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(54) Title: INHIBITORS OF BETA-SECRETASE

(57) Abstract: The present invention relates to spirocyclic acylguanidines and their use as inhibitors of the β- secretase enzyme (BACE1) activity, pharmaceutical compositions containing the same, and methods of using the same as therapeutic agents in the treatment of neurodegenerative disorders, disorders characterized by cognitive decline, cognitive impairment, dementia and diseases characterized by production of β-amyloid aggregates.

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INHIBITORS OF BETA-SECRETASE

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 61/693512, filed August 27, 2012, U.S. Provisional Application Serial No. 61/788839, filed March 15, 2013, and U.S. Provisional Application Serial No. 61/816458, filed April 26, 2013. The entire teachings of each of the above applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to spirocyclic acylguanidines and their use as inhibitors of the β-secretase enzyme (BACE1) activity, pharmaceutical compositions containing the same, and methods of using the same as therapeutic agents in the treatment of neurodegenerative disorders, disorders characterized by cognitive decline, cognitive impairment, dementia and diseases characterized by production of β-amyloid deposits and/or neurofibrillary tangles.

BACKGROUND OF THE INVENTION

β-Amyloid (also referred to herein as "Abeta" or "Aβ") deposits and neurofibrillary tangles are two major pathologic characterizations associated with Alzheimer's disease (AD). Clinically, AD is characterized by the loss of memory, cognition, reasoning, judgment, and orientation. Also affected, as the disease progresses, are motor, sensory and linguistic abilities until global impairment of multiple cognitive functions occurs. These cognitive losses take place gradually, but typically lead to severe impairment and eventual death in 4-12 years.

β-Amyloid deposits are predominantly an aggregate of Abeta peptide, which in turn is a product of the proteolysis of amyloid precursor protein (APP). More specifically, Aβ peptide results from the cleavage of APP at the C-terminals by one or more γ-secretases, and at the N-terminus by β-secretase enzyme (BACE1), also known as aspartyl protease and memapsin2, as part of the β-amyloidogenic pathway.

BACE activity is correlated directly to the generation of Aβ peptide from APP, and studies increasingly indicate that the inhibition of BACE inhibits the production of Aβ peptide.

Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of patients with Trisomy 21 (Down Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders. Neurofibrillary tangles also occur in other neurodegenerative disorders including dementia-inducing disorders.

Recently, Abeta has been reported to be implicated in the development of retinal ganglion cell (RGC) apoptosis in glaucoma, with evidence of caspase-3-mediated abnormal amyloid precursor protein processing, increased expression of Abeta in RGCs in experimental glaucoma and decreased vitreous Aβ levels (consistent with retinal Aβ deposition) in patients with glaucoma. Amyloid deposits have also been associated with macular degeneration in patients suffering from dry age-related macular degeneration (AMD) and in animal models of AMD.

WO2010/021680, WO2011/106414 and WO2010/105179 disclose spirocyclic acylguanidines with a spirocyclic scaffold as inhibitors of beta-secretase.

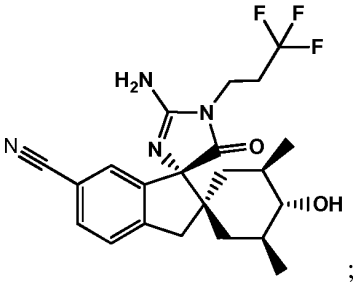
SUMMARY OF THE INVENTION

The present invention provides compounds that are BACE1 inhibitors and are useful as therapeutic agents in the treatment of a disease or disorder characterized by elevated β-amyloid deposits or β-amyloid levels in a patient. The disclosed BACE1 inhibitors have the following characteristics:

(1) High potency of inhibition of BACE1 enzyme activity (assay 1)
(2) High selectivity against the cardiac hERG channel in a cellular assay (assay 2)
(3) Low propensity to cause phospholipidosis in a cellular phospholipidosis assay (assay 3), and
(4) High stability against metabolic degradation in hepatocytes (assay 4).

Thus, the present invention provides compounds which show a combination of high potency as BACE1 inhibitors, high selectivity against the cardiac hERG channel, low phospholipidosis activity, and high stability against metabolic degradation.

One embodiment of the invention is a compound represented by a structural formula selected from: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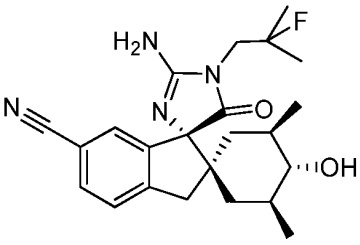
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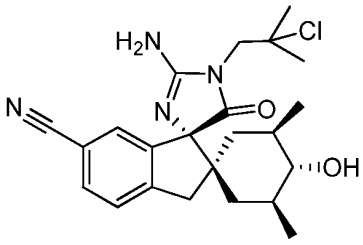
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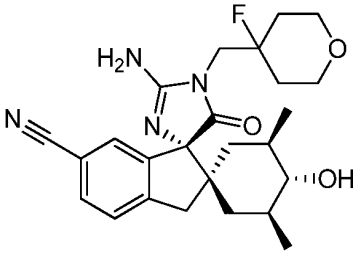
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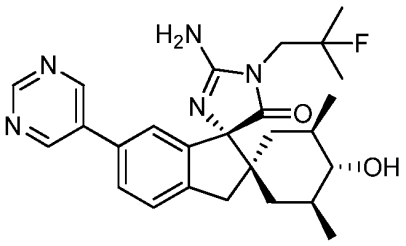
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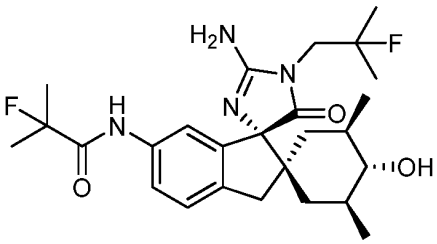
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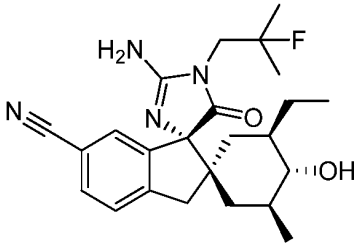
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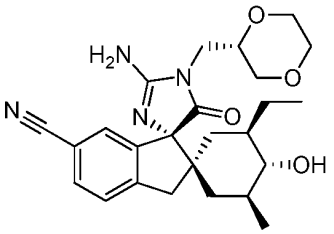
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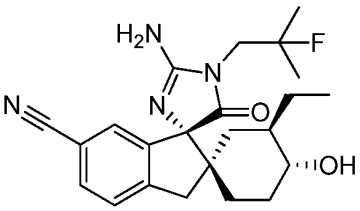
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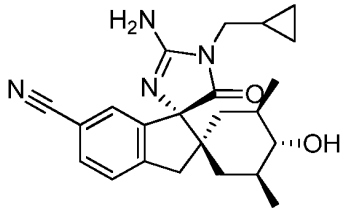
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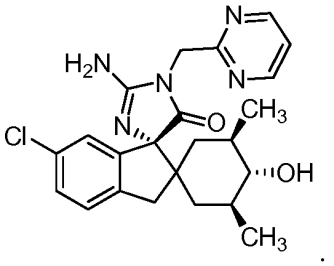
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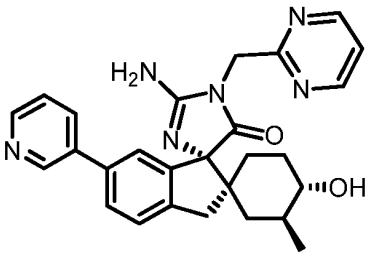
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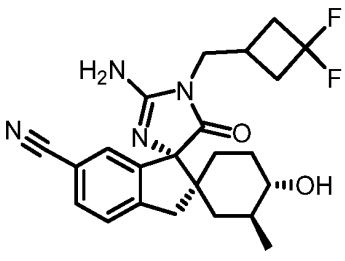
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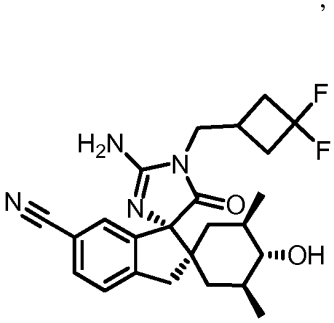
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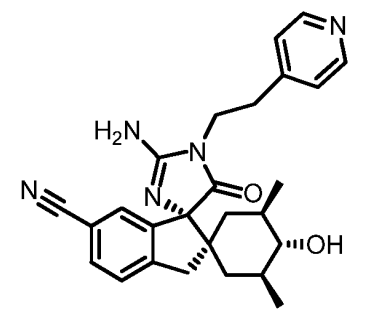
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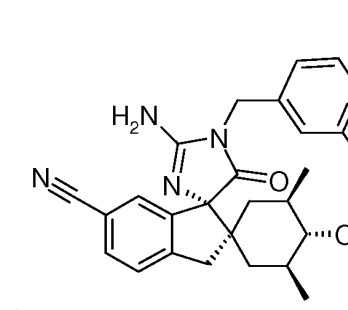
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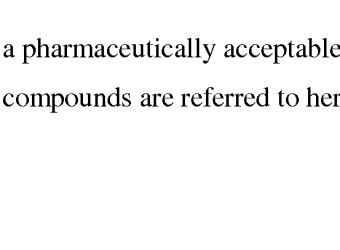
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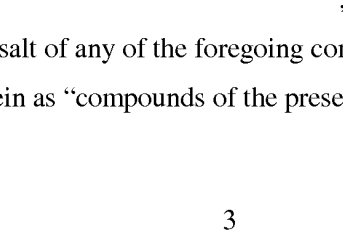
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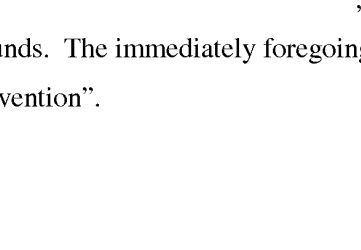

; or

a pharmaceutically acceptable salt of any of the foregoing compounds. The immediately foregoing compounds are referred to herein as “compounds of the present invention”.

Another embodiment of the invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use as a medicament.

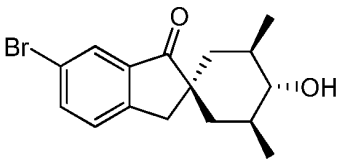
Another embodiment of the invention is a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Another embodiment of the invention is a compound of the present invention or a pharmaceutically acceptable salt thereof for use in the treatment of a BACE1 mediated disorder or disease in a subject.

Another embodiment of the invention is the use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a BACE1 mediated disorder in a subject.

Another embodiment of the invention is a method of treating a subject with a BACE1 mediated disease or disorder, comprising administering to the subject an effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof.

Yet another embodiment of the invention is an intermediate used in the preparation of a compound of the present invention. These intermediates are represented by a structural formula selected from:



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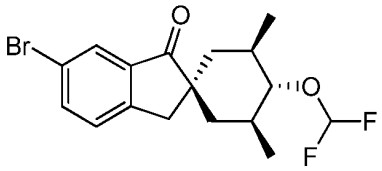

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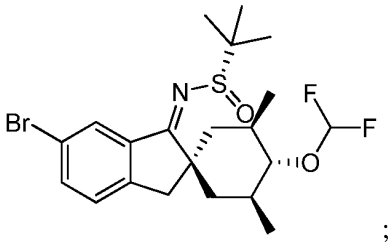

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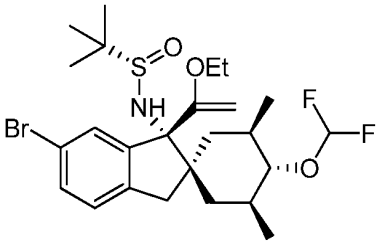

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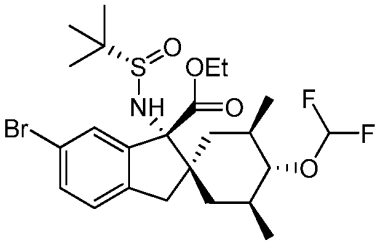

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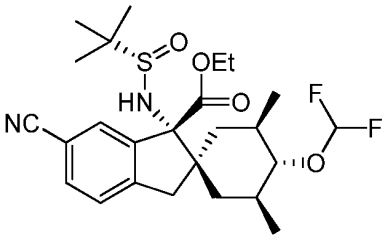

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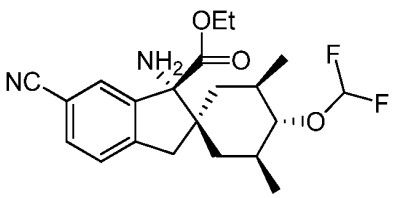

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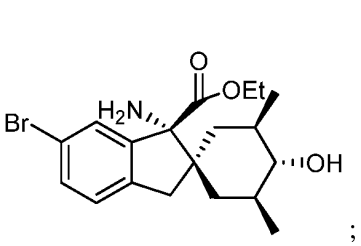
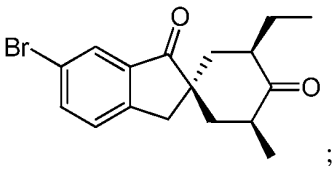
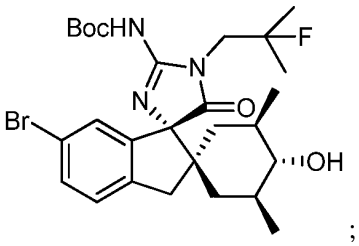
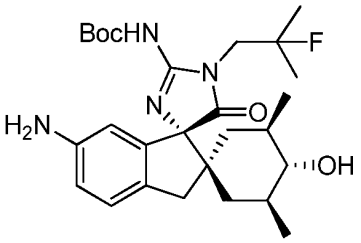
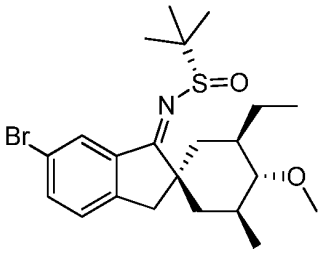
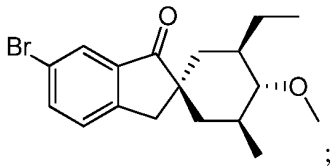
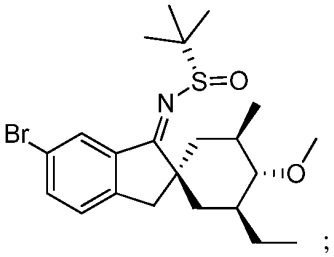
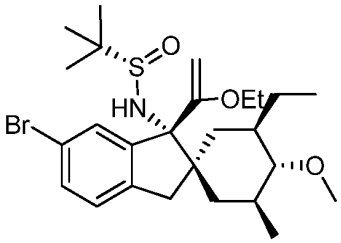
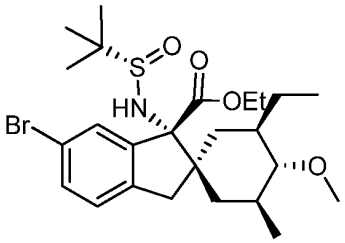
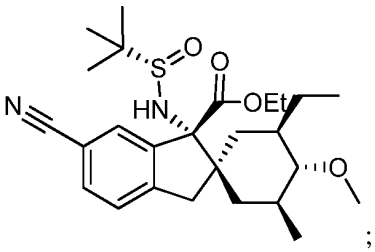
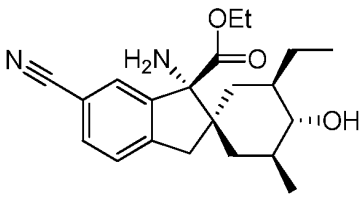
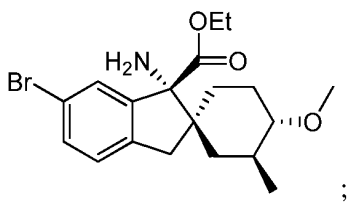
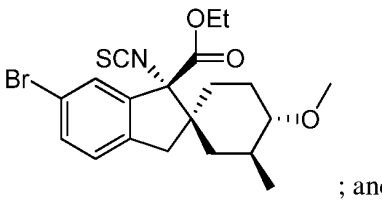














; and ; or a salt of any of the foregoing compounds.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention exhibit potent activity against the BACE1 enzyme and Abeta formation together with high selectivity against the hERG channel, low propensity to cause phospholipidosis, and high metabolic stability. For example, the compounds of the present invention show a BACE1 inhibition with an IC_{50} < 15 nM, a hERG inhibition of less than 35% at 10 μM, phospholipidosis with a First Effect Concentration (FEC) of at least 100 μM, and a metabolic stability of less than 25 percent of hepatic blood flow at 1 μM. These combined properties make the

compounds of the present invention useful for the treatment of pathological states in humans, in particular, for the treatment of Alzheimer's disease as well as other disorders and diseases mediated by BACE1.

Inhibition of the hERG (human Ether-à-go-go-Related Gene) channel by xenobiotics and subsequent delayed cardiac repolarization is associated with an increased risk for a specific polymorphic ventricular tachyarrhythmia, torsade de pointes, as established by Sanguinetti *et al.* (1995, Cell, Apr. 21, 81(2):299-307) and a large body of subsequent evidence. To avoid this risk early on, screening against hERG interaction in an *in vitro* system using heterologous expression of the hERG channel is common practice and an assay of this type is also an important part of later preclinical candidate profiling as recommended by the ICH guideline S7B (International Conference on Harmonization (2005): ICH Topic S 7 B; The nonclinical Evaluation of the Potential for delayed Ventricular Repolarization; (QT Interval Prolongation) by Human Pharmaceuticals (www.ich.org/products/guidelines/safety/article/safety-guidelines.html)). As such, low hERG channel inhibition, such as that shown by the compounds of the present invention, is highly desirable for therapeutics.

Phospholipidosis is a lipid storage disorder in which excess phospholipids accumulate within cells. Drug-induced phospholipidosis is an undesirable drug reaction. Therefore, in order to avoid detrimental side effects, compounds with low phospholipidosis potential are preferred for human therapeutic use.

Metabolic stability refers to the susceptibility of compounds to biotransformation in the context of selecting and/or designing drugs with favorable pharmacokinetic properties. The primary site of metabolism for many drugs is the liver. Intact hepatocytes contain the cytochrome P450s (CYPs), other non-P450 enzymes, and phase II enzymes such as sulfo- and glucuronosyltransferases, and thus represent a prime model system for studying drug metabolization *in vitro*. Enhanced metabolic stability is associated with several advantages, including increased bioavailability and longer half-life, which can enable lower and less frequent dosing of patients. Thus, enhanced metabolic stability is a favorable characteristic for compounds that are to be used for drugs.

Data provided in Table 1 below show that compounds of the present invention have the combination of potent BACE1 inhibitory activity, selectivity against cardiac hERG, low propensity to cause phospholipidosis, and high metabolic stability. Table 2 provides data showing that certain comparator compounds described in WO2010/105179 do not meet one or more of these criteria.

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

When a compound of the present invention is depicted by name or structure without indicating all tautomeric forms, it is to be understood that the compound and its pharmaceutically acceptable salts shall encompass all tautomers.

When a compound of the present invention is depicted by name or structure without indicating the stereochemistry, it is to be understood that the compound and its pharmaceutically acceptable salts shall encompass all stereo, optical and geometrical isomers (*e.g.*, enantiomers, diastereomers, E/Z isomers, etc.) and racemates thereof, as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms.

When a stereo, optical or geometric isomer is depicted by name or structure, it is to be understood that the stereo, optical and/or geometric isomeric purity of the named or depicted stereo, optical or geometric isomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% pure by weight. Stereo, optical and geometric isomeric purity is determined by dividing the weight of the named or depicted stereo, optical and geometric isomer in a mixture by the total weight of all stereo, optical and geometric isomers in the mixture.

When a compound of the present invention or its pharmaceutically acceptable salt is named or depicted by structure, it is to be understood that solvates, hydrates and the anhydrous form of the compound and solvates, hydrates and anhydrous form of its pharmaceutically acceptable salt are included in the invention. "Solvates" refer to crystalline forms wherein solvent molecules are incorporated into the crystal lattice during crystallization. Solvate may include water or nonaqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and EtOAc. Solvates, wherein water is the solvent molecule incorporated into the crystal lattice, are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. "Anhydrous form" refers to compounds with no solvent or water or substantially no solvent or water incorporated into the crystal structure (*e.g.*, less than 1:10, 1:20; 1:100; or 1:200 molar ratio of solvent or water to compound).

Salts

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and

the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2"-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2.2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Preferred salts are L-mandelic acid and maleic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like (see also Pharmaceutical salts, Berge, S.M. *et al.*, J. Pharm. Sci., (1977), 66:1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of acids other than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention (*e.g.*, trifluoro acetate salts) also comprise a part of the invention.

Biological Data

BACE1 Assay (Assay 1)

The inhibitory activity of compounds was assessed by a fluorescence quench assay of BACE1 activity using commercially available substrate HiLyte Fluor™488-Glu-Val-Asn-Leu-Asp-Ala-Glu-Phe-Lys-(QXL™ 520)-OH (SEQ ID NO:1) (AnaSpec, San Jose, CA) and truncated human beta-secretase, BACE1 (amino acids 1-454) fused to a myc-his tag and secreted from HEK293/$BACE_{ect.}$ cells into OptiMEM™ (Invitrogen). The substrate was dissolved at 1 mg/ml in DMSO.

The assay was performed in the presence of OptiMEM™ (supernatant collected over 24 h and cleared from cellular debris by centrifugation) containing the ectodomain of BACE1, 25 µl water containing the desired 2-fold concentration of test compound and 2% DMSO, 1 µM substrate peptide, 20 mM NaOAc, pH 4.4, and 0.04% Triton-X100 in a total assay volume of 50 µl in a 384 well plate. In general, 25 µl of compound dilution were added to the plate followed by the addition of 10 µl of BACE1 containing OptiMEM™ diluted 1:10 in water with 0.2% Triton X-100. The reaction was started with the addition of 15 µl substrate in NaOAc buffer. The reaction was incubated at rt (dark) in an Envision® multilabel reader (Perkin Elmer) and the cleavage of the substrate was recorded as kinetic for 60 min at ex: 485 nm, em: 538 nm. Blank wells containing no enzyme were included on each plate.

The intensity of fluorescence was regressed against time in order to derive velocities of reaction in all 384 wells. These velocities were used for calculating percent control using an uninhibited control containing 1% DMSO as 100% and a blank control performed in the absence of enzyme as 0%. IC_{50} values were calculated by fitting percent control *vs.* test compound concentration using Assay Explorer®.

hERG-Channel Assay (Assay 2)

Cells: HEK (human embryonic kidney) 293 cells were stably transfected with hERG cDNA.

Pipettes and solutions:

Cells were superfused with a bath solution containing (mM): NaCl (137), KCl (4.0), $MgCl_2$ (1.0), $CaCl_2$ (1.8), Glucose (10), HEPES (10), pH 7.4 with NaOH. Patch pipettes were made from borosilicate glass tubing using a horizontal puller and filled with pipette solution containing (mM): K-aspartate (130), $MgCl_2$ (5.0), EGTA (5.0), K_2ATP (4.0), HEPES (10.0), pH 7.2 with KOH. Resistance of the microelectrodes was in the range between 2 and 5 MΩ.

Stimulation and recording:

Membrane currents were recorded using an EPC-10 patch clamp amplifier and PatchMaster software. hERG-mediated membrane currents were recorded at 35 °C, using the whole-cell

configuration of the patch-clamp technique. Transfected HEK293 cells were clamped at a holding potential of -60 mV and hERG-mediated inactivating tail currents were elicited using a pulse pattern with fixed amplitudes (activation/inactivation: 40 mV for 2000 ms; recovery: -120 mV for 2 ms; ramp to 40 mV in 2 ms; inactivating tail current: 40 mV for 50 ms) repeated at 15 s intervals. During each inter-pulse interval, 4 pulses scaled down by a factor of 0.2 were recorded for a P/n leak subtraction procedure. R_s compensation was employed up to a level that safely allowed recording devoid of ringing.

Compound preparation and application:

The different concentrations of the test compounds were applied sequentially on each of the different cells investigated. A steady state level of baseline current was measured for at least 6 sweeps prior to the application of the first test compound concentration.

The test compound was dissolved in DMSO to yield a master stock solution which was diluted further in DMSO to stock solutions needed for the lower concentrations. Final dilutions in extracellular buffer were prepared freshly from these stocks by a 1:1000 dilution step each before starting the experiments.

Data analysis:

Peak current amplitudes were measured 3 ms after the ramp to +40 mV. For baseline and each concentration, the peak currents of the three last sweeps before application of the next concentration were averaged. Residual currents (I/I_0) were calculated for each cell as the fraction of actual average peak current and average baseline peak current.

***In vitro* Phospholipidosis Assay (Assay 3)**

The phospholipidogenic potential of test compounds was assayed using the human hematopoetic U937 cell line. The test principle was to analyze the phospholipid content by staining the cells with the fluorescent dye Nile red.

U937 cells were seeded into cell culture plates at 0.5 x 10^6 cells/mL in RPMI medium containing 10 % FBS, 1 % DMSO, and 0.005 % gentamicin. The cells were cultivated with or without different concentrations of test compound for 48 h under standard culture conditions.

For harvesting, the cells were centrifuged at 130x g for 4 min and washed once with PBS. Then, 2x 0.5 mL cell suspensions were prepared for non-fixed cell measurement (0.5 mL for propidium iodide (PI) viability measurement and 0.5 mL for Nile red measurement).

The remaining cells were fixed with 3.7 % formaldehyde for 30 min. After a further centrifugation step, cells were resuspended with 1.3 mL Nile red working solution (1 µg/mL) and incubated for 5 min at rt. The cell suspension was washed twice with 3 mL PBS and centrifuged with

130x g for 4 min. The supernatant was discarded and the cells were resuspended with 0.5 mL PBS and kept for flow cytometry measurement.

