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(54)

2-(2,4-DIFLUOROPHENYL)-1,1-DIFLUORO-1-(5-SUBSTITUTED-PYRIDIN-2-YL)-3-(1H-TETRAZOL-1-YL)PROPAN-2-OLS AND PROCESSES FOR THEIR PREPARATION

2-(2,4-DIFLUORPHENYL)-1,1-DIFLUOR-1-(5-SUBSTITUTIERTES-PYRIDIN-2-YL)-3-(1H-TETRAZOL-1-YL)PROPAN-2-OLE UND VERFAHREN ZU DEREN HERSTELLUNG

2-(2,4-DIFLUOROPHÉNYL)-1,1-DIFLUORO-1-(5-SUBSTITUTION-PYRIDINE-2-YL)-3-(1H-TETRAZOL-1-YL)PROPANE-2-OLES ET PROCÉDÉS DE PRÉPARATION CORRESPONDANTS

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WO-A1-2012/177725 **WO-A1-2013/110002**
WO-A1-2014/193974

EP 3 119 756 B9

Description

FIELD

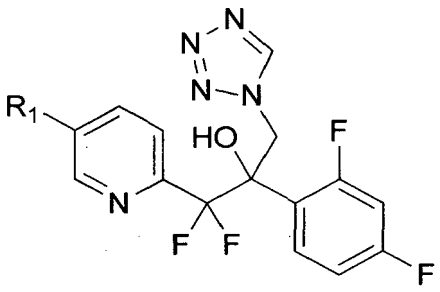
[0001] Provided herein are 2-(2,4-difluorophenyl)-1,1-difluoro-1-(5-substituted-pyridin-2-yl)-3-(1*H*-tetrazol-1-yl)propan-2-ols and processes for their preparation. In another embodiment provided herein are 1-(2,4-difluorophenyl)-2,2-difluoro-2-(5-substituted-pyridin-2-yl)ethanones and processes for their preparation.

BACKGROUND

[0002] International applications WO 2014/193974 A1 and WO 2013/110002 A1 as well as U.S. Patent applications 13/527,387, 13/527,426 and 13/528,283 describe *inter alia* certain metalloenzyme inhibitor compounds and their use as fungicides. Each of these patents describes the various routes to generate metalloenzyme inhibiting fungicides. It may be advantageous to provide more direct and efficient methods for the preparation of metalloenzyme inhibiting fungicides and related compounds, e.g., by the use of reagents and/or chemical intermediates which provide improved time and cost efficiency.

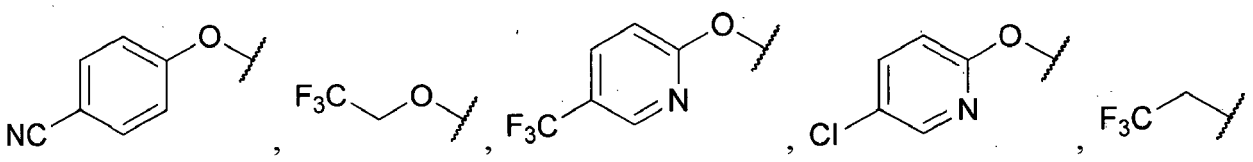
SUMMARY OF THE DISCLOSURE

[0003] Provided herein are 2-(2,4-difluorophenyl)-1,1-difluoro-1-(5-substituted-pyridin-2-yl)-3-(1H-tetrazol-1-yl)propan-2-ols and 1-(2,4-difluorophenyl)-2,2-difluoro-2-(5-substituted-pyridin-2-yl)ethanones and processes for their preparation. According to the disclosure, provided herein is a process for the preparation of a compound of the Formula VI:



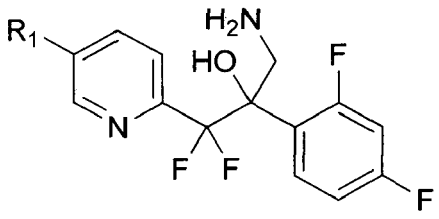
(VI)

wherein R_1 is selected from:



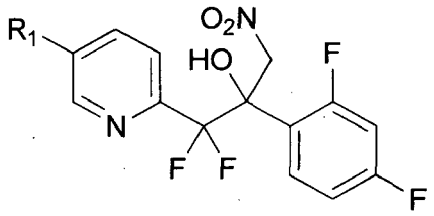
, and Br,

which comprises contacting compounds of Formula V with triethyl orthoformate and sodium azide in the presence of acetic acid.



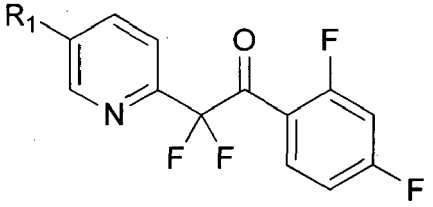
(V)

[0004] In another aspect of the disclosure, compounds of Formula V may be prepared by contacting compounds of Formula IV with a metal and an acid selected from acetic acid and hydrochloric acid.



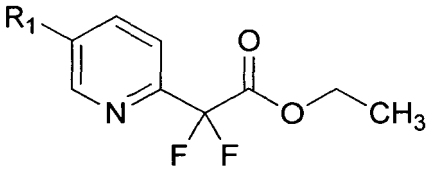
(IV)

[0005] In another embodiment, compounds of Formula IV may be prepared by contacting compounds of Formula III with nitromethane and a base.



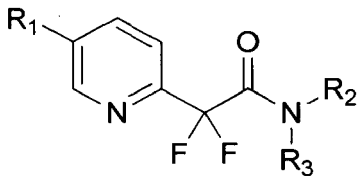
(III)

[0006] In another embodiment, compounds of Formula III may be prepared by contacting compounds of Formula II with a preformed organometallic reagent.



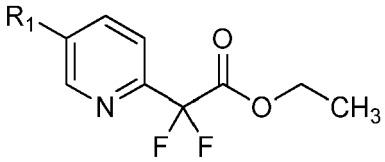
(II)

[0007] According to the invention, compounds of Formula III may be prepared by contacting compounds of Formula IIa with a preformed organometallic reagent, as defined in claim 1:



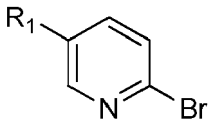
(IIa)

[0008] In another embodiment, compounds of Formula IIa may be prepared by contacting compounds of Formula II with an amine, a Lewis acid, and a solvent.



(II)

[0009] In another embodiment, compounds of Formula II may be prepared by contacting compounds of the Formula I with ethyl 2-bromo-2,2-difluoroacetate and a metal.



(I)

[0010] The term "cyano" refers to a -C≡N substituent.

[0011] The term "hydroxyl" refers to an -OH substituent.

[0012] The term "amino" refers to a -NH_2 substituent.

[0013] The term "alkylamino" refers to a -N(H)-R substituent.

[0014] The term "dialkylamino" refers to a -NR_2 substituent.

[0015] The term "halogen" or "halo" refers to one or more halogen atoms, defined as F, Cl, Br, and I.

[0016] The term "nitro" refers to a -NO_2 substituent.

[0017] The term "Lewis acid" refers to any substance that is an electron pair acceptor.

[0018] The term "organometallic" refers to an organic compound containing a metal, especially a compound in which a metal atom is bonded directly to a carbon atom.

[0019] Throughout the disclosure, references to the compounds of Formula VII, VI, V, and IV are read as also including optical isomers and salts. Specifically, when compounds of Formula VII, VI, V, or IV contain a branched chain alkyl group, it is understood that such compounds include optical isomers and racemates thereof. Exemplary salts may include: hydrochloride, hydrobromide, hydroiodide, and the like. Additionally, the compounds of Formula VII, VI, V, and IV may include tautomeric forms.

[0020] Certain compounds disclosed in this document can exist as one or more isomers. It will be appreciated by those skilled in the art that one isomer may be more active than the others. The structures disclosed in the present disclosure are drawn in only one geometric form for clarity, but are intended to represent all geometric and tautomeric forms of the molecule.

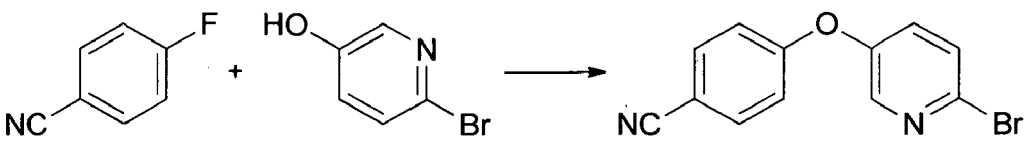
[0021] The embodiments described above are intended merely to be exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures.

DETAILED DESCRIPTION

[0022] 2-(2,4-Difluorophenyl)-1,1-difluoro-1-(5 -substituted-pyridin-2-yl)-3-(1*H*-tetrazol-1-yl)propan-2-ols and 1-(2,4-difluorophenyl)-2,2-difluoro-2-(5-substituted-pyridin-2-yl)ethanones provided herein may be prepared from 6-bromopyridin-3-ol as shown in Examples 1-8.

Example 1: Preparation of 4-((6-bromopyridin-3-yl)oxy)benzonitrile (1)

[0023]



[0024] **Method A:** To a stirred solution of 6-bromopyridin-3-ol (5.0 g, 28.7 mmol) and 4-fluorobenzonitrile (3.48 g, 28.7 mmol) in dry DMSO (57.5 mL) under nitrogen was added cesium carbonate (14.04 g, 43.1 mmol). The reaction mixture was stirred at 75°C for 18 h. The reaction was poured into ice water. The pH was adjusted to make the solution mildly acidic (pH = 6) using 1 N HC1. The resulting precipitate was filtered and washed with water followed by a minimum amount of ether to give the title compound as a brown solid (6.292 g, 76%).

[0025] **Method B:** To a stirred solution of 6-bromopyridin-3-ol (17.3 g, 100 mmol) and 4-fluorobenzonitrile (12.1 g, 120 mmol) in DMF (150 mL) under nitrogen was added Cs_2CO_3 (32.5 g, 120 mmol). The reaction mixture was stirred at 85-90 °C for 10-15 h. HPLC indicated the reaction was complete. Into the reaction mixture cooled to 10-15 °C (ice bath) was charged water (450 mL) to precipitate the product. The resulting precipitate was filtered, washed with acetonitrile-water (1:4) and water, and dried in a vacuum oven to give the title compound as a white solid (25 g, 91%). The product was slurried in EtOH (50 mL) at room temperature for 2-3 h to remove the side product. The suspension was filtered to collect the title compound as a white solid (23.5 g, 85%).

[0026] This reaction was also carried out as described in Example 1, Method A with the exception that potassium carbonate was used in place of cesium carbonate.

[0027] The following compounds **1-3** in Table 1a were made in accordance with the reaction depicted in Scheme 1 and the procedures described in Example 1. Characterization data for compounds **1-3** are shown in Table 1b.

