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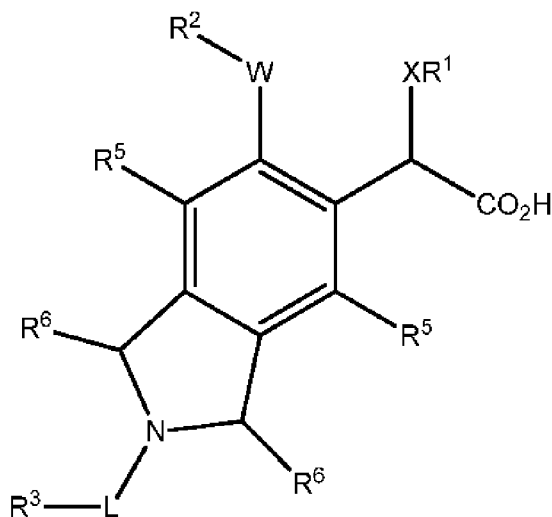
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[Continued on next page]

(54) Title: ISOINDOLINE DERIVATIVES



Formula I

(57) Abstract: Compounds of Formula (I) are disclosed and methods of treating viral infections with compositions comprising such compounds.

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## ISOINDOLINE DERIVATIVES

**FIELD OF THE INVENTION**

5           The present invention relates to substituted isoindoline compounds, pharmaceutical compositions, and methods of use thereof for (i) inhibiting HIV replication in a subject infected with HIV, or (ii) treating a subject infected with HIV, by administering such compounds.

**BACKGROUND OF THE INVENTION**

10           Human immunodeficiency virus type 1 (HIV-1) leads to the contraction of acquired immune deficiency disease (AIDS). The number of cases of HIV continues to rise, and currently over twenty-five million individuals worldwide suffer from the virus. Presently, long-term suppression of viral replication with antiretroviral drugs is the only option for treating  
15           HIV-1 infection. Indeed, the U.S. Food and Drug Administration has approved twenty-five drugs over six different inhibitor classes, which have been shown to greatly increase patient survival and quality of life. However, additional therapies are still required because of undesirable drug-drug interactions; drug-food interactions; non-adherence to therapy; and drug resistance due to mutation of the enzyme target.

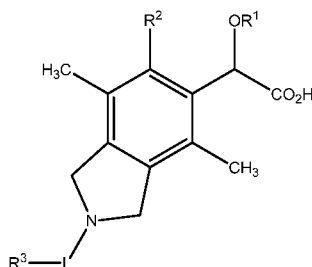
20           Currently, almost all HIV positive patients are treated with therapeutic regimens of antiretroviral drug combinations termed, highly active antiretroviral therapy ("HAART"). However, HAART therapies are often complex because a combination of different drugs must be administered often daily to the patient to avoid the rapid emergence of drug-resistant HIV-1 variants. Despite the positive impact of HAART on patient survival, drug  
25           resistance can still occur. The emergence of multidrug-resistant HIV-1 isolates has serious clinical consequences and must be suppressed with a new drug regimen, known as salvage therapy.

          Current guidelines recommend that salvage therapy includes at least two, and preferably three, fully active drugs. Typically, first-line therapies combine three to four drugs  
30           targeting the viral enzymes reverse transcriptase and protease. One option for salvage therapy is to administer different combinations of drugs from the same mechanistic class that remain active against the resistant isolates. However, the options for this approach are often limited, as resistant mutations frequently confer broad cross-resistance to different drugs in the same class. Alternative therapeutic strategies have recently become available with the  
35           development of fusion, entry, and integrase inhibitors. However, resistance to all three new drug classes has already been reported both in the lab and in patients. Sustained successful treatment of HIV-1-infected patients with antiretroviral drugs will therefore require the

continued development of new and improved drugs with new targets and mechanisms of action.

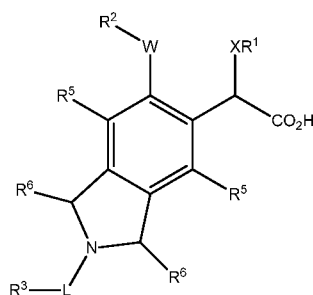
For example, over the last decade HIV inhibitors have been reported to target the protein-protein interaction between HIV-1 integrase and Lens Epithelium Derived Growth Factor/p75 ("LEDGF"). LEDGF is a cellular transcriptional cofactor of HIV-1 integrase that promotes viral integration of reverse transcribed viral cDNA into the host cell's genome by tethering the preintegration complex to the chromatin. Because of its crucial role in the early steps of HIV replication, the interaction between LEDGF and integrase represents another attractive target for HIV drug therapy.

US provisional patent application 62/027,359 discloses certain isoindoline compounds having the following formula:



### SUMMARY OF THE INVENTION

Briefly, in one aspect, the present invention discloses compounds of Formula I:



Formula I

wherein:

X is O or CH<sub>2</sub>;

R<sup>1</sup> is C<sub>1-6</sub>alkyl wherein said alkyl may contain cycloalkyl portions;

W is -CH=CH-, -C≡C-, C<sub>1-3</sub>alkylene, -CH<sub>2</sub>C(O)NH-, -NHC(O)-, -N(CH<sub>3</sub>)C(O)-, -N(CH<sub>3</sub>)C(O)CH<sub>2</sub>-, -C(O)-, -CH<sub>2</sub>C(O)-, or -NHC(O)CH<sub>2</sub>-, wherein each W is optionally substituted by 1 or 2 methyl groups;

R<sup>2</sup> is H, C<sub>1-6</sub>alkyl, C<sub>5-14</sub>aryl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-9</sub>heterocycle, or C<sub>5-9</sub>heteroaryl, wherein each R<sup>2</sup> group is optionally substituted by one to four substituents selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>heteroalkyl, or C<sub>1-6</sub>alkylene or C<sub>1-6</sub>heteroalkylene

wherein said C<sub>1-6</sub>alkylene or C<sub>1-6</sub>heteroalkylene is bonded to adjacent carbon atoms on said C<sub>5-14</sub>aryl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-9</sub>heterocycle, or C<sub>5-9</sub>heteroaryl to form a fused ring;

L is a bond, -CH<sub>2</sub>(CO)-, -C<sub>1-3</sub>alkylene-, -SO<sub>2</sub>-, -C(O)-, -C(S)-, -C(NH)-, -C(O)NH-, -C(O)NHCH<sub>2</sub>-, -C(O)N-, -C(O)OCH<sub>2</sub>-, -C(O)O-, -C(O)C(O)-, -SO<sub>2</sub>-NH-, or -CH<sub>2</sub>C(O)-;

R<sup>3</sup> is H, CN, oxo, C<sub>1-6</sub>alkyl, C<sub>5-14</sub>aryl, CH<sub>2</sub>C<sub>5-14</sub>aryl, CH<sub>2</sub>C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>spirocycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-9</sub>heterocycle, or C<sub>5-9</sub>heteroaryl, or R<sup>3</sup> may join together with an R<sup>6</sup> to form a fused 5-7 membered ring, and wherein each R<sup>3</sup> group is optionally substituted by one to four substituents selected from halo, oxo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-3</sub>fluoroalkyl, -OC<sub>1-6</sub>alkyl, -C(O)R<sup>4</sup>, -C(O)NR<sup>4</sup>, -C(O)NHR<sup>4</sup>, C<sub>5-14</sub>aryl, C<sub>1-6</sub>heteroalkyl, -B(OH)<sub>2</sub>, C<sub>3-9</sub>heterocycle, C<sub>5-9</sub>heteroaryl, -C(O)OC<sub>1-6</sub>alkyl, or two substituents may bond together to form a fused, spiro, or bridged ring and that fused, spiro, or bridged ring may optionally be substituted with R<sup>4</sup>;

R<sup>4</sup> is CN, halo, -OC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-9</sub>heterocycle, or C<sub>5-14</sub>aryl;

each R<sup>5</sup> is independently H, C<sub>1-3</sub>alkyl, C<sub>3-6</sub>cycloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, or CF<sub>3</sub>;

each R<sup>6</sup> is independently H, or C<sub>1-3</sub>alkyl, C<sub>5-14</sub>aryl, C<sub>3-9</sub>heterocycle, C<sub>5-9</sub>heteroaryl, -C(O)NR<sup>4</sup>, or -C(O)NHR<sup>4</sup>, or both R<sup>6</sup> may together comprise 2-4 carbon atoms and join together to form a bridged ring system;

and wherein each heterocycle, heteroaryl, heteroalkyl, and heteroalkylene comprises one to three heteroatoms selected from S, N, B, or O.

In another aspect the present invention discloses pharmaceutically acceptable salts of the compounds of Formula I.

In another aspect, the present invention discloses pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention discloses a method for treating a viral infection in a patient mediated at least in part by a virus in the *retrovirus* family of viruses, comprising administering to said patient a composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the viral infection is mediated by the HIV virus.

In another aspect, a particular embodiment of the present invention provides a method of treating a subject infected with HIV comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In yet another aspect, a particular embodiment of the present invention provides a method of inhibiting progression of HIV infection in a subject at risk for infection with HIV comprising administering to the subject a therapeutically effective amount of a compound of

Formula I, or a pharmaceutically acceptable salt thereof. Those and other embodiments are further described in the text that follows.

In accordance with another embodiment of the present invention, there is provided a method for preventing or treating a viral infection in a mammal mediated at least in part by a virus in the *retrovirus* family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound as defined in Formula I, wherein said virus is an HIV virus and further comprising administration of a therapeutically effective amount of one or more agents active against an HIV virus, wherein said agent active against the HIV virus is selected from the group consisting of Nucleotide reverse transcriptase inhibitors; Non-nucleotide reverse transcriptase inhibitors; Protease inhibitors; Entry, attachment and fusion inhibitors; Integrase inhibitors; Maturation inhibitors; CXCR4 inhibitors; and CCR5 inhibitors.

#### DETAILED DESCRIPTION OF THE INVENTION

Preferably R<sup>1</sup> is C<sub>1-6</sub>alkyl. Most preferably, R<sup>1</sup> is t-butyl.

Preferably X is O.

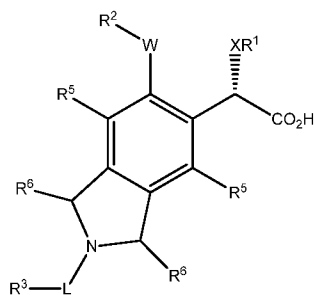
Preferably R<sup>2</sup> is optionally substituted phenyl. Most preferably, R<sup>2</sup> is phenyl substituted by one to four substituents selected from fluorine, methyl, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O- wherein said -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O- is bonded to adjacent carbon atoms on said phenyl to form a bicyclic ring, or -NHCH<sub>2</sub>CH<sub>2</sub>O- wherein said -NHCH<sub>2</sub>CH<sub>2</sub>O- is bonded to adjacent carbon atoms on said phenyl to form a bicyclic ring.

Preferably R<sup>3</sup> is C<sub>1-6</sub>alkyl, phenyl, naphthyl, cyclopentyl, cyclohexyl, pyridyl, or tetrahydropyranyl, each of which is optionally substituted by 1-3 substituents selected from halogen, C<sub>1-6</sub>alkyl, -OC<sub>1-6</sub>alkyl, C<sub>1-3</sub>fluoroalkyl, or phenyl.

Preferably each R<sup>5</sup> is methyl.

Preferably each R<sup>6</sup> is H.

Preferably the stereochemistry on the carbon to which XR<sup>1</sup> is bound is as depicted below.



“Pharmaceutically acceptable salt” refers to pharmaceutically acceptable salts derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium, and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate. Suitable salts include those described in P. Heinrich Stahl, Camille G. Wermuth (Eds.), Handbook of Pharmaceutical Salts Properties, Selection, and Use; 2002.

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### EXAMPLES

The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working examples.

The following examples serve to more fully describe the manner of making and using the above-described invention. It is understood that these examples in no way serve to limit the true scope of the invention, but rather are presented for illustrative purposes. In the examples below and the synthetic schemes above, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

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aq. = aqueous  
μL = microliters  
μM = micromolar  
NMR = nuclear magnetic resonance  
boc = tert-butoxycarbonyl

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br = broad  
Cbz = benzyloxycarbonyl  
d = doublet  
δ = chemical shift  
oC = degrees celcius

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DCM = dichloromethane  
dd = doublet of doublets  
DMEM = Dulbeco's Modified Eagle's Medium  
DMF = N,N-dimethylformamide  
DMSO = dimethylsulfoxide

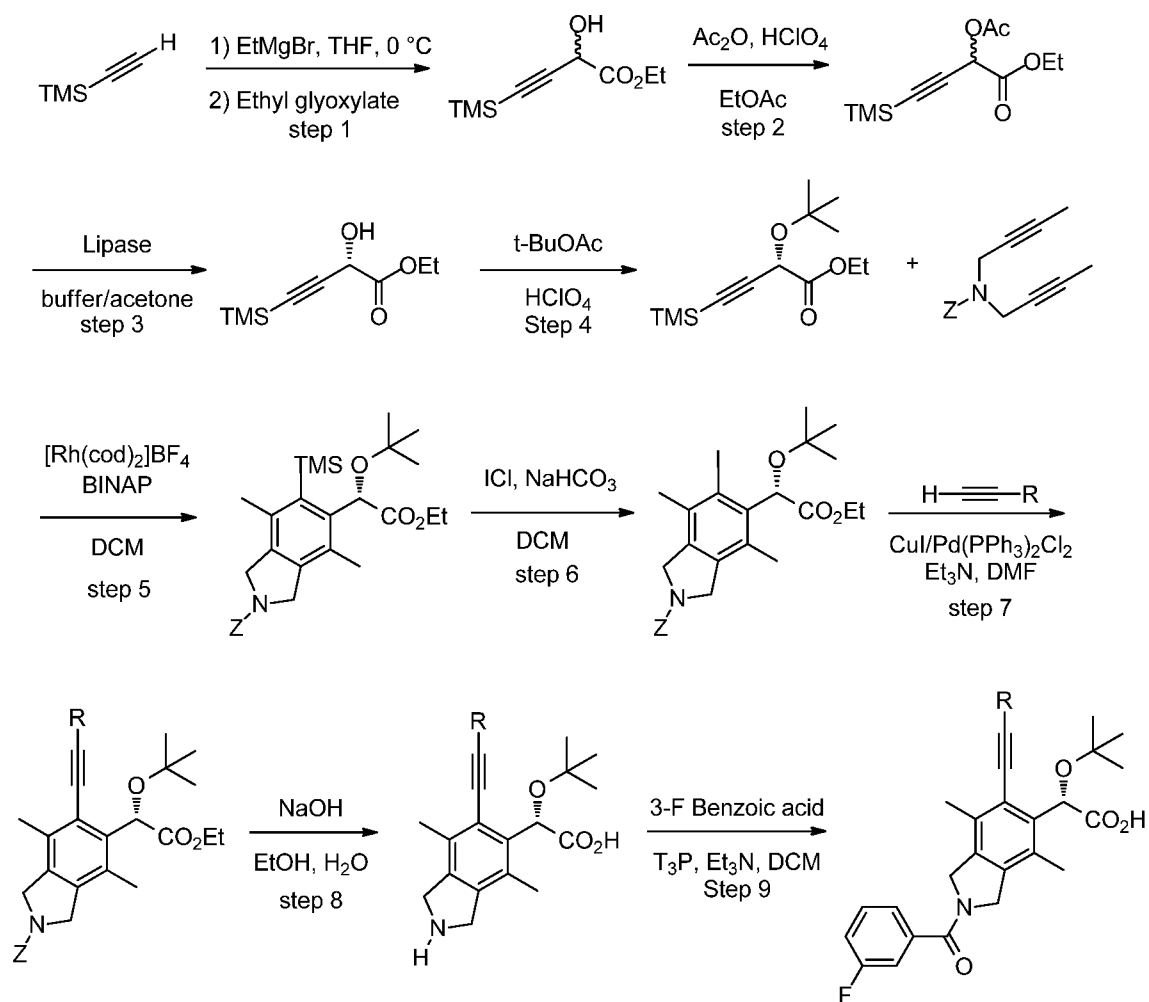
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EtOAc = ethyl acetate  
g = gram

	h or hr	=	hours
	HCV	=	hepatitis C virus
	HPLC	=	high performance liquid chromatography
	Hz	=	hertz
5	IU	=	International Units
	IC <sub>50</sub>	=	inhibitory concentration at 50% inhibition
	J	=	coupling constant (given in Hz unless otherwise indicated)
	m	=	multiplet
	M	=	molar
10	M+H <sup>+</sup>	=	parent mass spectrum peak plus H <sup>+</sup>
	mg	=	milligram
	min	=	minutes
	mL	=	milliliter
	mM	=	millimolar
15	mmol	=	millimole
	MS	=	mass spectrum
	nm	=	nanomolar
	ppm	=	parts per million
	q.s.	=	sufficient amount
20	s	=	singlet
	RT	=	room temperature
	sat.	=	saturated
	t	=	triplet
	TFA	=	trifluoroacetic acid
25	Z	=	benzyloxycarbonyl

