9.1, 4.6 Hz, 1H), 5.74 (br. s., 1H), 4.64 (s, 2H), 4.46 (d, *J*=6.1 Hz, 2H), 2.32 (s, 3H)

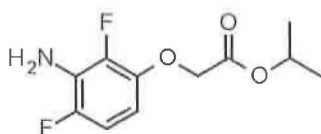
Example 4 – Compound I(d) synthesized according to scheme 4

2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetic acid (I(d))

20



Isopropyl 2-(3-amino-2,4-difluoro-phenoxy)acetate (intermediate IV(b))

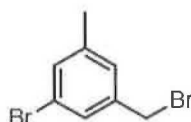


To a stirred solution of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (713 mg, 4.91 mmol, 1.0 eq) in DMF (20 mL) was added Na_2CO_3 (1.56 g, 14.8 mmol, 3.0 eq). The resulting mixture was stirred at room temperature for 35 min, then isopropyl bromoacetate (1.07 g, 5.90 mmol, 1.2 eq) was added and the reaction stirred at room temperature overnight. The reaction was diluted with water then extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:6) to give the title compound (intermediate IV(b)) as an oil (850 mg, 71 %).

10

LC-MS: m/z 246.1 $[\text{M}+\text{H}]^+$ 268.1 $[\text{M}+\text{Na}]^+$

1-Bromo-3-(bromomethyl)-5-methyl-benzene

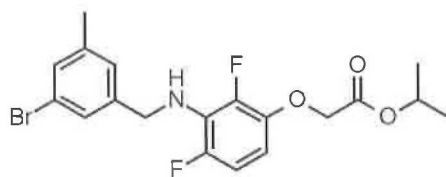


15

A solution of 1-bromo-3,5-dimethyl-benzene (1.0 g, 5.4 mmol, 1.0 eq), NBS (1.06 g, 5.94 mmol, 1.1 mmol) and AIBN (180 mg, 1.08 mmol, 0.2 eq) in CCl_4 (20 mL) was stirred at reflux overnight. The reaction was then diluted with water and extracted with CH_2Cl_2 . The organic extracts were combined and washed with aqueous NaHCO_3 , dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (Petroleum ether:EtOAc, 1:0 to 10:1) to give the title compound as a light yellow oil (1.2 g, 84%).

^1H NMR (400 MHz, DMSO) δ 7.36 (s, 1H), 7.28 (s, 1H), 7.19 (s, 1H), 4.47 (s, 2H), 2.31 (s, 3H)

25

Isopropyl 2-[3-[(3-bromo-5-methyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate

To a solution of isopropyl 2-(3-amino-2,4-difluoro-phenoxy)acetate (intermediate IV(b)) (350 mg, 1.43 mmol, 1.0 eq) and 1-bromo-3-(bromomethyl)-5-methyl-benzene (528 mg, 1.99 mmol, 1.4 eq) in DMSO (15 mL) was added K₂CO₃ (593 mg, 4.29 mmol, 3.0 eq). The reaction was heated at 100°C for 1h in a microwave reactor, then diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by chromatography (petroleum ether: EtOAc, 100:1 to 80:1) to give the title compound as a light yellow oil (192 mg, 16 %).

LC-MS: m/z 428.1, 430.1 [M+H]⁺

Isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetate (II(e))

To a solution of isopropyl 2-[3-[(3-bromo-5-methyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate (176 mg, 0.4 mmol, 1.0 eq) in acetonitrile (15 mL) was added 3-fluorophenylboronic acid (86 mg, 0.61 mmol, 1.5 eq), K₂CO₃ (142 mg, 1.03 mmol, 2.5 eq) and Pd(dppf)Cl₂ (15 mg, 0.02 mmol, 0.05 eq). The mixture was heated at reflux overnight then the solvent was removed *in vacuo*. The residue was diluted with CH₂Cl₂, washed with water, dried (MgSO₄), filtered and evaporated *in vacuo*. The residue was

purified by chromatography (petroleum ether: EtOAc, 150:1 to 60:1) to give the title compound as an oil (140 mg, 77 %).

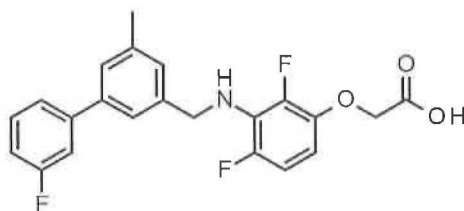
LC-MS : m/z 443.9 $[M+H]^+$

5

^1H NMR (300 MHz, DMSO- d_6): δ 7.56 - 7.32 (m, 5H), 7.24 - 7.11 (m, 1H), 7.13 (s, 1H), 6.78 (ddd, $J=11.6, 9.4, 2.1$ Hz, 1H), 6.28 (td, $J=9.0, 4.6$ Hz, 1H), 6.03 - 5.87 (m, 1H), 4.93 (spt, $J=6.3$ Hz, 1H), 4.69 (s, 2H), 4.42 (d, $J=7.2$ Hz, 2H), 2.32 (s, 3H), 1.15 (d, $J=6.2$ Hz, 6H)

10

2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetic acid (I(d))



To a stirred solution of isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methylphenyl]methylamino]phenoxy]acetate (127 mg, 0.29 mmol, 1.0 eq) in THF (3 mL) was added NaOH (2M aqueous solution, 0.57 mL, 1.15 mmol, 4.0 eq) at room temperature. The reaction was stirred at room temperature for 1h and then the THF removed *in vacuo* and the aqueous residue adjusted to pH 4 by addition of 1M HCl. The precipitate was collected by filtration, dried *in vacuo* and crystallized from CH_2Cl_2 and petroleum ether to give the title compound (I(d)) as a white solid (50 mg, 44 %).

20

LC-MS : m/z 401.9 $[M+H]^+$

^1H NMR (300MHz, DMSO- d_6) δ 13.05 (br. s., 1H), 7.58 - 7.28 (m, 5H), 7.24 - 7.04 (m, 2H), 6.77 (ddd, $J=11.7, 9.4, 2.0$ Hz, 1H), 6.27 (td, $J=9.1, 4.6$ Hz, 1H), 6.02 - 5.84 (m, 1H), 4.61 (s, 2H), 4.42 (d, $J=6.9$ Hz, 2H), 2.32 (s, 3H)

25

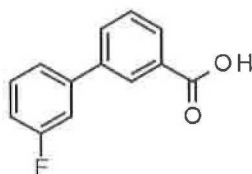
Example 5 – compound I(e) synthesized according to scheme 3

2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(e))



5

3-(3-Fluorophenyl)benzoic acid (intermediate III(c))

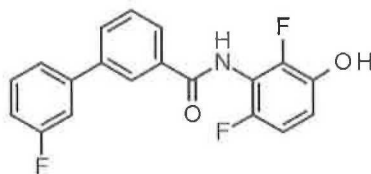


- 10 To a solution of (3-fluorophenyl)boronic acid (790 mg, 3.57 mmol, 1.0 eq), 3-bromobenzoic acid (790 mg, 3.93 mmol, 1.1eq) and Na₂CO₃ (142 mg, 1.03 mmol, 2.5 eq) in a mixture of EtOH (2.5 mL), DMF (10 mL) and H₂O (2.5 mL) was added Pd(PPh₃)₄ (170 mg, 0.18 mmol, 0.05 eq). The mixture was stirred at 100°C overnight. Water was added and the aqueous layer was extracted with EtOAc and the organic extract was
- 15 discarded. The aqueous layer was acidified to pH 4-5 with 1M HCl and extracted with EtOAc. The combined organic extracts were filtered through silica gel and evaporated *in vacuo* to give the title compound as a white solid (440 mg, 56 %).

LC-MS : m/z 239.1 [M+Na]⁺

20

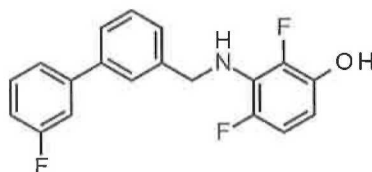
N-(2,6-Difluoro-3-hydroxy-phenyl)-3-(3-fluorophenyl)benzamide



To a stirred solution of 3-(3-fluorophenyl)benzoic acid (430 mg, 1.99 mmol, 1.1eq), in CH_2Cl_2 (10 mL) and DMF (0.15 mL) at 0°C was added $(\text{COCl})_2$ (760 mg, 5.97 mmol, 3.3 eq) dropwise. The reaction was stirred for 2 h, then the solvent removed. The residue dissolved in THF (6 mL) and added to a mixture of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (262.5 mg, 1.81 mmol, 1.0 eq) and NaHCO_3 (760 mg, 9.05 mmol, 5 eq) in THF (6 mL) at 0°C . The reaction was stirred for 3h then quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with Na_2CO_3 , water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude residue was crystallised from petroleum ether:EtOAc 3:1 to give the title compound (310 mg, 50 %). Evaporation of the filtrate provided a further 180 mg of impure material.

LC-MS : m/z 344.1 $[\text{M}+\text{H}]^+$

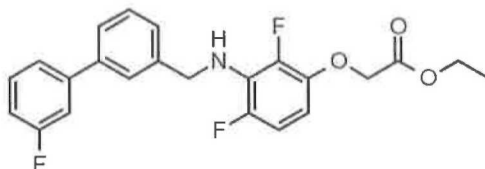
2,4-Difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-3-(3-fluorophenyl)benzamide (310 mg, 0.9 mmol, 1.0 eq) in THF (5 mL) was added BH_3 (5.4 mL, 1M in THF, 5.4 mmol, 6.0 eq) and the reaction heated at 60°C overnight. The reaction mixture was quenched with water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc 1:0 to 10:1) to give the title compound as an oil (255 mg, 86 %).

LC-MS : m/z 330.1 [M+H]⁺

Ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(u))



- 5 To a stirred solution of 2,4-difluoro-3-[[3-(3-fluorophenyl)phenyl] methylamino]phenol (250 mg, 0.76 mmol, 1.0 eq) in acetone (3 mL) was added Cs₂CO₃ (297 mg, 0.912 mmol, 1.2 eq). The resulting mixture was stirred for 40 min at room temperature then ethyl bromoacetate (139.4 mg, 0.84 mmol, 1.1 eq) was added. The resulting mixture was stirred overnight then partitioned against water and extracted with EtOAc. The combined
10 organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc 1:0 to 20:1) to give the title compound as an oil (270 mg, 86 %).

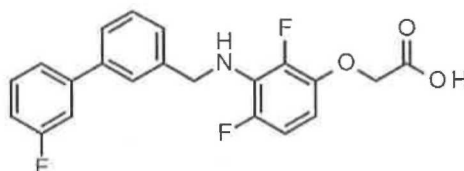
LC-MS : m/z 438.1 [M+Na]⁺

15

¹H NMR (400 MHz, DMSO-d₆) δ 7.65 (br s, 1H), 7.56 – 7.36 (m, 5H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.16 (m, 1H), 6.82 – 6.73 (m, 1H), 6.30 (td, *J* = 9.2, 4.6 Hz, 1H), 6.06 – 5.97 (m, 1H), 4.73 (s, 2H), 4.47 (d, *J* = 7.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

20

2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(e))



- To a stirred solution of intermediate ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl) phenyl]methylamino]phenoxy]acetate (270 mg, 0.65 mmol, 1.0 eq) in THF (4 mL) was
25 added NaOH (2 M aqueous solution, 2.5 mL, 5 mmol, 7.7 eq). The reaction was stirred at

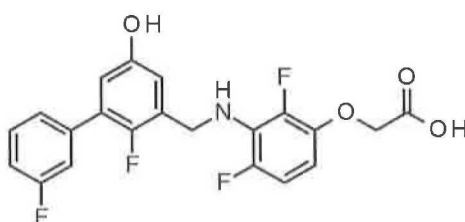
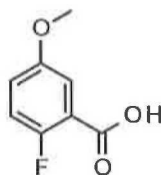
room temperature for 1h. Water was added and the THF removed *in vacuo*. The aqueous layer was extracted with EtOAc and the combined organic extracts washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude material obtained was crystallised from CH₂Cl₂/petroleum ether, collected by filtration and dried *in vacuo* to give the title compound (I(c)) as a white solid (190 mg, 75 %).

LC-MS : m/z 387.9 [M+H]⁺

¹H NMR (300MHz, DMSO-d₆) δ (13.03, br. s., 1H, COOH), 7.65 (s, 1H), 7.58 - 7.42 (m, 4H), 7.39 (t, *J*=7.7 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.19 (dddd, *J*=8.9, 7.6, 2.6, 1.5 Hz, 1H), 6.77 (ddd, *J*=11.8, 9.3, 2.2 Hz, 1H), 6.27 (td, *J*=9.1, 4.5 Hz, 1H), 6.11 - 5.90 (m, 1H), 4.61 (s, 2H), 4.46 (d, *J*=7.0 Hz, 2H)

Example 6 – compound I(f) synthesized according to scheme 3

15 **2-[2,4-Difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]
phenoxy] acetic acid (I(f))**

20 *2-Fluoro-5-methoxy-benzoic acid*

To a solution of 1-fluoro-4-methoxy-benzene (5 g, 39.6 mmol, 1.0 eq) and PMDTA (7.56 g, 43.62 mmol, 1.1eq) in dry THF (100 mL) at -60 °C under N₂ was added a solution of s-

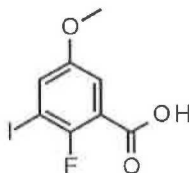
BuLi (1.3 M, 36.6 mL, 47.5 mmol, 1.2 eq) over a period of 1 h. The reaction mixture was stirred at -60 °C for 2h and then CO₂ (gas) was bubbled into the solution for 1 h. The reaction mixture was then warmed to room temperature, acidified by addition of 1M HCl and extracted with EtOAc. The combined organic extracts were washed with water and
5 brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:1) to give the title compound as a yellow solid (5.4 g, 80 %).

LC-MS : m/z 171.1 [M+H]⁺ 193.0 [M+Na]⁺

10

¹H NMR (400 MHz, DMSO-d₆) δ 13.33 (s, 1H), 7.31 (m, 1H), 7.24 (m, 1H), 7.20 – 7.16 (m, 1H), 3.78 (s, 3H)

2-Fluoro-3-iodo-5-methoxy-benzoic acid



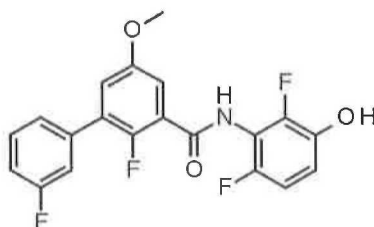
15

To a solution of 2,2,6,6-tetramethylpiperidine (42 g, 298 mmol, 2.5 eq) in THF at -60°C under N₂ was added n-BuLi (2.2 M, 141 mL, 309.3 mmol, 2.6 eq) dropwise over a period of 30 min. The reaction mixture was stirred at -60°C for 2h, then a solution of 2-fluoro-5-methoxy-benzoic acid (15 g, 119 mmol, 1.0 eq) in THF (300 mL) was added dropwise
20 with stirring. The reaction was stirred for a further 2 h at -60°C, then iodine (45 g, 179 mmol, 1.5 eq) was added in portions. The reaction was warmed to room temperature slowly and the resulting mixture acidified by addition of 1M HCl and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered
25 and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:1) to give the title compound as a yellow solid (5.6 g, 16 %).

2-Fluoro-3-(3-fluorophenyl)-5-methoxy-benzoic acid (intermediate III(d))

To a solution of 2-fluoro-3-iodo-5-methoxybenzoic acid (3.0 g 10.14 mmol, 1.0 eq) in a mixture of water (30 mL), EtOH (30 mL) and DMF (60 mL), was added 3-fluorophenylboronic acid (1.56 g 11.15 mmol, 1.1 eq) and Na₂CO₃ (4.3 g, 40.56 mmol, 4.0 eq). The mixture was stirred at room temperature under N₂ for 10 mins then Pd(PPh₃)₄ (1.17 g, 1.01 mmol, 0.1 eq) was added. The mixture was heated at 100°C for 5h then cooled to room temperature and acidified with 1M HCl. The aqueous layer was extracted with EtOAc and the combined extracts were washed with water, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:3) to give the title compound as a yellow solid (2.2 g, 81 %).

LC-MS: m/z 219.1 [M-COOH]⁺

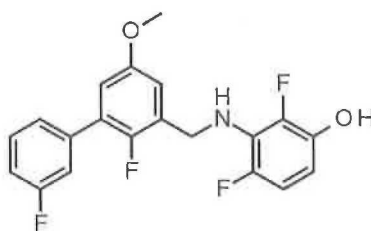
N-(2,6-Difluoro-3-hydroxy-phenyl)-2-fluoro-3-(3-fluorophenyl)-5-methoxybenzamide

To a solution of 2-fluoro-3-(3-fluorophenyl)-5-methoxybenzoic acid (402 mg, 1.52 mmol, 1.1 eq) in CH₂Cl₂ (20 mL) at 0 °C was added oxalylchloride (525 mg, 4.14 mmol, 3.0 eq) and DMF (5 drops). The solution was stirred at 0 °C for 2h then the solvent removed *in vacuo*. The residue was taken up in THF (10 mL) and added dropwise to a mixture of 3-amino-2,4-difluorophenol (intermediate X(a)) (200 mg, 1.38 mmol, 1.0 eq) and NaHCO₃

(348 mg, 4.14 mmol, 3.0 eq) in THF (10 mL) at 0°C. The mixture was stirred at 0°C for 4h then poured into water and extracted with EtOAc. The organic extract was washed with water, brine, dried (Na₂SO₄) filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:3) to give the title compound as a white solid (300 mg, 50 %).

LC-MS: m/z 392.1 [M+H]⁺

2,4-Difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenol



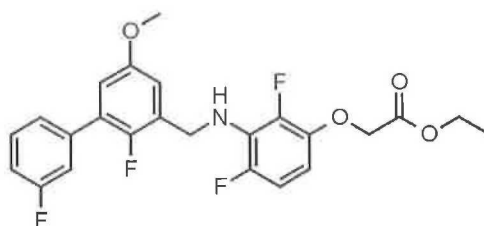
10

To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-2-fluoro-3-(3-fluorophenyl)-5-methoxy-benzamide (300 mg, 0.77 mmol, 1.0 eq) in THF (10 mL) at 0°C under N₂ was added a solution of BH₃ (1M in THF, 4 mL, 4.0 mmol, 5.2 eq) dropwise. The reaction mixture was heated to 60°C and stirred for 1.5h. The reaction was cooled to room temperature then quenched by addition of 1M HCl. The mixture was stirred at room temperature for 1.5 h, then extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as a yellow oil (180 mg, 62 %).

20

LC-MS: m/z 378.1 [M+H]⁺ 400.1 [M+Na]⁺

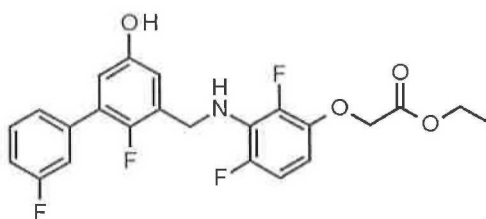
Ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenoxy]acetate



To a stirred solution of 2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methoxyphenyl]methylamino]phenol (180 mg, 0.48 mmol, 1.0 eq) in DMF (4 mL) was added Cs₂CO₃ (233 mg, 0.72 mmol, 1.5 eq). The resulting mixture was stirred for 40 min at room temperature then ethyl bromoacetate (96 mg, 0.57 mmol, 1.2 eq) was added. The resulting mixture was stirred at room temperature for 2h then water added and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (150 mg, 68 %).

LC-MS: m/z 486.1 [M+Na]⁺

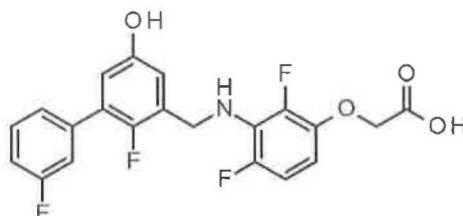
Ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetate (II(v))



To a solution of 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methoxyphenyl]methylamino]phenoxy]acetate (150 mg, 0.32 mmol, 1.0 eq) and AlCl₃ (259 mg, 1.94 mmol, 6.0 eq) in CH₂Cl₂ (5 mL) at 0°C was added ethanethiol (120 mg, 1.94 mmol, 6.0 eq). The reaction mixture was stirred at 0°C for 3h. The resulting mixture was poured into water and extracted with CH₂Cl₂. The organic extract was dried (Na₂SO₄), filtered and evaporated *in vacuo* and the residue purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:2) to give the title as a yellow oil (120 mg, 82 %).

LC-MS: m/z 472.1 [M+Na]⁺

2-[2,4-Difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]
5 phenoxy]acetic acid (I(f))



To a stirred solution of ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]phenoxy]acetate (120 mg, 0.27 mmol, 1.0 eq) in THF (6 mL) at room temperature was added NaOH (1M aqueous solution, 3 mL, 3.0 mmol, 11.1 eq).
10 The reaction was stirred at room temperature for 2h. The solvent was then removed *in vacuo* and the solid obtained taken up in water and the aqueous layer acidified to pH 3-6 by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound (I(f)) as a gummy solid (105 mg, 94 %).

15

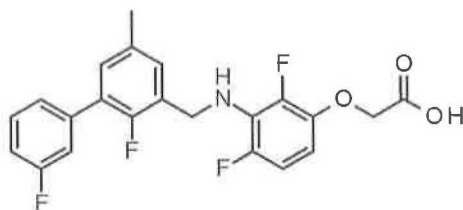
LC-MS : m/z 421.9 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ (13.08, bb, 1H, COOH); 9.44 (s, 1H); 7.50 (q, 1H); 7.39-7.20 (m, 3H); 6.89 (m, 1H); 6.79 (m, 1H); 6.68 (t, 1H); 6.19 (m, 1H); 5.72 (m, 1H);
20 4.68 (s, 2H); 4.47 (d, J=6 Hz, 2H)

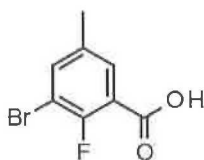
Example 7 – compound I(g) prepared according to scheme 3

**2-[2,4-Difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]
phenoxy]acetic acid (I(g))**

25

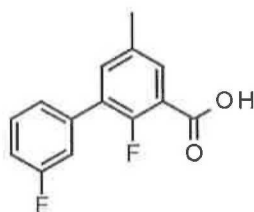


3-Bromo-2-fluoro-5-methyl-benzoic acid



- 5 To a solution of diisopropylamine (590 mg, 5.8 mmol, 1.1 eq) in dry THF (15 mL) at -78°C was added n-BuLi (2.6 mL, 5.8 mmol, 1.2 eq) dropwise. The solution was stirred at -78°C for 30 min, then a solution of 2-bromo-1-fluoro-4-methyl-benzene (1g, 5.3 mmol, 1.0 eq) in dry THF (5 mL) was added dropwise. After stirring for a further 1.5 h at -78°C, CO₂ gas was bubbled into the solution. The reaction was warmed to room temperature and allowed to stir for a further 1h. The reaction was then quenched by addition of aqueous NH₄Cl and the THF removed under reduced pressure. The aqueous residue was acidified to pH 5 and the solid that formed collected by filtration, washed with water and dried to give the title compound as a solid (700 mg, 58 %).
- 10
- 15 ¹H NMR (400 MHz, DMSO-d₆) δ 7.78 (dd, *J* = 6.0, 2.2 Hz, 1H), 7.66 (dd, *J* = 6.4, 2.2 Hz, 1H), 2.33 (s, 3H)

2-Fluoro-3-(3-fluorophenyl)-5-methyl-benzoic acid (intermediate III(e))



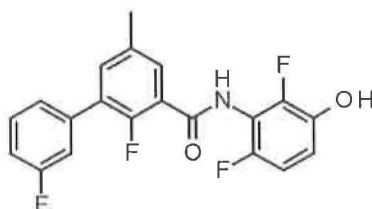
- 20 A mixture of 3-bromo-2-fluoro-5-methyl-benzoic acid (400 mg, 1.7 mmol, 1.0 eq), (3-fluorophenyl)boronic acid (720 mg, 5.2 mmol, 3.0 eq), K₂CO₃ (356 mg, 2.6 mmol, 1.5

eq) and $\text{Pd}(\text{PPh}_3)_4$ (396.0 mg, 0.40 mmol, 0.2 eq) in acetonitrile (5 mL) and H_2O (4 mL) was heated at reflux overnight. The reaction was acidified to pH 3 by addition of 1M HCl and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as a solid (160 mg, 75 %).

LC-MS: m/z 249.0 $[\text{M}+\text{H}]^+$ 271.0 $[\text{M}+\text{Na}]^+$

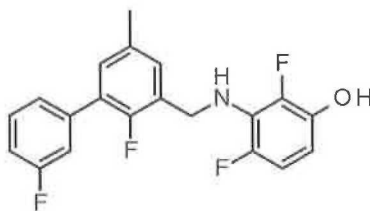
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.30 (br s, 1H), 7.67 (br d, $J = 6.3$ Hz, 1H), 7.59 – 7.48 (m, 2H), 7.38 (d, $J = 7.5$ Hz, 2H), 7.32 – 7.23 (m, 1H), 2.36 (s, 3H).

N-(2,6-Difluoro-3-hydroxy-phenyl)-2-fluoro-3-(3-fluorophenyl)-5-methyl-benzamide



To a stirred solution of 2-fluoro-3-(3-fluorophenyl)-5-methyl-benzoic acid (400 mg, 1.65 mmol, 1.1 eq) in CH_2Cl_2 (10 mL) was added oxalylchloride (0.5 mL, 5.9 mmol, 4.0 eq) and DMF (2 drops). The reaction was stirred for 1h, then the solvent removed *in vacuo* and the residue dissolved in THF (10 mL). The solution was then added dropwise to a mixture of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (212 mg, 1.50 mmol, 1.0 eq) and NaHCO_3 (492 mg, 5.90 mmol, 4.0 eq) in THF (10 mL) at room temperature. The reaction was stirred overnight then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:3) to give the title compound as a solid (130 mg, 24 %).

LC-MS: m/z 376.1 $[\text{M}+\text{H}]^+$ 398.1 $[\text{M}+\text{Na}]^+$

2,4-Difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenol

- To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-2-fluoro-3-(3-fluorophenyl)-5-methyl-benzamide (130 mg, 0.30 mmol, 1.0 eq) in THF (25 mL) was added dropwise a solution of borane (1M in THF, 1.2 mL, 1.2 mmol, 4 eq) under N₂. The reaction was heated at 60°C overnight. TLC showed the reaction was not complete so further borane (1 M in THF, 1.0 mL, 1 mmol) was added and heating continued at 60°C for 2h. The mixture was poured into water and extracted with EtOAc and the combined organic extracts washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as an oil (100 mg, 80 %).

LC-MS: m/z 362.1 [M+H]⁺

- Ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetate (II(w))*



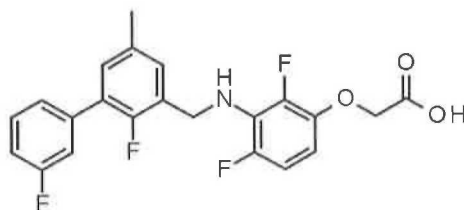
- To a stirred solution of 2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenol (100 mg, 0.30 mmol, 1.0 eq) and Na₂CO₃ (58 mg, 0.60 mmol, 2.0 eq) in 2-butanone (10 mL) was added ethyl bromoacetate (75.1 mg, 0.45 mmol, 1.5 eq). The mixture was stirred at room temperature for 3h. TLC showed the reaction to be incomplete so Cs₂CO₃ (50 mg, 0.15 mmol, 0.5 eq) was added and the reaction stirred a

further 3h. TLC showed the reaction was still not finished so ethyl bromoacetate (0.2 mL) was added and the reaction stirred for a further 1h. The solution was then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as a solid (100 mg, 81 %).

LC-MS: m/z 448.2 $[\text{M}+\text{H}]^+$ 470.1 $[\text{M}+\text{Na}]^+$

^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.35 (m, 1H), 7.34 – 7.20 (m, 2H), 7.13 (dd, $J = 9.6, 7.0$ Hz, 2H), 7.06 (td, $J = 8.3, 2.2$ Hz, 1H), 6.75 – 6.65 (m, 1H), 6.29 (td, $J = 8.9, 4.6$ Hz, 1H), 4.61 (s, 2H), 4.57 (s, 2H), 4.25 (q, $J = 7.1$ Hz, 2H), 2.33 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H).

2-[2,4-Difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetic acid (I(g))



To a stirred solution of ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetate (100 mg, 0.2 mmol, 1.0 eq) in a mixture of THF (20 mL) and water (20 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (38 mg, 0.9 mmol, 4.0 eq). The reaction was stirred at room temperature for 2h. The THF was then removed *in vacuo* and the aqueous residue acidified by addition of 1M HCl and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was washed with a mixture of petroleum ether : EtOAc, 10:1 to give the title compound (I(g)) as white solid (30 mg, 32 %).

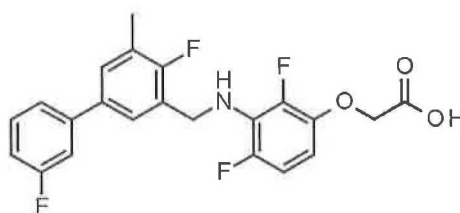
LC-MS : m/z 419.9 $[\text{M}+\text{H}]^+$

¹H NMR (300MHz, DMSO-d₆) δ 13.05 (br. s., 1H, COOH), 7.51 (td, *J*=8.0, 6.3 Hz, 1H), 7.41 - 7.29 (m, 2H), 7.28 - 7.12 (m, 3H), 6.80 (ddd, *J*=11.7, 9.4, 2.1 Hz, 1H), 6.31 (td, *J*=9.1, 4.6 Hz, 1H), 5.82 (s, 1H), 4.63 (s, 2H), 4.49 (d, *J*=7.0 Hz, 2H), 2.28 (s, 3H)

5

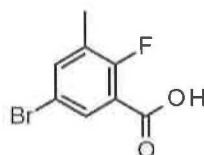
Example 8 – compound I(h) synthesized according to scheme 3

2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetic acid (I(h))



10

5-Bromo-2-fluoro-3-methyl-benzoic acid



To a solution of diisopropylamine (1.77g, 17.5 mmol, 1.1 eq) in THF (20 mL) was added
15 n-BuLi (7.3 mL, 2.4 M in THF, 17.5 mmol, 1.1 eq) at -78°C under N₂. The mixture was
stirred at -78°C for 1h, then a solution of 4-bromo-1-fluoro-2-methyl-benzene (3 g, 15.8
mmol, 1.0 eq) in THF (20 mL) was added dropwise. The reaction was stirred a further 2h
at -78°C then CO₂ gas was bubbled into the mixture for 30 min. The reaction was
quenched by addition of water and acidified to pH 3 by addition of 1M HCl. The aqueous
20 layer was extracted with EtOAc and the combined organic extracts were washed with
brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was
purified by chromatography to give the title compound as a white solid (697 mg, 21 %).

LC-MS : m/z 230.9, 232.9 [M-H]⁻

¹HNMR (400 MHz, DMSO-d₆) δ 7.94 – 7.59 (m, 2H), 2.26 (s, 3H)

2-Fluoro-5-(3-fluorophenyl)-3-methyl-benzoic acid (intermediate III(f))



5

To a solution of 5-bromo-2-fluoro-3-methyl-benzoic acid (697 mg, 2.99 mmol, 1.0 eq) and (3-fluorophenyl)boronic acid (502 mg, 3.59 mmol, 1.2 eq) in a mixture of EtOH (10 mL), dioxane (20 mL) and H₂O (10 mL) were added K₂CO₃ (142 mg, 1.03 mmol, 2.5 eq) and Pd(PPh₃)₄ (345 mg, 0.30 mmol, 0.1 eq). The mixture was heated at 85°C overnight.

10 The reaction was quenched by addition of 1M HCl and the aqueous phase extracted with EtOAc. The organic extract was dried (MgSO₄), filtered and evaporated *in vacuo*. The residue was purified by chromatography to give the title compound as a solid (558 mg, 73 %).

15 LC-MS : m/z 247.0 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ 7.95 – 7.86 (m, 2H), 7.58 – 7.47 (m, 3H), 7.27 – 7.18 (m, 1H), 2.34 (d, J = 1.9 Hz, 3H)

20 *N*-(2,6-difluoro-3-hydroxy-phenyl)-2-fluoro-5-(3-fluorophenyl)-3-methyl-benzamide



To a solution of 2-fluoro-5-(3-fluorophenyl)-3-methyl-benzoic acid (558 mg, 2.25 mmol, 1.0 eq) in DCM (30 mL) at 0°C was added (COCl)₂ (856 mg, 0.57 mL, 6.74 mmol, 3 eq)

and DMF (2 drops). The reaction was stirred at 0°C for 2h then the solvent was removed *in vacuo*. The residue was taken up in THF (30 mL) and added to a suspension of 3-amino-2,4-difluorophenol (intermediate X(a)) (330 mg, 2.36 mmol, 1.05 eq) and NaHCO₃ (566 mg, 6.74 mmol, 3.0 eq) in THF (30 mL) at 0°C. The reaction was stirred for 3h at 0°C then quenched by addition of 1 M HCl and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue was purified by chromatography (MeOH:DCM, 0:1 to 1:50) to give the title compound as a solid (360 mg, 43 %).

10 LC-MS: m/z 376.1 [M+H]⁺ 398.1 [M+Na]⁺

2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenol

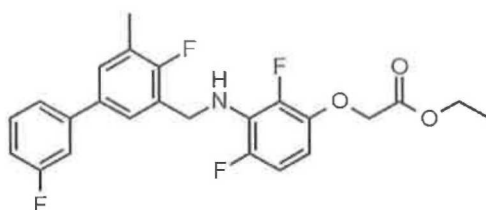


To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-2-fluoro-5-(3-fluorophenyl)-3-methyl-benzamide (200 mg, 0.53 mmol, 1.0 eq) in THF (8 mL) was added a solution of BH₃ (1M in THF, 5 mL, 5 mmol, 9.4 eq) dropwise. The reaction was heated at 55°C for 2h, then quenched by the addition of 1M HCl and EtOAc. The organic extract was separated, washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound (150 mg, 77 %). This material was used without further purification.

20 LCMS: m/z 362.1 [M+H]⁺ 384.1 [M+Na]⁺

Ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetate (II(h))

25

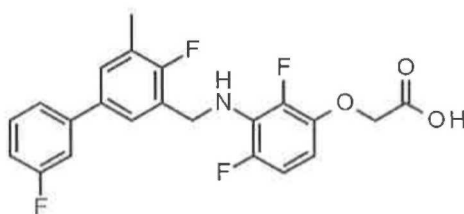


To a stirred solution of 2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenol (150 mg, 0.42 mmol, 1.0 eq) in 2-butanone (10 mL) was added Cs₂CO₃ (203 mg, 0.62 mmol, 1.5 eq). The resulting mixture was stirred at room temperature for 30 min then ethyl bromoacetate (83 mg, 0.50 mmol, 1.2 eq) was added. The reaction was stirred at room temperature 30 min then filtered and concentrated. The crude residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as a gum (150 mg, 81 %).

LC-MS : m/z 448.2 [M+H]⁺ 470.1 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.55 – 7.43 (m, 3H), 7.41 – 7.32 (m, 2H), 7.21 – 7.12 (m, 1H), 6.87 – 6.75 (m, 1H), 6.40 – 6.28 (m, 1H), 5.92 – 5.82 (m, 1H), 4.74 (s, 2H), 4.51 (d, *J* = 7.0 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H)

2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetic acid (*I(h)*)



To a stirred solution of ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetate (150 mg, 0.34 mmol, 1.0 eq) in THF (8 mL) was added NaOH (1M in water, 3.0 mL, 3.0 mmol) at room temperature. The reaction was stirred for 2h, then the THF was removed *in vacuo* and the aqueous layer acidified to pH

4 by addition of 1M HCl. The resultant precipitate was collected by filtration and dried *in vacuo* to give the title compound (I(h)) (120 mg, 85 %) as a white solid.

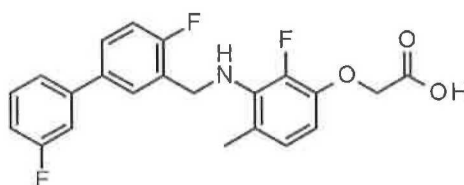
LC-MS : m/z 419.9 [M+H]⁺

5

¹H NMR (300 MHz, DMSO-d₆) δ 13.04 (br. s., 1H), 7.62 - 7.42 (m, 3H), 7.40 - 7.31 (m, 2H), 7.24 - 7.10 (m, 1H), 6.80 (ddd, *J*=11.7, 9.4, 2.1 Hz, 1H), 6.32 (td, *J*=9.1, 4.5 Hz, 1H), 5.84 (br. s., 1H), 4.63 (s, 2H), 4.51 (d, *J*=7.1 Hz, 2H), 2.27 (d, *J*=1.6 Hz, 3H)

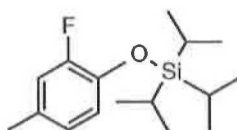
10 **Example 9 – compound I(i) synthesized according to scheme 3**

2-[2-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methyl-phenoxy]acetic acid (I(i))



15

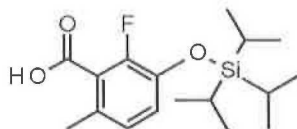
(2-Fluoro-4-methyl-phenoxy)-triisopropyl-silane



20

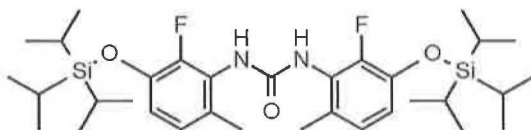
To a stirred solution of 2-fluoro-4-methyl-phenol (5 g, 39.6 mmol, 1.0 eq) and imidazole (3.24 g, 44.4 mmol, 1.2 eq) in DMF (50 mL) at 0 °C under N₂ was added TIPSCl (8.03 g, 41.6 mmol, 1.05 eq) dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 1h. The reaction was then poured into water and extracted with a mixture of EtOAc and petroleum ether (10:1). The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether) to give the title compound as a colourless oil (8 g, 62 %).

25

2-Fluoro-6-methyl-3-triisopropylsilyloxy-benzoic acid

To a solution of (2-fluoro-4-methyl-phenoxy)-triisopropyl-silane (5 g, 17.7 mmol, 1.0 eq)
 5 and PMDTA (3.4 g, 19.5 mmol, 1.1 eq) in dry THF (70 mL) at -78°C under N₂ was
 added a solution of n-BuLi (8 mL, 2.5 M in hexane, 20 mmol, 1.1 eq) over a period of 1h.
 The reaction mixture was stirred at -78°C for 2 h then CO₂ (gas) was bubbled into the
 mixture for 1h. The reaction mixture was then quenched with saturated 1M HCl and
 extracted with EtOAc. The organic extract was washed with water and brine, dried
 10 (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column
 chromatography (DCM:MeOH, 1:0 to 20:0) to give the title compound as a yellow oil (4
 g, 69 %).

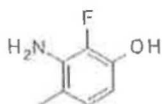
¹H NMR (400 MHz, CDCl₃) δ 7.05 – 6.85 (m, 2H), 2.24 (s, 3H), 1.34 – 1.15 (m, 3H),
 15 1.05 (d, *J* = 7.4 Hz, 18H)

1,3-Bis(2-fluoro-6-methyl-3-triisopropylsilyloxy-phenyl)urea

To a solution of 2-fluoro-6-methyl-3-triisopropylsilyloxy-benzoic acid (4 g, 12.2 mmol,
 20 1.0 eq) in a mixture of DCM (60 mL) and DMF (0.2 mL) at 0°C was added (COCl)₂ (4.67
 g, 36.75 mmol, 3.0 eq) dropwise. The mixture was warmed to room temperature and
 stirred for 1h. The reaction mixture was concentrated to dryness, and the residue obtained
 dissolved in acetone (50 mL). The resultant solution was added dropwise to a cooled
 solution of NaN₃ (3.19 g, 49.0 mol) in acetone (50 mL) and water (50 mL) at 0°C. The
 25 reaction was stirred for 1h at 0°C. Further water was then added (50 mL) and the reaction
 heated at 70 °C overnight. The acetone was evaporated *in vacuo* and the aqueous layer

extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give an oily residue, which was used directly without purification.

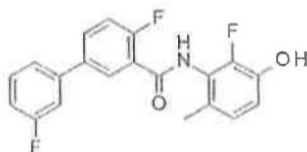
5 3-Amino-2-fluoro-4-methyl-phenol (intermediate X(b))



To a solution of 1,3-bis(2-fluoro-6-methyl-3-triisopropylsilyloxy-phenyl)urea (3 g, 4.83 mmol, 1.0 eq) in dioxane (60 mL) was added KOH (30% aqueous solution, 30 mL) at room temperature. The reaction mixture was heated at reflux overnight, then cooled and the resulting mixture acidified by addition of 1M HCl and extracted with EtOAc. The organic extract was washed with water, brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude residue was crystallized from DCM/petroleum ether (20 mL, 1/3, v/v) to give the title compound as a yellow solid (0.8 g, 59 %).

15 ^1H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 6.05 (app t, $J = 8.3$ Hz, 1H), 4.67 (s, 2H), 1.99 (s, 3H)

2-Fluoro-N-(2-fluoro-3-hydroxy-6-methyl-phenyl)-5-(3-fluorophenyl)benzamide



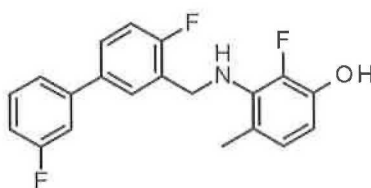
20 To a mixture of 2-fluoro-5-(3-fluorophenyl) benzoic acid (intermediate III(a)) (730 mg, 3.1 mmol, 1.1 eq) and $(\text{COCl})_2$ (1.1 g, 8.49 mmol, 3 eq) in DCM (20 mL) was added DMF (5 drops). The reaction mixture was stirred at 0°C for 1h and then concentrated *in vacuo*. The residue obtained was dissolved in THF (5 mL) and added dropwise to a solution of 3-amino-2-fluoro-4-methyl-phenol (400 mg, 2.83 mmol, 1 eq) and NaHCO_3 (951 mg, 11.3 mmol, 4 eq) in THF (15 mL) at 0°C . After the addition, the reaction mixture was stirred at room temperature for 3h. The resulting mixture was

poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as a yellow solid (600 mg, 60 %).

5

LC-MS: m/z 358.1 $[\text{M}+\text{H}]^+$ 380.1 $[\text{M}+\text{Na}]^+$

2-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methyl-phenol



- 10 To a solution of 2-fluoro-N-(2-fluoro-3-hydroxy-6-methyl-phenyl)-5-(3-fluorophenyl) benzamide (500 mg, 1.4 mmol, 1 eq) in THF (10 mL) under N_2 was added dropwise a solution of BH_3 (1M in THF, 7 mL, 7.0 mmol, 5 eq). The reaction mixture was heated at 50°C overnight. After cooling, the resulting mixture was quenched by addition of 1M HCl and extracted with EtOAc. The organic extract was washed with water and brine,
- 15 dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as an oil (300 mg, 42 %).

LC-MS: m/z 344.1 $[\text{M}+\text{H}]^+$ 366.1 $[\text{M}+\text{Na}]^+$

- 20 *Ethyl 2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methyl-phenoxy]acetate (II(x))*

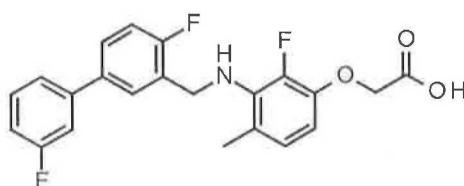


To a solution of 2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methylphenol (300 mg, 0.87 mmol, 1 eq) in DMF (6 mL) was added Cs_2CO_3 (425 mg, 1.31 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 1 h, then ethyl 2-bromoacetate (174 mg, 1.04 mmol, 1.2 eq) was added. The reaction mixture was stirred for 1 h then the reaction quenched by pouring into water. The mixture was extracted with EtOAc and the organic extract washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (260 mg, 70 %).