Scheme 1

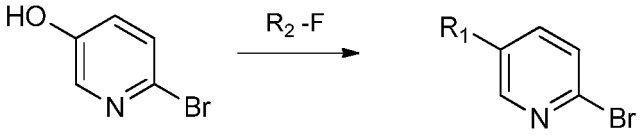
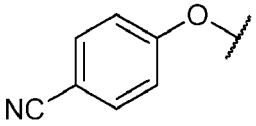
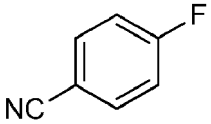
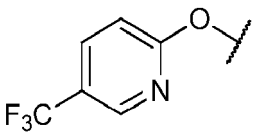
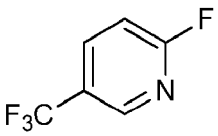


Table 1a

Compound No.	R_1	Appearance	Prepared as in Example(s):	R_2-F
1		Brown solid	Ex 1, Methods A and B	
2		Off-white solid	Ex 1, Method B	

(continued)

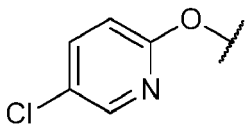
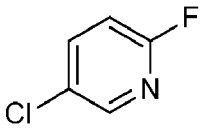
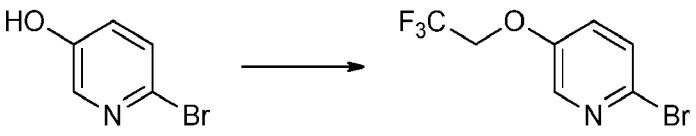
Compound No.	R_1	Appearance	Prepared as in Example(s):	R_2-F
3		White Solid	Ex 1, Method B	

Table 1b

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR (thin film) cm^{-1}
1	113	275 ([M]$^+$)	8.22 (d, *J* = 2.9 Hz, 1H), 7.70 - 7.63 (m, 2H), 7.56 - 7.51 (m, 1H), 7.28 (dd, *J* = 8.5, 2.9 Hz, 1H), 7.10 - 7.02 (m, 2H)		
2			8.39 - 8.32 (m, 1H), 8.27 - 8.22 (m, 1H), 7.97 - 7.85 (m, 1H), 7.49 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H)	^{13}C NMR (101 MHz, $CDCl_3$) δ 164.46 (s), 149.27 (s), 145.02 (q, *J* = 4.3 Hz), 143.88 (s), 139.03 - 134.92 (m), 132.18 (s), 128.54 (s), 124.81 (s), 122.54 (q, *J* = 33.3 Hz), 122.12 (s), 111.83 (s)	
3		284 ([M]$^+$)	8.27 (dd, *J* = 3.0, 0.6 Hz, 1H), 8.08 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.71 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.51 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.98 (dd, *J* = 8.7, 0.7 Hz, 1H)		
[a] All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Example 2. Preparation of 2-bromo-5-(2,2,2-trifluoroethoxy)pyridine

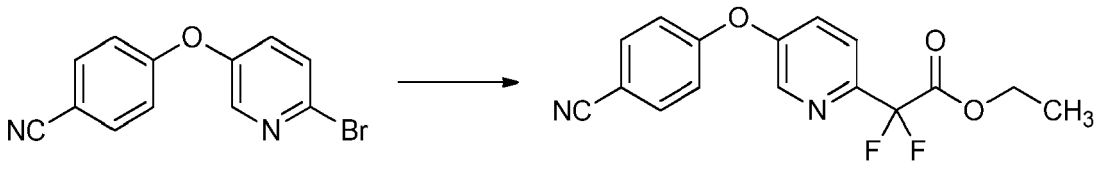
[0028]



6-Bromopyridin-3-ol (32.5 g, 187 mmol) and cesium carbonate (70.6 g, 217 mmol) were placed into a 1 L, 3-neck Morton flask equipped with a temperature probe, an overhead stirrer, and an addition funnel topped with a nitrogen line. A 9 °C cooling bath was applied before the solids were charged with DMF (325 mL). The temperature increased from 15°C to 20 °C when 2,2,2-trifluoroethyl trifluoromethanesulfonate (30.8 mL, 50.6 g, 212 mmol) was added by syringe over 27 min to the heterogeneous mixture of other components. The purple solution was stirred for 1 h 40 min before re-cooling with a 10 °C water bath. The solution was cooled to room temperature after the addition of water (650 mL). The mixture was extracted five times with 200 mL portions of 3:1 hexane-ethyl acetate. The combined organic layers were washed three times with 150 mL portions of water, dried over Na_2SO_4, filtered, and concentrated. The oil was then concentrated twice from 100 mL portions of hexane to give the title compound as a white solid (47.21 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 3.2 Hz, 1H), 7.44 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.19 (dd, *J* = 8.7, 3.2 Hz, 1H), 4.40 (q, *J* = 7.9 Hz, 2H); ^{19}F NMR -73.87; ESIMS *m/z* 256 ([M+H]$^+$).

Example 3: Preparation of ethyl 2-(5-(4-cyanophenoxy)pyridin-2-yl)-2,2-difluoroacetate (5)

[0029]



[0030] **Method A:** Crude 4-((6-bromopyridin-3-yl)oxy)benzonitrile was dried azeotropically with toluene to remove any possible trace water from the starting material. A magnetically stirred mixture of ethyl 2-bromo-2,2-difluoroacetate (3.08 mL, 23.99 mmol) and copper (2.98 g, 46.9 mmol) in dry DMSO (33.7 mL) was stirred at rt for 1 h, then 4-((6-bromopyridin-3-yl)oxy)benzonitrile (5.57 g, 20.25 mmol) was added in one portion. The reaction mixture was stirred at 60 °C for 3 days. The reaction was determined to be complete by TLC. The heat source was removed and the reaction diluted with EtOAc (100 mL) and stirred for 20 minutes. The reaction was filtered through a plug of celite and washed with EtOAc. The filtrate was washed with saturated NH_4Cl (3x) to remove any remaining copper. The solution was dried, and the solvent was removed under reduced pressure to produce crude product as a brown oil (5.947 g, 83%). The residue was purified by silica gel chromatography (0-20% EtOAc/hexanes) to give the title compound as a clear oil (two lots: (3.897 g, 59.9 %, 99% purity) and (804 mg, 11.23 %, 90% purity).

[0031] **Method B:** A magnetically stirred mixture of 4-((6-bromopyridin-3-yl)oxy)benzonitrile (27.5 g, 20 mmol), ethyl 2-bromo-2,2-difluoroacetate (4.47 g, 22 mmol), copper (2.67 g, 42 mmol) and methanesulfonic acid (38 mg, 0.4 mmol) in dry DMF (50 mL) was stirred at 40-45 °C. The reaction was complete by HPLC. The reaction mixture was cooled to room temperature, then diluted with toluene (200 mL) and stirred for 0.5 h at room temperature before filtration through celite and washing with additional toluene. The filtrate was washed with 20% NH_4Cl (50 mL) and water (25 mL x 2). The organic layer was concentrated with additional acetonitrile under reduced pressure to remove water. The solution was concentrated and dried under in vacuo to give the title compound as a brown oil (5.3 g, 83%).

[0032] The following compounds **5-10** in Table 3a were made in accordance with the reaction depicted in Scheme 3 and the procedures described in Example 3. Characterization data for compounds **5-10** are shown in Table 3b.

Scheme 3

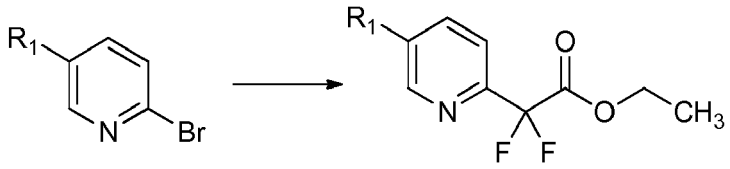
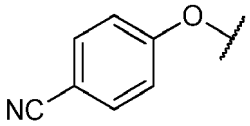
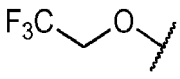
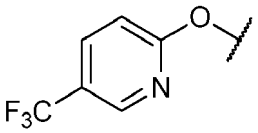


Table 3a

Compound No.	R_1	Appearance	Prepared as in Example(s):
5		Brown oil	Ex 3, Methods A and B
6		Amber oil	Ex 3, Method B
7		Colorless oil	Ex 3, Method B

(continued)

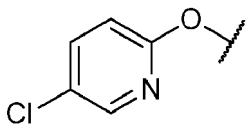
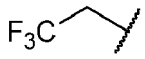
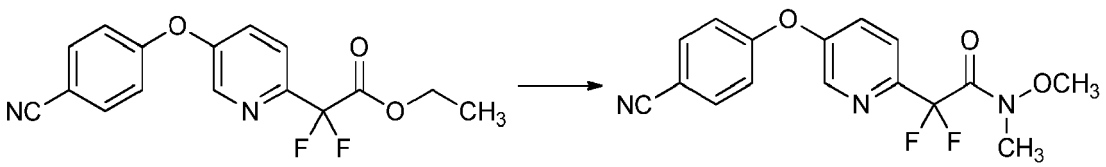
Compound No.	R_1	Appearance	Prepared as in Example(s):
8		Brown oil	Ex 3, Method B
9	Br	ClearColorless oil	Ex 3, Method A
10		Yellow oil	Ex 3, Method B

Table 3b

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR(thin film) cm^{-1}
5		319 ([M+H]$^+$)	(300 MHz, $CDCl_3$) δ 8.44 (d, J = 2.7 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.73 - 7.64 (m, 2H), 7.49 (dd, J = 8.6, 2.7 Hz, 1H), 7.16 - 7.07 (m, 2H), 4.39 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H)		2229, 1767
6		300 ([M+H]$^+$)	8.37 (dd, *J* = 2.9, 0.6 Hz, 1H), 7.72 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.39 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.46 (q, *J* = 7.9 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H)	^{19}F NMR -73.82 (s, 3F), - 104.24 (s, 2F)	
7		363 ([M+H]$^+$)	8.54 (d, *J* = 2.5 Hz, 1H), 8.48 - 8.37 (m, 1H), 8.06 - 7.93 (m, 1H), 7.82 (dd, *J* = 8.6, 0.6 Hz, 1H), 7.72 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H)		
8		328 ([M]$^+$)	8.51 (dd, *J* = 2.7, 0.7 Hz, 1H), 8.10 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.78 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.67 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.01 (dd, *J* = 8.7, 0.7 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H)		
9		281 ([M+H]$^+$)	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, *J* = 2.23, 0.57 Hz, 1H), 8.00 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.65 (dd, *J* = 8.4, 0.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H)	^{19}F NMR -105.2 (s)	
10			8.59 (s, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 10.5 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H)		2990, 1768
[a] All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Example 4: Preparation of 2-(5-(4-cyanophenoxy)pyridin-2-yl)-2,2-difluoro-*N*-methoxy-*N*-methylacetamide (11)

[0033]



[0034] To a 1L three neck round bottom flask equipped with an overhead stirrer, a temperature probe, a nitrogen inlet, and an addition funnel and cooled in an ice-water bath was charged *N,O*-dimethylhydroxylamine hydrochloride (6.15 g, 63 mmol) and dichloromethane (63 mL). A solution of dimethylaluminum chloride (63 mL, 63 mmol, 1M solution in hexane) was added slowly to keep the temperature below 15 °C. Upon the completion of addition, the ice-water bath was removed and the reaction allowed to warm to room temperature for 1h. A solution of ethyl 2-(5-(4-cyanophenoxy)pyridin-2-yl)-2,2-difluoroacetate (13.37 g, 42 mmol) in CH_2Cl_2 (21 mL) was added over 5-10 min and the mixture was stirred at rt for 3-5 h and the reaction proceeded to completion as indicated by HPLC. The reaction was cooled to 5 °C and quenched by a slow addition of 10% potassium sodium tartrate solution (400 mL). After addition of potassium sodium tartrate, the reaction mixture was stirred at room temperature for 1h. After separation of the organic layer, the aqueous layer was extracted with additional CH_2Cl_2. The combined organic layers were washed with 10% $NaHCO_3$ and water. The organic layer was concentrated and replaced with heptane to solidify the product. The product was filtered, washed with heptane and dried overnight *in vacuo* to give the title compound as a light yellow solid (12 g, 86%).

[0035] The following compounds **11-18** in Table 4a were made in accordance with the reaction depicted in Scheme 4 and the procedures described in Example 4. Characterization data for compounds **11-18** are shown in Table 4b.