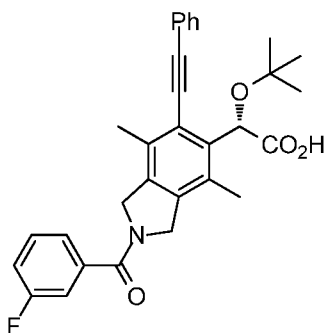


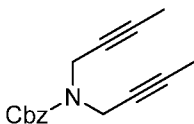
Scheme 1



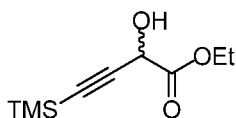
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**Example 1:** *(S)*-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(phenylethynyl)isoindolin-5-yl)acetic acid

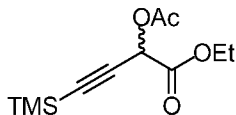


*Benzyl di(but-2-yn-1-yl)carbamate*

To an ice-cooled solution of 1-bromobut-2-yne (581 g, 2.2 eq) in DMF (3.5L) was added NaH (60%, 199 g, 2.5 eq) carefully and the mixture was stirred at 0°C under N<sub>2</sub> atmosphere for 15 min. Then a solution of benzyl carbamate (300 g, 1.985 mol, 1 eq) in DMF (500mL) was added dropwise at 0°C for 1h and the resulting mixture was allowed to warm to ambient temperature for 2h. After being quenched cautiously with H<sub>2</sub>O, the reaction was extracted with ether (x2). The organic layer was washed with H<sub>2</sub>O (x3), brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0 - 5% EtOAc in hexane) to afford the title compound (398 g, 79%).<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41 – 7.27 (m, 5H), 5.17 (s, 2H), 4.18 (s, 4H), 1.81 (t, J = 2.3 Hz, 6H). LC-MS (ESI+): m/z (M+H) =256.3

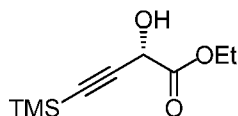
*Step 1: Ethyl 2-hydroxy-4-(trimethylsilyl)but-3-ynoate.*

To a solution of TMS-acetylene (250 g, 2.55 mol) in anhydrous THF (2.5 L) at 0 °C was added 3M EtMgBr/ether (933 mL, 2.80 mol) dropwise under an N<sub>2</sub> atmosphere while maintaining the inner temperature below 5 °C. After stirring at 0 °C for 30 min, the suspension was added to an ice cold solution of 50% ethyl glyoxylate/toluene (624 g, 3.05 mol) in anhydrous THF (5 L) via cannula. After stirring at 0 °C for 1 h, the mixture was quenched with saturated aqueous NH<sub>4</sub>Cl solution (3 L) and extracted with EtOAc (2x1 L). The combined EtOAc solutions were concentrated at reduced pressure. The residue was diluted with EtOAc (3 L). The solution was washed with water (2x1 L) and brine (2x1 L), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 0-10% EtOAc/petroleum ether) to give the title compound (285 g, 56%) as a yellow oil. <sup>1</sup>H NMR (400MHz, CHLOROFORM-d) δ = 4.83 (d, J=7.3 Hz, 1H), 4.34 (qq, J=7.2, 10.8 Hz, 2H), 3.02 (d, J=7.3 Hz, 1H), 1.34 (t, J=7.2 Hz, 3H), 0.22 - 0.16 (m, 9H).

*Step 2: Ethyl 2-acetoxy-4-(trimethylsilyl)but-3-ynoate*

To a 10 L flask was added EtOAc (7.5 L) followed by Ac<sub>2</sub>O (400 mL). After stirring at RT for 30 minutes the mixture was cooled to 0 °C and treated with another portion of Ac<sub>2</sub>O (2.1 L). After 1 hour at 0 °C, the solution was allowed to warm to RT. To the solution was added ethyl 2-hydroxy-4-(trimethylsilyl)but-3-ynoate (520 g, 2.60 mol). After stirring at RT for 5 1 hour the solution was washed with 1N aqueous NaOH (3x, 20 L total). The solution was then washed with brine (5 L), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to dryness at reduced pressure. The crude product was purified by flash chromatography (silica gel, 0-5% EtOAc/petroleum ether) to give the title compound (590 g, 94%) as a yellow oil. <sup>1</sup>H NMR (400MHz, CHLOROFORM-d) δ = 5.69 (s, 1H), 4.36 - 4.21 (m, 2H), 2.19 (s, 3H), 1.32 (t, 10 J=7.2 Hz, 3H), 0.25 - 0.15 (m, 9H).

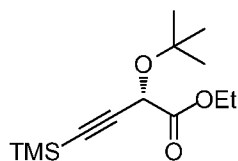
*Step 3: (S)-Ethyl 2-hydroxy-4-(trimethylsilyl)but-3-ynoate*



To a solution of ethyl 2-acetoxy-4-(trimethylsilyl)but-3-ynoate (150 g, 0.620 mol) in acetone (1.88 L) and phosphate buffer solution (pH 7.2, 7.5 L) was added Amano Lipase PS (75 g). After stirring at 20 °C overnight, the reaction mixture was diluted with water (2.5 L) and extracted with EtOAc (3 L). The layers were separated and the organic layer was washed with brine (3x, 10 L total volume), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated 20 under reduced pressure to give the crude product. This material was purified by flash chromatography (silica gel, 0-10% EtOAc/petroleum ether) to afford the title compound (55 g, 44%) as a yellow oil. <sup>1</sup>H NMR (400MHz, CHLOROFORM-d) δ = 4.83 (d, J=7.3 Hz, 1H), 4.34 (qq, J=7.2, 10.8 Hz, 2H), 3.02 (d, J=7.3 Hz, 1H), 1.34 (t, J=7.2 Hz, 3H), 0.22 - 0.16 (m, 9H).

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*Step 4: (S)-Ethyl 2-(tert-butoxy)-4-(trimethylsilyl)but-3-ynoate*

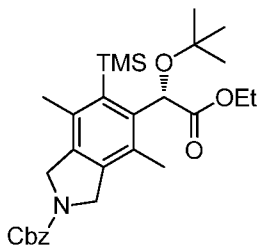


To a solution of (S)-ethyl 2-hydroxy-4-(trimethylsilyl)but-3-ynoate (100 g, 0.500 mol) 30 in t-BuOAc (2.5 L) was added HClO<sub>4</sub> (41 mL, 0.500 mol) dropwise at RT. After stirring for 40 minutes, the mixture was quenched with NaHCO<sub>3</sub> powder, diluted with water (2 L) and extracted with EtOAc (2L). The EtOAc solution was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>,

filtered and concentrated under reduced pressure to give the crude product. This material was purified by flash chromatography (silica gel, 0-5% EtOAc/petroleum ether) to afford the title compound (103 g, 81%) as a yellow oil. <sup>1</sup>H NMR (400MHz, CHLOROFORM-d) δ = 4.72 (s, 1H), 4.33 - 4.20 (m, 2H), 1.31 (t, J=7.2 Hz, 3H), 1.28 (s, 9H), 0.17 (s, 9H).

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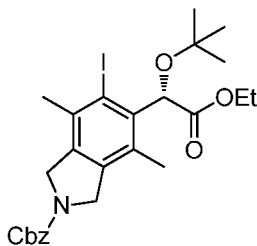
*Step 5: (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(trimethylsilyl)isoindoline-2-carboxylate*



A mixture of [Rh(cod)<sub>2</sub>]BF<sub>4</sub> (5 g, 12.313 mmol, 6.3% eq) and (R)-BINAP (7.67 g, 6.3% eq) in DCM (50 mL) was stirred at ambient temperature under H<sub>2</sub> atmosphere for 6 h until the solution turned dark. This mixture was charged with N<sub>2</sub> and a solution of (S)-ethyl 2-tert-butoxy-4-(trimethylsilyl)but-3-ynoate (50 g, 195 mmol, 1 eq) in DCM (100mL) was added. The mixture was heated to 40 °C. A solution of benzyl di(but-2-yn-1-yl)carbamate (100 g, 390 mmol, 2 eq) in DCM (400mL) was added to the above mixture under N<sub>2</sub> atmosphere dropwise for 3 h and the resulting mixture was kept stirring at 40 °C for 0.5 h. After being concentrated to dryness, the residue was purified by column chromatography (silica gel, 0 ~ 15% EtOAc in hexane) to afford the title compound (69 g, 69%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37 (ddd, J = 14.0, 9.2, 6.6 Hz, 5H), 5.60 (s, 1H), 5.23 (s, 2H), 4.74 – 4.61 (m, 4H), 4.24 (dd, J = 10.8, 7.1 Hz, 1H), 4.10 (s, 1H), 2.33 (d, J = 12.9 Hz, 3H), 2.21 (d, J = 10.6 Hz, 3H), 1.22 (td, J = 7.1, 1.1 Hz, 3H), 1.16 (s, 9H), 0.48 (s, 9H). LC-MS (ESI+): m/z (M+H) = 512.2

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*Step 6: (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate*

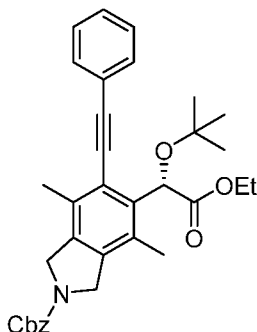


25

To an ice-cooled well-stirred suspension of (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(trimethylsilyl)isoindoline-2-carboxylate (90 g, 175.9 mmol, 1 eq) and sodium bicarbonate (296 g, 20 eq) in DCM (450mL) was added a solution of

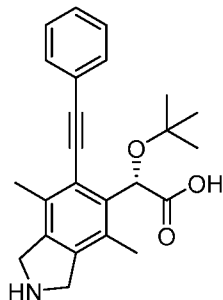
iodinemonochloride in DCM (1M, 194mL, 1.1 eq) at 0 °C under a N<sub>2</sub> atmosphere. The resulting mixture was stirred at 0 °C for 0.5 h. After being quenched with saturated sodium thiosulfate, the reaction mixture was extracted with EtOAc (1.5L) and the organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-15% EtOAc in hexane) to afford the title compound (74 g, 74%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45 – 7.29 (m, 5H), 5.87 (s, 1H), 5.22 (s, 2H), 4.69 (dd, J = 27.0, 15.3 Hz, 4H), 4.23 – 4.07 (m, 2H), 2.36 (d, J = 12.2 Hz, 3H), 2.29 (d, J = 10.7 Hz, 3H), 1.25 – 1.17 (m, 12H). LC-MS (ESI+): m/z (M+H) = 566.1

Step 7: *Benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(phenylethynyl)isoindoline-2-carboxylate*



A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (200 mg, 0.35 mmol), ethynylbenzene (145 mg, 1.41 mmol), Pd(dppf)Cl<sub>2</sub> (37.2 mg, 0.053 mmol) and CuI (20.2 mg, 0.106 mmol) in TEA (3 mL) was stirred at 60°C under N<sub>2</sub> atmosphere overnight. The resulting mixture was filtered through a pad of Celite and the filtrate was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product which was purified by silica gel chromatography (0-20% EtOAc in PE) to afford the title compound (35 mg, 18% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58 – 7.50 (m, 2H), 7.44 – 7.31 (m, 8H), 6.06 (s, 1H), 5.23 (s, 2H), 4.71 (d, J = 15.0 Hz, 4H), 4.22 – 4.08 (m, 2H), 2.41 (d, J = 11.6 Hz, 3H), 2.28 (d, J = 10.4 Hz, 3H), 1.25 (d, J = 1.2 Hz, 9H), 1.18 (td, J = 7.1, 2.1 Hz, 3H). LC/MS (m/z) ES+ = 540.6 (M+1).

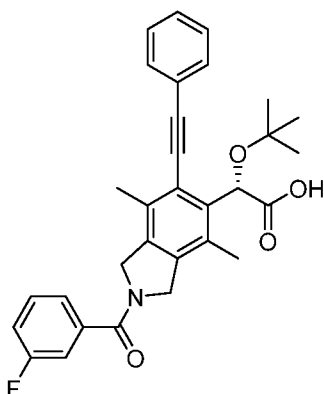
Step 8: (S)-2-(tert-butoxy)-2-(4,7-dimethyl-6-(phenylethynyl)isoindolin-5-yl)acetic acid



A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(phenylethynyl)iso indoline-2-carboxylate (35 mg, 0.065 mmol) and NaOH (78 mg, 1.95 mmol) in EtOH (0.8 mL) and H<sub>2</sub>O (0.4 mL) was stirred at 100 °C. After 2 h, the reaction mixture was cooled to ambient temperature acidified with 1N HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the title compound (25 mg, quant. yield) as a yellow oil which was used in the next step without further purification. LC/MS (m/z) ES+ = 378.4 (M+1).

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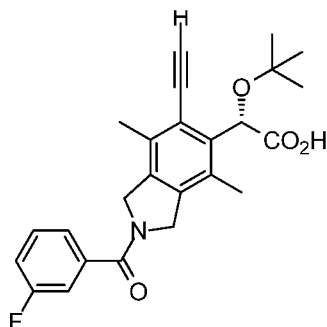
Step 9: (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(phenylethynyl)isoindolin-5-yl)acetic acid



To a solution of (S)-2-(tert-butoxy)-2-(4,7-dimethyl-6-(phenylethynyl)isoindolin-5-yl)acetic acid (19 mg, 0.05 mmol) and 3-fluorobenzoic acid (14 mg, 0.1 mmol) in EtOAc (2 mL) was added propane phosphonic acid anhydride (80 mg, 0.126 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (15 mg, 0.15 mmol). After 1 h, the reaction mixture was quenched with sat. NaHCO<sub>3</sub> aq. solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC (C18, 50-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (4.1 mg, 16% yield) as a yellow powder after lyophilization. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.29 (br, 1H), 7.49 (m, 9H), 5.87 (d, J = 4.3 Hz, 1H), 4.83 (m, 4H), 2.28 (m, 6H), 1.18 (d, J = 7.1 Hz, 9H). LC/MS (m/z) ES+ = 500.7 (M+1).