For Nile red staining of the 0.5 mL non-fixed cell samples, 50 µL of a ready to use Nile red solution (10 µg/mL) were added per sample. Samples were kept on ice for 5 min. Thereafter, they were washed once with 4 mL PBS (4 °C, 250x g for 8 min) and finally resuspended in 400 µL PBS and kept for flow cytometry measurement.

For the viability measurement, 12.5 µL of the ready to use PI solution (10 µg/mL) were added to the 0.5 mL non-fixed cell suspension. After 15 min of incubation on ice, the samples were measured by flow cytometry using a Coulter Epics XL/MCL flow cytometer.

The viability of the cells of each sample was determined by flow cytometry measurement of the PI content at channel 2 (568-590 nm). Cut-off gates for the fluorescence-dependent differentiation between live and dead cells were defined based on the analysis of cell culture medium control samples.

Only samples with a cell viability of >= 90 % relative to control samples were analyzed for phospholipidosis. Each Nile red sample (non-fixed and fixed samples) was measured by flow cytometry at channel 1 (504-541 nm) and channel 4 (660-680 nm).

For each channel, relative Nile red fluorescence intensity of a test sample was calculated compared to control samples and expressed as a percentage of control fluorescence intensity. The assessment of the phospholipidogenic potential and the first effective concentration (FEC) of a test compound was done manually based on the fluorescence intensities at both wavelengths for the fixed cells, as well as for the non-fixed cells.

***In vitro* Hepatocyte Stability Assay (Assay 4)**

The metabolic degradation of test compounds was assayed in a hepatocyte suspension. Cryopreserved hepatocytes were incubated in an appropriate buffer system (*e.g.*, Dulbecco´s modified eagle medium plus 3.5µg glucagon/500mL, 2.5mg insulin/500mL and 3.75mg/500mL hydrocortison) containing 5% species serum. Following a 30 min preincubation in an incubator (37 °C, 10% CO_2), 5 µl of test compound solution (80 µM; from 2mM in DMSO stock solution diluted 1:25 with medium) were added into 395 µl hepatocyte suspension (cell density in the range 0.25-5 x 10^6 cells/mL, typically 1 x 10^6 cells/mL; final concentration of test compound 1µM, final DMSO concentration 0.05%).

The cells were incubated for six h (incubator, orbital shaker) and samples (25µl) were taken at 0, 0.5, 1, 2, 4 and 6 h. Samples were transferred into acetonitrile and pelleted by centrifugation (5 min). The supernatant was transferred to a new 96 DeepWell™ plate, evaporated under nitrogen and

resuspended. Decline of compound was analyzed by HPLC-MS/MS. CL_{int} (*in vitro* hepatic intrinsic clearance) was calculated as follows:

CL_{int} = Dose / AUC = (C_0/CD) / (AUD + C_{last}/k) x 1000/60

C_0: initial concentration in the incubation [µM];

CD: cell density of vital cells [cells/mL];

AUD: area under the data [µM x h];

C_{last}: concentration of last data point [µM];

k: slope of the regression line for compound decline [h^{-1}].

The calculated *in vitro* hepatic intrinsic clearance was scaled up to the intrinsic *in vivo* hepatic clearance ($Cl_{int\ in\ vivo}$) and used to predict hepatic *in vivo* blood clearance (CL) by the use of a liver model (well-stirred model), as follows:

$CL_{int,\ in\ vivo}$ [mL/min/kg] = (CL_{int} [µL/min/10^6cells] x hepatocellularity [10^6 cells/g liver] x liver factor [g/kg body weight]) / 1000

CL [mL/min/kg] = $CL_{int,\ in\ vivo}$ [ml/min/kg] x hepatic blood flow [ml/min/kg] / ($CL_{int,\ in\ vivo}$ [ml/min/kg] + hepatic blood flow [mL/min/kg])

The *in vivo* blood clearance was transformed into percent of the hepatic blood flow (% Qh):

% Qh = CL [mL/min/kg] / hepatic blood flow [mL/min/kg]) x 100

Hepatocellularity, human: 1.2 x10^7 cells/g liver;

Liver factor, human: 25.7 g/kg body weight;

Hepatic blood flow, human: 21 mL/(min x kg).

***Rat Brain Aβ Lowering* Assay (Assay 5)**

The *in vivo* efficacy of compounds of the invention was demonstrated in a rat brain Aβ lowering (reduction) assay, and the data are presented in Table 3. Male Sprague-Dawley rats, 5 to 6 weeks of age, were used to demonstrate the ability of compounds of the invention to reduce brain amyloid peptides Aβ1-x. Compounds were administered via oral gavage in 1% Polysorbate-80 and 0.5% Natrosol®, at the single dosages indicated in Table 3. The animals were sacrificed 3 hrs after dosing, and brains were excised, dissected into cerebellum and left and right cerebra and flash-frozen in liquid nitrogen.

The cerebrum was homogenized (5 volumes per weight) in 20 mM Tris-HCL, pH 8.5, 0.2% Triton-X100 supplemented with protease inhibitors (cOmplete, Roche Applied Science) at 4°C using a glass Dounce homogenizer. The homogenate was centrifuged at 120,000×g for 60 min at 4°C, and

the supernatant was collected and analyzed for Ab1-x using immunoassay with chemiluminescent detection (Meso-Scale Discovery, Rockville, MD (MSD)).

Streptavidin 96-well plates (MSD) were pre-blocked with 5% Blocker A solution (MSD) for 1 hr at rt on an orbital shaker and washed 4 times with phosphate buffered saline (PBS). The wells were pre-coated with 20 ng/well of biotinylated antibody SIG-39155 (Clone M3.2, specific for amino acids 10-15 of the rodent Aβ) for 1 hr at rt and washed 4 times with PBS. For Aβ1-x analysis, 25 µl of either the cleared brain lysates or Aβ1-40 standards (8-500 pg/ml, with 2x increment) were incubated for 1 hr at rt with constant shaking. The wells were washed 4 times with PBS, and 25 µl of the detection antibody (Sulfo-TAG labeled anti-Aβ40 antibody supplied by MSD) was added and incubated for 1 hr at rt. After 4 washes with PBS, 150 µl of the chemiluminescence detection reagent (Read Buffer T, MSD) was added, and the plate was read on an MSD Sector Imager 6000 instrument. The calibration curve was fit into a non-linear four-parameter regression model, and the Aβ1-x concentrations were calculated for each well containing the cleared brain lysates. The percent of Aβ lowering was calculated based on the difference with the average Aβ concentration obtained for the brains from the animals treated with vehicle alone.

Table 1 shows the following properties of the compounds of the present invention: BACE1 inhibitory potency as measured in assay 1, hERG inhibition as measured in assay 2, first effect concentration (FEC) of phospholipidosis as measured in assay 3, and metabolic stability as measured in assay 4.

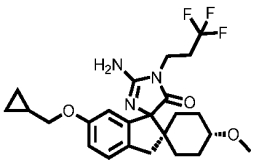
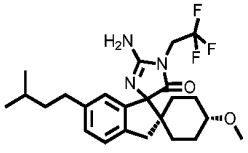
Table 1.

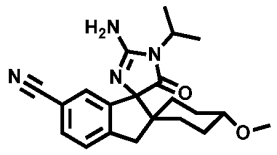
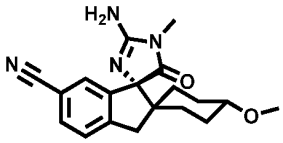
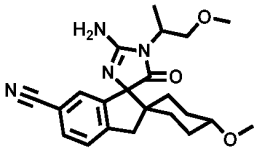
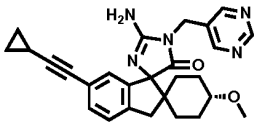
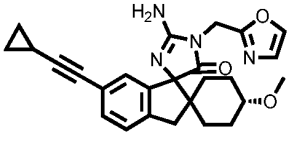
Example #	BACE1 IC_{50} nM (assay 1)	% Inhibition hERG @ 10 µM (assay 2)	Phospholipidosis FEC IC_{50} µM (assay 3)	*In vitro* Human Hepatocytes % Qh @ 1 µM (assay 4)
1	14.6	13	400	0
2	10.3	4.5	400	1.6
3	3.0	20	200	3.1
4	2.7	13	800	6.1
5	2.6	12	400	6.1
6	6.3	1.8	400	11
7	3.4	15	400	13
8	1.9	6	800	19.1
9	10.7	2.5	400	12.4
10	10.6	33	>100	0
11	14.6	19	200	0

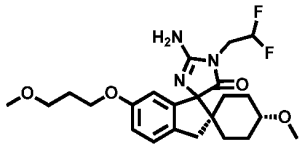
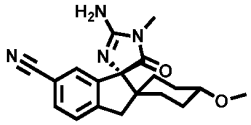
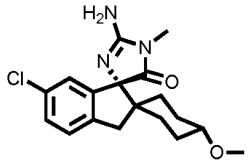
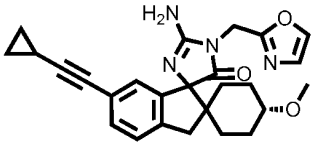
Example #	BACE1 IC_{50} nM (assay 1)	% Inhibition hERG @ 10 µM (assay 2)	Phospholipidosis FEC IC_{50} µM (assay 3)	*In vitro* Human Hepatocytes % Qh @ 1 µM (assay 4)
12	6.8	15	100	0
13	8.7	12	200	4.2
14	4.5	27	200	5.2
15	9.7	15.2	800	22.9
16	9.4	1.4	200	19

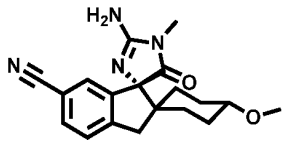
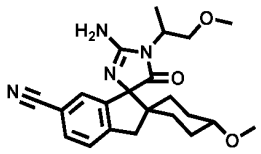
Table 2 provides data showing that compounds of the present invention have at least one of the following properties relative to certain comparator compounds described in WO2010/105179: 1) significantly lower IC_{50} inhibitory values in a BACE1 enzymatic assay, significantly lower percent inhibition of hERG, significantly lower propensity to cause phospholipidosis, and significantly greater metabolic stability relative.

Table 2.

Example #	BACE1 IC50 nM (Assay 1)	% Inhibition hERG @ 10 µM (Assay 2)	Phospholipidosis FEC IC50 µM (Assay 3)	*In vitro* Human Hepatocytes % Qh @ 1 µM (Assay 4)
Comparison 1				
1	14.6	13	400	0
 428 in WO2010/105179	8.3	87	-	-
 512 in WO2010/105179	3.5	89	-	88

Comparison 2				
10	10.6	33	>100	0
 121 in WO2010/105179	107	-	-	-
 174 in WO2010/105179	16	90	400	14
Comparison 3				
3	3.0	20	200	3.1
 251 in WO2010/105179	256	-	-	-
Comparison 4				
12	6.8	15	100	0
 255 in WO2010/105179	1.1	60	25	36
 249 in WO2010/105179	5.1	60	-	8.5

Comparison 5				
2	10.3	4.5	400	1.6
 602 in WO2010/105179	7.3	36	50	43
 174 in WO2010/105179	16	90	400	14
Comparison 6				
11	14.6	19	200	0
 172 in WO2010/105179	19	58	100	-
 249 in WO2010/105179	5.1	60	-	8.5

Comparison 7				
8	1.9	6	800	19.1
 174 in WO2010/105179	16	90	400	14
 251 in WO2010/105179	256	-	-	-

The ability of compounds of the invention to reduce brain Aβ was demonstrated in rats, as described in Assay 5, and the *in vivo* efficacy data are presented in Table 3.

Table 3.

Example	Dose (mg/kg)	% Aβ Reduction
1	25	25
2	12.5	40
4	12.5	21
7	25	58
9	25	42

Method of Treatment

The present invention is directed to compounds which are useful in the treatment of disorders or diseases characterized by elevated β-amyloid deposits or β-amyloid levels in a subject wherein the inhibition of the activity of the β-secretase enzyme (BACE1) is of therapeutic benefit, including but not limited to the treatment, amelioration or prevention of neurodegenerative disorders, disorders characterized by cognitive decline, cognitive impairment, dementia and diseases characterized by production of β-amyloid deposits and/or neurofibrillary tangles.

Compounds of the present invention are useful for treatment of Alzheimer's disease, Trisomy 21 (Down Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), senile dementia, cerebral amyloid angiopathy, degenerative dementia, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, dry age related macular degeneration (AMD), and glaucoma. The "dry" form of AMD, also known as "central geographic atrophy", results from atrophy to the retinal pigment epithelial layer below the neurosensory retina, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye. No medical or surgical treatment is currently available for this condition. Treatments available so far (*e.g.*, suggested by the National Eye Institute) include the use of vitamin supplements with high doses of antioxidants, lutein and zeaxanthin, which may slow the progression of dry macular degeneration. Glaucoma is a disease where fluid pressure inside the eye increases, causing irreversible damage to the optic nerve and loss of vision. Abeta colocalizes with apoptotic retinal ganglion cells in experimental glaucoma and induces significant retinal ganglion cell apoptosis in a dose- and time-dependent manner.

Accordingly, the present invention relates to a compound or a pharmaceutically acceptable salt thereof as a medicament.

Furthermore, the present invention relates to the use of a compound in the treatment of a disease and/or condition wherein the inhibition of the activity of the β-secretase enzyme (BACE1) is of therapeutic benefit.

Furthermore, the present invention relates to the use of a compound in the treatment of neurodegenerative disorders, disorders characterized by cognitive decline, cognitive impairment, dementia and diseases characterized by production of β-amyloid deposits or neurofibrillary tangles.

Therefore, the present invention relates to the use of a compound of the present invention in the treatment of Alzheimer's disease, Trisomy 21 (Down Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), senile dementia, cerebral amyloid angiopathy, degenerative dementia, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, dry AMD, and glaucoma.

The present invention also provides a method for the treatment of a disorder related to or associated with excessive BACE1 activity in a patient in need thereof which comprises administering to said patient an effective amount of a disclosed compound or a pharmaceutically acceptable salt thereof. The present invention also provides methods for inhibiting the activity of BACE1 in a subject in need thereof, comprising administering to a subject and/or contacting a receptor thereof

with an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof. The present invention also provides methods of ameliorating β-amyloid deposits in a subject in need thereof, comprising administering to said subject an effective amount of at least one disclosed compound or a pharmaceutically acceptable salt thereof.

The invention includes a therapeutic method for treating or ameliorating an BACE1 mediated disorder in a subject in need thereof comprising administering to a subject in need thereof an effective amount of a compound of the invention described herein, or pharmaceutically acceptable salts thereof or composition thereof.

As used herein, the term "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

As used herein, the term "treating" or 'treatment" refers to obtaining desired pharmacological and/or physiological effect. The effect can be prophylactic (*i.e.*, reducing the likelihood of developing the disorder or disease) or therapeutic, which includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator associated with the disorder; or delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome.

The dose range of the compounds according to the present invention applicable per day is usually from 0.1 to 3000 mg, preferably from 1 to 2000 mg , more preferably from 10 to 1000 mg, most preferably, 50 or 500 mg. Each dosage unit may conveniently contain from 0.1 to 1000 mg, preferably 25 to 250 mg.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

Pharmaceutical Compositions

Suitable preparations for administering the compounds of the present invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders, etc. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 95 wt.-%, preferably 5 to 90 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds of the invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

Combination Therapy

In one embodiment, the present invention includes combination therapy for treating or ameliorating a disease or a disorder described herein. The combination therapy comprises administering a combination of at least one compound of the present invention with one or more agent selected from the group of, for example, gamma-secretase inhibitors or modulators; amyloid aggregation inhibitors blocking the formation of Abeta oligomers or Abeta fibrils (*e.g.*, ELND-005); directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants (*e.g.*, vitamin E or ginkolide); anti-inflammatory substances (*e.g.*, Cox inhibitors, NSAIDs additionally or exclusively having Abeta lowering properties); HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors (*e.g.*, donepezil, rivastigmine, tacrine, and galantamine); NMDA receptor antagonists (*e.g.*, memantine); AMPA receptor agonists; AMPA receptor positive modulators, AMPAkines, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone (*e.g.*, ibutamoren mesylate and capromorelin); CB-1 receptor antagonists or inverse agonists; antibiotics (*e.g.*, minocyclin or rifampicin); PDE2, PDE4, PDE5, PDE9, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, antidepressants, such as citalopram, fluoxetine, paroxetine, sertraline and trazodone; anxiolytics, such as lorazepam and oxazepam; antiphychotics, such as aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced. The compounds according to the invention may also be used in combination with immunotherapies (*e.g.*, active immunization with Abeta or parts thereof or passive immunization with humanized anti-Abeta antibodies or nanobodies) for the treatment of the above-mentioned diseases and conditions.

Combination therapy includes co-administration of the compound of the invention with one or more other agent, sequential administration of the compound and one or more other agent, administration of a composition containing a compound and one or more other agent, or simultaneous administration of separate compositions containing the compound and one or more other agent.

EXPERIMENTAL SECTION

Methods of Preparation of Compounds

Compounds of the invention can be prepared employing conventional methods that utilize readily available reagents and starting materials. The reagents used in the preparation of the intermediates of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature.

Microwave reactions were carried out in CEM reactor using discovery SP system or in Biotage, Initiator 60 EXP. Where NMR data are presented, spectra were obtained in Varian -400 (400 MHz). Spectra are reported as ppm downfield from tetramethylsilane with number of proton, multiplicities and, in certain instances, coupling constants indicated parenthetically along with reference to deuterated solvent. Compounds were purified by basic preparative HPLC method as described below.

Method 1:

Mobile phase A: water with 0.05% NH_4OH; Mobile phase B: ACN; Flow rate: 25 mL/min; Detection: UV 220 nm / 254 nm; Column: Phenomenex Gemini C18 250*30mm*5um; Column temperature: 30 °C.

Time in min	%A	%B
0.0	68	32
12.00	38	62
12.20	0	100
13.5	0	100
13.7	90	10

Method 2:

Mobile phase A: water with 0.05% NH_4OH; Mobile phase B: ACN; Flow rate: 25 mL/min; Detection: UV 220 nm / 254 nm; Column: Durashell C18 250*30mm*5um; Column temperature: 30 °C.

Time in min	%A	%B
0.0	67	33
12.00	47	53
12.20	0	100
13.5	0	100
13.7	90	10

LC-MS data were obtained by utilizing the following chromatographic conditions:

Method 1:

HPLC System: Waters ACQUITY; Column: Waters ACQUITY CSH™ C18 1.7 µM.

Guard column: Waters Assy. Frit, 0.2 µM, 2.1 mm; Column tem: 40 °C.

Mobile Phase: A: TFA: Water (1 : 1000, v:v) Mobile phase B: TFA: ACN (1: 1000, v:v); Flow Rate: 0.65 mL/min; Injection Volume: 2 µL; Acquisition time: approximately 1.5 minute.

Gradient Program:

Time (min)	B%
0	10
0.8	90
1.20	90
1.21	10

Mass Spectrometer Parameters

Mass Spectrometer: Waters SQD; Ionization: Positive Electrospray Ionization (ESI); Mode Scan (100-1400 m/z in every 0.2 second); ES Capillary Voltage: 3.5 kV; ES Cone Voltage: 25 v.

Source Temperature: 120 °C; Disolvation Temperature: 500 °C; Desolvation Gas Flow: Nitrogen Setting 650 (L/h); Cone Gas Flow: Nitrogen Setting 50 (L/h).

Method 2:

HPLC System: Waters Alliance with DA- and MS-Detector; Column: Waters XBridge C18 4.6 x 30 mm, 3.5 µm; Column temp: 60 °C.

Mobile Phase: A: TFA: Water (1 : 1000, v:v) Mobile phase B: MeOH; Flow Rate: 4 mL/min.

Gradient Program:

Time (min)	B%
0	5
1.6	100
1.85	100
1.9	5

Method 3:

HPLC System: Waters Alliance with DA- and MS-Detector; Column: Waters XBridge C18 4.6 x 30 mm, 3.5 µm; Column temp: 60 °C.

Mobile Phase: A: TFA: Water (1: 1000, v:v) Mobile phase B: ACN; Flow Rate: 5 mL/min.

Gradient Program:

Time (min)	B%
0	3
0.2	3
1.6	100
1.7	100

Method 4:

HPLC System: Waters Alliance with DA- and MS-Detector; Column: Waters XBridge C18 4.6 x 30 mm, 3.5 µm; Column temp: 60 °C.

Mobile Phase: A: TFA: Water (1 : 1000, v:v) Mobile phase B: MeOH; Flow Rate: 4 mL/min.

Gradient Program:

Time (min)	B%
0	5
0.2	5
1.5	100
1.75	100
1.85	5

SFC separation and characterization of compounds were carried out under the following methods:

Method A:

Instrument: Thar SFC 80; Column: AD 250mm*30mm, 5um; Mobile phase: A: Supercritical CO_2, B: IPA (0.05% DEA), A: B =80:20 at 60ml/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220 nm.

Method B:

Instrument: SFC MG2; Column: OJ 250mm*30mm, 5um; Mobile phase: A: Supercritical CO_2, B: MeOH(0.05% DEA), A:B =90:10 at 70ml/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm.

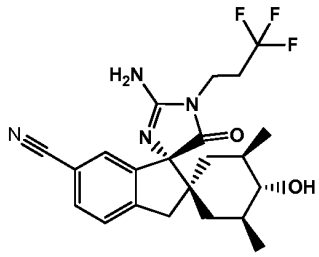
The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

Abbreviation	Meaning
ACN	acetonitrile
Boc	*tert*-butoxy carbonyl or *t*-butoxy carbonyl
Boc_2O	di-*tert*-butyl-dicarbnate
brine	saturated aqueous NaCl
DAST	(diethylamino) sulfur trifluoride
DCM	methylene chloride
DIEA	diisopropyl ethyl amine
DMA	dimethyl acetamide
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
Et	ethyl
dppf	1,1-bis(diphenylphosphino)ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiiimide hydrochloride
EtI	ethyl iodide
Et_3N	triethylamine
Et_2O	ethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HPLC	high performance liquid chromatography

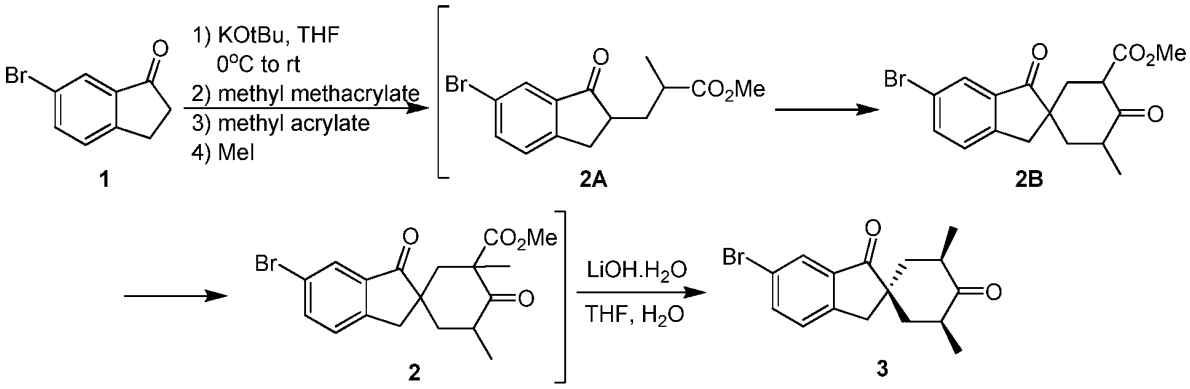
Abbreviation	Meaning
LDA	lithium diisopropylamide
min	minute
MeOH	methanol
MeI	methyl iodide
Me	methyl
Me_2S	dimethyl sulfide
MsCl	methane sulfonyl chloride
mL	milliliters
mmol	millimoles
mg	milligram
NaOMe	sodium methoxide
NCS	N-chlorosuccinamide
$PdCl_2dppf$	[1,1-bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$Pd2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
rt	room temperature
sat.	saturated
SFC	super critical fluid chromatography
t-BuOK	potassium tert butoxide
t-BuLi	tert butyl lithium
t-$BuNH_2$-BH3	tert butylamin-borane complex
t-BuOOH	tert butyl peroxide
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran

Abbreviation	Meaning
$Ti(OEt)_4$	titanium tetra ethoxide
TLC	thin layer chromatography
TMSI	trimethylsilyl iodide
v	volume
XPhos	dicyclohexylphosphino-2',4',6'-triiso-propyl-1,1'-biphenyl
$Zn(CN)_2$	zinc cyanide

Example 1



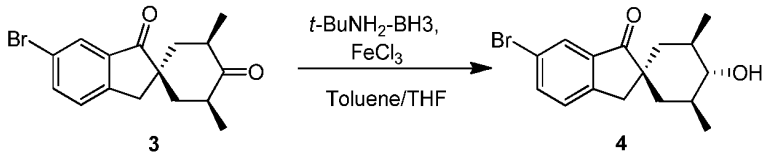
Step 1: Synthesis of intermediate 3.



To a mixture of 6-bromo-indan-1-one (100.00 g, 473.8 mmol) in anhydrous THF (1 L) at 0 °C was added *t*-BuOK (58.5 g, 521.2 mmol). After 5 minutes, the mixture was warmed to rt and was stirred for another 10 min before methyl methacrylate (49.8 g, 53.2 mL, 497.5 mmol, 1.05 eq) was added in one portion. After 2 h, methyl acrylate (49.0 g, 51.2 mL, 568.6 mmol, 1.2 eq) was added to the reaction mixture. After 3 h of stirring at rt, MeI (101 g, 44.3 mL, 710.7 mmol, 1.5 eq) was added to the reaction mixture, and the mixture was further stirred for 16 h. H_2O (1 L) was added followed by $LiOH*H_2O$ (79.5 g, 1895 mmol, 4.0 eq). The mixture was stirred for 28 h at rt. THF was removed

under reduced pressure. The residue was diluted with H_2O (1 L), filtered, and washed with H_2O until the filtrate was neutral. The product was washed with MeOH to afford 50 g of intermediate **3**.