10 LC-MS: m/z 430.2 $[M+H]^+$ 452.2 $[M+Na]^+$

¹H NMR (400 MHz, CDCl₃) δ 7.54 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.47 – 7.35 (m, 2H), 7.30 – 7.27 (m, 1H), 7.22 – 7.17 (m, 1H), 7.13 (dd, *J* = 9.6, 8.6 Hz, 1H), 7.08 – 7.00 (m, 1H), 6.76 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.38 (app t, *J* = 8.2 Hz, 1H), 4.63 (s, 2H), 4.53 (br s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.20 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H)

2-[2-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methylphenoxy]acetic acid (I(i))



20

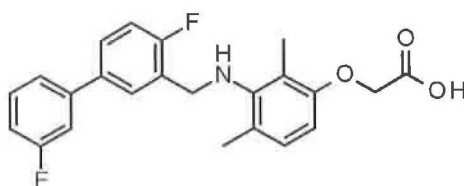
To a solution of ethyl 2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methyl-phenoxy]acetate (260 mg, 0.61 mmol, 1.0 eq) in THF (10 mL) was added NaOH (1M aqueous solution, 5 mL, 5 mmol, 8.2 eq) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1h. The organic solvent was evaporated *in vacuo* and the mixture that remained poured into water. The pH was adjusted to pH 4-6 with dilute HCl and the precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give title compound (I(i)) as a solid (200 mg, 82 %).

LC-MS : m/z 402.0 [M+H]⁺

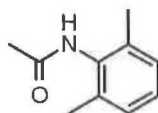
¹H NMR (300 MHz, DMSO-d₆) δ 7.72 (dd, *J*=7.2, 2.2 Hz, 1H), 7.63 - 7.54 (m, 1H), 7.53 - 7.44 (m, 1H), 7.40 (s, 1H), 7.39 - 7.34 (m, 1H), 7.30 - 7.18 (m, 1H), 7.21 - 7.09 (m, 1H), 6.67 (d, *J*=8.0 Hz, 1H), 6.25 (t, *J*=8.2 Hz, 1H), 4.48 (s, 2H), 4.44 (s, 2H), 2.12 (s, 3H)

Example 10 – compound I(j) synthesized according to scheme 3

2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic
10 acid (I(j))



N-(2,6-dimethylphenyl)acetamide

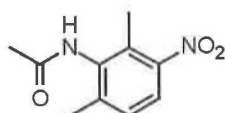


15

2,6-dimethylaniline (10 g, 82.5 mmol, 1.0 eq) was added to acetic anhydride (100 mL) at 0°C. The reaction mixture was then warmed to room temperature and stirred for 1h. The reaction was poured into ice water and the precipitate that formed collected by filtration to give the title compound as a yellow solid (10 g, 74 %).

20

N-(2,6-dimethyl-3-nitro-phenyl)acetamide



N-(2,6-dimethylphenyl)acetamide (10 g, 60 mmol, 1.0 eq) was dissolved in a mixture of H₂SO₄ (40 mL) and acetic acid (20 mL) at 0°C. A mixture of HNO₃ (10 mL) and H₂SO₄

(8 mL) was added dropwise with stirring. The reaction was allowed to warm to room temperature and stirred for a further 1h. The reaction was quenched by pouring into ice water, and the solid that formed collected by filtration to give the title compound as a yellow solid (12 g, 94 %).

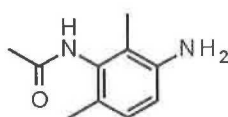
5

LC-MS: 209.1 $[M+H]^+$

^1H NMR (400 MHz, DMSO- d_6) δ 9.58 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 2.23 (s, 3H), 2.23 (s, 3H), 2.09 (s, 3H)

10

N-(3-amino-2,6-dimethyl-phenyl)acetamide

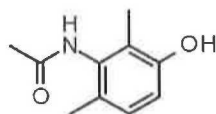


N-(2,6-dimethyl-3-nitro-phenyl)acetamide (12 g, 58 mmol, 1.0 eq) was dissolved in a mixture of MeOH (60 mL), EtOH (30 mL) and acetic acid (60 mL). Pd/C (1.6 g, 10%)
15 was added and the reaction stirred at room temperature under H_2 for 36 h. The catalyst was removed by filtration through celite and the filtrate collected. Water was added and the pH adjusted to pH 8 by addition of aqueous NaHCO_3 . The solution was concentrated *in vacuo* to remove methanol and ethanol. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4) filtered and evaporated *in vacuo*.
20 The crude product was purified by column chromatography (EtOAc:petroleum ether, 1:10 to 1:1) to give the title compound as a yellow solid (2 g, 19 %).

LC-MS: m/z 179.1 $[M+H]^+$

25

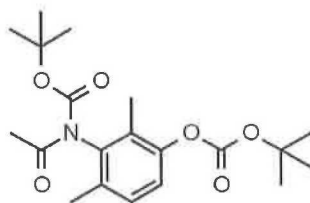
N-(3-hydroxy-2,6-dimethyl-phenyl)acetamide



To a solution of N-(3-amino-2,6-dimethyl-phenyl)acetamide (2 g, 11 mmol, 1.1 eq) in a mixture of H₂SO₄ (10 mL) and H₂O (70 mL) at 0°C was added a solution of NaNO₂ (1 g, 14.6 mmol, 1.3 eq) in H₂O (140 mL). The solution was stirred at 0 °C for 30 min then urea (425 mg, 7.1 mmol, 0.63 eq) was added. The reaction was poured into boiling water and the mixture stirred at 100°C for 2h. The aqueous phase was extracted with EtOAc, and the combined extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (MeOH:DCM, 0:1 to 1:20) to give the title compound as a white solid (800 mg, 40 %).

10 LC-MS: m/z 180.1 [M+H]⁺

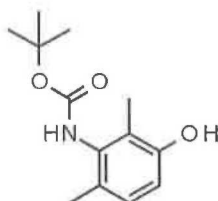
[3-(Acetyl(tert-butoxycarbonyl)amino)-2,4-dimethyl-phenyl] tert-butyl carbonate



To a solution of N-(3-hydroxy-2,6-dimethyl-phenyl)acetamide (614 mg, 3.43 mmol, 1.0 eq) in DMF (50 mL) was added (Boc)₂O (3.74 g, 17.2 mmol, 5.0 eq), Et₃N (1.04 g, 10.3 mmol, 3.0 eq) and DMAP (1.26 g, 10.3 mmol, 5.0 eq) and the solution stirred at 50 °C overnight. The reaction was cooled to room temperature, water was added and the aqueous layer was extracted with EtOAc. The organic extract was dried (Na₂SO₄), filtered and evaporated *in vacuo* and the residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as a yellow solid (800 mg, 62 %).

LC-MS: m/z 402.2 [M+Na]⁺

25 *Tert-butyl N-(3-hydroxy-2,6-dimethyl-phenyl)carbamate*

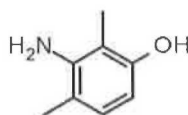


A solution of [3-(acetyl(tert-butoxycarbonyl)amino)-2,4-dimethyl-phenyl] tert-butyl carbonate (800 mg, 2.11 mmol, 1.0 eq) and hydrazine hydrate (5 mL) in t-BuOH (5 mL) was stirred under N₂ at 110°C overnight. The solution was adjusted to pH 6 by addition
5 of diluted HCl and the aqueous layer extracted with EtOAc. The organic extract was dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude solid was used in the next step without further purification (657 mg, 100 %).

LC-MS: m/z 260.1 [M+Na]⁺

10

3-Amino-2,4-dimethyl-phenol (intermediate X(c))



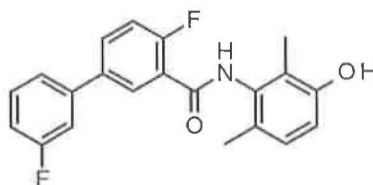
To a solution of tert-butyl N-(3-hydroxy-2,6-dimethyl-phenyl)carbamate (657 mg, 2.8 mmol, 1.0 eq) in DCM (5 mL) was added TFA (5 mL) and the reaction stirred at room
15 temperature overnight. The solvent was removed *in vacuo*. The residue was taken up in water and solution adjusted to pH 7 by addition of aqueous NaHCO₃. The aqueous phase was extracted with EtOAc and the organic extract dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a yellow solid (370 mg, 97 %) which was used without further purification.

20

LC-MS: 138.1 [M+H]⁺

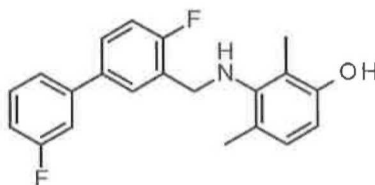
¹H NMR (400 MHz, DMSO-d₆) δ 8.58 (s, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.01 (d, *J* = 8.0 Hz, 1H), 4.36 (s, 2H), 1.96 (s, 3H), 1.89 (s, 3H)

25

2-Fluoro-5-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)benzamide

To a mixture of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (632 mg, 2.7 mmol, 1.0 eq) and oxalyl chloride (1.03 g, 8.1 mmol, 3.0 eq) in DCM (30 mL) was added DMF (0.3 mL). The reaction mixture was stirred at room temperature for 1h. The resulting mixture was concentrated to remove the solvent and excess oxalyl chloride then the residue obtained was dissolved in THF (20 mL). This solution was added dropwise to a suspension of 3-amino-2,4-dimethyl-phenol (370 mg, 2.7 mmol, 1.0 eq) and NaHCO₃ (680 mg, 8.1 mmol, 3.0 eq) in THF (20 mL). After addition was complete, the reaction mixture was stirred at room temperature for 30 min. The resulting mixture was adjusted to pH 3 by addition of 1M HCl and the aqueous layer extracted with EtOAc. The organic extract was dried (Na₂SO₄), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:1) to give the title compound as a yellow solid (400 mg, 42 %).

LC-MS: m/z 354.1 [M+H]⁺ 376.1 [M+Na]⁺

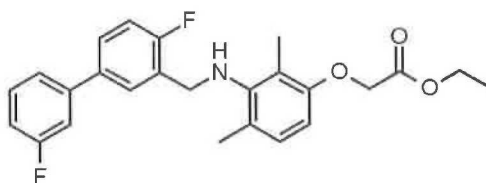
3-[[2-Fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenol

To a solution of 2-fluoro-5-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)benzamide (400 mg, 1.13 mmol, 1.0 eq) in THF under N₂ was added dropwise a solution of BH₃ (5.65 mL, 1M in THF, 5.65 mmol, 5.0 eq). The reaction mixture was heated to 60°C and stirred under N₂ for 3h. After cooling, the resulting mixture was quenched by addition of 1 M HCl and water and the aqueous layer extracted with EtOAc. The organic

extract was dried (Na_2SO_4), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title product as yellow oil (340 mg, 89 %).

5 LC-MS: 340.2 $[\text{M}+\text{H}]^+$ 362.1 $[\text{M}+\text{Na}]^+$

Ethyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate

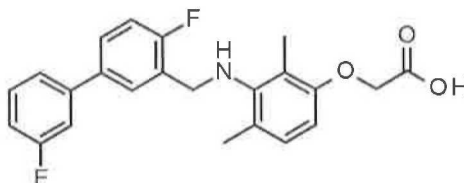


- 10 A solution of 3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenol (340 mg, 1.0 mmol, 1.0 eq) and Cs_2CO_3 (489 mg, 1.5 mmol, 1.5 eq) in 2-butanone (20 mL) was stirred at room temperature for 30 min. Ethyl 2-bromoacetate (167 mg, 1.0 mmol, 1.0 eq) was added and the reaction mixture was stirred at for 3h then quenched by addition of water. The aqueous layer was extracted with EtOAc and the organic extract
- 15 dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as a gummy solid (300 mg, 70 %).

LC-MS: 426.2 $[\text{M}+\text{H}]^+$ 448.2 $[\text{M}+\text{Na}]^+$

20

2-[3-[[2Fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(j))

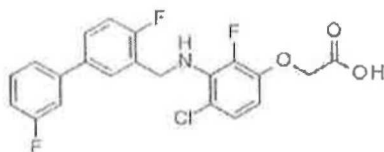


To a solution of ethyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (300 mg, 0.71 mmol, 1.0 eq) in THF (8 mL) was added a solution of NaOH (1M aqueous solution, 3 mL, 3 mmol, 4.2 eq) at room temperature. The reaction mixture was stirred 1h, then the THF was removed *in vacuo*. The remaining aqueous solution was poured into water and adjusted to pH 3 by addition of 1M HCl. The solid precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound (I(j)) as a solid (250 mg, 89 %).

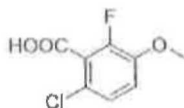
LC-MS : m/z 398.0 $[M+H]^+$

1H NMR (300 MHz, DMSO- d_6) δ 7.80 (dd, $J=7.1, 2.3$ Hz, 1H), 7.72 - 7.59 (m, 1H), 7.56 - 7.37 (m, 3H), 7.31 - 7.12 (m, 2H), 6.84 (d, $J=8.3$ Hz, 1H), 6.38 (d, $J=8.3$ Hz, 1H), 4.58 (s, 2H), 4.15 (s, 2H), 2.12 (d, 6H)

- 15 **Example 11 – compound I(k) synthesized according to scheme 3**
2-[4-Chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(k))



- 20 *6-Chloro-2-fluoro-3-methoxy-benzoic acid*



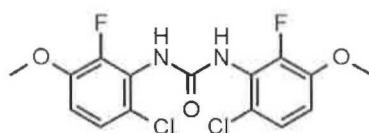
- To a solution of 4-chloro-2-fluoro-1-methoxy-benzene (800 mg, 5 mmol, 1.0 eq) in THF (20 mL) at $-78^\circ C$ was added *n*-BuLi (2.5M in THF, 3 mL, 7.5 mmol, 1.5 eq) dropwise under a nitrogen atmosphere. The mixture was stirred at this temperature for 30 min then CO_2 gas was bubbled through the solution for 1h. The reaction was warmed to room

temperature and quenched with water. The aqueous layer was acidified with 1M HCl and extracted with DCM. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a white solid (800 mg, 80 %), which was used in the next step without further purification.

5

^1H NMR (400 MHz, DMSO-d_6) δ 7.72 – 6.90 (m, 1H), 3.87 (s, 2H)

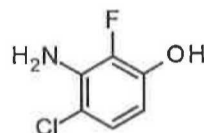
1,3-Bis(6-chloro-2-fluoro-3-methoxy-phenyl)urea



- 10 To a solution of 6-chloro-2-fluoro-3-methoxy-benzoic acid (600 mg, 2.93 mmol, 1.0 eq) in DCM (20 mL) at 0°C was added $(\text{COCl})_2$ (0.74 mL) and DMF (0.3 mL) and the reaction stirred for 2 h. The solvent was removed *in vacuo* and the residue dissolved in acetone (10 mL) and added to a solution of NaN_3 in a mixture of acetone (10 mL) and water (20 mL) at 0°C. The reaction was stirred at 0°C for 30 min, then heated at 70°C
- 15 overnight. The reaction was partitioned between water and EtOAc and the organic extract was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:20) to give the title compound as a yellow solid (400 mg, 36 %).

- 20 LC-MS: m/z 377.0, 379.0 $[\text{M}+\text{H}]^+$ 399.0 $[\text{M}+\text{Na}]^+$

3-Amino-4-chloro-2-fluoro-phenol (intermediate X(d))



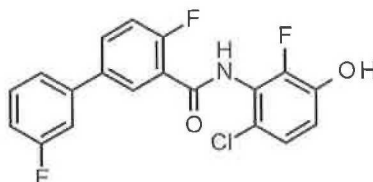
- 25 A solution of 1,3-bis(6-chloro-2-fluoro-3-methoxy-phenyl)urea (400 mg, 1.06 mmol, 1.0 eq) in HBr (48% aqueous solution, 20 mL) was stirred at 120°C overnight. The solution was then adjusted to pH 7 by addition of dilute aqueous NaOH and extracted with EtOAc.

The organic extract was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound (330 mg, 87 %) which was used without further purification.

LC-MS: m/z 162.0, 164.0 $[\text{M}+\text{H}]^+$

5

N-(6-chloro-2-fluoro-3-hydroxy-phenyl)-2-fluoro-5-(3-fluorophenyl)benzamide

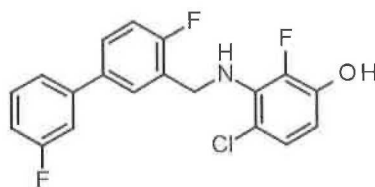


To a mixture of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (478 mg, 2.04 mmol, 1.0 eq) and $(\text{COCl})_2$ (777 mg, 6.13 mmol, 3.0 eq) in DCM (20 mL) was added DMF (0.3 mL). The reaction mixture was stirred at 0°C for 1 h, then the solvent removed *in vacuo*. The residue obtained was dissolved in THF (20 mL) and added dropwise to a solution of 3-amino-4-chloro-2-fluoro-phenol (intermediate X(d)) (330 mg, 2.04 mmol, 1.0 eq) and NaHCO_3 (515 mg, 6.13 mmol, 3.0 eq) in THF (20 mL). After the addition, the reaction mixture was stirred at room temperature for 30 min. The THF was evaporated *in vacuo* and the aqueous solution adjusted to pH 3 by addition of 1M HCl. The mixture was extracted with EtOAc and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:1) to give the title compound as a yellow solid (200 mg, 26 %).

20

LC-MS: m/z 378.0, 380.0 $[\text{M}+\text{H}]^+$ 400.0, 402.0 $[\text{M}+\text{Na}]^+$

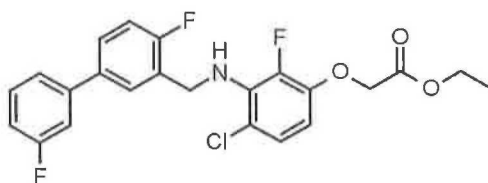
4-Chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol



To a solution of N-(6-chloro-2-fluoro-3-hydroxy-phenyl)-2-fluoro-5-(3-fluorophenyl) benzamide (200 mg, 0.53 mmol, 1.0 eq) in THF under N₂ was added dropwise a solution of BH₃ (1M in THF, 2.65 mL, 2.65 mmol, 5.0 eq) at room temperature. The reaction mixture was heated at 60°C for 3h. After cooling, the resulting mixture was quenched by addition of 1M HCl and the mixture extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as an oil (130 mg, 68 %).

LC-MS: m/z 364.0, 366.1 [M+H]⁺

Ethyl 2-[4-chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate



To a solution of 4-chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenol (130 mg, 0.36 mmol, 1.0 eq) and Cs₂CO₃ (175 mg, 0.54 mmol, 1.5 eq) in 2-butanone (20 mL) was added ethyl 2-bromoacetate (59.7 mg, 0.36 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 1h. Water was then added and the aqueous layer extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (80 mg, 50 %).

LC-MS: m/z 450.1, 452.1 [M+H]⁺ 472.1, 474.1 [M+Na]⁺

2-[4-Chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(k))



5

A solution of ethyl 2-[4-chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (80 mg, 0.18 mmol, 1.0 eq) in THF (6 mL) was added to a 1M solution of NaOH (2 mL, 2 mmol, 11.1 eq). The reaction mixture was stirred at room temperature for 2h. The organic solvent was removed *in vacuo* and the aqueous solution
 10 diluted with water. The solution was adjusted to pH 3 by addition of diluted HCl and the precipitate that formed collected by filtration, washed with water and dried *in vacuo* to give the title compound (I(k)) as white solid (65 mg, 87 %).

LC-MS : m/z 421.9, 423.9 [M+H]⁺

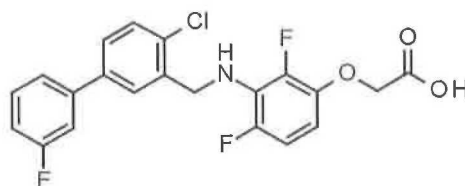
15

¹H NMR (300 MHz, DMSO-d₆) δ 7.70 (dd, *J*=7.2, 2.2 Hz, 1H), 7.64 - 7.55 (m, 1H), 7.53 - 7.42 (m, 1H), 7.42 - 7.32 (m, 2H), 7.30 - 7.19 (m, 1H), 7.23 - 7.12 (m, 1H), 7.03 (dd, *J*=8.9, 2.0 Hz, 1H), 6.41 (t, *J*=8.8 Hz, 1H), 5.67 (t, *J*=6.1 Hz, 1H), 4.65 (s, 2H), 4.60 (d, *J*=6.3 Hz, 2H)

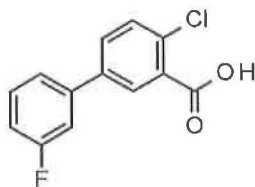
20

Example 12 – compound I(l) synthesized according to scheme 3

2-[3-[[2-Chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid (I(l))



2-Chloro-5-(3-fluorophenyl)benzoic acid (intermediate III(g))



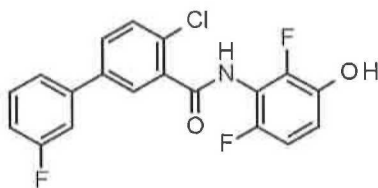
5

A solution of 3-fluorophenyl boronic acid (500 mg, 3.5 mmol, 1.2 eq), 5-bromo-2-chlorobenzoic acid (700 mg, 3.0 mmol, 1.0 eq), $\text{Pd}(\text{PPh}_3)_4$ (687 mg, 0.60 mmol, 0.2 eq) and Na_2CO_3 (2.52 g, 24 mmol, 8.0 eq) in a mixture of ethanol (5 mL), H_2O (5 mL) and DMF (20 mL) was stirred at 100°C under N_2 overnight. The reaction was quenched by addition of diluted HCl (to pH 3) and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) filtered and evaporated *in vacuo*. The residue was purified by chromatography (petroleum ether:EtOAc 20:1 to 1:1) to give the title compound as a white solid (500 mg, 67 %).

15 LC-MS : m/z 249.0, 251.0 $[\text{M}-\text{H}]^-$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.58 (br s, 1H), 8.06 (d, $J = 2.2$ Hz, 1H), 7.88 (dd, $J = 8.3, 2.4$ Hz, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.63 – 7.50 (m, 3H), 7.26 (br t, $J = 8.2$ Hz, 1H)

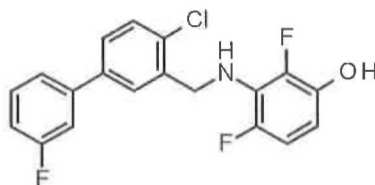
20 2-Chloro-N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)benzamide



- To a solution of 2-chloro-5-(3-fluorophenyl)benzoic acid (500 mg, 2.0 mmol, 1.0 eq) in DCM (20 mL) was added oxalyl chloride (761.6 mg, 6.0 mmol, 3.0 eq) and DMF (0.1 mL). The solution was stirred at room temperature for 1 h, then the solvent removed *in vacuo*. The resultant residue was dissolved in dry THF (30 mL) and added dropwise to a suspension of 3-amino-2,4-difluorophenol (intermediate X(a)) (290.2 mg, 2.0 mmol, 1.0 eq) and NaHCO₃ (504 mg, 6.0 mmol, 3.0 eq) in THF (30 mL). The mixture was warmed to room temperature and stirred for 30 min. The pH of the reaction was adjusted to pH 3 by addition of 1M HCl and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄) filtered and evaporated *in vacuo*. The residue was purified by chromatography to give the title compound as a white solid (200 mg, 27 %).

LC-MS: m/z 378.0, 380.0 [M+H]⁺ 400.0, 402.0 [M+Na]⁺

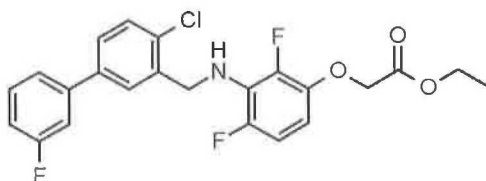
- 3-[[2-Chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenol



- To a solution of 2-chloro-N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl) benzamide (150 mg, 0.34 mmol, 1.0 eq) in THF (3 mL) was added a solution of BH₃ (1M in THF, 1.72 mL, 1.72 mmol, 5.0 eq). The reaction was heated at 60°C for 3h, then quenched by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the organic extract was washed with water and brine, dried (Na₂SO₄) filtered and evaporated *in vacuo*. The residue obtained was purified by flash chromatography (petroleum ether:EtOAc, 100:1 to 30:1) to give the title compound as a colourless oil (128 mg, 89 %).

- LC-MS : m/z 364.0, 366.1 [M+H]⁺

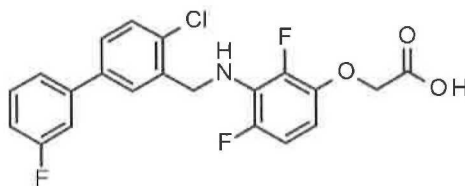
Ethyl 2-[3-[[2-chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy] acetate



To a solution of 3-[[2-chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenol (128 mg, 0.35 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃ (172 mg, 0.53 mmol, 1.5 eq). The reaction was stirred at room temperature for 30 min then
 5 ethylbromoacetate (70.5 mg, 0.42 mmol, 1.2 eq) was added dropwise. The reaction was stirred at room temperature for further 3h then water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered, evaporated *in vacuo* and the residue obtained purified by chromatography (petroleum ether:EtOAc, 100:1 to 20:1) to give the title compound as a
 10 colourless oil (120 mg, 76 %).

LC-MS: m/z 450.1, 452.1 [M+H]⁺ 472.1, 474.1 [M+Na]⁺

2-[3-[[2-Chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic
 15 acid (I(l))



To a solution of ethyl 2-[3-[[2-chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetate (120 mg, 0.27 mmol, 1.0 eq) in THF (8 mL) was added NaOH (1M aqueous solution, 3 mL, 3 mmol, 11.0 eq). The reaction was stirred at room
 20 temperature for 2h. The THF was removed *in vacuo* and the residue acidified to pH 5 by addition of 1M HCl. The precipitate that formed was collected by filtration, washed with water and dried to give the title compound (I(l)) (100 mg, 88 %).

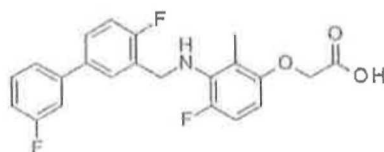
LC-MS : m/z 421.9, 423.9 [M+H]⁺

^1H NMR (300 MHz, DMSO- d_6) δ 7.74 (d, $J=2.0$ Hz, 1H), 7.65 - 7.56 (m, 1H), 7.55 - 7.45 (m, 2H), 7.43 - 7.35 (m, 2H), 7.31 - 7.09 (m, 1H), 6.82 (ddd, $J=11.7, 9.4, 2.1$ Hz, 1H), 6.33 (td, $J=9.1, 4.6$ Hz, 1H), 6.04 - 5.86 (m, 1H), 4.64 (s, 2H), 4.56 (d, $J=6.8$ Hz, 2H)

5

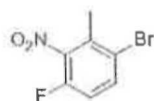
Example 13 - compound I(m) synthesized according to scheme 3

2-[4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methylphenoxy]acetic acid (I(m))



10

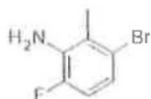
1-Bromo-4-fluoro-2-methyl-3-nitro-benzene



- 15 To a solution of 1-fluoro-3-methyl-2-nitro-benzene (5 g, 32.24 mmol, 1.0 eq) in TFA (25 mL) and conc. H_2SO_4 (10 mL) at 0°C was added NBS (6.31 g, 35.46 mmol, 1.1 eq) in portions. After addition, the mixture was stirred at room temperature for 2h. The resulting mixture was poured onto ice and the precipitate that formed collected by filtration, washed with water and dried *in vacuo* to give the title compound as a yellow solid (5 g, 67 %).
- 20

^1H NMR (400 MHz, DMSO- d_6) δ 7.98 (dd, $J = 9.0, 5.2$ Hz, 1H), 7.48 (app t, $J = 9.3$ Hz, 1H), 2.36 (s, 3H)

- 25 1-Bromo-4-fluoro-3-amino-2-methyl- benzene



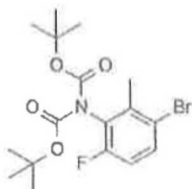
To a solution of 1-bromo-4-fluoro-2-methyl-3-nitro-benzene (3 g, 12.82 mmol, 1.0 eq) in EtOH (60 mL) was added NH₄Cl (30 mL), water (30 mL) and iron powder (2.87 g, 51.28 mmol, 4.0 eq). The reaction mixture was heated at reflux for 3h, then filtered through
 5 Celite. The filtrate was evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as a yellow solid (2 g, 77 %).

LC-MS: *m/z* 204.0, 206.0 [M+H]⁺

10

¹H NMR (400 MHz, CDCl₃) δ 6.91 (dd, *J* = 8.7, 5.0 Hz, 1H), 6.80 – 6.71 (m, 1H), 3.78 (br s, 2H), 2.28 (s, 3H)

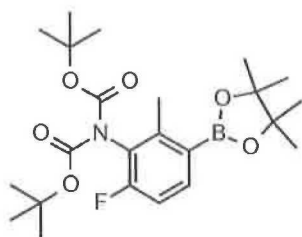
Tert-butyl N-(3-bromo-6-fluoro-2-methyl-phenyl)-N-tert-butoxycarbonyl-carbamate



15

To a solution of 1-bromo-4-fluoro-3-amino-2-methyl- benzene (6.09 g, 29.8 mmol, 1.0 eq) in DMF (60 mL) was added (Boc)₂O (32.5 g, 0.149 mol, 5.0 eq), TEA (6.14 g, 59.7 mmol, 2.0 eq) and DMAP (3.64 g, 29.8 mmol, 1.0 eq). The reaction mixture was stirred overnight then poured into water, and extracted with EtOAc. The organic
 20 extract was washed with water, brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography, (EtOAc:petroleum ether, 0:1 to 5:100) and triturated with petroleum ether to give the title compound as a white solid (6 g, 50 %).

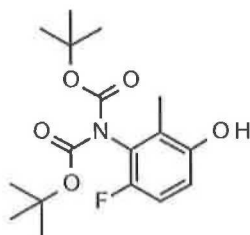
Tert-butyl N-tert-butoxycarbonyl-N-[6-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate



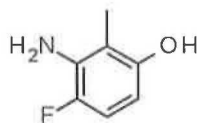
A mixture of tert-butyl N-(3-bromo-6-fluoro-2-methyl-phenyl)-N-tert-butoxycarbonyl-carbamate (1 g, 2.47 mmol, 1.0 eq), KOAc (0.73 g, 7.42 mmol, 3.0 eq), bis(pinacolato)diboron (753 mg, 2.96 mmol, 1.2 eq) and Pd(dppf)Cl₂ (188 mg, 0.247 mmol, 0.1 eq) in DMSO (10 mL) under N₂ was heated at 80°C for 4h. After cooling, the resultant mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (EtOAc:petroleum ether, 0:1, 1:30) to give the title product as a colourless oil (700 mg, 64 %).

10

Tert-butyl N-tert-butoxycarbonyl-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)carbamate



To a solution of tert-butyl N-tert-butoxycarbonyl-N-[6-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (800 mg, 41.7 mmol, 1.0 eq) in a mixture of THF (10 mL) and NaOH (1M aqueous solution, 5.3 mL, 5.3 mmol, 3.0 eq) at 0°C was added H₂O₂ (30% aqueous solution, 603 mg, 5.32 mmol, 3.0 eq). The reaction mixture was stirred at room temperature for 3h. The resulting mixture was acidified to pH 5-7 by addition of diluted HCl, and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography, (EtOAc:petroleum ether, 0:1 to 1:10) to give the title product as an oil (500 mg, 83 %).

3-Amino-4-fluoro-2-methyl-phenol (intermediate X(e))

To a solution of tert-butyl N-tert-butoxycarbonyl-N-(6-fluoro-3-hydroxy-2-methylphenyl)carbamate (500 mg, 1.46 mmol, 1.0 eq) in DCM (6 mL) was added TFA (2 mL).

- 5 The reaction was stirred at room temperature overnight, then the solvent was removed *in vacuo*, to give the title compound as yellow oil (200 mg, 97 %).

LC-MS: m/z 141.6 $[M+H]^+$

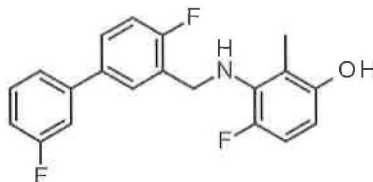
- 10 ^1H NMR (400 MHz, DMSO- d_6) δ 8.83 (s, 1H), 6.61 (dd, $J = 11.0, 8.7$ Hz, 1H), 5.99 (dd, $J = 8.7, 4.2$ Hz, 1H), 4.68 (br s, 2H), 1.91 (s, 3H)

2-Fluoro-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)benzamide

- 15 To a mixture of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (365 mg, 1.56 mmol, 1.1 eq) and $(\text{COCl})_2$ (541 mg, 4.26 mmol, 3.0 eq) in DCM (10 mL) was added DMF (3 drops). The reaction mixture was stirred at room temperature for 2h, then concentrated *in vacuo*. The residue obtained was dissolved in THF (5 mL) and added dropwise to a solution of 3-amino-4-fluoro-2-methylphenol (200 mg, 1.42 mmol, 1.0 eq)
- 20 in THF (15 mL) at 0°C . After the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for 2h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:3) to give the title compound as a
- 25 yellow solid (300 mg, 59 %).

LC-MS: m/z 358.1 [M+H]⁺ 380.1 [M+Na]⁺

4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenol



- 5 To a solution of 2-fluoro-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl) benzamide (300 mg, 0.84 mmol, 1.0 eq) in THF (10 mL) under N₂ was added dropwise a solution of BH₃ (1M in THF, 4.2 mL, 4.2 mmol, 5.0 eq). The reaction mixture was heated at 50°C overnight, then cooled and the reaction quenched by addition of 1M HCl. The mixture was extracted with EtOAc and the organic extract was washed with water and
- 10 brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title product as an oil (200 mg, 69 %).

LC-MS: m/z 344.1 [M+H]⁺

- 15 Ethyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl- phenoxy]acetate (II(y))



- To a solution of 4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl- phenol (200 mg, 0.58 mmol, 1.0 eq) in DMF (6 mL) was added Cs₂CO₃ (283 mg, 0.87
- 20 mmol, 1.5 eq). The reaction mixture was stirred for 1h at room temperature, then ethyl 2-bromoacetate (117 mg, 0.70 mmol, 1.2 eq) was added. The reaction mixture was stirred for a further 1h then poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The

residue obtained was purified by column chromatography to give the title compound as an oil (200 mg, 80 %).

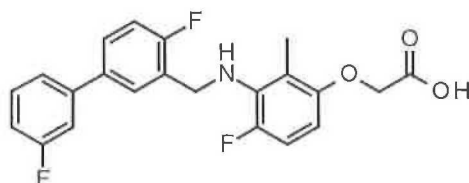
LC-MS: m/z 452.2 $[M+Na]^+$

5

1H NMR (400 MHz, DMSO- d_6) δ 7.71 (dd, $J = 7.1, 2.2$ Hz, 1H), 7.61 – 7.55 (m, 1H), 7.52 – 7.44 (m, 1H), 7.42 – 7.34 (m, 2H), 7.26 – 7.13 (m, 2H), 6.70 (d, $J = 8.5$ Hz, 1H), 6.30 (app t, $J = 8.2$ Hz, 1H), 4.68 (s, 2H), 4.49 (s, 2H), 4.11 (q, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 1.15 (t, $J = 7.1$ Hz, 3H)

10

2-[4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(m))



To a solution of ethyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenoxy]acetate (200 mg, 0.466 mmol, 1.0 eq) in THF (8 mL) was added NaOH (1M aqueous solution, 4 mL, 4.0 mmol, 9.0 eq) at 0°C. The reaction mixture was stirred at room temperature for 1h, then the organic solvent removed under reduced pressure and the aqueous solution diluted with water and adjusted to pH 4-6 by addition of diluted HCl. The precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound (I(m)) as a solid (150 mg, 80 %).

20

LC-MS : m/z 402.0 $[M+H]^+$

1H NMR (300 MHz, DMSO- d_6) δ 7.73 (dd, $J=7.2, 2.3$ Hz, 1H), 7.63 - 7.54 (m, 1H), 7.53 - 7.44 (m, 1H), 7.39 (d, $J=7.7$ Hz, 2H), 7.30 - 7.02 (m, 2H), 6.76 (dd, $J=12.3, 9.0$ Hz, 1H), 6.21 (dd, $J=9.0, 3.7$ Hz, 1H), 5.93 (m, 1H), 4.50 - 4.40 (m, 4H), 2.10 (s, 3H)

25

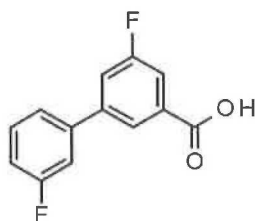
Example 14 – compound I(n) synthesized according to scheme 3

2-[2,4-Difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(n))



5

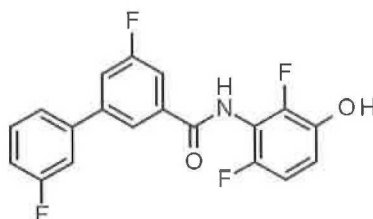
3-Fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(h))



To a solution of 3-fluorophenyl boronic acid (0.7 g, 5.0 mmol, 1.0 eq), 3-bromo-5-fluoro-
10 benzoic acid (1 g, 4.6 mmol, 1.1 eq) and Na_2CO_3 (1.45g, 13.7 mmol, 3 eq) in a mixture of
EtOH (5 mL), DMF (20 mL) and H_2O (5 mL) under N_2 was added $\text{Pd}(\text{PPh}_3)_4$ (200 mg,
0.17 mmol, 0.05 eq). The mixture was stirred at 100°C overnight then cooled to room
temperature. Water and ethyl acetate were added and the reaction was filtered through
Celite and the aqueous layer was extracted with EtOAc. The organic extract was
15 discarded and the aqueous layer was acidified to pH 4-5 by addition of 1M HCl and
extracted with EtOAc. The combined organic extracts were washed with water and brine,
dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a white
solid (970 mg, 90 %).

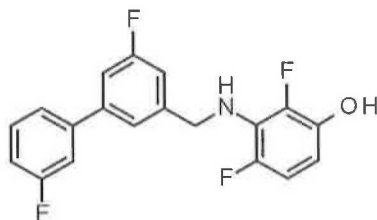
20 LC-MS : m/z 233.0 $[\text{M}-\text{H}]^-$

^1H NMR (400 MHz, $\text{MeOD}/\text{CDCl}_3$) δ 7.62 (t, $J = 1.5$ Hz, 1H), 7.29 – 7.23 (m, 1H), 7.10
– 6.97 (m, 3H), 6.93 – 6.87 (m, 1H), 6.72 – 6.64 (m, 1H)

N-(2,6-difluoro-3-hydroxy-phenyl)-3-fluoro-5-(3-fluorophenyl)benzamide

To a stirred solution of 3-fluoro-5-(3-fluorophenyl)benzoic acid (533 mg, 2.3 mmol, 1.1 eq) in DCM (10 mL) and DMF (3 drops) at 0°C was added oxalylchloride (866 mg, 6.8 mmol, 3.3 eq) dropwise. The reaction was warmed to room temperature and stirred for 2 h, and then the solvent removed. The residue that remained was dissolved in THF (6 mL) and added to a solution of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (300 mg, 2.07 mmol, 1.0 eq) and NaHCO₃ (868 mg, 10.34 mmol, 5.0 eq) in THF (6 mL) at 0°C. The reaction was warmed to room temperature and stirred for 1h then quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with 5% Na₂CO₃, water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue was recrystallised from DCM: petroleum ether (1:3) and collected by filtration to give the title compound as a solid (390 mg, 52%).

15

LC-MS: m/z 362.0 [M+H]⁺ 383.9 [M+Na]⁺*2,4-Difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol*

To a solution of *N*-(2,6-difluoro-3-hydroxy-phenyl)-3-fluoro-5-(3-fluorophenyl) benzamide (390 mg, 1.1 mmol, 1.0 eq) in THF (6 mL) at 0°C was added a solution of BH₃ (1M in THF, 6.47 mL, 6.5 mmol, 6.0 eq). The reaction was heated to 60°C and stirred overnight. The reaction mixture was quenched with water and extracted with

EtOAc. The organic extract was washed with 5% NaHCO₃, water and brine, dried (Na₂SO₄) and the solvent removed *in vacuo* to afford a crude residue which was purified by column chromatography (petroleum ether:EtOAc 1:0 to 10:1) to give the title compound as an oil (353 mg, 94 %).

5

LC-MS : m/z 348.1 [M-H]⁺

Ethyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(z))



10

To a stirred solution of 2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenol (350 mg, 1.0 mmol, 1.0 eq) in acetone (5 mL) was added Cs₂CO₃ (492.5 mg, 1.5 mmol, 1.5 eq). The resulting mixture was stirred for 30 min at room temperature then ethyl bromoacetate (202 mg, 1.21 mmol, 1.2 eq) was added. The resulting mixture was stirred 1h then water added and the mixture extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as an oil (385 mg, 88 %).

15

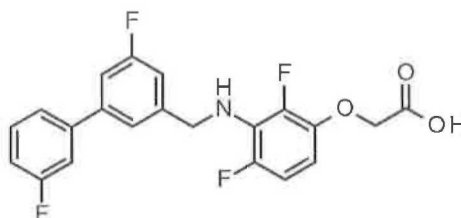
LC-MS : m/z calculated for C₂₃H₁₉F₄NO₃ [M+H]⁺ 434.14, [M+Na]⁺ 456.13, found 433.9, 456.0

20

¹H NMR (400 MHz, DMSO) δ 7.56 – 7.47 (m, 4H), 7.43 (d, *J* = 10.1 Hz, 1H), 7.29 – 7.19 (m, 1H), 7.14 (d, *J* = 9.8 Hz, 1H), 6.85 – 6.75 (m, 1H), 6.33 (td, *J* = 9.2, 4.7 Hz, 1H), 6.09 (br t, *J* = 7.1 Hz, 1H), 4.75 (s, 2H), 4.47 (br d, *J* = 7.0 Hz, 2H), 4.15 (q, *J* = 6.9 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H)

25

2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid
(I(n))



- 5 To a stirred solution of Ethyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (385 mg, 0.89 mmol, 1.0 eq) in THF (4 mL) was added an aqueous solution of LiOH (2M aqueous solution, 3 mL, 6 mmol, 6.7 eq). The reaction was stirred at room temperature for 1h. Water was added and the THF removed *in vacuo*. The aqueous residue was extracted with EtOAc and the combined organic extracts were
- 10 washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude material obtained was recrystallised from DCM/petroleum ether, collected by filtration and dried *in vacuo* to give (I(n)) (60 mg, 17 %) as a white solid.

LC-MS : m/z calculated for C₂₁H₁₅F₄NO₃ [M+H]⁺ 406.11, found 406.0

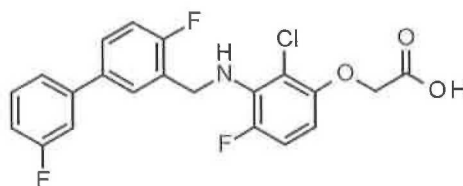
15

¹H NMR (300 MHz, DMSO-d₆) δ 7.63 - 7.46 (m, 4H), 7.40 (d, *J*=10.1 Hz, 1H), 7.29 - 7.17 (m, 1H), 7.13 (d, *J*=9.7 Hz, 1H), 6.70 (ddd, *J*=11.7, 9.4, 2.1 Hz, 1H), 6.15 (td, *J*=9.2, 4.7 Hz, 1H), 5.96 - 5.80 (m, 1H), 4.45 (d, *J*=7.3 Hz, 2H), 4.05 (s, 2H)

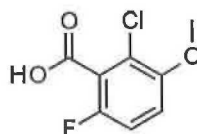
20

Example 15 – compound I(o) synthesized according to scheme 3

2-[2-Chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(o))



2-Chloro-6-fluoro-3-methoxy-benzoic acid



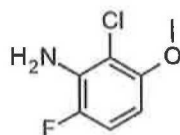
- 5 To a solution of 2-chloro-4-fluoro-1-methoxy-benzene (2.5 g, 15.6 mmol, 1 eq) in THF (25 mL) at -65 °C under N₂ was added a solution of *n*-BuLi (2.5 M, 17.1 mmol, 1.1 eq) dropwise. The reaction mixture was stirred at -65 °C for 1.5 h then CO₂ (gas) was bubbled into the solution for 10 min. The reaction mixture was then stirred at -60 to -20 °C for 30 min, then acidified with diluted HCl and extracted with EtOAc. The combined
- 10 organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound (2.7 g, 85 %) as a yellow solid which was used for next step without further purification.