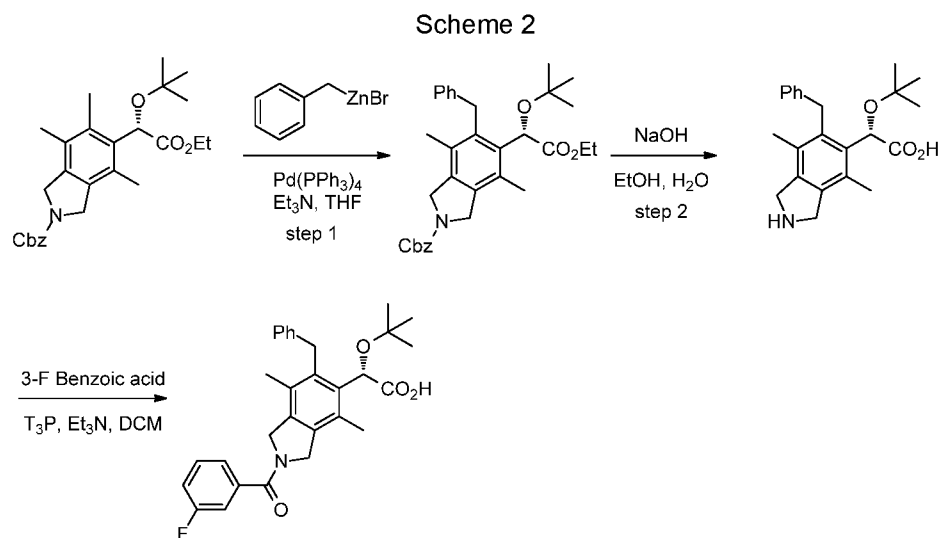
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**Example 2.** (S)-2-(tert-butoxy)-2-(6-ethynyl-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid

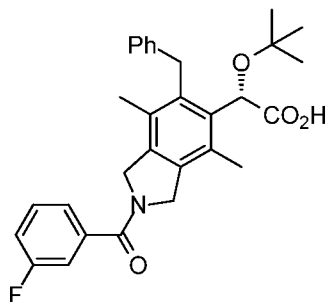


5 The title compound was made in a similar manner as Example 1 except using TMS-acetylene in Step 7. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.47 (br, 1H), 7.55 (m, 1H), 7.46 (m, 2H), 7.35 (m, 1H), 5.81 (d,  $J$  = 4.3 Hz, 1H), 4.76 (m, 5H), 2.21 (m, 6H), 1.15 (d,  $J$  = 7.0 Hz, 9H). LC/MS ( $m/z$ ) ES+ = 424.5 (M+1).

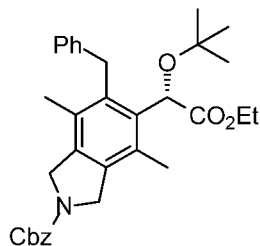
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**Example 3.** (S)-2-(6-benzyl-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)-2-(tert-butoxy)acetic acid

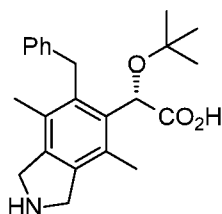


Step 1. (S)-benzyl 5-benzyl-6-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethylisoindoline-2-carboxylate



5 To an ice cold solution of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (135 mg, 0.24 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (56 mg, 0.0478 mmol) in THF (1 mL) was added benzylzinc(II) bromide (1M, 0.48 mL, 0.48 mmol) and the reaction mixture was heated to 65 °C. After 1 h, the reaction mixture was quenched with the addition of sat. NH<sub>4</sub>Cl aq. solution and extracted with EtOAc. The organic layer was washed  
10 with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in PE) to afford the title compound (122 mg, 97% yield) as a brown oil. LC/MS (m/z) ES+ = 530.7 (M+1).

15 Step 2: (S)-2-(6-benzyl-4,7-dimethylisoindolin-5-yl)-2-(tert-butoxy)acetic acid



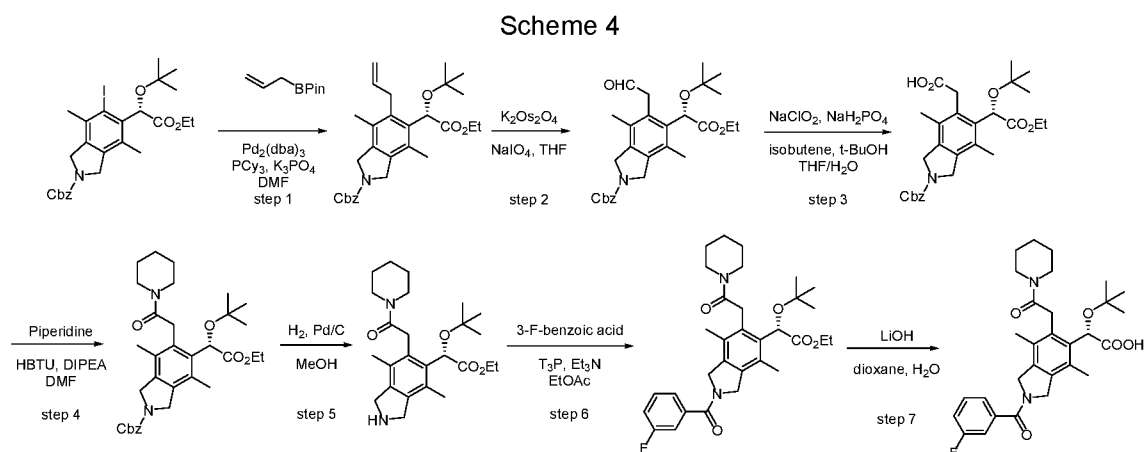
A mixture of benzyl (S)-5-benzyl-6-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethylisoindoline-2-carboxylate (115 mg, 0.16 mmol) and NaOH (193 mg, 4.8 mmol) in  
20 EtOH (2 mL) and H<sub>2</sub>O (1 mL) was stirred at 100°C under N<sub>2</sub> atmosphere. After 2 h, the reaction mixture was cooled to ambient temperature and the resulting mixture was acidified with 1N HCl and extracted with DCM/*i*-PrOH (85:15). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the title compound (80 mg, quant. yield) as a yellow oil which was used in the next step without  
25 further purification. LC/MS (m/z) ES+ = 368.5 (M+1).



*Step 3: (S)-2-(6-benzyl-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)-2-(tert-butoxy)acetic acid*

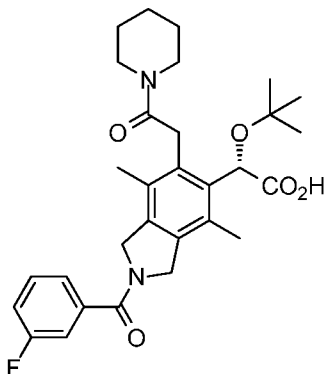
To a solution of (S)-2-(6-benzyl-4,7-dimethylisoindolin-5-yl)-2-(tert-butoxy)acetic acid  
 5 (80 mg, 0.218 mmol) and 3-fluorobenzoic acid (61 mg, 0.435 mmol) in DCM (4 mL) and EtOAc (2 mL) was added propane phosphonic acid anhydride (346 mg, 0.544 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (66 mg, 0.653 mmol). After 1 h, the reaction mixture was quenched with sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The  
 10 residue was purified by reverse phase HPLC (C18, 50-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (21 mg, 20% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.40 (br, 1H), 7.51 (m, 3H), 7.34 (m, 1H), 7.12 (m, 5H), 5.33 (s, 1H), 4.80 (dd, J = 33.3, 22.2 Hz, 4H), 4.20 (m, 2H), 2.31 (d, J = 66.6 Hz, 3H), 1.83 (d, J = 64.5 Hz, 3H), 0.92 (s, 9H). LC/MS (m/z) ES+ = 490.6 (M+1).

15

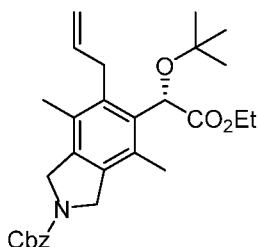


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**Example 4:** (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindolin-5-yl)acetic acid

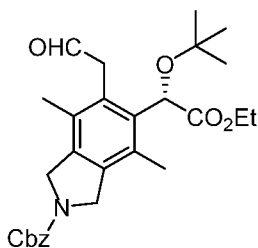


Step 1: (S)-benzyl 5-allyl-6-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethylisoindoline-2-carboxylate



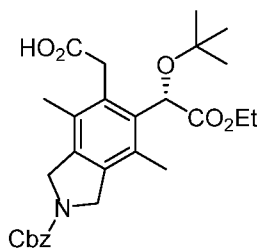
A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (1 g, 1.77 mmol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (386 mg, 2.3 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (324 mg, 0.35 mmol), PCy<sub>3</sub> (99 mg, 0.35 mmol) and K<sub>3</sub>PO<sub>4</sub> (1.1 g, 5.3 mmol) in DMF was stirred at 80°C. After 18 h, the reaction mixture was cooled to ambient temperature and partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product which was purified by ISCO (silica gel, 0-20% EtOAc in PE) to afford the title compound (680 mg, 80% yield) as a colorless oil. LC/MS (m/z) ES<sup>+</sup> = 480.6 (M+1).

Step 2: (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(2-oxoethyl)isoindoline-2-carboxylate



To a solution of benzyl (S)-5-allyl-6-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethylisoindoline-2-carboxylate (680 mg, 1.4 mmol) in THF (8 mL) and H<sub>2</sub>O (4 mL) was added NaIO<sub>4</sub> (1.2 g, 5.7 mmol) and K<sub>2</sub>Os<sub>2</sub>O<sub>4</sub> (80 mg, 0.21 mmol). After 18 h, the reaction mixture was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified on silica gel (silica gel, 0-30% EtOAc in PE) to afford the title compound (300 mg, 44% yield) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.72 (s, 1H), 7.47 – 7.30 (m, 5H), 5.44 (d, *J* = 5.9 Hz, 1H), 5.23 (s, 2H), 4.81 – 4.67 (m, 4H), 4.43 (dd, *J* = 18.0, 3.0 Hz, 1H), 4.22 – 4.13 (m, 1H), 4.07 – 3.97 (m, 1H), 3.87 (dd, *J* = 18.1, 4.1 Hz, 1H), 2.36 (d, *J* = 11.7 Hz, 3H), 2.04 (d, *J* = 12.5 Hz, 3H), 1.23 – 1.15 (m, 12H). LC/MS (m/z) ES<sup>+</sup> = 482.4 (M+1).

*Step 3: (S)-2-(2-((benzyloxy)carbonyl)-6-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethylisoindolin-5-yl)acetic acid*

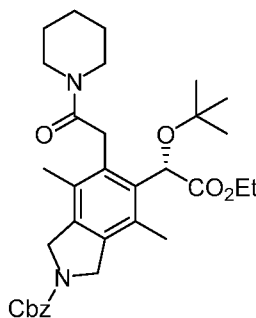


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A mixture of benzyl (S)-5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(2-oxoethyl)isoindoline-2-carboxylate (300 mg, 0.62 mmol), NaClO<sub>2</sub> (449 mg, 4.96 mmol), NaH<sub>2</sub>PO<sub>4</sub> (446 mg, 3.7 mmol) in isobutene (4 mL), THF (2 mL), *t*-BuOH (2 mL) and H<sub>2</sub>O (2 mL) was stirred at ambient temperature. After 2 h, the reaction mixture was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (silica gel, 0-10% MeOH in DCM) to afford the title compound (120 mg, 39% yield) as a colorless oil. LC/MS (m/z) ES<sup>+</sup> = 498.4 (M+1).

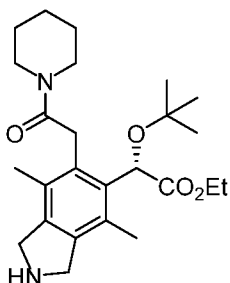
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Step 4: (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindoline-2-carboxylate



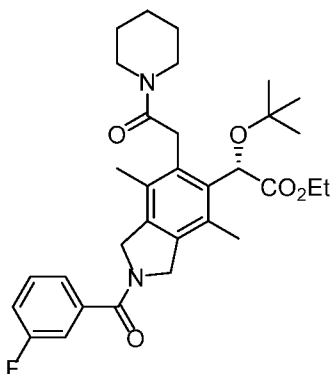
A mixture of (S)-2-(2-((benzyloxy)carbonyl)-6-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl isoindolin-5-yl)acetic acid (50 mg, 0.1 mmol), piperidine (10 mg, 0.12 mmol), HBTU (59 mg, 0.15 mmol) and DIPEA (0.5 mL) in DMF (2 mL) was stirred at ambient temperature. After 1 h, the resulting mixture was quenched with sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (silica gel, 0-30% EtOAc in PE) to afford the title compound (40 mg, 70% yield) as a yellow oil. LC/MS (m/z) ES+ = 565.7 (M+1).

Step 5: (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindolin-5-yl)acetic acid



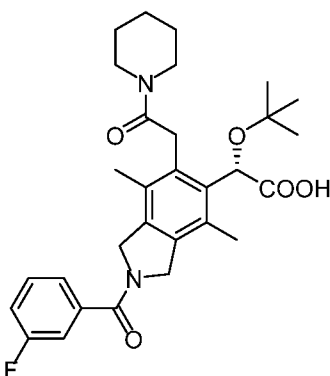
A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindoline-2-carboxylate (43 mg, 0.08 mmol) and 10% Pd/C (43 mg) in MeOH (4 mL) was hydrogenated under an atmosphere of H<sub>2</sub> (1 atm). After 1 h, the reaction mixture was filtered through a pad of Celite and the residue was concentrated under reduced pressure to give the crude title product (35 mg, quant. yield) as a brown oil which was used in the next step without further purification. LC/MS (m/z) ES+ = 431.4 (M+1).

Step 6: Ethyl (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindolin-5-yl)acetate



To a solution of (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindolin-5-yl)acetic acid (35 mg, 0.08 mmol, crude product from the previous step) and 3-fluorobenzoic acid (25 mg, 0.16 mmol) in EtOAc (3 mL) was added propane phosphonic acid anhydride (141 mg, 0.2 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (0.1, 0.49 mmol). After 1 h, the reaction mixture was quenched with sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with half saturated aq. citric acid and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in PE) to afford the title compound (22 mg, 50% yield) as a yellow oil. LC/MS (m/z) ES+ = 553.8 (M+1).

