Supporting Information

for

Novel Approach toward 3,3-Difluoropiperidines from Easily Available Starting Materials

and Synthesis of a New Phosphodiesterase Inhibitor

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General Experimental Procedures

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Commercially available dehydrated solvents, dimethyl sulfoxide (DMSO), dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), diethyl ether (Et₂O), ethyl acetate (EtOAc), methanol (MeOH), and acetic acid (AcOH) were used. Other all reagents were used as obtained from commercial sources. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 30°C unless otherwise stated. HRMS data were acquired with a Bruker Daltonic MicroTOF with internal calibration using ESI in the positive mode. NMR data were collected with a Bruker 600-Avance-III spectrometer equipped with a 5 mm TCI cryoprobe operating at 600 and 151 MHz for 1H and 13C, respectively. 19F NMR spectra were recorded with a Bruker 500-Avance spectrometer equipped with a 5 mm QNP probe operating at 470.6 Hz, using CFCl₃ as reference. The solvents used for NMR were CDCl₃, with reference signals for CHCl₃ (δ = 7.26 ppm, 1H) and (δ = 77.16 ppm, 13C), and DMSO-d₆ with the reference signals for residual DMSO (δ = 2.50 ppm, 1H) and (δ = 39.51 ppm, 13C) using TMS as internal reference. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) the number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), (3) and the coupling constant (J) quoted in hertz to the nearest 0.1 Hz. All compounds given below bear the same formula numbers as used in the main text.

Ethyl 4-cyano-2,2-difluorobutanoate (3)

To a stirred mixture of copper (5.03 g, 79 mmol), acrylonitrile (2 g, 37.7 mmol), and ethyl 2-bromo-2,2-difluoroacetate (8.7 mL, 67.9 mmol) in tetrahydrofuran (64.0 mL) was added at room temperature tetramethylethylenediamine (2.9 mL) and acetic acid (1.9 mL) in sequence. The mixture was stirred for 1 hour at room temperature, and then was filtered over celite using Et₂O as eluent. Saturated ammonium chloride solution was added to the mixture and the product was extracted with Et₂O (50 mL). The organic phase was washed several times with a saturated solution in water of ammonium chloride and bicarbonate to remove the last traces of copper salts. Then the organic layer was washed the last time with a saturated solution of NaCl. The product was purified using silica gel chromatography, heptane:EtOAc from 100:0 to 50:50 to yield the desired product (5.8 g, 37.7 mmol, 87% yield).

1H NMR (600 MHz, CDCl₃) δ: 4.37 (2H, q, J = 7.0 Hz), 2.68-2.58 (2H, m), 2.56-2.39 (2H, m), 1.38 (3H, t, J = 7.2 Hz).

13C NMR (151 MHz, CDCl₃) δ: 162.9 (C, t, J = 31.9 Hz), 118.1 (C, s), 114.6 (C, t, J = 252.4 Hz), 63.4 (CH₂, s), 30.8 (CH₂, t, J = 6.0 Hz).

The compound was already reported in literature.¹

General procedures addition of organolithium reagents to ethyl 4-cyano-2,2-difluorobutanoate (3)

General procedure A

To a solution of ethyl 4-cyano-2,2-difluorobutanoate (3) (1 equivalent, 0.3M) in Et₂O was added dropwise a solution of commercial available organolithium (1.1 equivalent) at -78°C. After 2h the reaction was quenched with a aqueous saturated solution of ammonium chloride, EtOAc was added and the phases were separated. The aqueous phase was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and purified using silica gel chromatography to provide the desired product.

General procedure B

To a solution of the bromoaryl compound (1.5 equivalent, 0.3M) in Et₂O and tetrahydrofuran (1:1) at -78°C was added dropwise n-BuLi 1.6M in hexane (1.4 equivalent). The formation of the organolithium species is followed by 1H-NMR. To the resulting solution, compound 3 (1eq, 1M) in Et₂O was added dropwise at -78°C. The mixture stirred at -78°C until full conversion of the starting material following the reaction by 1H-NMR and LC-MS. The reaction was quenched with a aqueous saturated solution of ammonium chloride, EtOAc was added and the phases were separated. The aqueous phase was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and purified using silica gel chromatography to provide the desired product.