LC-MS: *m/z* 203.0, 205.0 [M-H]⁻ 159.0, 161.0. [M-COOH]⁻

15

¹H NMR (400 MHz, DMSO-*d*₆) δ 14.06 (s, 1H), 7.31 (app t, *J* = 8.9 Hz, 1H), 7.24 (dd, *J* = 9.3, 5.0 Hz, 1H), 3.86 (s, 3H)

2-Chloro-6-fluoro-3-methoxy-aniline



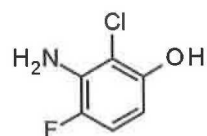
20

To a solution of 2-chloro-6-fluoro-3-methoxy-benzoic acid (2.7 g, 13.2 mmol, 1.0 eq) in a mixture of DCM (20 mL) and DMF (3 drops) at 0 °C was added (COCl)₂ (5.0 g, 39.6 mmol, 3.0 eq) dropwise. The reaction mixture was stirred at room temperature for 1h, and

then concentrated to dryness; the residue was dissolved in acetone (20 mL) and added dropwise to a solution of NaN_3 (2.6 g, 39.6 mmol, 3.0 eq) in water (15 mL) at 0 °C. The reaction was stirred 1h at 0 °C, water (50 mL) was added, then the reaction heated at 70°C overnight. The acetone was removed by distillation and the aqueous residue extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a residue, which was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:30) to give the title compound as a yellow oil (0.85 g, 37 %).

LC-MS: m/z 176.0, 178.0 $[\text{M}+\text{H}]^+$

3-Amino-2-chloro-4-fluoro-phenol (intermediate X(f))



To a solution of 2-chloro-6-fluoro-3-methoxy-aniline (0.85 g, 4.84 mmol, 1.0 eq) in DCM (8 mL) at 0°C was added BBr₃ (6.06 g, 24.2 mmol, 5.0 eq). The mixture was stirred at room temperature under N₂ overnight, then poured into ice-water. The pH of the solution was adjusted to pH 6 by addition of sat. NaHCO₃. The dichloromethane was removed under reduced pressure and the aqueous residue was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a pale yellow solid (0.74 g, 95 %).

LC-MS: m/z 162.0, 164.0 $[\text{M}+\text{H}]^+$

¹H NMR (400 MHz, DMSO-d₆) δ 9.67 (s, 1H), 6.80 (dd, J = 10.9, 8.9 Hz, 1H), 6.12 (dd, J = 8.9, 4.6 Hz, 1H), 5.20 (br s, 2H)

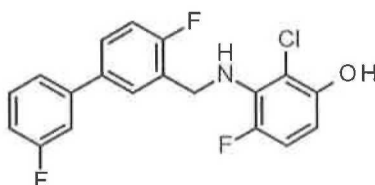
N-(2-chloro-6-fluoro-3-hydroxy-phenyl)-2-fluoro-5-(3-fluorophenyl)benzamide



To a solution of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (478 mg, 2.04 mmol, 1.1 eq) in DCM (9 mL) and DMF (3 drops) at 0 °C was added (COCl)₂ (779 mg, 6.14 mmol, 3.3 eq) dropwise. The reaction mixture was stirred at room temperature for 1.5h, then the solvent removed *in vacuo*. The residue obtained was dissolved in THF (7 mL) and added dropwise to a mixture of 3-amino-2-chloro-4-fluoro-phenol (intermediate X(f)) (300 mg, 1.86 mmol, 1.0 eq) and NaHCO₃ (781 mg, 9.3 mmol, 5.0 eq) in THF (7 mL) at 0°C. After addition was completed, the reaction mixture was warmed to room temperature and stirred overnight. Water was added and the aqueous mixture was extracted with EtOAc. The organic extract was washed with 5% Na₂CO₃, water and brine, dried (Na₂SO₄), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 3:20 to 1:4) to give the title as a yellow solid compound (180 mg, 26 %).

LC-MS: m/z 378.0 [M+H]⁺ 400.04, 402.04 [M+Na]⁺

2-Chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol



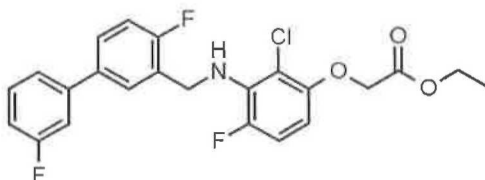
To a solution of N-(2-chloro-6-fluoro-3-hydroxyphenyl)-2-fluoro-5-(3-fluorophenyl) benzamide (180 mg, 0.48 mmol, 1.0 eq) in THF (2.5 mL) at 0 °C under N₂ was added dropwise a solution of BH₃ (1M in THF, 2.86 mL, 2.86 mmol, 6.0 eq). The reaction mixture was heated at 60 °C for 3h, then cooled and quenched by addition of water. The mixture was extracted with EtOAc and the organic extract was washed with NaHCO₃, water and brine, dried (Na₂SO₄), filtered, evaporated *in vacuo* and purified by column

chromatography (EtOAc:petroleum ether, 1:10, 1.2:10) to give the title compound as an oil (144 mg, 83 %).

LC-MS: m/z 364.1, 366.1 [M+H]⁺

5

Ethyl 2-[2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(aa))



To a solution of 2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenol (144 mg, 0.40 mmol, 1.0 eq) in acetone (3 mL) was added Cs₂CO₃ (193.5 mg, 0.59 mmol, 1.5 eq). The reaction mixture was stirred for 30 min, then ethyl 2-bromoacetate (79.3 mg, 0.48 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for 1 h and the resulting mixture poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered, and evaporated *in vacuo*. The residue obtained was purified by column chromatography (EtOAc:petroleum ether, 1:20 to 1:10) to give the title compound as an oil (155 mg, 87 %).

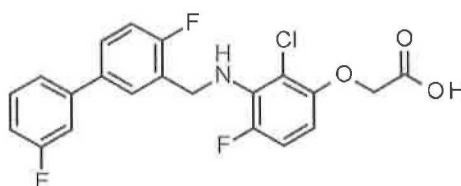
LC-MS: m/z 450.1, 452.1 [M+H]⁺ 472.1, 474.1 [M+Na]⁺

20

¹H NMR (400 MHz, DMSO-d₆) δ 7.68 (dd, *J* = 7.1, 2.4 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.49 (td, *J* = 7.9, 6.4 Hz, 1H), 7.40 – 7.32 (m, 2H), 7.26 – 7.14 (m, 2H), 6.95 (dd, *J* = 12.8, 9.2 Hz, 1H), 6.34 (dd, *J* = 9.2, 3.8 Hz, 1H), 5.83 – 5.74 (m, 1H), 4.79 (s, 2H), 4.61 (br d, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H)

25

2-[2-Chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(o))



To a solution of ethyl 2-[2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (155 mg, 0.34 mmol) in THF (2 mL) was added LiOH (2M aqueous solution, 2.5 mL, 2.5 mmol, 7.4 eq). The reaction mixture was stirred at room temperature for 2h, then the organic solvent was removed *in vacuo*. The residue that remained was diluted with water and adjusted to pH 4-6 by addition of diluted HCl. The solid precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to afford a crude product which was crystallized from DCM (1 mL) and hexane (20 mL) to give the title compound (I(o)) as a white solid (100 mg, 69 %).

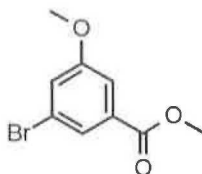
LC-MS : m/z 421.9, 423.9 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.69 (dd, J=7.2, 2.2 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.53 - 7.43 (m, 1H), 7.43 - 7.32 (m, 2H), 7.23 (dd, J=9.8, 8.6 Hz, 1H), 7.22 - 7.10 (m, 1H), 6.94 (dd, J=12.6, 9.2 Hz, 1H), 6.30 (dd, J=9.2, 3.8 Hz, 1H), 5.73 (t, J=7.1 Hz, 1H), 4.85 - 4.43 (m, 4H)

Example 16 – compound I(p) synthesized according to scheme 3 (amended by addition of hydrolysis step before last step)

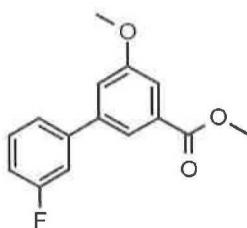
2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]phenoxy]acetic acid (I(p))



Methyl 3-bromo-5-methoxy-benzoate

- A mixture of 3-bromo-5-hydroxy-benzoic acid (3 g, 13.8 mmol, 1.0 eq) and Cs_2CO_3 (13.5 g, 41.5 mmol, 3.0 eq) in DMF (60 mL) was stirred at room temperature for 1h.
- 5 Methyl iodide (4.9 g, 34.6 mmol, 2.5 eq) was added and the reaction was stirred at room temperature overnight. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a colourless oil (3 g, 88 %).

- 10 LCMS: m/z 245.0, 247.0 $[\text{M}+\text{H}]^+$ 266.9, 269.0 $[\text{M}+\text{Na}]^+$

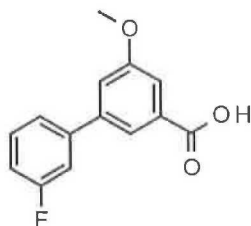
Methyl 3-(3-fluorophenyl)-5-methoxy-benzoate

- A suspension of methyl 3-bromo-5-methoxy-benzoate (3.2 g, 13.1 mmol, 1.0 eq), 3-fluorophenylboronic acid (2.0 g, 14.4 mmol, 1.1 eq) K_2CO_3 (7.2 g, 52.2 mmol, 4.0 eq) and $\text{Pd}(\text{PPh}_3)_4$ (754 mg, 0.65 mmol, 0.05 eq) in a mixture of methanol (10 mL) and dioxane (50 mL) was heated at 70°C for 4h under N_2 . After cooling, the resulting mixture was concentrated and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:20) to give the title compound as an oil (3.0 g, 88 %).

20

- LCMS: m/z 261.1 $[\text{M}+\text{H}]^+$ 283.1 $[\text{M}+\text{Na}]^+$

3-(3-Fluorophenyl)-5-methoxy-benzoic acid (intermediate III(i))

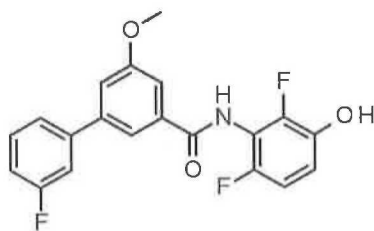


To a solution of methyl 3-(3-fluorophenyl)-5-methoxybenzoate (3 g, 11.5 mmol, 1.0 eq) in a mixture of methanol (20 mL) and THF (20 mL) at 0°C was added a solution of aqueous KOH (2M aqueous solution, 20 mL, 40 mmol, 3.5 eq). The reaction mixture was stirred at room temperature for 2h. The resulting mixture was concentrated to remove the methanol and THF then poured into water and the pH adjusted to pH 3-4 by addition of 1M HCl. The precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a white solid (2.5 g, 88 %).

LC-MS: m/z 247.1 $[M+H]^+$ 269.0 $[M+Na]^+$

1H NMR (400 MHz, DMSO- d_6) δ 13.20 (br. s., 1H), 7.78 (s, 1H), 7.62 – 7.50 (m, 3H), 7.50 – 7.44 (m, 2H), 7.28 – 7.20 (m, 1H), 3.89 (s, 3H)

N-(2,6-difluoro-3-hydroxyphenyl)-3-(3-fluorophenyl)-5-methoxybenzamide

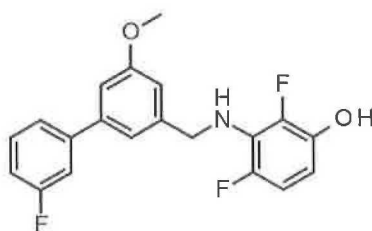


To a solution of 3-(3-fluorophenyl)-5-methoxybenzoic acid (747 mg, 3.0 mmol, 1.1 eq) in DCM (20 mL) was added oxalyl chloride (1.05 g, 8.3 mmol, 3.0 eq) and DMF (3 drops). The reaction mixture was stirred at room temperature for 2h, then concentrated. The oil obtained was dissolved in THF (5 mL) and added dropwise to a cooled solution of 3-Amino-2,4-difluorophenol (intermediate X(a)) (400 mg, 2.76 mmol, 1.0 eq) in THF (25 mL) at 0°C. After addition, the reaction mixture was stirred at room temperature for 2h. The resulting mixture was poured into water and extracted with EtOAc. The organic

extract was washed with water and brine, dried (Na_2SO_4), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:3) to give the title compound as a yellow solid (700 mg, 68 %).

5 LC-MS: m/z 374.1 $[\text{M}+\text{H}]^+$ 396.1 $[\text{M}+\text{Na}]^+$

2,4-Difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-3-(3-fluorophenyl)-5-methoxy-
10 benzamide (600 mg, 1.6 mmol, 1.0 eq) in THF under N_2 was added dropwise a solution
of BH_3 (1M in THF, 8 mL, 8.0 mmol, 8.0 eq) at room temperature. The reaction mixture
was heated at reflux for 4h, then cooled and the reaction quenched by addition of 1M HCl.
The aqueous layer was extracted with EtOAc and the combined organic extracts were
washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the
15 product (550 mg, 95 %) as yellow oil which was used directly to the next step without
further purification.

LC-MS : m/z 360.1 $[\text{M}+\text{H}]^+$

20 *Ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenoxy]
acetate (II(ab))*



To a solution of 2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenol (500 mg, 1.4 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃ (634 mg, 1.9 mmol, 1.4 eq). The reaction mixture was stirred for 1h, then ethyl 2-bromoacetate (279 mg, 1.7 mmol, 1.2 eq) was added. The reaction mixture was stirred for
5 a further 1h, then poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue obtained was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (500 mg, 80 %).

10 LC-MS: m/z 446.2 [M+H]⁺ 468.2 [M+Na]⁺

¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.32 (m, 2H), 7.28 – 7.22 (m, 1H), 7.13 (br s, 1H), 7.08 – 7.01 (m, 1H), 7.01 – 6.97 (m, 1H), 6.91 (br s, 1H), 6.70 (ddd, *J* = 11.3, 9.2, 2.2 Hz, 1H), 6.28 (ddd, *J* = 13.8, 9.1, 4.7 Hz, 1H), 4.61 (s, 2H), 4.54 (br s, 2H), 4.25 (q, *J* = 7.1
15 Hz, 2H), 3.85 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H)

Ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]phenoxy]acetate (II(b))



20 To a solution of ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenoxy]acetate (400 mg, 0.9 mmol, 1.0 eq) and AlCl₃ (718 mg, 5.4 mmol, 6.0 eq) in DCM (10 mL) at 0°C was added ethanethiol (315 mg, 5.4 mmol, 6.0 eq) under N₂. The reaction mixture was stirred at 0°C for 30 min. The resulting mixture was poured
25 into water and extracted with EtOAc. The organic extract was washed with brine, dried (Na₂SO₄), filtered, evaporated *in vacuo* and the crude residue obtained purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as an oil (260 mg, 67 %).

LC-MS: m/z 432.1 $[M+H]^+$ 454.1 $[M+Na]^+$

1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 2H), 7.28 – 7.22 (m, 1H), 7.11 (br s, 1H),
 5 7.08 – 7.02 (m, 1H), 6.96 (br s, 1H), 6.85 (br s, 1H), 6.72 (ddd, $J = 11.3, 9.2, 2.2$ Hz, 1H),
 6.31 (td, $J = 9.0, 4.7$ Hz, 1H), 4.66 (s, 2H), 4.53 (br s, 2H), 4.27 (q, $J = 7.1$ Hz, 2H), 1.31
 (t, $J = 7.1$ Hz, 3H)

10 2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]phenoxy]acetic
 acid (I(p))



To a solution of ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]
 methylamino]phenoxy]acetate (II(b)) (200 mg, 0.46 mmol, 1.0 eq) in THF (10 mL) was
 added NaOH (1M, 6 mL, 6 mmol, 13.0 eq) at 0°C. The reaction mixture was allowed to
 15 warm room temperature and was stirred for 3h. The THF was removed *in vacuo* and the
 remaining solution diluted with water and adjusted to pH 4-6 by addition of diluted HCl.
 The precipitate that formed was collected by filtration and dried *in vacuo* to give the title
 compound (I(p)) as a solid (170 mg, 91 %).

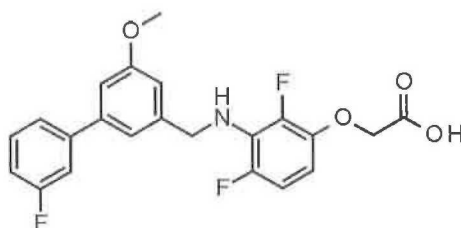
20 LC-MS : m/z 404.0 $[M+H]^+$

1H NMR (300 MHz, $CDCl_3$) δ 7.59 - 7.42 (m, 1H), 7.41 - 7.27 (m, 2H), 7.25 - 7.09 (m,
 1H), 7.05 (s, 1H), 6.86 (s, 1H), 6.82 - 6.75 (m, 1H), 6.74 (s, 1H), 6.27 (td, $J=9.0, 4.5$ Hz,
 1H), 5.92 (s, 1H), 4.62 (s, 2H), 4.38 (d, $J=6.9$ Hz, 2H)

25

Example 17 – compound I(q) synthesized according to scheme 3

2-[2,4-Difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenoxy]

acetic acid (I(q))

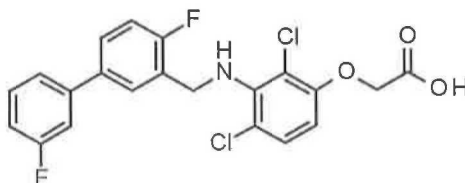
- 5 To a solution of ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenoxy]acetate (see example 16) (200 mg, 0.45 mmol, 1.0 eq) in THF (10 mL) was added an aqueous solution of NaOH (1M aqueous solution, 4 mL, 4 mmol, 8.9 eq) at 0°C. The reaction mixture was stirred at room temperature for 3h. The organic solvent was removed water added and the pH adjusted to pH 4-6 by addition of 1M HCl.
- 10 The solid that precipitated was collected by filtration and dried *in vacuo* to give the title compound as a solid (150 mg, 80 %).

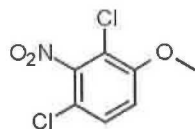
LC-MS : m/z 417.9 [M+H]⁺

- 15 ¹H NMR (400 MHz, DMSO-d₆) δ 7.61 - 7.36 (m, 3H), 7.36 - 7.14 (m, 2H), 7.05 (s, 1H), 6.89 (s, 1H), 6.85 - 6.64 (m, 1H), 6.28 (td, *J*=9.1, 4.6 Hz, 1H), 5.96 (s, 1H), 4.62 (s, 2H), 4.42 (d, *J*=6.9 Hz, 2H), 3.78 (s, 3H)

20 **Example 18 – compound I(r) synthesized according to scheme 2**

2-[2,4-Dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(r))

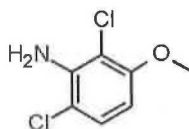


1,3-Dichloro-4-methoxy-2-nitro-benzene

To a solution of 2,4-dichloro-3-nitro-phenol (600 mg, 2.9 mmol, 1.0 eq) in acetone (30 mL), was added K_2CO_3 (1.2 g, 8.7 mmol, 3.0 eq) and the solution was stirred at room temperature for 30 min. Methyl iodide (1.2 g, 8.7 mmol, 3.0 eq) was added and the reaction was stirred at room temperature overnight. The reaction was filtered to remove the inorganic salts and the organic phase was evaporated *in vacuo* to give the title compound (550 mg, 86 %).

10

1H NMR (400 MHz, DMSO- d_6) δ 7.78 (d, $J = 9.3$ Hz, 1H), 7.47 (d, $J = 9.2$ Hz, 1H), 3.97 (s, 3H)

2,6-Dichloro-3-methoxy-aniline (intermediate VI(a))

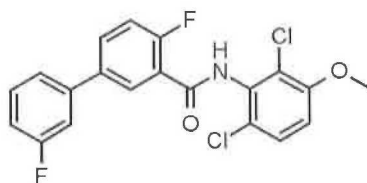
15

To a solution of 1,3-dichloro-4-methoxy-2-nitro-benzene (550 mg, 2.5 mmol, 1.0 eq) in EtOAc (20 mL) was added Pd/C (10% Pd, 50 mg) and the reaction was stirred under a hydrogen atmosphere overnight. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give the title compound (500 mg, 100 %).

20

LC-MS: m/z 192.0, 194.0, 196.0 $[M+H]^+$

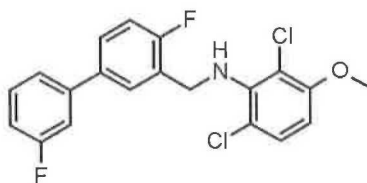
N-(2,6-dichloro-3-methoxy-phenyl)-2-fluoro-5-(3-fluorophenyl)benzamide



A solution of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (1.6 g, 7 mmol, 3.0 eq) in SOCl₂ (20 mL) was heated at reflux for 3 h. The excess thionyl chloride was removed *in vacuo* and the residue obtained dissolved in THF (10 mL) and added dropwise to a solution of 2,6-dichloro-3-methoxyaniline (450 mg, 2.3 mmol, 1.0 eq) and NaH (85 mg, 3.4 mmol, 1.5 eq) in THF (10 mL). The reaction was stirred at room temperature for 2h then quenched by addition of aqueous NH₄Cl. The mixture was extracted with EtOAc and the combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound (200 mg, 21 %).

LC-MS: m/z 430.0, 432.0, 434.0 [M+Na]⁺

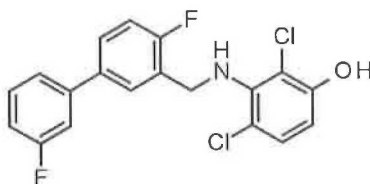
2,6-Dichloro-N-[[2-fluoro-5-(3-fluorophenyl)phenyl]methyl]-3-methoxyaniline



15

To a solution of N-(2,6-dichloro-3-methoxy-phenyl)-2-fluoro-5-(3-fluorophenyl) benzamide (200 mg, 0.5 mmol, 1.0 eq) in dry THF (10 mL) was added a solution of BH₃ (1M in THF, 2 mL, 2 mmol, 4.0 eq) dropwise. The solution was then heated at 60°C overnight. The reaction was quenched by addition of MeOH, then concentrated and the residue obtained was purified by column chromatography (Petroleum ether : EtOAc , 10:1) to give the title compound (150 mg, 77 %).

LC-MS: m/z 394.0, 396.0 [M+H]⁺

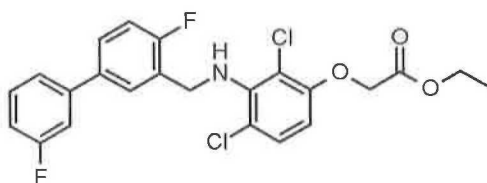
2,4-Dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol

To a solution of 2,6-dichloro-N-[[2-fluoro-5-(3-fluorophenyl)phenyl]methyl]-3-methoxy-
5 aniline (200 mg, 0.5 mmol, 1.0 eq) in DCM (15 mL) at 0°C was added borontribromide
(640 mg, 2.5 mmol, 5.0 eq) portion-wise. The reaction was stirred at room temperature
overnight then poured into ice. The mixture was extracted with EtOAc and the combined
organic extracts were dried, (Na₂SO₄) filtered and evaporated *in vacuo*. The residue
obtained was purified by column chromatography (Petroleum ether : EtOAc, 20:1) to
10 give the title compound (150 mg, 77 %).

LC-MS: m/z 380.1, 382.0, 384.1 [M+H]⁺

Ethyl 2-[2,4-dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]

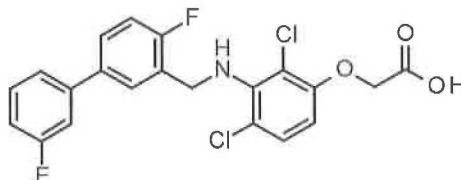
15 *acetate*



To a solution of 2,4-dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenol
(150 mg, 0.4 mmol, 1.0 eq) in DMF (50 mL), was added K₂CO₃ (220 mg, 0.6 mmol, 1.5
eq) and the solution was stirred at room temperature for 30 min. BrCH₂CO₂Et (100 mg,
20 1.6 mmol, 4.0 eq) was added dropwise and the reaction was stirred overnight. The
reaction was quenched by addition of water (200 mL) and extracted with EtOAc. The
combined organic extracts were dried (Mg₂SO₄), filtered and evaporated under reduced
pressure and the residue obtained purified by column chromatography (EtOAc:petroleum
ether, 0:1 to 1:10) to give the title compound (130 mg, 70 %).

LC-MS: m/z 466.1, 468.1, 470.1 [M+H]⁺ 488.1, 490.1, 490.0 [M+Na]⁺

2-[2,4-Dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic
5 acid (I(r))



To a solution of ethyl 2-[2,4-dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (130 mg, 0.28 mmol, 1.0 eq) in THF (20 mL), LiOH.H₂O (50 mg, 1.1 mmol, 4.0 eq) was added. After the addition of water (10 mL), the mixture
10 was heated to 60°C overnight. The THF was then removed *in vacuo* and the water phase was adjusted to pH 6 by addition of 1M HCl. The precipitate was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a solid (80 mg, 65 %).

LC-MS : m/z 437.9, 439.1, 441.1 [M+H]⁺

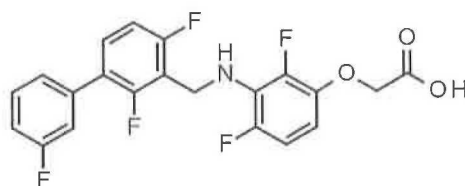
15

¹H NMR (300 MHz, DMSO-d₆) δ 7.96 - 7.73 (m, 1H), 7.59 (td, *J*=5.4, 2.4 Hz, 1H), 7.54 - 7.45 (m, 1H), 7.44 - 7.33 (m, 2H), 7.31 - 7.00 (m, 3H), 6.49 (d, *J*=9.0 Hz, 1H), 5.52 - 5.18 (m, 1H), 4.62 (d, *J*=5.6 Hz, 2H), 4.58 (s, 2H)

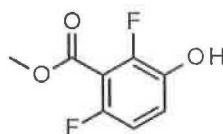
20

Example 19 – compound I(s) synthesized according to scheme 3

2-[3-[[2,6-Difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenoxy]acetic acid (I(s))



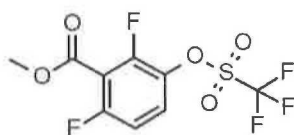
Methyl 2,6-difluoro-3-hydroxy-benzoate



- 5 To a solution of 2,6-difluoro-3-triisopropylsilyloxy-benzoic acid (see example 2) (7 g, 21.1 mmol, 1.0 eq) in MeOH (100 mL) was added SOCl₂ (10 mL) dropwise. The reaction mixture was heated at reflux for 3h, then cooled and the solvent removed *in vacuo*. Water was added and the aqueous layer was extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the
- 10 title compound as a solid (3 g, 75 %) which was used in the next step without further purification.

LC-MS: m/z 189.0 [M+H]⁺ 211.0 [M+Na]⁺

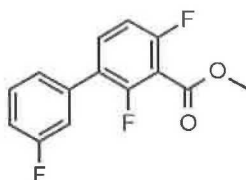
- 15 *Methyl 2,6-difluoro-3-(trifluoromethylsulfonyloxy)benzoate*



- To a solution of Methyl 2,6-difluoro-3-hydroxy-benzoate (2 g, 10.6 mmol, 1.0 eq) and pyridine (2.1 g, 26.8 mmol, 2.5 eq) in DCM (30 mL) at 0°C under N₂ was added dropwise triflic anhydride (4.5 g, 15.95 mmol, 1.5 eq). After addition was completed, the
- 20 reaction was allowed to warm to room temperature and stirred at room temperature for 4h. The resulting mixture was poured into water and adjusted to pH 5-6 by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the organic extract washed with water and brine, dried (Na₂SO₄), filtered, evaporated *in vacuo* and purified by flash

column chromatography (EtOAc:petroleum ether, 0:1 to 1:20) to give the title compound as a colourless oil (3 g, 88%).

Methyl 2,6-difluoro-3-(3-fluorophenyl)benzoate



5

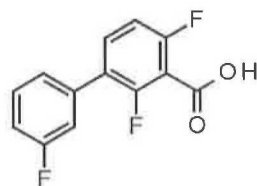
A mixture of methyl 2,6-difluoro-3-(trifluoromethylsulfonyloxy)benzoate (3.0 g, 9.4 mmol, 1.0 eq), 3-fluorophenylboronic acid (1.57 g, 11.2 mmol, 1.2 eq), K_2CO_3 (5.2 g, 37.6 mmol, 4.0 eq) and $Pd(PPh_3)_4$ (543 mg, 0.47 mmol, 0.05 eq) in a mixture of MeOH (10 mL) and dioxane (30 mL) was heated to 80°C under N_2 overnight. After cooling, the resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (1.7 g, 68 %).

10

LC-MS: m/z 267.1 $[M+H]^+$ 289.1 $[M+Na]^+$

15

2,6-difluoro-3-(3-fluorophenyl)benzoic acid (intermediate III(j))



To a solution of methyl 2,6-difluoro-3-(3-fluorophenyl)benzoate (1.7 g, 6.4 mmol, 1.0 eq) in mixture of MeOH (20 mL) and THF (20 mL) was added a solution of aqueous NaOH (1M aqueous solution, 20 mL, 20 mmol, 3.1 eq) at room temperature. The reaction mixture was heated to reflux for 30 mins, then cooled and the resulting mixture concentrated *in vacuo* to remove the organic solvent. The residue was diluted with water and adjusted to pH 5-6, by addition of 1M HCl. The precipitate that formed was collected

20

by filtration, washed with water and dried *in vacuo* to give the title compound as a white solid (1.4 g, 87 %).

LC-MS: m/z 253.0 $[M+H]^+$ 275.0 $[M+Na]^+$

5

1H NMR (400 MHz, DMSO- d_6) δ 14.15 (br s, 1H), 7.77 – 7.68 (m, 1H), 7.58 – 7.50 (m, 1H), 7.43 – 7.36 (m, 2H), 7.36 – 7.24 (m, 2H)

N-(2,6-difluoro-3-hydroxy-phenyl)-2,6-difluoro-3-(3-fluorophenyl)benzamide



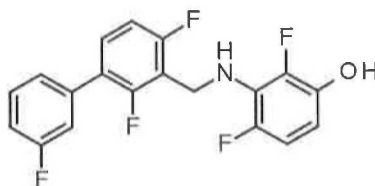
10

To a solution of 2,6-difluoro-3-(3-fluorophenyl)benzoic acid (765 mg, 3.03 mmol, 1.1 eq) and oxalyl chloride (1.05 g, 8.5 mmol, 3.0 eq) in DCM (20 mL) was added DMF (0.1 mL). The reaction mixture was stirred at room temperature for 2h, then concentrated *in vacuo*. The residue obtained was dissolved in THF (5 mL) and added dropwise to a solution of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (400 mg, 2.76 mmol, 1.0 eq) in THF (25 mL) at 0°C over 10 min. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 3h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:4) to give the title compound as a yellow solid (600 mg, 61 %).

15

20

3-[[2,6-Difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-2,6-difluoro-3-(3-fluorophenyl) benzamide (500 mg, 1.32 mmol, 1.0 eq) in THF (10 mL) under N₂ was added dropwise a solution of BH₃ (1M in THF, 7 mL, 7.0 mmol, 5.3 eq) at room temperature. The reaction mixture was heated at reflux for 4h then cooled and the reaction was quenched by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound (400 mg, 83 %) as an oil which was used in the next step without purification.

- 10 Ethyl 2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenoxy]acetate (II(ac))

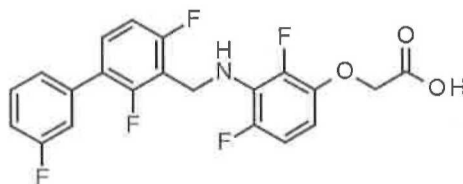


- To a solution of 3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenol (300 mg, 0.82 mmol, 1.0 eq) in DMF (5 mL) was added Cs₂CO₃ (375 mg, 1.15 mmol, 1.4 eq) at room temperature. The reaction mixture was stirred for 1h, then ethyl 2-bromoacetate (151 mg, 0.90 mmol, 1.1 eq) was added. The reaction mixture was stirred for a further 1h and the resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered, evaporated *in vacuo* and purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (240 mg, 65 %).

LC-MS: m/z 452.1 [M+H]⁺ 474.1 [M+Na]⁺

- ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.36 (m, 1H), 7.35 – 7.27 (m, 1H), 7.26 – 7.22 (m, 1H), 7.18 (br d, *J* = 10.0 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.98 – 6.92 (m, 1H), 6.73 – 6.66 (m, 1H), 6.34 (td, *J* = 9.0, 4.7 Hz, 1H), 4.66 (s, 2H), 4.60 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H)

2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid (I(s))



5

To a solution of ethyl 2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetate (240 mg, 0.53 mmol, 1.0 eq) in THF (10 mL) was added a solution of aqueous NaOH (1M aqueous solution, 5 mL, 5 mmol, 9.4 eq). The reaction mixture was stirred at room temperature for 3h. The organic solvent was removed *in vacuo* and the residue diluted with water and adjusted to pH 5-6 by addition of diluted HCl. The precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a solid (180 mg, 80 %).

10

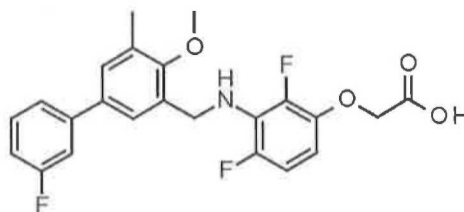
LC-MS : m/z 423.9 [M+H]⁺

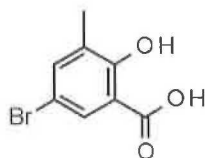
15

¹H NMR (300 MHz, DMSO-d₆) δ 7.63 - 7.43 (m, 2H), 7.39 - 7.29 (m, 2H), 7.29 - 7.21 (m, 1H), 7.16 (td, *J*=8.9, 1.3 Hz, 1H), 6.82 (ddd, *J*=11.5, 9.3, 2.2 Hz, 1H), 6.39 (td, *J*=9.1, 4.7 Hz, 1H), 5.56 - 5.21 (m, 1H), 4.64 (s, 2H), 4.55 (d, *J*=6.5 Hz, 2H)

20 **Example 20 – compound I(t) synthesized according to scheme 3**

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]phenoxy]acetic acid (I(t))



5-Bromo-2-hydroxy-3-methyl-benzoic acid

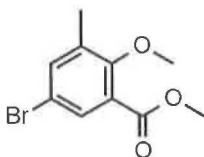
To a solution of 2-hydroxy-3-methyl-benzoic acid (10 g, 66.7 mmol, 1.0 eq) in acetic acid (100 mL) was added bromine (10.66 g, 66.7 mmol, 1.0 eq) slowly over 5 min. The mixture was stirred at room temperature for 24h, then water was added slowly and the mixture was stirred for a further 30 min. The precipitate was collected by filtration and was washed with water and dried to give the title compound as a white solid (13.7 g, 90 %).

10

LC-MS : m/z 229.0, 231.0 [M-H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 7.71 (dd, *J* = 2.6, 0.6 Hz, 1H), 7.60 (dd, *J* = 2.6, 0.8 Hz, 1H), 2.18 (s, 3H)

15

Methyl 5-bromo-2-methoxy-3-methyl-benzoate

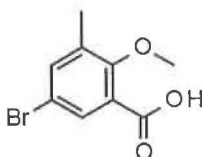
To a solution of 5-bromo-2-hydroxy-3-methyl-benzoic acid (3 g, 12.9 mmol, 1.0 eq) and K₂CO₃ (5.38g, 38.9 mmol, 3.0 eq) in acetone (15 mL) was added MeI (5.53 g, 38.9 mmol, 3.0 eq). The mixture was stirred at 58°C overnight. TLC indicated that the reaction was not completed. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄) filtered and evaporated *in vacuo*. The crude solid obtained was dissolved in DMF (20 mL) and Cs₂CO₃ (6 g, 18.4 mmol, 1.4 eq) added. To the mixture was added MeI (2 mL, 38.95 mmol, 3eq). The mixture was stirred for 1h at room temperature, water was added and the aqueous layer

25

was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a white solid (2.6 g, 77 %).

- 5 LC-MS: m/z 259.0, 260.9 $[\text{M}+\text{H}]^+$ 280.9, 282.9 $[\text{M}+\text{Na}]^+$

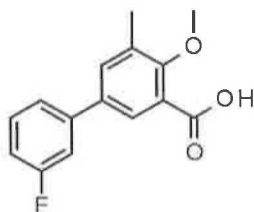
5-Bromo-2-methoxy-3-methyl-benzoic acid



- To a solution of methyl 5-bromo-2-methoxy-3-methyl-benzoate (2.6 g, 10.0 mmol, 1.0 eq) in THF (20 mL) was added an aqueous solution of NaOH (2M, 20 mL, 40 mmol, 4.0 eq). The mixture was stirred at room temperature for 5h. Water was added and the aqueous layer was acidified to pH 9 by addition of 1M HCl. The THF was removed *in vacuo* and the aqueous layer was further acidified to pH 4-5 with 1M HCl. The solid that precipitated from the reaction was collected by filtration and dried to give the title compound as a white solid (1.8 g, 73 %).

LC-MS: m/z 245.0, 247.0 $[\text{M}+\text{H}]^+$ 267.0, 269.0 $[\text{M}+\text{Na}]^+$

5-(3-Fluorophenyl)-2-methoxy-3-methyl-benzoic acid (intermediate III(k))



- To a solution of 3-fluorophenylboronic acid (0.75 g, 5.39 mmol, 1.1 eq), 5-bromo-2-methoxy-3-methyl-benzoic acid (1.2 g, 4.90 mmol, 1.0 eq) and Na_2CO_3 (1.56g, 14.69 mmol, 3 eq) in a mixture of EtOH (6 mL), DMF (24 mL) and H_2O (6 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (300 mg, 0.26 mmol, 0.05 eq). The mixture was stirred at 100°C overnight.

Water was added, the reaction was filtered and the filtrate was extracted with EtOAc. The organic extract was discarded and the aqueous phase was acidified to pH 4-5 with 1M HCl and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to provide the title compound as a white solid (1.09 g, 86 %).

LC-MS: m/z 261.1 $[\text{M}+\text{H}]^+$ 283.1 $[\text{M}+\text{Na}]^+$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.02 (s, 1H), 7.77 (d, $J = 5.0$ Hz, 2H), 7.56 – 7.45 (m, 3H), 7.25 – 7.15 (m, 1H), 3.78 (s, 2H), 2.33 (s, 2H)

N-(2,6-Difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)-2-methoxy-3-methyl-benzamide



To 5-(3-fluorophenyl)-2-methoxy-3-methyl-benzoic acid (1.09 g, 4.19 mmol, 1.1 eq) was added SOCl_2 (10 mL, 12.6 mmol, 3.0 eq). The reaction was heated to 70°C and stirred for 6h, then the solvent was removed. The residue obtained was dissolved in THF (10 mL) and added to a mixture of 3-amino-2,4-difluorophenol (intermediate X(a)) (0.405 g, 2.8 mmol, 1.0 eq) and NaHCO_3 (1.17 g, 13.9 mmol, 5 eq) in THF (8 mL) at 0°C . The reaction was warmed to room temperature, stirred for 2h then quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue obtained was purified by column chromatography (petroleum ether:EtOAc 1:0 to 10:1) to give the title compound as a white solid (209 mg, 19 %).

LC-MS : m/z 388.1 $[\text{M}+\text{H}]^+$ 410.1 $[\text{M}+\text{Na}]^+$

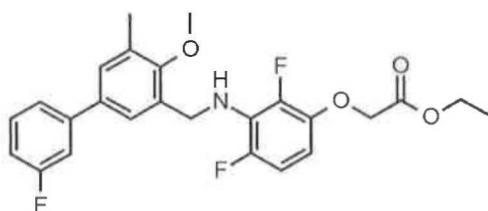
2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)-2-methoxy-3-methyl-benzamide (150 mg, 0.39 mmol, 1.0 eq) in THF (3 mL) at 0°C was added a solution of BH_3 (1M in THF, 2.32 mL, 2.32 mmol, 5.9 eq). The reaction was heated at 60°C overnight, then quenched by addition of water. The aqueous layer was extracted with EtOAc and the organic extract was washed with 5% Na_2CO_3 , water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether:EtOAc, 1:0 to 10:1) to give the title compound as an oil (47 mg, 33 %).

LC-MS : m/z 374.2 $[\text{M}+\text{H}]^+$ 396.1, $[\text{M}+\text{Na}]^+$

Ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]phenoxy]acetate



To a stirred solution of 2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]phenol (47 mg, 0.13 mmol, 1.0 eq) in acetone (5 mL) was added Cs_2CO_3 (61.5 mg, 0.19 mmol, 1.5 eq). The resulting mixture was stirred for 30 min at room temperature then ethyl bromoacetate (25.2 mg, 0.15 mmol, 1.2 eq) was added. The resulting mixture was stirred for 1h then diluted with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 1:0 to 20:1) to give the title compound as an oil (64 mg, 86 %).

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]phenoxy] acetic acid (I(t))



To a stirred solution of ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methylphenyl]methylamino]phenoxy]acetate (64 mg, 0.14 mmol, 1.0 eq) in THF (3 mL) was added an aqueous solution of LiOH (2M aqueous solution, 2 mL, 4 mmol). The reaction was stirred at room temperature for 1h. Water was added and the THF removed *in vacuo*. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* give the title compound as a white solid (32 mg, 53 %).

LC-MS : m/z 431.9 [M+H]⁺

15 ¹H NMR (400 MHz, DMSO-d₆) δ = 7.47 (s, 2H), 7.42 (s, 1H), 7.38 - 7.27 (m, 2H), 7.20 - 7.09 (m, 1H), 6.87 - 6.72 (m, 1H), 6.28 (d, *J*=4.9 Hz, 1H), 5.66 (s, 1H), 4.70 - 4.38 (m, 4H), 3.71 (s, 3H), 2.29 (s, 3H)

Example 21 – compound I(u) synthesized according to scheme 3 (amended by
addition of hydrolysis step before last step)

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methyl-phenyl]methylamino]phenoxy]acetic acid (I(u))



Ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methyl-phenyl]methylamino]phenoxy]acetate (II(ad))



- 5 To a stirred solution of ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]phenoxy]acetate (see example 20) (190 mg, 0.414 mmol, 1.0 eq) in DCM (5 mL) at 0°C under N₂ was added AlCl₃ (330.8 mg, 2.48 mmol, 6.0 eq) and EtSH (154.2 mg, 2.48mmol, 6.0 eq). The resulting mixture was stirred for 1.5h at room temperature then the reaction was quenched by dropwise addition of water. The aqueous
- 10 layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄) filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc 1:0 to 10:1 v/v) to give the title compound as an oil (90 mg, 49 %).

15 LC-MS : m/z 468.2 [M+Na]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (br s, 1H), 7.46 – 7.38 (m, 1H), 7.36 – 7.25 (m, 4H), 7.12 – 7.05 (m, 1H), 6.82 (t, *J* = 10.3 Hz, 1H), 6.34 (td, *J* = 8.9, 4.1 Hz, 1H), 5.58 (br s, 1H), 4.75 (s, 2H), 4.47 (d, *J* = 6.8 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 3H),

20 1.16 (t, *J* = 7.1 Hz, 3H)

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methyl-phenyl]methylamino]phenoxy]acetic acid (I(u))



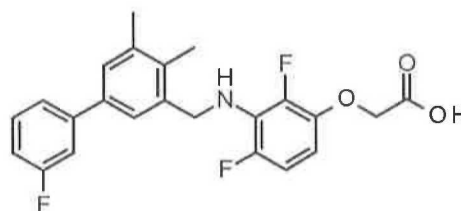
To a stirred solution of ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methyl-phenyl]methylamino]phenoxy]acetate (90 mg, 0.20 mmol, 1.0 eq) in THF (3 mL) was added a solution of LiOH (2M aqueous solution, 3 mL, 6 mmol, 30 eq). The reaction was stirred at room temperature for 3h. Water was added and the mixture acidified to pH 4-5 with diluted HCl then extracted with EtOAc. The combined organic extracts were washed with water and brine, dried and evaporated *in vacuo* to give the title compound (as a white solid (73 mg, 86 %).