Scheme 4

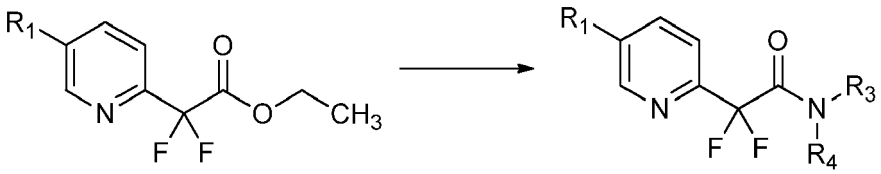
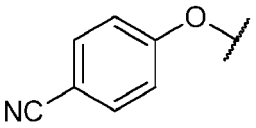
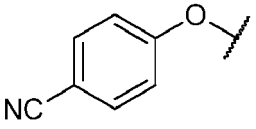
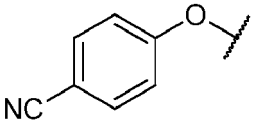
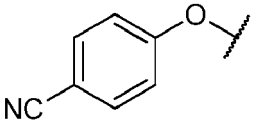
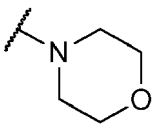
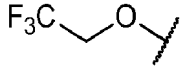


Table 4a

Comp ound No.	R_1	$-N(R_3)(R_4)$	Appearance	Prepared as in Example(s):
11		$-N(OCH_3)(CH_3)$	Light yellow solid	Ex 4
12		$-N(CH_3)(CH_3)$	Oil	Ex 4
13		$N(CH_2CH_3)(CH_2\ CH_3)$	Oil	Ex 4
14			Clear oil	Ex 4
15		$-N(OCH_3)(CH_3)$	Off-white solid	Ex 4

(continued)

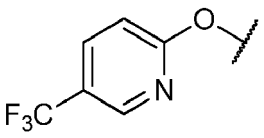
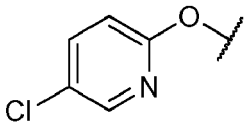
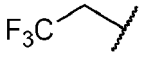
Compound No.	R_1	$-N(R_3)(R_4)$	Appearance	Prepared as in Example(s):
16		$-N(OCH_3)(CH_3)$	Light yellow solid	Ex 4
17		$-N(OCH_3)(CH_3)$	Yellow solid	Ex 4
18		$-N(OCH_3)(CH_3)$	Oil	Ex 4

Table 4b

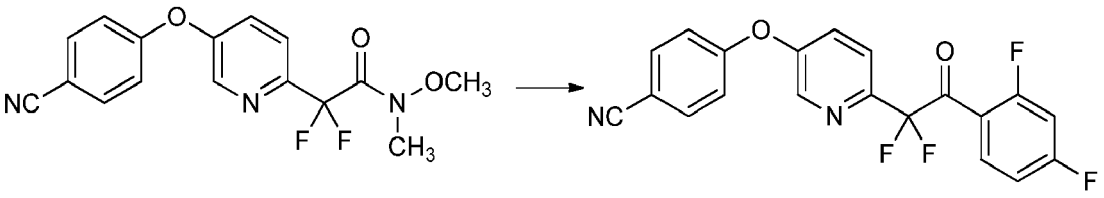
Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR(thin film) cm^{-1}
11	101	334	8.42 (d, *J* = 4.0 Hz, 1H), 7.71 (m, 3H), 7.49 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.10 (m, 2H), 3.56 (s, 3H), 3.29 (s, 3H)		
12		319	8.45 (dd, *J* = 2.8, 0.7 Hz, 1H), 7.81-7.63 (m, 3H), 7.50 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.18 -7.05 (m, 2H), 3.15 (t, *J* = 1.9 Hz, 3H), 3.07 (t, *J* = 0.8 Hz, 3H)	^{19}F NMR (376 MHz, $CDCl_3$) δ -97.58 (s)	
13		346	8.45 (d, *J* = 4.0 Hz, 1H), 7.72 (m, 3H), 7.49 (dd, *J* = 12.0, 4.0 Hz, 1H), 7.10 (m, 2H), 3.47 (m, 4H), 1.20 (m, 6H)	162.28, 159.65, 153.10, 148.85, 141.36, 134.53, 127.39, 122.22, 118.95, 118.23, 114.24, 107.89, 42.24, 41.73, 14.16, 12.27	
14		359	(300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.7 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.69 (m, 2H), 7.49 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.11 (m, 2H), 3.70 (m, 8H)		
15		315 ($[M+H]^+$)	8.34 (d, *J* = 2.9 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.46 (q, *J* = 7.9 Hz, 2H), 3.49 (s, 3H), 3.27 (s, 3H)	^{19}F NMR -73.79 (s, 3F), -100.76 (s, 2F)	
16		378 ($[M+H]^+$)	8.52 (d, *J* = 2.4 Hz, 1H), 8.46 - 8.38 (m, 1H), 8.03 -7.94 (m, 1H), 7.78 (dd, *J* = 8.6, 0.4 Hz, 1H), 7.72 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 3.50 (s, 3H), 3.29 (s, 3H)		
17		343 ($[M]^+$)	8.49 (dd, *J* = 2.6, 0.8 Hz, 1H), 8.10 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.78 - 7.70 (m, 2H), 7.67 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.00 (dd, *J* = 8.7, 0.7 Hz, 1H), 3.50 (s, 3H), 3.29 (s, 3H)		

(continued)

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR(thin film) cm^{-1}
18		299 ([M+H]$^+$)	8.56 (s, 1H), 7.83 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 3.46 (m, 5H), 3.28 (s, 3H)		
[a]All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Example 5: Preparation of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-oxoethyl)pyridin-3-yl)oxy)benzonitrile (19)

[0036]



[0037] To a magnetically stirred mixture of magnesium (2.43 g, 100 mmol) in THF (50 mL) under N_2 atmosphere was added a part of solution of 1-bromo-2,4-difluorobenzene (19.30 g, 11.3 mL, 100 mmol) in THF (25 mL) at 45 °C. The solution was stirred for 0.5 h at 50-55 °C and cooled to 30 °C. The rest of solution was charged slowly over 1 h at 30-40 °C, and then the mixture was stirred for additional 1-2 h at room temperature.

[0038] Into the solution of 2-(5-(4-cyanophenoxy)pyridin-2-yl)-2,2-difluoro-*N*-methoxy-*N*-methylacetamide (16.6 g, 50 mmol) in THF (75 mL) at 0 °C was added the above freshly prepared Grignard solution slowly, and then the mixture was stirred for 0.5 h. After completion of reaction by HPLC, the reaction mixture was cooled to 5 °C (ice-water bath), followed by addition of 6N HCl (10 mL) and 20% NH_4Cl (200 mL). The product was extracted with CH_2Cl_2 (400 mL). The organic layer was washed with additional 20% NH_4Cl, 10% K_2CO_3 and water. The separated organic layer was concentrated and replaced with EtOH to give the title compound (19.3 g, 100%) that was used in the next step without further purification.

[0039] This reaction was also carried out as described in Example 5 with the exception of generating the arylmagnesium bromide reagent by reaction of the aryl bromide with isopropylmagnesium chloride.

[0040] The following compounds 19-23 in Table 5a were made in accordance with the reaction depicted in Scheme 5 and the procedures described in Example 5. Characterization data for compounds **19-23** are shown in Table 5b.

Scheme 5

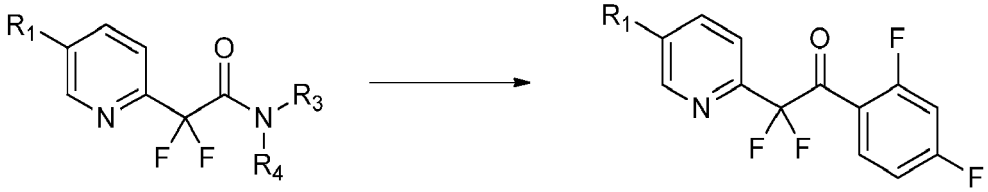
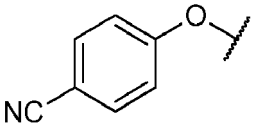


Table 5a

Compound No.	R_1	Appearance	Prepared as in Example(s):
19		Yellow solid	Ex 5

(continued)

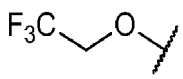
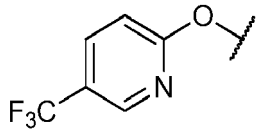
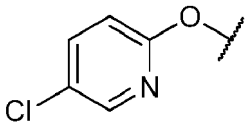
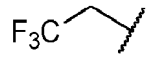
Compound No.	R_1	Appearance	Prepared as in Example(s):
20		Amber solid	Ex 5
21		Brown oil	Ex 5
22		Brown Oil	Ex 5
23		Yellow oil	Ex 5

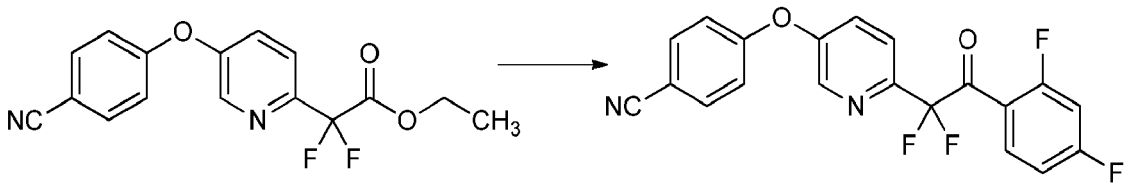
Table 5b

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR(thin film) cm^{-1}
19		387 ([M+H]$^+$)	(300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.7 Hz, 1H), 8.15 - 8.02 (m, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.74 - 7.65 (m, 2H), 7.53 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.16 - 7.06 (m, 2H), 7.05 - 6.96 (m, 1H), 6.84 (ddd, *J* = 10.9, 8.6, 2.4 Hz, 1H)	^{19}F NMR (376 MHz, $CDCl_3$) δ - 99.13 (d, *J* = 13.5 Hz), -100.67 (d, *J* = 14.9 Hz), - 101.82 (dd, *J* = 28.5, 14.2 Hz)	
20		368 ([M+H]$^+$)	8.29 (d, *J* = 2.8 Hz, 1H), 8.04 (td, *J* = 8.4, 6.4 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.99 (dddd, *J* = 8.7, 7.6, 2.4, 0.9 Hz, 1H), 6.82 (ddd, *J* = 11.0, 8.6, 2.4 Hz, 1H), 4.45 (q, *J* = 7.8 Hz, 2H)		
21		431 ([M+H]$^+$)	8.53 - 8.37 (m, 1H), 8.09 (td, *J* = 8.4, 6.6 Hz, 1H), 8.05 - 7.97 (m, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.05 - 6.90 (m, 1H), 6.84 (ddd, *J* = 11.0, 8.7, 2.4 Hz, 1H)		
22		396 ([M]$^+$)	8.44 (dd, *J* = 2.6, 0.7 Hz, 1H), 8.12 - 8.03 (m, 2H), 7.86 (dd, *J* = 8.6, 0.7 Hz, 1H), 7.72 (ddd, *J* = 8.7, 4.4, 2.6 Hz, 2H), 7.04 - 6.96 (m, 2H), 6.84 (ddd, *J* = 11.0, 8.7,2.4 Hz, 1H)		
23		352 ([M+H]$^+$)	8.51 (s, 1H), 8.08 (m, 1H), 7.88 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.84 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.00 (m, 1H), 6.83 (ddd, *J* = 10.8, 8.6, 2.4 Hz, 1H), 3.46 (q, *J* = 10.4 Hz, 2H)		

[a]All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted

Example 6. Preparation of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-oxoethyl)pyridin-3-yl)oxy)benzonitrile (19)

[0041]



[0042] To a magnetically stirred mixture of 1-bromo-2,4-difluorobenzene (0.923 mL, 8.17 mmol) in Et_2O (21 mL) under N_2 atmosphere at -78 °C was added slowly n-butyllithium (2.5 M in hexanes, 3.27 mL, 8.17 mmol). After completion of the addition, ethyl 2-(5-(4-cyanophenoxy)pyridin-2-yl)-2,2-difluoroacetate (2.00 g, 6.28 mmol) in Et_2O (15 mL) was added, and the reaction was stirred at -60 to -50 °C for 1 h. The reaction was quenched with 2 N HCl until reaction mixture was acidic. The reaction was allowed to warm to room temperature, and the mixture then made basic with sat. aq. $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was dried on the rotavap under vacuum for 4 h to give the title compound as a yellow oil (2.515 g, 88 %).