Step 7: (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindolin-5-yl)acetic acid



A mixture of ethyl (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(piperidin-1-yl)ethyl)isoindolin-5-yl)acetate (22 mg, 0.04 mmol) in LiOH (0.24 mL, 2.5 N) and dioxane (1.5 mL) was stirred at 80 °C. After 18 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc and washed with 1N HCl. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, 40-100% MeCN in H<sub>2</sub>O with 0.1% formic

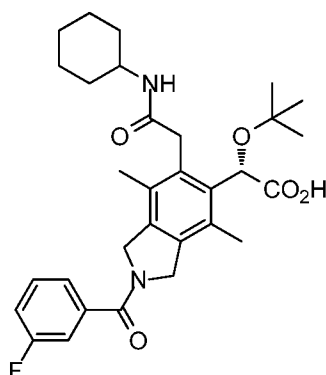
acid) to afford the title compound (9 mg, 44% yield) as a white powder.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.61 (br, 1H), 7.58 – 7.31 (m, 4H), 5.25 (d,  $J$  = 18.1 Hz, 1H), 4.78 (dd,  $J$  = 35.2, 11.6 Hz, 4H), 3.69 – 3.37 (m, 6H), 2.27 (d,  $J$  = 66.5 Hz, 3H), 1.92 (d,  $J$  = 64.8 Hz, 3H), 1.66 – 1.37 (m, 6H), 1.06 (d,  $J$  = 6.9 Hz, 9H). LC/MS ( $m/z$ ) ES+ = 525.6 (M+1).

5

Examples 5 - 7 were prepared in a manner similar to the procedures described for Example 4.

**Example 5.** (S)-2-(tert-butoxy)-2-(6-(2-(cyclohexylamino)-2-oxoethyl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid

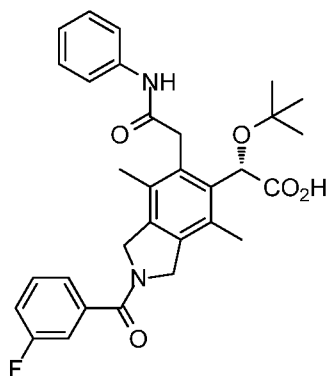
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$^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.29 (br, 1H), 7.54 (dd,  $J$  = 13.7, 8.0 Hz, 1H), 7.45 (m, 2H), 7.35 (t,  $J$  = 8.3 Hz, 1H), 7.20 (s, 1H), 6.65 (s, 1H), 5.30 (m, 2H), 4.76 (d,  $J$  = 34.8 Hz, 4H), 3.97 (m, 1H), 2.26 (d,  $J$  = 67.1 Hz, 3H), 2.00 (m, 5H), 1.49 (m, 7H), 1.10 (d,  $J$  = 8.6 Hz, 9H), 0.86 (m, 1H). LC/MS ( $m/z$ ) ES+ = 539.3 (M+1).

15

**Example 6.** (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-oxo-2-(phenylamino)ethyl)isoindolin-5-yl)acetic acid

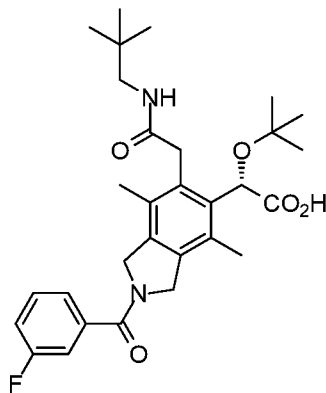


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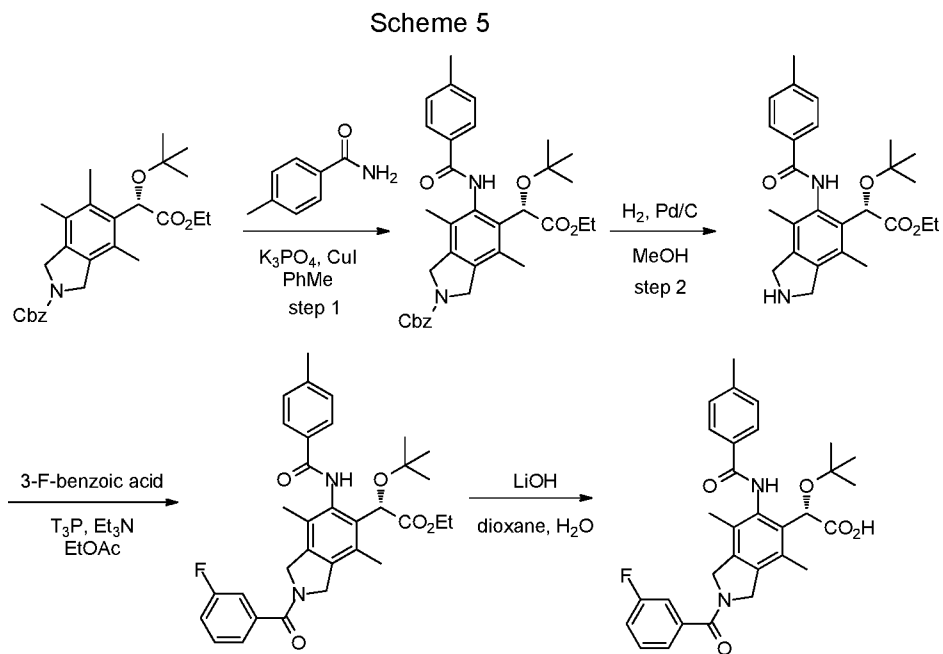
$^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.41 (br, 1H), 9.79 (br, 1H), 7.62 – 7.50 (m, 3H), 7.50 – 7.42 (m, 2H), 7.35 (t,  $J$  = 8.1 Hz, 1H), 7.26 (dd,  $J$  = 13.5, 7.5 Hz, 2H), 6.98 (dd,  $J$  = 12.5, 6.7 Hz, 1H), 5.37 (d,  $J$  = 16.7 Hz, 1H), 4.92 – 4.68 (m, 4H), 4.16 – 3.80 (m, 2H), 2.37 – 1.93 (m, 6H), 1.05 (d,  $J$  = 8.0 Hz, 9H). LC/MS (m/z) ES+ = 533.1 (M+1).

5

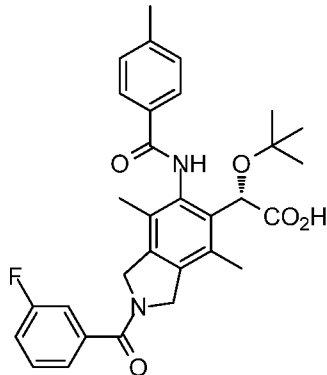
**Example 7.** (*S*)-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-(*neopentylamino*)-2-oxoethyl)isoindolin-5-yl)acetic acid



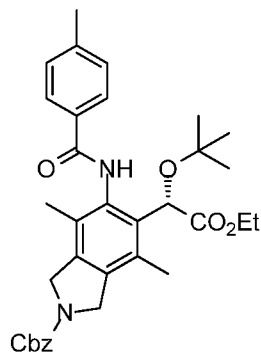
10  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.45 (br, 1H), 8.20 (br, 1H), 7.57 – 7.51 (m, 1H), 7.49 – 7.41 (m, 2H), 7.35 (t,  $J$  = 8.0 Hz, 1H), 5.36 (d,  $J$  = 13.8 Hz, 1H), 4.88 – 4.67 (m, 4H), 4.01 – 3.72 (m, 2H), 2.88 (d, 2H), 2.34 – 1.92 (m, 6H), 1.10 (d,  $J$  = 8.7 Hz, 9H), 0.82 (d,  $J$  = 9.2 Hz, 9H). LC/MS (m/z) ES+ = 527.2 (M+1).



5 **Example 8:** *(S)*-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylbenzamido)isoindolin-5-yl)acetic acid



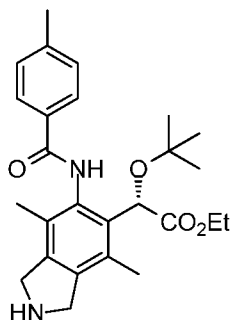
Step 1: *(S)*-benzyl 5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(4-methylbenzamido)isoindoline-2-carboxylate





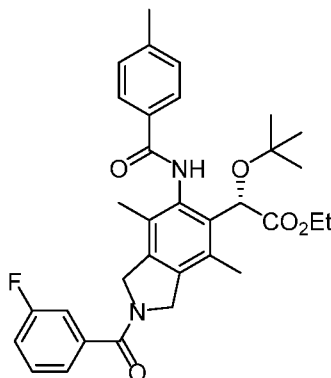
A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (300 mg, 0.53 mmol), 4-methylbenzamide (143 mg, 1.06 mmol), *N*<sup>1</sup>,*N*<sup>2</sup>-dimethylethane-1,2-diamine (18 mg, 0.21 mmol), CuI (20 mg, 0.11 mmol) and K<sub>3</sub>PO<sub>4</sub> (338 mg, 1.59 mmol) in toluene (6 mL) was stirred at 110 °C. After 24 h, the reaction mixture was cooled to ambient temperature and partitioned between EtOAc and H<sub>2</sub>O. The layers were separated and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in PE) to afford the title compound (80 mg, 48% yield) as a light yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.46 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.46 – 7.28 (m, 7H), 5.41 (d, *J* = 4.0 Hz, 1H), 5.24 (s, 2H), 4.82 – 4.67 (m, 4H), 4.02 – 3.91 (m, 2H), 2.42 (s, 3H), 2.34 (d, *J* = 11.6 Hz, 3H), 2.12 (d, *J* = 11.2 Hz, 3H), 1.27 – 1.18 (m, 12H). LC/MS (*m/z*) ES<sup>+</sup> = 573.7 (*M*+1).

Step 2: (S)-ethyl 2-(tert-butoxy)-2-(4,7-dimethyl-6-(4-methylbenzamido)isoindolin-5-yl)acetate



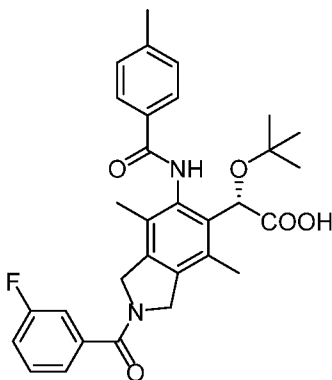
A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(4-methyl benzamido)isoindoline-2-carboxylate (80 mg, 0.14 mmol) and 10% Pd/C (80 mg) in MeOH (6 mL) was hydrogenated under a H<sub>2</sub> atmosphere (1 atm). After 1 h, the resulting mixture was filtered through a pad of Celite and the residue was concentrated under reduced pressure to give the crude title product (50 mg, 81% yield) as a brown oil which was used in the next step without further purification. LC/MS (*m/z*) ES<sup>+</sup> = 439.5 (*M*+1).

Step 3: Ethyl (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylbenzamido)isoindolin-5-yl)acetate



To a solution of ethyl (S)-2-(tert-butoxy)-2-(4,7-dimethyl-6-(4-methylbenzamido)isoindolin-5-yl)acetate (50 mg, 0.11 mmol, crude product from the previous step) and 3-fluorobenzoic acid (32 mg, 0.23 mmol) in EtOAc (3 mL) was added propane phosphonic acid anhydride (181 mg, 0.29 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (87 mg, 0.86 mmol). After 2 h, the reaction mixture was quenched with sat. aq. NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was washed with half saturated aq. citric acid and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-40% EtOAc in PE) to afford the title compound (35 mg, 55% yield) as a yellow oil. LC/MS (m/z) ES+ = 561.6 (M+1).

Step 4: (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylbenzamido)isoindolin-5-yl)acetic acid

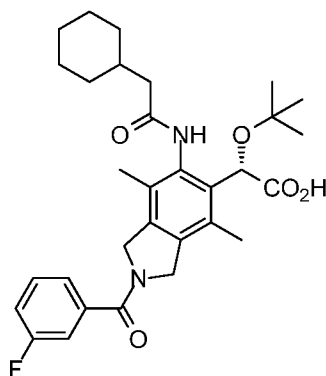


A mixture of ethyl (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylbenzamido)isoindolin-5-yl)acetate (35 mg, 0.06 mmol) and LiOH (23 mg, 0.94 mmol) in dioxane (2 mL) and H<sub>2</sub>O (0.5 mL) was stirred at 80 °C. After 18 h, the resulting mixture was diluted with EtOAc and acidified with 1N HCl. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was

purified by reverse phase HPLC (C18, 0-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (13 mg, 39% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.62 (br, 1H), 9.73 (br, 1H), 7.90 (t, *J* = 7.5 Hz, 2H), 7.53 (m, 3H), 7.34 (m, 3H), 5.35 (d, *J* = 11.7 Hz, 1H), 4.82 (dd, *J* = 31.7, 5.6 Hz, 4H), 2.33 (m, 6H), 1.97 (d, *J* = 62.2 Hz, 3H), 1.09 (d, *J* = 5.6 Hz, 9H). LC/MS (m/z) ES+ = 533.6 (M+1).

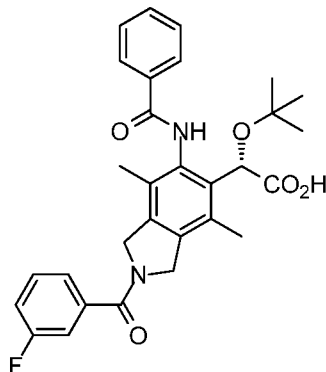
Examples 9-11 were prepared in a manner similar to the procedures described for Example 8.

10 **Example 9.** (*S*)-2-(*tert*-butoxy)-2-(6-(2-cyclohexylacetamido)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



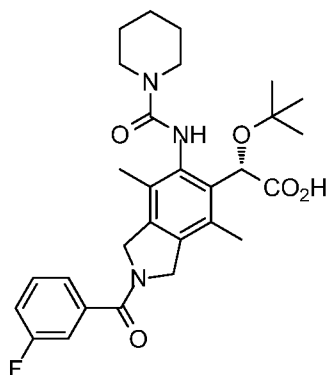
15 <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.32 (br, 1H), 9.12 (br, 1H), 7.54 (dd, *J* = 13.8, 7.4 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 8.1 Hz, 1H), 5.31 (s, 1H), 4.78 (d, *J* = 32.2 Hz, 4H), 2.23 (m, 5H), 1.94 (d, *J* = 63.4 Hz, 3H), 1.70 (m, 6H), 1.11 (m, 14H). LC/MS (m/z) ES+ = 539.8 (M+1).

**Example 10.** (S)-2-(6-benzamido-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)-2-(tert-butoxy)acetic acid



5  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.66 (br, 1H), 8.13 (m, 3H), 7.53 (m,  $J = 26.7, 13.8, 7.6$  Hz, 6H), 7.35 (t,  $J = 8.5$  Hz, 1H), 5.23 (s, 1H), 4.82 (m, 4H), 2.28 (d,  $J = 65.3$  Hz, 3H), 1.98 (d,  $J = 62.2$  Hz, 3H), 1.00 (s, 9H). LC/MS (m/z) ES+ = 519.6 (M+1).