General procedure C

To a solution of the bromo-etheroaryl compound (1.5 equivalent, 0.3M) in Et₂O and tetrahydrofuran (1:1) at -78°C was added dropwise n-BuLi 1.6 M in hexane (1.4 equivalent). The formation of the organolithium species is followed by 1H-NMR. To the resulting solution, compound 3 (1eq, 1M) in Et₂O was added dropwise at -78°C. The mixture stirred at -78°C until full conversion of the starting material following the reaction by 1H-NMR and LC-MS. The reaction was quenched with a aqueous saturated solution of ammonium chloride, EtOAc was added and the phases were separated. The aqueous phase was further extracted with EtOAc (2 x 5 mL). The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and purified using silica gel chromatography to provide the desired product.
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4,4-difluoro-5-oxo-5-phenylpentanenitrile (5a)

Using general procedure A: to a solution of 3 (1 g, 5.56 mmol, 0.3 M) in Et₂O, was added dropwise phenyl lithium (3.45 mL, 6.21 mmol, 1.8 molar in n-dibutyl ether) at -78°C.

The crude residue was purified by flash column chromatography (heptane:EtOAc) from 100:0 to 50:50, to yield product 5a as a yellow oil (1.51 g, 5.02 mmol, 89% yield).

1H NMR (CDCl₃, 600 MHz) δ: 8.17-8.12 (2H, m), 7.69-7.66 (1H, m), 7.54-7.51 (2H, m), 2.71 -2.68 (2H, m), 2.66-2.58 (2H, m).

19F NMR (CDCl₃, 471 MHz) δ: -101.1 (t, J = 16.0 Hz).

13C NMR (CDCl₃, 151 MHz) δ: 187.8 (C, t, J = 31.6 Hz), 135.0 (CH, s), 131.4 (C, t, J = 3.3 Hz), 130.4 (CH, t, J = 3.4 Hz), 128.9 (CH, s), 118.1 (C, s), 120.0-116.0 (CF₂, t, J = 255.8 Hz), 30.0-29.6 (CH₂, t, J = 23.5 Hz), 10.7-10.5 (CH₂, t, J = 6.7 Hz).

4,4-difluoro-5-(4-fluorophenyl)-5-oxopentanenitrile (5b)

Using general procedure B: to a solution of 1-bromo-4-fluorobenzene (741 mg, 0.465 mL, 4.23 mmol, 0.3M) in Et₂O and THF (1:1) at -78°C added dropwise n-BuLi (2.47 mL, 3.95 mmol, 1.6 molar in hexane). After the generation of the organolithium species, a solution of 3 (500 mg, 2.82 mmol, 1M)  in Et₂O was added.

The crude residue was purified by flash column chromatography (heptane:EtOAc) from 100:0 to 50:50 to yield the desired product as a yellow oil 4,4-difluoro-5-(4-fluorophenyl)-5-oxopentanenitrile (520 mg, 2.289 mmol, 81 % yield).

1H NMR (CDCl₃, 600 MHz) δ: 8.19-8.14 (2H, m), 7.22-7.18 (2H, t, J = 8.54 Hz), 2.72-2.56 (4H, m).

19F NMR (CDCl₃, 471 MHz) δ: -100.7 (t, J = 16.5 Hz), -101.3 (m).

13C NMR (CDCl₃, 151 MHz) δ: 186.3 (C, s), 166.77 (C, d, J = 258.8 Hz), 133.5 (CH, dt, J = 9.8, 3.3 Hz), 127.7 (C, s), 120.1-116.0 (CF₂, t, J = 255.8 Hz), 118.0 (C, s), 116.5 (CH, d, J = 22.0 Hz), 30.3-29.8 (CH₂, t, J = 23.7 Hz), 10.8-10.5 (CH₂, t, J = 6.7 Hz).

5-(4-(benzyloxy)phenyl)-4,4-difluoro-5-oxopentanenitrile (5c)

Using general procedure B: to a solution of 1-(benzyloxy)-4-bromobenzene (510 µL, 2.66 mmol, 0.3M) in Et₂O and THF (1:1) at -78°C added dropwise n-BuLi (1.8 mL, 2.90 mmol, 1.6 molar in hexane). After the generation of the organolithium reagent a solution of 3 (400 mg, 2.258 mmol, 1M)  in Et₂O was added.

The crude residue was purified by flash column chromatography (heptane:EtOAc) from 100:0 to 50:50, to yield the desired product as a yellow oil (700 mg, 2.258 mmol, 72% yield).