[0043] Compounds **19** and **25** in Table 6a were made in accordance with the reaction depicted in Scheme 6 and the procedures described in Example 6. Characterization data for compound **25** is shown in Table 6b.

Scheme 6

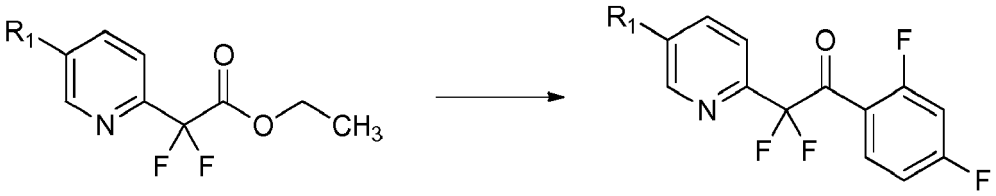


Table 6a

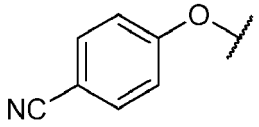
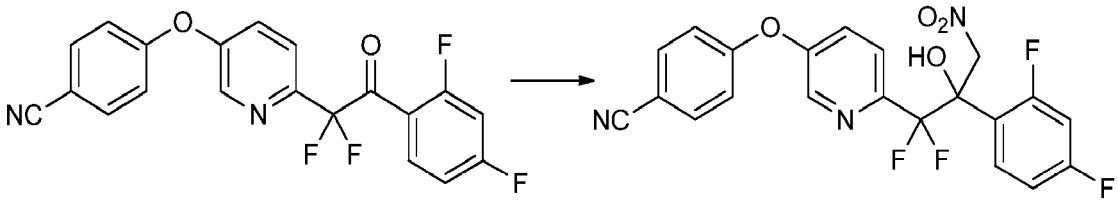
Compound No.	R_1	Appearance	Prepared as in Example(s):
19		Yellow solid	Ex 6
25	Br	White solid	Ex 6

Table 6b

Compou nd No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR(thin film) cm^{-1}
25		349 ($[M+1]^+$)	8.67 - 8.58 (m, 1H), 8.10 - 7.99 (m, 2H), 7.73 (dd, *J* = 8.4, 0.4 Hz, 1H), 7.05 - 6.94 (m, 1H), 6.83 (ddd, *J* = 10.7, 5.5, 1.4 Hz, 1H)		
[a]All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Example 7. Preparation of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-nitropropyl)pyridin-3-yl)oxy)benzonitrile (26)

[0044]



[0045] **Method A**: To a magnetically stirred solution of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-oxoethyl)pyridin-3-yl)oxy)benzonitrile (0.385 g, 0.897 mmol) in nitromethane (1.016 mL, 18.84 mmol) was added potassium carbonate (0.285 g, 2.063 mmol) under N_2 atmosphere. The reaction mixture was stirred at 40 °C for 2 h. The reaction was quenched with acetic acid (2.0 mL) in water (15 mL). The mixture was extracted with Et_2O, and the combined organic phases were washed with brine, sat. aq. $NaHCO_3$, and water, dried ($MgSO_4$) and concentrated to give the title compound as a yellow oil (427 mg, 99 %).

[0046] **Method B**: Into the mixture of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-oxoethyl)pyridin-3-yl)oxy)benzonitrile (50 mmol) and K_2CO_3 (6.9 g, 50 mmol) in EtOH (150 mL, 190 proof) at rt was charged nitromethane (9.16 g, 150 mmol) and the suspension was stirred at rt. Into the reaction mixture cooled to -10 °C was added 20% NH_4Cl (150 mL). The mixture was stirred until a solid formed, followed by adding additional 20% NH_4Cl (300 mL). The suspension was stirred for 1-2 h at room temperature. The product was isolated through filtration and washed with water and dried *in vacuo* to give the title compound (19.3 g, 86%).

[0047] This reaction was also carried out as described in Example 7, Method A with the exception of potassium hydroxide being used in place of potassium carbonate and dimethylformamide being used as a solvent instead of neat nitromethane.

[0048] The following compounds **26-31** in Table 7a were made in accordance with the reaction depicted in Scheme 7 and the procedures described in Example 7. Characterization data for compounds **26-31** are shown in Table 7b.

Scheme 7

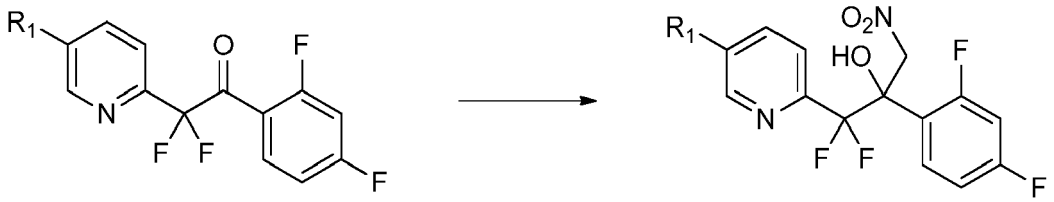
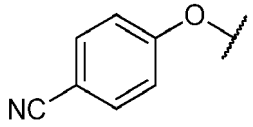
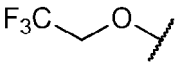
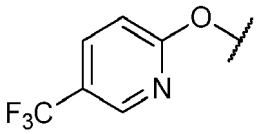
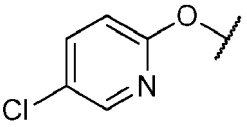


Table 7a

Compound No.	R_1	Appearance	Prepared as in Example(s):
26		White solid	Ex 7, Methods A and B
27		Tan solid	Ex 7, Method B
28		Vanilla color solid	Ex 7, Method B
29		Black oil	Ex 7, Method B

(continued)

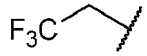
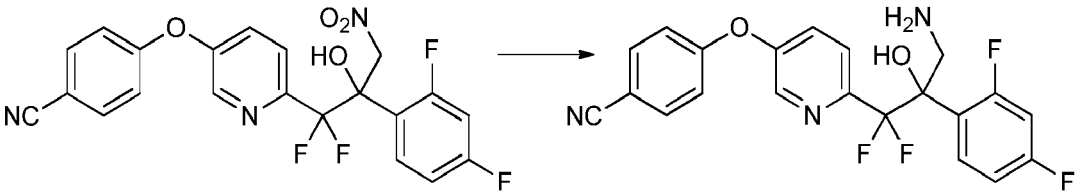
Compound No.	R_1	Appearance	Prepared as in Example(s):
30	Br	White solid	Ex 7, Method A
31		Solid	Ex 7, Method B

Table 7b

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR (thin film) cm^{-1}
26		448 ($[M+H]^+$)	(300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.7 Hz, 1H), 7.71 (m, 2H), 7.54 (m, 2H), 7.41 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.10 (m, 2H), 6.83 (m, 2H), 6.16 (s, 1H), 5.63 (d, *J* = 12.7 Hz, 1H), 5.10 (dd, *J* = 12.7, 1.7 Hz, 1H)		3337, 2229
27		429 ($[M+H]^+$)	8.35 (d, *J* = 2.9 Hz, 1H), 7.57 - 7.45 (m, 2H), 7.32 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.87 - 6.75 (m, 2H), 6.36 (s, 1H), 5.62 (d, *J* = 12.6 Hz, 1H), 5.06 (dd, *J* = 12.6, 1.6 Hz, 1H), 4.45 (q, *J* = 7.8 Hz, 2H)	^{19}F NMR (376 MHz, $CDCl_3$) δ - 78.68 (br), -104.97 (dd, *J* = 255.68, 15.04 Hz), -105.54 (m), -108.44 (d, *J* = 7.52 Hz), - 109.49 (dd, *J* = 255.68, 15.04 Hz)	
28		492 ($[M+1]^+$)	8.53 (d, *J* = 2.5 Hz, 1H), 8.41 (dd, *J* = 1.5, 0.8 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.68 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.63 -7.51 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 6.94 - 6.79 (m, 2H), 6.48 (s, 1H), 5.66 (d, *J* = 12.6 Hz, 1H), 5.09 (dd, *J* = 12.6, 1.1 Hz, 1H)	^{19}F NMR (376 MHz, $CDCl_3$) δ - 104.97 (d, *J* = 19.7 Hz), -105.43 - 105.73 (m), - 108.53 (d, *J* = 9.0 Hz), -108.76 - 109.77 (m), 61.82 (s)	
29		457 ($[M]^+$)	8.50 (d, *J* = 2.6 Hz, 1H), 8.15 - 8.06 (m, 1H), 7.75 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.57 (dd, *J* = 8.7, 0.8 Hz, 2H), 7.02 (dd, *J* = 8.7, 0.6 Hz, 1H), 6.89 - 6.78 (m, 2H), 6.57 (s, 1H), 5.64 (d, *J* = 12.5 Hz, 1H), 5.14 - 5.00 (m, 1H)		
30		409 ($[M]^+$)	8.68 (d, *J* = 2.2 Hz, 1H), 7.94 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.53 - 7.45 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.87 - 6.77 (m, 2H), 5.93 (s, 1H), 5.65 (d, *J* = 12.8 Hz, 1H), 5.08 (dd, *J* = 12.8, 1.7 Hz, 1H)	^{19}F NMR (376 MHz, $CDCl_3$) δ - 105.51 (ddd, *J* = 30.0, 17.6, 9.5 Hz), -106.02 (dd, *J* = 258.3, 17.4 Hz), -108.03 (d, *J* = 9.5 Hz), -110.56 (dd, *J* = 258.2, 30.5 Hz)	
31		413 ($[M+H]^+$)	8.56 (s, 1H), 7.78 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.51 (m, 2H), 6.81 (m, 2H), 6.40 (s, 1H), 5.64 (d, *J* = 12.6 Hz, 1H), 5.08 (dd, *J* = 12.6, 1.4 Hz, 1H), 3.46 (q, *J* = 10.3 Hz, 2H)		
[a]All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Example 8. Preparation of 4-((6-(3-amino-2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxypropyl)pyridin-3-yl)oxy)benzonitrile (32)

[0049]



[0050] **Method A. By reduction with Zinc powder:** To a solution of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-nitropropyl)pyridin-3-yl)oxy)benzonitrile (0.412 g, 0.921 mmol) in acetic acid (3.68 mL) was added zinc powder (0.602 g, 9.21 mmol). The reaction was stirred at rt. After 1 h, LCMS indicated a complete conversion to the desired product. The reaction was filtered through a plug of celite and washed with acetic acid. The filtrate was concentrated to 1 mL by co-evaporating with acetonitrile and was neutralized with sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated to give the acetic acid salt of the desired product. The residue was diluted with CH_2Cl_2, and the organic phase was washed with saturated aqueous $NaHCO_3$, brine, and then dried ($MgSO_4$) and concentrated to give the title compound as a faint yellow foam (296 mg, 77 %).

[0051] **Method B. By reduction with Tin(II) chloride:** To a magnetically stirred solution of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-nitropropyl)pyridin-3-yl)oxy)benzonitrile (0.208 g, 0.465 mmol) (contaminated by 29 mg of nitromethane = 0.47 mmol) in ethanol (4.65 mL) was added a solution of anhydrous tin(II) chloride (0.529 g, 2.79 mmol) in HCl (0.848 mL, 27.9 mmol). The reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was poured into ice water and was neutralized with sat. aq. $NaHCO_3$. The mixture was filtered through celite while washing with EtOAc. The filtrate was extracted with EtOAc, and the combined organic phases were washed with brine and water, dried ($MgSO_4$) and concentrated. Purification by silica gel chromatography (0-15% MeOH/DCM) gave the title compound as a faint yellow oil (62 mg, 31.9 %).

[0052] **Method C. By reduction with Zinc powder:** Into the flask (500 mL) containing Zn (13.08 g, 200 mmol) in AcOH (40 mL) at 23 °C was added slowly a solution of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-nitropropyl)pyridin-3-yl)oxy)benzonitrile (8.95g, 20 mmol) in MeOH (160 mL) at 30-35 °C over 20 min. The mixture was stirred at rt. After completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and filtered through celite which was rinsed with additional CH_2Cl_2. The resulting solution was washed with 10% NH_4Cl solution. After separation, the aq. layer was extracted with additional CH_2Cl_2. The combined organic layers were washed with 10% KOH (100 mL) and water (50 mL). The organic layer was concentrated with acetonitrile, and the crude title compound was used in the next step without further purification.