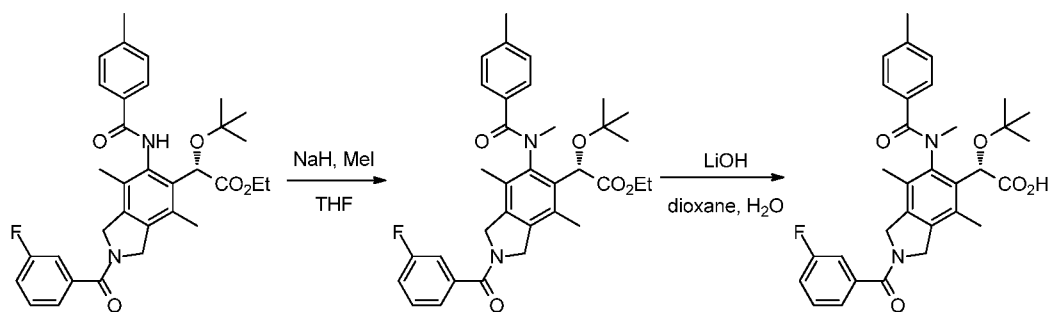
10 **Example 11.** (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(piperidine-1-carboxamido)isoindolin-5-yl)acetic acid



15  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  12.49 (br, 1H), 8.36 (br, 1H), 7.54 (m, 1H), 7.46 (d,  $J = 7.9$  Hz, 2H), 7.35 (dd,  $J = 9.7, 7.3$  Hz, 1H), 5.30 (m, 1H), 4.77 (m, 4H), 3.42 (m, 4H), 2.24 (d,  $J = 65.7$  Hz, 3H), 1.92 (d,  $J = 67.1$  Hz, 3H), 1.57 (m, 6H), 1.12 (d,  $J = 6.3$  Hz, 9H). LC/MS (m/z) ES+ = 526.6 (M+1).

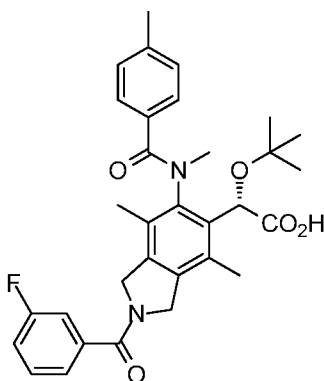
20

Scheme 6

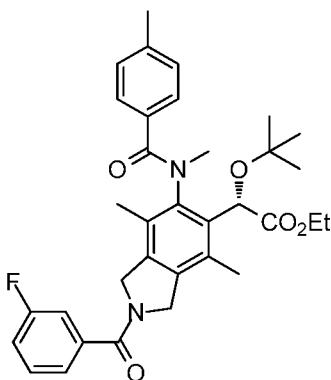


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**Example 12:** (S)-2-(tert-butoxy)-2-(6-(N,4-dimethylbenzamido)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



10 **Step 1:** (S)-ethyl 2-(tert-butoxy)-2-(6-(N,4-dimethylbenzamido)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetate

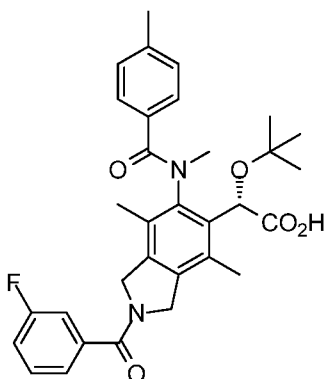


An ice cold solution of ethyl (S)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methyl benzamido)isoindolin-5-yl)acetate (50 mg, 0.09 mmol) in THF (2 mL) was treated with NaH (60%, 18 mg, 0.45 mmol). After 30 min, MeI (126 mg, 0.89 mmol) was added and

15

the reaction mixture was warmed to ambient temperature. After 1 h, the reaction mixture was quenched with sat. aq. NH<sub>4</sub>Cl and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in PE) to afford the title compound (30 mg, 59% yield) as a yellow oil. LC/MS (m/z) ES+ = 575.8 (M+1).

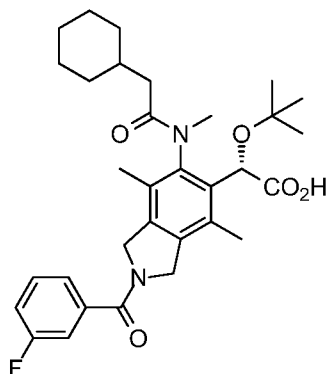
Step 2: *(S)*-2-(*tert*-butoxy)-2-(6-(*N*,4-dimethylbenzamido)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



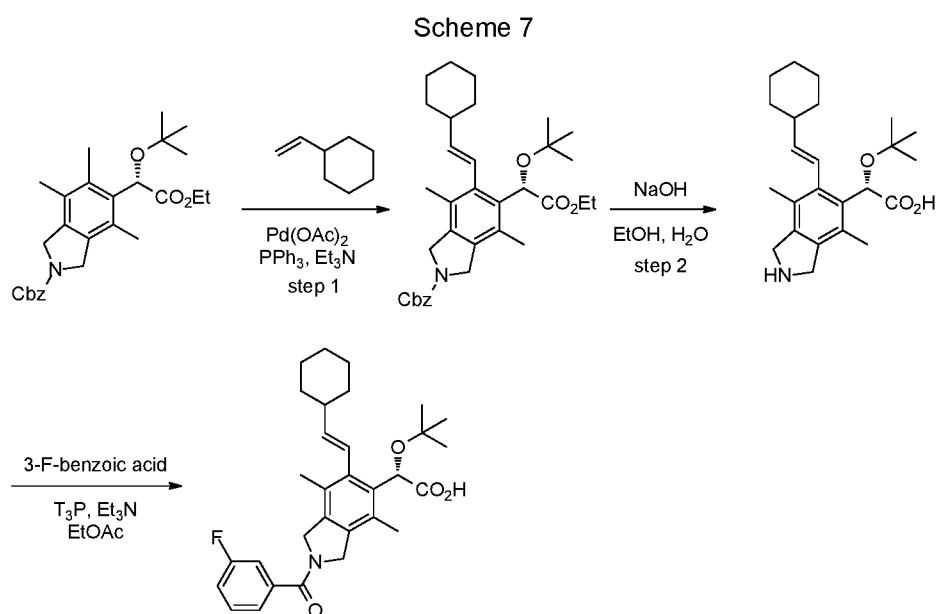
A mixture of ethyl *(S)*-2-(*tert*-butoxy)-2-(6-(*N*,4-dimethylbenzamido)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetate (60 mg, 0.10 mmol) and LiOH (38 mg, 1.57 mmol) in dioxane (3 mL) and H<sub>2</sub>O (0.7 mL) was stirred at 80 °C. After 18 h, the reaction mixture was diluted with EtOAc and acidified with 1N HCl. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, 0-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (24 mg, 41% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47 (m, 3H), 7.34 (m, 1H), 7.29 (m, 3H), 7.19 (m, 1H), 5.62 (s, 1H), 5.00 (d, *J* = 11.1 Hz, 2H), 4.73 (m, 2H), 3.36 (m, 3H), 2.26 (m, 9H), 1.25 (d, *J* = 7.2 Hz, 9H). LC/MS (m/z) ES+ = 547.6 (M+1).

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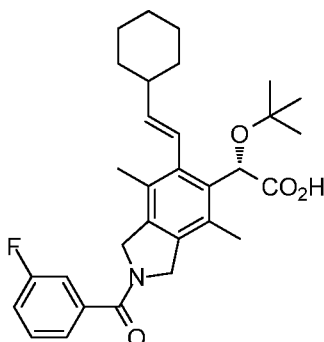
**Example 13.** (S)-2-(tert-butoxy)-2-(6-(2-cyclohexyl-N-methylacetamido)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



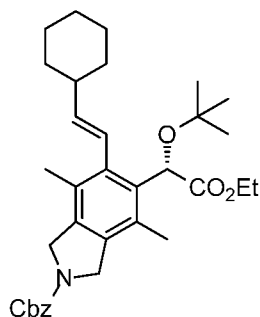
The title compound was made in a similar manner as Example 12. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.07 (br. 1H), 7.54 (m, 1H), 7.46 (d, *J* = 6.9 Hz, 2H), 7.35 (t, *J* = 8.6 Hz, 1H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.80 (m, 4H), 2.97 (d, *J* = 11.6 Hz, 3H), 2.31 (m, 5H), 1.94 (d, *J* = 63.7 Hz, 3H), 1.60 (m, 5H), 1.17 (m, 12H), 0.84 (m, 3H). LC/MS (*m/z*) ES+ = 553.7 (M+1).



**Example 14:** (S,E)-2-(tert-butoxy)-2-(6-(2-cyclohexylvinyl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



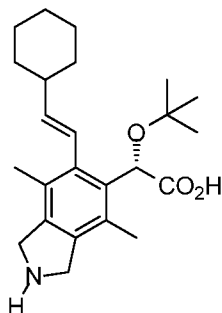
Step 1: (S,E)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-(2-cyclohexylvinyl)-4,7-dimethylisoindoline-2-carboxylate



A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (300 mg, 0.53 mmol), vinylcyclohexane (292 mg, 2.7 mmol), Pd(OAc)<sub>2</sub> (24 mg, 0.11 mmol) and PPh<sub>3</sub> (56 mg, 0.21 mmol) in Et<sub>3</sub>N (3 mL) was stirred at 100°C. After 18 h, the reaction mixture was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, 65-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (12 mg, 4% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.43 – 7.33 (m, 5H), 6.40 (d, J = 16.2 Hz, 1H), 5.72 – 5.63 (m, 1H), 5.59 (s, 1H), 5.22 (s, 2H), 4.69 (d, J = 16.7 Hz, 4H), 4.24 – 4.06 (m, 2H), 2.27 – 2.09 (m, 7H), 1.91 – 1.76 (m, 4H), 1.25 – 1.10 (m, 18H). LC/MS (m/z) ES+ = 548.8 (M+1).



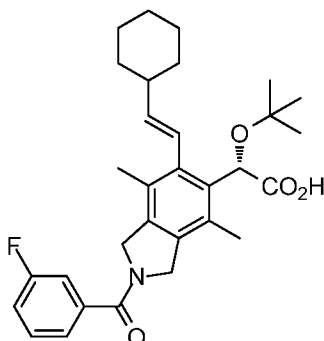
Step 2: *(S,E)*-2-(*tert*-butoxy)-2-(6-(2-cyclohexylvinyl)-4,7-dimethylisoindolin-5-yl)acetic acid



A mixture of *(S,E)*-benzyl 5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-6-(2-cyclohexylvinyl)-4,7-dimethylisoindoline-2-carboxylate (12 mg, 0.02 mmol) in NaOH (0.15 mL, 5 N) and EtOH (0.3 mL) was stirred at 100 °C. After 18 h, the reaction mixture was cooled to ambient temperature and was neutralized with 1N HCl and extracted with DCM/*i*-PrOH (85:15). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give title compound (10 mg, quant. yield) which was used in the next step without further purification. LC/MS (*m/z*) ES<sup>+</sup> = 386.4 (M+1).

10

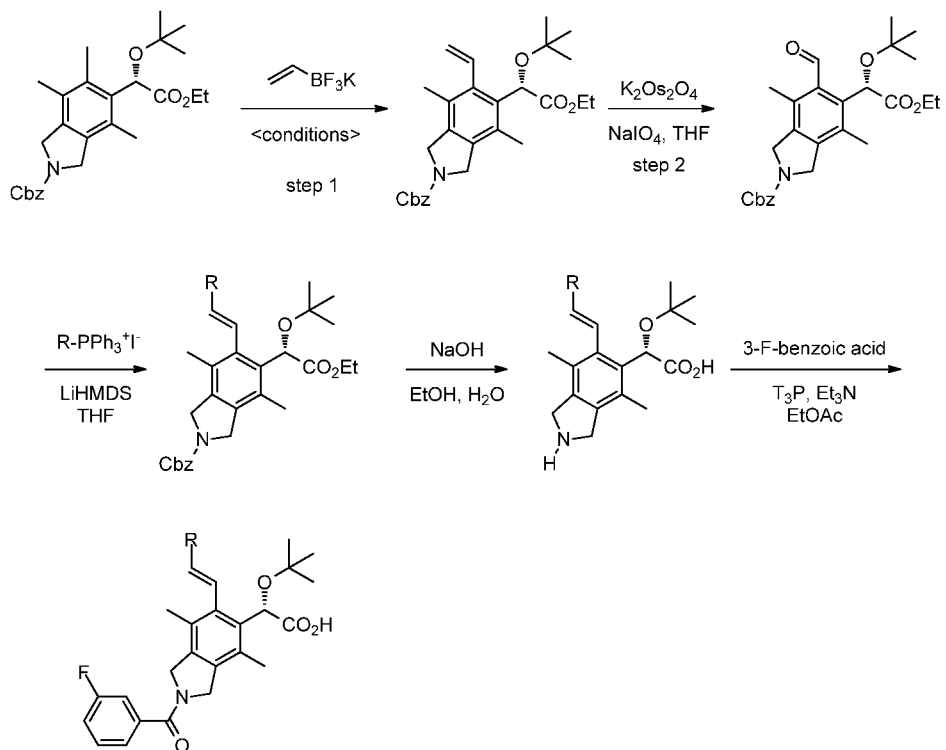
Step 3: *(S,E)*-2-(*tert*-butoxy)-2-(6-(2-cyclohexylvinyl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



To a solution of *(S,E)*-2-(*tert*-butoxy)-2-(6-(2-cyclohexylvinyl)-4,7-dimethylisoindolin-5-yl)acetic acid (10 mg, 0.026 mmol) and 3-fluorobenzoic acid (7.3 mg, 0.05 mmol) in EtOAc (0.5 mL) and DCM (1 mL) was added propane phosphonic acid anhydride (41 mg, 0.065 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (16 mg, 0.16 mmol). After 1 h, the reaction mixture was quenched with sat. aq. NaHCO<sub>3</sub> and extracted with DCM. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, 60-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (5.5 mg, 42% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.32 (br, 1H), 7.54 (m, 1H), 7.45 (m, 2H), 7.34 (t, *J* = 8.7 Hz, 1H), 6.43 (m, 1H), 5.66 (m, 1H), 5.47 (d, *J* = 5.2 Hz, 1H), 4.77 (m, 4H), 2.10 (m, 6H), 1.72 (m, 5H), 1.19 (m, 15H). LC/MS (*m/z*) ES<sup>+</sup> = 508.6 (M+1).

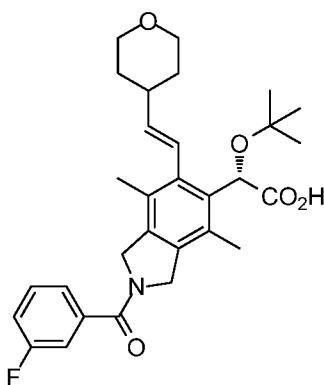
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Scheme 8

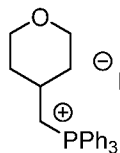


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**Example 15:** (S,E)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-(tetrahydro-2H-pyran-4-yl)vinyloxy)isoindolin-5-yl)acetic acid

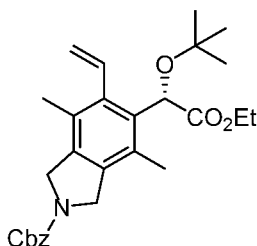


10 Triphenyl((tetrahydro-2H-pyran-4-yl)methyl)phosphonium



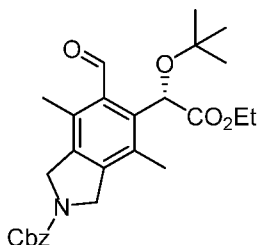
The title compound was prepared from the known procedure as described in *J. Med. Chem.* **2008**, *51*, 4340 - 4345 and references therein.