Step 2: Synthesis of intermediate 4.



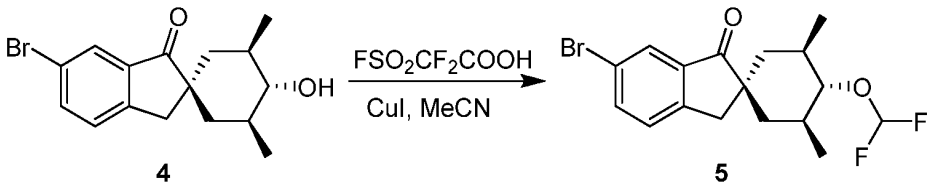
3 4

A mixture of $FeCl_3$ (6.0 g, 37.0 mmol) and toluene (60 mL) was cooled to 0 °C. A mixture of intermediate **3** (11.9 g, 37.0 mmol) in THF (48 mL) was added to the mixture. The mixture was stirred for 5 min at 0 °C and then cooled to -10 °C. A solution of *t*-$BuNH_2$-BH_3 (3.5 g, 40.7 mmol) in THF (12 mL) was added dropwise to the reaction mixture at -10 °C. The reaction mixture was stirred at about -10 °C for 30 min, quenched with aqueous HCl solution (6N, 10 mL), stirred at about 0 °C for 30 min, and then allowed to warm to rt. The mixture was concentrated to remove THF, and toluene (60 mL) was added. The aqueous layer was removed, and the organic phase was washed with water (3 x 60 mL). The organic phase was concentrated to half volume, heated to 50 °C to obtain a solution, and then cooled to 0 °C over 1 h and held at 0 °C for 1 h. The solid was filtered and washed with cold (0 °C) toluene (12 mL), and dried under vacuum to give compound **4** (9.93 g).

LC-MS (method 1): tR = 1.24 min, MS (ESI) m/z 323.1 $[M+H]^+$.

^{1}H-NMR ($CDCl_3$): δ: 7.889-7.894 (s, 1H), 7.671-7.696 (d, 1H), 7.311-7.332 (d, 1H), 3.605 (s, 1H), 2.981 (s, 2H), 1.769-1.797 (m, 4H), 1.072-1.082 (m, 2H), 1.019-1.056 (m, 6H).

Step 3: Synthesis of intermediate 5.

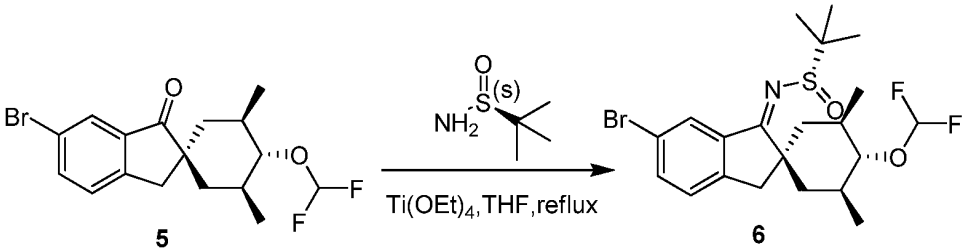


4 5

A mixture of intermediate **4** (6.0 g, 18.6 mmol) and CuI (0.71 g, 3.72 mmol, 0.2 eq) in ACN (120 mL) was heated to 60 °C and 2-(fluorosulfonyl)difluotoacetic acid (13.2 g, 74.4 mmol) was added. The mixture was stirred at 60 °C for 20 min. The mixture was cooled, quenched with H_2O and extracted with EtOAc. The combined organic phases were washed with H_2O and brine, dried

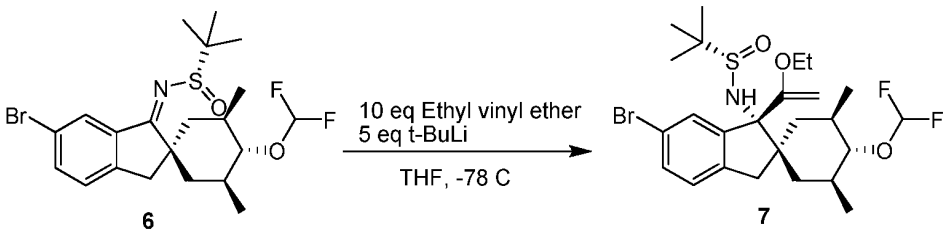
over anhydrous Na_2SO_4, concentrated to afford 15 g crude product, which was purified by column on slica gel (eluent: petroleum ether: ethyl acetate from 300: 1 to 50: 1) to afford intermediate **5** (4.6 g).

Step 4: Synthesis of intermediate 6.



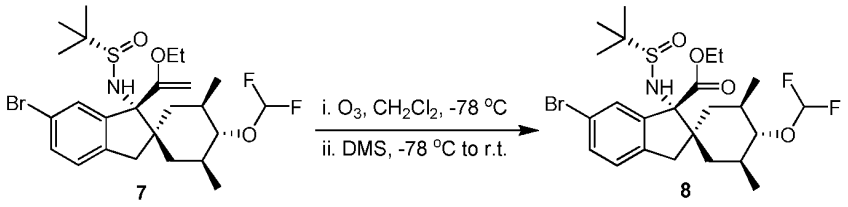
The mixture of intermediate **5** (3.4 g, 9.2 mmol) and titanium (IV) ethoxide (21 g, 92 mmol) in dry THF (40 mL) was stirred at rt for 1 h. (*S*)-*N*-tert-butylsulfinamide (4.5 g, 36.8 mmol) was added and the resulting mixture was stirred at 80 °C under N_2 atmosphere for 12 h. The reaction mixture was cooled and water (400 mL) was added. The mixture was filtered and the aqueous layer was extracted with ethyl acetate (3 × 400 mL). The separated organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1) to yield intermediate **6** (3.9 g).

Step 5: Synthesis of intermediate 7.



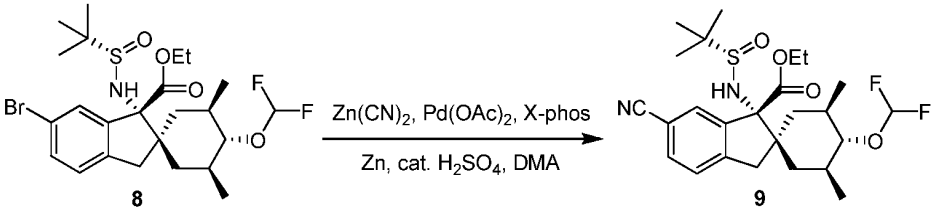
A *t*-BuLi solution (32 mL, 41.0 mmol, 1.3 M in hexane) was added dropwise to a solution of ethyl vinyl ether (7.05 g, 82 mmol) in anhydrous THF (50 mL) at -78 °C under N_2 atmosphere and the mixture was stirred for 20 min. The resulting mixture was stirred at 0 °C for another 45 min and then cooled to -78 °C. A pre-cooled solution at -78 °C, containing intermediate **6** (3.9 g, 8.2 mmol) in anhydrous THF (80 mL) was added dropwise and the mixture was stirred for 2 h at -78 °C. The reaction was quenched with sat. NH_4Cl (50 mL) aqueous solution and extracted with ethyl acetate (3 × 300 mL). The organic phases were combined and concentrated under reduced pressure. The crude product was purified by preparative HPLC (method 2) to afford intermediate **7** (3.3 g).

Step 6: Synthesis of intermediate 8.



Intermediate **7** (10 g, 18.2 mmol) was added to a solution of MeOH in DCM (5:1, 100 mL) and cooled to -78 °C. Ozone was bubbled through the mixture for 20 min. After 10 minutes of additional stirring, the mixture was purged with N_2 for 15 minutes and then treated with Me_2S (20 mL) at -78 °C. It was allowed to warm to rt and stirred for 3 h at rt. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1 to 5:1) to yield intermediate **8** (6 g).

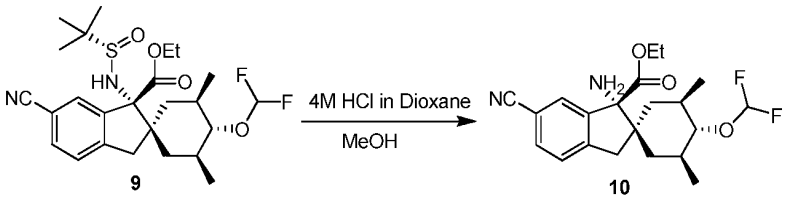
Step 7: Synthesis of intermediate 9.



Concentrated sulfuric acid (48 µL) was added to DMA (20 mL) and the solvent was purged with N_2 for 20 min. A 50 mL round bottom flask was charged with $Pd(OAc)_2$ (0.3 g) and Xphos (1.25 g) under N_2, then the above solvent was transferred in. The resulting mixture was heated at 80 °C for 30 min to give mixture **A**.

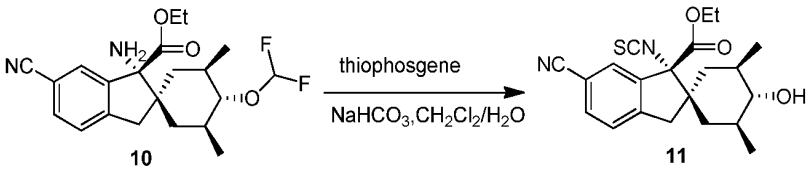
In an another flask, DMA (50 mL) was purged with N_2 and intermediate **8** (2.2 g, 4.0 mmol), $Zn(CN)_2$ (0.5 g, 4.0 mmol) and zinc dust (14.1 mg) were added. The mixture A was added to this solution, and the resulting mixture was heated at 90 °C for 1 h. The reaction mixture was cooled to rt, diluted with water (100 mL) and ethyl acetate (100 mL) and stirred for 10 minutes. The mixture was filtered through celite, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layer was washed with water, brine and dried and the solvent was removed under reduced pressure. The residue was purified on flash column on silica gel (petroleum ether: ethyl acetate; 20:1 to 3:1) to yield intermediate **9** (1.5 g).

Step 8: Synthesis of intermediate 10.



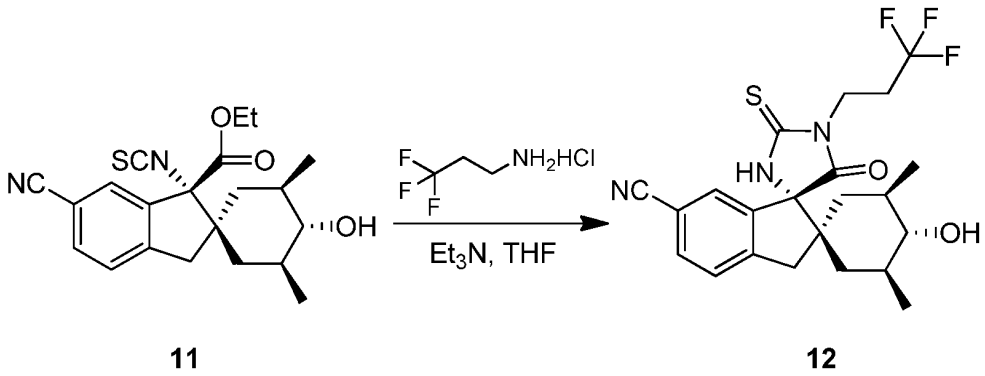
To a mixture of intermediate **9** (0.5 g, 1.01 mmol) in MeOH (11 mL) was added HCl in dioxane (4 M, 2.25 mL). The resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure to afford crude intermediate **10** (529 mg) which was used for the next step without further purification.

Step 9: Synthesis of intermediate 11.



To a solution of intermediate **10** (529 mg, 1.35 mmol) in DCM (6 mL), H_2O (6 mL) and $NaHCO_3$ (1.13 g, 13.5 mmol) were added at rt. Thiophosgene (310 mg, 2.7 mmol) was added with vigorous stirring and the mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 40 mL). The organic layers were combined and washed with brine (2 × 40 mL), dried and the solvent was removed under reduced pressure to afford crude intermediate **11** (520 mg), which was used for the next step without further purification.

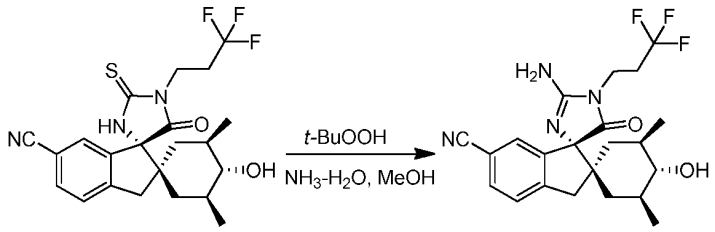
Step 10: Synthesis of intermediate 12.



To a mixture of intermediate **11** (200 mg, 0.52 mmol) in THF (10 mL) was added 3, 3, 3-trifluoro-propylamine hydrochloride (156 mg, 1.04 mmol) and TEA (526 mg, 5.2 mmol). The mixture was stirred overnight at rt. The reaction was diluted with water and extracted with EtOAc (30

mL). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude product. The residue was purified by preparative TLC (petroleum ether: ethyl acetate; 1: 1) to afford intermediate **12** (265 mg).

Step 11: Synthesis of Example 1.



To a mixture of intermediate **12** (265 mg, 0.59 mmol) in MeOH (10 ml), aqueous ammonium hydroxide (1.5 mL) and *t*-BuO_2H (0.8 mL, 5.0 M solution in nonane) were added. The mixture was stirred at rt for 16 h and then quenched with sat. aqueous $Na_2S_2O_3$ solution (0.5 mL). The residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (method 2) to give Example **1** (86.9 mg).

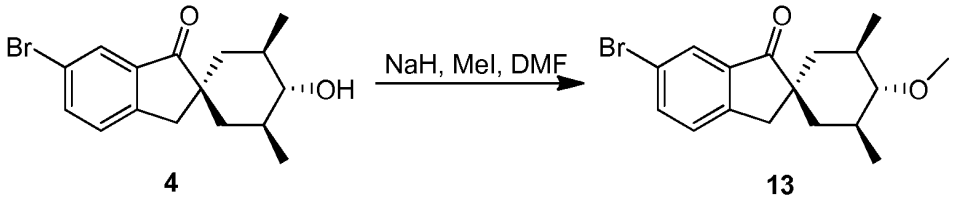
LC-MS (method 1): tR = 0.92 min, MS (ESI) m/z 435.2 $[M+H]^+$.

^{1}H-NMR (CD_3OD): δ 7.65 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.30 (s, 1H), 3.82-3.85 (t, J = 7.6 Hz, 2H), 3.24 (s, 1H), 3.15 (d, J = 16.0 Hz, 1H), 2.56 (m, 3H), 1.23-1.79 (m, 5H), 0.956-1.02 (m, 7H).

^{19}F NMR: δ -66.64.

Synthesis of Intermediate 20

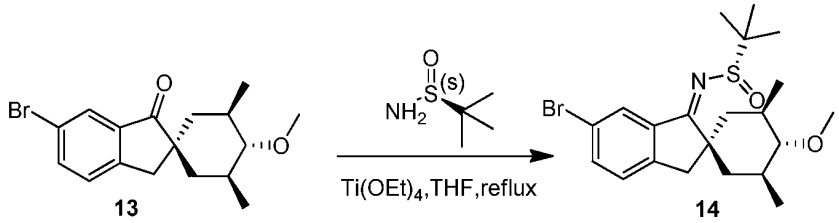
Step 1: Synthesis of intermediate 13.



To a mixture of intermediate **4** (20.0 g, 61.9 mmol) in DMF (200 mL) was added NaH (5.0 g, 123.8 mmol) at 0 °C and the mixture was stirred for 15 min at 0 °C. Methyl iodide (17.6 g, 123.8

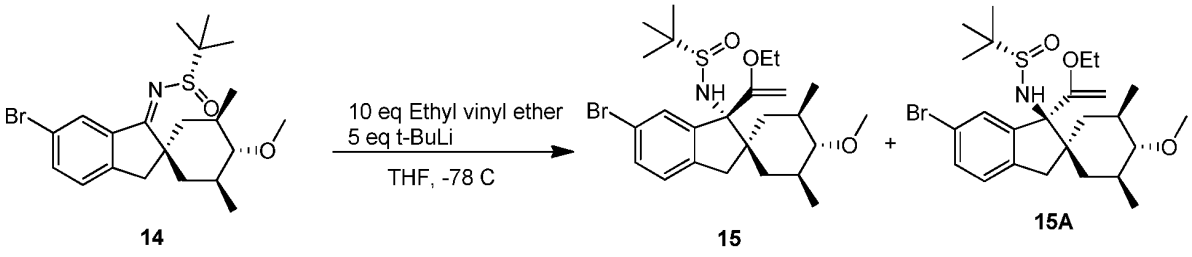
mmol) was added at 0 °C and the mixture was warmed to rt and stirred for 1.5 h at rt. The mixture was quenched with H_2O and extracted with EtOAc. The combined organic phases were washed with H_2O followed by brine, dried and concentrated to afford crude product, which was purified by column on silica gel (petroleum ether: ethyl acetate; 30:1 to 5:1) to afford intermediate **13** (20 g).

Step 2: Synthesis of intermediate 14.



A mixture of intermediate **13** (20.0 g, 59.3 mmol) and titanium (IV) ethoxide (108.2 g, 474.4 mmol) in dry THF (200 ml) was stirred at rt for 1 h. (*S*)-N-tert-butylsulfinamide (29 g, 237.2 mmol) was added and the resulting mixture was stirred at 80 °C under N_2 atmosphere overnight. The reaction mixture was cooled and water (400 ml) was added. The mixture was filtered and the aqueous layer was extracted with ethyl acetate (3 × 400 mL). The combined organic phase was dried and concentrated under reduced pressure to give crude intermediate. This was purified by column chromatography on silica gel (petroleum ether: ethyl acetate; 20:1) to yield intermediate **14** (18.4 g).

Step 3: Synthesis of intermediate 15.



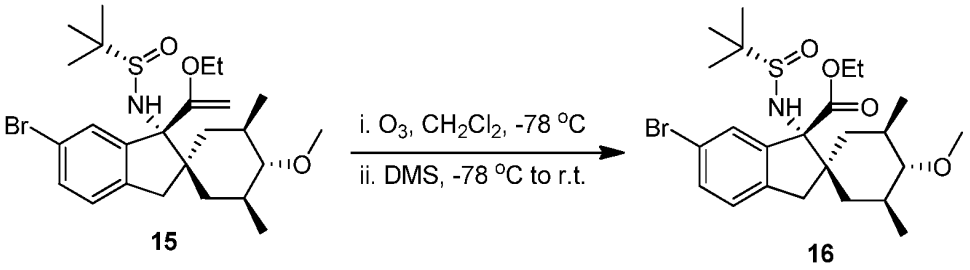
t-BuLi (131 mL, 170.3 mmol, 1.3 M in hexane) was added dropwise to a solution of ethyl vinyl ether (12.3 g, 170.3 mmol, 5.0 eq) in anhydrous THF (100 mL) at -78 °C under N_2 and the mixture was stirred for 20 min. The resulting mixture was stirred at 0 °C for another 45 min and re-cooled to -78 °C. A pre-cooled solution of intermediate **14** (15.0 g, 34.1 mmol) in anhydrous THF (50 mL) at -78 °C was added dropwise and the mixture was stirred for 2 h at -78 °C. The reaction mixture was quenched with sat. NH_4Cl aqueous solution (50 mL) and extracted with EtOAc (3 × 300 mL). The organic phases were combined and concentrated under reduced pressure to give the residue,

which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate; 50:1 to 3:1) to afford intermediates **15** (11 g) and **15A** (1.44 g), respectively.

LC-MS (method 1) tR = 5.67 min; MS (ESI) m/z 514.2 $[M+H]^+$.

^{1}H-NMR (CD_3OD): δ 7.546 (s, 1H), 7.454-7.479 (d, 1H), 7.208-7.228 (d, 1H), 4.620-4.755 (d, 1H), 4.373-4.381 (m, 1H),4.048-4.055 (m, 1H), 3.844-3.903 (m, 2H), 3.458-3.474 (s, 3H), 2.986-3.000 (m, 2H), 2.326-2.377 (m, 1H), 1.969-2.001 (m, 1H), 1.671 (s, 1H), 1.457-1.520 (t, J = 12 Hz, 3H),1.373-1.408 (m, 2H), 1.328 (s, 9H), 1.169-1.278 (m, 5H), 1.073-1.106(d, 3H).

Step 4: Synthesis of intermediate 16.

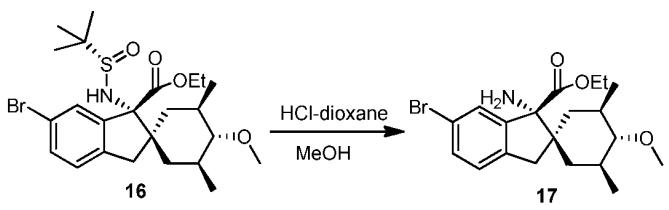


Intermediate **15** (4.8 g, 9.37 mmol) was added to a mixture of DCM in MeOH (5:1, 40 mL), and the mixture was cooled to -78 °C. Ozone was bubbled through the mixture for 20 min. The mixture was purged with N_2 for 10 minutes and treated with Me_2S (10 mL) at -78 °C. The mixture was allowed to warm up to rt and stirred at rt for 3 h. The solvent was removed under vacuum, the residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate; 20:1 to 8:1) to give intermediate **16** (3.5 g).

LC-MS (method 1): tR = 1.30 min; MS (ESI) m/z 516.1 $[M+H]^+$.

^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.42-7.44 (d, J = 8.0 Hz, 1H), 7.09-7.11 (d, J = 8.0 Hz, 1H), 4.40 (s, 1H), 4.26-4.39 (m, 2H), 3.44 (s, 3H), 2.93-2.97 (d, J = 15.6 Hz, 1H), 2.70-2.74 (d, J = 15.2 Hz, 1H), 2.22-2.30 (t, J = 10.0 Hz, 1H), 1.75-1.79 (m, 1H), 1.61-1.66 (m, 1H), 1.54-1.57 (m, 2H), 1.32-1.38 (m, 4H), 1.14 (s, 9H), 1.06-1.08 (d, J = 6.0 Hz, 3H), 0.89-0.91 (d, J = 6.0 Hz, 3H), 0.67-0.74 (m, 1H).

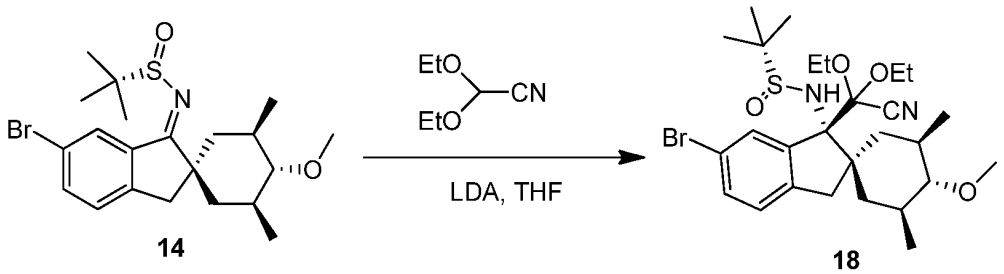
Step 5: Synthesis of intermediate 17.



To a mixture of intermediate **16** (5.1 g, 10 mmol) in MeOH (10 mL) was added HCl in dioxane (4.0M, 8.0 mL). The resulting mixture was stirred for 1 h. Solvent was removed under reduced pressure to afford crude intermediate **17** (6.0 g), which was used for the next step without further purification.

Alternative synthesis of intermediate 17

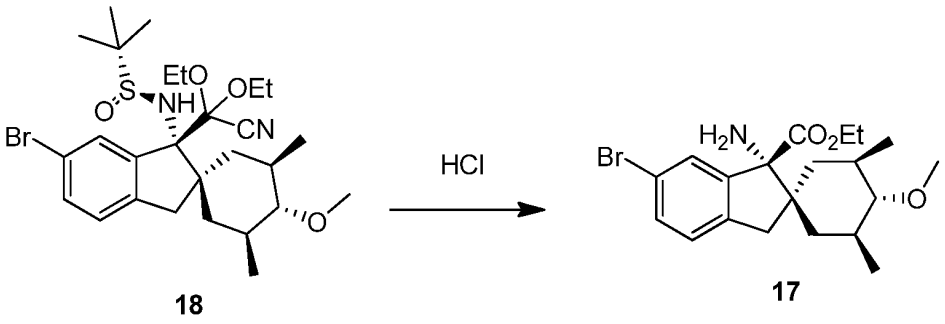
Step 1. Synthesis of intermediate 18.



A mixture of intermediate **14** (5.00 g, 11.4 mmol), diethoxyacetonitrile (3.5 mL, 24.4 mmol) and THF (50 mL) was cooled to -7 °C and treated dropwise with LDA (25.0 mL, 45.0 mmol, 1.8M in THF/heptane/ethylbenzene). The mixture was stirred at -7 to -2 °C for 2 h, and then quenched with water (50 mL) and sat. aqueous NH_4Cl (25 mL). Hexanes (100 mL) was added, and the layers were separated. The organic layer was washed with water, brine, and was concentrated under reduced pressure to give crude intermediate **18** (9.00 g) which was used directly in the next step.

LC-MS (method 1): tR = 3.74 min, MS (ESI) m/z 523.2/525.2 $[M\text{-}OEt+H]^+$

Step 2. Synthesis of intermediate 17.