[0053] The following compounds **32-37** in Table 8a were made in accordance with the reaction depicted in Scheme 8 and the procedures described in Example 8. Characterization data for compounds **32-37** are shown in Table 8b.

Scheme 8

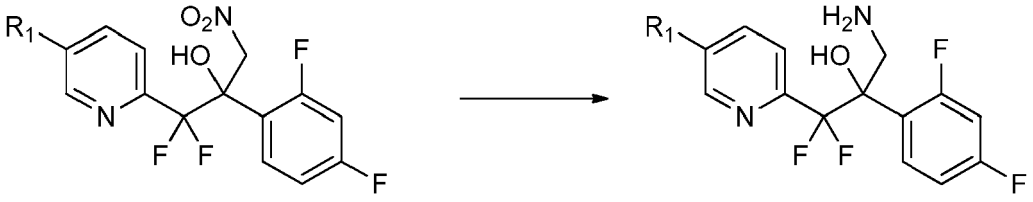
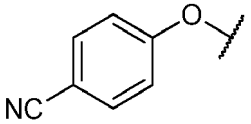


Table 8a

Compound No.	R_1	Appearance	Prepared as in Example(s):
32		Faint yellow foam	Ex 8, Methods A, B and C

(continued)

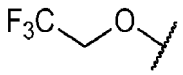
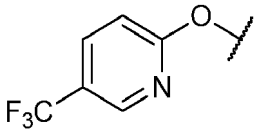
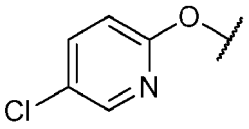
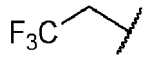
Compound No.	R_1	Appearance	Prepared as in Example(s):
33		Oil	Ex 8, Method C
34		Light brown oil	Ex 8, Method C
35		Light Yellow solid	Ex 8, Method C
36	Br	Colorless oil	Ex 8, Method A
37		Nearly white solid	Ex 8, Method C

Table 8b

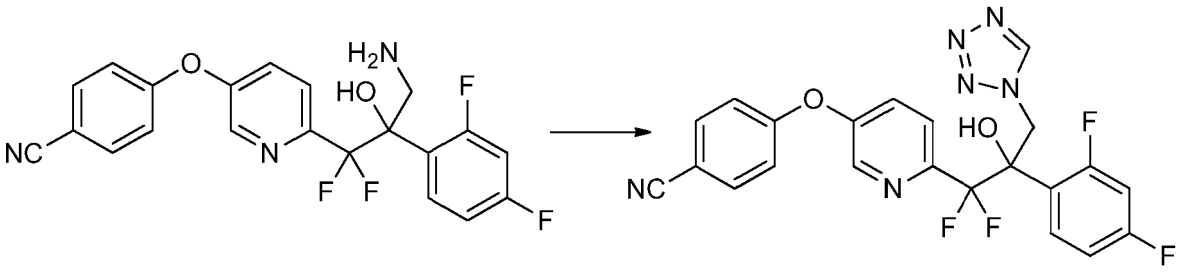
Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR (thin film) cm^{-1}
32		418 ($[M+H]^+$)	(300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.6 Hz, 1H), 7.67 (m, 2H), 7.50 (m, 1H), 7.44 (app d, *J* = 8.6 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.05 (m, 2H), 6.76 (m, 2H), 3.84 (dd, *J* = 13.7, 4.2 Hz, 1H), 3.21 (d, J = 13.5 Hz, 1H), 2.47 (br s, 2H)		3419, 3076, 2228
33			8.31 (d, *J* = 2.9 Hz, 1H), 7.50 (td, *J* = 8.7, 6.6 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.29 - 7.21 (m, 1H), 6.76 (dddd, *J* = 14.3, 11.5, 8.5, 2.6 Hz, 2H), 6.29 (s, 1H), 4.43 (q, *J* = 7.9 Hz, 2H), 3.79 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.22 (d, *J* = 13.8 Hz, 1H), 1.44 - 1.07 (m, 2H)		
34		460 ($[M-1]^-$)	8.48 (d, *J* = 2.5 Hz, 1H), 8.41 (dd, *J* = 1.6,0.8 Hz, 1H), 8.02 - 7.92 (m, 1H), 7.62 - 7.47 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.88-6.72 (m, 2H), 6.35 - 6.33 (m, 1H), 3.80 (dd, *J* = 13.7, 4.2 Hz, 1H), 3.26 (d, *J* = 13.7 Hz, 1H), 0.9 - 1.6 (br, 2H)		
35		457 ($[M]^+$)	8.45 (d, *J* = 2.7 Hz, 1H), 8.09 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.72 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.62 - 7.53 (m, 2H), 7.49 (dd, *J* = 8.6, 0.7 Hz, 1H), 6.99 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.79 (dddd, *J* = 20.5, 11.5, 8.7, 2.4 Hz, 2H), 5.30 (s, 2H), 3.83 - 3.63 (m, 1H), 3.28 (d, *J* = 12.6 Hz, 1H), 1.47 (s, 1H)		

(continued)

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR (thin film) cm^{-1}
36		379 ([M]$^+$)	8.62 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.85 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.52 - 7.41 (m, 1H), 7.30 (dd, *J* = 8.4, 0.5 Hz, 1H), 6.84 - 6.68 (m, 2H), 3.87 (dd, *J* = 13.7, 4.7 Hz, 1H), 3.19 (d, *J* = 13.7 Hz, 1H), 1.0 - 1.9 (br, 2H), 0.8 - 0.9 (br, 1H)	^{19}F NMR (376 MHz, $CDCl_3$) δ - 106.15 (ddd, *J* = 23.2, 15.0, 8.3 Hz), -109.39 (dd, *J* = 252.1, 23.3 Hz), -110.47 (d, *J* = 8.8 Hz), - 110.99 (dd, *J* = 252.2, 14.9 Hz)	
37		383 ([M+H]$^+$)	8.53 - 8.49 (m, 1H), 7.69 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.55 - 7.41 (m, 2H), 6.82 - 6.70 (m, 2H), 3.80 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.43 (q, *J* = 10.5 Hz, 2H), 3.23 (dq, *J* = 13.8, 1.1 Hz, 1H)	^{19}F NMR -65.75 (s, 3F), ABX: X = - 106.29 (ddd, *J* = 22.0, 15.9, 8.6 Hz, IF), B = - 109.27 (*JAB* = 254.7 Hz, *JBX* = 21.9 Hz, IF), - 110.61 (d, *J* = 8.4 Hz, IF), A = - 111.04 (*JAB* = 254.7, *JAX* = 15.9 Hz, 1F)	
[a]All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Example 9. Preparation of 4-((6-(2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxy-3-(1H-tetrazol-1-yl)propyl)pyridin-3-yl)oxy)benzonitrile (38)

[0054]



[0055] **Method A:** To a magnetically stirred solution of 4-((6-(3-amino-2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxypropyl)pyridin-3-yl)oxy)benzonitrile (0.060 g, 0.144 mmol) in acetic acid (0.288 mL) was added sodium azide (0.019 g, 0.288 mmol) and triethyl orthoformate (0.072 mL, 0.431 mmol). The reaction mixture was stirred at 90 °C for 5 h. The reaction mixture was poured into water and then made basic by addition of sat. aq. $NaHCO_3$ and the mixture extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated to give the title compound as a faint yellow oil (45 mg, 63.2%).

[0056] **Method B:** To a magnetically stirred solution of 4-((6-(3-amino-2-(2,4-difluorophenyl)-1,1-difluoro-2-hydroxypropyl)pyridin-3-yl)oxy)benzonitrile (20 mmol) in acetonitrile was added AcOH (80 mL), sodium azide (2.6 g, 40 mmol) and triethyl orthoformate (8.89 g, 60 mmol) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h and heated to 35-40 °C for 20 hours. After completion of reaction by HPLC, the reaction mixture was concentrated with additional acetonitrile and MeOH. The resulting residual oil was dissolved in MeOH (40 mL), and then the solution was charged slowly to water (300 mL) at room temperature. The precipitated solid was stirred for 2-3 h at room temperature. The suspension was filtered and washed with water. The cake was dried under vaccum at room temperature to give the title compound (9.02 g, 94%).

[0057] The following compounds **38-43** in Table 9a were made in accordance with the reaction depicted in Scheme 9 and the procedures described in Example 9. Characterization data for compounds **38-43** are shown in Table 9b.

Scheme 9

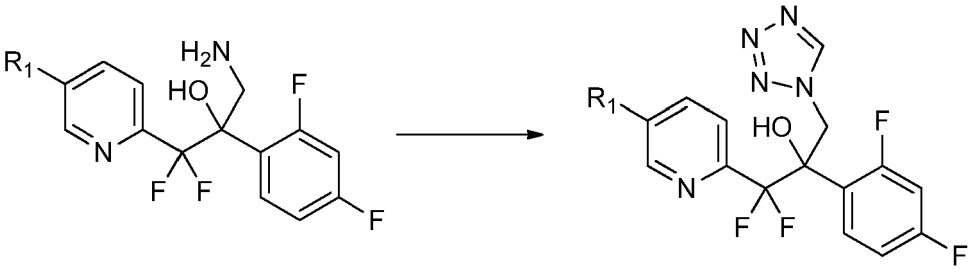


Table 9a

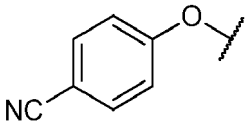
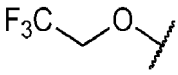
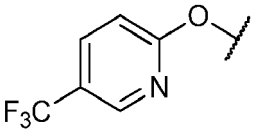
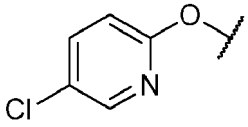
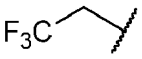
Compound No.	R_1	Appearance	Prepared as in Example(s):
38		off-white solid	Ex 9, Methods A and B
39		Foam	Ex 9, Method B
40		Pink colored foam	Ex 9, Method B
41		Dark yellow solid	Ex 9, Method B
42	Br	Light brown thick oil	Ex 9, Method A
43		Slightly yellowed glass	Ex 9, Method B

Table 9b

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR (thin film) cm^{-1}
38		469 ([M-H]$^-$)	(300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.26 (d, *J* = 2.7 Hz, 1H), 7.71 (m, 2H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.43 (m, 2H), 7.19 (s, 1H), 7.12 (m, 2H), 6.76 (m, 2H), 5.44 (d, *J* = 14.4 Hz, 1H), 5.23 (dd, *J* = 14.4, 1.5 Hz, 1H)	^{19}F NMR (376 MHz, $CDCl_3$) δ -104.05 (m), -105.67 (dd, *J* = 263.9, 20.1 Hz),-107.32 (dd, *J* = 264.1, 34.3 Hz), - 107.83 (d, *J* = 9.6 Hz)	

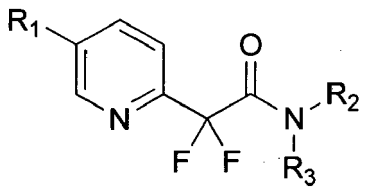
(continued)