- 5 *Step 1: (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-vinylisoindoline-2-carboxylate*



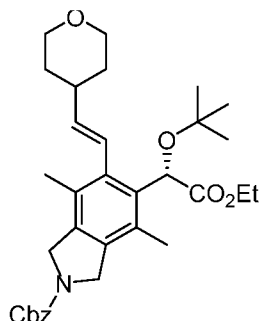
- A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (10 g, 17.7 mmol), vinylBF<sub>3</sub>K (3.8 g, 28.3 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3.2 g, 3.54 mmol), MePhos (1.3 g, 3.54 mmol) and K<sub>3</sub>PO<sub>4</sub> (11 g, 53.1 mmol) in DMF (110 mL) was stirred at 80 °C. After 18 h, the reaction mixture was filtered through a pad of Celite and the filtrate was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in PE) to afford the title compound (6.1 g, 67% yield) as a yellow solid. LC/MS (m/z) ES<sup>+</sup> = 466.4 (M+1).
- 10  
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*Step 2: (S)-benzyl 5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-6-formyl-4,7-dimethylisoindoline-2-carboxylate*



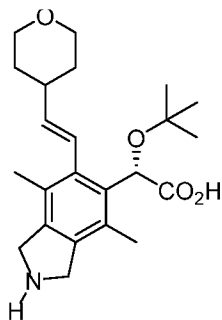
- A mixture of benzyl (S)-5-(1-(tert-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-vinylisoindoline-2-carboxylate (300 mg, 0.64 mmol), NaIO<sub>4</sub> (413 mg, 1.93 mmol) and K<sub>2</sub>Os<sub>2</sub>O<sub>4</sub> (24 mg, 0.064 mmol) in THF (4 mL) and H<sub>2</sub>O (2 mL) was stirred at ambient temperature. After 18 h, the reaction mixture was quenched with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-40% EtOAc in PE) to afford the title compound (170 mg, 56% yield) as a yellow oil. LC/MS (m/z) ES<sup>+</sup> = 490.6 (M+Na).
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Step 3: (*S,E*)-benzyl 5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(2-(tetrahydro-2H-pyran-4-yl)vinyl)isoindoline-2-carboxylate



5 A -78°C suspension of triphenyl((tetrahydro-2H-pyran-4-yl)methyl)phosphonium iodide (409 mg, 0.84 mmol) in THF (2 mL) was treated with LiHMDS (0.8 mL, 0.8 mmol, 1.0 M). After 30 min, a solution of benzyl (*S*)-5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-6-formyl-4,7-dimethylisoindoline-2-carboxylate (98 mg, 0.21 mmol) in THF was added dropwise. The reaction mixture was warmed to ambient temperature and was quenched with sat. aq. NH<sub>4</sub>Cl  
10 solution and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in PE) to afford the title compound (50 mg, 43% yield) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42 – 7.34 (m, 5H), 6.48 (d, *J* = 16.3 Hz, 1H), 5.72 – 5.65 (m, 1H), 5.54 (s, 1H), 5.22 (s, 2H), 4.73 – 4.65 (m, 4H), 4.22 – 4.09 (m, 2H),  
15 4.07 – 4.00 (m, 2H), 3.50 (td, *J* = 11.8, 1.2 Hz, 2H), 2.53 – 2.45 (m, 1H), 2.27 (d, *J* = 10.9 Hz, 3H), 2.11 (d, *J* = 12.3 Hz, 3H), 1.77 – 1.64 (m, 4H), 1.20 – 1.11 (m, 12H). LC/MS (*m/z*) ES+ = 550.7 (*M*+1).

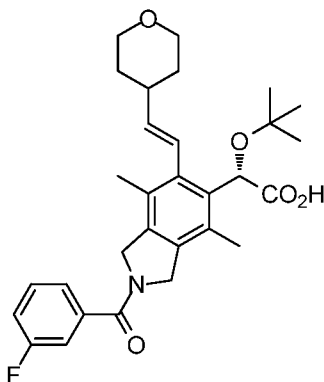
Step 4: (*S,E*)-2-(*tert*-butoxy)-2-(4,7-dimethyl-6-(2-(tetrahydro-2H-pyran-4-yl)vinyl)isoindolin-  
20 5-yl)acetic acid



A mixture of (*S,E*)-benzyl 5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-6-(2-cyclohexylvinyl)-4,7-dimethylisoindoline-2-carboxylate (50 mg, 0.09 mmol) and NaOH (108 mg, 2.7 mmol) in EtOH (1.1 mL) and H<sub>2</sub>O (0.55 mL) was stirred at 100°C under N<sub>2</sub>

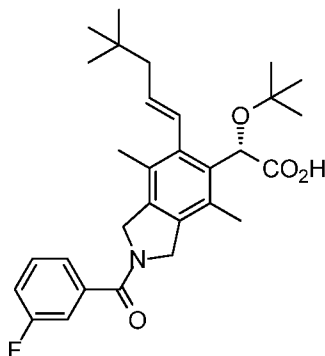
atmosphere overnight. After cooled down to r.t., the resulting mixture was neutralized with 1N HCl and extracted with DCM/*i*-PrOH (85:15). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give title compound (31 mg, 89% yield) which was used in the next step without further purification. LC/MS (m/z)  
 5 ES+ = 388.3 (M+1).

*Step 5: (S,E)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-(tetrahydro-2H-pyran-4-yl)vinyl)isoindolin-5-yl)acetic acid*



10 A solution of *(S,E)-2-(tert-butoxy)-2-(4,7-dimethyl-6-(2-(tetrahydro-2H-pyran-4-yl)vinyl)iso indolin-5-yl)acetic acid* (31 mg, 0.08 mmol) and 3-fluorobenzoic acid (22 mg, 0.16 mmol) in EtOAc (2 mL) and DCM (2 mL) was added propane phosphonic acid anhydride (127 mg, 0.2 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (29 mg, 0.48 mmol). After 1 h, the resulting mixture was quenched with sat. NaHCO<sub>3</sub> aq. solution and extracted with DCM. The  
 15 organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, 50-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (10 mg, 24% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.55 (br, 1H), 7.59 – 7.50 (m, 1H), 7.49 – 7.40 (m, 2H), 7.34 (t, *J* = 8.8 Hz, 1H), 6.49 (dd, *J* = 15.9, 13.0 Hz, 1H), 5.76 – 5.62 (m, 1H), 5.42 (d, *J*  
 20 = 5.6 Hz, 1H), 4.90 – 4.57 (m, 4H), 3.89 (dd, *J* = 9.3, 4.7 Hz, 2H), 3.45 – 3.36 (m, 3H), 2.30 – 1.94 (m, 6H), 1.78 – 1.61 (m, 2H), 1.50 – 1.35 (m, 2H), 1.05 (d, *J* = 7.7 Hz, 9H). LC/MS (m/z) ES+ = 510.2 (M+1).

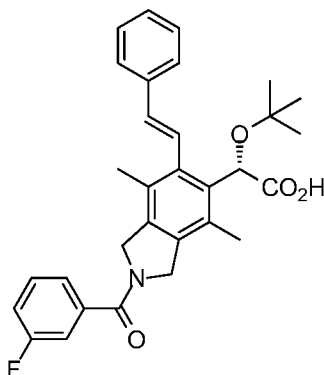
**Example 16.** *(S,E)-2-(tert-butoxy)-2-(6-(4,4-dimethylpent-1-en-1-yl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid*



The title compound was made in a similar manner as Example 15 except using (3,3-Dimethylbutyl)triphenylphosphonium (WO200463179A1) in Step 3. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.79 (br, 1H), 7.49 – 7.41 (m, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.22 – 7.15 (m, 1H), 6.50 – 6.41 (m, 1H), 5.96 – 5.83 (m, 1H), 5.75 (s, 1H), 5.03 – 4.88 (m, 2H), 4.74 – 4.64 (m, 2H), 2.29 – 2.03 (m, 8H), 1.14 (d, *J* = 7.6 Hz, 9H), 0.96 (d, *J* = 7.6 Hz, 9H). LC/MS (*m/z*) ES+ = 496.2 (M+1).

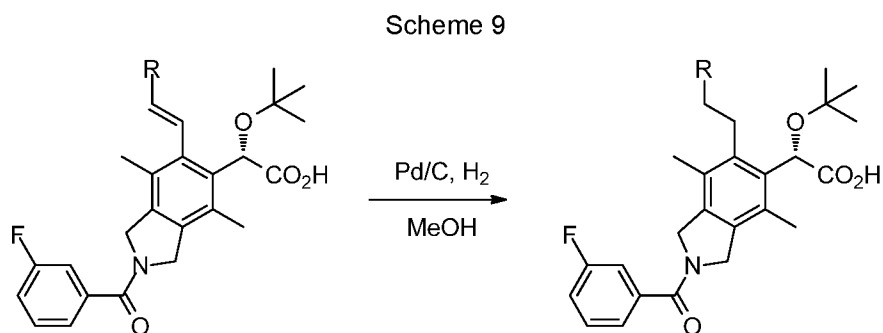
10

**Example 17.** *(S,E)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-styrylisoindolin-5-yl)acetic acid*

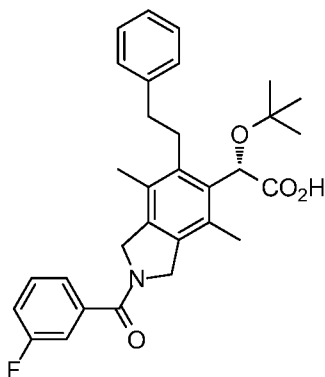


The title compound was made in a similar manner as Example 15 except using Benzyltriphenylphosphonium bromide in Step 3. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.41 (s, 1H), 7.42 (m, 10H), 6.62 (m, 1H), 5.48 (d, *J* = 6.7 Hz, 1H), 4.82 (m, 4H), 2.18 (m, 6H), 1.05 (t, *J* = 8.9 Hz, 9H). LC/MS (*m/z*) ES+ = 502.5 (M+1).

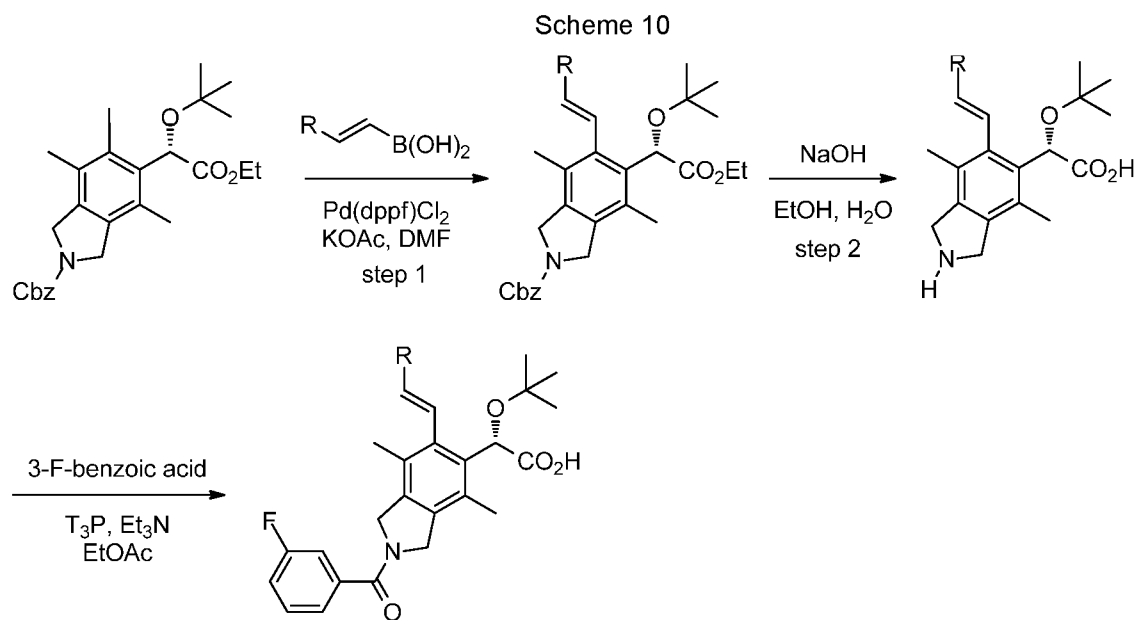
15



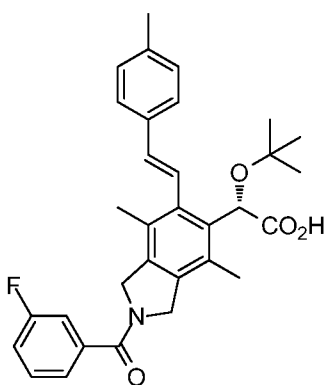
- 5 **Example 18.** *(S)*-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-phenethylisoindolin-5-yl)acetic acid



A mixture of *(S,E)*-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-  
 10 styrylisoindolin-5-yl)acetic acid (20 mg, 0.04 mmol) and 10% Pd/C (20 mg) in MeOH (1 mL)  
 was hydrogenated under H<sub>2</sub> atmosphere (1 atm). After 1 h, the resulting mixture was filtered  
 through a pad of Celite and the residue was concentrated under reduced pressure. The  
 residue was purified by reverse phase HPLC to afford the title compound (12 mg, 60%  
 15 yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.51 (br, 1H), 7.55 (m, 1H), 7.46 (d,  
*J* = 7.7 Hz, 2H), 7.35 (m, 5H), 7.21 (m, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 4.79 (m, 4H), 2.98 (m,  
 4H), 2.24 (m, 6H), 1.19 (d, *J* = 8.3 Hz, 9H). LC/MS (*m/z*) ES<sup>+</sup> = 504.5 (*M*+1).

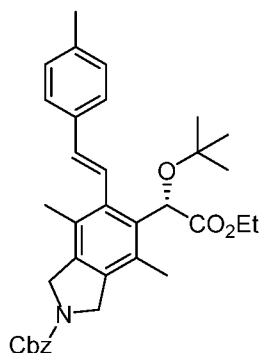


5 **Example 19:** (S,E)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylstyryl)isoindolin-5-yl)acetic acid



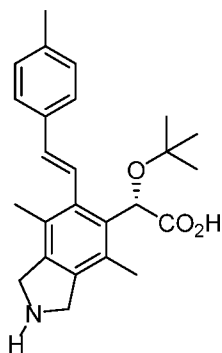


Step 1: *(S,E)*-benzyl 5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(4-methylstyryl)isoindoline-2-carboxylate



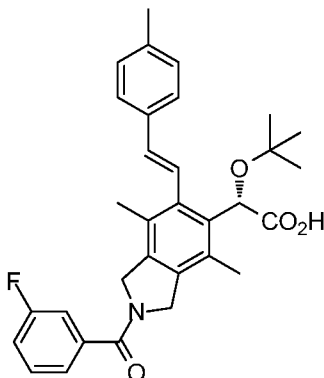
A mixture of benzyl *(S)*-5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-6-iodo-4,7-dimethylisoindoline-2-carboxylate (150 mg, 0.27 mmol), *(E)*-(4-methylstyryl)boronic acid (87 mg, 0.53 mmol) Pd(dppf)Cl<sub>2</sub> (22 mg, 0.127 mmol), KOAc (80 mg, 0.81 mmol) in DMF (1.5 mL) was stirred at 80 °C. After 18 h, the reaction mixture was cooled to ambient temperature and the resulting mixture was partitioned between EtOAc and H<sub>2</sub>O. The layers were separated and the organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (silica gel, 0-20% EtOAc in PE) to afford the title compound (120 mg, 82% yield) as a yellow solid. LC/MS (*m/z*) ES<sup>+</sup> = 556.4 (*M*+1).