LC-MS : m/z 417.9 $[M+H]^+$

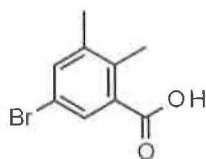
1H NMR (300 MHz, DMSO- d_6) δ = 8.77 (s, 1H), 7.52 - 7.36 (m, 1H), 7.36 - 7.23 (m, 4H), 7.18 - 6.97 (m, 1H), 6.89 - 6.67 (m, 1H), 6.30 (dt, $J=4.6, 9.1$ Hz, 1H), 4.59 (s, 2H), 4.46 (d, $J=6.7$ Hz, 2H), 2.23 (s, 3H)

Example 22 – compound I(v) synthesized according to scheme 3

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenoxy]acetic acid (I(v))



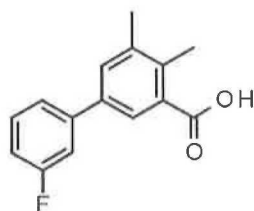
5-Bromo-2,3-dimethyl-benzoic acid



To a solution of 2,3-dimethylbenzoic acid (5 g, 33.3 mmol, 1.0 eq) in acetic acid (167 mL) at room temperature was added a solution of conc. nitric acid (25.2 g, 399 mmol, 12 eq), water (15 g, 0.83 mmol, 25 eq) and bromine (5.85 g, 36.6 mmol, 1.1 eq). A solution of silver nitrate (7.35 g, 43 mmol, 1.3 eq) in water (43 mL) was then added dropwise over 30 min. Once addition was completed, the reaction was stirred at room temperature for 1 h, then quenched by addition of water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a yellow solid (6.4 g, 83 %).

LC-MS: m/z 228.4 $[\text{M}+\text{H}]^+$

5-(3-Fluorophenyl)-2,3-dimethyl-benzoic acid (intermediate III(m))



To a solution of 3-fluorophenylboronic acid (2.20g, 15.7 mmol, 1.2 eq) 5-bromo-2,3-dimethylbenzoic acid (3 g, 13.1 mmol, 1.0 eq) in DMF (30 mL) and H_2O (15 mL) was added Na_2CO_3 (5.56 g, 52.3 mmol, 4.0 eq) and $\text{Pd}(\text{PPh}_3)_4$ (0.76 g, 0.66 mmol, 0.05 eq). The reaction was heated at 95°C overnight under N_2 . Water was added and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a white solid (3.82 g, 100 %).

LC-MS: m/z 245.1 $[\text{M}+\text{H}]^+$ 267.1 $[\text{M}+\text{Na}]^+$

¹H NMR (400 MHz, DMSO-d₆) δ 12.99 (br s, 1H), 7.80 (d, *J* = 1.7 Hz, 1H), 7.70 (d, *J* = 1.4 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.23 – 7.15 (m, 1H), 2.41 (s, 3H), 2.35 (s, 3H)

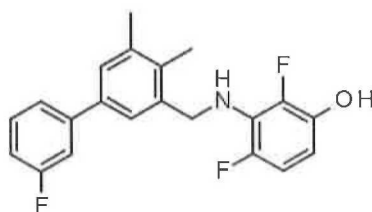
5 *N*-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)-2,3-dimethyl-benzamide



To a solution of 5-(3-fluorophenyl)-2,3-dimethyl-benzoic acid (3.82 g, 15.6 mmol, 5.8 eq) in DCM (30 mL) was added (COCl)₂ (5.96g, 46.8 mmol, 17.0 eq) and DMF (0.5 mL). The mixture was stirred at room temperature under N₂ for 2h then the solvent removed *in vacuo*. The residue obtained was dissolved in THF (10 mL) and added to a mixture of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (0.4 g, 2.75 mmol, 1.0 eq) and Na₂CO₃ (0.87g, 8.26 mmol, 3.0 eq) in THF. The reaction was stirred at room temperature overnight then water and EtOAc were added. The organic extract was washed with water, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (DCM:MeOH, 0:1 to 1:50) to give the title compound as a solid (0.16 g, 15 %).

LC-MS: *m/z* 372.1 [M+H]⁺ 394.1 [M+Na]⁺

20 *2,4-Difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenol*

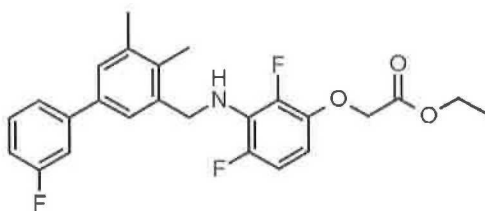


To a solution of *N*-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)-2,3-dimethyl-benzamide (160 mg, 0.4 mmol, 1.0 eq) in THF (15 mL) was added a solution of BH₃ (1M

in THF, 180 mg, 2.1 mmol, 5.0 eq). The solution was stirred for 30 min then heated at 60 °C overnight. The reaction was quenched by addition of 1M HCl and the aqueous layer extracted with EtOAc. The organic extract was washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a white solid (137 mg, 89 %).

LC-MS: m/z 358.2 [M+H]⁺ 380.1 [M+Na]⁺

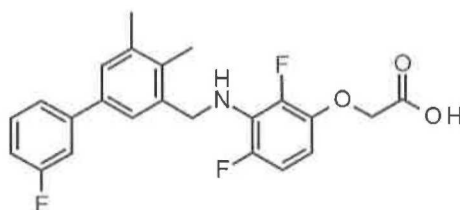
Ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenoxy]acetate



To a stirred solution of 2,4-difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenol (137 mg, 0.38 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃ (170 mg, 0.5 mmol, 1.4 eq). The resulting mixture was stirred for 30 min at room temperature, then ethyl 2-bromoacetate (77 mg, 0.46 mmol, 1.2 eq) was added. The mixture was stirred at room temperature for 2.5h and then diluted in water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as an oil (120 mg, 70 %).

LC-MS: m/z 444.1 [M+H]⁺ 466.2 [M+Na]⁺

2-[2,4-Difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenoxy]acetic acid (I(v))



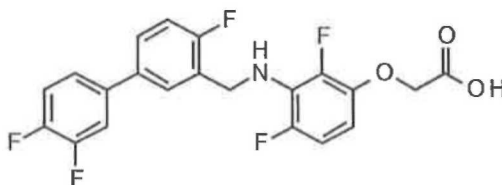
To a stirred solution of ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethylphenyl]methylamino]phenoxy]acetate (120 mg, 0.27 mmol, 1.0 eq.) in a mixture of THF (5 mL) and MeOH (5 mL) at room temperature was added NaOH (2M aqueous solution, 5 mL, 10 mmol). The reaction was stirred at room temperature for 3h. The reaction was then diluted with EtOAc and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄) filtered and evaporated *in vacuo* to give the title compound as a gummy solid (112 mg, 94 %).

LC-MS : m/z 415.9 [M+H]⁺

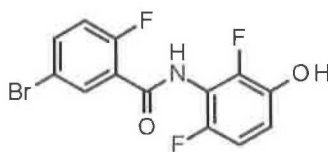
¹H NMR (300 MHz, DMSO-d₆) δ 7.59 - 7.27 (m, 6H), 7.21 - 7.03 (m, 1H), 6.79 (t, *J*=10.6 Hz, 1H), 6.29 (td, *J*=9.0, 4.7 Hz, 1H), 4.58 (s, 2H), 4.48 (d, *J*=6.2 Hz, 2H), 2.31 (s, 3H), 2.22 (s, 3H)

Example 23 – compound I(w) synthesized according to scheme 4

2-[3-[[5-(3,4-difluorophenyl)-2-fluoro-phenyl]methylamino]-2,4-difluorophenoxy]acetic acid (I(w))



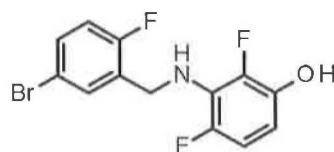
5-Bromo-N-(2,6-difluoro-3-hydroxy-phenyl)-2-fluoro-benzamide



To a solution of 5-bromo-2-fluoro-benzoic acid (5.1 g, 23.3 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) were added $(\text{COCl})_2$ (8.8 g, 69.9 mmol, 3.0 eq) and DMF (0.07 mL). The reaction mixture was stirred at room temperature for 1.5h then the solvent and excess reagent were removed under reduced pressure. The residue obtained was dissolved in THF (30 mL) and added dropwise to a mixture of 3-amino-2,4-difluorophenol (intermediate X(a)) (3.0 g, 20.9 mmol, 1.0 eq) and NaHCO_3 (5.3 g, 62.9 mmol, 3.0 eq) in THF (3 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1h then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH_2Cl_2 :MeOH, 500:1 to 300:1) to give the title compound as a white solid (5.78 g 79 %).

LC-MS: m/z 346.0, 348.0 $[\text{M}+\text{H}]^+$

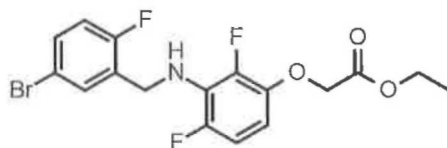
3-[(5-Bromo-2-fluoro-phenyl)methylamino]-2,4-difluoro-phenol



To a solution of 5-bromo-N-(2,6-difluoro-3-hydroxy-phenyl)-2-fluoro-benzamide (5.78 g, 7.1 mmol, 1.0 eq) in THF (100 mL) at 0 °C under N_2 was added a solution of BH_3 (1M in THF, 83.5 mL, 83.5 mmol, 5.0 eq) dropwise. The reaction mixture was heated at 60 °C overnight then cooled to room temperature and quenched with water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 30:1 to 20:1) to give the title compound as a brown oil (5.26 g, 94 %).

LC-MS: m/z 332.0, 334.0 [M+H]⁺

Ethyl 2-[3-[(5-bromo-2-fluoro-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate

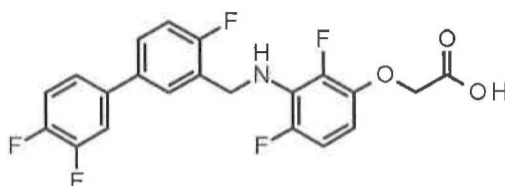


- 5 To a solution of 3-[(5-bromo-2-fluoro-phenyl)methylamino]-2,4-difluoro-phenol (5.26 g, 15.8 mmol, 1.0 eq) in DMF (50 mL) was added Na₂CO₃ (2.35 g, 22.2 mmol, 1.4 eq). The reaction was stirred at room temperature for 30 min then ethyl bromoacetate (2.91 g, 17.4 mmol, 1.1 eq) was added. The reaction mixture was stirred at room temperature for 1h then poured into water and extracted with EtOAc. The combined organic extracts were
- 10 washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 40:1 to 30:1) to give the title compound as a colorless oil (5 g, 75 %).

LC-MS: m/z 418.0, 420.0 [M+H]⁺

15

2-[3-[[5-(3,4-Difluorophenyl)-2-fluoro-phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid (I(w))



- 20 To a solution of ethyl 2-[3-[(5-bromo-2-fluoro-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate (100 mg, 0.24 mmol, 1.0 eq) in acetonitrile (3 mL) and water (1 mL) under N₂ was added Na₂CO₃ (100 mg, 0.96 mmol, 4.0 eq) and Pd(PPh₃)₄ (14 mg, 0.012 mmol, 0.05eq). The reaction was heated at 90 °C overnight then diluted HCl was added and the aqueous layer extracted with EtOAc. The combined organic extracts were washed
- 25 with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue

obtained was purified by column chromatography (CH₂Cl₂:MeOH, 1:0 to 80:1) to give the title compound as a white solid (20 mg, 44 %).

LC-MS: m/z 451.3 [M-H]⁻

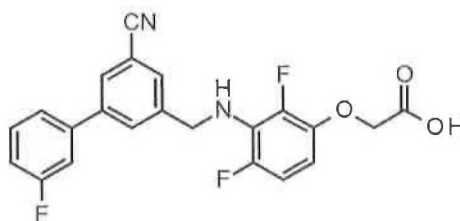
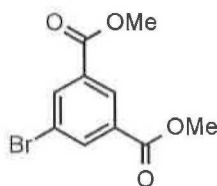
5

¹H NMR (400 MHz, DMSO) δ 7.73 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.64 (ddd, *J* = 9.9, 7.5, 1.9 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.45 – 7.34 (m, 1H), 7.28 – 7.17 (m, 1H), 6.72 (t, *J* = 10.1 Hz, 1H), 6.20 (td, *J* = 8.9, 4.6 Hz, 1H), 5.70 (br s, 1H), 4.49 (d, *J* = 7.1 Hz, 2H), 4.16 (s, 2H).

10

Example 24 – compound I(x) synthesized according to scheme 3

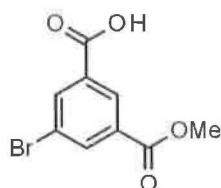
2-[3-[[3-cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid (I(x))

15 *Dimethyl 5-bromobenzene-1,3-dicarboxylate*

5-bromobenzene-1,3-dicarboxylic acid (5 g, 20.4 mmol, 1.0 eq) was dissolved in DMF (150 mL). Cs₂CO₃ (33.2 g, 102 mmol, 5.0 eq) was added and the reaction stirred for 30 min. MeI (7.2 g, 51 mmol, 2.5 eq) was added dropwise and the solution was stirred at room temperature overnight. Water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a colourless oil (5 g, 90 %).

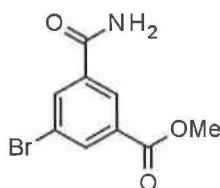
20

LC-MS: m/z 274.9 [M+H]⁺

3-Bromo-5-methoxycarbonyl-benzoic acid

Dimethyl 5-bromobenzene-1,3-dicarboxylate (5 g, 18.3 mmol, 1.0 eq) was dissolved in THF (50 mL) and LiOH.H₂O (1.1 g, 27.5 mmol, 1.5 eq) and H₂O (10 mL) were added. The mixture was stirred at room temperature overnight. The THF was removed *in vacuo* and the aqueous phase acidified with diluted HCl. The aqueous phase was extracted with EtOAc, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂: MeOH, 50:1) to give the title compound as a white solid (3 g, 63 %).

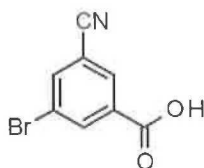
LC-MS: m/z 259.0, 261.0 [M+H]⁺

Methyl 3-bromo-5-carbamoyl-benzoate

To 3-bromo-5-methoxycarbonyl-benzoic acid (3 g, 11.6 mmol, 1 eq) was added SOCl₂ (20 mL) and the reaction heated at reflux overnight. The excess SOCl₂ was removed *in vacuo* and the residue obtained was dissolved in THF (15 mL) and added dropwise to a solution of NH₃ (38 % aqueous, 30 mL). The precipitate that formed was collected by filtration, washed with water and dried to give the title compound as a white solid (2.8 g, 94 %).

LC-MS: m/z 255.9, 257.9 [M-H]⁻

3-Bromo-5-cyano-benzoic acid



To methyl 3-bromo-5-carbamoyl-benzoate (2.8 g, 10.8 mmol, 1.0 eq) was added POCl₃ (30 mL) and the reaction heated at 100 °C overnight. The POCl₃ was removed under reduced pressure, water was added and the aqueous layer extracted with EtOAc. The
5 combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo* to afford a crude residue which was purified by column chromatography (petroleum ether:EtOAc, 20:1) to give methyl 3-bromo-5-cyano-benzoate (2.5 g, 96 %). This material was dissolved in THF (30 mL) and LiOH.H₂O (1.7 g, 41.6 mmol, 1.54 eq) and H₂O (10 mL) were added. The mixture was stirred at room temperature overnight. The
10 THF was removed under reduced pressure and the aqueous phase acidified with diluted HCl and extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂: MeOH, 50:1) to give the title compound as a white solid (2 g, 85 %).

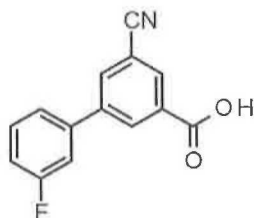
15

LC-MS: m/z 248.0, 249.9 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 13.67 (br s, 1H), 8.40 (s, 1H), 8.24 (s, 1H), 8.24 (s, 1H).

20

3-Cyano-5-(3-fluorophenyl)benzoic acid (III(n))

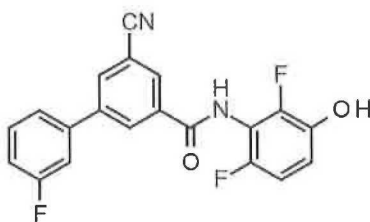


To a solution of 3-Bromo-5-cyano-benzoic acid (2 g, 8.8 mmol, 1 eq) and 3-fluorophenylboronic acid (1.6 g, 11.5 mmol, 1.3 eq) in DMF (100 mL) under nitrogen were added Pd(PPh₃)₄ (500 mg, 0.44 mmol, 0.05 eq) and K₂CO₃ (3.6 g, 26.4 mmol, 3 eq).

The solution was heated at 100 °C overnight, then water and EtOAc were added. The aqueous layer was acidified by addition of diluted HCl and extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂: MeOH, 25:1) to give the title compound as a white solid (1.2 g, 56 %).

LC-MS: m/z 264.1 [M+Na]⁺

10 3-Cyano-N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl)benzamide

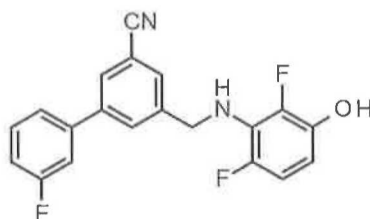


3-Cyano-5-(3-fluorophenyl)benzoic acid (500 mg, 2.1 mmol, 1 eq) was dissolved in SOCl₂ (15 mL) and heated at reflux overnight. The excess SOCl₂ was removed under reduced pressure and the residue that remained dissolved in THF (10 mL) and added dropwise to a mixture of 3-amino-2,4-difluorophenol (280 mg, 2 mmol, 0.95 eq) and NaHCO₃ (880 mg, 10.5 mmol, 5 eq) in THF (40 mL). The reaction was stirred at room temperature for 3h, then filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 10:1) to give the title compound as a white solid (500 mg, 64 %).

20

LC-MS: m/z 369.1 [M+H]⁺ 391.1 [M+Na]⁺

3-[(2,6-Difluoro-3-hydroxy-anilino)methyl]-5-(3-fluorophenyl)benzonitrile



To a solution of 3-Cyano-N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3-fluorophenyl) benzamide (500 mg, 2.7 mmol, 1.0 eq) in THF (30 mL) at 0 °C was added a solution of BH₃ (1M in THF, 10.8 mL, 10.8 mmol, 4.0 eq) dropwise. The reaction was then heated at 50 °C for 6h. The reaction was cooled to room temperature and quenched by addition of aqueous NH₄Cl. The aqueous layer was extracted with EtOAc and the combined organic extracts dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 7:1) to give the title compound as white solid (280 g, 58 %).

10

LC-MS: m/z 355.1 [M+H]⁺, 377.1 [M+Na]⁺

Ethyl 2-[3-[[3-cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetate



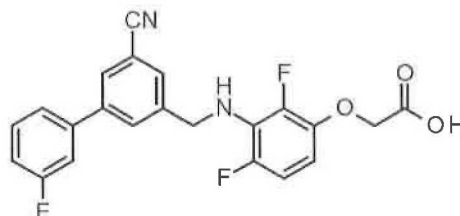
15

To a solution of 3-[(2,6-Difluoro-3-hydroxy-anilino)methyl]-5-(3-fluorophenyl) benzonitrile (280 mg, 0.8 mmol, 1 eq) in DMF (10 mL) was added K₂CO₃ (550 mg, 4 mmol, 5 eq). The solution was stirred at room temperature for 30 min, then ethyl bromoacetate (200 mg, 1.2 mmol, 1.5 eq) was added dropwise. The reaction was stirred overnight, then water was added and the aqueous phase extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 15:1) to give the title compound as colorless oil (300 mg, 86 %).

20

LC-MS: m/z 441.1 [M+H]⁺ 463.1 [M+Na]⁺

2-[3-[[3-Cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic
5 acid (I(x))



Ethyl 2-[3-[[3-cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]
acetate (300 mg, 0.68 mmol, 1.0 eq) was dissolved in THF (20 mL). Water (10 mL) and
LiOH.H₂O (110 mg, 2.7 mmol, 4 eq) were added and the solution heated at 40 °C
10 overnight. The THF was removed *in vacuo* and the aqueous phase acidified to pH 6 by
addition of diluted HCl. The precipitate that formed was collected by filtration, washed
with water and dried to give the title compound as a white solid (70 mg, 25 %).

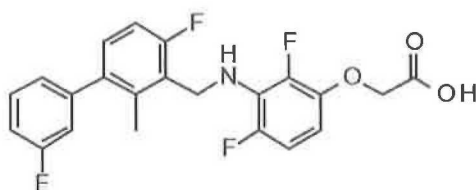
LC-MS: m/z 413.1 [M+H]⁺ 435.1 [M+Na]⁺

15

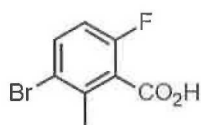
¹H NMR (400 MHz, DMSO) δ 8.06 (s, 1H), 8.01 (s, 1H), 7.75 (s, 1H), 7.62 – 7.49 (m,
3H), 7.30 – 7.21 (m, 1H), 6.83 – 6.74 (m, 1H), 6.30 (td, *J* = 9.1, 4.4 Hz, 1H), 6.09 (br t, *J*
= 7.2 Hz, 1H), 4.60 (s, 2H), 4.50 (d, *J* = 6.8 Hz, 2H).

20

Example 25 – compound I(y) synthesized according to scheme 3
2-[2,4-difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]
methylamino]phenoxy]acetic acid (I(y))



3-Bromo-6-fluoro-2-methylbenzoic acid

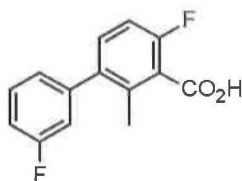


To a stirred solution of 2-fluoro-6-methylbenzoic acid (1 g, 6.4 mmol, 1.0 eq) in acetic acid (32 mL) was added nitric acid (3.27 mL), water (3 mL) and bromine (0.36 mL). A solution of silver nitrate (1.43 g, 8.4 mmol 1.3 eq) in water (10 mL) was then added dropwise over a period of 15 min. After the addition was completed, stirring was continued a further 1.5h at room temperature. The reaction was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to afford a crude product, which was triturated with hexane to give the title compound as a yellow solid (1.35 g, 90 %).

LC-MS: m/z 232.9 [M-H]⁻

¹H NMR (400 MHz, CDCl₃) δ 7.72 (dd, *J* = 8.9, 5.4 Hz, 1H), 7.15 (app t, *J* = 8.9 Hz, 1H), 2.34 (s, 3H).

6-Fluoro-3-(3-fluorophenyl)-2-methylbenzoic acid (III(o))

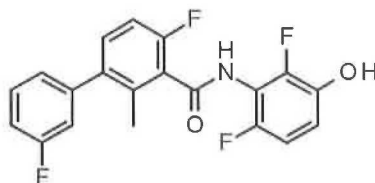


To a solution of 3-bromo-6-fluoro-2-methylbenzoic acid (1.35 g, 5.8 mmol, 1.0 eq) and 3-fluorophenyl boronic acid (970 mg, 6.9 mmol, 1.2 eq) in DMF (25 mL) under N₂ were added Na₂CO₃ (2.45 g, 23.1 mmol, 4 eq) and Pd(PPh₃)₄ (0.33 g, 0.29 mmol, 0.05 eq). The

reaction was heated at 95 °C overnight, then the reaction acidified by addition of 4M HCl to a final pH of 4. The reaction mixture was filtered through celite and extracted with EtOAc. The organic extract was washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound (680 mg, 48%). This material was used without further purification.

LC-MS: m/z 247.0 [M-H]⁻

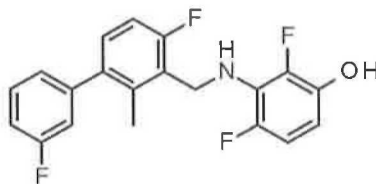
10 *N*-(2,6-Difluoro-3-hydroxy-phenyl)-6-fluoro-3-(3-fluorophenyl)-2-methyl-benzamide



To 6-fluoro-3-(3-fluorophenyl)-2-methyl-benzoic acid (3 g, 12.0 mmol, 1 eq) was added SOCl₂ (60 mL) and the reaction heated at 80 °C overnight. The resulting mixture was concentrated *in vacuo* and the residue that remained dissolved in THF (20 mL) and added dropwise to a mixture of 3-amino-2,4-difluoro-phenol (1.93 g, 13.2 mmol, 1.1 eq) and NaHCO₃ (2.32 g, 36.2 mmol, 3 eq) in THF (5 mL). After the addition, the reaction mixture was stirred at room temperature for 30 min. Water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound (500 mg, 11 %) which was used without further purification.

LC-MS: m/z 376.1 [M+H]⁺, 398.1 [M+Na]⁺

2,4-Difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-6-fluoro-3-(3-fluorophenyl)-2-methyl-benzamide (400 mg, 1.06 mmol, 1.0 eq) in THF (5 mL) under N₂ was added a solution of BH₃ (1M in THF, 5.3 mL, 5.3 mmol, 5.0 eq). The reaction mixture was heated at 60 °C overnight, then quenched by addition of methanol and concentrated *in vacuo*.
5 The residue was purified by column chromatography (petroleum ether: EtOAc, 50:1 to 20:1) to give title compound as colorless oil (230 mg, 59 %).

LC-MS: m/z 362.1 [M+H]⁺ 384.1 [M+Na]⁺

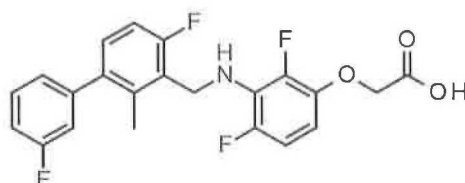
- 10 *Ethyl 2-[2,4-difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy] acetate*



- To a solution of 2,4-difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenol (230 mg, 0.63 mmol, 1.0 eq) in DMF (4 mL) was added Cs₂CO₃
15 (420 mg, 1.2 mmol, 2 eq). The reaction was stirred for 10 min, then ethyl bromoacetate (130 mg, 0.76 mmol, 1.2 eq) was added. The reaction mixture was stirred for a further 30 min, then water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum
20 ether: EtOAc, 25:1) to give title compound as a colourless oil (240 mg, 85 %).

LC-MS: m/z 448.2 [M+H]⁺ 470.2 [M+Na]⁺

- 25 *2-[2,4-Difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl]methylamino] phenoxy] acetic acid (I(y))*



To a solution of ethyl 2-[2,4-difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methylphenyl]methylamino]phenoxy]acetate (240 mg, 0.53 mmol, 1.0 eq) in a mixture of THF (2 mL) and MeOH (2 mL) was added NaOH (2M aqueous solution, 2 mL, 4.0 mmol).

- 5 The reaction mixture was stirred at room temperature for 3 h. The THF and MeOH were evaporated *in vacuo* and the pH of the aqueous phase adjusted to pH 3 by addition of diluted HCl. The solid that formed was collected by filtration, washed with water and dried to give the title compound as a white solid (150 mg, 68 %).

- 10 LC-MS: m/z 418.1 $[M-H]^+$

1H NMR (400 MHz, DMSO) δ 7.54 – 7.44 (m, 1H), 7.26 – 7.15 (m, 2H), 7.15 – 7.05 (m, 3H), 6.83 – 6.72 (m, 1H), 6.26 (td, $J = 9.2, 5.0$ Hz, 1H), 4.70 (br s, 1H), 4.47 (d, $J = 5.3$ Hz, 2H), 4.08 (s, 2H), 2.27 (s, 3H).

15

Example 26

2-[3-[[3-carbamoyl-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenoxy]acetic acid (I(z))



20

To a mixture of ethyl 2-[3-[[3-cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluorophenoxy]acetate (see example 24) (200 mg, 0.45 mmol, 1 eq) and K_2CO_3 (310

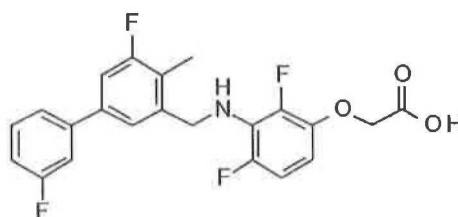
mg, 2.3 mmol, 5 eq) in DMSO (10 mL) at 40 °C was added H₂O₂ (30% aqueous solution, 10 mL) dropwise. The mixture was stirred for 20 min then cooled to room temperature. Water was added, and the reaction neutralised by addition of diluted HCl. The solid precipitate that formed was collected by filtration, washed with water and dried to give
 5 the title compound as white solid (90 mg, 46 %).

LC-MS: m/z 431.1 [M+H]⁺ 453.1 [M+Na]⁺

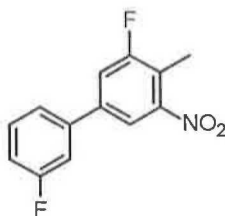
¹H NMR (400 MHz, DMSO) δ 8.10 (s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.82 (s, 1H), 7.62
 10 – 7.48 (m, 3H), 7.44 (s, 1H), 7.30 – 7.18 (m, 1H), 6.78 (t, *J* = 10.0 Hz, 1H), 6.28 (td, *J* =
 9.1, 4.8 Hz, 1H), 6.05 (br t, *J* = 7.4 Hz, 1H), 4.60 (s, 2H), 4.50 (d, *J* = 6.4 Hz, 2H).

Example 27 – compound I(aa) synthesized according to scheme 3

15 **2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methylphenyl]methylamino]phenoxy] acetic acid (I(aa))**



1-Fluoro-5-(3-fluorophenyl)-2-methyl-3-nitro-benzene



20

A mixture of 5-bromo-1-fluoro-2-methyl-3-nitro-benzene (5.0 g, 21.31 mmol, 1.0 eq), 3-fluorophenylboronic acid (3.29 g, 23.8 mmol, 1.1 eq), Pd(PPh₃)₄ (1.2 g, 1.07 mmol, 0.05 eq) and K₂CO₃ (11.8 g, 85.5 mmol, 4 eq) in a mixture of dioxane (150 mL) and EtOH (50

mL) was heated at 80 °C under N₂ overnight. After cooling to room temperature the reaction was poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as an oil (4.0 g, 75 %). This material was used without further purification.

3-Fluoro-5-(3-fluorophenyl)-2-methyl-aniline



A solution of 1-fluoro-5-(3-fluorophenyl)-2-methyl-3-nitro-benzene (4.0 g, 16.0 mmol, 1.0 eq) in EtOH (80 mL) was added to Pd/C (10%, 0.8 g) and the mixture stirred under hydrogen for 48h. The catalyst was removed by filtration through celite and the compound purified by silica gel chromatography (petroleum ether:EtOAc, 20:1 to 10:1) to give the title compound as a white solid (1.54 g, 44 %).

LC-MS: m/z, 220.1 [M+1]⁺

1-Bromo-3-fluoro-5-(3-fluorophenyl)-2-methyl-benzene

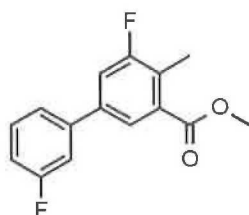


Copper(II)bromide (1.88 g, 8.4 mmol, 1.2 eq) and tert-butyl nitrite (1.81 g, 17.5 mmol, 2.5 eq) were suspended in acetonitrile (15 mL), the mixture was cooled to 0 °C and a solution of 3-fluoro-5-(3-fluorophenyl)-2-methyl-aniline (1.54 g, 7.0 mmol, 1 eq) in acetonitrile was added dropwise. The solution was stirred at 0°C for 1h, water was added and the aqueous layer extracted with EtOAc. The organic phase

was dried (Na_2SO_4), filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography (petroleum ether:EtOAc, 1:0 to 50:1) to give the title compound as a colourless oil (1.88 g, 94 %).

- 5 LC-MS: m/z No target MS observed by LCMS.

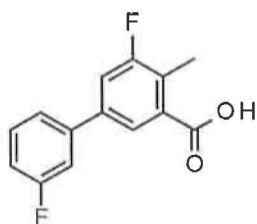
Methyl 3-fluoro-5-(3-fluorophenyl)-2-methyl-benzoate



- 10 A mixture of 1-bromo-3-fluoro-5-(3-fluorophenyl)-2-methyl-benzene (1.88 g, 6.6 mmol, 1 eq), potassium acetate (3.25 g, 33.2 mmol, 5 eq), palladium (II) acetate (0.12 g, 0.5 mmol, 0.075 eq) and dppf (0.41 g, 0.9 mmol, 0.15 eq) in a mixture of MeOH (50 mL) and THF (50 mL) was placed in a high pressure reactor and pressurized with carbon monoxide gas to 50 bar. The reaction mixture was heated at 125 °C for 16h, then cooled, filtered and the solvent evaporated *in vacuo*. The residue was partitioned
- 15 between water and CH_2Cl_2 and extracted with CH_2Cl_2 . The combined organic extracts were dried (MgSO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc 1:0 to 50:1) to give the title compound as a white solid (1 g, 57 %).

- 20 LC-MS: m/z 263.1 $[\text{M}+1]^+$ 285.1 $[\text{M}+\text{Na}]^+$

3-Fluoro-5-(3-fluorophenyl)-2-methyl-benzoic acid (III(p))

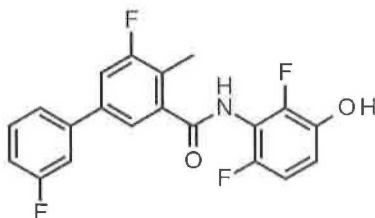


To a solution of methyl 3-fluoro-5-(3-fluorophenyl)-2-methyl-benzoate (1.0 g, 3.1 mmol, 1.0 eq) in a mixture of THF (4 mL) and MeOH (4 mL) was added NaOH (2 M aqueous solution, 10 mL, 20 mmol). The reaction mixture was stirred at room temperature for 3h. The THF and MeOH were evaporated *in vacuo* and the pH of the aqueous phase was adjusted to pH 4-6 by addition of diluted HCl. The solid precipitate that formed was collected by filtration, washed with water and dried to give the title compound as a white solid (1.1 g, 100 %).

LC-MS: m/z , 247.1 $[M-1]^-$

^1H NMR (400 MHz, DMSO) δ 7.93 – 7.85 (m, 2H), 7.56 – 7.48 (m, 3H), 7.25 – 7.18 (m, 1H), 2.33 (d, $J = 1.9$ Hz, 3H).

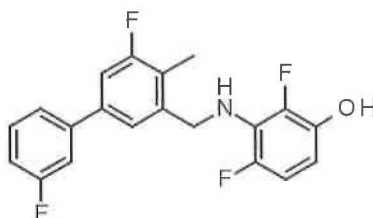
N-(2,6-Difluoro-3-hydroxy-phenyl)-3-fluoro-5-(3-fluorophenyl)-2-methyl-benzamide



To a solution of 3-fluoro-5-(3-fluorophenyl)-2-methyl-benzoic acid (1.1 g, 4.4 mmol, 1 eq) in CH_2Cl_2 (15 mL) at 0 °C was added DMF (0.05 mL), and $(\text{COCl})_2$ (1.68 g, 13.2 mmol, 3 eq). The reaction mixture was stirred at room temperature for 3h. The resulting mixture was concentrated to dryness under reduced pressure and the residue obtained dissolved in THF (10 mL) and added dropwise to a solution of 3-amino-2,4-difluorophenol (intermediate X(a)) (770 mg, 5.3 mmol, 1.2 eq) and K_2CO_3 (3 g, 22.1 mmol, 5 eq) in THF (20 mL) at 0 °C. After the addition, the reaction mixture was stirred for 2h and then water added and the aqueous layer extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 10:1 to 3:1) to give the title compound as a white solid (0.9 g, 54 %).

LC-MS: m/z, 376.1 [M+H]⁺ 398.1 [M+Na]⁺

2,4-Difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenol



5

To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-3-fluoro-5-(3-fluorophenyl)-2-methyl-benzamide (0.9 g, 2.4 mmol, 1.0 eq) in THF (20 mL) under N₂ was added a solution of BH₃ (1 M in THF, 11.9 mL, 11.9 mmol, 5.0 eq). The reaction mixture was heated at reflux overnight. Methanol was added to quench the reaction and the solution
10 was then concentrated *in vacuo* to give the title compound (900 mg, 100 %) which was used without further purification.

LC-MS: m/z, 362.1 [M+H]⁺ 384.1 [M+Na]⁺

15 *Isopropyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetate (II(ae))*



To a solution 2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino] phenol (900 mg, 2.5 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃
20 (1.62 g, 4.9 mmol, 2 eq). The reaction mixture was stirred for 30 min, then isopropyl bromoacetate (540 mg, 2.9 mmol, 1.2 eq) was added dropwise. The reaction was stirred at room temperature for 30 min, then water was added and the aqueous layer was extracted with EtOAc. The organic extract was washed with water, dried (Na₂SO₄),

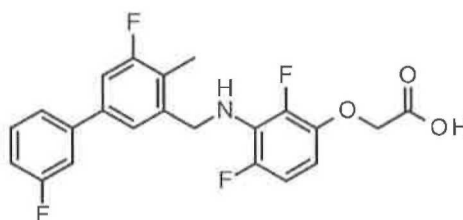
filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc 20:1 to 5:1) to give the title compound (300 mg, 26 %).

5 LC-MS: m/z 462.2 $[M+H]^+$, 484.1 $[M+Na]^+$

1H NMR (400 MHz, DMSO) δ 8.30 – 8.22 (m), 8.20 (d, $J = 7.8$ Hz), 8.16 – 8.05 (m), 7.92 (td, $J = 8.5, 2.3$ Hz), 7.66 – 7.56 (m), 7.18 (td, $J = 9.0, 4.7$ Hz), 6.06 – 5.94 (m), 5.47 (s), 5.44 (br d, $J = 3.2$ Hz), 4.69 (br s), 3.21 (d, $J = 1.5$ Hz), 2.14 (d, $J = 6.3$ Hz).

10

2-[2,4-Difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetic acid (I(aa))



15 To a solution of isopropyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]acetate (300 mg, 0.65 mmol, 1.0 eq) in a mixture of THF (10 mL) and MeOH (10 mL) was added NaOH (2M aqueous solution, 10 mL). The reaction mixture was stirred at room temperature for 3h. The THF was evaporated *in vacuo* and the pH of the aqueous phase adjusted pH 3 with diluted HCl. The solid
20 precipitate that formed was collected by filtration, washed with water and dried to give the title compound as a white solid (104 mg, 38 %).

LC-MS: m/z 417.2 $[M-1]^-$

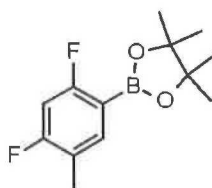
25 1H NMR (400 MHz, DMSO) δ 7.54 – 7.36 (m, 5H), 7.23 – 7.14 (m, 1H), 6.86 – 6.74 (m, 1H), 6.30 (td, $J = 9.1, 4.6$ Hz, 1H), 5.79 (br t, $J = 5.9$ Hz, 1H), 4.59 (s, 2H), 4.48 (d, $J = 6.2$ Hz, 2H), 2.22 (s, 3H).

Example 28 – compound I(ab) synthesized according to scheme 3

2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-
5 phenoxy]acetic acid (I(ab))



2-(2,4-Difluoro-5-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

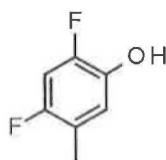


A mixture of 1-bromo-2,4-difluoro-5-methylbenzene (5 g, 24.15 mmol, 1.0 eq),
10 Pd(dppf)Cl₂ (844 mg, 1.22 mmol, 0.05 eq), KOAc (7.11 g, 72.46 mmol, 3 eq) and
bis(pinacolato) diboron (7.36 g, 29 mmol, 1.2 eq) in DMSO (30 mL) under N₂ was stirred
at 90 °C overnight. The reaction was then poured into water and extracted with EtOAc.
The combined organic extracts were washed with water and brine, dried (Na₂SO₄),
filtered and evaporated *in vacuo* to give the title compound as colorless oil (2.24 g, 36 %).

15

LC-MS: *m/z* 277.1 [M+Na]⁺

2,4-Difluoro-5-methyl-phenol



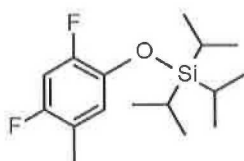
20 To a solution of 2-(2,4-difluoro-5-methyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-
dioxaborolane (2.24 g, 8.82 mmol, 1.0 eq) in a mixture of NaOH (1M aqueous solution,

26.4 mL, 26.4 mmol, 3.0 eq) and THF (20 mL) at 0 °C was added H₂O₂ (3 g, 26.4 mmol, 3 eq). The reaction mixture was stirred at room temperature for 4h, then the pH of the reaction mixture was adjusted to pH 5 by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and
5 brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue obtained was purified by column chromatography (petroleum ether: EtOAc, 100:1 to 50:1) to give the title compound as a colorless oil (850 mg, 65 %).

LC-MS: m/z 143.1 [M-H]⁻

10

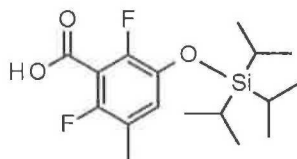
(2,4-Difluoro-5-methyl-phenoxy)-triisopropyl-silane



To a stirred solution of 2,4-difluoro-5-methylphenol (780 mg, 5.41 mmol, 1.0 eq) and imidazole (442 mg, 6.5 mmol, 1.2 eq) in DMF (10 mL) at 0 °C was added TIPSCl (1.15 g,
15 5.95 mmol, 1.1 eq) dropwise. After the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude residue, which was purified by column chromatography (petroleum ether: EtOAc, 100:1) to give the title
20 compound as a colorless oil (1.2 g, 80 %).

¹H NMR (400 MHz, DMSO) δ 7.16 (t, *J* = 10.2 Hz, 1H), 6.91 – 6.85 (m, 1H), 2.15 (s, 3H), 1.31 – 1.15 (m, 3H), 1.04 (d, *J* = 7.4 Hz, 18H).

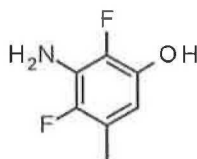
25 2,6-Difluoro-3-methyl-5-triisopropylsilyloxy-benzoic acid



To a solution of (2,4-difluoro-5-methyl-phenoxy)-triisopropyl-silane (1.15 g, 3.83 mmol, 1.0 eq) in dry THF (20 mL) under N₂ at -60 °C was added a solution of n-BuLi (1.7 mL, 2.5 M in hexane, 4.21 mmol, 1.1 eq) over a period of 5 min. The reaction mixture was stirred at -60°C for 2h, then CO₂ (gas) was bubbled into the mixture. The reaction was warmed to room temperature and stirred for 1h, then quenched with water. The aqueous layer was extracted with EtOAc and the organic extract was discarded. The aqueous layer was then acidified to pH 5 with diluted HCl and extracted with ethyl acetate. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a white solid (1.08 g, 82 %).

¹H NMR (400 MHz, DMSO) δ 13.87 (br s, 1H), 7.07 – 6.98 (m, 1H), 2.18 (s, 3H), 1.31 – 1.18 (m, 3H), 1.05 (d, *J* = 7.4 Hz, 18H).

15 *3-Amino-2,4-difluoro-5-methyl-phenol* (X(g))



To a solution of 2,6-difluoro-3-methyl-5-triisopropylsilyloxy-benzoic acid (1.08 g, 3.14 mmol, 1.0 eq) in CH₂Cl₂ (15 mL) was added (COCl)₂ (1.19 g, 9.40 mmol, 3.0 eq) dropwise at 0 °C. DMF (3 drops) was added and the mixture warmed to room temperature and stirred for 1h. The reaction mixture was concentrated to dryness, and the residue obtained was dissolved in acetone (20 mL) and added dropwise to a cooled solution of NaN₃ (815 mg, 12.5 mol, 4 eq) in a mixture of acetone (10 mL) and water (10 mL) at 0 °C. The reaction was stirred for 1h at 0 °C, further water (20 mL) was then added and the reaction heated at 70 °C overnight. The reaction was partitioned between EtOAc and water and extracted with EtOAc, the combined organic extracts were washed

with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was dissolved in dioxane (25 mL), aqueous KOH (25% aqueous solution, 12 mL) was added and the reaction heated at reflux overnight. The reaction was then cooled to room temperature and acidified to pH 5-6 with 1M HCl. The aqueous layer was
5 extracted with EtOAc and the combined organic extracts washed with water, brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum Ether: EtOAc, 50:1 to 20:1) to give the title compound as a white solid (270 mg, 87 %).