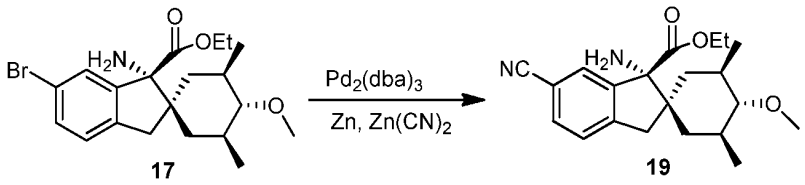


A mixture of above intermediate **18** (9.00 g, 11.4 mmol) in EtOH (30 mL) was treated with aqueous HCl (6 N, 20 mL). The reaction mixture was heated at 75 °C for 24 h and cooled to rt. The reaction was extracted with toluene (50 mL), and the aqueous phase was basified (pH = 8) with

aqueous NaOH (2 N, ~60 mL). Toluene (100 mL) was added and the mixture was stirred for 10 minutes. The organic layer was separated and washed with aqueous $NaHCO_3$, brine and concentrated under reduced pressure. Hexanes was added and the solution was concentrated under reduced pressure to give crude intermediate **17** (3.47 g) which was used directly in the next step.

LC-MS: tR = 0.86 min, MS (ESI) m/z 410.2/412.2 $[M+H]^+$

Step 6: Synthesis of intermediate 19.

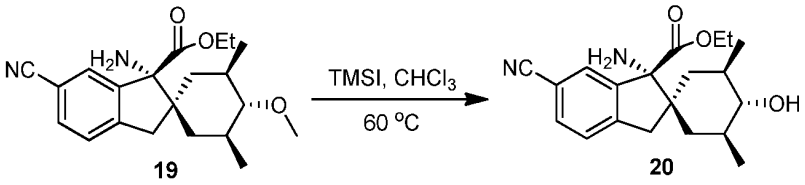


17 19

A mixture of compound **17** (500 mg, 1.9 mmol) under nitrogen, $Zn(CN)_2$ (300 mg, 2.6 mmol), $Pd_2(dba)_3$ (150 mg, 0.16 mmol), dppf (160 mg, 0.32 mmol) and Zn dust (60 mg, 0.9 mmol) in DMF (15 mL) was heated to 120 °C for 3 h in CEM microwave reactor. The mixture was concentrated under vacuum and the residue was purified by column on silica gel (eluent: petroleum ether: ethyl acetate; 20: 1 to 8: 1) to afford intermediate **19** (300 mg).

LC-MS: t_R = 0.880; MS (ESI) m/z 308.1 $[M+H]^+$.

Step 7: Synthesis of intermediate 20.

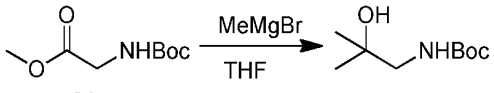


19 20

To a solution of intermediate **19** (3.1 g, 7.4 mmol) in $CHCl_3$ (20 ml) was added TMSI (10 ml) and stirred at 65 °C for 2 h. The mixture was cooled to rt and sat. $Na_2S_2O_3$ (10 mL), sat. $NaHCO_3$ aqueous solution (10 mL) were added, and the mixture was stirred for 10 minutes. The residue was partitioned between DCM (40 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford crude intermediate **20** (2.6 g), which was used for the next step without further purification.

Synthesis of intermediate 26

Step 1: Synthesis intermediate 22.

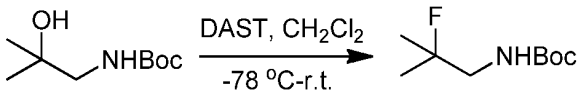


21 **22**

A mixture of intermediate **21** (2.0 g, 10.6 mmol) in anhydrous THF (20 mL) was added to methyl magnesium bromide (14 mL, 42 mmol, 3.0 M in Et_2O) at -30 °C under a N_2 atmosphere. The mixture was stirred at -30 °C for 4 h, and then quenched by addition of H_2O (40 mL) and aqueous HCl (1 M, 50 mL) with stirring at 0 °C. The mixture was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried, filtered and concentrated under vacuum to give the crude intermediate **22** (2.1 g), which was used directly in the next step without purification.

^{1}H NMR: ($CDCl_3$): δ 4.97 (br, 1H), 3.10 (s, 2H), 2.17 (br, 1H), 1.44 (s, 9H), 1.20 (s, 6H).

Step 2: Synthesis of intermediate 23.



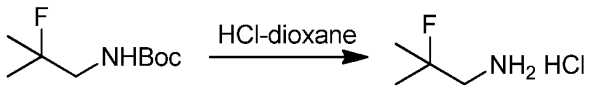
22 **23**

To a mixture of intermediate **22** (3.0 g, 15.9 mmol) in anhydrous DCM (50 mL) was added DAST (2.3 mL, 17.4 mmol) at -78 °C under a N_2 atmosphere. The mixture was stirred at -78 °C for 1 h, and then allowed to warm to rt overnight. The mixture was cooled to 0 °C, and quenched by slow addition of sat. aqueous layer $NaHCO_3$ (30 mL) with stirring at 0 °C. The mixture was separated, and the aqueous layer was extracted with DCM (2× 20 mL). The combined organic layer was washed with brine (2 × 30 mL), dried, filtered and concentrated under vacuum to yield the crude intermediate **23** (2.5 g), which was used directly in the next step without purification.

^{1}H NMR: ($CDCl_3$): δ 4.82 (br, 1H), 3.30-3.35 (d, J = 6.0 Hz, 1H), 3.24-3.26 (d, J = 6.0 Hz, 1H), 1.44 (s, 9H), 1.37 (s, 3H), 1.35 (s, 3H).

^{19}F NMR: ($CDCl_3$): δ -144.93.

Step 3: Synthesis of intermediate 24.



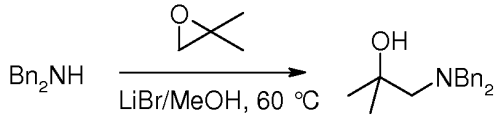
23 **24**

To a mixture of intermediate **23** (2.0 g, 10.5 mmol, crude) in anhydrous DCM (10 mL) was added HCl in dioxane (4 M, 10 mL, 40 mmol) with stirring. The mixture was stirred at rt for 2 h after which time the solvent was removed under reduced pressure. The residue was treated with a mixture of DCM-petroleum ether (1:1, 3 × 10 mL) and the precipitate was collected and dried under vacuum to yield the crude intermediate **24** (1.1 g), which was used directly in the next step without purification.

^{1}H NMR: (CD_3OD): δ 3.15-3.25 (d, J = 20.0 Hz, 2H), 1.51 (s, 3H), 1.48 (s, 3H). ^{19}F NMR: ($CDCl_3$): δ -147.59.

Intermediate **24** can alternatively be obtained from dibenzyl amine according to the following procedure:

Step 1: Synthesis of Intermediate 22a

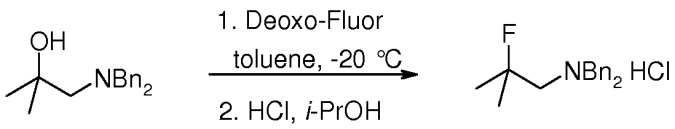


22a

To a slurry of LiBr (1.66 g, 19.06 mmol, 0.2 equiv) in MeOH (3.8 mL) was added Bn_2NH (18.80 g, 95.30 mmol, 1.0 equiv) at about 20-25°C. Isobutylene oxide (10.31 g, 142.95 mmol, 1.5 equiv) was added at a rate to maintain the temperature below 65 °C. After the addition was complete, the batch was stirred at about 60 °C for 6 h. The batch was cooled to about 20°C, and toluene (37.6 mL) and water (18.8 mL) were added. After stirring for about 5 min, the layers were separated. The organic phase was concentrated under vacuum to an oil, and toluene was added and the solution was again distilled to an oil. Compound **22a** was obtained as a toluene solution (33.88 g, 75.1 wt.%) in 99% yield and used directly in the next step.

^{1}H NMR: ($CDCl_3$): δ 1.11 (s, 6H), 2.42 (s, 1H), 2.56 (s, 2H), 3.70 (s, 4H), 7.23-7.35 (m, 10H).

Step 2: Synthesis of Intermediate 23a



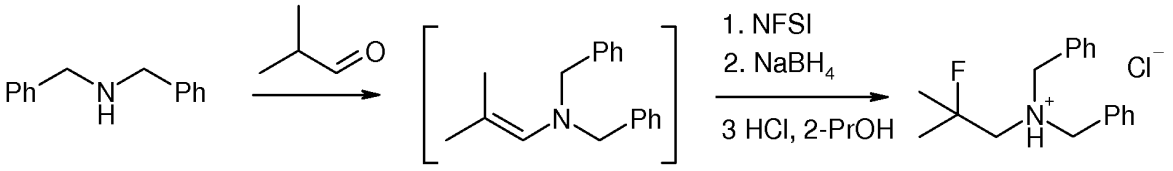
22a **23a**

A solution of intermediate **22a** (10.32 g, 75.1 wt.%, 28.77 mmol) in anhydrous toluene (40 mL) was cooled to -20 °C. Deoxo-Fluor (7.0 g, 31.64 mmol, 1.10 eq) was added dropwise while keeping the temperature below -10°C. The mixture was stirred at -20 °C to -10°C for 3 h. The reaction was then quenched by the addition of aqueous KOH solution (6.46 g of 85 wt.% KOH pellets, 96.86 mmol, 3.40 eq in 25.84 g of water) while keeping the temperature below 10°C. The mixture was warmed to rt and the layers were separated. The organic layer was washed with water (3 x 25 mL). The organic phase was concentrated under vacuum and repeatedly distilled with heptane until the water content was < 200 ppm. The crude product was diluted with heptane (25 mL) and filtered through a silica gel pad (8 g silica gel). The silica gel pad was rinsed with heptane (2 x 20 mL) and the combined heptane filtrates were distilled under vacuum to the minimum volume and repeatedly distilled with isopropanol. Isopropanol (40 mL) was added and the solution was cooled to -10 °C. Hydrogen chloride solution in isopropanol (8.3 mL, 5.2 N, 43.16 mmol, 1.50 eq) was added while keeping the temperature below 30 °C. After stirring at 20-25 °C for 1 h, the mixture was heated to 75 °C to get a clear solution and held at this temperature for 15 min. The mixture was cooled to 20-25 °C and stirred at this temperature for 2-3 h. The solid was filtered, washed with heptane, and dried under vacuum at 20-25 °C to give the product as a white solid (5.74 g, 91 wt.%) in 65% yield.

^{1}H NMR: ($CDCl_3$): δ 1.31-1.35 (d, J = 21.5 Hz, 6H), 3.35-3.38 (d, J = 18.8 Hz, 2H), 4.39-4.45 (dd, J = 18.6 Hz, J = 3.5 Hz, 4H), 7.50-7.62 (m, 10H).

^{19}F NMR: ($CDCl_3$): δ -143.58.

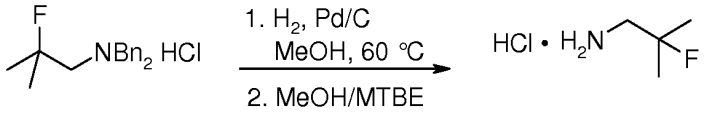
Intermediate **23a** can alternatively be obtained from dibenzyl amine according to the following procedure:



23a

To a reaction vessel equipped with a Dean-Stark trap (prefilled with isobutyraldehyde) was charged dibenzylamine (40.06 g, 203.06 mmol), isobutyraldehyde (19.04 g, 264.98 mmol, 1.30 equiv) and toluene (20 mL). The mixture was heated to reflux under nitrogen to remove water (~ 3.8 mL) in ~ 4 h, while the temperature was gradually raised to ~ 115 °C). The excess of isobutyraldehyde and toluene was then distilled under reduced pressure. The crude liquid was cooled to –10 °C and a solution of N-fluorobenzenesulfonimide (NFSI, 76.84 g, 243.67 mmol, 1.20 equiv) in *N,N*,-dimethyl acetamide (100 mL) was slowly added below 20 °C. The mixture was stirred at room temperature until complete conversion (5–20 h). The mixture was cooled to 0 °C and a solution of $NaBH_4$ (4.22 g, 111.68 mmol, 0.55 equiv) in *N,N*,-dimethyl acetamide (48 mL) was added below 20 °C. After addition, the mixture was stirred at room temperature for 2.5 h. The mixture was cooled to 10 °C and a solution of NaOH (10.56 g, 263.98, 1.50 equiv) in water (40 mL) was slowly added (gas was released), followed by 200 mL of water. The mixture was stirred at room temperature for 0.5 h, and extracted with heptane (250 mL). The organic layer was washed with water (2 x 150 mL) and distilled at normal pressure (up to 115 °C). 2-Propanol (150 mL) was added and the mixture was distilled to remove solvents (50 mL). Acetic anhydride (2.07 g, 20.29 mmol, 0.10 equiv) was added at ~30 °C and stirred for 0.5 h. To the mixture was added 4.5 M HCl in 2-propanol (54 mL, 243.67 mol, 1.20 equiv) at ~30 °C. The resulting suspension was stirred at 60 °C for 1 h, and then cooled to 20 °C in 1 h. The solid was filtered, rinsed with 2-propanol (50 mL), and dried to give a white solid (**23a**) (47.46 g, 97.7 % purity) in 74 % yield.

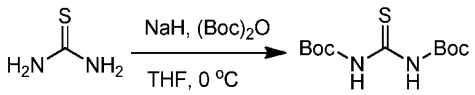
Step 3: Synthesis of Intermediate 24



23a **24**

To a hydrogenation vessel was charged 10% palladium on carbon (50% wet with water, 0.53 g, 0.25 mmol, 0.01 equiv), **23a** (8.74 g, 89.5 wt.%, 25.41 mmol, 1.00 equiv) and methanol (24 mL). The mixture was hydrogenated at 60 °C and 400 psi of H_2 for 5-8 h. After cooling to 20-25 °C, the mixture was filtered through a Celite pad, and the pad was rinsed with MeOH. The solvent was distilled under vacuum at 50°C to a volume of 4-5 mL. MTBE (25 mL) was added to the batch dropwise with stirring to form a slurry. After stirring for 30 min at 50°C, the batch was cooled to 20-25°C, held at this temperature for 1 h, and filtered. The solid was rinsed with MTBE and then dried at 25°C under vacuum for 4 h. Compound **24** was obtained as a white solid (3.24 g, 96 wt.%) in 96% yield. ^{1}H NMR: (CD_3OD): δ 1.44-1.49 (d, J = 21.2 Hz, 6H), 3.13-3.18 (d, J = 19.7 Hz, 2H). ^{19}F NMR: ($CDCl_3$): δ -147.55.

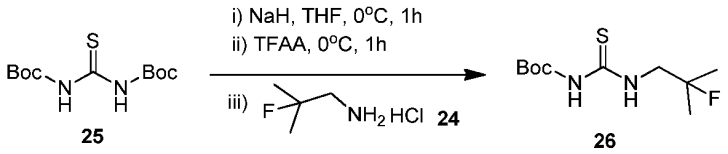
Step 4: Synthesis of intermediate 25.



25

To a stirred mixture of thiourea (23.0 g, 302 mmol) in THF (5.0 L) under argon at 0 °C was added NaH (29.9 g, 755 mmol, 60% in mineral oil). After 5 min, the ice bath was removed, and the reaction mixture was stirred at rt for 10 min. The mixture was cooled to 0 °C and Boc_2O (138 g, 635 mmol) was added. The ice bath was removed after 30 min of stirring at that temperature. The resulting slurry was stirred for another 2 h at rt. The reaction was quenched with an aqueous solution of sat. $NaHCO_3$ (500 mL) and poured into water (5.0 L) and extracted with EtOAc (3 × 2.0 L). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford intermediate **25** (80.0 g), which was used for the next step without further purification.
LCMS (method 1)**:** t_R = 1.15 min, MS (ESI) *m/z* 575.2 $[2M+Na]^+$.

Step 5: Synthesis of intermediate 26.



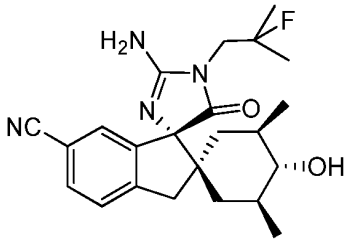
To a mixture of intermediate **25** (3.9 g, 14.2 mmol) and anhydrous THF (285 mL) was added NaH (0.68 g, 17.0 mmol, 60% in mineral oil) at 0 °C and the mixture was stirred for 1 h, then TFAA (2.20 mL, 15.6 mmol) was added and the stirring continued for an additional 1 h. A pre-mixed mixture of intermediate **24** (2.0 g, 15.6 mmol) and Et_3N (3.96 mL, 28.40 mmol) in anhydrous THF (130 mL) was added and the resulting mixture was stirred at rt overnight. Water (150 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic layer was dried, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: petroleum ether: ethyl acetate from 50: 1 to 8: 1) to afford intermediate **26** (2.49 g).

LC-MS (method 1): t_R = 1.08 min, MS (ESI) m/z 194.8 $[M-55]^+$.

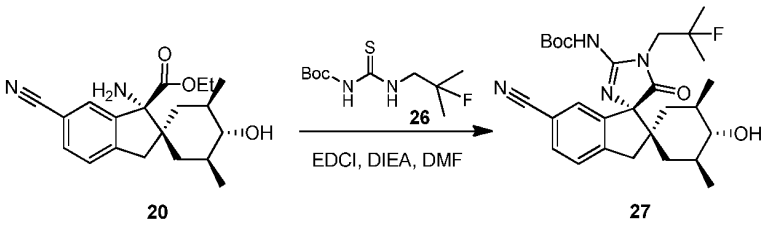
^{1}H NMR (CD_3OD): δ 3.88-3.93 (m, 2H), 1.53 (s, 9H), 1.43 (s, 3H), 1.38 (s, 3H)

^{19}F NMR (CD_3OD): δ -144.15

Example 2



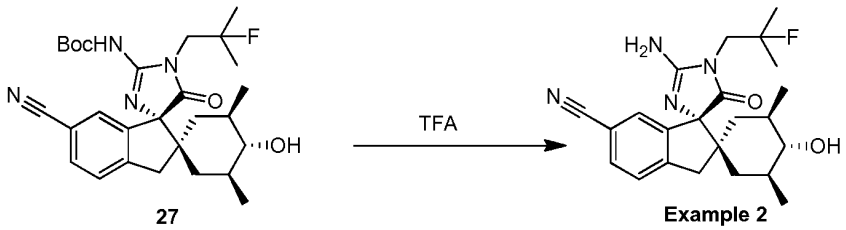
Step 1: Synthesis of intermediate 27.



To a solution of intermediate **20** (550 mg, 1.61 mmol) in DMF (5 mL), intermediate **26** (425 mg, 1.69 mmol), EDCI (614 mg, 3.22 mmol) and DIEA (416 mg, 3.22 mmol) were added. The mixture was stirred at rt for 36 h. EtOAc (200 mL) was added, followed by water (20 mL), and the mixture was stirred for 10 minutes. The organic layer was separated and washed with water (3 X 20 mL), brine (3 × 50 mL), dried, and solvent was removed under reduced pressure to afford crude product. The residue was purified by column chromatography (petroleum ether: ethyl acetate; 5: 1) to afford intermediate **27** (547 mg).

LC-MS: t_R = 1.14; MS (ESI) m/z 513.3 $[M+H]^+$.

Step 2: Synthesis of Example 2.



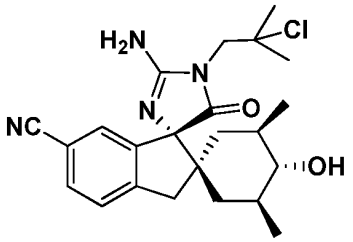
To a mixture of intermediate **27** (400 mg, 0.56 mmol) in DCM (5 mL) was added TFA (1 mL) and the mixture was stirred at rt for 2 h. To this mixture, a sat. $NaHCO_3$ solution (10 mL) was added and stirred for 10 minutes. The mixture was partitioned between DCM (10 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4 and

concentrated under reduced pressure. The residue was purified by preparative HPLC (basic method 1) and SFC method A to give compound Example **2** (303.9 mg).

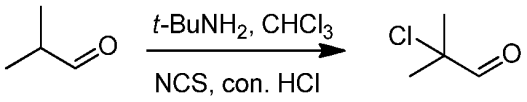
LC-MS (method 1): t_R = 0.90 min, MS (ESI) m/z 413.2$[M+H]^+$.

^{1}H-NMR (CD_3OD): δ 7.63-7.65 (dd, J = 8.0, 1.6 Hz, 1H), 7.49-7.51 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 3.69-3.76 (m, 2H), 3.26-3.30 (m, 1H), 3.15-3.19 (m, 1H), 2.55-2.59 (t, J = 8.0 Hz, 1H), 1.79-1.84 (m, 1H), 1.27-1.63 (m, 11H), 1.03-1.09 (t, J = 12.0 Hz, 1H), 1.00-1.01 (t, J = 4.0 Hz, 3H), 0.96-0.97 (d, J = 4.0 Hz, 3H). ^{19}F NMR**:** (CD_3OD): δ -139.5.

Example 3



Step 1: Synthesis of intermediate 28.

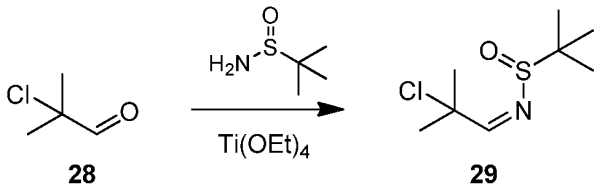


28

2-methylproponal (9.3 g, 129 mmol) was added to t-$BuNH_2$ (4.75 g, 129 mmol) at 0 °C and stirred at rt for 2 h. To this mixture $CHCl_3$ (130 mL) was added, and the mixture was dried over Na_2SO_4 and filtered. To the resultant solution, NCS (18.20 g, 136 mmol) was added at 0 °C, followed by stirring at rt for 5 h. Water (100 mL) was poured into the reaction mixture and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layer was washed with water (200 mL), dried, and concentrated under reduced pressure. To the resultant residue, concentrated HCl was added. The mixture was stirred at rt for 5 h, and sat. $NaHCO_3$ (200 mL) was added. The product was extracted with $CHCl_3$ and the residue was distilled at atmospheric pressure to obtain intermediate **28** (2 g).

^{1}H NMR ($CDCl_3$): δ 9.44 (s, 1H), 1.65 (s, 6H).

Step 2: Synthesis of intermediate 29.

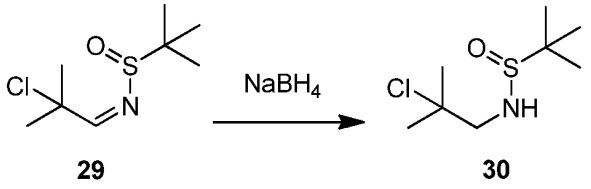


28 **29**

The mixture of intermediate **28** (1.06 g, 10 mmol) and titanium (IV) ethoxide (2.72 mL, 12 mmol) in anhydrous THF (22 mL), (±) *N*-tert-butylsulfinamide (1.21 g, 9 mmol) was added. The resulting mixture was stirred at reflux under N_2 atmosphere for 4 h. The reaction mixture was cooled and water (20 mL) was added. The resulting mixture was filtered and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give intermediate **29** (1 g).

^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 1.71 (s, 6H), 1.14(s, 9H).

Step 3: Synthesis of intermediate 30.

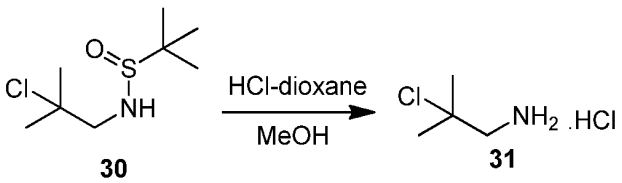


29 **30**

To a solution of intermediate **29** (0.7 g, 3.33 mmol) in anhydrous THF (5 mL) was added $NaBH_4$ (0.25 g, 6.66 mmol) at 0 °C. The reaction mixture was stirred at rt for 16 h, the reaction was quenched with sat. NH_4Cl solution (5 mL), aqueous $KHCO_3$ (20 mL), and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was dried, and concentrated under reduced pressure to yield crude intermediate **30** (260 mg), which was used for the next step without further purification.

^{1}H NMR ($CDCl_3$): δ 3.40-3.45 (m, 1H), 3.11-3.17 (m, 1H), 1.55-1.57 (m, 6H), 1.23 (s, 9H).

Step 4: Synthesis of intermediate 31.



30 **31**

To the mixture of intermediate **30** (450 mg, 2.12 mmol) in dry MeOH (3 mL) was added HCl in dioxane (4 M, 2 mL). The resulting mixture was stirred at rt for 2 h. The solvent was removed

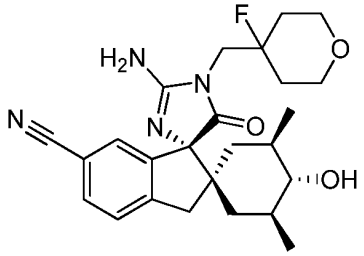
under reduced pressure to afford crude product **31**, which was used for the next step without further purification.

Example **3** was synthesized in a manner similar to Example **1**, using intermediate **31** in step 10.

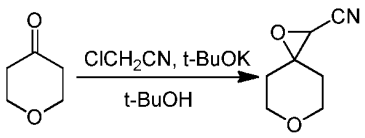
LC-MS (method 1): t_R = 0.86 min, MS (ESI) m/z 429.2 $[M+H]^+$.