Step 2: *(S,E)*-2-(*tert*-butoxy)-2-(4,7-dimethyl-6-(4-methylstyryl)isoindolin-5-yl)acetic acid



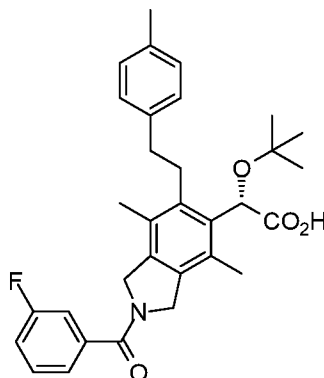
A mixture of benzyl *(S,E)*-5-(1-(*tert*-butoxy)-2-ethoxy-2-oxoethyl)-4,7-dimethyl-6-(4-methylstyryl) isoindoline-2-carboxylate (160 mg, 0.29 mmol) and NaOH (346 mg, 8.64 mmol) in EtOH (3 mL) and H<sub>2</sub>O (1.5 mL) was stirred at 100°C. After 18 h, the reaction mixture was cooled to ambient temperature and acidified with 6 N HCl and extracted with DCM/*i*-PrOH (85:15). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give the title compound (110 mg, quant. yield) as a brown oil which was used in the next step without further purification. LC/MS (*m/z*) ES<sup>+</sup> = 394.4 (*M*+1).

Step 3. *(S,E)*-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylstyryl)isoindolin-5-yl)acetic acid



5 A solution of *(S,E)*-2-(*tert*-butoxy)-2-(4,7-dimethyl-6-(4-methylstyryl)isoindolin-5-yl)acetic acid (115 mg, 0.29 mmol) and 3-fluorobenzoic acid (82 mg, 0.58 mmol) in DCM (3 mL) was treated with propane phosphonic acid anhydride (464 mg, 0.73 mmol, 50% EtOAc solution) and Et<sub>3</sub>N (118 mg, 1.17 mmol). After 30 min, the resulting mixture was quenched with sat. aq. NaHCO<sub>3</sub> and extracted with DCM. The organic layer was washed with half sat.  
10 aq. citric acid and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (C18, 50-100% MeCN in H<sub>2</sub>O with 0.1% formic acid) to afford the title compound (70 mg, 47% yield) as a white powder. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.46 (br, 1H), 7.55 (dd, *J* = 13.9, 7.6 Hz, 1H), 7.46 (m, 4H), 7.32 (m, 2H), 7.21 (m, 2H), 6.57 (m, 1H), 5.49 (d, *J* = 6.4 Hz, 1H), 4.79 (m, 4H), 2.22 (m, 9H),  
15 1.03 (d, *J* = 7.5 Hz, 9H). LC/MS (*m/z*) ES<sup>+</sup> = 516.6 (M+1).

**Example 20.** *(S)*-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(4-methylphenethyl)isoindolin-5-yl)acetic acid

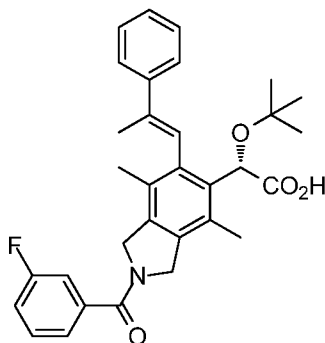


20

The title compound was made in a similar manner as Example 18. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.44 (br, 1H), 7.55 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 2H), 5.41 (d, *J* = 17.3 Hz, 1H), 4.79 (d, *J* = 36.1 Hz, 4H), 2.86 (m, 4H), 2.26 (m, 9H), 1.20 (d, *J* = 12.4 Hz, 9H). LC/MS (*m/z*) ES+ = 518.5 (M+1).

5

**Example 21.** (*S,E*)-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(2-phenylprop-1-en-1-yl)isoindolin-5-yl)acetic acid

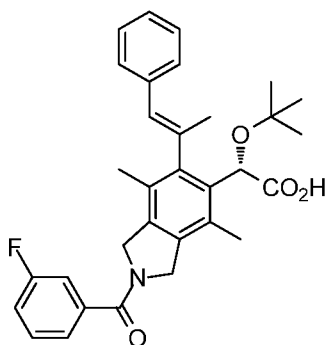


10

The title compound was made in a similar manner as Example 14 except using prop-1-en-2-ylbenzene in Step 1. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.33 (br, 1H), 7.46 (m, 9H), 6.86 (m, 1H), 5.37 (m, 1H), 4.79 (m, 4H), 2.08 (m, 9H), 1.09 (m, 9H). LC/MS (*m/z*) ES+ = 516.6 (M+1).

15

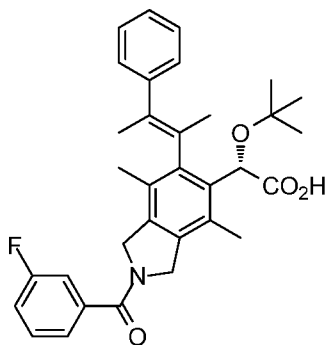
**Example 22.** (*S,E*)-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(1-phenylprop-1-en-2-yl)isoindolin-5-yl)acetic acid



20 The title compound was made in a similar manner as Example 19 except using (*Z*)-4,4,5,5-tetramethyl-2-(1-phenylprop-1-en-2-yl)-1,3,2-dioxaborolane (*J. Org. Chem.* **2013**, *78*, 12837) in Step 1. <sup>1</sup>H NMR (400 MHz, DMSO) δ 12.37 (br, 1H), 7.41 (m, 9H), 6.24 (d, *J* = 11.8 Hz,

1H), 5.30 (d,  $J = 4.9$  Hz, 1H), 4.79 (m, 4H), 2.15 (m, 9H), 1.12 (d,  $J = 8.7$  Hz, 9H). LC/MS (m/z) ES+ = 516.6 (M+1).

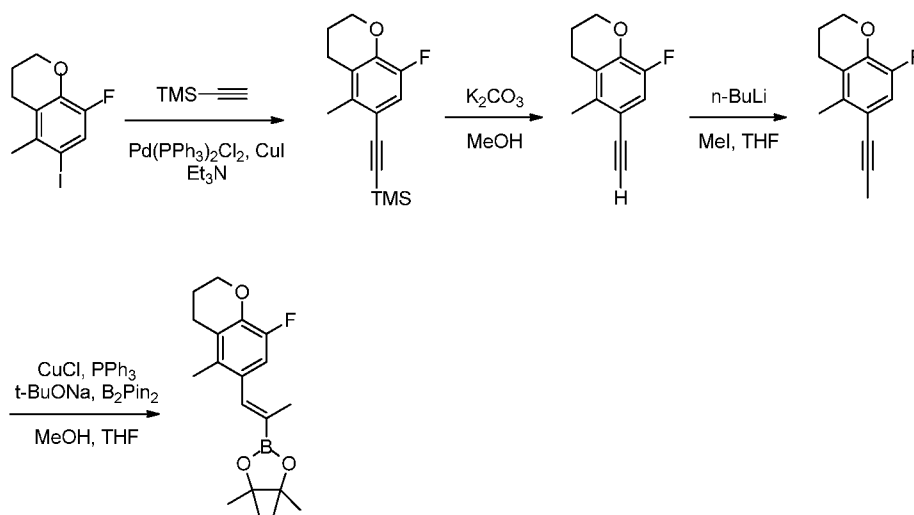
5 **Example 23.** (*S,E*)-2-(*tert*-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-(3-phenylbut-2-en-2-yl)isoindolin-5-yl)acetic acid



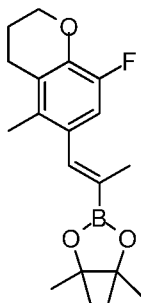
The title compound was made in a similar manner as Example 19 except using (*Z*)-4,4,5,5-tetramethyl-2-(3-phenylbut-2-en-2-yl)-1,3,2-dioxaborolane (*J. Am. Chem. Soc.* **2012**, 134, 15168) in Step 1. <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  12.38 (br, 1H), 7.41 (m, 9H), 5.33 (dd,  $J = 18.8, 4.2$  Hz, 1H), 4.79 (m, 4H), 2.20 (m, 6H), 1.67 (m, 6H), 1.21 (m, 9H). LC/MS (m/z) ES+ = 530.6 (M+1).

15

Scheme 11

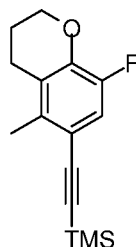


(Z)-2-(1-(8-fluoro-5-methylchroman-6-yl)prop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



5

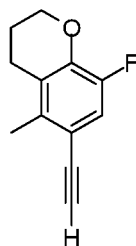
Step 1. ((8-fluoro-5-methylchroman-6-yl)ethynyl)trimethylsilane



A mixture of 8-fluoro-6-iodo-5-methylchromane (2.5 g, 8.59 mmol), ethynyltrimethylsilane (4.2 g, 43 mmol), Pd(dppf)Cl<sub>2</sub> (600 mg, 0.859 mmol) and Cul (326 mg, 1.72 mmol) in Et<sub>3</sub>N (20 mL) was stirred at ambient temperature. After 18 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography ISCO (0-5% EtOAc in PE) to afford the title compound (2.0 g, 90% yield) as a yellow solid. LC/MS (m/z) ES+ = 263.1 (M+1).

15

Step 2. 6-ethynyl-8-fluoro-5-methylchroman

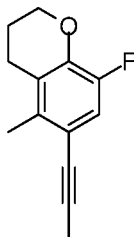


A solution of ((8-fluoro-5-methylchroman-6-yl)ethynyl)trimethylsilane (2.0 g, 8 mmol) in MeOH (20 mL) was treated with K<sub>2</sub>CO<sub>3</sub> (2.2 g, 16 mmol). After 3 h, the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-10% EtOAc in PE) to afford the title compound (1.2 g, 75% yield) as a

white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.05 (d,  $J = 11.2$  Hz, 1H), 4.26 – 4.13 (m, 2H), 3.18 (s, 1H), 2.66 (t,  $J = 6.6$  Hz, 2H), 2.30 (d,  $J = 0.6$  Hz, 3H), 2.17 – 2.02 (m, 2H). LC/MS (m/z)  $\text{ES}^+ = 191.4$  (M+1).

5

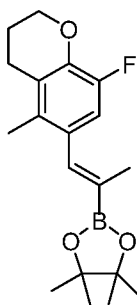
Step 3. 8-fluoro-5-methyl-6-(prop-1-yn-1-yl)chroman



A  $-30$  °C solution of 6-ethynyl-8-fluoro-5-methylchromane (600 mg, 3.15 mmol) in THF (8 mL) was treated with *n*-BuLi (2.5 M, 1.86 mL, 4.7 mmol). After 30 min, iodomethane was added and the reaction mixture was warmed to ambient temperature. After 2 h, the reaction mixture was quenched with sat. aq.  $\text{NH}_4\text{Cl}$  solution and extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAc in PE) to afford the title compound (560 mg, 87% yield) as a white solid. LC/MS (m/z)  $\text{ES}^+ = 205.3$  (M+1).

15

Step 4. (Z)-2-(1-(8-fluoro-5-methylchroman-6-yl)prop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



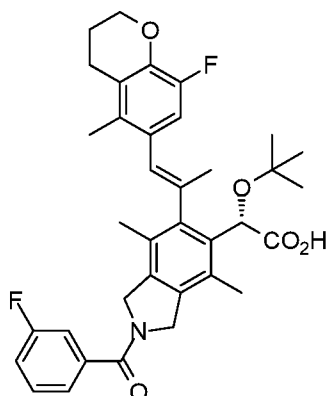
20

A mixture of  $\text{CuCl}$  (20 mg, 0.196 mmol),  $\text{PPh}_3$  (51.5 mg, 0.196 mmol) and *t*-BuONa (226 mg, 2.35 mmol) in THF was stirred at ambient temperature. After 30 min, a solution of 8-fluoro-5-methyl-6-(prop-1-yn-1-yl)chromane (400 mg, 1.96 mmol) was added, followed by the addition of MeOH (157 mg, 3.92 mmol). After 18 h, the resulting mixture was partitioned between EtOAc and  $\text{H}_2\text{O}$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by silica gel

25

chromatography (silica gel, 0-5% EtOAc in PE) to afford the title compound (200 mg, 31% yield) as a white solid. LC/MS (m/z) ES+ = 333.4 (M+1).

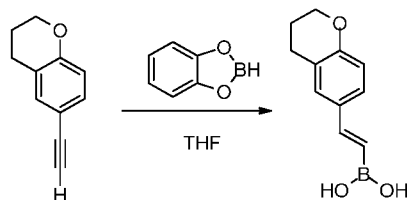
5           **Example 24.** *(S,E)-2-(tert-butoxy)-2-(6-(1-(8-fluoro-5-methylchroman-6-yl)prop-1-en-2-yl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid*



The title compound was made in a similar manner as Example 19 except using *(Z)-2-(1-(8-fluoro-5-methylchroman-6-yl)prop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane*  
 10 in Step 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.80 (br, 1H), 7.46 (dd, *J* = 13.6, 7.8 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 20.1, 8.3 Hz, 1H), 6.29 (s, 1H), 5.52 (s, 1H), 5.10 – 4.87 (m, 2H), 4.71 (d, *J* = 7.0 Hz, 2H), 4.22 (dd, *J* = 9.7, 4.6 Hz, 2H), 2.69 (dd, *J* = 11.3, 5.6 Hz, 2H), 2.38 – 2.03 (m, 14H), 1.40 – 1.11 (m, 9H). LC/MS (m/z) ES+ = 604.7 (M+1).

15

Scheme 12

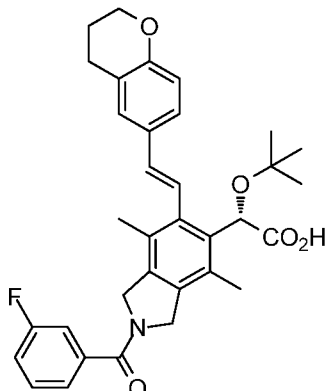


*(E)-2-(chroman-6-yl)vinylboronic acid*

20           A solution of 6-ethynylchromane (200 mg, 1.27 mmol) (made according to WO200876043/A1) in THF (2.5 mL) was treated with pinacolborane (303 mg, 2.53 mmol) and heated to 70 °C. After 1.5 h, the reaction mixture was quenched with MeOH (1 mL) and partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by  
 25 silica gel chromatography (0-10% EtOAc in PE) to afford the title compound (90 mg, 37%

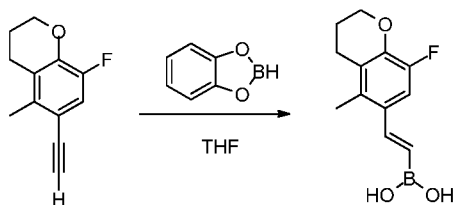
yield) as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17 (dd,  $J = 8.5, 2.0$  Hz, 1H), 7.14 – 7.09 (m, 2H), 6.76 (d,  $J = 8.4$  Hz, 1H), 4.22 – 4.14 (m, 2H), 2.78 (t,  $J = 6.5$  Hz, 2H), 2.03 – 1.97 (m, 5H), 1.56 (s, 3H), 1.30 (s, 12H). LC/MS ( $m/z$ ) ES- = 249.3 (M+HCOOH-1).