Compound No.	Mp (°C)	ESIMS *m/z*	^{1}H NMR (δ)[a]	^{13}C NMR or ^{19}F NMR (δ)	IR (thin film) cm^{-1}
39		452 ([M+H]$^+$)	8.75 (s, 1H), 8.27 (d, *J* = 2.9 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.36 - 7.28 (m, 2H), 7.26 (s, 1H), 6.76 (ddd, *J* = 12.0, 8.5, 2.6 Hz, 1H), 6.71- 6.62 (m, 1H), 5.57 (dd, *J* = 14.3, 0.8 Hz, 1H), 5.12 (dd, *J* = 14.3, 1.5 Hz, 1H), 4.44 (q, *J* = 7.8 Hz, 2H)	^{19}F NMR (376 MHz, $CDCl_3$) δ -73.68 (m), -103.79 (dd, *J* = 263.2, 41.46 Hz), - 104.93 (m), 108.00 (d, *J* = 11.28 Hz), - 110.45 (dd, *J* = 263.2, 41.46 Hz)	
40		515 ([M+H]$^+$)	8.79 (s, 1H), 8.48 (d, *J* = 2.4 Hz, 1H), 8.41 (dd, *J* = 1.6, 0.8 Hz, 1H), 8.01 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.68 (dt, *J* = 18.4, 5.5 Hz, 2H), 7.37 (td, *J* = 8.9, 6.5 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.82 - 6.72 (m, 1H), 6.72-6.62 (m, 1H), 5.64 (d, *J* = 14.3 Hz, 1H), 5.13 (d, *J* = 14.4 Hz, 1H)		
41	61-63	480 ([M]$^+$)	8.76 (s, 1H), 8.53 - 8.39 (m, 1H), 8.09 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.71 - 7.53 (m, 2H), 7.35 (td, *J* = 8.9, 6.4 Hz, 1H), 7.02 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.77 (ddd, *J* = 12.0, 8.5, 2.6 Hz, 1H), 6.72 - 6.66 (m, 1H), 5.68 - 5.58 (m, 1H), 5.14 - 5.07 (m, 1H), 2.10 (s, 1H)		
42		432.11 ([M]$^+$)	8.76 (s, 1H), 8.63 (d, *J* = 1.4 Hz, 1H), 7.95 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.34 - 7.23 (m, 1H), 6.93 (s, 1H), 6.81 - 6.72 (m, 1H), 6.72 - 6.62 (m, 1H), 5.61 (d, *J* = 14.3 Hz, 1H), 5.12 (d, *J* = 14.8 Hz, 1H)	^{19}F NMR (376 MHz, $CDCl_3$) δ -103.52 -- 103.97 (m), -103.96 --104.40(m), - 107.62 (d, *J* = 9.7 Hz), -112.16 (dd, *J* = 263.2, 43.0 Hz)	
43		436 ([M+H]$^+$)	8.76 (s, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 7.79 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.37 - 7.28 (m, 2H), 6.76 (ddd, *J* = 12.1, 8.5, 2.6 Hz, 1H), 6.65 (dddd, *J* = 8.7, 7.5, 2.6, 0.9 Hz, 1H), 5.59 (dd, *J* = 14.3, 0.9 Hz, 1H), 5.13 (dd, *J* = 14.1, 1.4 Hz, 1H), 3.45 (q, *J* = 10.3 Hz, 2H)	^{19}F NMR (376 MHz, $CDCl_3$) δ -65.61 (s, 3F), ABX: X= - 103.93 (ddd, *JAX* = 41.9 Hz, *JAB* = 15.4, 9.8 Hz, IF), B = - 104.75 (*JAB* = 262.9 Hz, *JBX* = 15.5 Hz, IF), -107.91 (d, *J* = 9.7 Hz, IF), A = - 111.65 (*JAB* = 262.9 Hz, *JAX* = 41.6 Hz, 1F)	
[a]All ^{1}H NMR data measured in $CDCl_3$ at 400 MHz unless otherwise noted					

Claims

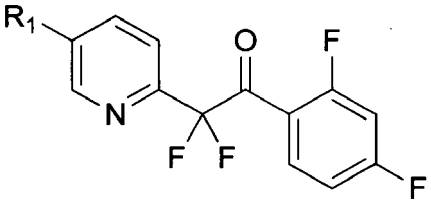
1. A method of making compounds of Formula III, or salts thereof, including the step of:

contacting compounds of Formula IIa with a preformed organometallic reagent,



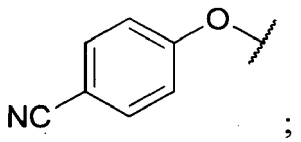
(IIa)

to afford compounds of Formula III, or salts thereof;



(III)

wherein R_1 is



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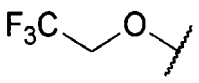

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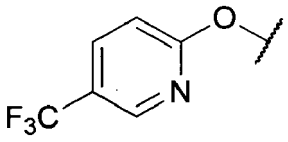

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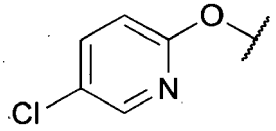

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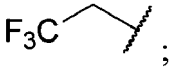


;

or Br;

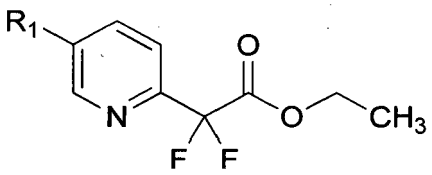
wherein R_2 and R_3 are selected from $-OCH_3$, $-CH_3$, $-CH_2CH_3$ or joined together to form a morpholine ring; preferably

wherein the preformed organometallic reagent is formed by a metal halogen exchange reaction of 1-bromo-2,4-difluorobenzene with one of magnesium, *n*-butyllithium, and isopropylmagnesium chloride; or

wherein the step of contacting compounds of Formula IIa with the preformed organometallic reagent further includes an aprotic solvent; or

wherein the aprotic solvent is one of diethyl ether and tetrahydrofuran; or wherein the step of contacting compounds of Formula IIa with the preformed organometallic reagent is carried out at 0°C.

2. The method of claim 1, further comprising the step of:
contacting compounds of Formula II with an amine, a Lewis acid, and a solvent

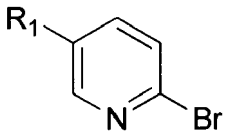


(II);

to afford compounds of Formula IIa; preferably
wherein the amine is selected from *N*,*O*-dimethylhydroxylamine, dimethylamine, diethylamine and morpholine; or
wherein the Lewis acid is dimethylaluminum chloride; or
wherein the solvent is dichloromethane; or
wherein the step of contacting compounds of Formula II with the amine, the Lewis acid, and the solvent is carried out in such a manner as to maintain a temperature below 15°C.

3. The method of claim 2, further comprising the step of:

contacting compounds of the Formula I with ethyl 2-bromo-2,2-difluoroacetate and a metal,



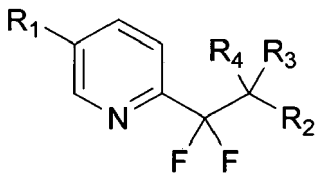
(I);

to afford compounds of Formula II; preferably
wherein the metal is copper; or
wherein the step of contacting I with ethyl 2-bromo-2,2-difluoroacetate and a metal further includes a solvent; or
wherein the step of contacting I with ethyl 2-bromo-2,2-difluoroacetate and a metal further includes a solvent selected from dimethyl sulfoxide, dimethylformamide, and mixtures thereof.

4. The method of claim 3, further comprising the step of:

contacting 6-bromopyridin-3-ol with one of 2,2,2-trifluoroethyl trifluoromethanesulfonate, 5-chloro-2-fluoropyridine and 2-fluoro-5-(trifluoromethyl)pyridine to afford compounds of Formula I; preferably
wherein the step of contacting 6-bromopyridin-3-ol with one of 5-chloro-2-fluoropyridine and 2-fluoro-5-(trifluoromethyl)pyridine further includes a base; or
wherein the step of contacting 6-bromopyridin-3-ol with one of 5-chloro-2-fluoropyridine and 2-fluoro-5-(trifluoromethyl)pyridine further includes a base that is one of cesium carbonate and potassium carbonate; or
wherein the step of contacting 6-bromopyridin-3-ol with one of 5-chloro-2-fluoropyridine and 2-fluoro-5-(trifluoromethyl)pyridine further includes a solvent; or
wherein the step of contacting 6-bromopyridin-3-ol with one of 5-chloro-2-fluoropyridine and 2-fluoro-5-(trifluoromethyl)pyridine further includes a solvent that is one of dimethyl sulfoxide and dimethylformamide; or
wherein the step of contacting 6-bromopyridin-3-ol with one of 5-chloro-2-fluoropyridine and 2-fluoro-5-(trifluoromethyl)pyridine is carried out between 65°C and 100 °C.

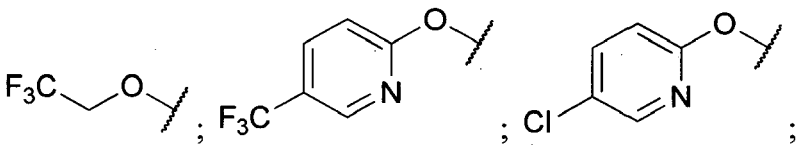
5. A compound of Formula VII or salt thereof:



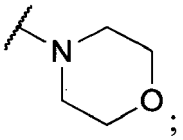
(VII)

wherein

R_1 is



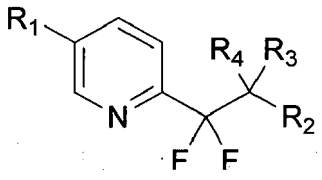
or Br;
R_2 is ethoxy; 2,4-difluorophenyl; -N(OCH_3)(CH_3); -N(CH_3)(CH_3); - N(CH_2CH_3)(CH_2CH_3); or



R_3 is -OH;
R_4 is nitromethyl or aminomethyl;

alternatively R_3 and R_4 may be taken together to form a carbonyl.

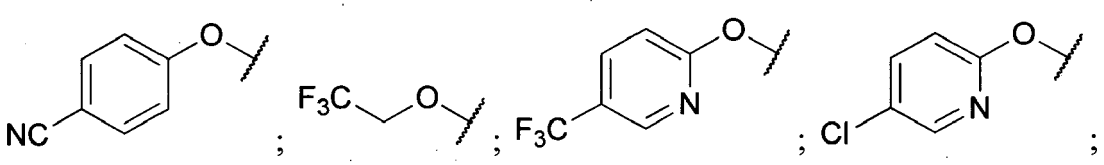
6. A compound of Formula VII or salt thereof:

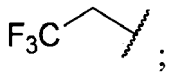


(VII)

wherein

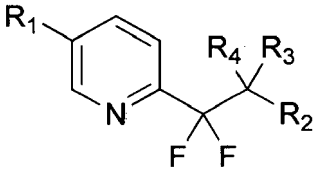
R_1 is





or Br;
R_2 is 2,4-difluorophenyl;
R_3 is -OH;
R_4 is nitromethyl or aminomethyl.

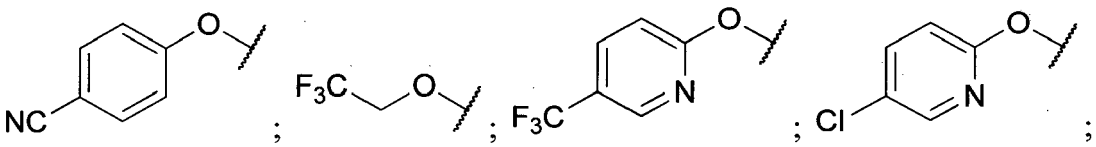
7. A compound of Formula VII or salt thereof:

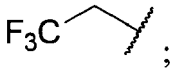


(VII)

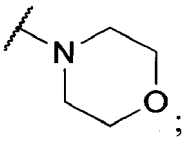
wherein

R_1 is



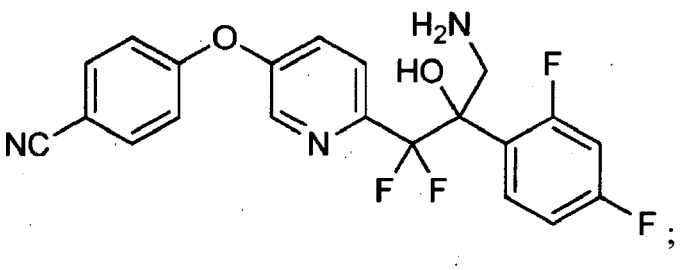


or Br;
R_2 is -N(OCH_3)(CH_3); -N(CH_3)(CH_3); -N(CH_2CH_3)(CH_2CH_3); or



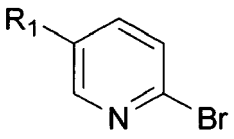
and
R_3 and R_4 are taken together to form a carbonyl.