10 LC-MS: m/z 160.1 $[\text{M}+\text{H}]^+$

N-(2,6-Difluoro-3-hydroxy-5-methyl-phenyl)-2-fluoro-5-(3-fluorophenyl)benzamide

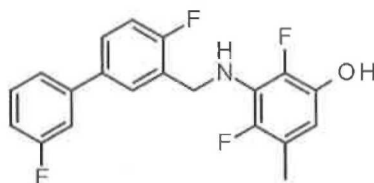


To a solution of 2-fluoro-5-(3-fluorophenyl)benzoic acid (Intermediate III(a)) (437 mg,
15 1.87 mmol, 1.1 eq) in CH_2Cl_2 (10 mL) and DMF (3 drops) was added SOCl_2 (15 mL) dropwise at 0 °C. The solution was stirred at room temperature for 1h, then concentrated *in vacuo*. The residue obtained was dissolved in THF (20 mL) and added dropwise to a solution of 3-amino-2,4-difluoro-5- methyl-phenol (270 mg, 1.70 mmol, 1.0 eq) in THF (10 mL) at 0 °C. After addition was completed, the reaction mixture was stirred at room
20 temperature for 2h, then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 10:1 to 3:1) to give the title compound as a white solid (285 mg, 45 %).

25

LC-MS: m/z 376.1 $[\text{M}+\text{H}]^+$ 398.1 $[\text{M}+\text{Na}]^+$

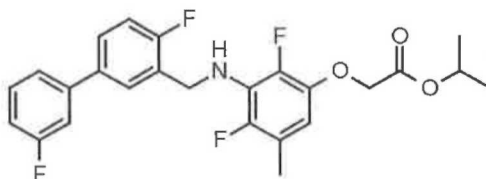
2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenol



N-(2,6-difluoro-3-hydroxy-5-methyl-phenyl)-2-fluoro-5-(3-fluorophenyl)benzamide (285 mg, 0.76 mmol, 1.0 eq) was dissolved in THF (20 mL). A solution of BH_3 (1M in THF, 4.56 mL, 4.56 mmol, 6.0 eq) was added and the reaction mixture heated at 60 °C under nitrogen for 2h. After cooling, the reaction was quenched with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 30:1 to 20:1) to give the title compound as a colorless oil (206 mg, 75 %).

LC-MS: m/z 362.1 $[\text{M}+\text{H}]^+$ 384.1 $[\text{M}+\text{Na}]^+$

Isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenoxy]acetate (II(af))

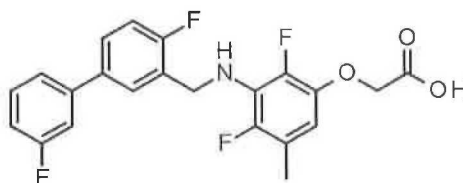


2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenol (206 mg, 0.57 mmol, 1.0 eq) was dissolved in DMF (15 mL). Cs_2CO_3 (279 mg, 0.86 mmol, 1.5 eq) was added and the reaction mixture stirred for 30 min at room temperature. Isopropyl bromoacetate (124 mg, 0.68 mmol, 1.2 eq) was added and the reaction stirred a further 1h at room temperature. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 50:1 to 30:1) to give the title compound as a colorless oil (200 mg, 76 %).

LC-MS: m/z 462.2 $[M+H]^+$ 484.2 $[M+Na]^+$

1H NMR (400 MHz, DMSO) δ 7.72 (d, $J = 5.3$ Hz, 1H), 7.58 (br s, 1H), 7.54 – 7.45 (m, 1H), 7.44 – 7.33 (m, 2H), 7.29 – 7.13 (m, 2H), 6.26 (t, $J = 7.1$ Hz, 1H), 5.80 (br s, 1H), 5.01 – 4.87 (m, 1H), 4.66 (s, 2H), 4.51 (d, $J = 6.6$ Hz, 2H), 2.07 (s, 3H), 1.14 (d, $J = 5.9$ Hz, 6H).

2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenoxy]
10 acetic acid (I(ab))



To a solution of isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenoxy]acetate (194 mg, 0.42 mmol, 1.0 eq) in THF (10 mL) was added LiOH (2M aqueous solution, 5 mL, 5 mmol). The reaction mixture was stirred
15 at room temperature overnight. The THF was removed under reduced pressure and the pH of the aqueous phase adjusted to pH 5 by addition of diluted HCl. The solid that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a white solid (61 mg, 91%).

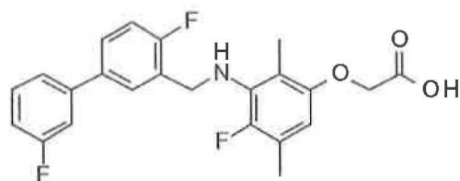
20 LC-MS: m/z 420.1 $[M+H]^+$ 442.1 $[M+Na]^+$

1H NMR (400 MHz, DMSO) δ 7.74 (dd, $J = 7.1, 2.2$ Hz, 1H), 7.62 – 7.54 (m, 1H), 7.54 – 7.46 (m, 1H), 7.43 – 7.35 (m, 2H), 7.27 – 7.14 (m, 2H), 6.12 (t, $J = 7.8$ Hz, 1H), 5.65 (br s, 1H), 4.50 (d, $J = 7.0$ Hz, 2H), 4.20 (s, 2H), 2.04 (s, 3H)

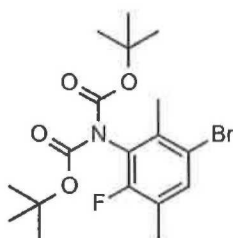
25

Example 29 – compound I(ac) synthesized according to scheme 3

2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenoxy]acetic acid (I(ac))



Tert-butyl N-tert-butoxycarbonyl-N-(3-bromo-6-fluoro-2,5-dimethylphenyl)carbamate



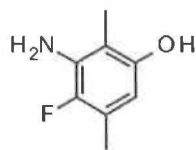
5

To a stirred solution of 2,2,6,6-tetramethylpiperidine (699 mg, 4.9 mmol, 2.0 eq) in THF (7.5 mL) at -50 °C was added *sec*-BuLi (3.8 mL, 1.3 M, 4.9 mmol, 2.0 eq) dropwise. The reaction was stirred for 20 min at -15 °C to -10 °C, then cooled to -65 °C and a solution of *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-(3-bromo-6-fluoro-2-methylphenyl)carbamate (See example 13) (1 g, 2.47 mmol, 1.0 eq) in THF (7.5 mL) added dropwise. The reaction was stirred a further 2h at -65 °C. Iodomethane (1.05 g, 7.41 mmol, 3.0 eq) was added in one portion and the reaction allowed to warm to -10 °C over 30 min. The reaction was then poured into saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄) filtered and evaporated *in vacuo* to give a crude residue, which was purified by column chromatography (petroleum ether:EtOAc, 100:0 to 30:1) to give the title compound as a white solid (880 mg, 85 %).

15

LC-MS: *m/z* 340.0, 342.0 [M-Boc+Na]⁺

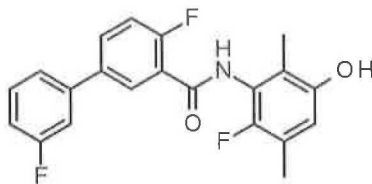
20 *3-amino-4-fluoro-2,5-dimethylphenol* (*X(h)*)



A mixture of tert-butyl N-tert-butoxycarbonyl-N-(3-bromo-6-fluoro-2,5-dimethylphenyl)carbamate (0.81 g, 1.94 mmol, 1.0 eq), Pd(dppf)Cl₂ (763 mg, 0.19 mmol, 0.1 eq), KOAc (571 mg, 5.82 mmol, 3.0 eq) and bis(pinacolato)diboron (591 mg, 2.33 mmol, 1.2 eq) in DMSO (10 mL) under N₂ was stirred at 80 °C overnight. After cooling to room temperature, the reaction was poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to afford a crude residue. The residue obtained was dissolved in THF (10 mL) and the solution cooled to 0 °C. H₂O₂ (30% aqueous solution, 660 mg, 5.82 mmol, 3.0 eq) was added, followed by NaOH (1M aqueous solution, 5.82 mL, 5.82 mmol, 3.0 eq) the mixture was stirred for 10 min and allowed to warm to 10 °C. The pH was adjusted to pH 5~7 by addition of 3M HCl and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was dissolved in MeOH (8 mL) and cooled to 0 °C. HCl in dioxane (4M, 12 mL, 48 mmol, 24.7 eq) was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred for 1h. The reaction was then cooled to 0 °C and the pH adjusted to 5-6 by addition of 1M NaOH. The dioxane was removed *in vacuo* and the aqueous phase extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give a crude residue, which was purified by column chromatography (petroleum ether: EtOAc, 10:1) to give the title compound as a yellow solid (157 mg, 52 %).

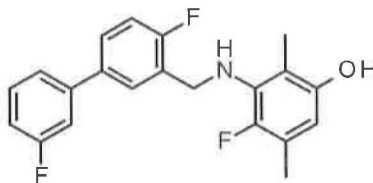
LC-MS: m/z 156.1 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ 8.67 (s, 1H), 5.88 (d, *J* = 6.3 Hz, 1H), 4.57 (s, 2H), 2.04 (d, *J* = 1.9 Hz, 3H), 1.88 (s, 3H).

2-Fluoro-N-(2-fluoro-5-hydroxy-3,6-dimethyl-phenyl)-5-(3-fluorophenyl)benzamide

To a solution of 2-fluoro-5-(3-fluorophenyl)benzoic acid (Intermediate III(a)) (248 mg, 1.06 mmol, 1.1 eq) in CH_2Cl_2 (4 mL) and DMF (1 drop) at 0 °C was added $(\text{COCl})_2$ (403 mg, 3.18 mmol, 3.3 eq) dropwise. The reaction mixture was stirred at room temperature for 2h. The solvent and excess reagent were then removed under reduced pressure and the residue obtained dissolved in THF (4 mL) and added dropwise to a mixture of 3-amino-4-fluoro-2,5-dimethylphenol (X(h)) (150 mg, 0.97 mmol, 1.0 eq) and NaHCO_3 (407 mg, 4.85 mmol, 5.0 eq) in THF (3 mL) at 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 30 min. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with aqueous NaHCO_3 , water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 6:1 to 5:1) to give an impure product. The crude material was triturated with a mixture of petroleum ether and EtOAc (3 mL:1 mL) and the solid collected by filtration to afford the title compound as a white solid (233 mg, 65 %).

LC-MS: m/z 372.1 $[\text{M}+\text{H}]^+$ 394.1 $[\text{M}+\text{Na}]^+$

4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenol

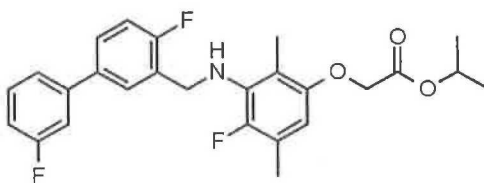
To a solution of 2-fluoro-N-(2-fluoro-5-hydroxy-3,6-dimethyl-phenyl)-5-(3-fluorophenyl)benzamide (230 mg, 0.62 mmol, 1.0 eq) in THF (3 mL) at 0 °C under N_2 was added a solution of BH_3 (1M in THF, 3.7 mL, 3.7 mmol, 6.0 eq) dropwise. The

reaction mixture was heated at 60 °C overnight. After cooling, the reaction was quenched by addition of water and extracted with EtOAc. The organic extract was washed with aqueous NaHCO₃, water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a white solid (220 mg, 99 %).

5

LC-MS: m/z 358.1 [M+H]⁺

Isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethylphenoxy]acetate (II(ag))



10

To a solution of 4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenol (220 mg, 0.62 mmol, 1.0 eq) in DMF (6 mL) was added Cs₂CO₃ (301 mg, 0.92 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred for 30 min, then isopropyl bromoacetate (134 mg, 0.74 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for 1h. TLC showed the starting material was not consumed. A further portion of Cs₂CO₃ (300 mg, 0.92 mmol, 1.5 eq) was added and the reaction stirred for 1h, then a further portion of isopropyl bromoacetate (134 mg, 0.74 mmol, 1.2 eq) was added and the reaction stirred for 4h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 50:1 to 20:1) to give the title compound as a colorless oil (225 mg, 80 %).

15

20

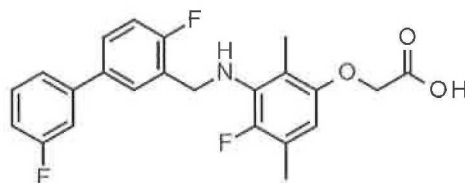
LC-MS: m/z 458.2 [M+H]⁺

25

¹H NMR (400 MHz, DMSO) δ 7.73 (dd, *J* = 7.1, 2.3 Hz, 1H), 7.58 (ddd, *J* = 8.2, 4.9, 2.6 Hz, 1H), 7.54 – 7.44 (m, 1H), 7.43 – 7.34 (m, 2H), 7.28 – 7.13 (m, 2H), 6.18 (d, *J* = 5.7

Hz, 1H), 5.12 – 5.02 (m, 1H), 4.99 – 4.89 (m, 1H), 4.61 (s, 2H), 4.43 (d, $J = 7.0$ Hz, 2H), 2.09 – 2.04 (m, 6H), 1.16 (d, $J = 6.3$ Hz, 6H)

2-[4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenoxy]
5 acetic acid (I(ac))



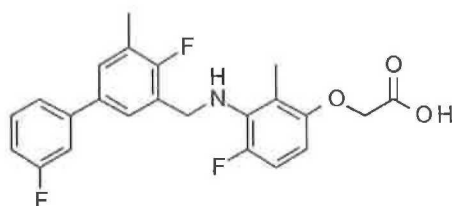
To a solution of isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methyl
amino]-2,5-dimethyl-phenoxy]acetate (130 mg, 0.28 mmol, 1.0 eq) in THF (2 mL) was
added LiOH (2M aqueous solution, 2 mL, 4 mmol, 14 eq) at room temperature. The
10 reaction mixture was stirred at room temperature for 2h. Water was added and THF was
removed under reduced pressure. The aqueous layer was washed with MTBE and the
organic extract was discarded. The aqueous layer was adjusted to pH 3-4 by addition of
3M HCl and then extracted with EtOAc. The combined organic extracts were washed
with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude product was
15 recrystallized from CH_2Cl_2 (1 mL) and petroleum ether (3 mL) to give the target
compound as an off-white solid (85 mg, 72 %).

LC-MS: m/z 398.2 $[\text{M}+\text{H}]^+$

20 ^1H NMR (400 MHz, DMSO-d_6) δ 12.89 (br s, 1H), 7.74 (dd, $J = 7.0, 2.2$ Hz, 1H), 7.58
(ddd, $J = 7.7, 4.7, 2.3$ Hz, 1H), 7.53 – 7.46 (m, 1H), 7.43 – 7.35 (m, 2H), 7.26 – 7.15 (m,
2H), 6.18 (d, $J = 5.8$ Hz, 1H), 5.05 (br s, 1H), 4.55 (s, 2H), 4.43 (s, 2H), 2.07 (s, 6H)LC-
MS: m/z 416.1 $[\text{M}+\text{H}]^+$

25 **Example 30 – compound I(ad) synthesized according to scheme 3**

2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-
methyl-phenoxy]acetic acid (I(ad))



2-Fluoro-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)-3-methyl-benzamide

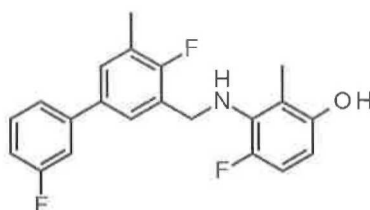


- 5 To a solution of 2-fluoro-5-(3-fluorophenyl)-3-methyl-benzoic acid (intermediate III(f)) (528 mg, 2.1 mmol, 1.0 eq), in CH₂Cl₂ (20 mL) and DMF (3 drops) was added (COCl)₂ (0.5 mL). The reaction was stirred at room temperature for 1h then the solvent and excess reagent were removed under reduced pressure. The residue obtained was dissolved in THF (20 mL) and added to a mixture of 3-amino-4-fluoro-2-methylphenol (intermediate
- 10 X(e)) (300 mg, 2.1 mmol, 1.0 eq) and NaHCO₃ (536 mg, 6.38 mmol, 3 eq) in THF (20 mL) at 0 °C. After addition was completed, the reaction mixture was stirred at room temperature for 30 min. Water was added and the aqueous phase was adjusted to pH 3 by addition of diluted HCl. The aqueous solution was extracted with EtOAc and the combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The
- 15 residue obtained was purified by column chromatography (petroleum ether:EtOAc, 100:1 to 1:1) to give the title compound as a white solid (420 mg, 53 %).

LC-MS: m/z 372.1 [M+H]⁺ 394.1 [M+Na]⁺

20

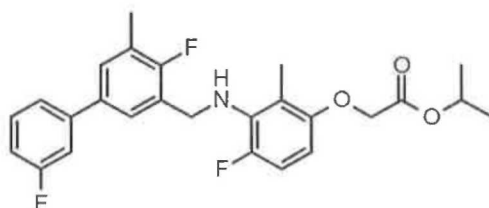
4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-methyl-phenol



To a solution of 2-fluoro-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)-3-methyl-benzamide (404 mg, 1.1 mmol, 1.0 eq) in THF (10 mL) under N₂ was added a solution of BH₃ (1M in THF, 5.5 mL, 5.5 mmol, 5.0 eq) at room temperature. The reaction mixture was heated at 60 °C for 3h, then cooled to room temperature and quenched with 1 M HCl. Water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude residue obtained was purified by column chromatography (petroleum ether:EtOAc, 100:1 to 15:1) to give the title compound as a yellow oil (269 mg, 69 %).

LC-MS: m/z 378.2 [M+H]⁺

Isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (II(ah))

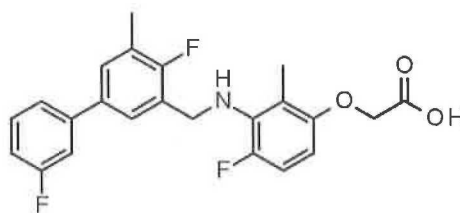


To a solution of 4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methyl amino]-2-methyl-phenol (269 mg, 0.8 mmol, 1 eq), in 2-butanone (10 mL) was added Cs₂CO₃ (368 mg, 0.9 mmol, 1.5eq) and isopropyl 2-bromoacetate (163.5 mg, 0.9 mmol, 1.2 eq). The reaction mixture was stirred at room temperature for 2h, then filtered to remove the solids. The filtrate was evaporated *in vacuo* and the crude residue obtained purified by column chromatography (petroleum ether:EtOAc, 100:1 to 15:1) to give the title compound as a yellow oil (300 mg, 87 %).

LC-MS: m/z 458.2 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 7.55 – 7.43 (m, 3H), 7.40 – 7.32 (m, 2H), 7.16 (td, J = 8.4, 2.1 Hz, 1H), 6.78 (dd, J = 12.4, 9.0 Hz, 1H), 6.24 (dd, J = 9.1, 3.6 Hz, 1H), 5.19 – 5.11 (m, 1H), 4.94 (hept, J = 6.3 Hz, 1H), 4.63 (s, 2H), 4.44 (d, J = 6.9 Hz, 2H), 2.26 (d, J = 1.4 Hz, 3H), 2.12 (s, 3H), 1.15 (d, J = 6.3 Hz, 6H).

2-[4-Fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ad))



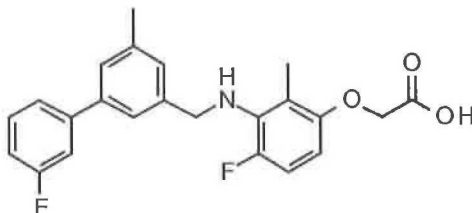
To a solution of isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (150 mg, 0.33 mmol) in THF (6 mL) was added NaOH (1M aqueous solution, 4.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 2h, then the THF removed under reduced pressure. The remaining aqueous solution was adjusted to pH 3-4 with diluted HCl and the solid that precipitated collected by filtration, washed with water and dried *in vacuo* to give the title compound as a white solid (100 mg, 74 %).

LC-MS: m/z 414.1 $[M-H]^-$

1H NMR (400 MHz, DMSO) δ 12.94 (br s, 1H), 7.56 – 7.50 (m, 1H), 7.50 – 7.44 (m, 2H), 7.40 – 7.33 (m, 2H), 7.20 – 7.12 (m, 1H), 6.79 (dd, J = 12.3, 9.1 Hz, 1H), 6.24 (dd, J = 9.0, 3.7 Hz, 1H), 5.13 (br s, 1H), 4.57 (s, 2H), 4.44 (s, 2H), 2.26 (s, 3H), 2.11 (s, 3H).

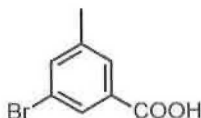
Example 31 – compound I(ae) synthesized according to scheme 3

2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ae))



5

3-Bromo-5-methylbenzoic acid



1-bromo-3,5-dimethylbenzene (15 g, 81 mmol, 1.0 eq) in a mixture of pyridine (133 mL) and H₂O (83 mL) was heated to 80°C. KMnO₄ (25.6 g, 162 mmol, 2.0 eq) was added in portions over 45 min. After the addition was completed, heating was continued at 80°C for 1.5 h. The hot solution was then filtered, and the filtrate was acidified by addition of concentrated hydrochloric acid. The aqueous solution was extracted with EtOAc and the combined organic extracts washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (CH₂Cl₂: MeOH, 80:1 to 40:1) to give the title compound as a white solid (5.2 g, 29 %)

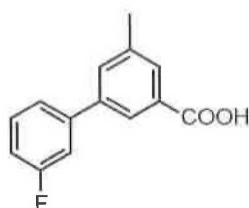
15

LC-MS: m/z 212.9, 215 [M+H]⁺

¹H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.79 (s, 1H), 7.57 (s, 1H), 2.38 (s, 3H).

20

3-(3-Fluorophenyl)-5-methyl-benzoic acid (III(q))



To a solution of 3-bromo-5-methylbenzoic acid (3.0 g, 13.95 mmol, 1.0 eq), 3-fluorophenylboronic acid (2.34 g, 16.74 mmol, 1.2 eq) and Na_2CO_3 (5.91 g, 55.8 mmol, 4.0 eq) in a mixture of EtOH (10 mL), DMF (40 mL) and H_2O (10 mL) was added
5 $\text{Pd}(\text{PPh}_3)_4$ (806 mg, 0.7 mmol, 0.05 eq). The mixture was stirred at 100 °C overnight. Water was added and the aqueous layer extracted with EtOAc. The organic extract was discarded and the aqueous layer was acidified to pH 4-5 by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were filtered through silica gel and concentrated to give the title compound as a white solid (2.0 g,
10 62 %)

LC-MS: m/z 229.1 $[\text{M}-\text{H}]^-$

^1H NMR (400 MHz, DMSO) δ 13.07 (s, 1H), 7.99 (s, 1H), 7.78 (s, 2H), 7.57 – 7.48 (m,
15 3H), 7.26 – 7.19 (m, 1H), 2.44 (s, 3H).

N-(6-Fluoro-3-hydroxy-2-methyl-phenyl)-3-(3-fluorophenyl)-5-methyl-benzamide

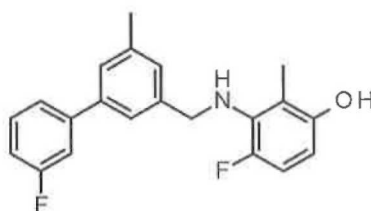


20 To a solution of 3-(3-fluorophenyl)-5-methyl-benzoic acid (448 mg, 1.95 mmol, 1.1 eq) in CH_2Cl_2 (10 mL) was added $(\text{COCl})_2$ (742 mg, 5.85 mmol, 3.3 eq) and DMF (3 drops) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. The resulting mixture was concentrated *in vacuo* to remove the solvent and excess reagent. The solid

obtained was dissolved in THF (10 mL) and added dropwise to a mixture of 3-amino-4-fluoro-2-methylphenol (intermediate X(c)) (250 mg, 1.77 mmol, 1.0 eq) and NaHCO₃ (744 mg, 8.86 mmol, 5.0 eq) in THF (15 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂:MeOH, 500:1 to 300:1) to give the title compound as a white solid (396 mg, 63 %).

10 LC-MS: m/z 354.1 [M+H]⁺ 376.1 [M+Na]⁺

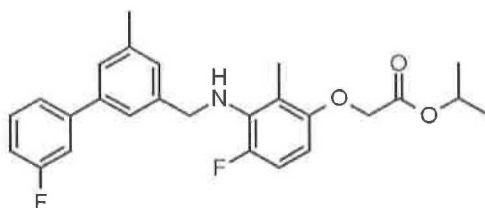
4-Fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenol



To a solution of N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-3-(3-fluorophenyl)-5-methyl-benzamide (394 mg, 1.11 mmol, 1.0 eq) in THF (15 mL) under N₂ was added a solution of BH₃ (1M in THF, 6.7 mL, 6.7 mmol, 6.0 eq) dropwise. The reaction mixture was heated at 60 °C overnight. After cooling, the reaction was quenched by addition of water and the aqueous layer was extracted with EtOAc. The extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 30:1 to 20:1) to give the title compound as a brown oil (324 mg, 86 %).

LC-MS: m/z 340.2 [M+H]⁺ 362.1 [M+Na]⁺

25 *Isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (II(ai))*

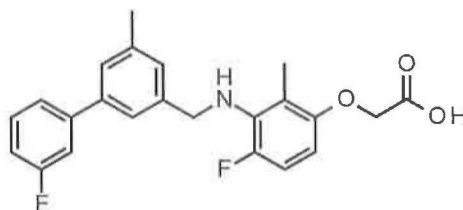


To a solution of 4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenol (324 mg, 0.95 mmol, 1.0 eq) in DMF (15 mL) was added Cs₂CO₃ (467 mg, 1.43 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 30 min,
 5 then isopropyl bromoacetate (207 mg, 1.15 mmol, 1.2 eq) was added and stirring continued for a further 1h. Water was added and the aqueous layer was extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 50:1 to 40:1) to give the title compound as a colorless oil (317
 10 mg, 76 %).

LC-MS: m/z 440.2 [M+H]⁺ 462.2 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.52 – 7.44 (m, 1H), 7.44 – 7.36 (m, 3H), 7.33 (s, 1H),
 15 7.17 (td, *J* = 8.4, 1.9 Hz, 1H), 7.13 (s, 1H), 6.77 (dd, *J* = 12.4, 9.0 Hz, 1H), 6.21 (dd, *J* = 9.0, 3.6 Hz, 1H), 5.22 (t, *J* = 6.8 Hz, 1H), 4.94 (hept, *J* = 6.2 Hz, 1H), 4.62 (s, 2H), 4.37 (d, *J* = 6.8 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 6H).

20 2-[4-Fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ae))



To a solution of isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl] methylamino]-2-methyl-phenoxy]acetate (200 mg, 0.46 mmol, 1.0 eq) in THF (10 mL) was added LiOH (2M aqueous solution, 4 mL, 8.0 mmol). The reaction mixture was stirred at room temperature for 2h then the THF was removed *in vacuo*. The pH of the aqueous solution that remained was adjusted to pH 5 by addition of 3M HCl. The solid precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a yellow solid (150 mg, 83 %).

LC-MS: m/z 398.2 $[M+H]^+$

10

^1H NMR (400 MHz, DMSO) δ 7.54 – 7.36 (m, 4H), 7.33 (s, 1H), 7.22 – 7.09 (m, 2H), 6.74 (dd, $J = 12.3, 9.0$ Hz, 1H), 6.17 (dd, $J = 8.9, 3.5$ Hz, 1H), 5.15 (br s, 1H), 4.41 (s, 2H), 4.36 (s, 2H), 2.32 (s, 3H), 2.10 (s, 3H).

15

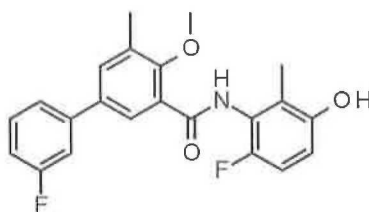
Example 32 – compound I(af) synthesized according to scheme 3

2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(af))



20

N-(6-Fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)-2-methoxy-3-methyl-benzamide



To a solution of 5-(3-fluorophenyl)-2-methoxy-3-methyl-benzoic acid (intermediate III(k)) (500 mg, 1.92 mmol, 1.1 eq) in CH_2Cl_2 (10 mL) was added $(\text{COCl})_2$ (731.6 mg, 5.76 mmol, 3.3 eq) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1h. The resulting mixture was concentrated under reduced pressure and the residue that remained dissolved in THF (6 mL) and added to a mixture of 3-amino-4-fluoro-2-methylphenol (intermediate X(c)) (246.5 mg, 1.75 mmol, 1.0 eq) and NaHCO_3 (733.5 mg, 8.73 mmol, 5.0 eq) in THF (8 mL). After the addition, the reaction mixture was stirred for a further 2h. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with 5% Na_2CO_3 , dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 10:1 to 5:1 then CH_2Cl_2 :MeOH, 20:1) to give the title compound as a white solid (540 mg, 80 %).

LC-MS: m/z 384.1 $[\text{M}+\text{H}]^+$ 406.1 $[\text{M}+\text{Na}]^+$

4-Fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenol



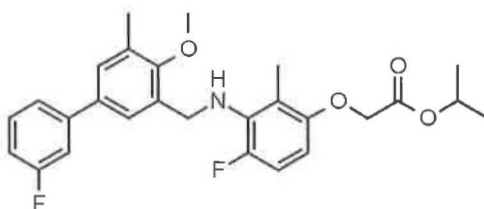
To a solution of N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)-2-methoxy-3-methyl-benzamide (450 mg, 1.17 mmol, 1.0 eq) in THF (6 mL) at 0 °C under N_2 was added a solution of BH_3 (1M in THF, 7.04 mL, 7.04 mmol, 6.0 eq). The reaction mixture was heated at 60 °C for 1h. After cooling to 0 °C, water was added dropwise and

the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 20:1 to 10:1) to give the title compound as a colorless oil (94 mg, 22 %).

5

LC-MS: m/z 370.1 $[\text{M}+\text{H}]^+$ 392.1 $[\text{M}+\text{Na}]^+$

Isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl] methylamino]-2-methyl-phenoxy]acetate (II(qj))



10

To a solution of 4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl] methylamino]-2-methyl-phenol (94 mg, 0.25 mmol, 1.0 eq) in acetone (4 mL) at room temperature was added Cs_2CO_3 (124.4 mg, 0.38 mmol, 1.5 eq). The reaction mixture was stirred for 30 min, then isopropyl bromoacetate (55.3 mg, 1.2 mmol, 1.2 eq) was added and stirring continued for a further 2h. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 20:1) to give the title compound as a colorless oil (65 mg, 54 %).

15

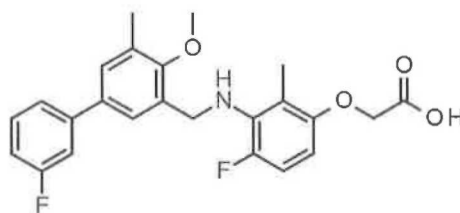
20 LC-MS: m/z 470.2 $[\text{M}+\text{H}]^+$ 492.2 $[\text{M}+\text{Na}]^+$

^1H NMR (400 MHz, DMSO) δ 7.52 – 7.39 (m, 3H), 7.39 – 7.30 (m, 2H), 7.14 (td, $J = 8.5$, 2.3 Hz, 1H), 6.79 (dd, $J = 12.0$, 9.1 Hz, 1H), 6.25 (dd, $J = 9.0$, 3.6 Hz, 1H), 5.01 – 4.90 (m, 2H), 4.65 (s, 2H), 4.44 (s, 2H), 3.71 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 1.17 (d, $J =$

25

6.3 Hz, 6H).

2-[4-Fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(af))



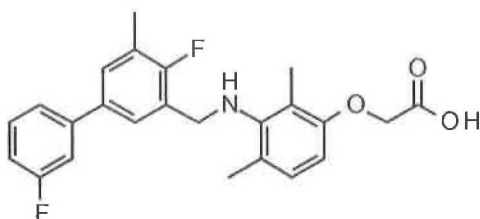
To a solution of isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (64 mg, 0.2 mmol, 1.0 eq) in THF (2 mL) was added LiOH (2M aqueous solution, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at room temperature for 1 h. The THF was removed and the pH of the aqueous solution that remained adjusted to pH 4-5 with diluted HCl. The aqueous layer was extracted with EtOAc, the organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a white solid (30 mg, 50 %).

LC-MS: m/z 428.2 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 7.51 – 7.40 (m, 3H), 7.40 – 7.30 (m, 2H), 7.14 (td, *J* = 8.7, 2.2 Hz, 1H), 6.79 (dd, *J* = 12.4, 9.1 Hz, 1H), 6.24 (dd, *J* = 9.1, 3.6 Hz, 1H), 4.57 (s, 2H), 4.43 (s, 2H), 3.70 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H).

Example 33 – compound I(ag) synthesized according to scheme 3

2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(ag))



2-Fluoro-5-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-3-methyl-benzamide



- 5 To a solution of 2-fluoro-5-(3-fluorophenyl)-3-methyl-benzoic acid (intermediate III(f)) (597 mg, 2.41 mmol, 1.1 eq) in CH_2Cl_2 (15 mL) and DMF (5 drops) was added $(\text{COCl})_2$ (916 mg, 7.22 mmol, 3.3 eq) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. The resulting mixture was concentrated under reduced pressure to remove the solvent and excess reagent and the residue obtained dissolved in THF (20
- 10 mL) and added dropwise to a solution of 3-amino-2,4-dimethylphenol (intermediate X(c)) (300 mg, 2.18 mmol, 1.0 eq) and NaHCO_3 (920 mg, 10.9 mmol, 5 eq) in THF (20 mL) at 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 1h. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered, and
- 15 evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2 :MeOH, 500:1 to 300:1) to give the title compound as a white solid (270 mg, 34 %).

LC-MS: m/z 368.1 $[\text{M}+\text{H}]^+$ 390.2 $[\text{M}+\text{Na}]^+$

20

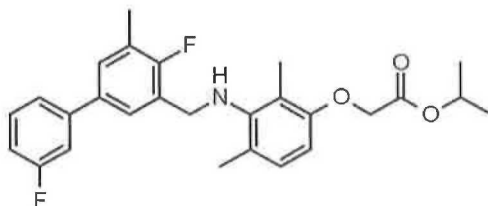
3-[[2-Fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenol



To a solution of 2-fluoro-5-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-3-methyl- benzamide (270 mg, 0.7 mmol, 1.0 eq) in THF (15 mL) was added a solution of BH_3 (1M in THF, 4.4 mL, 4.4 mmol, 6.0 eq) dropwise under N_2 . The reaction mixture was heated at 60 °C overnight. After cooling, the resulting mixture was quenched by the addition of water and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 30:1 to 20:1) to give the title compound as a colorless oil (106 mg, 41 %).

LC-MS: m/z 354.2 $[\text{M}+\text{H}]^+$

Isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (II(ak))



To a solution of 3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenol (106 mg, 0.30 mmol, 1.0 eq) in DMF (6 mL) was added Cs_2CO_3 (147 mg, 0.45 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred for 30 min, then isopropyl bromoacetate (65 mg, 0.136 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for 1h. Water was added and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column

chromatography (petroleum ether:EtOAc, 50:1 to 40:1) to give the title compound as a colorless oil (90 mg, 66 %).

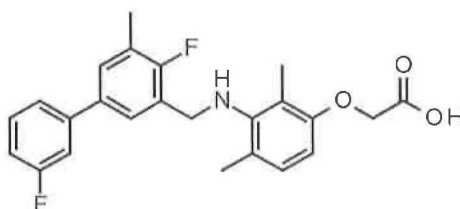
LC-MS: m/z 454.2 $[M+H]^+$ 476.2 $[M+Na]^+$

5

1H NMR (400 MHz, DMSO) δ 7.60 (dd, $J = 6.5, 2.2$ Hz, 1H), 7.56 – 7.51 (m, 1H), 7.51 – 7.39 (m, 3H), 7.22 – 7.13 (m, 1H), 6.84 (d, $J = 8.3$ Hz, 1H), 6.38 (d, $J = 8.3$ Hz, 1H), 5.01 – 4.90 (m, 1H), 4.64 (s, 2H), 4.25 (t, $J = 7.5$ Hz, 1H), 4.13 (d, $J = 7.3$ Hz, 2H), 2.28 (d, $J = 1.3$ Hz, 3H), 2.14 (s, 3H), 2.13 (s, 3H), 1.19 (d, $J = 6.3$ Hz, 6H).

10

2-[3-[[2-Fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid (I(ag))



- 15 To a solution of isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methyl amino]- 2,4-dimethyl-phenoxy]acetate (70 mg, 0.15 mmol, 1.0 eq) in THF (5 mL) at 0 °C was added LiOH (2M aqueous solution, 2.0 mL, 4.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2h. The THF was removed *in vacuo* and the remaining aqueous mixture diluted with water and adjusted to pH 5 by addition of
- 20 3M HCl. The solid that precipitated was collected by filtration and dried *in vacuo* to give the title compound as a yellow solid (40 mg, 63 %).

LC-MS: m/z 412.2 $[M+H]^+$

- 25 1H NMR (400 MHz, DMSO) δ 7.61 (dd, $J = 6.5, 2.2$ Hz, 1H), 7.52 (dd, $J = 6.5, 2.4$ Hz, 1H), 7.50 – 7.39 (m, 3H), 7.20 – 7.12 (m, 1H), 6.81 (d, $J = 8.3$ Hz, 1H), 6.35 (d, $J = 8.3$ Hz, 1H), 4.38 (s, 2H), 4.12 (s, 2H), 2.28 (d, $J = 1.2$ Hz, 3H), 2.13 (s, 6H).

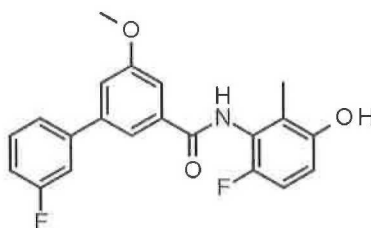
Example 34 – compound I(ah) synthesized according to scheme 3

2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ah))

5



N-(6-Fluoro-3-hydroxy-2-methyl-phenyl)-3-(3-fluorophenyl)-5-methoxy-benzamide

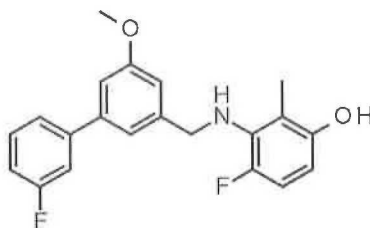


To a solution of 3-(3-fluorophenyl)-5-methoxy-benzoic acid (524 mg, 2.1 mmol, 1.0 eq) in CH₂Cl₂ (10 mL) was added dropwise (COCl)₂ (810 mg, 6.4 mmol, 3 eq) at 0 °C. DMF (0.1 mL) was added and the reaction mixture stirred at room temperature for 3h. The solvent was removed under reduced pressure and the residue obtained was dissolved in THF (20 mL) and added dropwise to a mixture of 3-amino-4-fluoro-2-methyl-phenol (300 mg, 2.1 mmol, 1 eq) and K₂CO₃ (1.47 g, 10.6 mmol, 5 eq.) in THF (20 mL) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 3h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 20:1) to give the title compound as yellow solid (500 mg, 63 %).

20

LC-MS: m/z 370.1 [M+H]⁺ 392.1 [M+Na]⁺

4-Fluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2-methyl-phenol



To a stirred solution of N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-3-(3-fluorophenyl)-5-methoxy-benzamide (500 mg, 1.35 mmol, 1.0 eq) in anhydrous THF (10 mL) under N₂ was added a solution of BH₃ (1M in THF, 7 mL, 6.77 mmol, 5.0 eq) dropwise over 5 min.

- 5 The reaction mixture was heated to 60 °C overnight. After cooling, the resulting mixture was quenched by addition of saturated aqueous NH₄Cl. Water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc, 100:1 to 20:1) to give the title compound as a
- 10 colorless oil (390 mg, 81 %).

LC-MS: m/z 356.1 [M+H]⁺

- 15 *Isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2-methyl-phenoxy]acetate*



- To a solution of 4-fluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2-methyl-phenol (390 mg, 1.1 mmol, 1.0 eq) in DMF (6 mL) was added Cs₂CO₃ (538 mg, 1.65 mmol, 1.5 eq). The reaction was stirred 30 min, then isopropyl 2-bromoacetate (239 mg, 1.32 mmol, 1.2 eq) was added at room temperature. The reaction mixture was stirred
- 20 at room temperature for a further 1h, then water was added and the aqueous layer was extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude product was purified by column

chromatography (petroleum ether:EtOAc, 1:0, 100:1, to 20:1) to give the title compound as a colorless oil (400 mg, 80 %).

LC-MS: m/z 456.2 $[M+H]^+$, 478.2 $[M+Na]^+$

5

Isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl-phenoxy]acetate (II(al))



To a solution of isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2-methyl-phenoxy]acetate (300 mg, 0.66 mmol, 1 eq) and $AlCl_3$ (526 mg, 3.95 mmol, 6 eq) in CH_2Cl_2 (10 mL) was added ethanethiol (245 mg, 3.95 mmol, 5 eq) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 2h and the resulting mixture was quenched by the addition of water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (petroleum ether:EtOAc, 15:1) to give the title compound as a colorless oil (120 mg, 41 %).

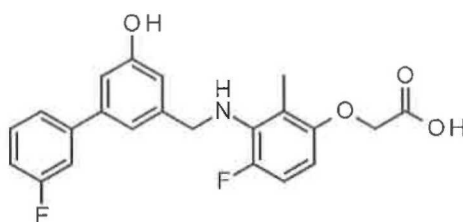
20

LC-MS: m/z 442.2 $[M+H]^+$ 465.2 $[M+Na]^+$

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.33 (m, 1H), 7.32 – 7.28 (m, 1H), 7.24 – 7.18 (m, 1H), 7.08 (s, 1H), 7.06 – 6.99 (m, 1H), 6.95 – 6.91 (m, 1H), 6.83 – 6.75 (m, 2H), 6.26 (dd, J = 9.0, 3.8 Hz, 1H), 5.19 – 5.06 (m, 1H), 4.56 (s, 2H), 4.34 (s, 2H), 2.20 (s, 3H), 1.27 (d, J = 6.3 Hz, 6H).

25

2-[4-Fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ah))

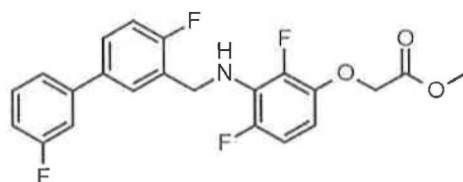


To a solution of isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]-2-methylphenoxy]acetate (90 mg, 0.2 mmol, 1 eq) in a mixture of MeOH (3 mL) and THF (3 mL) was added NaOH (1 M aqueous solution, 3 mL, 3 mmol) and the reaction was stirred at room temperature for 3h. The MeOH and THF were removed under reduced pressure and the aqueous phase was acidified to pH 3-6 by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as yellow oil (30 mg, 37 %).

LC-MS: m/z 400.1 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 9.52 (br s, 1H), 7.52 – 7.42 (m, 1H), 7.42 – 7.29 (m, 2H), 7.21 – 7.12 (m, 1H), 7.04 (s, 1H), 6.85 (s, 1H), 6.81 – 6.70 (m, 2H), 6.19 (dd, *J* = 8.9, 3.5 Hz, 1H), 5.20 (br s, 1H), 4.55 (s, 2H), 4.34 (s, 2H), 2.11 (s, 3H).

Example 35 - Methyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(c)), prepared via scheme 7



To a stirred solution of ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(a)) (290 mg, 0.7 mmol, 1.0 eq) in MeOH (30 mL) was added K₂CO₃ (28 mg, 0.2 mmol 0.3 eq). The reaction was heated at reflux overnight. The solvent was removed *in vacuo* and the residue obtained was diluted with water and neutralized by addition of 1M HCl. The aqueous layer was further extracted with EtOAc

and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by chromatography (EtOAc:petroleum ether, 0:1 to 1:20) to give the title compound an oil (130 mg, 46 %).