- 5           **Example 25.** (S,E)-2-(tert-butoxy)-2-(6-(2-(chroman-6-yl)vinyl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



The title compound was made in a similar manner as Example 19 except using (*E*)-  
 10    (*E*)-2-(chroman-6-yl)vinyl)boronic acid in Step 1.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.75 (br, 1H),  
 7.50 – 7.40 (m, 1H), 7.36 (d,  $J = 7.3$  Hz, 1H), 7.29 (d,  $J = 4.9$  Hz, 2H), 7.24 – 7.11 (m, 2H),  
 7.01 (dd,  $J = 16.4, 12.4$  Hz, 1H), 6.80 (dd,  $J = 8.4, 5.6$  Hz, 1H), 6.72 – 6.53 (m, 1H), 5.77 (s,  
 1H), 5.09 – 4.87 (m, 2H), 4.80 – 4.60 (m, 2H), 4.21 (dd,  $J = 9.8, 4.2$  Hz, 2H), 2.81 (dd,  $J =$   
 15    11.8, 6.0 Hz, 2H), 2.35 – 1.98 (m, 8H), 1.12 (d,  $J = 8.1$  Hz, 9H). LC/MS ( $m/z$ ) ES+ = 558.6  
 (M+1).

Scheme 13



20

(*E*)-2-(8-fluoro-5-methylchroman-6-yl)vinyl)boronic acid.

To a solution of 6-ethynyl-8-fluoro-5-methylchromane (200 mg, 1.05 mmol) in THF (3 mL) was added catacolborane (235 mg, 2.10 mmol) and heated to 70 °C. After 1.5 h, the resulting mixture was quenched with MeOH (1 mL) and partitioned between EtOAc and  $\text{H}_2\text{O}$ .

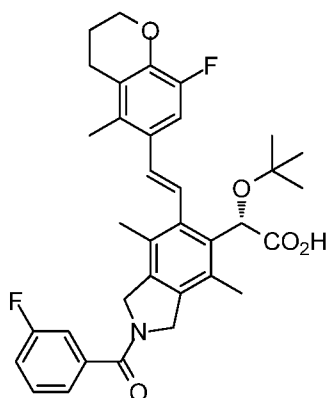
25    The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated



under reduced pressure. The residue was purified by silica gel chromatography (silica gel, 0-10% EtOAc in PE) to afford the title compound (50 mg, 22% yield) as a white solid. LC/MS (m/z) ES<sup>-</sup> = 281.4 (M+HCOOH-1).

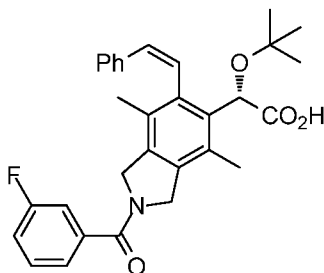
5

**Example 26.** (S)-2-(tert-butoxy)-2-(6-(2-(8-fluoro-5-methylchroman-6-yl)vinyl)-2-(3-fluorobenzoyl)-4,7-dimethylisoindolin-5-yl)acetic acid



10 The title compound was made in a similar manner as Example 19 except using (*E*)-*(2-(8-fluoro-5-methylchroman-6-yl)vinyl)boronic acid* in Step 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.80 (br, 1H), 7.51 – 7.41 (m, 1H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.31 – 7.28 (m, *J* = 1.5 Hz, 1H), 7.25 – 7.15 (m, 2H), 7.09 – 6.84 (m, 2H), 5.78 (s, 1H), 5.12 – 4.87 (m, 2H), 4.80 – 4.64 (m, 2H), 4.23 (dd, *J* = 9.7, 4.0 Hz, 2H), 2.70 (dd, *J* = 10.7, 6.4 Hz, 2H), 2.41 – 1.96 (m, 11H),  
15 1.14 (d, *J* = 6.9 Hz, 9H). LC/MS (m/z) ES<sup>+</sup> = 590.4 (M+1).

**Example 27:** (S,Z)-2-(tert-butoxy)-2-(2-(3-fluorobenzoyl)-4,7-dimethyl-6-styrylisoindolin-5-yl)acetic acid



20 The title compound was made in a similar manner as Example 19 except using (*Z*)-*styrylboronic acid* (*J. Am. Chem. Soc.* **2015**, 137, 3233 – 3236) in Step 1. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.56 (br, 1H), 7.54 – 7.26 (m, 4H), 7.23 – 7.08 (m, 4H), 7.01 (d, *J* = 10.2 Hz,

1H), 6.84 – 6.50 (m, 2H), 5.63 (d,  $J = 48.8$  Hz, 1H), 5.11 – 4.61 (m, 4H), 2.43 – 1.83 (m, 6H), 1.14 (d,  $J = 10.7$  Hz, 9H). LC/MS (m/z) ES+ = 502.1 (M+1).

#### ANTI-HIV ACTIVITY

##### MT4 Assay

5 Antiviral HIV activity and cytotoxicity values for compounds of the invention from Table 1 were measured in parallel in the HTLV-1 transformed cell line MT-4 based on the method previously described (Hazen et al., 2007, *In vitro* antiviral activity of the novel, tyrosyl-based human immunodeficiency virus (HIV) type 1 protease inhibitor brecanavir (GW640385) in combination with other antiretrovirals and against a panel of protease  
10 inhibitor-resistant HIV (Hazen et al., “In vitro antiviral activity of the novel, tyrosyl-based human immunodeficiency virus (HIV) type 1 protease inhibitor brecanavir (GW640385) in combination with other antiretrovirals and against a panel of protease inhibitor-resistant HIV”, *Antimicrob. Agents Chemother.* 2007, 51: 3147-3154; and Pauwels et al., “Sensitive and rapid assay on MT-4 cells for the detection of antiviral compounds against the AIDS virus”, *J. of Virological Methods* 1987, 16: 171-185).

15 Luciferase activity was measured 96 hours later by adding a cell titer glo (Promega, Madison, Wis.). Percent inhibition of cell protection data was plotted relative to no compound control. Under the same condition, cytotoxicity of the compounds was determined using cell titer Glo™ (Promega, Madison, Wis). IC<sub>50</sub>s were determined from a  
20 10 point dose response curve using 3-4-fold serial dilution for each compound, which spans a concentration range > 1000 fold.

These values are plotted against the molar compound concentrations using the standard four parameter logistic equation:

25 
$$y = ((V_{max} * x^n) / (K^n + x^n)) + Y_2$$

where:

Y<sub>2</sub> = minimum y                      n = slope factor

V<sub>max</sub> = maximum y                  x = compound concentration [M]

K = EC<sub>50</sub>

30

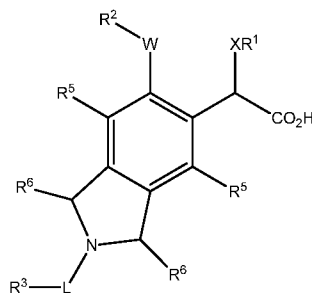
When tested in the MT4 assay compounds were found to have IC<sub>50</sub> values listed in Table 1.

Table 1

Example	IC50 ( $\mu$ M)
1	1.03
2	3.68
3	0.651
4	10.18
5	50
6	9.63
7	38
8	50
9	50
10	4.10
11	3.12
12	33.9
13	44.64
14	0.086
15	1.31
16	0.120
17	0.124
18	1.09
19	50
20	50
21	0.103
22	0.039
23	0.044
24	50
25	33.9
26	50
27	0.868

**What is claimed is:**

1. A compounds of Formula I:



Formula I

5

wherein:

X is O or CH<sub>2</sub>;

R<sup>1</sup> is C<sub>1-6</sub>alkyl wherein said alkyl may contain cycloalkyl portions;

10 W is -CH=CH-, -C≡C-, C<sub>1-3</sub>alkylene, -CH<sub>2</sub>C(O)NH-, -NHC(O)-, -N(CH<sub>3</sub>)C(O)-, -N(CH<sub>3</sub>)C(O)CH<sub>2</sub>-, -C(O)-, -CH<sub>2</sub>C(O)-, or -NHC(O)CH<sub>2</sub>-, wherein each W is optionally substituted by 1 or 2 methyl groups;

15 R<sup>2</sup> is H, C<sub>1-6</sub>alkyl, C<sub>5-14</sub>aryl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-9</sub>heterocycle, or C<sub>5-9</sub>heteroaryl, wherein each R<sup>2</sup> group is optionally substituted by one to four substituents selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>heteroalkyl, or C<sub>1-6</sub>alkylene or C<sub>1-6</sub>heteroalkylene wherein said C<sub>1-6</sub>alkylene or C<sub>1-6</sub>heteroalkylene is bonded to adjacent carbon atoms on said C<sub>5-14</sub>aryl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-9</sub>heterocycle, or C<sub>5-9</sub>heteroaryl to form a fused ring;

L is a bond, -CH<sub>2</sub>(CO)-, -C<sub>1-3</sub>alkylene-, -SO<sub>2</sub>-, -C(O)-, -C(S)-, -C(NH)-, -C(O)NH-, -C(O)NHCH<sub>2</sub>-, -C(O)N-, -C(O)OCH<sub>2</sub>-, -C(O)O-, -C(O)C(O)-, -SO<sub>2</sub>-NH-, or -CH<sub>2</sub>C(O)-;

20 R<sup>3</sup> is H, CN, C<sub>1-6</sub>alkyl, C<sub>5-14</sub>aryl, CH<sub>2</sub>C<sub>5-14</sub>aryl, CH<sub>2</sub>C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>spirocycloalkyl, C<sub>3-7</sub>cycloalkenyl, C<sub>3-9</sub>heterocycle, or C<sub>5-9</sub>heteroaryl, oxo, or R<sup>3</sup> may join together with one R<sup>6</sup> to form a fused 5-7 membered ring, and wherein each R<sup>3</sup> group is optionally substituted by one to four substituents selected from halo, oxo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-3</sub>fluoroalkyl, -OC<sub>1-6</sub>alkyl, -C(O)R<sup>4</sup>, -C(O)NR<sup>4</sup>, -C(O)NHR<sup>4</sup>, C<sub>5-14</sub>aryl, C<sub>1-6</sub>heteroalkyl, -B(OH)<sub>2</sub>, C<sub>3-9</sub>heterocycle, C<sub>5-9</sub>heteroaryl, -C(O)OC<sub>1-6</sub>alkyl, or two substituents may bond together to form a fused, spiro, or bridged ring and that fused, spiro, or bridged ring may optionally be substituted with R<sup>4</sup>;

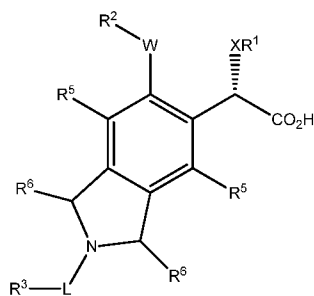
R<sup>4</sup> is CN, halo, -OC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-9</sub>heterocycle, or C<sub>5-14</sub>aryl;

each R<sup>5</sup> is independently H, C<sub>1-3</sub>alkyl, C<sub>3-6</sub>cycloalkyl, CH<sub>2</sub>F, CHF<sub>2</sub>, or CF<sub>3</sub>;

each R<sup>6</sup> is independently H, or C<sub>1-3</sub>alkyl, C<sub>5-14</sub>aryl, C<sub>3-9</sub>heterocycle, C<sub>5-9</sub>heteroaryl, -C(O)NR<sup>4</sup>, or -C(O)NHR<sup>4</sup>, or both R<sup>6</sup> may together comprise 2-4 carbon atoms and join together to form a bridged ring system;

and wherein each heterocycle, heteroaryl, heteroalkyl, and heteroalkylene comprises  
5 one to three heteroatoms selected from S, N, B, or O.

2. A compound according to Claim 1 wherein R<sup>1</sup> is C<sub>1-6</sub>alkyl.
3. A compound according to Claim 1 or Claim 2 wherein X is O.
- 10 4. A compound according to any of Claims 1-3 wherein each R<sup>6</sup> is H.
5. A compound according to any of Claims 1-4 wherein R<sup>2</sup> is optionally substituted phenyl.
- 15 6. A compound according to Claim 5 wherein R<sup>2</sup> is phenyl substituted by one to four substituents selected from fluorine, methyl, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O- wherein said -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O- is bonded to adjacent carbon atoms on said phenyl to form a bicyclic ring, or -NHCH<sub>2</sub>CH<sub>2</sub>O- wherein said -NHCH<sub>2</sub>CH<sub>2</sub>O- is bonded to adjacent carbon atoms on said phenyl to form a bicyclic ring.
- 20 7. A compound according to any of Claims 1-6 wherein R<sup>3</sup> is C<sub>1-6</sub>alkyl, phenyl, naphthyl, cyclopentyl, cyclohexyl, pyridyl, or tetrahydropyranyl, each of which is optionally substituted by 1-3 substituents selected from halogen, C<sub>1-6</sub>alkyl, -OC<sub>1-6</sub>alkyl, C<sub>1-3</sub>fluoroalkyl, or phenyl.
- 25 8. A compound according to any of Claims 1-7 wherein each R<sup>5</sup> is methyl.
9. A compound according to any of Claims 1-8 wherein the stereochemistry on the carbon to which XR<sup>1</sup> is bound is as depicted below.



30

10. A pharmaceutically acceptable salt of a compound according to any of Claims 1-9.
11. A pharmaceutical composition comprising a compound or salt according to any of  
5 Claims 1-10.
12. A method for treating a viral infection in a patient mediated at least in part by a virus in the *retrovirus* family of viruses, comprising administering to said patient a composition according to Claim 11.  
10
13. The method of Claim 12 wherein said viral infection is mediated by the HIV virus.
14. A compound or salt as defined in any of Claims 1-10 for use in medical therapy.
15. A compound or salt as defined in any of Claims 1-10 for use in the treatment of a viral  
15 infection in a human.
16. The use of a compound or salt as defined in any of Claims 1-10 in the manufacture of a  
20 medicament for use in the treatment of a viral infection in a human.

INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2016/057262

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D405/06 C07D209/44 A61K31/4035 A61P31/18  
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

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/044027 A2 (ASTEX THERAPEUTICS LTD [GB]; CONGREVE MILES STUART [GB]; FAZAL LYNDSEY) 17 April 2008 (2008-04-17) compounds of the examples; page 83, line 14 - page 85, line 24; claims 1,75,111	1-16
A	WO 2014/119636 A1 (SHIONOGI & CO LTD) 7 August 2014 (2014-08-07) abstract	1-16
A,P	& EP 2 952 503 A1 (SHIONOGI & CO [JP]) 9 December 2015 (2015-12-09) compounds of the examples, Experimental Example 1; paragraphs [0001], [0012], [0047], [0172], [0173], [0575]; claims 1,33,34,44-47; tables A-1 - A-9	1-16
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Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search <b>27 January 2017</b>	Date of mailing of the international search report <b>08/02/2017</b>
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer <b>Guspanová, Jana</b>
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2016/057262

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2016/005878 A1 (VIIV HEALTHCARE UK LTD [GB]) 14 January 2016 (2016-01-14) compounds of the examples; page 1, paragraph 1; claims 1,11,12,15-17; table 1  -----	1-16



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/057262

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		JP 2010505927 A	25-02-2010
		US 2010152184 A1	17-06-2010
		WO 2008044027 A2	17-04-2008
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		WO 2016005878 A1	14-01-2016
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