^{1}H NMR: (CD_3OD): δ 7.60-7.62 (d, J = 7.6 Hz, 1H), 7.45-7.47 (d, J = 7.6 Hz, 1H), 7.27 (s, 1H), 3.76-3.85 (m, 2H), 3.11-3.25 (m, 2H), 2.51-2.56 (m, 1H), 1.57-1.58 (d, J = 4.0 Hz, 1H), 1.42-1.52 (m, 9H), 1.23-1.26 (m, 1H), 1.03-1.09 (m, 1H), 0.97-0.99 (m, 3H), 0.93-0.94 (m, 3H) ppm.

Example 4



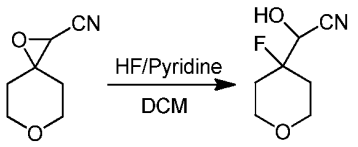
Step 1: Synthesis of intermediate 32.



32

A mixture of dihydro-2H-pyran-4(3H)-one (50.0 g, 500 mmol) and 2-chloroacetonitrile (35.0 g, 350 mmol) in tert-butanol (50 mL) was stirred for 30 min. To this mixture was added a solution of *t*-BuOK (60 g, 550 mmol) in tert-butanol (500 mL) over 40 minutes. The reaction mixture was stirred at rt for 16 h. It was diluted with water (100 mL) and quenched with HCl (10% aqueous, 20 mL). The reaction mixture was concentrated to one-third of its original volume, and extracted with Et_2O (3 x 200 mL). The combined organic layer was washed with brine, dried, and concentrated to afford crude intermediate **32** (57 g), which was used directly in the next step without purification.

Step 2: Synthesis of intermediate 33.

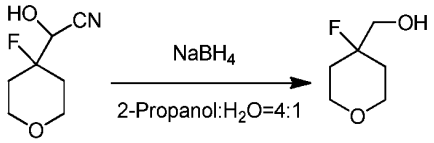


32 **33**

To a mixture of intermediate **32** (57 g) in DCM (200 mL) in a polypropylene bottle at 0 °C, 70% hydrogen fluoride-pyridine (50 mL) was added slowly. The mixture was allowed to warm to rt overnight. The reaction mixture was diluted with EtOAc (500 mL) and poured into sat. aqueous $NaHCO_3$ (200 mL). Additional solid $NaHCO_3$ was used to neutralize the mixture carefully until bubbling ceased. The aqueous layer was extracted with EtOAc (3 × 500 mL). The combined organic layer was washed with aqueous HCl (1%, 200 mL) brine, dried and concentrated to give crude intermediate **33** (54 g), which was used directly in the next step without purification.

^{1}H NMR: ($CDCl_3$): δ 4.37 (m, 2H), 3.96-2.70 (m, 4H), 1.97 – 1.81 (m, 4H).

Step 3: Synthesis of intermediate 34.

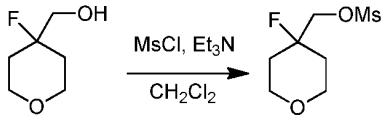


33 **34**

To a mixture of intermediate **33** (54 g; 340 mmol) in 2-propanol (1000 mL) and water (250 mL) at 0 °C, $NaBH_4$ (20 g, 509 mmol) was added. The mixture was stirred and allowed to warm to rt over 3 h. The reaction was quenched with acetone (50 mL), and stirred for another 1 h. The clear liquid was separated from solid by decantation. EtOAc (100 mL) was used to wash the solid, and the filtrates were combined. The combined organic solution was concentrated under reduced pressure and purified with flash column chromatography on silica gel (5-20% ethyl acetate in hexanes) to give intermediate **34** (22 g).

^{1}H NMR: ($CDCl_3$): δ:3.82–3.77 (m, 4H), 3.72-3.52 (dd, J = 20.8, 6.4 Hz, 2H), 2.69(s, 1H), 1.82-1.60 (m, 4H).

Step 4: Synthesis of intermediate 35.

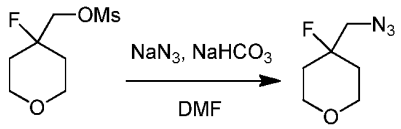


34 **35**

MsCl (25.8 g, 225 mmol) was added to a mixture of intermediate **34** (20 g, 150 mmol) and TEA (22.7 g, 225 mmol) in DCM (200 mL) at 0 °C. The mixture was stirred at rt for 2 h, and then water (100 mL) was added. The aqueous layer was extracted with DCM (2 × 200 mL), organic phases were combined, dried and solvent was removed under reduced pressure to afford crude intermediate **35** (30 g), which was used for the next step without further purification.

^{1}H NMR: ($CDCl_3$): δ:4.22 (d, J = 20.0 Hz, 2H), 3.87-3.82 (m, 4H), 3.06(s, 3H), 1.88-1.68 (m, 4H).

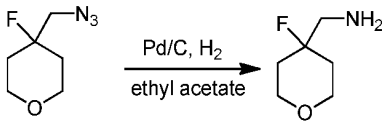
Step 5: Synthesis of intermediate 36.



35 **36**

To a mixture of intermediate **35** (10 g, 47 mmol) in DMF (150 mL) was added NaN_3 (16 g, 250 mmol) and $NaHCO_3$ (9.3 g, 100 mmol) at rt. The mixture was stirred at 120 °C for 20 h. The reaction quenched with water at rt, extracted with EtOAc (2 × 200 mL). The organic phases were combined, dried and solvent was removed under vacuum to afford crude intermediate **36** (8 g), which was used for the next step without further purification.

Step 6: Synthesis of intermediate 37.



36 **37**

To a mixture of intermediate **36** (8 g, 50 mmol) in EtOAc (100 mL) was added 10% Pd/C (0.8 g) under a N_2 atmosphere, the mixture was degassed and exchanged with hydrogen for 3 times. The final mixture was stirred at rt under 1 atm. hydrogen atmosphere for 24 h. The catalyst was filtered off through a pad of celite and washed with EtOAc (2 × 50 mL). The combined filtrate was concentrated under reduced pressure to yield intermediate **37** (5.3 g).

^{1}H NMR: (CD_3OD): δ 3.83-3.79 (m, 4H), 2.76-2.71 (d, *J* = 8.0 Hz, 2H), 1.83-1.65 (m, 4H).

^{19}F NMR: (CD_3OD) δ: -169.66.

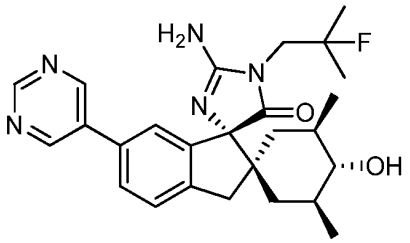
Example **4** was synthesized in a manner similar to Example **1**, using intermediate **37** in step 10.

LC-MS (method 1): t_R = 0.80 min, MS (ESI) m/z 455.2 $[M+H]^+$.

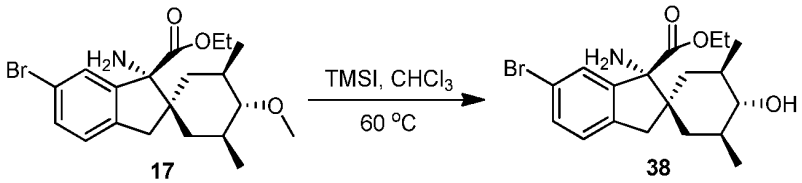
^{1}H-NMR: (CD_3OD): *δ* 7.61-7.63 (d, *J* = 7.6 Hz, 1H), 7.47-7.49 (d, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 3.63-3.83 (m, 6H), 3.23-3.27 (m, 1H), 3.12-3.16 (m, 1H), 2.52-2.57 (t, *J* = 10.0 Hz, 1H), 1.48-1.82 (m, 7H), 1.38-1.44 (t, *J* = 12.0 Hz, 1H), 1.23-1.28 (m, 1H), 0.97-1.05 (m, 4H), 0.94-0.95 (d, *J* = 4.0 Hz, 3H).

^{19}F NMR: (CD_3OD): *δ* -160.48

Example 5



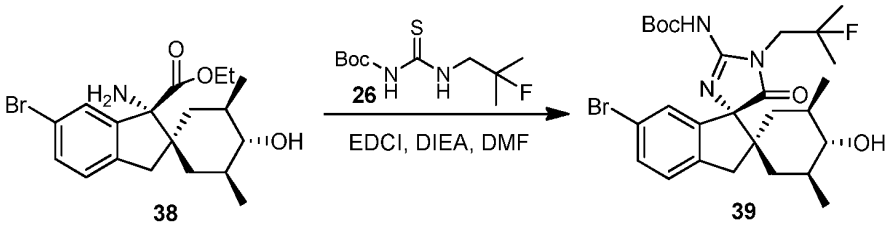
Step 1: Synthesis of intermediate 38.



To a solution of intermediate **17** (3.6 g, 7.4 mmol) in $CHCl_3$ (25 ml) was added TMSI (10 ml) and the mixture was stirred at 65 °C for 2 h. The mixture was cooled to rt, sat. $Na_2S_2O_3$ (10 mL), and sat. $NaHCO_3$ aqueous solution (10 mL) were added, and the mixture was stirred for 10 minutes. The mixture was partitioned between DCM (50 mL) and H_2O (10 mL). The organic layer was separated

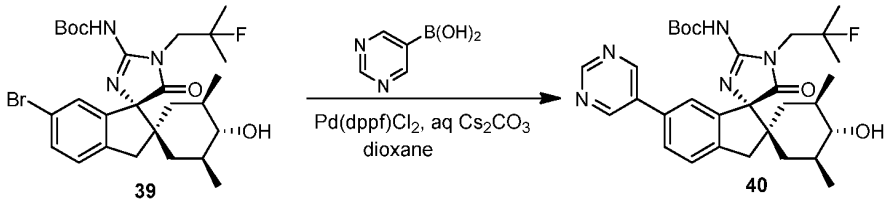
and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude intermediate **38** (2.6 g), which was used for the next step without further purification.

Step 2: Synthesis of intermediate 39.



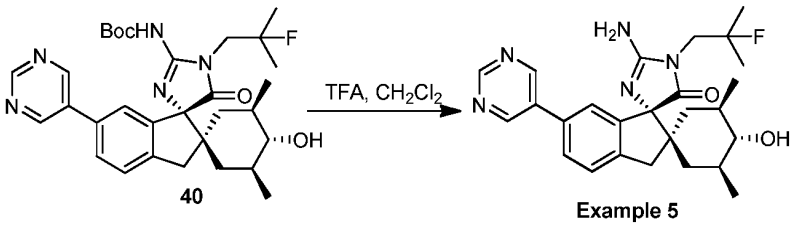
To a mixture of intermediate **38** (2.5 g, 6.4 mmol) in DMF (20 mL) was added intermediate **26** (1.8 g, 7.0 mmol, 1.1 eq), EDCI (2.5 g, 13 mmol) and DIEA (1.7 g, 13 mmol). The mixture was stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried, the solvent was removed under reduced pressure to afford crude product, which was purified by column (petroleum ether: ethyl acetate = 20: 1 to 5: 1) to give intermediate **39** (2.8 g).

Step 3: Synthesis of intermediate 40.



To a solution of intermediate **39** (350 mg, 0.6 mmol) in dioxane (5 mL) under N_2 atmosphere, 5-pyrimidine boronic acid (90 mg, 0.66 mmol) and aqueous Cs_2CO_3 solution (2 mL, 2 M in water) were added. The mixture was purged by bubbling a steam of N_2 for 5 min, then $Pd(dppf)Cl_2$ (40 mg, 0.06 mmol) was added. The mixture was stirred for 2 h at 110 °C under a N_2 atmosphere. The reaction was cooled to rt, diluted with EtOAc and filtered. The filtrate was washed with aqueous Na_2CO_3 (5 mL) and concentrated under reduced pressure to afford crude intermediate **40** (300 mg) which was used for the next step without further purification.

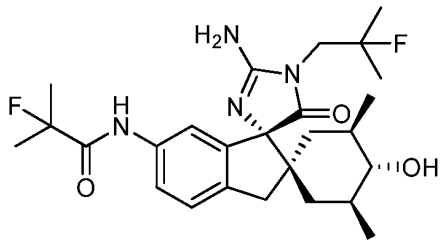
Step 4: Synthesis of Example 5.



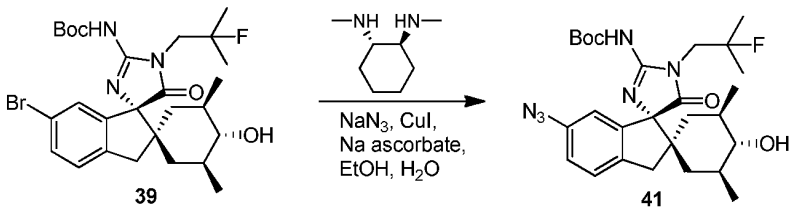
40 Example 5

To a solution of intermediate **40** (300 mg, 0.53 mmol) in DCM (5 mL) was added TFA (1 mL) and the mixture was stirred at rt for 2 h. To this mixture, sat. $NaHCO_3$ solution (10 mL) was added and stirred for 10 minutes. The residue was partitioned between DCM (10 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (basic, method 1) to give Example **5** (141 mg). LC-MS (method 1): MS (ESI) m/z 466.2$[M+H]^+$. ^1H NMR: (CD_3OD): δ 9.12 (s, 1H), 9.02 (s, 2H), 7.64-7.62 (dd, J = 7.6, 1.6 Hz,1H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 3.80-3.66 (m, 2H), 3.30-3.13 (m, 2H), 2.59 (t, J = 10.0 Hz, 1H), 1.85 (d, J = 12.4 Hz, 1H), 1.65-1.32 (m, 10H), 1.11-1.05 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H), 1.02(d, J = 6.4 Hz, 3H). ^{19}F NMR: (CD_3OD): δ -139.27.

Example 6



Step 1:. Synthesis of intermediate 41.

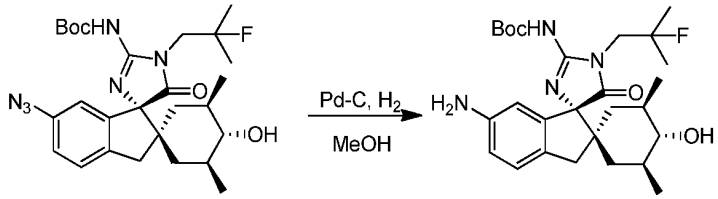


39 41

To a mixture of intermediate **39** (1.0 g, 1.8 mmol) in ethanol (23 mL) and water (10 mL), NaN_3 (300 mg, 3.6 mmol), CuI (40 mg, 10%) sodium ascorbate (40 mg, 0.20 mmol, 5%) and N,N'-dimethyl-cyclohexane-1,2-diamine (40 mg, 0.28 mmol, 15%) were added under N_2 atmosphere. The mixture was stirred for 3h at 90 °C under a N_2 atmosphere. The mixture was cooled to rt, diluted with

EtOAc and filtered. The filtrate was concentrated to afford crude intermediate **41** (830 mg) which was used for the next step without further purification.

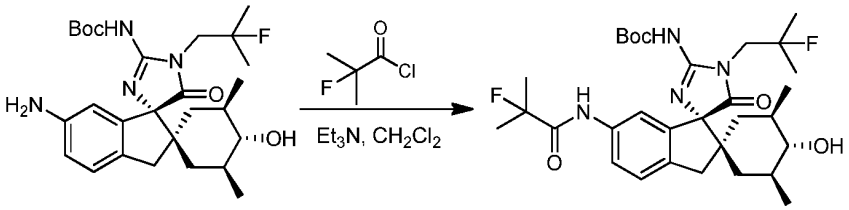
Step 2: Synthesis of intermediate 42.



41 42

To a mixture of intermediate **41** (830 mg, 1.6 mmol) in MeOH (10 mL) was added 10% Pd/C (0.1 g) under a nitrogen atmosphere, the mixture was degassed and exchanged with hydrogen for 3 times. The mixture was stirred at rt under 1 atm hydrogen atmosphere for 4 h. The mixture was filtered through a pad of celite and washed with EtOAc (2 × 10 mL). The combined filtrate and washing were concentrated under reduced pressure to give intermediate **42** (0.7 g), which was used for the next step without further purification. LC-MS (method 1): t_R = 0.99 min, MS (ESI) m/z 503.2 $[M+H]^+$.

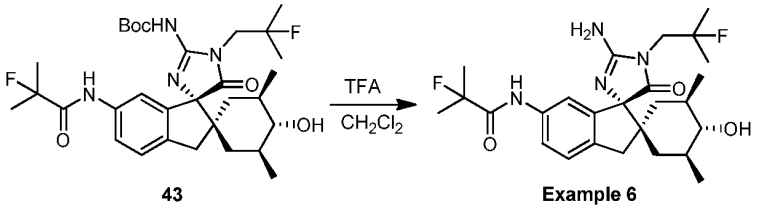
Step 3: Synthesis of intermediate 43.



42 43

To a mixture of intermediate **42** (350 mg, 0.7 mmol) in DCM (5 mL) was added Et_3N (0.2 mL, 1.2 mmol, 2.0 eq) and 2-fluoro-2-methylpropanoyl chloride (150 mg, 2 mmol). The mixture was stirred at rt for 3 h. The reaction was quenched with water and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine (3 × 15 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to afford crude intermediate **43** (320 mg) which was used for the next step without further purification.

Step 4: Synthesis of Example 6.



43 Example 6

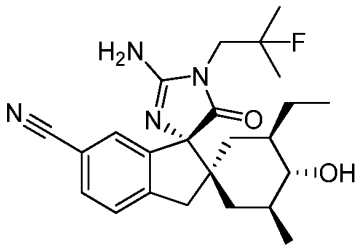
To a mixture of intermediate **43** (320 mg, 0.54 mmol) in DCM (5 mL) TFA (1 mL) was added and the mixture was stirred at rt for 2 h. The reaction was quenched with sat. $NaHCO_3$ aqueous solution (10 mL). The mixture was partitioned between DCM (10 mL) and H_2O (10 mL). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (basic method 1) to give Example **6** (179.9 mg).

LC-MS (method 1): LC-MS t_R = 0.86 min, MS (ESI) m/z 491.2$[M+H]^+$.

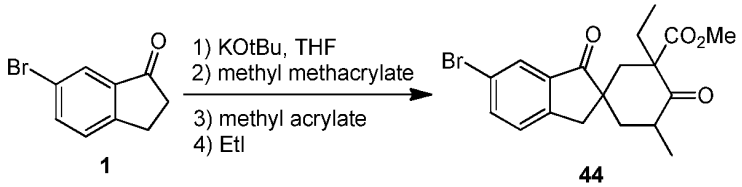
^{1}H NMR: (CD_3OD): δ 7.42 (m 1H), 7.30 (m, 2H), 3.78-3.71 (m, 2H), 3.17-3.05 (m, 2H), 2.59 (t, J = 10.0 Hz, 1H), 1.80 (d, J = 12.0 Hz, 1H), 1.64-1.53 (m, 8H), 1.42-1.34 (m, 8H), 1.08-0.96 (m, 7H).

^{19}F NMR: (CD_3OD): δ -138.95, -147.61.

Example 7



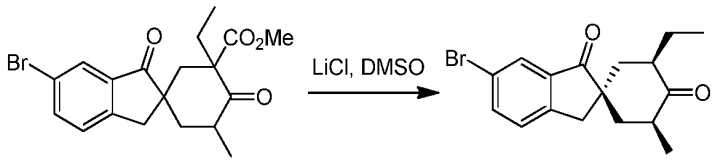
Step 1: Synthesis of intermediate 44.



1 44

To a solution of 6-bromo-indan-1-one (100.0 g, 0.48 mol) dissolved in THF (2.0 L, 0.24 M) was added *t*-BuOK (64.0 g, 0.57 mol) in one portion at 0 °C. The reaction was stirred for 5 min at 0 °C and stirred for an additional 10 min at rt. Methyl methacrylate (56.0 mL, 0.53 mol) was added in one portion. After 30 min, methyl acrylate (52.0 mL, 0.57 mol) was added in one portion and the mixture stirred overnight. To this reaction mixture, DMF (260 mL, 1.8 M) and EtI (76.0 mL, 0.96 mol) were added and the mixture was stirred overnight. The reaction was quenched with sat. aqueous citric acid solution (200 mL) and the organic layer was separated. The EtOAc was removed under reduced pressure and the crude material was diluted with H_2O (3 L) and extracted with EtOAc (3 × 3L). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure to afford crude intermediate **44** (200 g), which was used for the next step without further purification.

Step 2: Synthesis of intermediate 45.

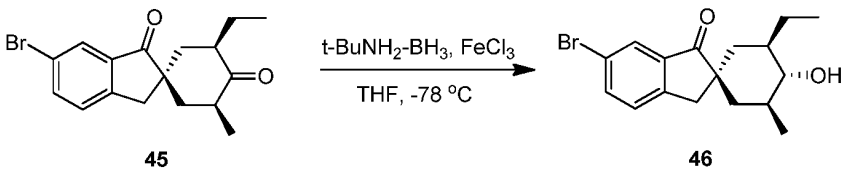


44 **45**

Intermediate **44** (200.0 g, 0.51 mol) was mixed with DMSO (1.0 L, 0.5 M) and LiCl (215.0 g, 5.1 mol) was added. The mixture was heated to 120 °C for 4 days. The mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc=30: 1) to afford the crude intermediate. The intermediate was dissolved in minimal amount of MeOH, and NaOMe in MeOH (30%, 20 mL) was added. After 20 min, the mixture was filtered to give intermediate **45** (40 g).

^{1}H-NMR: ($CDCl_3$): δ 7.93 (d, J = 1.6 Hz, 1H), 7.77 (dd, J = 10.8, 2.4 Hz, 1H), 7.42-7.45 (d, J = 10.8 Hz, 1H), 3.34 (s, 2H), 2.60-2.70 (m, 1H), 2.36-2.47 (m, 1H), 1.76-1.99 (m, 5H), 1.21-1.30 (m, 1H), 1.07 (d, J = 8.8 Hz, 3H), 0.90 (t, J = 9.6 Hz, 3H) ppm.

Step 3: Synthesis of intermediate 46.

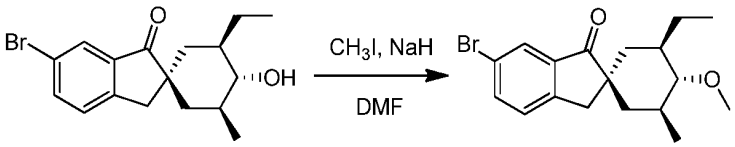


45 **46**

Intermediate **46** was synthesized from intermediate **45** by a method similar to that described in step 2 of Example **1**.

^{1}H-NMR: ($CDCl_3$): δ 7.81 (d, J = 1.8 Hz, 1H), 7.63 (dd, J = 8.1, 2.1 Hz, 1H), 7.42-7.45 (d, J = 8.4 Hz, 1H), 3.34 (s, 2H), 2.60-2.70 (m, 1H), 2.36-2.47 (m, 1H), 1.76-1.99 (m, 5H), 1.21-1.30 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H) ppm.

Step 4: Synthesis of intermediate 47.

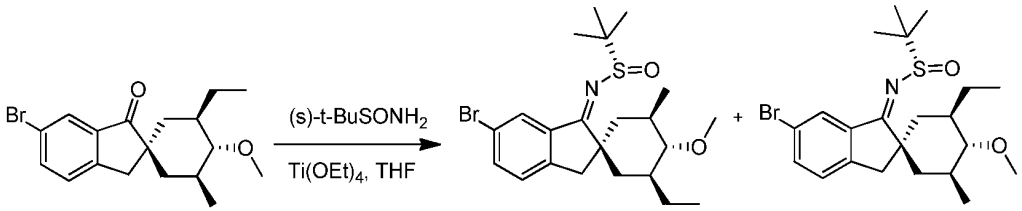


46 **47**

To a solution of intermediate **46** (30.0 g, 0.08 mol) in DMF (500 mL) was added NaH (8.0 g, 0.16 mol) at 0 °C. The mixture was stirred at 0 °C 30 min, and then MeI (25.0 mL, 0.4 mol) was added and the mixture was stirred at rt overnight. The mixture was quenched with H_2O (100 mL), extracted with EtOAc (3 × 300 mL). The organic layer was concentrated and purified by column chromatography (petroleum ether/EtOAc = 20/ 1) to afford intermediate **47** (22.0 g).

^{1}H-NMR: ($CDCl_3$): δ 7.81 (d, J = 1.8 Hz, 1H), 7.63 (m, J = 8.1, 1.8 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 3.41 (s, 3H), 2.91 (s, 2H), 2.46-2.52 (m, 1H), 1.75-1.79 (m, 1H), 1.59-1.62 (m, 1H), 1.29-1.47 (m, 5H), 1.08-1.15 (m, 1H), 0.98 (d, J = 6.3 Hz, 3H), 0.78 (t, J = 7.5 Hz, 3H).

Step 5: Synthesis of intermediate 48.

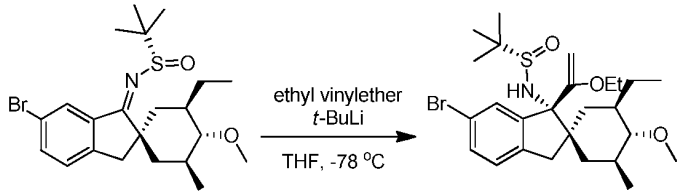


47 **48A** **48**

A mixture of intermediate **47** (22.0 g, 0.06 mol) and titanium (IV) ethoxide (130 mL, 0.62 mol) in dry THF (400 mL) was stirred at rt for 1 h. (*S*)-*N*-tert-butylsulfinamide (30.0 g, 0.25 mol) was added and the resulting mixture was stirred at 80 °C under N_2 overnight. The reaction mixture was cooled and water (200 ml) was added. The mixture was filtered and the aqueous layer was

extracted with EtOAc (3 × 400 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 20: 1) to give intermediate **48A** (7.0 g) and **48** (10.0 g) respectively.