5 LC-MS : m/z 419.9 $[\text{M}+\text{H}]^+$

^1H NMR (300MHz, $\text{DMSO}-d_6$) δ 7.73 (dd, $J=7.2, 2.4$ Hz, 1H), 7.66 - 7.56 (m, 1H), 7.54 - 7.44 (m, 1H), 7.43 - 7.36 (m, 2H), 7.24 (dd, $J=9.8, 8.6$ Hz, 1H), 7.23 - 7.13 (m, 1H), 6.80 (ddd, $J=11.6, 9.3, 2.1$ Hz, 1H), 6.36 (td, $J=9.1, 4.6$ Hz, 1H), 6.03 - 5.75 (m, 1H), 4.76 (s, 2H), 4.52 (d, $J=7.1$ Hz, 2H), 3.65 (s, 3H)

Example 36 - Isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate (II(d)) , prepared via scheme 6



2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(b)) (70 mg, 0.17 mmol, 1.0 eq) was dissolved in iPrOH (5 mL). Concentrated sulphuric acid (2 drops) was added and the solution was stirred at room temperature overnight. The reaction was quenched by addition of aqueous NaHCO_3 and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (MgSO_4), filtered and evaporated *in vacuo* to give the crude product. The compound was triturated in a mixture of petroleum ether and DCM and dried under vacuum to give the title compound (II(d)) as a gummy solid (52 mg, 68 %).

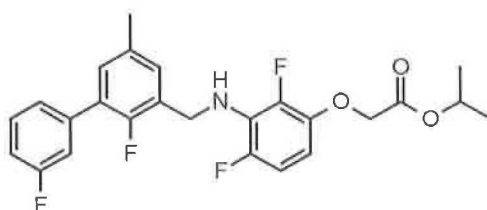
25

LC-MS : m/z 448.0 $[\text{M}+\text{H}]^+$

^1H NMR (300MHz, $\text{DMSO}-d_6$) δ 7.73 (dd, $J=7.3, 2.3$ Hz, 1H), 7.63 - 7.56 (m, 1H), 7.54 -

7.45 (m, 1H), 7.43 - 7.35 (m, 2H), 7.23 (dd, $J=9.9, 8.6$ Hz, 1H), 7.23 - 7.13 (m, 1H), 6.80 (ddd, $J=11.6, 9.3, 2.1$ Hz, 1H), 6.33 (td, $J=9.1, 4.5$ Hz, 1H), 5.88 (s, 1H), 4.93 (spt, $J=6.3$ Hz, 1H), 4.70 (s, 2H), 4.52 (d, $J=7.0$ Hz, 2H), 1.14 (d, $J=6.2$ Hz, 6H)

5 **Example 37 - Isopropyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetate (II(f)), prepared via scheme 6**

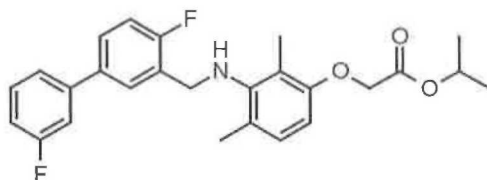


10 A mixture of 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetic acid (I(g)) (300 mg, 0.83 mmol, 1.0 eq) and Cs_2CO_3 (407 mg, 1.25 mmol, 1.5 eq) in DMF (5 mL) was stirred at room temperature for 1h, then isopropyl bromoacetate (171 mg, 0.91 mmol, 1.1 eq) was added. The mixture was stirred at room temperature for 1h. The resulting mixture was poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:10) to give the title compound as an oil (310 mg, 81 %).

20 LC-MS : m/z 462.0 $[\text{M}+\text{H}]^+$

^1H NMR (300 MHz, DMSO-d_6) δ 7.58 - 7.45 (m, 1H), 7.41 - 7.29 (m, 2H), 7.28 - 7.16 (m, 3H), 6.81 (ddd, $J=11.7, 9.4, 2.1$ Hz, 1H), 6.32 (td, $J=9.1, 4.5$ Hz, 1H), 5.91 - 5.77 (m, 1H), 4.95 (spt, $J=6.3$ Hz, 1H), 4.71 (s, 2H), 4.50 (d, $J=6.9$ Hz, 2H), 2.28 (s, 3H), 1.17 (d, $J=6.2$ Hz, 6H)

Example 38 – Isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (II(g)) , prepared via scheme 6



- 5 A solution of 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(j)) (120 mg, 0.3 mmol, 1eq) and SOCl_2 (1 mL) in i-PrOH (4 mL) was heated at reflux for 2h. The solvent was evaporated *in vacuo* and the residue was taken up in water and basified to pH 8 by addition of aqueous NaHCO_3 . The mixture was extracted with EtOAc and the organic extract was dried (Na_2SO_4) filtered and evaporated
- 10 *in vacuo*. The residue obtained was purified by column chromatography to give the title compound as an oil (120 mg, 90 %).

LC-MS : m/z 440.1 $[\text{M}+\text{H}]^+$

- 15 ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.79 (dd, $J=7.2, 2.3$ Hz, 1H), 7.69 - 7.58 (m, 1H), 7.56 - 7.38 (m, 3H), 7.34 - 7.06 (m, 2H), 6.84 (d, $J=8.3$ Hz, 1H), 6.37 (d, $J=8.4$ Hz, 1H), 5.09 - 4.87 (m, 1H), 4.64 (s, 2H), 4.41 - 4.25 (m, 1H), 4.16 (d, $J=6.1$ Hz, 2H), 2.12 (d, $J=4.5$ Hz, 6H), 1.19 (d, $J=6.2$ Hz, 6H)

20

Example 39 - Isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenoxy]acetate (II(i)) , prepared via scheme 3



To a solution of 4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenol (see example 13) (150 mg, 0.44 mmol, 1.0 eq) in DMF (2 mL) was added Cs₂CO₃ (214 mg, 0.66 mmol, 1.5 eq) and the reaction mixture was stirred for 1h. Isopropyl 2-bromoacetate (80 mg, 0.44 mmol, 1.0 eq) was then added and the reaction was stirred for
5 a further 1h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:20) to give the title compound as a colourless oil (130 mg, 80 %).

10 LC-MS : m/z 444.1 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.72 (dd, *J*=7.2, 2.3 Hz, 1H), 7.57 (ddd, *J*=8.2, 5.3, 2.5 Hz, 1H), 7.53 - 7.43 (m, 1H), 7.42 - 7.33 (m, 2H), 7.29 - 7.11 (m, 2H), 6.78 (dd, *J*=12.2, 9.0 Hz, 1H), 6.24 (dd, *J*=9.0, 3.7 Hz, 1H), 5.53 - 5.06 (m, 1H), 4.94 (spt, *J*=1.0 Hz, 1H),
15 4.63 (s, 2H), 4.45 (d, *J*=7.0 Hz, 2H), 2.11 (s, 3H), 1.15 (d, *J*=6.2 Hz, 6H)

Example 40 - 2-Hydroxyethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(j)) , prepared via scheme 7



20

To a solution of isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate (II(d)) (0.63 g, 1.41 mmol, 1.0 eq) in ethylene glycol (30 mL) at room temperature was added H₂SO₄ (0.4 mL, 7.5 mmol, 5.3 eq) dropwise. The reaction mixture was stirred overnight at 10 °C then heated at 40 °C for 3h. The reaction
25 was then cooled to room temperature and poured into water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with 5% Na₂CO₃, water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was

purified by column chromatography (EtOAc:petroleum ether, 1:5 to 1:1) to give the title compound as an oil, which crystallised on standing to give a white solid (0.54 g, 85 %).

LC-MS : m/z 450.0 $[M+H]^+$

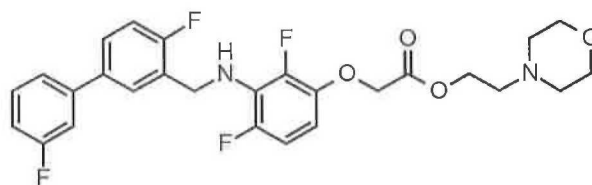
5

1H NMR (300 MHz, DMSO- d_6) δ 7.74 (dd, $J=7.2, 2.2$ Hz, 1H), 7.65 - 7.55 (m, 1H), 7.54 - 7.44 (m, 1H), 7.43 - 7.34 (m, 2H), 7.29 - 7.20 (m, 1H), 7.18 (dt, $J=8.8, 1.6$ Hz, 1H), 6.80 (ddd, $J=11.6, 9.4, 2.0$ Hz, 1H), 6.36 (td, $J=9.1, 4.6$ Hz, 1H), 5.88 (t, $J=6.9$ Hz, 1H), 4.84 (t, $J=5.6$ Hz, 1H), 4.76 (s, 2H), 4.53 (d, $J=7.1$ Hz, 2H), 4.11 (t, $J=5.0$ Hz, 2H), 3.56 (q, $J=5.4$ Hz, 2H)

10

Example 41 - 2-Morpholinoethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenoxy]acetate (II(k)) , prepared via scheme 6

15



A mixture of 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenoxy]acetic acid (I(b)) (800 mg, 1.97 mmol, 1.0 eq), 2-morpholinoethanol (284 mg, 2.17 mmol, 1.1 eq), HATU (974 mg, 2.56 mmol, 1.3 eq), and TEA (598 mg, 5.91 mmol, 3 eq) in DCM (10 mL) and DMF (10 mL) was stirred at room temperature overnight under N_2 . The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* and the residue purified by column chromatography, (MeOH:DCM 0:1 to 1:50) to give the title compound as a yellow oil (710 mg, 70 %).

25

LC-MS : m/z 519.2 $[M+H]^+$

1H NMR (300 MHz, DMSO- d_6) δ 7.74 (dd, $J=2.2, 7.1$ Hz, 1H), 7.64 - 7.55 (m, 1H), 7.54

- 7.44 (m, 1H), 7.43 - 7.33 (m, 2H), 7.29 - 7.19 (m, 1H), 7.22 - 7.12 (m, 1H), 6.94 - 6.67 (m, 1H), 6.35 (td, $J=9.1, 4.6$ Hz, 1H), 4.76 (s, 2H), 4.52 (d, $J=7.1$ Hz, 2H), 4.18 (t, $J=5.6$ Hz, 2H), 3.56 - 3.46 (m, 4H), 2.46 (s, 3H), 2.39 - 2.27 (m, 4H)

5 **Example 42 - 2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetamide (II(l)), prepared via scheme 7**



To a mixture of isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate (II(d)) (1.0 g, 2.24 mmol, 1.0 eq) in dioxane (10 mL) was added NH_3 (35% aqueous solution, 30 mL). The reaction was then heated to 100°C and stirred overnight. The resulting mixture was concentrated *in vacuo*. Water was added and the aqueous layer was extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a white solid (320 mg, 36 %).

15

LC-MS : m/z 405.0 $[\text{M}+\text{H}]^+$

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.74 (dd, $J=7.1, 2.3$ Hz, 1H), 7.66 - 7.55 (m, 1H), 7.54 - 7.43 (m, 1H), 7.44 - 7.31 (m, 4H), 7.24 (dd, $J=9.7, 8.6$ Hz, 1H), 7.22 - 7.07 (m, 1H), 6.82 (ddd, $J=11.6, 9.4, 2.1$ Hz, 1H), 6.32 (td, $J=9.1, 4.7$ Hz, 1H), 6.03 - 5.80 (m, 1H), 4.53 (d, $J=7.1$ Hz, 2H), 4.39 (s, 2H)

20

Example 43 - 2-[2,4-Difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]-N-ethyl-acetamide (II(m)), prepared via scheme 7

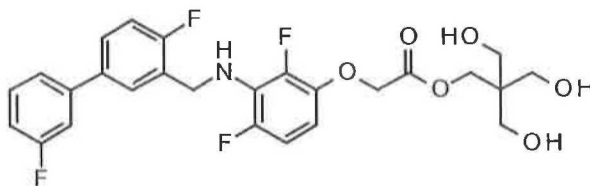


A solution of isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate (II(d)) (0.2 g, 0.45 mmol, 1.0 eq) in ethylamine (6 mL, 60-70% aqueous solution) was stirred at 100°C overnight in a sealed tube. The reaction mixture was then cooled to room temperature and poured into water. The mixture was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 1:20 to 1:4, v/v) to give the title compound as a white solid (0.15 g, 80 %).

LC-MS : m/z 433.1 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.98 (t, J=5.2 Hz, 1H), 7.74 (dd, J=7.2, 2.2 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.55 - 7.44 (m, 1H), 7.43 - 7.32 (m, 2H), 7.24 (dd, J=9.7, 8.6 Hz, 1H), 7.22 - 7.08 (m, 1H), 6.82 (ddd, J=11.6, 9.3, 2.0 Hz, 1H), 6.33 (td, J=9.1, 4.6 Hz, 1H), 5.88 (t, J=6.9 Hz, 1H), 4.53 (d, J=7.1 Hz, 2H), 4.40 (s, 2H), 3.19 - 2.89 (m, 2H), 1.00 (t, J=7.2 Hz, 3H)

Example 44 - [3-Hydroxy-2,2-bis(hydroxymethyl)propyl] 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(n)), prepared via scheme 6

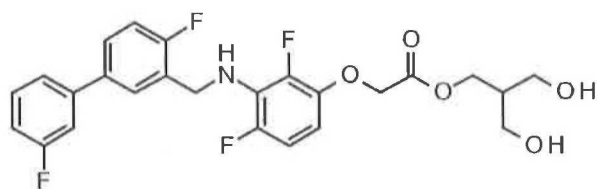


To a stirred solution of 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(b)) (700 mg, 1.73 mmol, 1.0 eq) in DMF (30 mL) was added pentaerythritol (470 mg, 3.45 mmol, 2.0 eq), TEA (699 mg, 6.91 mmol, 4.0 eq) and HATU (985 mg, 2.60 mmol, 1.5 eq). The resulting mixture was stirred at room temperature overnight under N₂. The reaction was diluted with water then extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by column chromatography (DCM:MeOH=100:1-20:1) to give the title compound as a colourless oil (370 mg, 41 %).

LC-MS : m/z 524.1 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.74 (dd, *J*=7.3, 2.3 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.54 - 7.45 (m, 1H), 7.43 - 7.34 (m, 2H), 7.24 (dd, *J*=9.8, 8.6 Hz, 1H), 7.22 - 7.13 (m, 1H), 6.80 (ddd, *J*=11.6, 9.3, 2.1 Hz, 1H), 6.36 (td, *J*=9.1, 4.6 Hz, 1H), 5.96 - 5.81 (m, 1H), 4.73 (s, 2H), 4.52 (d, *J*=7.1 Hz, 2H), 4.44 - 4.19 (m, 3H), 4.01 (s, 2H), 3.32 (d, *J*=5.6 Hz, 6H)

Example 45 - [3-Hydroxy-2-(hydroxymethyl)propyl] 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl) phenyl]methylamino]phenoxy]acetate (II(o)), prepared via scheme



To a stirred solution of triethyl methanetricarboxylate (700 mg, 1.73 mmol, 1.0 eq) in DMF (40 mL) was added 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(b)) (367 mg, 1.73 mmol, 1.0 eq), TEA (699 mg, 6.91 mmol, 4.0 eq) and HATU (985 mg, 2.60 mmol, 1.5 eq). The resulting mixture was stirred at room temperature overnight under N₂. The reaction was diluted with water then extracted with EtOAc. The combined organic extracts were washed with brine, dried

(Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (DCM:MeOH=100:1-20:1) to give the title compound as a colourless oil (475 mg, 49 %).

5 LC-MS : m/z 494.1 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.74 (dd, *J*=7.2, 2.3 Hz, 1H), 7.64 - 7.55 (m, 1H), 7.54 - 7.44 (m, 1H), 7.43 - 7.35 (m, 2H), 7.23 (dd, *J*=9.8, 8.6 Hz, 1H), 7.22 - 7.12 (m, 1H), 6.80 (ddd, *J*=11.6, 9.3, 2.1 Hz, 1H), 6.36 (td, *J*=9.1, 4.6 Hz, 1H), 6.07 - 5.80 (m, 1H),
10 4.75 (s, 2H), 4.54 (d, *J*=1.0 Hz, 2H), 4.50 (t, *J*=1.0 Hz, 2H), 4.11 (d, *J*=6.1 Hz, 2H), 3.50 - 3.29 (m, 4H), 1.82 (spt, *J*=6.0 Hz, 1H)

Example 46 - 1-Acetoxyethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(p)), prepared via scheme 6

15



1-bromoethyl acetate (700 mg, 1.7 mmol, 1.0 eq) was dissolved in DMA (10 mL) at room temperature. K₂CO₃ (120 mg, 0.9 mmol, 0.5 mmol) was added and the mixture stirred for 90 min at 30°C under a nitrogen atmosphere. The reaction was cooled to -5°C and 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(b))
20 (350 mg, 2.1 mmol, 1.2 eq) was added. The reaction was warmed to 30°C over 30 min and stirred for a further 30 min. The reaction was quenched by addition of water and extracted with ethyl acetate. The organic extract was dried (Na₂SO₄), filtered and evaporated *in vacuo* and the residue obtained purified by column chromatography
25 (petroleum ether: EtOAc, 10:1) to give the title compound as a colourless oil (200 mg, 23 %).

LC-MS : m/z 492.1 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.74 (dd, *J*=7.2, 2.3 Hz, 1H), 7.65 - 7.55 (m, 1H), 7.54 - 7.45 (m, 1H), 7.41 (d, *J*=1.7 Hz, 1H), 7.39 - 7.29 (m, 1H), 7.23 (dd, *J*=9.9, 8.6 Hz, 1H), 7.22 - 7.12 (m, 1H), 6.88 - 6.74 (m, 2H), 6.35 (td, *J*=9.1, 4.6 Hz, 1H), 4.79 (s, 2H), 4.53 (br. s., 2H), 2.01 (s, 3H), 1.39 (d, *J*=5.4 Hz, 3H)

Example 47 - Isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino] phenoxy]acetate (II(q)), prepared via scheme 3



To a solution of 2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino] phenol (see example 16) (1.0 g, 2.78 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃ (1.36 g, 3.34 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred for 1h, then isopropyl 2-bromoacetate (624 mg, 3.34 mmol, 1.2 eq) was added and the reaction mixture was stirred for 1h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄) and evaporated *in vacuo*. The residue obtained was purified by column chromatography, (EtOAc:petroleum ether 0:1 to 1:20) to give the title compound as a colourless oil (0.8 g, 62 %).

LC-MS : m/z 460.0 [M+H]⁺

¹H NMR (300 MHz, DMSO-d₆) δ 7.60 - 7.39 (m, 3H), 7.31 - 7.12 (m, 2H), 7.11 - 7.00 (m, 1H), 6.89 (s, 1H), 6.78 (ddd, *J*=11.7, 9.3, 2.1 Hz, 1H), 6.29 (td, *J*=9.1, 4.6 Hz, 1H), 6.08 - 5.86 (m, 1H), 4.93 (spt, *J*=6.3 Hz, 1H), 4.69 (s, 2H), 4.42 (d, *J*=7.2 Hz, 2H), 3.78 (s, 3H), 1.15 (d, *J*=6.2 Hz, 6H)

Example 48 - Isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino] phenoxy]acetate (II(r))



- 5 To a solution of isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino] phenoxy]acetate (II(q)) (700 mg, 1.52 mmol, 1.0 eq) in DCM (20 mL) at 0°C was added AlCl₃ (1.2 g, 9.12 mmol, 6.0 eq) and ethanethiol (566 mg, 9.12 mmol, 6.0 eq) under N₂. The reaction mixture was stirred at room temperature for 3h and the resulting mixture was poured into aqueous NaHCO₃ and extracted with EtOAc. The
- 10 organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (EtOAc:petroleum ether, 0:1 to 1:20) to give the title compound as a yellow oil (500 mg, 74 %).

LC-MS : m/z 446.0 [M+H]⁺

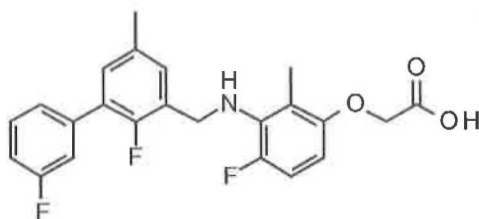
15

¹H NMR (300 MHz, DMSO-d₆) δ 9.59 (d, *J*=1.3 Hz, 1H), 7.67 - 7.47 (m, 1H), 7.46 - 7.34 (m, 2H), 7.31 - 7.17 (m, 1H), 7.11 (s, 1H), 6.92 (d, *J*=1.5 Hz, 1H), 6.89 - 6.75 (m, 2H), 6.34 (td, *J*=9.0, 4.6 Hz, 1H), 6.01 (br. s., 1H), 5.01 (spt, *J*=1.0 Hz, 1H), 4.75 (s, 2H), 4.44 (d, *J*=6.8 Hz, 2H), 1.22 (d, *J*=6.2 Hz, 6H)

20

Example 49 – compound I(ai) synthesized according to scheme 3

2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ai))



2-Fluoro-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-3-(3-fluorophenyl)-5-methyl-benzamide

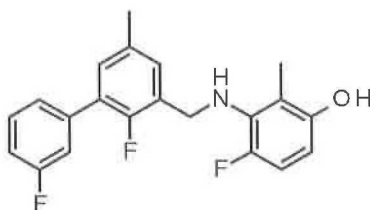


5

- To a solution of 2-fluoro-3-(3-fluorophenyl)-5-methyl-benzoic acid (intermediate III(e)) (580 mg, 2.3 mmol, 1.1 eq) in CH₂Cl₂ (10 mL) at 0 °C, was added oxalyl chloride (812 mg, 6.4 mmol, 3 eq) dropwise. DMF (10 drops) was added and the mixture was stirred at room temperature for 3h. The organic solvent and excess reagent were removed under reduced pressure. The residue that remained was dissolved in THF (10 mL) and added dropwise to a mixture of 3-amino-4-fluoro-2-methylphenol (intermediate X(e)) (300 mg, 2.1 mmol, 1 eq) and K₂CO₃ (1.47 g, 10.6 mmol, 5 eq) in THF (20 mL) at 0 °C. After addition was completed, the reaction was allowed to warm to room temperature and stirred for 3h. The resulting mixture was poured into water and extracted with EtOAc.
- The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 100:1 to 10:1) to give the title compound as a white solid (200 mg, 25 %).

LC-MS: m/z 372.1 [M+H]⁺ 394.2 [M+Na]⁺

4-Fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenol



To a stirred solution of 2-fluoro-N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-3-(3-fluorophenyl)-5-methyl-benzamide (200 mg, 0.54 mmol, 1.0 eq) in THF (5 mL) under nitrogen was added a solution of BH_3 (1M in THF, 3.0 mL, 3.0 mmol, 5.6 eq) dropwise over 5 min. the mixture was heated at 60 °C overnight, then the reaction cooled to room temperature and quenched by addition of aqueous NH_4Cl . The reaction was further diluted with water and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 100:1 to 25:1) to give the title compound as a colorless oil (180 mg, 93 %).

LC-MS: m/z 358.1 $[\text{M}+\text{H}]^+$

Isopropyl 2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl] methylamino]-2-methyl-phenoxy]acetate (II(am))



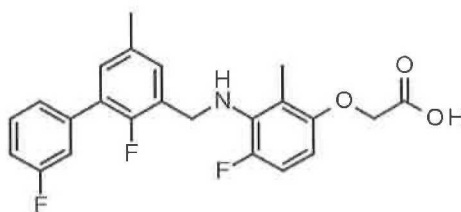
To a solution of 4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl] methylamino]-2-methyl-phenol (180 mg, 0.5 mmol, 1.0 eq) in DMF (3 mL) was added Cs_2CO_3 (246 mg, 0.75 mmol, 1.5 eq). The reaction was stirred for 30 min at room temperature then isopropyl 2-bromoacetate (99 mg, 0.55 mmol, 1.1 eq) was added. The reaction was stirred a further 1h then diluted with water and extracted with EtOAc. The organic extract

was washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 1:0 to 25:1) to give the title compound as a colorless oil (100 mg, 43 %).

5 LC-MS: m/z 458.2 [M+H]⁺ 480.2 [M+Na]⁺

¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.35 (m, 1H), 7.29 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.15 – 7.09 (m, 2H), 7.09 – 7.02 (m, 1H), 6.78 (dd, *J* = 11.1, 9.1 Hz, 1H), 6.25 (dd, *J* = 8.9, 3.8 Hz, 1H), 5.17 – 5.07 (m, 1H), 4.53 (s, 2H), 4.40 (s, 2H), 2.32 (s, 3H), 2.21 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 6H).

2-[4-Fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(ai))



15 To a stirred solution of isopropyl 2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (100 mg, 0.22 mmol, 1.0 eq) in a mixture of THF (10 mL) and H₂O (10 mL) was added NaOH (17 mg, 0.44 mmol, 2.0 eq). The reaction was stirred for 2h then acidified to pH 4 by addition of 1M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed
20 with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂:MeOH, 20:1) to give a partially purified material. Further purification by preparative HPLC provided the title compound as yellow solid (9 mg, 10 %).

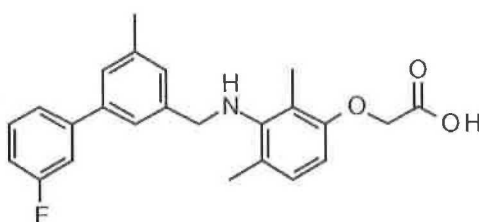
25 LC-MS: m/z 416.1 [M+H]⁺ 430.2 [M+Na]⁺

¹H NMR (400 MHz, MeOD) δ 7.47 – 7.40 (m, 1H), 7.28 (dd, J = 7.8, 0.9 Hz, 1H), 7.22 – 7.13 (m, 3H), 7.13 – 7.05 (m, 1H), 6.84 (dd, J = 11.2, 9.1 Hz, 1H), 6.47 (dd, J = 9.0, 3.9 Hz, 1H), 4.62 (s, 2H), 4.45 (s, 2H), 2.30 (s, 3H), 2.19 (s, 3H).

5

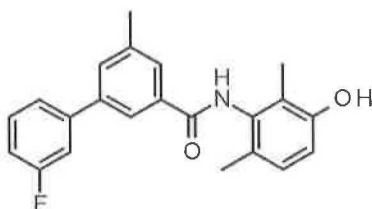
Example 50 – compound I(aj) synthesized according to scheme 3

2-[3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(aj))



10

3-(3-Fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-5-methyl-benzamide



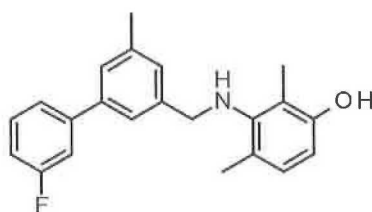
To a solution of 3-(3-fluorophenyl)-5-methyl-benzoic acid (300 mg, 1.30 mmol, 1.1 eq) (III(q)) in CH₂Cl₂ (10 mL) was added (COCl)₂ (610 mg, 4.81 mmol, 3.3 eq) and DMF (5 drops). The reaction mixture was stirred at room temperature for 2h. The resulting mixture was concentrated under reduced pressure to remove the solvent and excess reagent. The residue obtained was dissolved in THF (10 mL) and added dropwise to a mixture of 3-amino-2,4-dimethylphenol (intermediate X(c)) (163 mg, 1.18 mmol, 1.0 eq) and NaHCO₃ (612 mg, 7.30 mmol, 5.0 eq) in THF (20 mL) at 0 °C. After addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for 1h. The resulting mixture was poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered, and evaporated *in vacuo*. The crude product obtained was purified by column

chromatography (CH₂Cl₂: MeOH, 500:1 to 300:1) to give the title compound as a white solid (290 mg, 57 %).

LC-MS: m/z 350.2 [M+H]⁺ 372.1 [M+Na]⁺

5

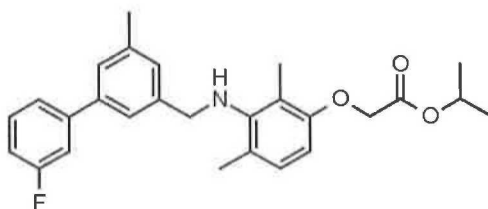
3-[[3-(3-Fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenol



To a solution of 3-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-5-methyl-benzamide (288 mg, 0.82 mmol, 1.0 eq) in THF (10 mL) under N₂ was added a solution
10 of BH₃ (1M in THF, 5.0 mL, 5.0 mmol, 6.0 eq) at 0 °C. The reaction mixture was heated at 60 °C overnight. After cooling, the resulting mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 50:1 to 20:1) to give the title compound as a
15 colorless oil (168 mg, 61 %).

LC-MS: m/z 336.2 [M+H]⁺ 358.1 [M+Na]⁺

Isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-
20 phenoxy] acetate (II(an))



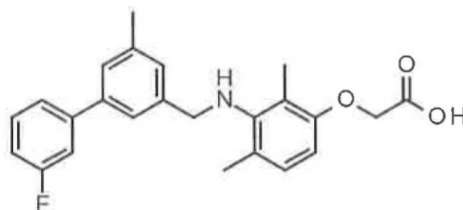
To a solution of 3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenol (168 mg, 0.50 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃ (245 mg, 0.75

mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 30 min then isopropyl bromoacetate (109 mg, 0.6 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for a further 1h then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried
5 (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 40:1 to 30:1) to give the title compound as a colorless oil (151 mg, 69 %).

LC-MS: m/z 436.2 [M+H]⁺ 458.2 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.53 – 7.34 (m, 5H), 7.21 – 7.13 (m, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 5.02 – 4.90 (m, 1H), 4.64 (s, 2H), 4.30 (br t, *J* = 7.4 Hz, 1H), 4.09 (d, *J* = 6.7 Hz, 2H), 2.34 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 6H).
15

2-[3-[[3-(3-Fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid (1*ajj*)



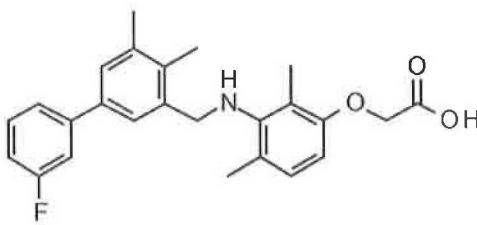
To a solution of isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (114 mg, 0.26 mmol, 1.0 eq) in THF (10 mL) at 0 °C was added LiOH (2M aqueous solution, 4 mL, 8 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The THF was removed under reduced pressure and the aqueous solution that remained was diluted with water and adjusted to
25 pH 4-6 by the addition of dilute HCl. The solid precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give title compound as a yellow solid (70 mg, 68 %).

LC-MS : m/z 394.1 $[M+H]^+$

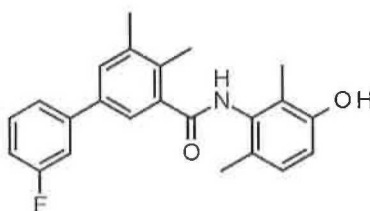
1H NMR (400 MHz, DMSO) δ 7.52 – 7.35 (m, 5H), 7.21 – 7.12 (m, 2H), 6.80 (d, J = 8.3 Hz, 1H), 6.32 (d, J = 8.3 Hz, 1H), 4.35 (s, 2H), 4.07 (s, 2H), 2.34 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H).

Example 51 – compound I(ak) synthesized according to scheme 3

10 **2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(ak))**



5-(3-Fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-2,3-dimethyl-benzamide



15 To a solution of 5-(3-fluorophenyl)-2,3-dimethyl-benzoic acid (intermediate III(m)) (0.4 g, 1.6 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) was added $(COCl)_2$ (0.62 g, 4.9 mmol, 3.0 eq) and DMF (0.01 mL). The reaction mixture was stirred at room temperature for 1.5 h, then the solvent and excess reagent were removed under reduced pressure. The residue obtained was dissolved in THF (20 mL) and added dropwise to a mixture of 3-amino-2,4-dimethylphenol (intermediate X(c)) (260 mg, 1.9 mmol, 1.2 eq) and K_2CO_3 (0.9 g, 6.5 mmol, 4.0 eq) in THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1h, then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and

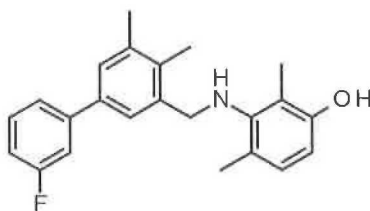
20

evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 15:1 to 3:1) to give the title compound as a colorless oil (300 mg, 51 %)

LC-MS: m/z 363.2 $[M+H]^+$

5

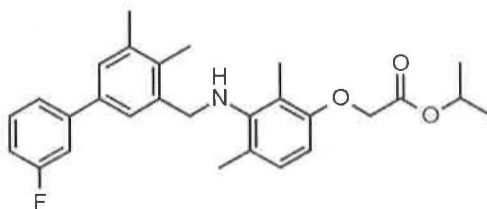
3-[[5-(3-Fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenol



To a solution of 5-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-2,3-dimethyl-benzamide (300 mg, 0.82 mmol, 1.0 eq) in THF (10 mL) under N_2 was added a solution
10 of BH_3 (1M in THF, 4.1 mL, 4.1 mmol, 5.0 eq) dropwise at 0 °C. The reaction mixture was heated at 60 °C overnight. After cooling, the reaction was quenched by addition of water and the aqueous layer extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 30:1 to 20:1) to give the
15 title compound as a colorless oil (90 mg, 32 %).

LC-MS: m/z 350.2 $[M+H]^+$

Isopropyl 2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-
20 phenoxy] acetate (II(ao))



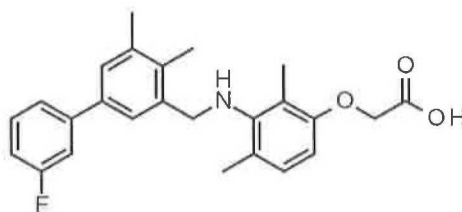
To a solution 3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenol (87.5 mg, 0.25 mmol, 1.0 eq) in DMF (10 mL) was added Cs_2CO_3 (0.16 g, 0.51

mmol, 2.0 eq). The reaction mixture was stirred at room temperature for 30 min then isopropyl bromoacetate (56 mg, 0.3 mmol, 1.2 eq) was added and the reaction stirred for a further 1h. The resulting mixture was poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated
5 *in vacuo*. The residue was purified by column chromatography (petroleum ether: EtOAc, 100:1 to 30:1) to give the title compound as a colorless oil (80 mg, 69 %).

LC-MS: m/z 450.2 $[\text{M}+\text{H}]^+$

10 ^1H NMR (400 MHz, DMSO) δ 7.58 (d, $J = 1.5$ Hz, 1H), 7.52 – 7.41 (m, 3H), 7.20 – 7.09 (m, 1H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.39 (d, $J = 8.3$ Hz, 1H), 5.06 – 4.89 (m, 1H), 4.65 (s, 2H), 4.08 (d, $J = 5.7$ Hz, 2H), 3.99 (br s, 1H), 2.32 (s, 3H), 2.20 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 1.20 (d, $J = 6.3$ Hz, 6H).

15 2-[3-[[5-(3-Fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(ak))



To a solution of isopropyl 2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl] methylamino]-2,4-dimethyl-phenoxy]acetate (80 mg, 0.17 mmol, 1.0 eq) in a mixture of THF (5 mL)
20 and MeOH (5 mL) was added NaOH (2M aqueous solution, 3 mL, 6.0 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2h. The organic solvent was removed *in vacuo* and the remaining aqueous solution diluted with water and acidified to pH 4-6 with diluted HCl. The solid precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give the title compound
25 as a white solid (20 mg, 27 %).

LC-MS: m/z 406.2 $[\text{M}-\text{H}]^-$

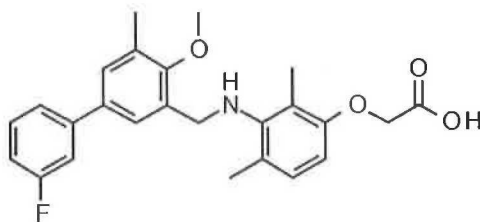
¹H NMR (400 MHz, MeOD) δ 7.45 – 7.36 (m, 2H), 7.36 – 7.31 (m, 2H), 7.26 – 7.20 (m, 1H), 7.06 – 6.99 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 4.62 (s, 2H), 4.30 (s, 2H), 2.35 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H).

5

Example 52 – compound I(al) synthesized according to scheme 3

2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(al))

10



5-(3-Fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-2-methoxy-3-methyl- benzamide

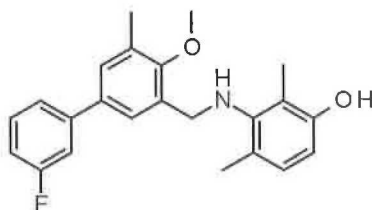


To a solution of 5-(3-fluorophenyl)-2-methoxy-3-methyl-benzoic acid (intermediate
15 III(k)) (400 mg, 1.5 mmol, 1.1eq) in CH₂Cl₂ (8 mL) was added (COCl)₂ (585 mg, 4.6
mmol, 3.3 eq) and DMF (3 drops). The reaction mixture was stirred at room temperature
for 1h. The resulting mixture was concentrated under reduced pressure to remove the
solvent and excess reagent and the residue obtained was dissolved in THF (8 mL) and
added dropwise to a solution of 3-amino-2,4-dimethylphenol (intermediate X(c)) (192 mg,
20 1.4 mmol, 1.0 eq) and NaHCO₃ (587 mg, 7.0 mmol, 5.0 eq) in THF (6 mL) at 0 °C. After
the addition was complete the reaction mixture was allowed to warm to room temperature
and was stirred for 2h. The resulting mixture was poured into water and extracted with
EtOAc. The combined organic extracts were washed with water and brine, dried

(Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 10:1 to 5:1, then DCM: MeOH, 20:1) to give the title compound as a yellow solid (436 mg 82 %).

5 LC-MS: m/z 380.2 [M+H]⁺

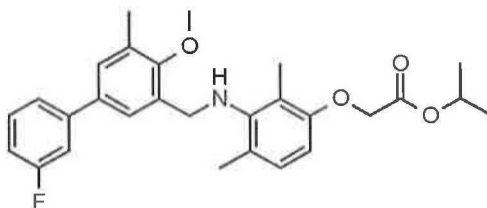
3-[[5-(3-Fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenol



To a solution of 5-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-2-methoxy-3-methyl-benzamide (270 mg, 0.71 mmol, 1.0 eq) in THF (5 mL) at 0°C under N₂ was added a solution of BH₃ (1M in THF, 1.07 mL, 1.07 mmol, 1.5 eq) dropwise. The reaction mixture was heated at 60 °C for 4h, then cooled and quenched with water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc 30:1 to 20:1) to give the title compound as a yellow oil (115 mg, 44 %)

LC-MS: m/z 366.2 [M+H]⁺

20 Isopropyl 2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (II(ap))

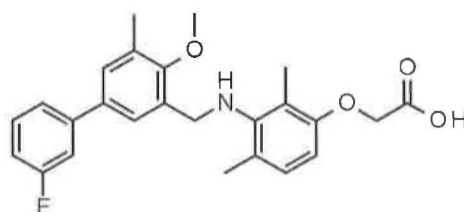


To a solution of 3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenol (115 mg, 0.31 mmol, 1.0 eq) in acetone (4 mL) was added Cs₂CO₃ (154 mg, 0.47 mmol, 1.5 eq). The reaction mixture was stirred for 30 min at room temperature then isopropyl bromoacetate (68.4 mg, 0.38 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for a further 2h then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc 30:1 to 20:1) to give the title compound as a colorless oil (155 mg, 100 %).

LC-MS: m/z 466.2 [M+H]⁺ 488.2 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.59 (d, *J* = 2.0 Hz, 1H), 7.52 – 7.37 (m, 4H), 7.20 – 7.10 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.65 (s, 2H), 4.21 – 4.14 (m, 1H), 4.11 (d, *J* = 6.5 Hz, 2H), 3.68 (s, 3H), 2.31 (s, 3H), 2.15 (s, 6H), 1.19 (d, *J* = 6.2 Hz, 6H).

2-[3-[[5-(3-Fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(al))



To a solution of isopropyl 2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (155 mg, 0.33 mmol, 1.0 eq) in THF (4 mL) was added LiOH (2M aqueous solution, 4 mL, 8 mmol). The reaction mixture was stirred at room temperature for 2h then the THF was removed under reduced pressure. The aqueous solution that remained was diluted with water and the pH adjusted to 4-6 with diluted HCl. The solid precipitate that formed was collected by filtration, washed with

water and dried *in vacuo* to give a partially purified product. This material was further purified by preparative HPLC to give the title compound as a yellow solid (30 mg, 21 %).

LC-MS: m/z 424.2 $[M+H]^+$

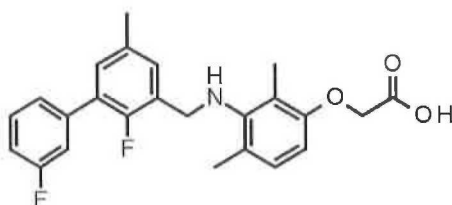
5

^1H NMR (400 MHz, DMSO) δ 7.66 (s, 1H), 7.55 (s, 1H), 7.54 – 7.41 (m, 3H), 7.17 (t, J = 8.3 Hz, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 4.64 (s, 2H), 4.22 (s, 2H), 3.72 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H).

10

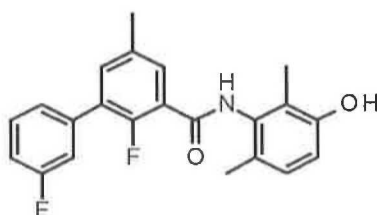
Example 53 – compound I(am) synthesized according to scheme 3

2-[3-[[2-Fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(am))



15

2-Fluoro-3-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-5-methyl-benzamide



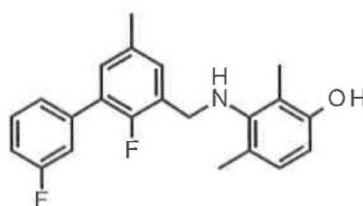
To a solution of 2-fluoro-3-(3-fluorophenyl)-5-methyl-benzoic acid (intermediate III(e))
20 (597 mg, 2.4 mmol, 1.1 eq) in CH_2Cl_2 (15 mL) was added $(\text{COCl})_2$ (916 mg, 7.2 mmol, 3.3 eq) and DMF (5 drops). The reaction mixture was stirred at room temperature for 2 h, then the solvent and excess reagent were removed under reduced pressure. The residue obtained was dissolved in THF (20 mL) and added dropwise to a mixture of 3-amino-2,4-

dimethylphenol (intermediate X(c)) (300 mg, 2.2 mmol, 1.0 eq) and NaHCO₃ (920 mg, 10.9 mmol, 5.0 eq) in THF (20 mL) at 0 °C. After the addition was completed, the reaction was allowed to warm to room temperature and stirred for a further 1 h. The reaction was then poured into water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered, and evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂:MeOH, 500:1 to 300:1) to give the title compound as a white solid (588 mg, 73 %).

LC-MS: m/z 368.1 [M+H]⁺

10

3-[[2-Fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenol



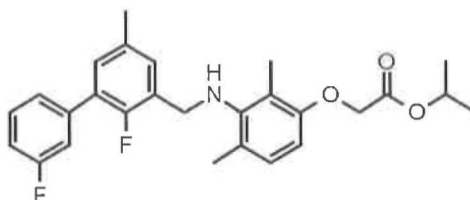
To a solution of 2-fluoro-3-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-5-methyl-benzamide (588 mg, 1.6 mmol, 1.0 eq) in THF (10 mL) at 0 °C under N₂ was added a solution of BH₃ (1M in THF, 9.6 mL, 9.6 mmol, 6.0 eq) dropwise. The reaction mixture was heated at 60 °C overnight. The reaction was cooled to room temperature, quenched with H₂O and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 50:1 to 20:1) to give the title compound as white solid (220 mg, 39 %).

20

LC-MS: m/z 354.1 [M+H]⁺

Isopropyl 2-[3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (II(bb))

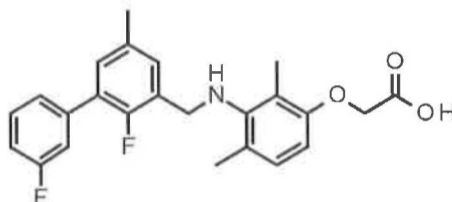
25



To a solution of 3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenol (114 mg, 0.32 mmol, 1.0 eq) in DMF (10 mL) was added Cs₂CO₃ (158 mg, 0.48 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 30 min
5 the isopropyl bromoacetate (70 mg, 0.39 mmol, 1.2 eq) was added. The reaction mixture was stirred a further 1 h then poured into water and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 30:1 to 20:1) to give the title compound as colorless oil (108 mg, 76 %).

¹H NMR (400 MHz, DMSO) δ 7.51 (td, *J* = 8.1, 6.4 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.27 – 7.19 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 4.96 (hept, *J* = 6.3 Hz, 1H), 4.65 (s, 2H), 4.17 (br t, *J* = 7.5 Hz, 1H), 4.09 (d, *J* = 6.3 Hz, 2H), 2.31 (s, 3H), 2.14 (br s, 6H), 1.19 (d, *J* = 6.3 Hz, 6H).