8. A compound selected from:



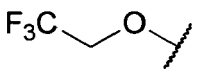
and salts thereof.

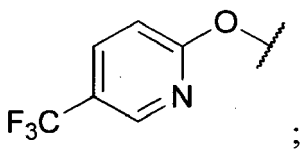
9. A compound of Formula VIII or salt thereof:



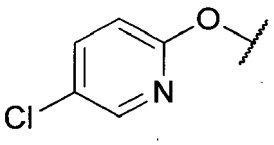
(VIII)

wherein
R_1 is





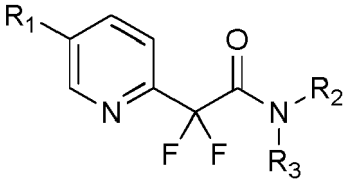
or



Patentansprüche

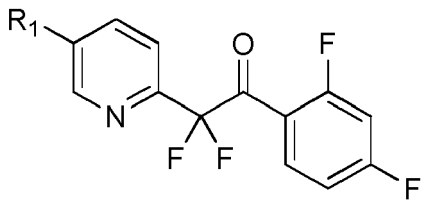
1. Verfahren zur Herstellung von Verbindungen der Formel III oder von Salzen davon, umfassend die folgenden Stufen:

das Inkontaktbringen von Verbindungen der Formel IIa mit einem zuvor gebildeten organometallischen Reagens,



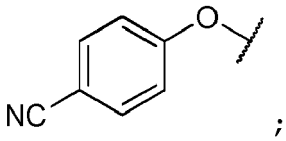
(IIa)

um Verbindungen der Formel III oder Salze davon zu ergeben;



(III)

wobei gilt: R_1 ist



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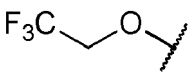

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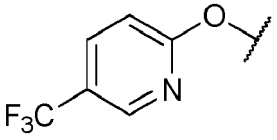

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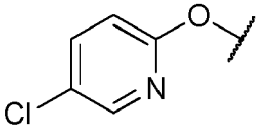

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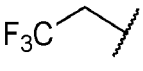
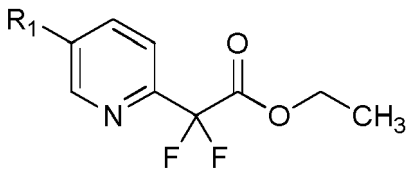


;

oder Br;
wobei gilt: R_2 und R_3 sind ausgewählt aus $-OCH_3$, $-CH_3$, $-CH_2CH_3$ oder sind miteinander verbunden, um einen Morpholinring zu bilden; bevorzugt
wobei gilt: das zuvor gebildete organometallische Reagens ist gebildet durch eine Metallhalogenaustauschreaktion von 1-Brom-2,4-difluorbenzol mit einem von Magnesium, n-Butyllithium und Isopropylmagnesiumchlorid; oder
wobei gilt: die Stufe des Inkontaktbringens von Verbindungen der Formel IIa mit dem zuvor gebildeten organometallischen Reagens umfasst des Weiteren ein aprotisches Lösungsmittel; oder
wobei gilt: das aprotische Lösungsmittel ist eines von Diethylether und Tetrahydrofuran; oder
wobei gilt: die Stufe des Inkontaktbringens von Verbindungen der Formel IIa mit dem zuvor gebildeten organometallischen Reagens wird bei 0°C durchgeführt.

2. Verfahren nach Anspruch 1, des Weiteren umfassend die folgende Stufe:

das Inkontaktbringen der Formel II mit einem Amin, einer Lewis-Säure und einem Lösungsmittel

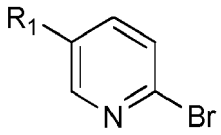


(II);

um Verbindungen der Formel IIa zu ergeben; bevorzugt
wobei gilt: das Amin ist ausgewählt aus *N*,*O*-Dimethylhydroxylamin, Dimethylamin, Diethylamin und Morpholin; oder
wobei gilt: die Lewis-Säure ist Dimethylaluminiumchlorid; oder
wobei gilt: das Lösungsmittel ist Dichlormethan; oder
wobei gilt: die Stufe des Inkontaktbringens von Verbindungen der Formen II mit dem Amin, der Lewis-Säure und dem Lösungsmittel wird durchgeführt in einer solchen Weise, dass die Temperatur unterhalb von 15°C gehalten wird.

3. Verfahren nach Anspruch 2, des Weiteren umfassend die folgende Stufe:

das Inkontaktbringen von Verbindungen der Formel I mit Ethyl-2-brom-2,2-difluoracetat und einem Metall,



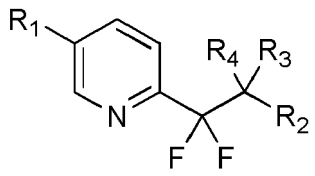
(I);

um Verbindungen der Formel II zu ergeben; bevorzugt
wobei gilt: das Metall ist Kupfer; oder
wobei gilt: die Stufe des Inkontaktbringens von I mit Ethyl-2-brom-2,2-difluoracetat und einem Metall umfasst des Weiteren ein Lösungsmittel; oder
wobei gilt: die Stufe des Inkontaktbringens von I mit Ethyl-2-brom-2,2-difluoracetat und einem Metall umfasst des Weiteren ein Lösungsmittel, ausgewählt aus Dimethylsulfoxid, Dimethylformamid und Gemischen davon.

4. Verfahren nach Anspruch 3, des Weiteren umfassend die folgende Stufe:

das Inkontaktbringen von 6-Brompyridin-3-ol mit einem von 2,2,2-Trifluorethyltrifluormethansulfonat, 5-Chlor-2-fluorpyridin und 2-Fluor-5-(trifluormethyl)pyridin, um Verbindungen der Formel I zu ergeben; bevorzugt
wobei gilt: die Stufe des Inkontaktbringens von 6-Brompyridin-3-ol mit einem von 5-Chlor-2-fluorpyridin und 2-Fluor-5-(trifluormethyl)pyridin umfasst des Weiteren eine Base; oder
wobei gilt: die Stufe des Inkontaktbringens von 6-Brompyridin-3-ol mit einem von 5-Chlor-2-fluorpyridin und 2-Fluor-5-(trifluormethyl)pyridin umfasst des Weiteren eine Base, die eines von Cäsiumcarbonat und Kaliumcarbonat ist; oder
wobei gilt: die Stufe des Inkontaktbringens von 6-Brompyridin-3-ol mit einem von 5-Chlor-2-fluorpyridin und 2-Fluor-5-(trifluormethyl)pyridin umfasst des Weiteren ein Lösungsmittel; oder
wobei gilt: die Stufe des Inkontaktbringens von 6-Brompyridin-3-ol mit einem von 5-Chlor-2-fluorpyridin und 2-Fluor-5-(trifluormethyl)pyridin umfasst des Weiteren ein Lösungsmittel, das eines von Dimethylsulfoxid und Dimethylformamid ist; oder
wobei gilt: die Stufe des Inkontaktbringens von 6-Brompyridin-3-ol mit einem von 5-Chlor-2-fluorpyridin und 2-Fluor-5-(trifluormethyl)pyridin wird durchgeführt zwischen 65°C und 100°C.

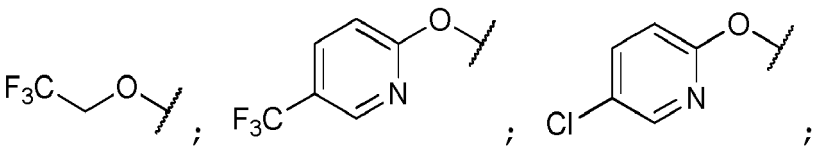
5. Verbindung der Formel VII oder Salz davon:



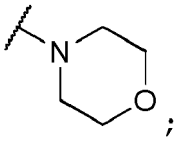
(VII)

wobei gilt:

R_1 ist

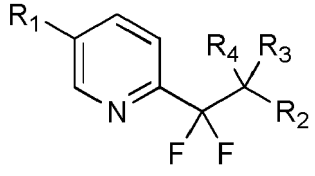


oder Br;
R_2 ist Ethoxy; 2,4-Difluorphenyl; -N(OCH_3)(CH_3); -N(CH_3)(CH_3); -N(CH_2CH_3)(CH_2CH_3); oder



R_3 ist -OH;
R_4 ist Nitromethyl oder Aminomethyl;
alternative können R_3 uand R_4 zusammengenommen sein, um ein Carbonyl zu bilden;

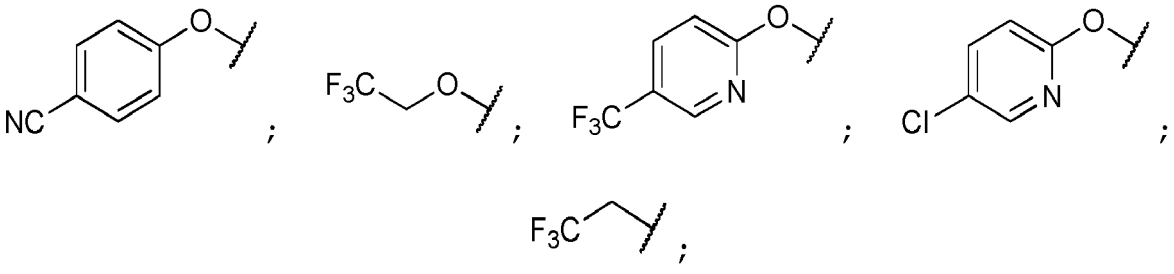
6. Verbindung der Formel VII oder Salz davon:



(VII)

wobei gilt:

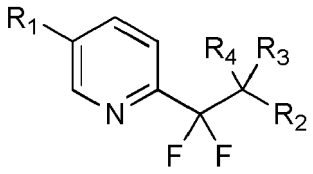
R_1 ist



oder Br;

R_2 ist 2,4-Ddifluorphenyl;
R_3 ist -OH;
R_4 ist Nitromethyl oder Aminomethyl.

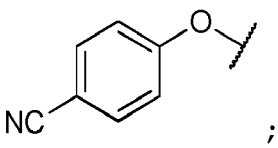
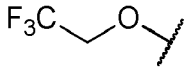
7. Verbindung der Formel VII oder Salz davon:



(VII)

wobei gilt:

R_1 ist


;

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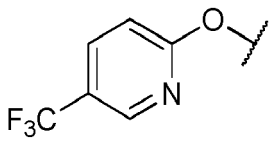
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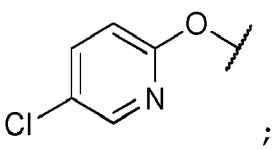
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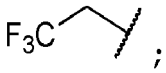
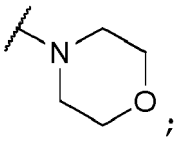
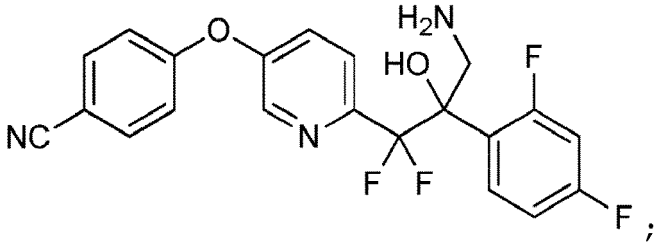

;

oder Br;
R_2 ist -N(OCH_3)(CH_3); -N (CH_3)(CH_3); -N (CH_2CH_3)(CH_2CH_3); oder


;

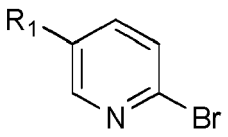
und
R_3 und R_4 sind zusammengenommen, um ein Carbonyl zu bilden.

8. Verbindung ausgewählt aus:


;

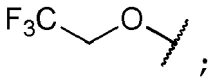
und Salze davon.