Step 6: Synthesis of intermediate 49.



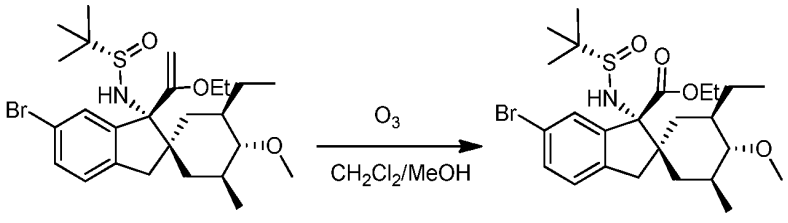
48 **49**

To a mixture of ethoxy-ethene (4.7 mL, 49.5 mmol) in anhydrous THF (50 mL) at -78 °C was added *t*-BuLi (38.0 mL, 49.5 mmol, 1.3 M in hexane) dropwise over 20 minutes and the mixture was stirred for 20 min. The resulting mixture was stirred at 0 °C for another 45 min and then cooled back to -78 °C.

A pre-cooled solution of intermediate **48** (4.5 g, 9.9 mmol) in anhydrous THF (60 mL) at -78 °C was added to the above solution, dropwise over 30 minutes and the mixture was stirred for 2.5 h at -78 °C. The reaction was quenched with sat. NH_4Cl (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phase was concentrated under reduced pressure to give the residue, which was purified by column chromatography (petroleum ether: EtOAc = 20: 1) to afford intermediate **49** (3.5 g).

LC-MS (method 1): t_R = 5.94 min, MS (ESI) m/z 528.1 $[M+H]^+$.

Step 7: Synthesis of intermediate 50.



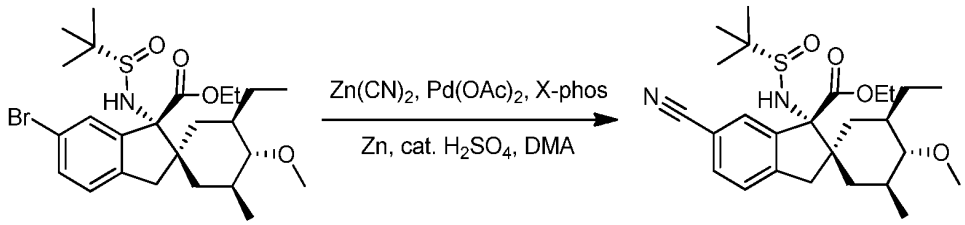
49 **50**

Intermediate **49** (3.5 g, 6.60 mmol) was dissolved in a mixture of DCM and MeOH (5: 1; 40 mL), and cooled to -78 °C. Ozone was bubbled through the mixture for 20 min. The reaction was stirred for an additional 10 minutes, after which the mixture was purged with N_2 and treated with Me_2S at -78 °C. The reaction was allowed to warm to rt and stirred for an additional 3 h. The

solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum/ EtOAc = 15/1) to give intermediate **50** (2.3 g).

^{1}H-NMR: ($CDCl_3$): δ 7.83 (s, 1H), 7.43 (dd, J = 8.0, 2.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 4.26-4.43 (m, 3H), 3.42 (s, 3H), 2.95 (d, J = 16.0 Hz, 1H), 2.68 (d, J = 16.0 Hz, 1H), 2.32-2.37 (m, 1H), 2.17 (s, 1H), 1.91-1.97 (m, 1H), 1.82-1.89 (m, 1H), 1.63-1.68 (m, 1H), 1.31-1.40 (m, 6H), 1.13 (s, 9H), 0.90-0.95 (m, 6H), 0.68 (t, J = 12.0 Hz, 1H).

Step 8: Synthesis of intermediate 51.

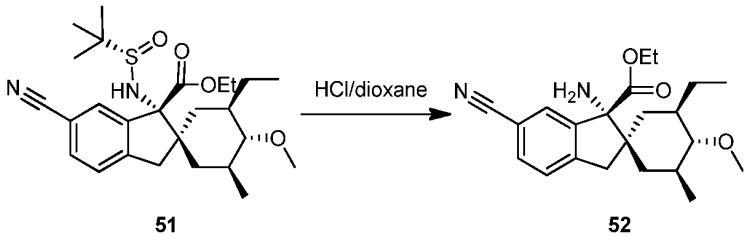


Concentrated sulfuric acid (49 µL), was added to DMA (20 mL) and the solvent was purged with N_2 for 20 min. A 50 mL round bottom flask was charged with Pd $(OAc)_2$ (1.35 g) and Xphos (3.15 g) under N_2, and transferred to the above solution. The resulting mixture was heated at 80 °C for 30 min to give mixture **A**.

In an another flask, DMA (30 mL) was purged under N_2 for 20 min and intermediate **50** (2.3 g, 4.50 mmol), Zn $(CN)_2$ (527 mg, 4.50 mmol) and Zn dust (15 mg) were added followed by mixture **A**. The resulting mixture was heated at 90 °C for 40 min. The reaction mixture was cooled to rt, diluted with water (80 mL) and EtOAc (100 mL). After stirring for 10 minutes, the mixture was filtered through celite, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum: EtOAc= 10:1) to afford intermediate **51** (1.8 g).

LC-MS (method 1): t_R = 1.19 min, MS (ESI) m/z 475.2 $[M+H]^+$.

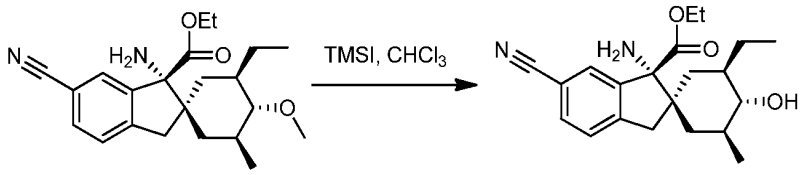
Step 9: Synthesis of intermediate 52.



To a mixture of intermediate **51** (590 mg, 1.24 mmol) in MeOH (10 mL) was added a 4 M HCl solution in dioxane (2 mL). The resulting mixture was stirred for 30 min. Solvent was removed under reduced pressure to afford crude intermediate **52** (550 mg), which was used for the next step without further purification.

LC-MS (method 1): t_R = 0.88 min, MS (ESI) m/z 322.1 $[M-48]^+$.

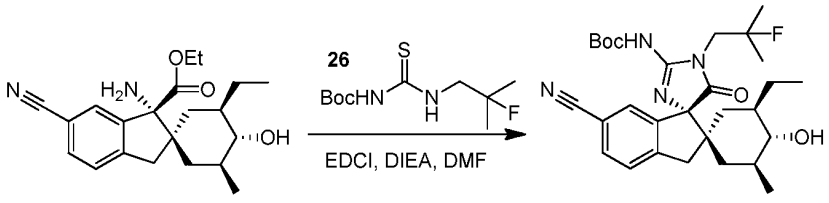
Step 10: Synthesis of intermediate 53.



52 **53**

To a mixture of intermediate **52** (550 mg, 1.59 mmol) in $CHCl_3$ (10 mL) was added TMSI (2.5 mL, 15.9 mmol) slowly at rt. The mixture was stirred at 60 °C for 2 h and then allowed to cool to rt. MeOH (5 mL) and sat. $Na_2S_2O_3$ (5 mL) solution was added over 10 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined, washed with water (2 × 40 mL), dried and solvent was removed under reduced pressure to yield crude intermediate **53** (400 mg).

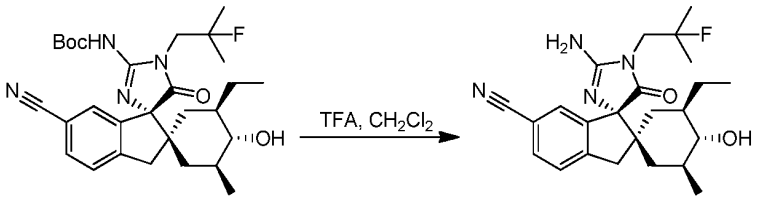
Step 11: Synthesis of intermediate 54.



53 **54**

To a mixture of intermediate **53** (1.2 g, 3.30 mmol) in DMF (15 mL), intermediate **26** (850 mg, 3.30 mmol), EDCI (1.28 g, 6.60 mmol) and DIEA (1.2 mL, 6.60 mmol) were added. The mixture was stirred at 30 °C overnight. The solution was cooled to rt and EtOAc (20 mL) and water (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (3 × 50 mL), dried and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ EtOAc = 5/1) to afford **54** (760 mg).

Step 12: Synthesis of Example 7.



54 **Example 7**

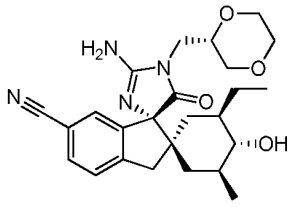
To a mixture of intermediate **54** (750 mg, 1.43 mmol) in DCM (8 mL) was added TFA (2 mL) and stirred at rt for 1 h. The pH of the reaction mixture was adjusted to 8.5 by addition of sat. $NaHCO_3$ solution. The organic layer was separated and concentrated under reduced pressure to yield crude product. The residue was purified by preparative HPLC (basic, method 2) to give Example **7** (465 mg).

LC-MS (method 1): t_R = 0.85 min, MS (ESI) m/z 427.2 $[M+H]^+$.

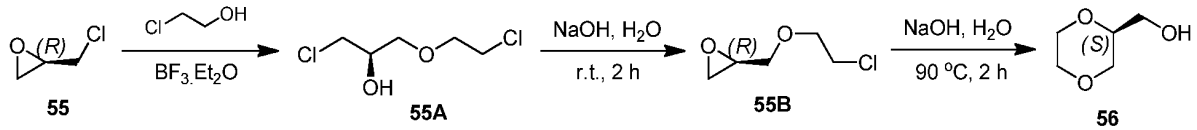
^{1}H-NMR: (CD_3OD): 7.65 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.30 (s, 1H), 3.65-3.80 (m, 2H), 3.12-3.29 (m, 2H), 2.64-2.69 (m, 1H), 1.79-1.84 (m, 2H), 1.51-1.55 (m, 1H), 1.32-1.50 (m, 9H), 1.32-1.42 (m, 1H), 1.00-1.20 (m, 4H), 0.78 (t, *J* = 7.6 Hz, 3H).

^{19}F-NMR: (CD_3OD): -139.444.

Example 8



Step 1: Synthesis of intermediate 56.



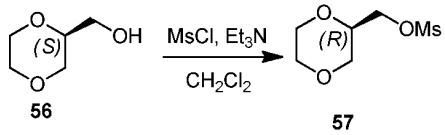
55 **55A** **55B** **56**

A mixture of (*R*)-2-(chloromethyl)oxirane (**55,** 109 mL, 1.62 mol) and $BF_3.OEt_2$ (3.4 mL, 0.027 mol) in toluene (200 mL) was heated to an internal temperature of 30 °C and 2-choloroethanol (49 g, 0.53 mol) was added dropwise at a rate sufficient to main the reaction temperature at 36-38 °C. The resulting mixture was aged at 36 °C for 20 min. The mixture was cooled to 16 °C and aqueous

NaOH (250 mL, 23%) was added with vigorous stirring over 1h, maintaining the reaction temperature below 20 °C. The mixture was aged for 1 h at rt. The two layers were separated, and the aqueous phase was extracted with toluene (130 mL). The combined organic layers were washed with water (100 mL), the resulting organic layer was distilled to low volume, monitoring the distillate for loss of product to give the final intermediate **56** (23 g).

^{1}H-NMR: (CDCl3): δ 3.33-3.84 (m, 9H).

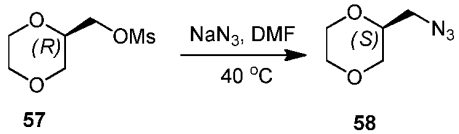
Step 2: Synthesis of intermediate 57.



56 **57**

To a mixture of intermediate **56** (81.0 g, 0.686 mol) in DCM (500 mL) was added TEA (196 mL, 1.37 mol) and MsCl (80 mL, 1.029 mol) at 0 °C. The mixture was stirred for 5 h at rt, and quenched with water (200 mL), extracted with dichloromethane (2 × 200 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford crude intermediate **57** (132.8 g), which was used for the next step directly without purification.

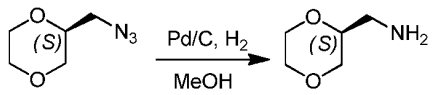
Step 3: Synthesis of intermediate 58.



57 **58**

To a mixture of intermediate **57** (132.8 g, 0.677 mol) in DMF (640 mL), NaN_3 (88.0 g, 1.35 mol), $NaHCO_3$ (170.6 g, 2.03 mol) and NaI (20.3 g, 0.135 mol) were added. The mixture was stirred at rt overnight. The reaction mixture was quenched with water (300 mL), and then extracted with ethyl acetate (2 × 300 mL). The combined organic layer was washed with water and then brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford crude intermediate **58** (96 g), which was used for the next step directly without purification.

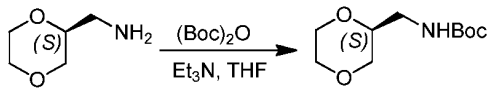
Step 4: Synthesis of intermediate 59.



58 **59**

To a mixture of intermediate **58** (3.6 g, 25.48 mmol) in MeOH (100 mL) was added Pd/C (0.4 g, 10% content) under a nitrogen atmosphere, the mixture was degassed and exchanged with hydrogen for 3 times. The final mixture was stirred at rt under hydrogen balloon for 24 h. The catalyst was filtered off through a pad of celite and washed with MeOH (2 × 50 mL). The combined filtrate and washing were concentrated under reduced pressure to give crude intermediate **59** (2.93 g).

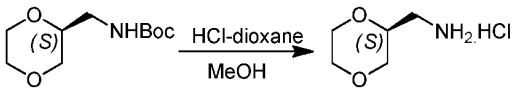
Step 5: Synthesis of intermediate 60.



59 **60**

To a solution of intermediate **59** (1.1 g, 10 mmol) in THF (50 mL) was added Et_3N (3.0 g, 30 mmol) and $(Boc)_2O$ (2.6 g, 12 mmol). The mixture was stirred at rt overnight. The reaction was quenched with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give crude product, which was purified by column chromatography on silica gel (petroleum ether: ethyl acetate; 100: 1 to 20: 1) to afford pure intermediate **60** (500 mg).

Step 6: Synthesis of intermediate 61.

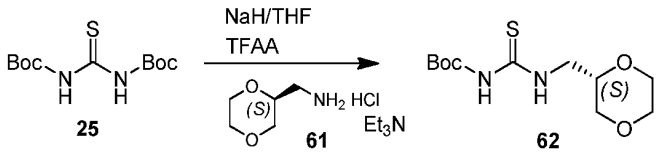


60 **61**

Intermediate **60** (20 g, 92 mmol) was dissolved in MeOH (150 mL), and then a solution of HCl in dioxane (4 M, 30 mL, 120 mmol,) was added. The reaction mixture was stirred at rt for 18 h. MeOH was removed under vacuum to yield pure intermediate **61** (14 g), which was used for the next step without further purification.

^{1}H NMR (CD_3OD): δ 3.62-3.90 (m, 6H), 3.32-3.35 (m, 1H), 3.01-3.04 (m, 1H), 2.85-2.90 (m, 1H).

Step 7: Synthesis of intermediate 62.



To a mixture of intermediate **25** (12.3 g, 44.55 mmol) in anhydrous THF (600 mL) was added NaH (2.1 g, 53.46 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred for 1 h, followed by addition of TFAA (6.9 mL, 49.0 mmol) and the stirring was continued for additional 1 h. Intermediate **61** (7.5 g, 49.0 mmol) and Et_3N (12.4 mL, 89.1 mmol) in anhydrous THF (300 mL) were added and the resulting reaction mixture was stirred at rt overnight. H_2O (300 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3 × 350 mL). The combined organic layers were dried, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (5-50% ethyl acetate in hexane) to afford intermediate **62** (7.95 g).

LCMS (method 1): t_R = 0.90 min, MS (ESI) *m/z* 221.1 $[M-55]^+$.

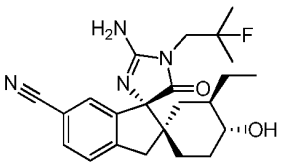
^{1}H NMR (CD_3OD): δ 3.80-3.90 (m, 4H), 3.70-3.80 (m, 2H), 3.55-3.65 (m 2H), 3.35-3.40 (m, 1H), 1.57 (s, 9H).

Example **8** was synthesized from intermediate **53** and intermediate **62** in accordance with the method described in steps 11 and 12 for Example **7**.

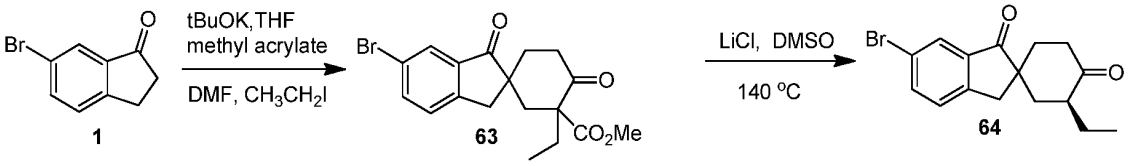
LC-MS (method 1): t_R = 0.87 min, MS (ESI) m/z 453.2$[M+H]^+$.

^{1}H-NMR (CD_3OD): 7.64 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 3.51-3.86 (m, 8H), 3.11-3.35 (m, 3H), 2.64-2.69 (m, 1H), 1.78-1.84 (m, 2H), 1.49-1.55 (m, 1H), 1.39 (s, 3H), 1.13-1.20 (m, 1H), 0.99-1.06 (m, 4H), 0.78 (t, *J* = 7.6 Hz, 3H).

Example 9



Step 1: Synthesis of intermediate 62.

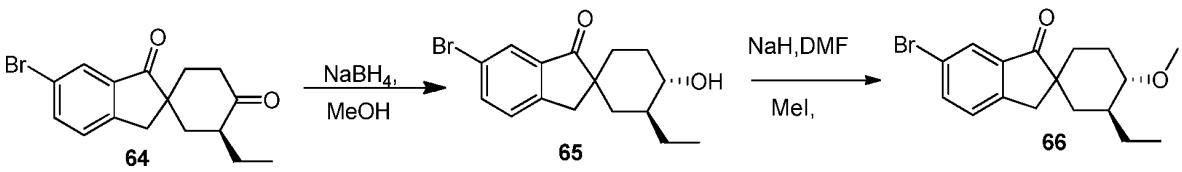


A mixture of 6-bromo-indan-1-one **1** (50.0 g, 236 mmol) and methyl acrylate (42.0 g, 472 mmol) in anhydrous THF (900 mL) was pre-cooled to 0 °C and *t*-BuOK (31.8 g, 284 mmol, 1.1 eq) was added portion wise over 30 min. The mixture was warmed to rt over 1 h and stirred for an additional 40 min at rt. DMF (200mL) and EtI (74 g, 472 mmol) were added to this reaction mixture, and the mixture was stirred at rt overnight. THF was removed under reduced pressure. The residue was diluted with H_2O (300 mL) and extracted with EtOAc (300 mL). The organic layer was concentrated under reduced pressure to afford the crude intermediate **63** (120.0 g). This product was used as is for the next step.

A mixture of intermediate **63** (120.0 g, 310 mmol) and LiCl (130.0 g, 3100 mmol) in DMSO (900 mL) was refluxed overnight. The mixture was quenched with water (3 L) and extracted with EtOAc (3 × 400 mL). The combined organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc; 20:1) to give intermediate **64** (15 g).

^{1}H NMR: ($CDCl_3$): δ 7.91 (s, 1H), 7.74 (dd, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 2H), 2.48-2.53 (m, 2H), 2.33-2.49 (m, 1H), 2.15-2.23 (m, 1H), 1.75-1.95 (m, 4H), 1.21-1.40 (m, 1H), 0.88 (t, *J* = 8.0 Hz, 3H).

Step 2: Synthesis of intermediate 66.



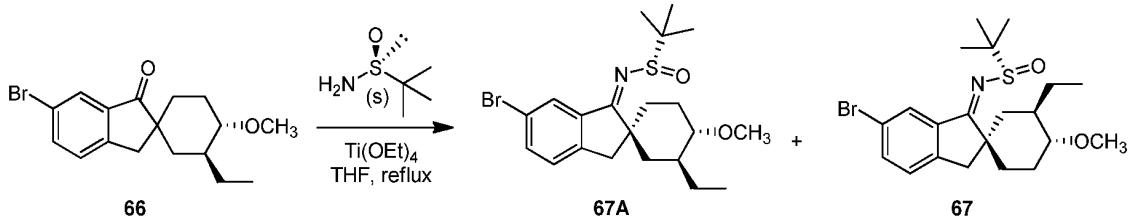
To a mixture of THF (20 mL) and MeOH (5 mL) at -78 °C was added intermediate **64** (6.0 g, 18.7 mmol), $NaBH_4$ (355 mg, 9.3 mmol) and $CeCl_3.7H_2O$ (70 mg, 0.19 mmol). The mixture was stirred at -78 °C for 20 min, quenched with satd. NH_4Cl solution (30 mL), and extracted with EtOAc (400 mL X 4). The organic layers were combined and concentrated under reduced pressure to afford a crude intermediate **65** (6.5 g).

To a mixture of intermediate **65** (6.5 g, 20.0 mmol) and NaH (3.2 g, 80.0 mmol) in DMF (100 mL) was added MeI (11.4 g, 80.0 mmol) at 0 °C. The mixture was stirred at rt overnight. The mixture was quenched with H_2O, extracted with EtOAc, and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel (eluent: petroleum ether: ethyl acetate; 20: 1 to 15: 1) to afford intermediate **66** (3.5 g).

LC-MS (method 1): t_R = 1.32 min, MS (ESI) m/z 339.1 $[M+H]^+$.

^1H NMR: ($CDCl_3$): δ 7.88 (s, 1H), 7.69 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.39 (s, 3H), 2.97 (s, 2H), 2.88-2.94 (m, 1H), 2.21-2.26 (m, 1H), 1.81-1.87 (m, 1H), 1.70-1.78 (m, 1H), 1.40-1.59 (m, 4H), 1.12-1.39 (m, 2H), 0.88 (t, *J* = 8.0 Hz, 3H).

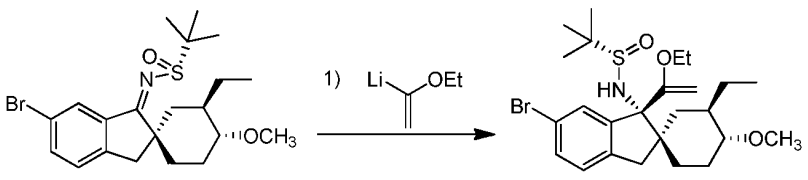
Step 3: Synthesis of intermediate 67 & 67A.



66 67A 67

The mixture of intermediate **66** (3.5 g, 10.4 mmol) and titanium (IV) ethoxide (23.7 g, 104 mmol) in dry THF (40 mL) was stirred at rt for 1 hour. (*S*)-*N*-tert-butylsulfinamide (1.6 g, 11.6 mmol) was added and the resulting mixture was stirred at 80 °C under N_2 atmosphere overnight. The reaction mixture was cooled and water (400 mL) was added and filtered. The aqueous layer was extracted with EtOAc (3 × 200 mL). The separated organic phases were combined and dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc; 20:1) and compounds eluted in the following order to give intermediate **67A** (1.5 g) and **67** (1.5 g) respectively.

Step 4: Synthesis of intermediate 68.

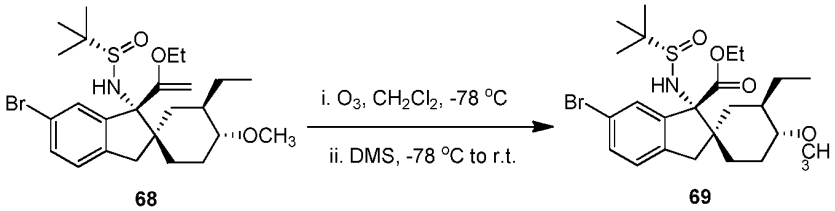


67 68

To a mixture of ethoxy-ethene (1.3 g, 17.0 mmol) in anhydrous THF (20 mL) at -78 °C under a N_2 atmosphere, *t*-BuLi (13.0 mL, 17.0 mmol, 1.3 M in hexane) was added dropwise and stirred for 20 min. The resulting mixture was stirred at 0 °C for an additional 45 min and then cooled back to -

78 °C. To this mixture, a pre-cooled solution of intermediate **67** (1.5 g, 3.4 mmol) in anhydrous THF (20 mL) at -78 °C was added dropwise and stirred for 2.5 h. The reaction was quenched with sat. NH_4Cl (50 mL) and then extracted with EtOAc (3 × 100 mL). The organic phases were combined and concentrated under reduced pressure to afford the crude product, which was purified by column on silica gel (petroleum ether: ethyl acetate; 20: 1) to afford intermediate **68** (1.2 g).

Step 5: Synthesis of intermediate 69.