2-[3-[[2-Fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid



To a solution of isopropyl 2-[3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (80 mg, 0.18 mmol, 1.0 eq) in THF (8 mL) at 0°C was added LiOH (2M aqueous solution, 4 mL, 8.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The THF was removed

and the remaining aqueous solution was diluted with water. The pH was adjusted to pH 4-6 by addition of diluted HCl. The solid precipitate that formed was collected by filtration, washed with water and dried *in vacuo* to give target compound as a yellow solid (30 mg, 41 %).

5

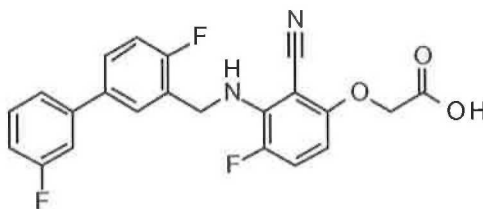
LC-MS: m/z 412.1 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 7.57 – 7.48 (m, 1H), 7.44 – 7.35 (m, 2H), 7.35 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 7.00 (d, $J = 8.7$ Hz, 1H), 6.72 – 6.62 (m, 1H), 4.67 (s, 2H), 4.31 (s, 2H), 2.34 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H).

10

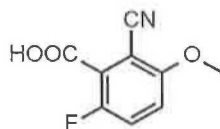
Example 54 – compound I(an) synthesized according to scheme 5

2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(an))



15

2-Cyano-6-fluoro-3-methoxy-benzoic acid



20

To a solution of N,N-diisopropylamine (5.6 mL, 39.7 mmol, 1.2 eq) in THF (100 mL) at -78 °C was added n-BuLi (2.5M in hexanes, 15.9 mL, 39.7 mmol, 1.2 eq) dropwise. The mixture was stirred for 30 min at -78 °C, then a solution of 5-fluoro-2-methoxybenzonitrile (5.0 g, 33.1 mmol, 1.0 eq) in THF (20 mL) was added. The resulting mixture was stirred for a further 1.5h at -78 °C then CO₂ was bubbled into the mixture for 30 min. The reaction was quenched by addition of saturated aqueous NH₄Cl and water and the resulting solution acidified to pH 4 with 3M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na₂SO₄)

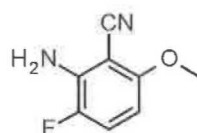
25

filtered and evaporated *in vacuo*. The residue obtained was triturated with 2-methoxy-2-methylpropane (20 mL) to give title compound as an off-white solid (3.5 g, 54 %).

LC-MS: m/z 196.1 $[M+H]^+$ 218.0 $[M+Na]^+$

5

2-Amino-3-fluoro-6-methoxy-benzonitrile



To a stirred solution of 2-cyano-6-fluoro-3-methoxy-benzoic acid (2 g, 10.3 mmol, 1.0 eq) in THF (40 mL) were added Et_3N (3.6 mL, 25.8 mmol, 2.5 eq) and DPPA (2.97 g, 10.8 mmol, 1.05 eq). The reaction was stirred at room temperature 3h then water (10 mL) was added and the mixture was heated at reflux for 2h. The THF was removed *in vacuo* and the aqueous solution diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 5:1) to give the title compound as an off-white solid (900 mg, 53 %).

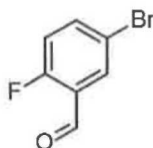
15

LC-MS: m/z 167.0 $[M+H]^+$

1H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, $J = 10.7, 9.0$ Hz, 1H), 6.10 (dd, $J = 9.0, 3.3$ Hz, 1H), 4.49 (br s, 2H), 3.84 (s, 3H).

20

5-Bromo-2-fluoro-benzaldehyde



To a solution of N,N -diisopropylamine (8.87 mL, 62.9 mmol, 1.1 eq) in dry THF (80 mL) at $-78^\circ C$ was added $n-BuLi$ (2.5M in hexane, 27.5 mL, 68.5 mmol, 1.2 eq). The resulting mixture was stirred for 30 min then 1-bromo-4-fluoro-benzene (10 g, 57.1 mmol, 1 eq) in

25

dry THF (20 mL) was added. The resultant mixture was stirred at -78 °C for 2h then methyl formate (3.8 g, 62.9 mmol, 1.1 eq) was added and the reaction was stirred a further 30 min at -78 °C. The reaction was allowed to warm to room temperature and stirred a further 1h. The reaction was then diluted with water (100 mL), and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 20:1) to give the title compound as a yellow oil (6.25 g, 54 %).

¹H NMR (400 MHz, CDCl₃) δ 10.29 (s, 1H), 7.97 (dd, *J* = 6.1, 2.6 Hz, 1H), 7.70 (ddd, *J* = 8.8, 4.7, 2.6 Hz, 1H), 7.09 (dd, *J* = 9.6, 8.9 Hz, 1H).

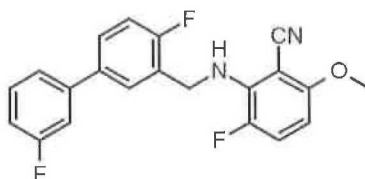
2-Fluoro-5-(3-fluorophenyl)benzaldehyde



To a stirred mixture of 5-bromo-2-fluoro-benzaldehyde (3.0 g, 14.8 mmol, 1 eq), (3-fluorophenyl)boronic acid (2.48 g, 17.7 mmol, 1.2 eq) and K₂CO₃ (4.13 g, 44.4 mmol, 3 eq) in a mixture of EtOH (30 mL), DMF (30 mL) and water (10 mL) under N₂ was added Pd(PPh₃)₄ (1.71 g, 1.48 mmol, 0.1 eq). The reaction was heated at 100 °C for 3h, then filtered through Celite. The filtrate was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 300:1) to give the title compound as a yellow oil (1.1 g, 34 %).

¹H NMR (400 MHz, CDCl₃) δ 10.38 (s, 1H), 8.03 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.77 (ddd, *J* = 8.6, 5.0, 2.6 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.33 – 7.29 (m, 1H), 7.25 – 7.20 (m, 2H), 7.05 (tdd, *J* = 8.4, 2.5, 1.0 Hz, 1H).

3-Fluoro-2-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-6-methoxy-benzonitrile

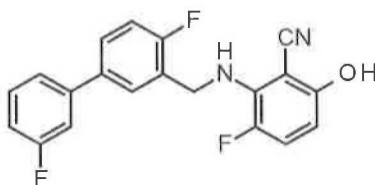


To a solution of 2-fluoro-5-(3-fluorophenyl)benzaldehyde (505 mg, 2.32 mmol, 1.2 eq) and 2-amino-3-fluoro-6-methoxy-benzonitrile (320 mg, 1.93 mmol, 1 eq) in toluene (30 mL) was added 4Å molecular sieves (10 g). The mixture was heated at reflux for 4 h, then filtered to remove the molecular sieves. The filtrate was concentrated and the residue obtained was dissolved in methanol (30 mL). NaBH₄ (109.6 mg, 2.9 mmol, 1.5 eq) was added and the reaction stirred for 2 h at room temperature. The reaction was quenched by addition of water, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 50:1) to give the title compound as an off-white solid (610 mg, 72 %).

LC-MS: m/z 368.9 [M+H]⁺, 390.9 [M+Na]⁺

¹H NMR (400 MHz, CDCl₃) δ 7.57 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.46 (ddd, *J* = 8.3, 4.9, 2.4 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.32 – 7.27 (m, 1H), 7.23 – 7.18 (m, 1H), 7.14 (dd, *J* = 9.6, 8.6 Hz, 1H), 7.10 – 7.00 (m, 2H), 6.15 (dd, *J* = 9.0, 3.2 Hz, 1H), 4.82 (d, *J* = 6.6 Hz, 2H), 4.69 (br s, 1H), 3.84 (s, 3H).

3-Fluoro-2-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-6-hydroxy-benzonitrile



To a solution of 3-fluoro-2-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-6-methoxy-benzonitrile (560 mg, 1.5 mmol, 1 eq) in CH₂Cl₂ (30 mL) was added BBr₃ (1.14 g, 4.5 mmol, 3 eq) and the reaction was stirred overnight. The mixture was then poured

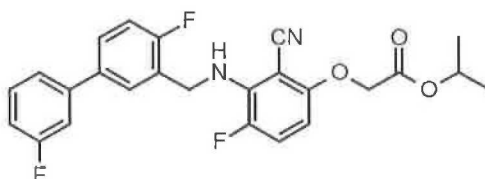
into water, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 10:1 to 5:1) to give the title compound as a yellow oil (360 mg, 68 %).

5

LC-MS: m/z 376.9 [M+Na]⁺

Isopropyl 2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (II(ar))

10



To a solution of 3-fluoro-2-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-6-hydroxy-benzonitrile (360 mg, 1.0 mmol, 1 eq) in acetone was added Cs₂CO₃ (651.6 mg, 2.0 mmol, 2 eq). The reaction was stirred for 30 min at room temperature then isopropyl 2-bromoacetate (221 mg, 1.2 mmol, 1.2 eq) was added. The reaction was stirred for a further 2h, then quenched with water and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 50:1 to 10:1) to give the title compound as a colorless oil (270 mg, 59 %).

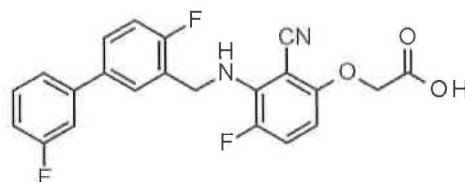
20

LC-MS: m/z 455.1 [M+H]⁺ 477.1 [M+Na]⁺

¹H NMR (400 MHz, CDCl₃) δ 7.58 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.46 (ddd, *J* = 8.5, 4.9, 2.4 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.32 – 7.27 (m, 1H), 7.24 – 7.18 (m, 1H), 7.14 (dd, *J* = 9.6, 8.6 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.02 (dd, *J* = 9.0, 3.1 Hz, 1H), 5.15 – 5.04 (m, 1H), 4.83 (d, *J* = 4.8 Hz, 2H), 4.73 (br s, 1H), 4.63 (s, 2H), 1.24 (d, *J* = 6.3 Hz, 6H).

25

2-[2-Cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid (I(an))

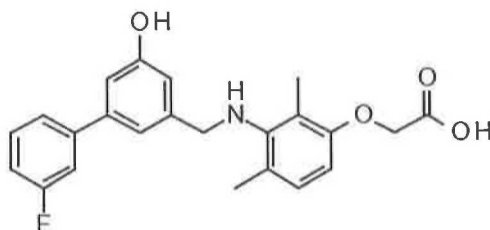


To a solution of isopropyl 2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate (220 mg, 0.48 mmol, 1 eq) in a mixture of THF (10 mL) and water (10 mL) was added LiOH (20 mg, 0.96 mmol, 2 eq). The reaction was stirred for 3h then the THF removed *in vacuo*. The aqueous solution that remained was acidified to pH 4 with 3M HCl and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was triturated with a mixture of 2-methoxy-2-methylpropane (5 mL) and petroleum ether (20 mL) to give the desired product as an off-white solid (110 mg, 56 %).

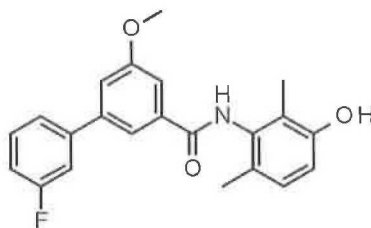
LC-MS: m/z 413.1 [M+H]⁺ 435.1 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.69 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.54 – 7.45 (m, 1H), 7.44 – 7.38 (m, 2H), 7.31 – 7.22 (m, 2H), 7.22 – 7.15 (m, 1H), 6.62 (td, *J* = 6.7, 2.7 Hz, 1H), 6.21 (dd, *J* = 9.1, 3.0 Hz, 1H), 4.83 – 4.68 (m, 4H).

Example 55 – compound I(ao) synthesized according to scheme 3
2-[3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethylphenoxy]acetic acid (I(ao))



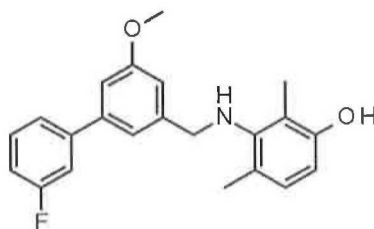
3-(3-Fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-5-methoxy-benzamide



To a solution of 3-(3-(3-fluorophenyl)-5-methoxy-benzoic acid (intermediate III(i)) (1.4 g, 5.7 mmol, 1.0 eq) in CH_2Cl_2 (15 mL) were added $(\text{COCl})_2$ (2.2 g, 17.3 mmol, 3.0 eq) and DMF (0.01 mL). The reaction mixture was stirred at room temperature for 1.5h then the solvent and excess reagent removed under reduced pressure. The residue obtained was dissolved in THF (20 mL) and added dropwise to a solution of 3-amino-2,4-dimethylphenol (intermediate X(c)) (791 mg, 5.77 mmol, 1.0 eq) in THF (20 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 1h. The reaction mixture was poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 100:1 to 1:1) to give the title compound as a white solid (1.2 g, 57 %).

LC-MS: m/z 365.4 $[\text{M}+\text{H}]^+$

3-[[3-(3-Fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenol



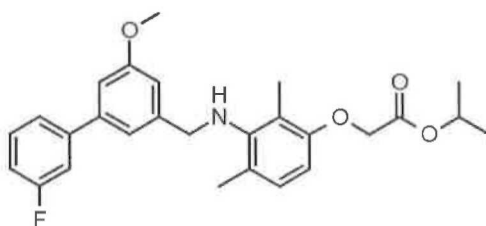
To a solution of 3-(3-(3-fluorophenyl)-N-(3-hydroxy-2,6-dimethyl-phenyl)-5-methoxy-benzamide (1.2 g, 3.3 mmol, 1.0 eq) in THF (50 mL) at 0 °C under N_2 was added a solution of BH_3 (1M in THF, 16.0 mL, 16.0 mmol, 5.0 eq) dropwise. The reaction mixture was heated at 60 °C overnight then cooled to room temperature and quenched with water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in*

vacuo. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 100:1 to 5:1) to give the title compound as a colorless oil (700 mg, 60 %).

LC-MS: m/z 351.4 [M+1].

5

Isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (II(at))



To a solution of 3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenol (700 mg, 2.0 mmol, 1.0 eq) in 2-butanone (4 mL) was added Cs_2CO_3 (973 mg, 3 mmol, 1.5 eq). The reaction mixture was stirred for 30 min then isopropyl bromoacetate (432 mg, 2.4 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for a further 1h then poured into water and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 100:0 to 30:1) to give the title compound as a colorless oil (570 mg, 63 %).

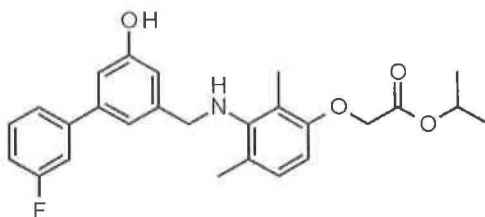
LC-MS: m/z 451.5 [M+H]⁺

20

¹H NMR (400 MHz, DMSO) δ 7.53 – 7.41 (m, 3H), 7.23 – 7.15 (m, 2H), 7.08 (s, 1H), 6.92 (s, 1H), 6.82 (d, $J = 8.4$ Hz, 1H), 6.34 (d, $J = 8.3$ Hz, 1H), 4.96 (hept, $J = 6.3$ Hz, 1H), 4.64 (s, 2H), 4.38 (br t, $J = 7.1$ Hz, 1H), 4.11 (d, $J = 5.2$ Hz, 2H), 3.78 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 1.19 (d, $J = 6.3$ Hz, 6H).

25

Isopropyl 2-[3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (II(as))

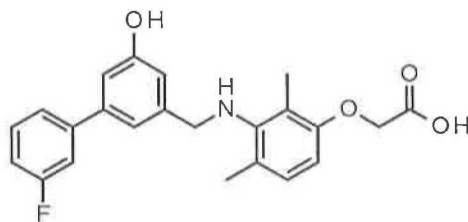


To a solution of isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl] methylamino]-2,4-dimethyl-phenoxy]acetate (390 mg, 0.9 mmol, 1.0 eq) in CH₂Cl₂ (10 mL) at 0 °C was added dropwise ethyl mercaptan (321 mg, 5.2 mmol, 6.0 eq) and AlCl₃ (690 mg, 5.2 mmol, 6.0 eq). The reaction mixture was stirred at room temperature for 1h then poured into water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 100:1 to 10:1) to give the title compound as a white solid (200 g, 53 %).

LC-MS: *m/z* 437.5 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 9.54 (s, 1H), 7.54 – 7.43 (m, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.17 (td, *J* = 8.3, 1.8 Hz, 1H), 7.06 (s, 1H), 6.89 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 6.34 (d, *J* = 8.3 Hz, 1H), 5.02 – 4.90 (m, 1H), 4.63 (s, 2H), 4.28 (br t, *J* = 6.9 Hz, 1H), 4.05 (d, *J* = 6.6 Hz, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 6H).

2-[3-[[3-(3-Fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid (I(ao))



To a solution of isopropyl 2-[3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate (100 mg, 0.22 mmol, 1.0 eq) in THF (10 mL) at 0 °C was

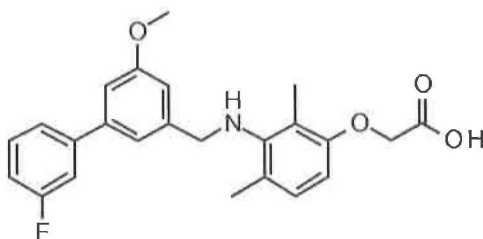
added NaOH (1M aqueous solution, 3 mL, 3 mmol). The reaction mixture was stirred at room temperature overnight then the THF was removed under reduced pressure. The remaining aqueous solution was poured into water and adjusted to pH 4-6 by addition of diluted HCl. The solid that precipitated was collected by filtration, washed with water and
5 dried *in vacuo* to give the title compound as a yellow solid (60 mg, 66 %).

LC-MS: m/z 409.5 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 9.60 (br s, 1H), 7.53 – 7.44 (m, 1H), 7.43 – 7.32 (m, 2H),
10 7.18 (td, *J* = 8.3, 2.3 Hz, 1H), 7.08 (s, 1H), 6.93 (s, 1H), 6.90 – 6.84 (m, 1H), 6.82 (s, 1H),
6.44 (br s, 1H), 4.60 (s, 2H), 4.11 (br s, 2H), 2.16 (s, 6H).

Example 56 – compound I(ap) synthesized according to scheme 3

15 **2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetic acid (I(ap))**



To a solution of isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl] methylamino]-2,4-dimethyl-phenoxy]acetate (II(at)) (100 mg, 0.22 mmol, 1.0 eq) in THF (10 mL) was
20 added NaOH (1M aqueous solution, 3.0 mL, 3.0 mmol). The reaction mixture was stirred at room temperature for 2h, then the THF was removed under reduced pressure. The remaining aqueous solution was adjusted to pH 3-4 by the addition of diluted HCl. The solid that precipitated was collected by filtration, washed with water and dried *in vacuo* to give the title compound as a yellow solid (60 mg, 66 %).

25

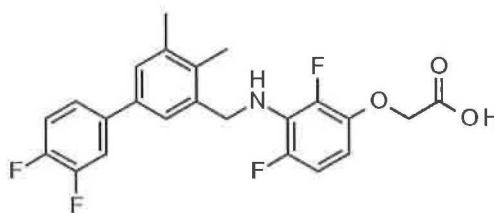
LC-MS: m/z 409.5 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 7.55 – 7.42 (m, 3H), 7.27 – 7.11 (m, 3H), 6.99 – 6.88 (m, 2H), 6.54 (br s, 1H), 4.63 (s, 2H), 4.24 (br s, 2H), 3.79 (s, 3H), 2.17 (s, 6H).

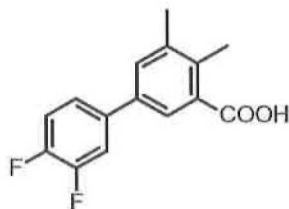
5

Example 57 – compound I(aq) synthesized according to scheme 3

2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluorophenoxy]acetic acid (I(aq))



10 **5-(3,4-Difluorophenyl)-2,3-dimethyl-benzoic acid (III(s))**

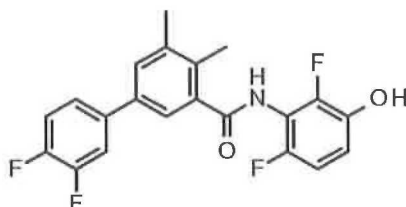


To a mixture of 5-bromo-2,3-dimethyl-benzoic acid (500 mg, 2.18 mmol, 1.0 eq), (3,4-difluorophenyl)boronic acid (378.6 mg, 2.40 mmol, 1.1 eq) and Na₂CO₃ (693 mg, 6.54 mmol, 3.0 eq) in a mixture of EtOH (2.5 mL), DMF (10 mL) and H₂O (2.5 mL) was added Pd(PPh₃)₄ (126 mg, 0.11 mmol, 0.05 eq) under nitrogen. The mixture was stirred at 100 °C overnight. After cooling to room temperature, water was added and the diluted reaction mixture filtered through celite. The aqueous layer was extracted with EtOAc and the organic extract was discarded. The remaining aqueous layer was acidified to pH 2 by addition of 3M HCl. The resulting mixture was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a white solid (400 mg, 70 %).

LC-MS: m/z 261.1 [M-H]⁻

¹H NMR (400 MHz, DMSO) δ 7.84 – 7.74 (m, 2H), 7.68 (s, 1H), 7.57 – 7.46 (m, 2H), 2.41 (s, 3H), 2.37 (d, J = 8.7 Hz, 3H).

5 *N*-(2,6-Difluoro-3-hydroxy-phenyl)-5-(3,4-difluorophenyl)-2,3-dimethyl-benzamide

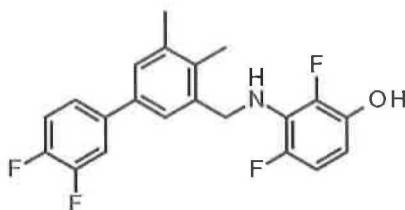


To a solution of 5-(3,4-difluorophenyl)-2,3-dimethyl-benzoic acid (395 mg, 1.51 mmol, 1.1 eq) in CH₂Cl₂ (5 mL) was added (COCl)₂ (521.6 mg, 4.11 mmol, 3.0 eq) dropwise at 0 °C. DMF (10 mg, 0.14 mmol, 0.1 eq) was added and the reaction mixture was stirred at room temperature for 2h. The resulting mixture was concentrated under reduced pressure to remove the solvent and excess reagent. The residue obtained was dissolved in THF (4 mL) and added dropwise to a mixture of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (198 mg, 1.37 mmol, 1.0 eq) and NaHCO₃ (575 mg, 6.85 mmol, 5.0 eq) in THF (4 mL) at 0 °C. After addition was completed the reaction mixture was stirred at room temperature for 30 min. Water was added and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with saturated NaHCO₃, water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 10:1 to 4:1) to give the title compound as a white solid (100 mg, 19 %).

20

LC-MS: m/z 388.3 [M-H]⁻

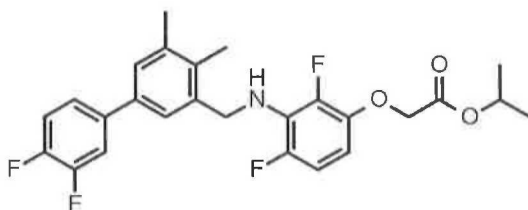
3-[[5-(3,4-Difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3,4-difluorophenyl)-2,3-dimethyl-benzamide (90 mg, 0.23 mmol, 1.0 eq) in THF (1.5 mL) under N₂ was added
5 dropwise a solution of BH₃ (1M in THF, 1.03 mL, 1.03 mmol, 4.6 eq) at 0 °C. The reaction mixture was heated at 60 °C overnight then cooled and the reaction quenched with water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 30:1
10 to 15:1) to give the title compound as a colorless oil (70 mg, 81 %).

LC-MS: m/z 376.1 [M+H]⁺

Isopropyl 2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetate (II(au))
15



To a solution of 3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenol (70 mg, 0.19 mmol, 1.0 eq) in acetone (2 mL) was added Cs₂CO₃ (90 mg, 0.28 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred for 10 min then
20 isopropyl bromoacetate (40 mg, 0.22 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for a further 30 min then water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column

chromatography (petroleum ether:EtOAc, 100:0 to 20:1) to give the title compound as a colorless oil (73 mg, 82 %).

LC-MS: m/z 498.2 $[M+H]^+$

5

^1H NMR (400 MHz, DMSO) δ 7.58 (ddd, $J = 12.3, 7.8, 2.2$ Hz, 1H), 7.48 (dt, $J = 10.6, 8.6$ Hz, 1H), 7.43 – 7.35 (m, 3H), 6.81 (ddd, $J = 11.5, 9.3, 2.0$ Hz, 1H), 6.31 (td, $J = 9.1, 4.5$ Hz, 1H), 5.61 (br s, 1H), 5.00 – 4.87 (m, 1H), 4.70 (s, 2H), 4.47 (d, $J = 5.1$ Hz, 2H), 2.30 (s, 3H), 2.21 (s, 3H), 1.15 (d, $J = 6.3$ Hz, 6H).

10

2-[3-[[5-(3,4-Difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluorophenoxy]acetic acid (*I(aq)*)



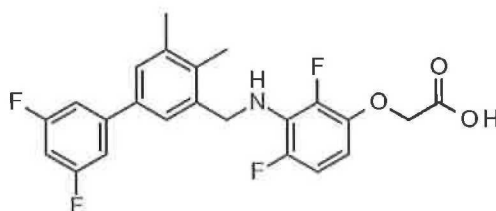
To a solution of isopropyl 2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluorophenoxy]acetate (70 mg, 0.15 mmol, 1.0 eq) in a mixture of THF (1.5 mL) and MeOH (0.5 mL) was added LiOH (2M aqueous solution, 1.5 mL, 3.0 mmol). The reaction was stirred at room temperature for 1h then the organic solvent was removed under reduced pressure. The remaining aqueous solution was diluted with water and the solution acidified to pH 4-5 with 3M HCl. The mixture was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a white solid (63 mg, 99 %).

25

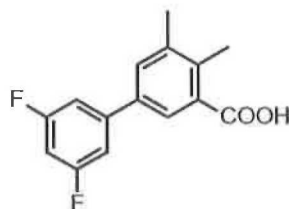
LC-MS: m/z 434.1 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 7.60 (ddd, $J = 12.3, 7.8, 2.1$ Hz, 1H), 7.48 (dt, $J = 10.4, 8.6$ Hz, 1H), 7.43 (s, 1H), 7.41 – 7.34 (m, 2H), 6.82 – 6.68 (m, 1H), 6.20 (br s, 1H), 5.41 (br s, 1H), 4.45 (d, $J = 6.5$ Hz, 2H), 4.23 (br s, 2H), 2.30 (s, 3H), 2.21 (s, 3H).

- 5 **Example 58 – compound I(ar) synthesized according to scheme 3**
2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluorophenoxy]acetic acid (I(ar))



- 10 5-(3,5-Difluorophenyl)-2,3-dimethyl-benzoic acid (III(t))



- To a solution of 5-bromo-2,3-dimethylbenzoic acid (500 mg, 2.18 mmol, 1.0 eq), (3,5-difluorophenyl)boronic acid (414 mg, 2.62 mmol, 1.2 eq) and Na_2CO_3 (925 mg, 8.73 mmol, 4.0 eq) in a mixture of EtOH (5 mL), DMF (20 mL) and water (5 mL) was added
15 $\text{Pd}(\text{PPh}_3)_4$ (252 mg, 0.22 mmol, 0.1 eq) under nitrogen. The mixture was stirred at 100 °C overnight. Water was added and the mixture acidified to pH 3 by addition of 3M HCl. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2 :MeOH, 300:1 to 200:1) to give
20 the title compound as a white solid (184 mg, 32 %).

LC-MS: m/z 261.1 $[\text{M}-\text{H}]^-$

¹H NMR (400 MHz, DMSO) δ 12.99 (br s), 7.82 (s), 7.74 (s), 7.44 (d, $J = 7.1$ Hz), 7.27 – 7.17 (m), 2.41 (s), 2.36 (s).

N-(2,6-Difluoro-3-hydroxy-phenyl)-5-(3,5-difluorophenyl)-2,3-dimethyl-benzamide



5

To a solution of 5-(3,5-difluorophenyl)-2,3-dimethyl-benzoic acid (240 mg, 0.92 mmol, 1.1 eq) in CH₂Cl₂ (12 mL) was added (COCl)₂ (348 mg, 2.75 mmol, 3.3 eq) and DMF (5 drops). The reaction mixture was stirred at room temperature for 1.5h, then concentrated under reduced pressure to remove the organic solvent and excess reagent. The residue obtained was dissolved in THF (10 mL) and added dropwise to a solution of 3-amino-2,4-difluorophenol (intermediate X(a)) (121 mg, 0.83 mmol, 1.0 eq) and NaHCO₃ (386 mg, 4.6 mmol, 5.0 eq) in THF (10 mL) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 1h. The resulting mixture was diluted with water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (CH₂Cl₂:MeOH, 500:1 to 200:1) to give the title compound as a yellow solid (50 mg, 15 %).

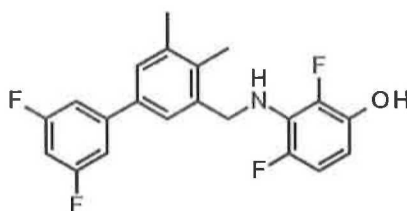
10

15

LC-MS: m/z 390.1 [M+H]⁺ 412.1 [M+Na]⁺

20

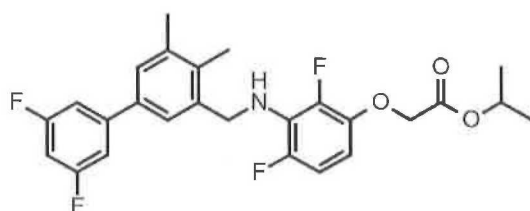
3-[[5-(3,5-Difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-5-(3,5-difluorophenyl)-2,3-dimethyl-benzamide (46 mg, 0.12 mmol, 1.0 eq) in THF (5 mL) under N₂ was added dropwise a solution of BH₃ (1M in THF, 0.72 mL, 0.72 mmol, 6.0 eq). The reaction mixture was heated at 60 °C overnight. After cooling, the resulting mixture was quenched with water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 40:1 to 20:1) to give the title compound as a colorless oil (20 mg, 45 %).

10 LC-MS: m/z 376.2 [M+H]⁺

Isopropyl 2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluorophenoxy]acetate (II(av))



15 To a solution of 3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenol (20 mg, 0.05 mmol, 1.0 eq) in DMF (3 mL) was added Cs₂CO₃ (26 mg, 0.075 mmol, 1.5 eq). The mixture was stirred at room temperature for 30 min then isopropyl bromoacetate (11 mg, 0.06 mmol, 1.2 eq) was added. The reaction mixture was stirred at room temperature for a further 1h then diluted with water and extracted with

20 EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 30:1) to give the title compound as a colorless oil (23 mg, 92 %).

25 LC-MS: m/z 476.1 [M+H]⁺

2-[3-[[5-(3,5-Difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid (I(ar))



To a solution of isopropyl 2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetate (23 mg, 0.048 mmol, 1.0 eq) in THF (3 mL) at 0 °C was added LiOH (2M aqueous solution, 1 mL, 2.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The THF was removed under reduced pressure and the remaining aqueous solution was adjusted to pH 3 by addition of 3M HCl. The resulting mixture was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the title compound as a yellow solid (20 mg, 95 %).

LC-MS: m/z 434.1 [M+H]⁺ 456.1 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.48 (s, 1H), 7.45 (s, 1H), 7.32 – 7.23 (m, 2H), 7.17 (tt, *J* = 9.3, 2.3 Hz, 1H), 6.81 (ddd, *J* = 11.5, 9.3, 2.1 Hz, 1H), 6.32 (td, *J* = 9.1, 4.6 Hz, 1H), 5.56 (br s, 1H), 4.63 (s, 2H), 4.48 (d, *J* = 6.6 Hz, 2H), 2.31 (s, 3H), 2.22 (s, 3H).

Example 59 – compound I(as) synthesized according to scheme 5

(R,S)-2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy]acetic acid (I(as))



2-Fluoro-5-(3-fluorophenyl)-N-methoxy-N-methyl-benzamide

To a solution of 2-fluoro-5-(3-fluorophenyl)benzoic acid (intermediate III(a)) (2 g, 8.5 mmol, 1.0 eq) and N-methoxymethanamine hydrochloride (916 mg, 9.4 mmol, 1.1 eq) in DMF (20 mL) was added triethylamine (3.6 mL, 25.6 mmol, 3.0 eq) at 0 °C. HOBt (1.51g, 11.1 mmol, 1.3 eq) and EDC (2.13 g, 11.1 mmol, 1.3 eq) were added and the solution was stirred for 2 days. Water was added and the aqueous layer was extracted with EtOAc. The organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 20:1 to 10:1 then CH₂Cl₂) to give the title compound as a colorless oil (2.03 g, 85 %).

LC-MS: m/z 278.1 [M+H]⁺ 300.1 [M+Na]⁺

15

1-[2-Fluoro-5-(3-fluorophenyl)phenyl]ethanone

To a solution of 2-fluoro-5-(3-fluorophenyl)-N-methoxy-N-methyl-benzamide (1.8 g, 6.5 mmol, 1.0 eq) in THF (14 mL) at -20 °C was added MeMgBr (3.2 mL, 9.7 mmol, 1.5 eq). The mixture was stirred at 0 °C for 2h then water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether: EtOAc, 20:1 to 10:1) to give the title compound as a white solid (1.3 g, 86 %).

25

LC-MS: m/z 233.1 [M+H]⁺ 255.1 [M+Na]⁺

2,4-Difluoro-3-[(E)-1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylideneamino]phenol

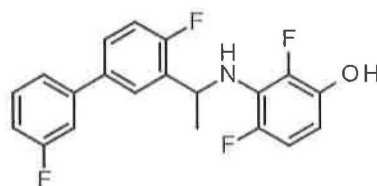


- 5 To a mixture of compound 1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethanone (500 mg, 2.1 mmol, 1 eq) and 3-amino-2,4-difluorophenol (intermediate X(a)) (375 mg, 2.5 mmol, 1 eq) in toluene (50 mL) was added 4Å molecule sieves (30 grains) and AlCl₃ (28 mg, 0.21 mmol, 0.1 eq). The reaction was heated at reflux overnight, the sieves were removed by filtration and the filtrate evaporated under reduced pressure. The residue obtained was
- 10 purified by column chromatography (petroleum ether: EtOAc, 25:1) to give the title compound as a colorless oil (500 mg, 66 %).

LC-MS: m/z 360.1 [M+H]⁺ 382.1 [M+Na]⁺

15

(R,S)-2,4-Difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenol



- 2,4-difluoro-3-[(E)-1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylideneamino] phenol (300 mg, 0.8 mmol, 1.0 eq) was dissolved in THF (20 mL) and a solution of BH₃ (1M in THF, 3.2 mL, 3.2 mmol, 4.0 eq) was added dropwise. The solution was then heated at 60 °C
- 20 overnight. The reaction was quenched with methanol and the solvent was removed *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 15:1) with a second batch of the same reaction (50 mg scale) to give the title compound as a colorless oil (320 mg, 91 %).

25

LC-MS: m/z 362.1 $[M+H]^+$ 384.1 $[M+Na]^+$

(*R,S*)-Isopropyl 2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy]acetate (II(*aw*))



5

To a solution of (*R,S*)-2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino] phenol (320 mg, 0.88 mmol, 1 eq) in DMF (20 mL) was added K_2CO_3 (486 mg, 1.1 mmol, 4 eq) and the mixture stirred for 30 min. Isopropyl bromoacetate (190 mg, 1.1 mmol, 1.2 eq) was added dropwise to the reaction and the mixture stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic extract was washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 50:1) to give the title compound as a colorless oil (380 mg, 93 %).

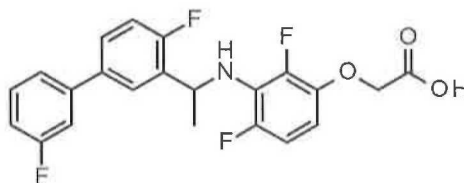
10

15 LC-MS: m/z 484.1 $[M+Na]^+$

1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, $J = 7.1, 2.3$ Hz), 7.41 – 7.34 (m), 7.25 (d, $J = 8.3$ Hz), 7.20 – 7.14 (m), 7.07 (dd, $J = 10.3, 8.6$ Hz), 7.04 – 6.99 (m), 6.65 (ddd, $J = 11.2, 9.2, 2.2$ Hz), 6.25 (td, $J = 9.0, 4.7$ Hz), 5.21 – 5.13 (m), 5.13 – 5.04 (m), 4.53 (s), 4.13 (br d, $J = 9.6$ Hz), 1.62 (d, $J = 6.7$ Hz), 1.22 (d, $J = 6.3$ Hz).

20

(*R,S*)-2-[2,4-Difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy]acetic acid (I(*as*))



25

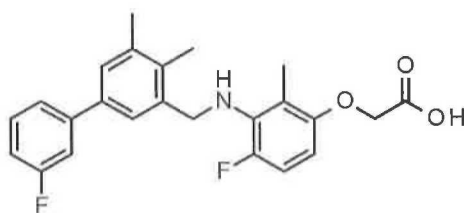
To a solution of (R,S)-isopropyl 2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy]acetate (130 mg, 0.28 mmol, 1 eq) in THF (10 mL) was added a solution of LiOH.H₂O (24 mg, 0.56 mmol, 2 eq) in H₂O (10 mL) and the mixture was stirred overnight at room temperature. The solution was acidified to pH 1 by addition of 1N HCl and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and evaporated *in vacuo* to give the title compound as a yellow solid (85 mg, 72 %).

LC-MS: m/z 420.1 [M+H]⁺ 442.1 [M+Na]⁺

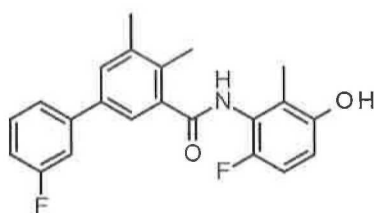
¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, *J* = 7.1, 2.2 Hz, 1H), 7.41 – 7.31 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.18 – 7.11 (m, 1H), 7.10 – 6.97 (m, 2H), 6.70 – 6.61 (m, 1H), 6.25 (td, *J* = 8.9, 4.6 Hz, 1H), 5.15 (q, *J* = 6.6 Hz, 1H), 4.58 (s, 2H), 1.61 (d, *J* = 6.8 Hz, 3H).

Example 60 – compound I(at) synthesized according to scheme 3

2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (I(at))



N-(6-Fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)-2,3-dimethyl-benzamide



To a solution of 5-(3-fluorophenyl)-2,3-dimethyl-benzoic acid (intermediate III(m)) (500 mg, 2.0 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at 0 °C was added oxalyl chloride (770 mg, 6.1 mmol, 3.0 eq) and DMF (0.1 mL) and the reaction was stirred for 1h. The solvent and excess reagent were removed under reduced pressure and the residue obtained was dissolved in THF (10 mL) and added to a mixture of 3-amino-4-fluoro-2-methyl-phenol (intermediate X(c)) (280 mg, 2.0 mmol, 1.0 eq) and Na_2CO_3 (860 mg, 8.1 mmol, 4.0 eq) in THF (10 mL) at 0 °C. The reaction was stirred for 3h, then filtered and concentrated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 400:1 to 4:3) to give the title compound as a brown solid (300 mg, 40 %).

LC-MS: m/z 368.2 $[\text{M}+\text{H}]^+$ 390.2 $[\text{M}+\text{Na}]^+$

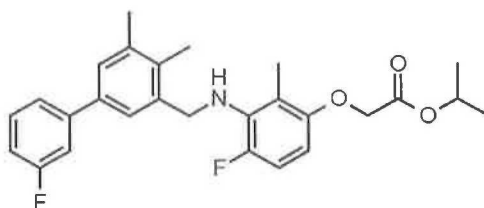
4-Fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenol



To a solution of N-(6-fluoro-3-hydroxy-2-methyl-phenyl)-5-(3-fluorophenyl)-2,3-dimethyl-benzamide (290 mg, 0.78 mmol, 1.0 eq) in THF (10 mL) was added a solution of BH_3 (1M in THF, 5 mL, 5.0 mmol, 6.4 eq) under nitrogen. The mixture was heated at 60 °C overnight then the reaction quenched by addition of methanol. The mixture was evaporated *in vacuo* and the residue obtained purified by column chromatography (petroleum ether:EtOAc, 400:1 to 20:1) to give the title compound as a pale red oil (230 mg, 85 %).

LC-MS: m/z 376.1 $[\text{M}+\text{Na}]^+$

Isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (II(ax))



To a solution of 4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenol (230 mg, 0.65 mmol, 1.0 eq) in DMF (5 mL) was added Cs₂CO₃ (420 mg, 1.3 mmol, 2.0 eq) and isopropyl 2-bromoacetate (140 mg, 0.78 mmol, 1.2 eq). The reaction was stirred at room temperature for 1 h then water and EtOAc were added. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 400:1 to 40:7) to give the title compound as a colorless oil (180 mg, 62 %).

LC-MS: m/z 454.2 [M+H]⁺ 476.2 [M+Na]⁺

¹H NMR (400 MHz, DMSO) δ 7.50 – 7.42 (m, 2H), 7.42 – 7.32 (m, 3H), 7.17 – 7.10 (m, 1H), 6.80 (dd, *J* = 12.3, 9.0 Hz, 1H), 6.25 (dd, *J* = 9.0, 3.6 Hz, 1H), 5.00 – 4.89 (m, 1H), 4.89 – 4.82 (m, 1H), 4.64 (s, 2H), 4.40 (d, *J* = 6.3 Hz, 2H), 2.31 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H), 1.17 (d, *J* = 6.2 Hz, 6H).

2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid (*I(at)*)



To a solution of isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenoxy]acetate (80 mg, 0.17 mmol, 1.0 eq) in a mixture of THF

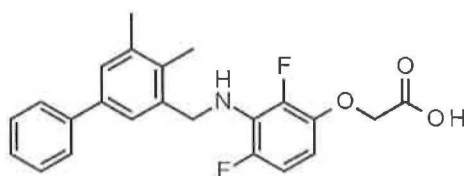
(5 mL) and MeOH (5 mL) was added NaOH (2M aqueous solution, 5 mL, 10 mmol). The reaction was stirred for 3h then the organic solvent was removed under reduced pressure. The remaining aqueous solution was adjusted to pH 5 with diluted HCl and the mixture extracted with EtOAc. The combined organic extracts were dried (Na₂SO₄), filtered and
5 evaporated *in vacuo*. The residue obtained was purified by column chromatography (CH₂Cl₂:MeOH, 400:1 to 4:1) to give the title compound as a white solid (74 mg, 97 %).

LC-MS: m/z 410.2 [M-H]⁻

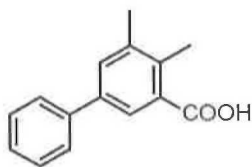
10 ¹H NMR (400 MHz, DMSO) δ 7.52 (s, 1H), 7.50 – 7.35 (m, 4H), 7.14 (app t, *J* = 7.7 Hz, 1H), 6.97 – 6.88 (m, 1H), 6.48 (dd, *J* = 8.9, 3.3 Hz, 1H), 4.63 (s, 2H), 4.46 (s, 2H), 2.29 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H).

Example 61 – compound I(au) synthesized according to scheme 3

15 **2-[3-[(2,3-dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetic acid (I(au))**



2,3-Dimethyl-5-phenyl-benzoic acid (III(u))



20

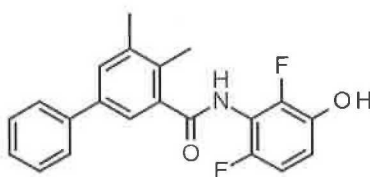
To a solution of 5-bromo-2,3-dimethyl-benzoic acid (690 mg, 3.0 mmol, 1.0 eq), phenylboronic acid (404 mg, 3.3 mmol, 1.1 eq) and Na₂CO₃ (958 mg, 9.0 mmol, 3.0 eq) in a mixture of EtOH (5 mL), DMF (20 mL) and water (5 mL) was added Pd(PPh₃)₄ (0.17 g, 0.15 mmol, 0.05 eq). The reaction was heated at 100 °C overnight then diluted with
25 EtOAc and filtered through celite. The aqueous layer was acidified to pH 4-5 with diluted

HCl and extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 10:1 then CH₂Cl₂:MeOH, 400:0 to 20:1) to give the title compound as a white solid (315 mg, 46 %).