9. Verbindung der Formel VIII oder Salz davon:

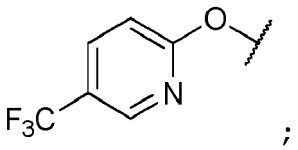


(VIII)

wobei gilt:
R_1 ist

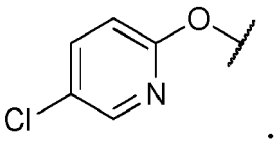


;



;

oder

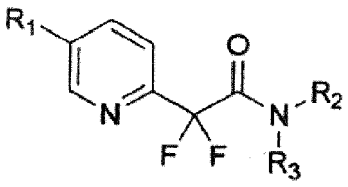


.

Revendications

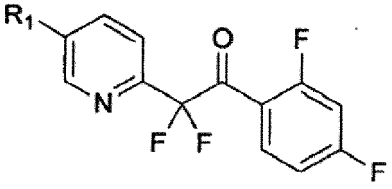
1. Procédé de préparation de composés de formule III, ou de leurs sels, comprenant l'étape consistant à :

mettre en contact des composés de formule IIa avec un réactif organométallique préformé,



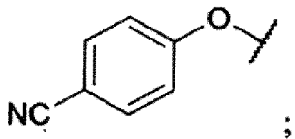
(IIa)

pour obtenir des composés de Formule III, ou des sels de ceux-ci ;



(III)

dans lequel R_1 représente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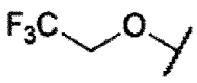
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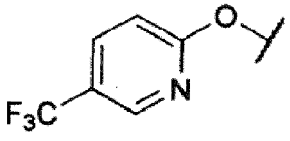
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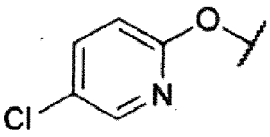
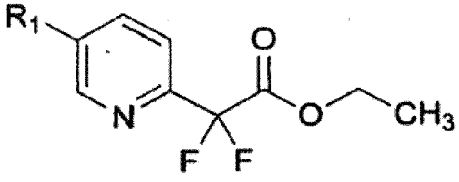

;


;

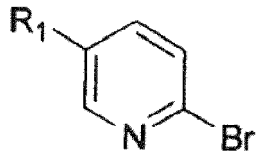
ou Br;
où R_2 et R_3 sont choisis parmi $-OCH_3$, $-CH_3$, $-CH_2CH_3$ ou sont reliés ensemble pour former un cycle morpholine ; de préférence
dans lequel le réactif organométallique préformé est formé par une réaction d'échange d'halogène métallique de 1-bromo-2,4-difluorobenzène avec un des éléments suivants : magnésium, n-butyllithium et chlorure d'isopropylmagnésium ; ou
dans lequel l'étape consistant à mettre en contact des composés de formule IIa avec le réactif organométallique préformé comprend en outre un solvant aprotique ; ou
dans lequel le solvant aprotique est un des éléments suivants : éther diéthylique et tétrahydrofuranne ; ou
dans lequel l'étape consistant à mettre en contact des composés de formule IIa avec le réactif organométallique préformé est effectuée à 0 °C.

2. Procédé selon la revendication 1, comprenant en outre l'étape consistant à mettre en contact des composés de formule II avec une amine, un acide de Lewis et un solvant


(II);

pour obtenir des composés de formule IIa ; de préférence
dans lequel l'amine est choisie parmi la *N*, *O*-diméthylhydroxylamine, la diméthylamine, la diéthylamine et la morpholine ; ou
dans lequel l'acide de Lewis est le chlorure de diméthylaluminium ; ou
dans lequel le solvant est le dichlorométhane ; ou
dans lequel l'étape consistant à mettre en contact des composés de formule II avec l'amine, l'acide de Lewis et le solvant est effectuée de manière à maintenir une température inférieure à 15° C.

3. Procédé selon la revendication 2, comprenant en outre l'étape consistant à mettre en contact des composés de formule I avec du 2-bromo-2,2-difluoroacétate d'éthyle et un métal,



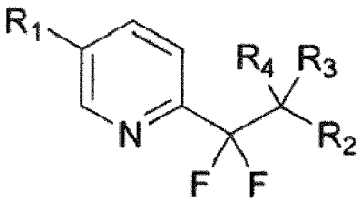
(I);

pour obtenir des composés de formule II ; de préférence où le métal est du cuivre ; ou
dans lequel l'étape consistant à mettre en contact I avec du 2-bromo-2,2-difluoroacétate d'éthyle et un métal comprend en outre un solvant ; ou
dans lequel l'étape consistant à mettre en contact I avec du 2-bromo-2,2-difluoroacétate d'éthyle et un métal comprend en outre un solvant choisi parmi le diméthylsulfoxyde, le diméthylformamide et leurs mélanges.

4. Procédé selon la revendication 3, comprenant en outre l'étape consistant à :

mettre en contact du 6-bromopyridin-3-ol avec un des éléments suivants : 2,2,2-trifluoroéthyl trifluorométhanesulfonate, 5-chloro-2-fluoropyridine et 2-fluoro-5-(trifluorométhyl)pyridine pour obtenir des composés de formule I ; de préférence
dans lequel l'étape consistant à mettre en contact du 6-bromopyridin-3-ol avec un des éléments suivants : 5-chloro-2-fluoropyridine et 2-fluoro-5-(trifluorométhyl)pyridine, comprend en outre une base ; ou
dans lequel l'étape consistant à mettre en contact du 6-bromopyridin-3-ol avec un des éléments suivants : 5-chloro-2-fluoropyridine et 2-fluoro-5-(trifluorométhyl)pyridine, comprend en outre une base qui est un des éléments suivants : carbonate de césium et carbonate de potassium ; ou
dans lequel l'étape consistant à mettre en contact du 6-bromopyridin-3-ol avec un des éléments suivants : 5-chloro-2-fluoropyridine et 2-fluoro-5-(trifluorométhyl)pyridine, comprend en outre un solvant ; ou
dans lequel l'étape consistant à mettre en contact du 6-bromopyridin-3-ol avec un des éléments suivants : 5-chloro-2-fluoropyridine et 2-fluoro-5-(trifluorométhyl)pyridine, comprend en outre un solvant qui est un des éléments suivants : diméthylsulfoxyde et diméthylformamide ; ou
dans lequel l'étape consistant à mettre en contact du 6-bromopyridin-3-ol avec un des éléments suivants : 5-chloro-2-fluoropyridine et 2-fluoro-5-(trifluorométhyl)pyridine est effectuée entre 65 °C et 100 °C.

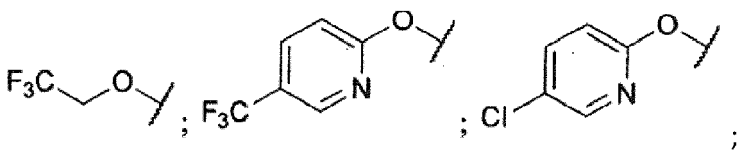
5. Composé de formule VII ou un de ses sels :



(VII)

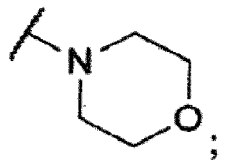
dans lequel

R_1 représente



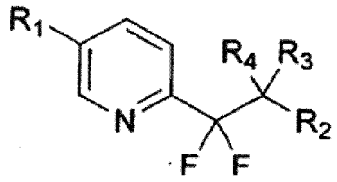
;

ou Br ;
R_2 représente un groupe éthoxy; 2,4-difluorophényl ; -N(OCH_3)(CH_3) ; - N(CH_3)(CH_3); -N(CH_2CH_3)(CH_2CH_3); ou



R_3 représente -OH ;
R_4 représente un nitrométhyle ou un aminométhyle ; alternativement R_3 et R_4 peuvent être pris ensemble pour former un carbonyle.

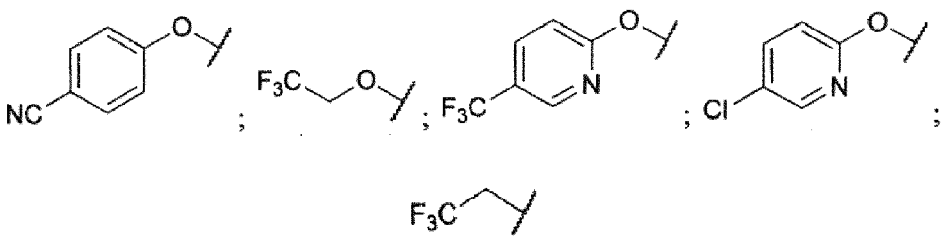
6. Composé de formule VII ou un de ses sels :



(VII)

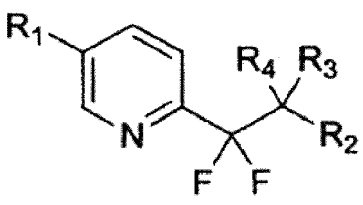
dans lequel

R_1 représente



ou Br ;
R_2 représente le 2,4-difluorophényle ;
R_3 représente -OH ;
R_4 représente un groupe nitrométhyle ou aminométhyle.

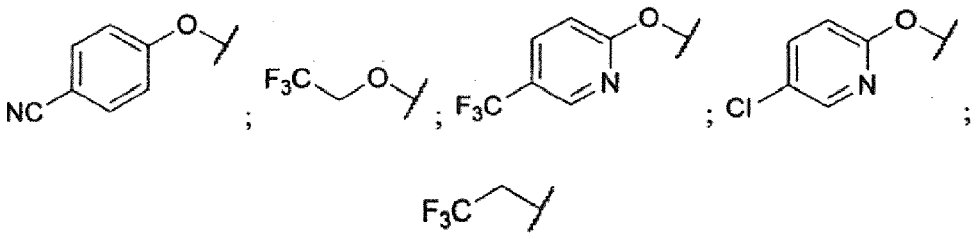
7. Composé de formule VII ou un de ses sels :



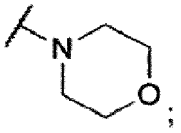
(VII)

dans lequel

R_1 représente

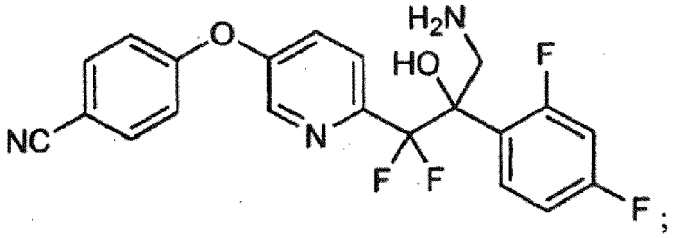


ou Br ;
R_2 représente -N(OCH_3)(CH_3); -N(CH_3)(CH_3); -N(CH_2CH_3)(CH_2CH_3); ou



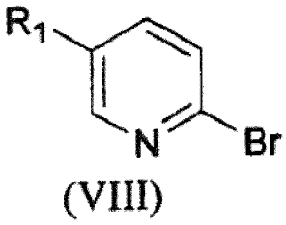
et
R_3 et R_4 sont pris ensemble pour former un carbonyle.

8. Composé choisi parmi :



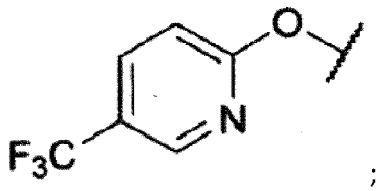
et ses sels.

9. Composé de formule VIII ou un de ses sels :



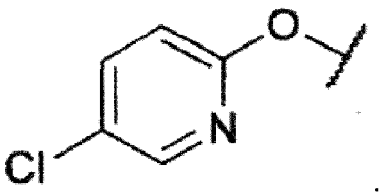
(VIII)

dans lequel
R_1 représente



;

ou



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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2014193974 A1 **[0002]**
- WO 2013110002 A1 **[0002]**
- US 527387 **[0002]**
- US 13527426 B **[0002]**
- US 13528283 B **[0002]**