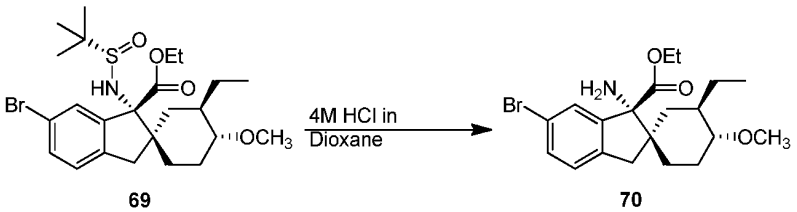


68 **69**

The intermediate **68** (1.2 g, 2.4 mmol) was added to a mixture of methanol in DCM (5:1, 20 mL), and cooled to -78 °C. Ozone was bubbled through the mixture for 20 min. The mixture was purged with N_2 and treated with Me_2S (5 mL) at -78 °C. The reaction was allowed to warm to rt and stirred for an additional 3 h. The solvent was removed under vacuum, the residue was purified by preparative TLC (petroleum ether: ethyl acetate; 3: 1) to afford intermediate **69** (860 mg).

LC-MS (method 1): t_R = 1.35 min, MS (ESI) m/z 516.1 $[M+H]^+$.

Step 6: Synthesis of intermediate 70.



69 **70**

To intermediate **69** (860 mg, 1.7 mmol) in MeOH (10 mL) was added HCl in dioxane (4 M, 2 mL). The resulting mixture was stirred for 30 min at rt. The solvent was removed under reduced pressure to afford crude intermediate **70** (800 mg) which was used for the next step without further purification.

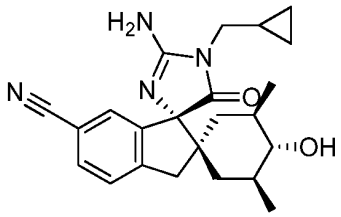
Example **9** was synthesized from intermediate **70** by the method described in Example **7,** from step 10 through step 12.

LC-MS (method 1): t_R = 0.79 min, MS (ESI) m/z 413.2 $[M+H]^+$.

^{1}H-NMR (CD_3OD): 7.66 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 3.69-3.76 (m, 2H), 3.12-3.27 (m, 3H), 1.78-1.95 (m, 3H), 1.32-1.42 (m, 11H), 1.11-1.18 (m, 1H), 0.78 (t, *J* = 7.6 Hz, 3H).

^{19}F-NMR (CD_3OD): -139.768.

Example 10

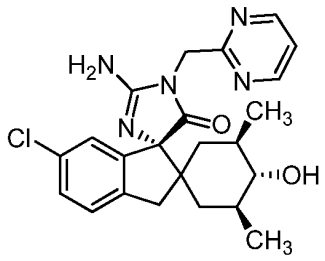


Example **10** was prepared by the method described in Example **1**, using cyclopropyl methyl amine in step 10.

LC-MS (method 1): t_R = 1.02 min; $[M+H]^+$ = 393.

^{1}HNMR (CD_3OD) δ (ppm)**:** 7.62 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 2.0 Hz, 1 H), 3.47 (dd, *J* = 14.8, 6.4 Hz , 1 H), 3.34 (dd, *J* = 14.8, 6.4 Hz, 1 H), 3.24 (d, *J* =16.0 Hz, 1 H), 3.12 (d, *J* = 16.0 Hz, 1 H), 2.54 (t, *J* = 10.0 Hz, 1 H), 1.79, (d, *J* = 12.4 Hz, 1 H), 1.60 -1.40 (m, 3 H), 1.22 (m, 2 H), 1.03 (m ,1 H), 0.99 (d, *J* = 6.4 Hz, 3 H), 0.94 (d, *J* = 6.0 Hz, 3 H), 0.49 (m, 2H), 0.32 (m, 2 H).

Example 11

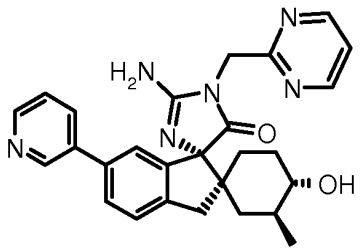


Example 11 was prepared by the method described in Example **1**, using 6-chloro indan-1-one in the first step and 2-aminomethyl pyrimidine in step 10.

LC-MS (method 1) t_R = 0.90 min. *m/z* 440, 442 (MH^+)

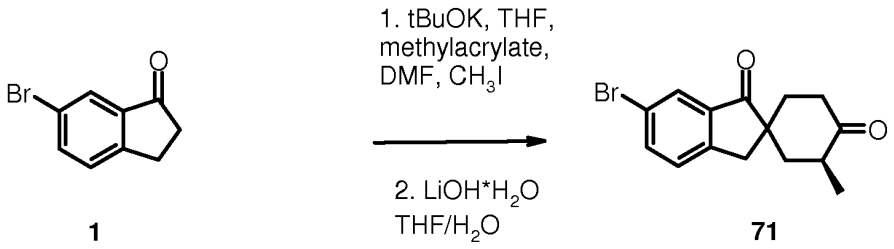
^{1}H NMR (CD_3OD) δ 8.73 (d, *J* = 4.7 Hz, 2H), 7.38 (t, *J* = 4.7 Hz, 1H), 7.27-7.24 (m, 2H), 5.01 (s, 2H), 3.14-3.05 (m, 2H), 2.60 (t, *J* = 9.8 Hz, 1H), 1.77-1.74 (m, 1H), 1.67-1.58 (m, 1H), 1.55-1.45 (m, 1H), 1.40-1.24 (m, 3H), 1.01-0.97 (m, 6H).

Example 12



Example 12

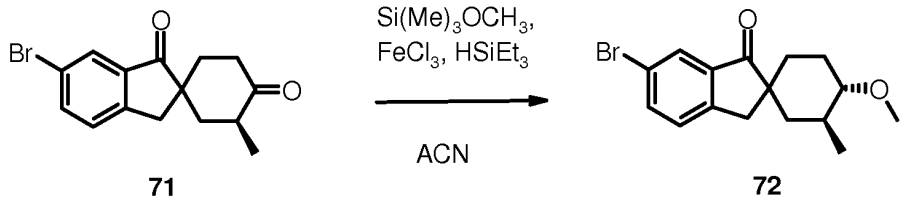
Step 1: Synthesis of intermediate 71.



1 **71**

6-bromo-indan-1-one **1** (100 g, 474 mmol) and methyl acrylate (86.4 g, 995 mmol) were mixed with 800 mL THF and t-BuOK (1.0 g) was added in two portions under ice cooling. The cooling bath was removed and the remaining t-BuOK (63.0 g) was added in even portions over 20 min (total of 64.0 g, 569 mmol). The mixture was stirred for 2 h at rt. DMF (240 mL) was added to the reaction mixture, followed by MeI (135 g, 948 mmol) and the mixture was stirred for 2 h. The reaction was quenched with 10% citric acid solution. The reaction mixture was concentrated under reduced pressure and filtered. The cake was washed with water, followed by MeOH to give a crude intermediate which was mixed with THF/H_2O (1.8 L/1.8 L). LiOH*H_2O (92.0 g, 2.19 mol) was added. The mixture was stirred for 16 h at rt and then 12 h at 70 °C. The reaction mixture was concentrated under reduced procedure and filtered. The cake was washed with H_2O, and then it was stirred with MeOH (50 mL) for 5 min, filtered again, and washed with additional amount of MeOH (50 mL). The solid was collected to give 75 g intermediate **71** which was used as such in the next step.

Step 2: Synthesis of intemediate 72.



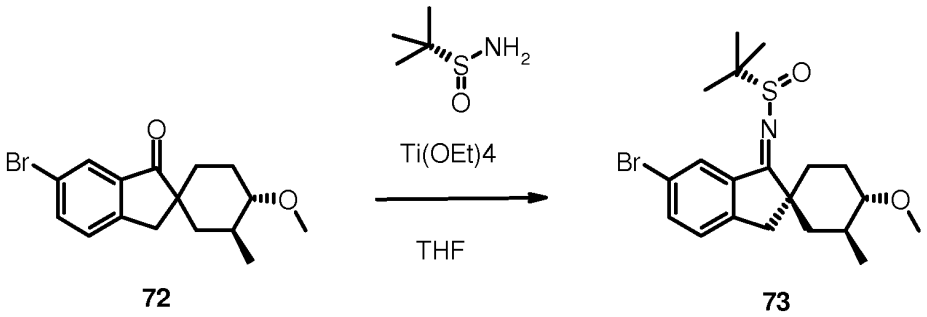
71 72

10.0 g (32.5 mmol) of intermediate **71** and 530 mg (3.27 mmol) ferric chloride were mixed with of 200 ml THF. To the stirred mixture 14.0 mL (102 mmol) methoxy trimethylsilane and 16.0 mL (100 mmol) triethylsilane were added and the mixture was stirred for 35 min at ambient temperature. The mixture was added to phosphate buffer (pH 7) and stirred for 14 h. The mixture was extracted with ethyl acetate, the organic phase dried and evaporated. The residue was purified by MPLC (340 g silica, cyclohexanes/ethyl acetate (100/0 to 85/15 in 60 min). Fractions containing the product were combined and the solvent was evaporated to yield 3.69 g of intermediate **72**.

LC-MS (method 2): t_R = 1.53 min. *m/z* 323/5 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 3: Synthesis of intemediate 73.



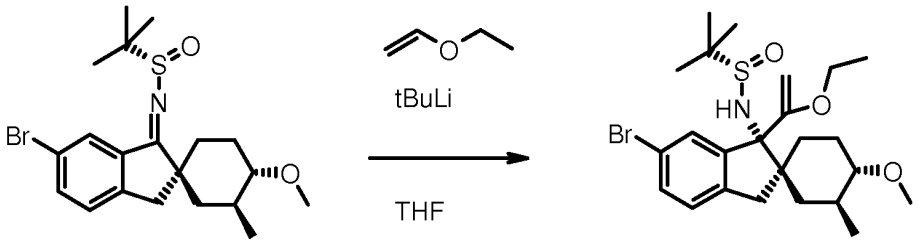
72 73

16.0 g (49.5 mmol) of intermediate **72** were mixed with 100 mL THF, 57.0 g (249 mmol) titanium (IV)-ethoxide were added and the mixture was stirred for 1 h at ambient temperature. After this, 12.0 g (99.0 mmol) of (S)-2-methyl-2-propanesulfinamide were added and mixture was refluxed under nitrogen for 3 days. 200 mL of water and 200 mL of DCM were added and the mixture filtered through celite. The organic layer was separated, and the solvent removed under vacuum. The residue was purified by MPLC (600 g silica, cyclohexanes/ethyl acetate (100/0 to 75/25 in 3 h, 95/5 to 85/15 in 15 min, 0/100 for 10 min). Fractions containing the product were combined. Mixed fractions were again chromatographed by MPLC. The desired product eluted first. The solvent was evaporated to yield 3.69 g of intermediate **73**.

LC-MS (method 2): t_R = 1.61 min. *m/z* 426/8 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 4: Synthesis of intemediate 74.



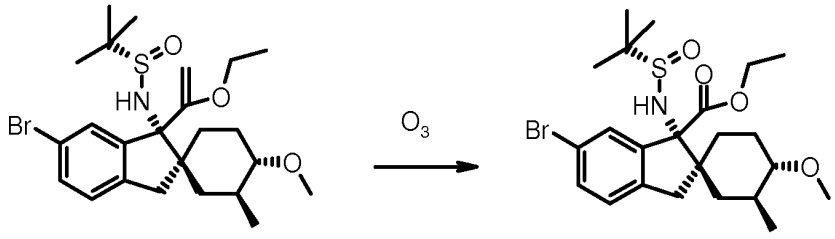
73 **74**

Under nitrogen 4.14 mL g (43.3 mmol) of ethylvinyl ether mixed with 70 mL THF were cooled to -78 °C and 25 mL tert-butyllithium (1.7 M in pentane, 43.4 mmol) were added. The mixture was warmed to 0 °C and stirred for 30 min. The mixture was transferred by a cannula to a mixture of 3.69 g (8.65 mmol) intermediate **73** in 130 mL THF at -78 °C. The mixture was stirred for 30 min at this temperature 100 mL sat. aqueous solution of ammonium chloride were added and the mixture extracted with ethyl acetate. The solvent was removed under vacuum and the residue purified by MPLC (340 g silica, cyclohexanes/ethyl acetate (90/10 to 60/40 in 70 min). Fractions containing the product were combined and the solvent was evaporated to yield 3.62 g of intermediate **74**.

LC-MS (method 2): t_R = 1.20 min. *m/z* 598/500 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 5: Synthesis of intemediate 75.



74 **75**

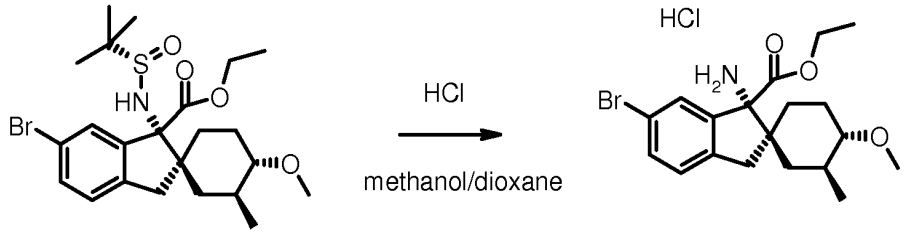
3.62 g (95%, 6.89 mmol) of intermediate **74** were mixed with 60 mL DCM and 15 mL methanol and cooled to -78 °C. Ozone was bubbled through the mixture for 20 min. The mixture was purged with N_2 and treated with 5 ml (68.4 mmol) Me_2S at -78 °C. The reaction was allowed to warm

to rt. The solvent was removed under vacuum, the residue was purified by MPLC (340 g silica, cyclohexanes/ethyl acetate (95/25 to 65/35 in 35 min). Fractions containing the product were combined and the solvent was evaporated to yield 2.50 g of intermediate **75**.

LC-MS (method 2): t_R = 1.20 min. *m/z* 500/2 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 6: Synthesis of intemediate 76.



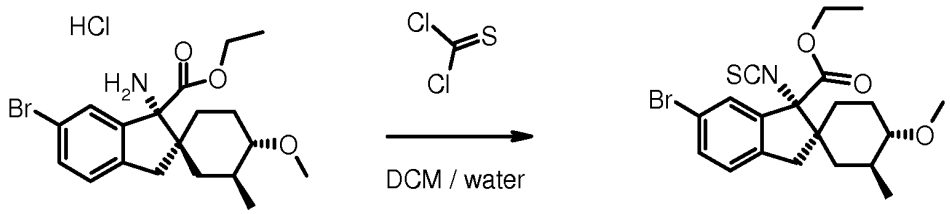
75 **76**

650 mg (0.98 mmol) of intermediate **75** were mixed with 8 ml methanol and 1 ml of a 4 M solution of HCl in 1,4-dioxan was added at 0 °C. The mixture was stirred for 2 h at the same temperature. The mixture was evaporated and the remaining crude product **76** used as such for the next step.

LC-MS (method 2): t_R = 1.20 min. *m/z* 396/8 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 7: Synthesis of intemediate 77.

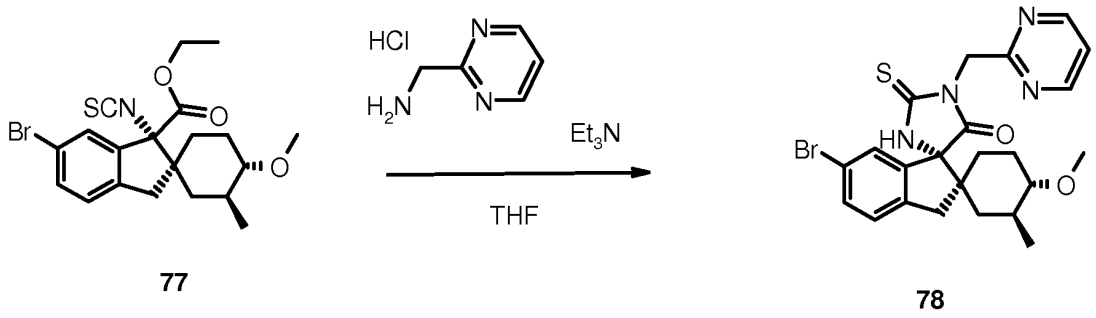


76 **77**

530 mg (1.23 mmol) of intermediate **76** and 675 mg (8.04 mmol) $NaHCO_3$ were mixed with 8 mL water and 4 ml DCM. 188 µL (2.54 mmol) thiophosgene were added at 0 °C while stirring. The mixture was stirred at 0 °C for 1 h. The mixture was extracted with DCM, the solvent evaporated and the remaining crude product **77** used as such for the next step.

LC-MS (method 2) t_R = 1.74 min. *m/z* 347/9 Br ($M+H^+$)

Step 8: Synthesis of intemediate 78.



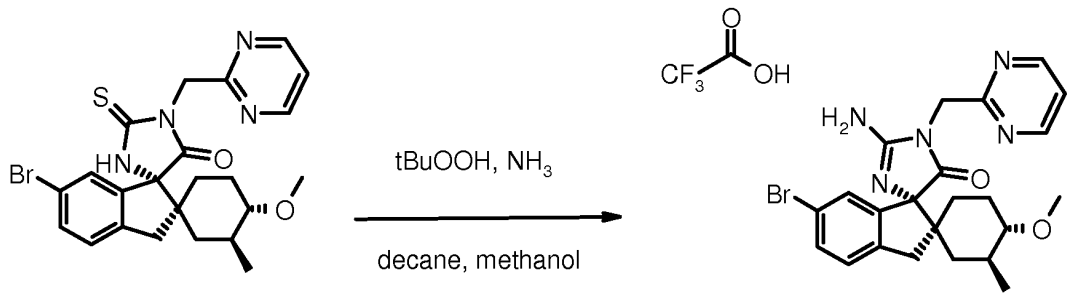
77 **78**

510 mg (80 %, 0.93 mmol) of 2-aminomethylpyrimidine hydrochloride was mixed with 3 mL THF and 290 µL (2.07 mmol) triethylamine were added. After 5 min, intermediate **77** mixed with 7 mL THF was added, and the mixture was stirred at ambient temperature for 2 h. 290 µL (2.07 mmol) triethylamine were added and the mixture was stirred for an additional 2 h. The mixture was evaporated and the residue purified by MPLC (25 g silica, cyclohexanes/ethyl acetate (110/0 to 70/30 in 50 min). Fractions containing the product were combined and the solvent was evaporated to yield 305 mg of intermediate **78**.

LC-MS (method 2): t_R = 1.00 min. *m/z* 501/3 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 9: Synthesis of intemediate 79.



78 **79**

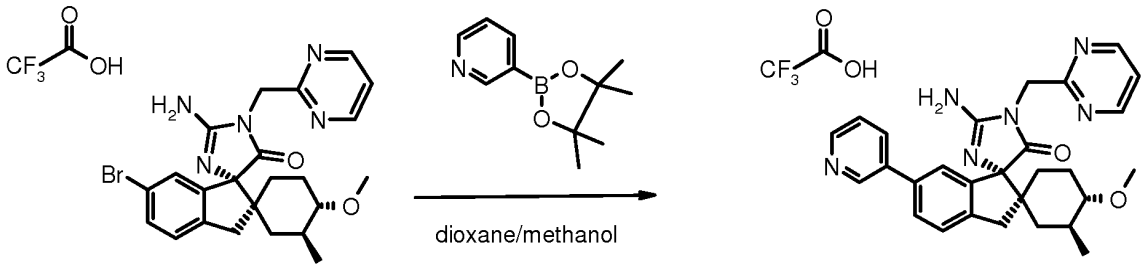
303 mg (0.60 mmol) of intermediate **78**, 2.65 mL (14.6 mmol, 5.5 M in decane) tert-butyhydroperoxide, 10 mL (70.0 mmol, 7 M in methanol) ammonia were mixed and stirred for 14 h at rt. The mixture was evaporated and the residue purified by HPLC (column: Waters Sunfire; eluent A: water + 0.1% TFA; eluent B: MeOH). Fractions containing the product were combined, the methanol

was evaporated and the residue lyophilized to yield 155 mg of the intermediate **79** as trifluoro acetic acid salt.

LC-MS (method 2): t_R = 1.00 min. *m/z* 484/6 Br ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 10: Synthesis of intemediate 80.



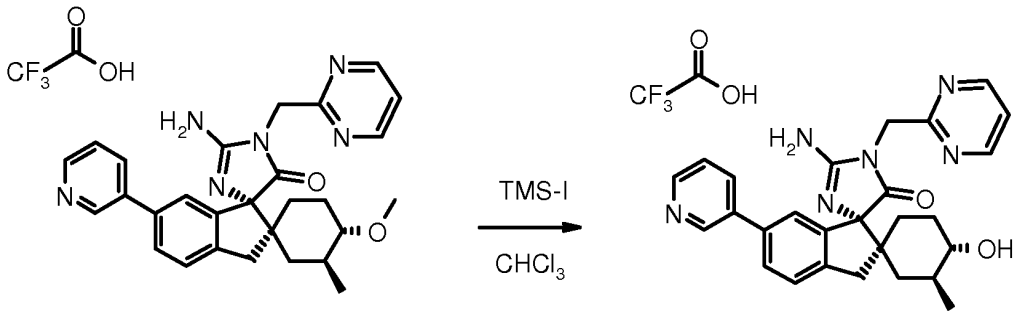
79 **80**

70 mg (90 %, 0.11 mmol) of intermediate **79**, 52.5 mg (0.26 mmol) 2-(3-pyridyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 16.1 mg 0.022 mmol) chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II), 210 µL 2 M aqueous Na_2CO_3 solution, 1.4 mL dioxane and 0.75 mL methanol were mixed in a microwave vial which was charged with argon. The mixture was stirred 30 min at 140 °C in a microwave oven (Biotage). The mixture was filtered over a thiol cartridge (Agilent Technologies, 500 mg, PL-Thiol MP SPE), the methanol evaporated and the residue purified by HPLC (column: Waters Sunfire; eluent A: water + 0.1% TFA; eluent B: MeOH). Fractions containing the product were combined, the methanol was evaporated and the residue lyophilized to yield 56.5 mg of the intermediate **80** as trifluoro acetic acid salt.

LC-MS (method 2): t_R = 1.00 min. *m/z* 483 ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 11: Synthesis of Example 12.



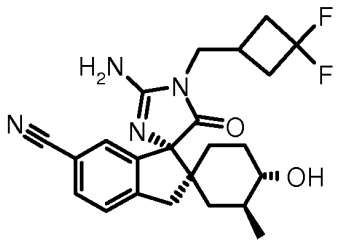
80 **Example 12**

To a suspension of 25 mg (0.042 mmol) of intermediate **80** in 1 mL chloroform were added 30 µL (97 %, 0.21 mmol) iodotrimethylsilane and the mixture was stirred for 60 min. The reaction was quenched with 0.5 mL methanol and 5 mL sat. $NaHCO_3$ aqueous solution and 5 mL 10 % Na_2SO_3 aqueous solution were added. The mixture was extracted with ethyl acetate and the combined organic layers dried, evaporated and the residue purified by HPLC (column: Waters Sunfire; eluent A: water + 0.1% TFA; eluent B: MeOH). Fractions containing the product were combined, the methanol was evaporated and the remaining residue lyophilized to yield 15.9 mg of Example **12** as trifluoro acetic acid salt.

LC-MS (method 2): t_R = 0.84 min. *m/z* 469 ($M+H^+$)

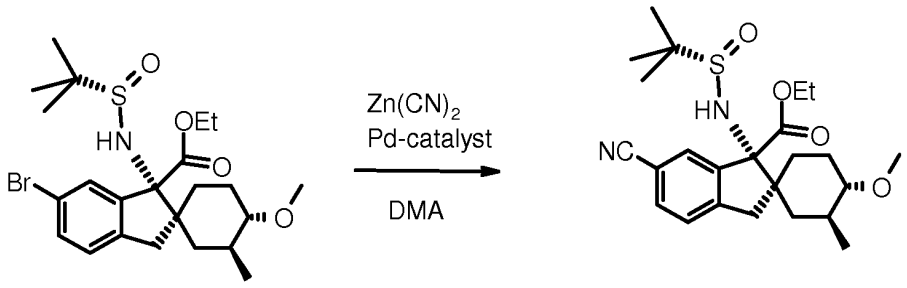
^{1}HNMR (DMSO-d6): δ 10.96 (br s, 1H), 9.58 (br s, 2H), 8.93 (d, 1H), 8.79 (d, 2H), 8.63 (dd, 1H), 8.14 (br d, 1H), 7.76 (dd, 1H), 7.70 (br s, 1H, 7.59 (dd, 1H), 7.51 (m, 2H), 5.18 (d, 1H), 5.08 (d, 1H), 4.30 (br s, OH) 3.16 (d, 1H), 3.02 (d, 1H), 2.94 (m, 1H), 1.78 (m, 1H), 1.58 - 1. 24 (m, 6H), 0.92 (d, 3H).

Example 13



Example 13

Step 1: Synthesis of intermediate 81.



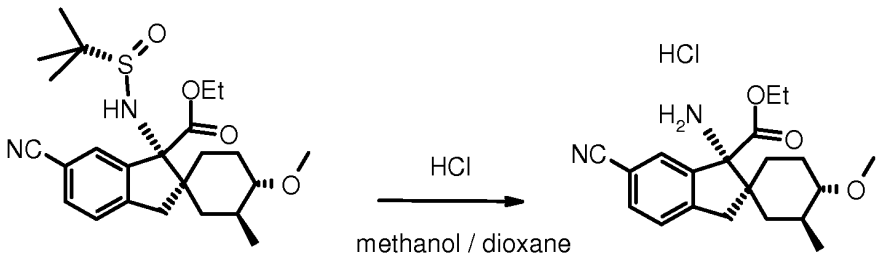
75 81

1.58 g (90 %, 2.84 mmol) of intermediate **75** were mixed with 60 mL DMA and argon was bubbled through the mixture. Zinc cyanide (556 mg, 4.74 mmol) and chloro(2-dicyclohexylphosphino-2',4',6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) (690 mg, 0.93 mmol) were added at rt. The mixture was stirred for 20 min at 120 °C. After this, the mixture was evaporated at 3 mbar at 70 °C, and the residue was mixed with water and ethyl acetate, filtered over celite, and the phases separated. The aqueous phase was extracted with ethyl acetate, and the organic phases were combined, dried and evaporated. The residue was purified by MPLC (100 g silica, CH/EE 80/20 to 55/45 in 70 min). Fractions containing the product were combined to give 1.17 g of intermediate **81**.