5

LC-MS: m/z 225.1 [M-H]⁻

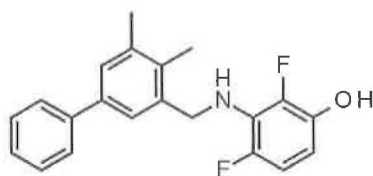
N-(2,6-Difluoro-3-hydroxy-phenyl)-2,3-dimethyl-5-phenyl-benzamide



- 10 To a solution of 2,3-dimethyl-5-phenyl-benzoic acid (315 mg, 1.4 mmol, 1.1 eq) in CH₂Cl₂ (10 mL) was added oxalyl chloride (530 mg, 4.2 mmol, 3.3 eq) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1h. The solvent and excess reagent were removed under reduced pressure and the residue that remained dissolved in THF (10 mL) and added dropwise to a mixture of 3-amino-2,4-difluoro-phenol (intermediate X(a)) (184 mg, 1.3 mmol, 1.0 eq) and NaHCO₃ (532 mg, 6.3 mmol, 5.0 eq) in THF (8 mL) at 0 °C. The reaction was stirred at room temperature for 2h, water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered, and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether:EtOAc, 20:1 to 10:1, then CH₂Cl₂:MeOH, 500:1 to 100:1) to give the title compound as a yellow solid (220 mg, 49 %).

LC-MS:m/z 354.1[M+H]⁺ 376.1[M+Na]⁺

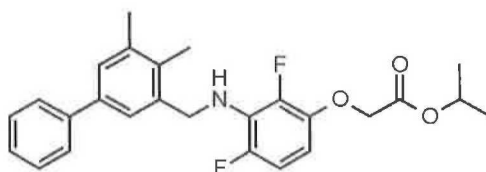
25 3-[(2,3-Dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenol



To a solution of N-(2,6-difluoro-3-hydroxy-phenyl)-2,3-dimethyl-5-phenyl-benzamide (210 mg, 0.6 mmol, 1.0 eq) in THF (4 mL) at 0 °C was added dropwise a solution of BH₃ (1M in THF, 3.6 mL, 3.6 mmol, 6.0 eq). The reaction mixture was heated at 60 °C for 5h, then cooled and quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 100:0 to 10:1) to give the title compound as colorless oil (120 mg, 60 %).

LC-MS: m/z 362.1 [M+Na]⁺

Isopropyl 2-[3-[(2,3-dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenoxy] acetate (II(ay))



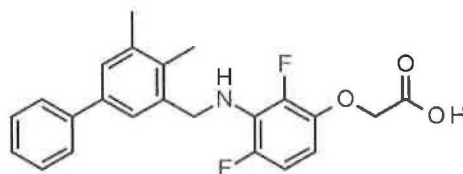
To a solution of 3-[(2,3-dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenol (120 mg, 0.4 mmol, 1.0 eq) in acetone (4 mL) was added Cs₂CO₃ (173 mg, 0.5 mmol, 1.5 eq) and the reaction was stirred at room temperature for 30 min. Isopropyl bromoacetate (76 mg, 0.42 mmol, 1.2 eq) was added and the reaction was stirred at room temperature for 1h. Water was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried (Na₂SO₄), filtered and evaporated *in vacuo*. The residue obtained was purified by column chromatography (petroleum ether:EtOAc, 20:1) to give the title compound as a colorless oil (117 mg, 75 %).

LC-MS: m/z 462.2 $[M+Na]^+$

1H NMR (400 MHz, DMSO) δ 7.55 – 7.49 (m, 2H), 7.45 – 7.37 (m, 3H), 7.36 – 7.27 (m, 2H), 6.80 (ddd, $J = 11.6, 9.2, 2.1$ Hz, 1H), 6.30 (td, $J = 9.1, 4.5$ Hz, 1H), 5.65 (br s, 1H),
5 5.00 – 4.88 (m, 1H), 4.70 (s, 2H), 4.48 (d, $J = 6.2$ Hz, 2H), 2.31 (s, 3H), 2.21 (s, 3H),
1.15 (d, $J = 6.3$ Hz, 6H).

2-[3-[(2,3-Dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetic acid

10 (I(au))



To a solution of isopropyl 2-[3-[(2,3-dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate (110 mg, 0.25 mmol, 1.0 eq) in THF (4 mL) was added LiOH (52 mg, 1.2 mmol, 5 eq) and water (3 mL) and the reaction mixture stirred at room
15 temperature for 1h. The THF was removed under reduced pressure and the remaining aqueous solution was adjusted to pH 4-5 by addition of 1M HCl. The mixture was extracted with EtOAc and the combined organic extracts washed with water and brine, dried (Na_2SO_4), filtered and evaporated *in vacuo* to give the title compound as a yellow
oil (80 mg, 80 %).

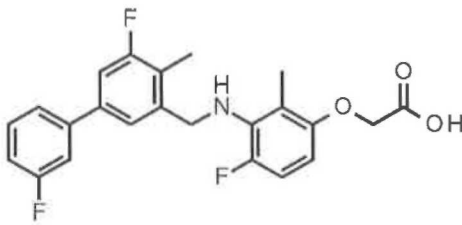
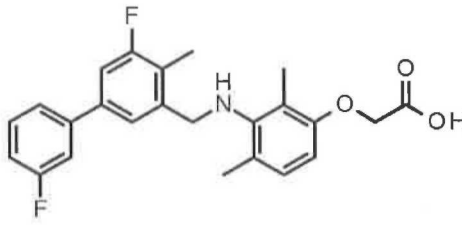
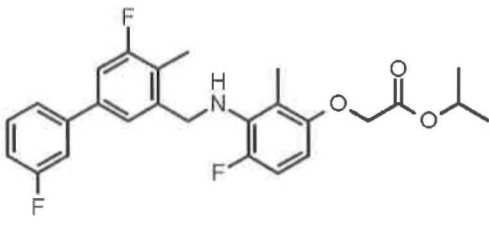
20

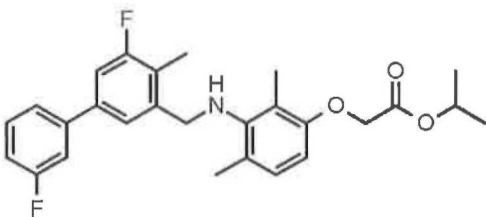
LC-MS: m/z 398.2 $[M+H]^+$ 420.1 $[M+Na]^+$

1H NMR (400 MHz, DMSO) δ 13.02 (br s, 1H), 7.57 – 7.49 (m, 2H), 7.47 – 7.38 (m, 3H),
7.37 – 7.27 (m, 2H), 6.81 (ddd, $J = 11.5, 9.3, 2.0$ Hz, 1H), 6.31 (td, $J = 9.1, 4.5$ Hz, 1H),
25 5.62 (br s, 1H), 4.65 (s, 2H), 4.49 (d, $J = 6.1$ Hz, 2H), 2.32 (s, 3H), 2.22 (s, 3H).

The following compounds according to the invention were made according to scheme 3 in a similar manner to the compounds described above.

Table 3:

Compound number	Structure	LC-MS ¹ H NMR
I(av)		m/z 416.2 $[M+H]^+$ ¹ H NMR (400 MHz, DMSO) δ 7.54 – 7.37 (m, 5H), 7.23 – 7.14 (m, 1H), 6.80 (dd, J = 12.3, 9.0 Hz, 1H), 6.26 (dd, J = 9.0, 3.6 Hz, 1H), 5.01 (br s, 1H), 4.57 (s, 2H), 4.40 (s, 2H), 2.21 (d, J = 1.3 Hz, 3H), 2.12 (s, 3H).
I(aw)		m/z 412.2 $[M+H]^+$ ¹ H NMR (400 MHz, DMSO) δ 7.64 (d, J = 1.4 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.44 (dd, J = 11.0, 1.6 Hz, 1H), 7.25 – 7.16 (m, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.3 Hz, 1H), 4.24 (s, 2H), 4.07 (s, 2H), 2.18 (d, J = 1.5 Hz, 3H), 2.10 (s, 6H).
II(az)		m/z 458.2 $[M+H]^+$ 480.2 $[M+Na]^+$ ¹ H NMR (400 MHz, DMSO) δ 7.53 – 7.36 (m, 5H), 7.18 (td, J = 7.9, 1.3 Hz, 1H), 6.80 (dd, J = 12.3, 9.0 Hz, 1H), 6.26 (dd, J = 9.0, 3.7 Hz, 1H), 5.08 – 5.00 (m, 1H), 5.00 – 4.89 (m, 1H), 4.64 (s, 2H), 4.41 (d, J = 6.8 Hz, 2H), 2.21

		(d, $J = 1.6$ Hz, 3H), 2.12 (s, 3H), 1.16 (d, $J = 6.3$ Hz, 6H).
II(ba)		m/z 454.2 $[M+H]^+$ 476.2 $[M+Na]^+$ 1H NMR (400 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.41 – 7.36 (m, 1H), 7.35 – 7.30 (m, 1H), 7.25 – 7.16 (m, 2H), 7.08 – 7.00 (m, 1H), 6.93 (d, $J = 8.3$ Hz, 1H), 6.40 (d, $J = 8.3$ Hz, 1H), 5.14 (hept, $J = 6.2$ Hz, 1H), 4.58 (s, 2H), 4.15 (s, 2H), 2.28 (d, $J = 1.9$ Hz, 3H), 2.27 (s, 3H), 2.19 (s, 3H), 1.28 (d, $J = 6.3$ Hz, 6H).

Tests

- Compounds according to the table 4 were subjected to pharmacological tests for determining their agonist effect on EP2 receptors. Tests involved measuring the *in vitro* activity of the compounds of the invention on EP2 receptors.

Test 1: binding assays

Test 1.1: Human prostanoid EP₄ receptor binding assay

10 Protocol

Cell membrane homogenate from Human embryonic kidney HEK-293(T) cells expressing recombinant human prostanoid EP₄ receptor was used to perform Prostanoid receptor radioligand binding assays.

The competition reaction was initiated by incubation of membrane protein homogenate (20 µg protein) for 120 min at 22°C with 0.5 nM [³H]PGE₂ ligand in the absence or presence of the test compound in a buffer containing 10 mM MES/KOH (pH 6.0), 10 mM MgCl₂ and 1 mM EDTA.

- 5 Non-specific binding was determined in the presence of 10 µM PGE₂ (the corresponding non-radioactive prostanoid). Affinity of the compound binding to hEP4 receptor was measured by displacement of the radiolabeled ligand in the presence of varying doses of tested compound.
- 10 Incubations were terminated by rapid filtration under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% PEI and washed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard).
- The filters were dried and the residual radioactivity bound to the individual filters determined with addition of scintillation cocktail (Microscint 0, Packard) by a
- 15 scintillation counter (Topcount, Packard).
- The results were expressed as a percent inhibition of the control radioligand specific binding.
- The standard reference compound PGE₂, was tested in at several concentrations to obtain a competition curve to determined IC₅₀.

20

Analysis and expression of results

- The specific ligand binding to the receptors is defined as the difference between the total binding and the nonspecific binding determined in the presence of an excess of unlabelled ligand. The results are expressed as a percent of control specific binding ((measured
- 25 specific binding/control specific binding) x 100) obtained in the presence of the test compounds. The IC₅₀ values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (nH) were determined by non-linear regression analysis of the competition curves generated with mean replicate values using Hill equation curve fitting ($Y = D + [(A - D)/(1 + (C/IC_{50})^{nH})]$, where Y = specific binding,
- 30 D = minimum specific binding, A = maximum specific binding, C = compound concentration, IC₅₀ = IC₅₀, and nH = slope factor). This analysis was performed using a

software developed at Cerep (Hill software) and validated by comparison with data generated by the commercial software SigmaPlot® 4.0 for Windows® (© 1997 by SPSS Inc.). The inhibition constants (K_i) were calculated using the Cheng Prusoff equation ($K_i = IC_{50}/(1+(L/KD))$), where L – concentration of radioligand in the assay, and KD – affinity of the radioligand for the receptor). A scatchard plot is used to determine the K_d .

Test 1.2: Human prostanoid EP₂ receptor cellular functional assay

Protocol

Human CHO cells expressing the recombinant human prostanoid EP₂ receptor were suspended in assay medium (HBSS buffer (Invitrogen) containing 20 mM HEPES (pH7.4) and 500 μ M isobutyl-methylxanthine IBMX) and plated out to yield approximately 1×10^4 cells/well in a 96-well. Following this, cells were incubated with agonists for 30 min in the presence of the test compounds. For stimulated control measurements, separate assay wells contain 10 μ M PGF₂ (control specific agonist). All incubations were carried out at 37 °C in a 5% CO₂ atmosphere. Following incubation, the amount of cAMP in each well was determined by HTRF method. The cells are lysed and the fluorescence acceptor (D2-labeled cAMP) and fluorescence donor (anti-cAMP antibody labeled with europium cryptate) are added. After 60 min at room temperature, the fluorescence transfer is measured at λ_{ex} =337 nm and λ_{em} =620 and 665 nm using a microplate reader (Rbystar, BMG).

The cAMP concentration is determined by dividing the signal measured at 665 nm by that measured at 620 nm (ratio).

The standard reference agonist PGE₂ was tested at several concentrations to generate a concentration-response curve to determine EC₅₀.

Analysis and expression of results

The results are expressed as a percent of control specific agonist response ((measured specific response/control specific agonist response) x 100) obtained in the presence of the test compounds. The EC₅₀ values (concentration producing a half-maximal specific response) were determined by non-linear regression analysis of the concentration-response curves generated with mean replicate values using Hill equation curve fitting (Y

= $D + [(A - D)/(1 + (C/C_{50})^{nH})]$, where Y = specific response, D = minimum specific response, A = maximum specific response, C = compound concentration, and C₅₀ = EC₅₀ and nH = slope factor). This analysis was performed using a software developed at Cerep (Hill software) and validated by comparison with data generated by the commercial software SigmaPlot® 4.0 for Windows® (© 1997 by SPSS Inc.).

Table 4:

Compound number	<i>In vitro</i> functional assay EP2 (h) EC ₅₀ (nM)	% response	<i>In vitro</i> potency EP4 (h) IC ₅₀ (nM)
I(a)	110	74%	NC
I(b)	28	82%	NC
I(c)	69	66%	NC
I(d)	35	74%	NC
I(e)	160	65%	NC
I(f)	160	61%	NC
I(g)	55	80%	NC
I(h)	13	88%	NC
I(i)	99	73%	NC
I(j)	26	80%	NC
I(k)	73	77%	> 300
I(l)	24	76%	NC
I(m)	10	89%	NC
I(n)	52	86%	NC
I(o)	34	74%	NC
I(p)	17	70%	NC
I(q)	18	70%	NC
I(r)	45	78%	> 300
I(s)	17	72%	NC

Compound number	<i>In vitro</i> functional assay EP2 (h) EC ₅₀ (nM)	% response	<i>In vitro</i> potency EP4 (h) IC ₅₀ (nM)
I(t)	17	73%	NC
I(u)	9	78%	NC
I(v)	2	85%	NC
I(w)	14	40%	NC
I(x)	27	45%	NC
I(y)	130	62%	NC
I(z)	4	53%	NC
I(aa)	3	97%	> 300
I(ab)	50	105%	NC
I(ac)	18	117%	NC
I(ad)	2	101%	> 300
I(ae)	3	83%	NC
I(af)	5	70%	NC
I(ag)	< 1	85%	> 300
I(ah)	8	74%	NC
I(ai)	35	80%	NC
I(aj)	7	79%	NC
I(ak)	2	113%	> 300
I(al)	0.9	70%	> 300
I(am)	3	87%	NC
I(an)	9	91%	NC

Compound number	<i>In vitro</i> functional assay EP2 (h) EC ₅₀ (nM)	% response	<i>In vitro</i> potency EP4 (h) IC ₅₀ (nM)
I(ao)	1	76%	NC
I(ap)	3	89%	NC
I(aq)	2	31%	NC
I(ar)	8	130%	NC
I(as)	11	107%	NC
I(at)	6	91%	> 300
I(au)	15	81%	NC
I(av)	5	97%	NC
I(aw)	3	80%	>300
II(d)	>300	44%	
I(as) (+ isomer)*	18	124%	NC
CP-544326	46	72%	NC

* Isolated by prep chiral HPLC using the following conditions: Column : Chiralcel OJ-H 5µm; Dimension: 2 x 25cm; Mobile phase: CO₂ 90% MeOH 10%; Flow rate 55 ml/min; Pressure=100 bars; Column=35°C; Detection :254 nm. $[\alpha]_D = +171 \pm 3$

5 NC: not calculable

CP-544326 corresponds to the acid of taprenepag.

Taprenepag is a prodrug which was until recently in Phase II for the treatment of glaucoma.

It is apparent from the results above that compounds above are very potent and very selective EP2 agonists.

5 Test 2: Solubility

Solubility of the test materials was evaluated on n=1 trial, following the procedure below:

2.5 mg of each compound for solubility testing were dissolved in 5 mL of the diluent, an initial concentration of 500ug/mL. The mixture was first vortexed for 15 seconds to allow a good wetting of the API, then sonicated for 5 minutes to promote solubilisation. The vortex/sonication cycle was repeated 3 times. The suspension was stirred at room temperature using a magnetic stirrer at 300 rpm. This mixture is observed at 4h, 24h and 48h to determine if the test compound has dissolved. At each time point if the compound is completely solubilised a further 5mg of the test compound is added and the process repeated.

When no more test compound will dissolve in the diluent, an aliquot of 0.5 mL of the suspension was withdrawn and centrifuged 3x2min at 13400 rpm. The supernatant for HPLC quantification was filtered using 0.2µm Pall Acrodisc Nylon 13mm membrane and quantified by comparing to the calibration curve, using the method: column: Nucleodur C18 ISIS 3 µm 4.6 X 125 mm, Mobile Phase (CH₃COOH 0.05% in H₂O and ACN), Flow rate: 1 ml/min, Wavelength: λ=240 nm (IIa and IIc) or 240 nm (IId), Injected volume: 10 µl, Gradient of concentration: from 30% B to 100%B in 6 min.

Table 5:

Compound	Solubility at equilibrium (µg/mL)
PF-04217329	542
II(a)	8117

II(c)	6780
II(d)	711

PF-04217329 corresponds to the prodrug: taprenepag.

It is apparent from the results above that prodrugs of the invention are more soluble than taprenepag.

5 Test 3: *In vivo* activity of compounds according to the invention:

Test 3.1: monkey

Laser-induced hypertensive cynomolgus monkey

Ten adult female cynomolgus monkeys, each weighing 3-5 kg, in which glaucoma had
10 been induced unilaterally by diode laser photocoagulation of the mid-trabecular meshwork, were used in this study.

Intraocular pressure (IOP) was measured at 0 hr (before drug administration) and then hourly until 6 hrs after drug administration on one baseline day, one vehicle-treatment
15 day, and treatment days 1, 3, and 5 with 0.01% of compound II(d).

Compound II(d) was tested in two groups of 4 monkeys for a total of 8 monkeys.
Following one baseline day (untreated) and one vehicle-treatment day (50 μ l (25 μ l x 2),
drop of vehicle to the glaucomatous eye at 9:30 (a 50 μ l drop (25 μ l x 2) of compound
20 (II(d)) were topically applied to the glaucomatous eye *only* once daily at 9:30 am *for 5 consecutive days*.

Slit-lamp examination for the detection of aqueous humor flare and cells was performed
in a dark room before drug administration and at 1, 3 and 5 hrs after dosing on baseline
25 day and at the same times on treatment days 1, 3 and 5.

Two-tailed paired and unpaired t test and the ANOVA test were used for statistical analysis.

Results are presented in Fig. 1, and show that the overall IOP is reduced by 22% after a daily administration over 5 days.

It is therefore apparent that the compounds of the invention are potent and efficacious
5 agonists on EP2 receptors and are selective over EP4 receptors.

It is therefore apparent that the compounds of the invention have an agonist activity for EP2 receptors. The compounds according to the invention can therefore be used for preparing medicaments, especially medicaments which are agonists of EP2 receptors.

10

Accordingly, in another of its aspects, the invention provides medicaments which comprise a prodrug of formula (II), or a drug of formula (I), or an addition salt thereof with a pharmaceutically acceptable organic base or inorganic cation, or else a co-crystal or a solvate (*to be adapted on a case-by-case basis*) of the compound of formula (I) or
15 (II).

These medicaments are employed therapeutically, especially in the treatment [*and the prevention*] of Glaucoma, or ocular hypertension. Glaucoma, according to the present invention, as to be understood as absolute glaucoma, congenital glaucoma, traumatic
20 glaucoma due to birth injury, but also primary open-angle glaucoma, including capsular with pseudoexfoliation of lens, chronic simple, low-tension, pigmentary.

Glaucoma also includes Primary angle-closure glaucoma, which comprises both primary and residual stage of angle closure glaucoma, in its acute, chronic or intermittent forms. It also includes Glaucoma secondary to eye trauma, Glaucoma secondary to eye
25 inflammation, Glaucoma secondary to other eye disorders, Glaucoma secondary to drugs, other Glaucoma as well as unspecified Glaucoma.

According to another of its aspects, the present invention relates to pharmaceutical compositions comprising as active principle a compound according to the invention. In an
30 aspect, the compound according to the invention is a compound of formula (I) or one of its prodrugs. In another aspect, the compounds according to the invention are compounds

of formula II. These pharmaceutical compositions comprise an effective dose of at least one compound according to the invention, or one of its prodrugs, and also at least one pharmaceutically acceptable excipient.

- 5 The said excipients are selected, in accordance with the pharmaceutical form and method of administration desired, from the customary excipients, which are known to a person skilled in the art.

10 In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intra-tracheal, intranasal, transdermal, intraocular or rectal administration, the active principle of formula (I) above, or one of its prodrugs, may be administered in a unit administration form, in a mixture with conventional pharmaceutical excipients, to animals and to human beings for the prophylaxis and/or treatment of the above disorders or diseases.

15 The unit administration appropriate forms include oral forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intra-ocular and intranasal administration forms, forms for inhalative, topical, transdermal, subcutaneous, intra-muscular or intravenous administration, rectal
20 administration forms and implants. For topical application it is possible to use the compounds or their prodrugs according to the invention in creams, gels, ointments, eye drops or lotions.

As an example, a unit administration form of a compound according to the invention in
25 eye drop form may comprise the following components:

Compound according to the invention:	1% w/v
Dimethyl sulfoxide + PVP K-30:	1% w/v
Benzalkonium chloride:	0.01-0.02 % w/v
30 Edated disodium:	0.005-0.1% w/v
Boric acid:	quantity sufficient (QS) to buffer capacity

	Sodium borate:	NMT 0.5%
	Sodium chloride:	QS to osmolality 308 mOsm/kg
	Polysorbate 80	0.1-3%
	HPMC 4000 cps	0.45-1%
5	HCl/NaOH	QS to pH 5-6
	Purified water	QS to required volume

Drugs and prodrugs according to the present invention can also be given in combination, and in particular, as a non limitative list, in combination with beta-blockers, prostaglandins, sympathomimetic collyres, inhibitors of carbonic anhydrase, or
 10 parasympathomimetic collyres, for example.

Suitable beta blockers include timolol, Alprenolol, Bucindolol, Carteolol, Carvedilol, Labetalol, Nadolol, Oxprenolol, Penbutolol, Pindolol, Propranolol, Sotalol, Eucommia bark (herb), Acebutolol, Atenolol, Betaxolol, Bisoprolol, Celiprolol, Esmolol, Metoprolol,
 15 Nebivolol, Butaxamine, ICI-118,551, or SR 59230A.

Suitable prostaglandins include, for example latanoprost, bimatoprost, travoprost or tafluprost.

Suitable sympathomimetic eye-drops include for example brimonidine (Alphagan), apraclonidine (Iopidine), dipivefrin (Propine, AKPro), and epinephrine (Eppy, Glaucon,
 20 Epinal, Epifrin).

Suitable inhibitors of carbonic anhydrase include Acetazolamide, Methazolamide, Dorzolamide, or Topiramate, for example.

Suitable parasympathomimetic collyres include pilocarpine.
 25

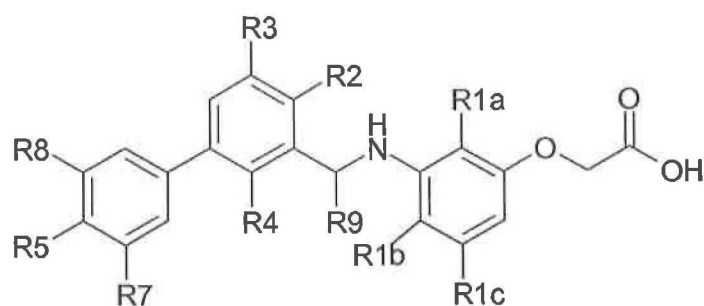
The present invention, according to another of its aspects, also provides a method of treating the pathologies indicated above, which comprises administering to a patient an effective dose of a compound according to the invention, or one of its prodrugs.

CLAIMS

5

CLAIMS

1. Compound of formula (I), or one of its prodrugs, in which:



I

10

R1a represents H, an halogen, a (C₁-C₆)alkyl or a CN;

R1b represents H, an halogen or a (C₁-C₆)alkyl;

R1c represents H or a (C₁-C₆)alkyl;

15 R2 represents H, an halogen, an OH, an O-(C₁-C₆)alkyl or a (C₁-C₆)alkyl;

R3 represents H, an halogen, a (C₁-C₆)alkyl, an OH, an O-(C₁-C₆)alkyl, a CONH₂ or a CN;

R4 represents H, an halogen or a (C₁-C₆)alkyl;

R5 represents H or F;

20 R7 represents H or F;

R8 represents H or F;

R9 represents H or a (C₁-C₆)alkyl,

or one of its enantiomers.

2. Compound according to claim 1, in which compounds of formula (I) are not:
- 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)phenyl]methylamino]phenoxy]
acetic acid;
- 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy]
acetic acid;
- 2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetic
acid;
- 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic
acid;
- 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-phenyl]methylamino]phenoxy]
acetic acid;
- 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-phenyl]methylamino]phenoxy]
acetic acid;
- 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-2,5-dimethyl-phenyl] methylamino]
phenoxy] acetic acid;
- 2-[2,4-difluoro-3-[[5-fluoro-3-(3-fluorophenyl)-2-methylphenyl]methylamino]
phenoxy]acetic acid;
- 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-6-hydroxy-phenyl]methylamino]
phenoxy]acetic acid;
- 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-6-methoxy-phenyl]methylamino]
phenoxy]acetic acid;
- 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-isopropyl-phenyl]methylamino]phenoxy]
acetic acid;
- 2-[3-[[3-ethyl-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]
acetic acid;
- 2-[2-ethyl-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]
acetic acid;
- 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-isopropyl-
phenoxy]acetic acid.
- 2-[2,4-difluoro-3-[[2-fluoro-5-(4-fluorophenyl)phenyl]methylamino]phenoxy]
acetic acid

2-[2,4-difluoro-3-[(2-fluoro-5-phenyl-phenyl)methylamino]phenoxy]acetic acid

2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-6-methyl-phenyl]methylamino]phenoxy] acetic acid

2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenoxy]acetic acid

5 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]phenoxy] acetic acid

2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetic acid

or one of its enantiomers.

10

3. Compound according to any preceding claim, selected from the following list:

I(ai): 2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetic acid

15 I(aj): 2-[3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid

I(ak): 2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid

I(al): 2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid

20 I(am): 2-[3-[[2-Fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl- phenoxy] acetic acid

I(an): 2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetic acid

25 I(ao): 2-[3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid

I(ap): 2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid

I(aq): 2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy] acetic acid

30 I(ar): 2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy] acetic acid

- I(as): 2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino]phenoxy] acetic acid
- I(at): 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenoxy] acetic acid
- 5 I(au): 2-[3-[(2,3-dimethyl-5-phcnyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetic acid
- I(av): 2-[4-fluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]-2-methyl-phenoxy] acetic acid
- I(aw): 2-[3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid,
- 10 or one of its enantiomers.
4. Compound according to any preceeding claim, selected from the following list:
- I(h): 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino] phenoxy] acetic acid,
- 15 I(i): 2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methyl-phenoxy] acetic acid,
- I(j): 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid,
- 20 I(k): 2-[4-chloro-2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl] methylamino] phenoxy] acetic acid,
- I(l): 2-[3-[[2-chloro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy] acetic acid,
- I(m): 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenoxy] acetic acid,
- 25 I(n): 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid,
- I(o): 2-[2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl] methylamino] phenoxy] acetic acid,
- 30 I(p): 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl] methylamino] phenoxy] acetic acid,
- I(q) : 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl] methylamino] phenoxy] acetic acid,

- I(r): 2-[2,4-dichloro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl] methylamino] phenoxy] acetic acid,
- I(s): 2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid,
- 5 I(t) : 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl] methylamino] phenoxy] acetic acid,
- I(u): 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methyl-phenyl] methylamino] phenoxy] acetic acid,
- I(v) : 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl] methylamino]phenoxy]acetic acid,
- 10 I(w): 2-[3-[[5-(3,4-difluorophenyl)-2-fluoro-phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid,
- I(x): 2-[3-[[3-cyano-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetic acid,
- 15 I(y) : 2-[2,4-difluoro-3-[[6-fluoro-3-(3-fluorophenyl)-2-methyl-phenyl] methylamino] phenoxy] acetic acid,
- I(z) : 2-[3-[[3-carbamoyl-5-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy] acetic acid,
- I(aa): 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl] methylamino] phenoxy] acetic acid,
- 20 I(ab): 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl-phenoxy] acetic acid,
- I(ac) : 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl-phenoxy] acetic acid,
- 25 I(ad): 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2-methyl-phenoxy] acetic acid,
- I(ac): 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy] acetic acid,
- I(af): 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy] acetic acid,
- 30 I(ag): 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetic acid, and
- I(ah): 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl-phenoxy] acetic acid,
- 35 or one of its enantiomers.

5. Compound according to any preceding claim, selected from the following list:

I(a): 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid

I(b): 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid

5 I(c): 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methylphenyl]methylamino]phenoxy]acetic acid

I(d): 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methylphenyl]methylamino]phenoxy]acetic acid

10 I(e): 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid

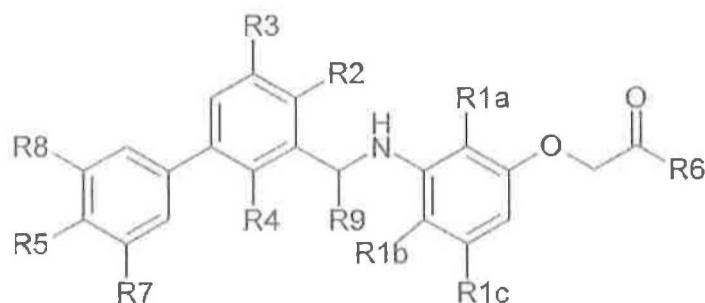
I(f): 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxyphenyl]methylamino]phenoxy]acetic acid

I(g): 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methylphenyl]methylamino]phenoxy]acetic acid,

15 or one of its enantiomers,

6. Compound according to any preceding claim, where the compound is 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetic acid.

20 7. Compound of formula (I) or one of its prodrugs according to any preceding claim, wherein the prodrug of the drug of formula (I) is a compound of formula (II):



II

25

R1a represents H, an halogen, a (C1-C6)alkyl or a CN;

R1b represents H, an halogen or a (C1-C6)alkyl;

R1c represents H or a (C1-C6)alkyl;

R2 represents H, an halogen, an OH, an O-(C1-C6)alkyl or a (C1-C6)alkyl;

5 R3 represents H, an halogen, a (C1-C6)alkyl, an OH, an O-(C1-C6)alkyl, a CONH₂, or a CN;

R4 represents H, an halogen or a (C1-C6)alkyl;

R5 represents H or F;

10 R6 represents an O-(C1-C6)alkyl, an O-(C1-C6)alkyl-heterocycloalkyl, a NH₂, a NH-(C1-C6)alkyl, an O-(C1-C6)alkyl optionally substituted by one to three hydroxyl groups, O-(C1-C6)alkyl-O-CO(C1-C6)alkyl);

R7 represents H or F;

R8 represents H or F;

R9 represents H or (C1-C6)alkyl,

or one of its enantiomers.

15

8. Compound of formula (II) according to claim 7, selected from the following list:

II(s): ethyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate

20 II(t): ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]phenoxy] acetate

II(u): ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate

II(v): ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino] phenoxy] acetate

25 II(w): ethyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino] phenoxy] acetate

II(x): ethyl 2-[2-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-4-methyl-phenoxy]acetate

30 II(y): ethyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenoxy]acetate

- II(z): ethyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate
- II(aa): ethyl 2-[2-chloro-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenoxy] acetate
- 5 II(ab): ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino] phenoxy] acetate
- II(ac): ethyl 2-[3-[[2,6-difluoro-3-(3-fluorophenyl)phenyl]methylamino]-2,4-difluoro-phenoxy]acetate
- II(ad): ethyl 2-[2,4-difluoro-3-[[5-(3-fluorophenyl)-2-hydroxy-3-methyl-phenyl]methylamino] phenoxy] acetate
- 10 II(ae): isopropyl 2-[2,4-difluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino] phenoxy] acetate
- II(af): isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-5-methyl -phenoxy]acetate
- 15 II(ag): isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,5-dimethyl- phenoxy]acetate
- II(ah): isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2- methyl-phenoxy] acetate
- II(ai): isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
- 20 II(aj): isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
- II(ak): isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl- phenoxy]acetate
- 25 II(al): isopropyl 2-[4-fluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2-methyl- phenoxy]acetate
- II(am): isopropyl 2-[4-fluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
- II(an): isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
- 30

- II(ao): isopropyl 2-[3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
- II(ap): isopropyl 2-[3-[[5-(3-fluorophenyl)-2-methoxy-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
- 5 II(aq): isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
- II(ar): isopropyl 2-[2-cyano-4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino] phenoxy] acetate
- II(as): isopropyl 2-[3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]-2,4-dimethyl-phenoxy] acetate
- 10 II(at): isopropyl 2-[3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
- II(au): isopropyl 2-[3-[[5-(3,4-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetate
- 15 II(av): isopropyl 2-[3-[[5-(3,5-difluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2,4-difluoro-phenoxy]acetate
- II(aw): isopropyl 2-[2,4-difluoro-3-[1-[2-fluoro-5-(3-fluorophenyl)phenyl]ethylamino] phenoxy] acetate
- II(ax): isopropyl 2-[4-fluoro-3-[[5-(3-fluorophenyl)-2,3-dimethyl-phenyl]methylamino]-2-methyl-phenoxy] acetate
- 20 II(ay): isopropyl 2-[3-[(2,3-dimethyl-5-phenyl-phenyl)methylamino]-2,4-difluoro-phenoxy]acetate
- II(az): isopropyl 2-[4-fluoro-3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]-2-methyl-phenoxy]acetate
- 25 II(ba): isopropyl 2-[3-[[3-fluoro-5-(3-fluorophenyl)-2-methyl-phenyl]methylamino]-2,4-dimethyl-phenoxy]acetate
- II(bb): isopropyl 2-[3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]-2,4- dimethyl-phenoxy]acetate,
or one of its enantiomers.
- 30

9. Compound of formula (II) according to any one of claims 7 and 8, selected from the

following list:

- II(b): ethyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]phenoxy] acetate,
- II(e): isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy] acetate,
- II(f): isopropyl 2-[2,4-difluoro-3-[[2-fluoro-3-(3-fluorophenyl)-5-methyl-phenyl]methylamino]phenoxy]acetate,
- II(g): isopropyl 2-[3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2,4-dimethyl-phenoxy] acetate,
- II(h): ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)-3-methyl-phenyl]methylamino]phenoxy]acetate,
- II(i): isopropyl 2-[4-fluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]-2-methyl-phenoxy]acetate,
- II(j): 2-hydroxyethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate,
- II(k): 2-morpholinoethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate,
- II(l) : 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetamide,
- II(m): 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]-N-ethyl-acetamide,
- II(n): [3-hydroxy-2,2-bis(hydroxymethyl)propyl] 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate,
- II(o) : [3-hydroxy-2-(hydroxymethyl)propyl] 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate,
- II(p): 1-acetoxyethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate,
- II(q): isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-methoxy-phenyl]methylamino]phenoxy]acetate, and
- II(r): isopropyl 2-[2,4-difluoro-3-[[3-(3-fluorophenyl)-5-hydroxy-phenyl]methylamino]phenoxy]acetate.
- or one of its enantiomers.

10. Compound of formula (II) according to any one of claims 7 to 9, selected from the following list:

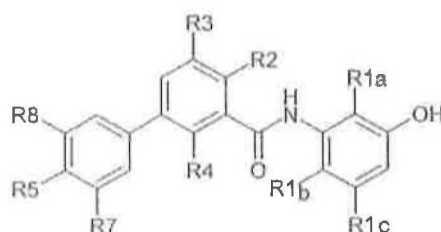
II(a): ethyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate

II(c): methyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy] acetate

5 II(d): isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl) phenyl]methylamino] phenoxy]acetate,
or one of its enantiomers

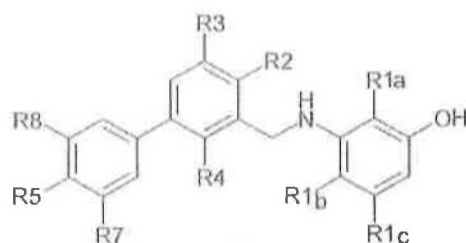
10 11. Compound according to any one of claims 7 to 10, where the compound is isopropyl 2-[2,4-difluoro-3-[[2-fluoro-5-(3-fluorophenyl)phenyl]methylamino]phenoxy]acetate.

15 12. Process for preparing a compound of formula (I) or one of its prodrugs according to any one of claims 1 to 11, wherein a compound of formula (XI):



XI

is reduced to give a compound of formula (IX),:



IX

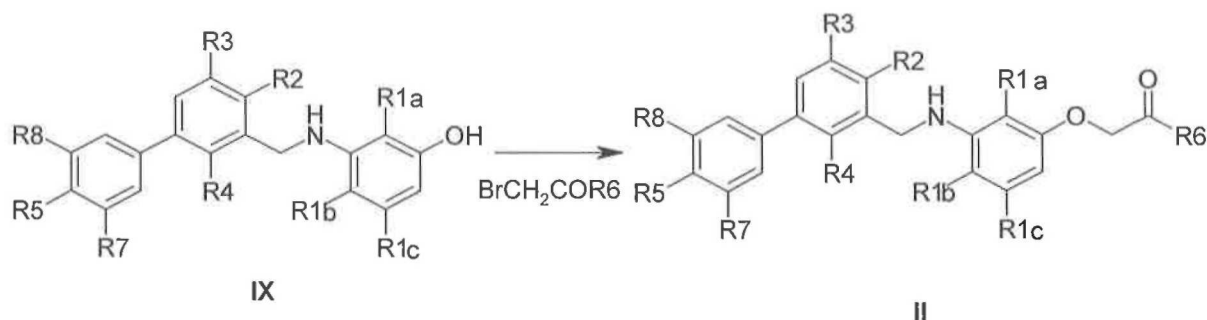
20

which is reacted with $\text{BrCH}_2\text{COR}_6$ to give a compound of formula (II),
in which R1a, R1b, R1c, R2, R3, R4, R5, R7, R8 and R6 are as defined in claims
1 to 11.

13. Compound of formula:

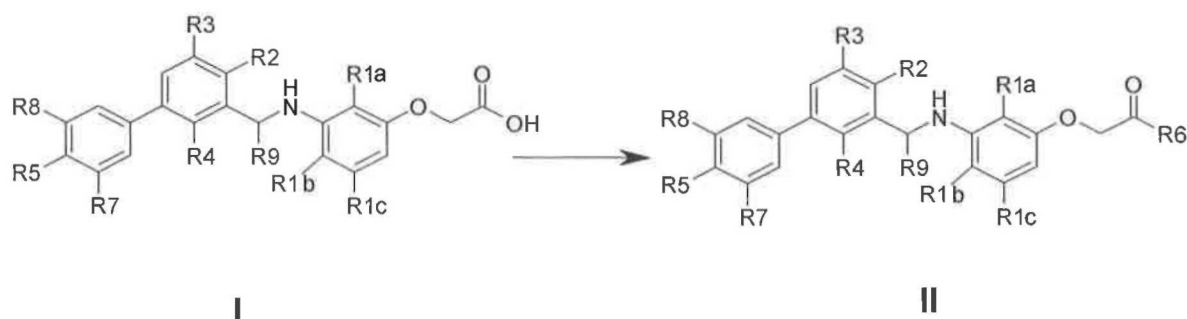
- III(b): 5-(3-Fluorophenyl)-2-methyl-benzoic acid;
 - III(d): 2-Fluoro-3-(3-fluorophenyl)-5-methoxy-benzoic acid;
 - III(e): 2-Fluoro-3-(3-fluorophenyl)-5-methyl-benzoic acid;
 - III(f): 2-Fluoro-5-(3-fluorophenyl)-3-methyl-benzoic acid;
 - III(g): 2-Chloro-5-(3-fluorophenyl)benzoic acid;
 - III(i): 3-(3-Fluorophenyl)-5-methoxy-benzoic acid;
 - III(j): 2,6-difluoro-3-(3-fluorophenyl)benzoic acid;
 - III(k): 5-(3-Fluorophenyl)-2-methoxy-3-methyl-benzoic acid;
 - III(m): 5-(3-Fluorophenyl)-2,3-dimethyl-benzoic acid;
 - III(n): 3-Cyano-5-(3-fluorophenyl)benzoic acid;
 - III(o): 6-Fluoro-3-(3-fluorophenyl)-2-methyl-benzoic acid;
 - III(p): 3-Fluoro-5-(3-fluorophenyl)-2-methyl-benzoic acid;
 - III(q): 3-(3-Fluorophenyl)-5-methyl-benzoic acid;
 - III(s): 5-(3,4-Difluorophenyl)-2,3-dimethyl-benzoic acid;
 - III(t): 5-(3,5-Difluorophenyl)-2,3-dimethyl-benzoic acid;
 - III(u): 2,3-Dimethyl-5-phenyl-benzoic acid;
 - IV(a): Ethyl 2-(3-amino-2,4-difluorophenoxy)acetate;
 - IV(b): Isopropyl 2-(3-amino-2,4-difluoro-phenoxy)acetate;
 - 2-Chloro-6-fluoro-3-methoxy-aniline;
 - 2-Amino-3-fluoro-6-methoxy-benzonitrile;
 - X(a): 3-Amino-2,4-difluoro-phenol;
 - X(b): 3-Amino-2-fluoro-4-methyl-phenol;
 - X(d): 3-Amino-4-chloro-2-fluoro-phenol;
 - X(e): 3-Amino-4-fluoro-2-methyl-phenol;
 - X(f): 3-Amino-2-chloro-4-fluoro-phenol;
 - X(g): 3-Amino-2,4-difluoro-5-methyl-phenol;
 - X(h): 3-amino-4-fluoro-2,5-dimethyl-phenol;
- or one of its enantiomers.

14. Process for the manufacture of a compound of formula (II), wherein said process comprises the following step:



in which R1a, R1b, R1c, R2, R3, R4, R5, R7, R8 and R6 are as defined in any one of claims 1 to 11.

15. Process for the manufacture of a compound of formula (II), wherein said process comprises the following step:



in which R1a, R1b, R1c, R2, R3, R4, R5, R7, R8 and R6 are as defined in any one of claims 1 to 11.

16. Medicament, wherein it comprises a compound of formula (I) or one of its prodrugs according to any one of claims 1 to 11.
17. Medicament according to claim 16 wherein the prodrug is a compound of formula (II) as defined in claims 7 to 11.
18. Pharmaceutical composition, wherein it comprises a compound of formula (I) or one of its prodrugs according to any one of claims 1 to 11, and also at least one pharmaceutically acceptable excipient.
19. Use of a compound of formula (I) or one of its prodrugs according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment of glaucoma.

20. Compound of formula (I) or one of its prodrugs according to any one of claims 1 to 11, as EP2 agonist.
21. Compound of formula (I) or one of its prodrugs according to any one of claims 1 to 11 as a medicament.
22. Combination of a compound of formula (I) or one of its prodrugs with beta-blockers, prostaglandins, sympathomimetic collyres, inhibitors of carbonic anhydrase, or parasympathomimetic collyres.