LC-MS (method 2): t_R = 1.40 min. *m/z* 447 ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 2: Synthesis of intermediate 82.



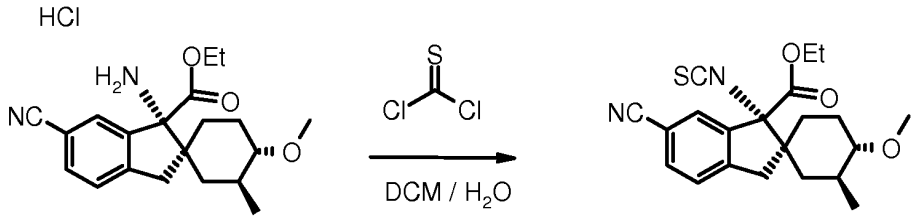
81 82

Intermediate **82** was synthesized by a method described in Example **12** step 6 from 4.00 g (80%, 7.17 mmol) intermediate **81**. 4.13 g of the crude product were obtained and used as such in the next step.

LC-MS (method 2): t_R = 1.11 min. *m/z* 343 ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 3: Synthesis of intermediate 83.

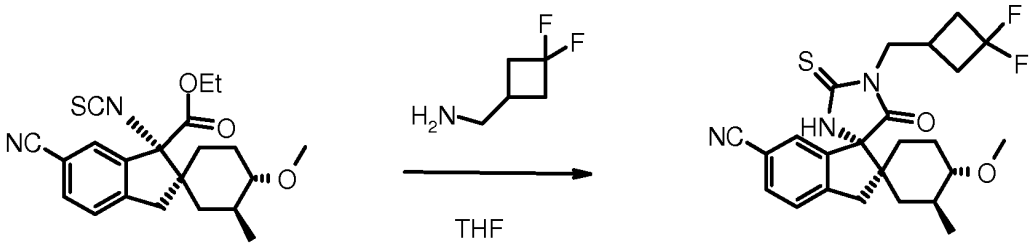


82 **83**

Intermediate **83** was synthesized by a method described in Example **12** step 7 from 4.13 g (70%, 7.63 mmol) intermediate **82**. 4.6 g of the crude product were obtained and used as such in the next step.

LC-MS (method 2): t_R = 1.58 min. *m/z* 294 ($M+H^+$)

Step 4: Synthesis of intermediate 84.

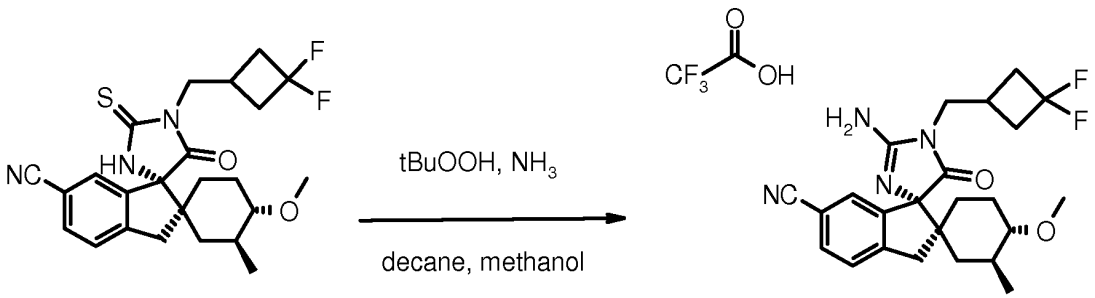


83 **84**

Intermediate **84** was synthesized in accordance with the method described in Example **12**, step 8, from 200 mg (0.33 mmol) intermediate **83**. Instead of 2-aminomethylpyrimidine hydrochloride, 63 mg (0.49 mmol) 3,3-difluorocyclobutyl)methanamine and 3 equivalents of trieethylamine were used. The crude product was purified by MPLC (25 g silica, CH/EE 65/35 in 45 min) to yield 141 mg of intermediate **84**.

LC-MS (method 2): t_R = 1.53 min. *m/z* 460 ($M+H^+$)

Step 5: Synthesis of intermediate 85.



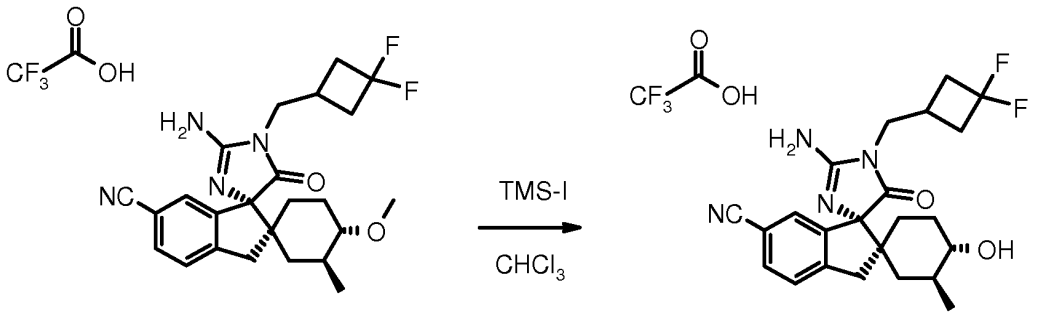
84 85

Intermediate **85** was synthesized by in accordance with the method described in Example **12**, step 9 using 139 mg (0.30 mmol) of intermediate **84**. The crude product was purified by HPLC (column: Waters Sunfire; eluent A: water + 0.1% TFA; eluent B: MeOH) to yield 96.8 mg of intermediate **85** as trifluoroacetic acid salt.

LC-MS (method 2): t_R = 1.19 min. *m/z* 443 ($M+H^+$)

^{1}HNMR (DMSO-d6) corresponds with the desired product.

Step 6: Synthesis of Example 13.



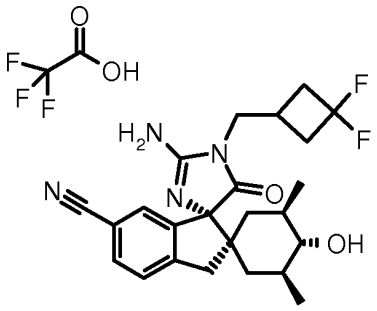
85 Example 13

Example **13** was synthesized in accordance with the method described in Example **12,** step 11 using 40 mg (0.072 mmol) of intermediate **85**. The crude product was purified by HPLC (column: Waters Sunfire; eluent A: water + 0.1% TFA; eluent B: MeOH) to yield 20 mg of Example **13**.

LC-MS (method 2): t_R = 0.88 min. *m/z* 429 ($M+H^+$)

^{1}HNMR (DMSO-d6): δ 10.83 (br s, 1H), 9.65 (br s, 2H), 7.90 (d, 1H), 7.84 (dd, 1H), 7.59 (d, 1H), 4.35 (br s, OH), 3.78 (m, 2H), 3.20 (d, 1H), 3.03 (d, 1H), 2.88 (m, 1H), 2.68 - 2.26 (m, 5H), 1.72 (m, 1H), 1.54 (m, 1H), 1.45 - 1. 28 (m, 3H), 1.16 (m, 1H), 1.05 (t, 1H), 0.91 (d, 3H).

Example 14



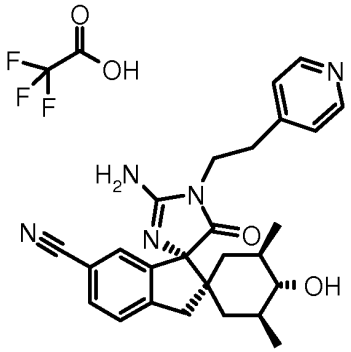
Example 14

Example **14** was synthesized by the method described in Example **13** using intermediate **17** instead of intermediate **75** in step 1.

LC-MS (method 3): t_R = 0.96 min. *m/z* 443 ($M+H^+$)

^{1}HNMR (DMSO-d6): δ 10.85 (br s, 1H), 9.65 (br s, 2H), 7.88 (d, 1H), 7.84 (dd, 1H), 7.59 (d, 1H), 4.40 (br s, OH), 3.78 (m, 2H), 3.20 (d, 1H), 3.06 (d, 1H), 2.68 - 2.26 (m, 6H), 1.60 - 1. 04(m, 6H), 0.92 (d, 3H), 0.88 (d, 3H).

Example 15



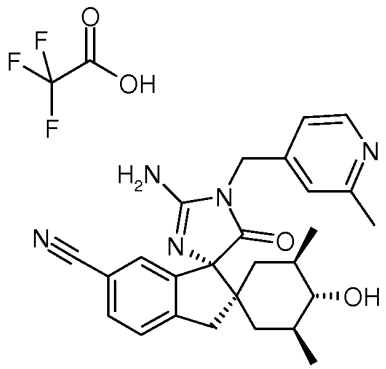
Example 15

Example **15** was synthesized by the method described in Example **13** using intermediate **17** instead of intermediate **75** in step 1 and 2-pyridin-4-yl-ethylamine instead of 3,3-difluorocyclobutyl)methanamine in step 4.

LC-MS (method 3): t_R = 0.96 min. *m/z* 444.5 ($M+H^+$)

^{1}HNMR (DMSO-d6): δ 10.81 (br s, 1H), 9.70 (br s, 2H), 8.55 (d, 2H), 7.84 (br s, 1H), 7.83 (dd, 1H), 7.55 (m, 3H), 4.30 (br s, OH), 4.06 - 3.90 (m, 2H), 3.16 - 2.96 (m, 4H), 2.40 (t, 1H), 1.49 (m, 1H), 1.35 (m, 2H), 1.18 (m, 1H), 1.02 - 0.90 (m, 2H), 0.88 (d, 3H), 0.86 (d, 3H).

Example 16



Example 16

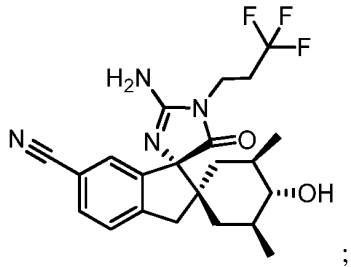
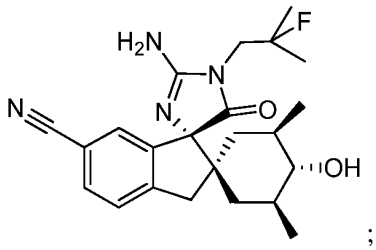
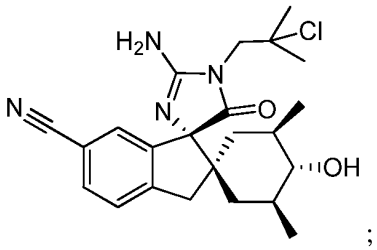
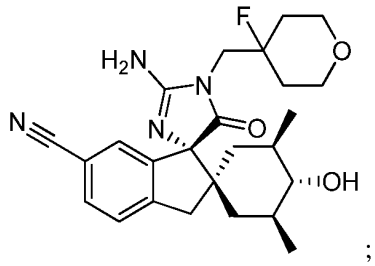
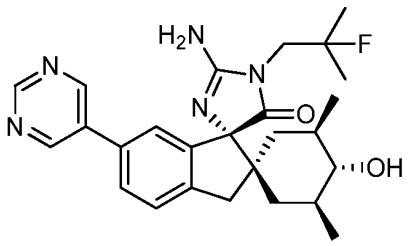
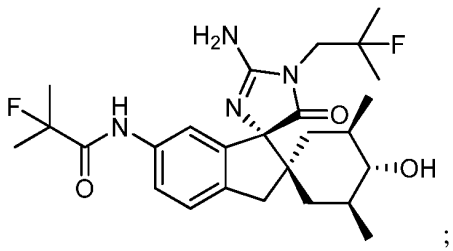
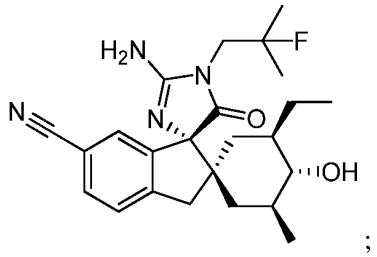
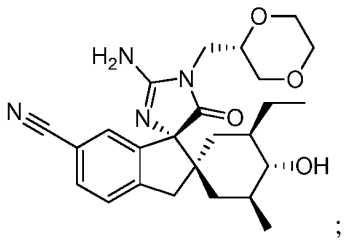
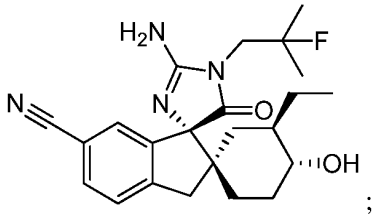
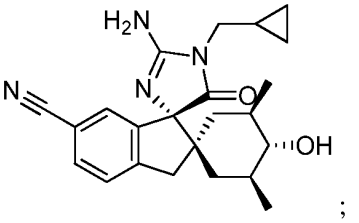
Example **16** was synthesized by the method described in Example **13** using intermediate **17** instead of intermediate **75** in step 1 and (2-methyl-pyridin-4-yl)-methylamine instead of 3,3-difluorocyclobutyl)methanamine in step 4.

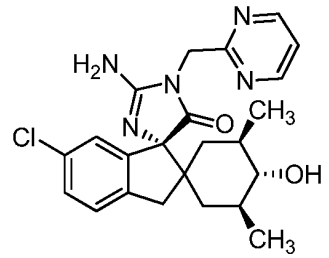
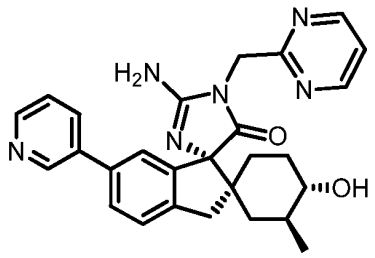
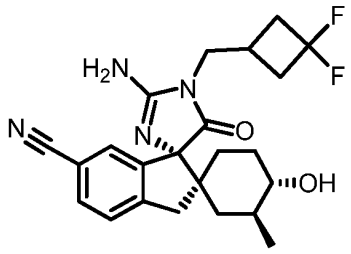
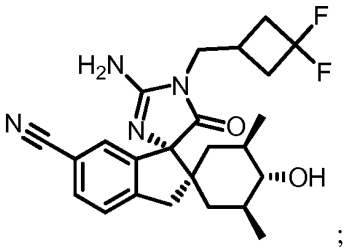
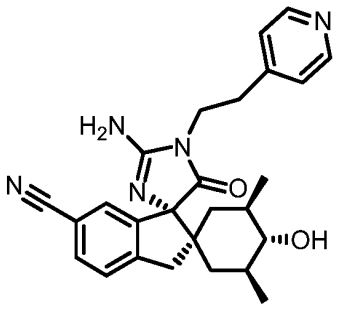
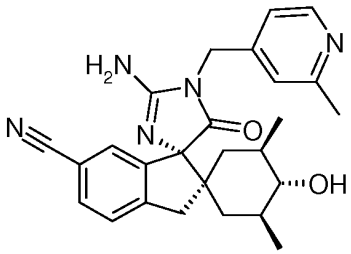
LC-MS (method 4): t_R = 0.82 min. *m/z* 444 ($M+H^+$)

^{1}HNMR (DMSO-d6): δ 10.96 (br s, 1H), 9.70 (br s, 2H), 8.52 (d, 1H), 7.98 (d, 1H), 7.85 (dd, 1H), 7.60 (d, 1H), 7.32 (d, 1H), 7.28 (br s, 1H), 4.93 (s, 2H), 4.30 (br s, OH), 3.20 (d, 1H), 3.03 (d, 1H), 2.52 (s, 3H), 2.47 (m, 1H), 1.59 - 1. 10 (m, 6H), 0.90 (d, 3H), 0.88 (d, 3H).

CLAIMS

1. A compound represented by a structural formula selected from:

 ;	 ;
 ;	 ;
 ;	 ;
 ;	 ;
 ;	 ;

 ;	 ;
 ;	 ;
 ; and	 ;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

3. A pharmaceutical composition comprising at least one compound according to claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

4. A compound according to claim 1 or a pharmaceutically acceptable salt thereof for use in the treatment of a BACE1 mediated disorder or disease.

5. A compound or a pharmaceutically acceptable salt thereof for use according to claim 4, wherein the BACE1 mediated disorder or disease is selected from the group consisting of a neurodegenerative disorder, cognitive decline, cognitive impairment, dementia and disease characterized by the production of β-amyloid deposits or neurofibrillary tangles.

6. A compound or a pharmaceutically acceptable salt thereof for use according to claim 5, wherein the disorder or disease is selected from the group consisting of Alzheimer's disease, Trisomy 21 (Down Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), senile dementia, cerebral amyloid angiopathy, degenerative dementia, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, dry age related macular degeneration (AMD), and glaucoma.

7. A compound or a pharmaceutically acceptable salt thereof for use according to claim 6, wherein the disease or disorder is Alzheimer's disease.

8. A compound or a pharmaceutically acceptable salt thereof for use according to claim 6, wherein the disease or disorder is glaucoma.

9. Use of a compound according to claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a BACE1 mediated disorder in a subject.

10. Use of a compound according to claim 9 or a pharmaceutically acceptable salt thereof, wherein the BACE1 mediated disease or disorder is selected from the group consisting of a neurodegenerative disorder, cognitive decline, cognitive impairment, dementia and disease characterized by the production of β-amyloid deposits or neurofibrillary tangles.

11. Use of a compound according to claim 10 or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is selected from the group consisting of Alzheimer's disease, Trisomy 21 (Down Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), senile dementia, cerebral amyloid angiopathy, degenerative dementia, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, dry age related macular degeneration (AMD), and glaucoma.

12. Use of a compound according to claim 11or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is Alzheimer's disease.

13. Use of a compound according to claim 11or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is glaucoma.

14. A method of treating a BACE1 mediated disorder or disease in a subject, comprising administering to the subject an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

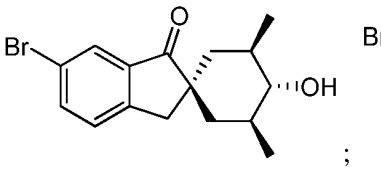
15. The method of claim 14, wherein the BACE1 mediated disorder or disease is selected from the group consisting of neurodegenerative disorder, cognitive decline, cognitive impairment, dementia and disease characterized by the production of β-amyloid deposits or neurofibrillary tangles.

16. The method of claim 15, wherein the disorder or disease is selected from the group consisting of Alzheimer's disease, Trisomy 21 (Down Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), senile dementia, cerebral amyloid angiopathy, degenerative dementia, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, dry age related macular degeneration (AMD), and glaucoma.

17. The method of claim 16, wherein the disorder or disease is Alzheimer's disease.

18. The method according to claim 16, wherein the disorder or disease is glaucoma.

19. A compound selected from the group consisting of: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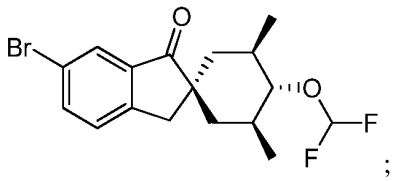
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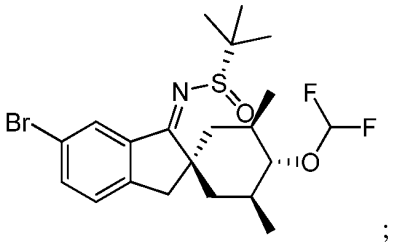
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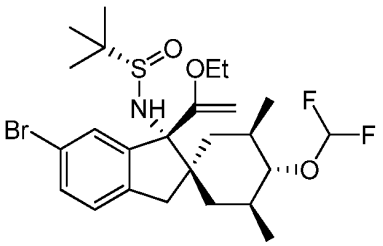
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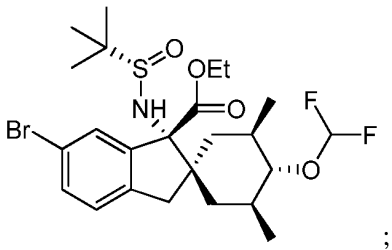
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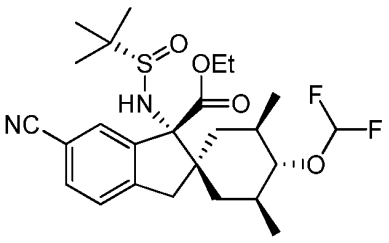
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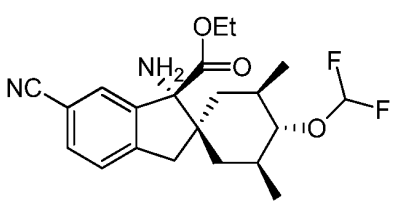
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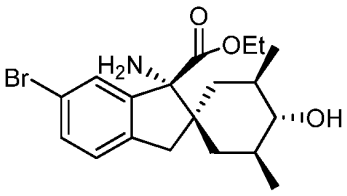

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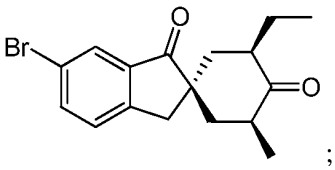

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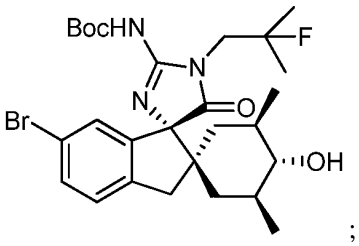

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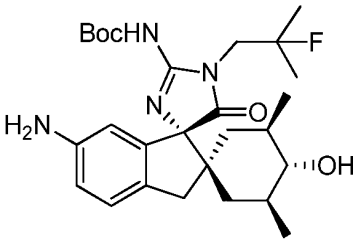

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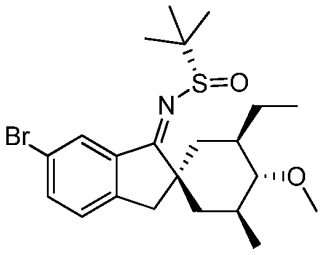

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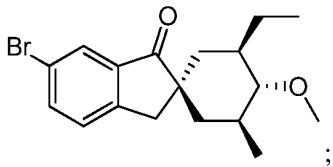

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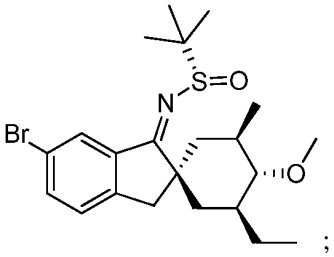

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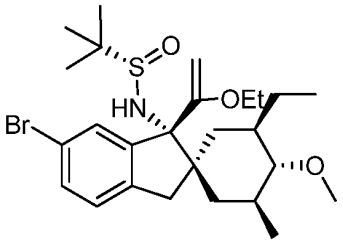

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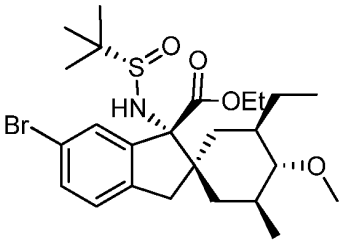

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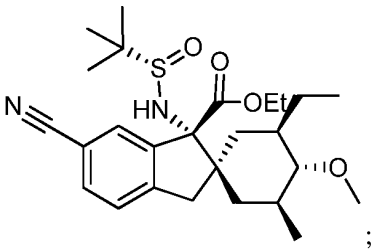

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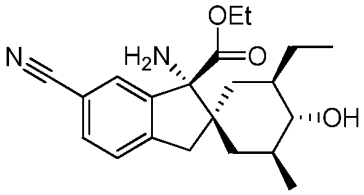

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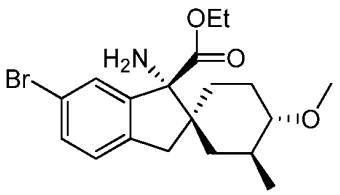

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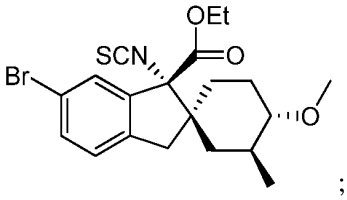

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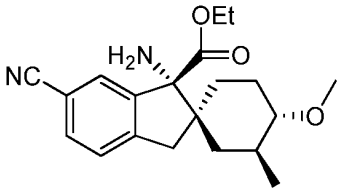

; or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/056566

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D235/02 C07D401/06 C07D403/04 A61K31/4184 A61P25/28
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/105179 A2 (VITAE PHARMACEUTICALS INC [US]; BOEHRINGER INGELHEIM INT [DE]; CACATIA) 16 September 2010 (2010-09-16) cited in the application See the examples	1-19
A	WO 2011/106414 A1 (DILLARD LAWRENCE W [US]; YUAN JING [US]; LEFTHERIS KATERINA [US]; VENK) 1 September 2011 (2011-09-01) cited in the application the whole document	1-19
E	WO 2013/134085 A1 (BOEHRINGER INGELHEIM INT [DE]; VITAE PHARMACEUTICALS INC [US]) 12 September 2013 (2013-09-12) the whole document	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 November 2013	08/11/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Menchaca, Roberto

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/056566

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		UY 34654 A	30-09-2013
		WO 2013134085 A1	12-09-2013

摘要

本發明涉及螺環醯基胍及其作爲 β-分泌酶（BACE1）活性抑制劑的用途，含有該螺環醯基胍的藥物組合物和使用該螺環醯基胍作爲治療藥劑的方法，該方法用於治療神經退行性病症，具有認知減退、認知損傷、痴呆特徵的病症和具有產生β-澱粉樣蛋白聚集特徵的疾病。