1H NMR (CDCl₃, 600 MHz) δ: 8.12-8.08 (2H, d, J = 8.94 Hz), 7.44-7.34 (5H, m), 7.06-7.03 (2H, d, J = 9.02 Hz), 5.16 (2H, s); 2.70-2.66 (2H, m), 2.64-2.56 (2H, m).

19F NMR (CDCl₃, 471 MHz) δ: -100.6 (t, J = 16.2 Hz).

13C NMR (CDCl₃, 151 MHz) δ: 184.6 (C, s), 164.1 (C, s), 135.7 (C, s), 133.0 (CH, s), 128.8 (CH, s), 128.5 (CH, s), 127.5 (CH, s), 124.2 (C, s), 120.1-115.4 (CF₂, t, J = 253.2 Hz), 115.0 (CH, s), 70.3 (CH₂, s), 30.2-29.6 (CH₂, t, J = 23.8 Hz), 10.8-10.5 (CH₂, t, J = 6.5 Hz).
4,4-difluoro-5-(1-methyl-1H-pyrazol-4-yl)-5-oxopentanenitrile (5d)

Using general procedure C: to a solution of 4-bromo-1-methyl-1H-pyrazole (136 mg, 847 µmol, 0.3 M) in Et₂O and THF (1:1) at -95°C added dropwise n-BuLi (600 µL, 960 µmol, 1.6 molar in hexane). After the generation of the organolithium reagent a solution of 3 (100 mg, 564 µmol, 1 M) in Et₂O was added. The crude residue was purified by flash column chromatography AcOEt: AcOEt/MeOH/Et₃N (85/10/5) from 100:0 to 80:20 to yield the desired product as a yellow oil (77 mg, 0.36 mmol, 64% yield).

**1H NMR** (CDCl₃, 600 MHz) δ: 8.08 (1H, s), 8.07 (1H, s), 3.98 (3H, s), 2.64-2.68 (2H, t, J = 7.47 Hz), 2.50-2.60 (2H, m).

**19F NMR** (CDCl₃, 471 MHz) δ: -102.1 (t, J = 16.6 Hz).

**13C NMR** (CDCl₃, 151 MHz) δ: 182.0-182.6 (C, t, J = 32.1 Hz), 142.1-142.2 (CH, t, J = 2.8 Hz), 134.9-135.0 (CH, t, J = 2.8 Hz), 115.5-119.0 (CF₂, t, J = 253.0 Hz), 118.0 (C, s), 117.0 (C, t, J = 2.3 Hz), 39.6 (CH₃, s), 29.1-29.5 (CH₂, t, J = 23.6 Hz), 10.5-10.6 (CH₂, t, J = 5.9 Hz).

4,4-difluoro-5-oxohexanenitrile (5e)

Using general procedure A: To a solution of 3 (120 mg, 0.680 mmol, 0.3 M) in Et₂O was added dropwise methyllithium (250 µL, 0.748 mmol, 3 molar in diethoxymethane) at -78°C. After the quenching with a saturated solution of NH₄Cl, the reaction was extracted with Et₂O, the organic phases gently concentrated in vacuum. The product was not purified but used directly in the next step.

**1H NMR** (600 MHz, CDCl₃) δ: 2.62-2.59 (m, 2H), 2.45-2.36 (m, 2H), 2.38 (t, J = 1.6 Hz, 3H).

**19F NMR** (CDCl₃, 471 MHz) δ: -108.3 (t, J = 16.5 Hz).

**13C NMR** (151 MHz, CDCl₃) δ: 197.25 (C, t, J = 32.7 Hz), 117.86 (C, s, 1C), 115.74 (CF₂, t, J = 253.7 Hz), 28.19 (CH₂, t, J = 23.5 Hz, 11C), 23.45 (CH₃, s), 10.33 (CH₂, t, J = 6.0 Hz).

4,4-difluoro-5-oxo-5-(thiophen-2-yl)pentanenitrile (5f)

Using general procedure A: to a solution of 3 (500 mg, 2.82 mmol, 0.3 M) in Et₂O, was added dropwise 2-thienyllithium (3.10 ml, 3.10 mmol, 1 molar in THF) at -78°C. The crude residue was purified by flash column chromatography (heptane:EtOAc) from 100:0 to 0:100, to yield the expected product as an oil (528 mg, 2.453 mmol, 87 % yield).

**1H NMR** (CDCl₃, 600 MHz) δ: 8.06-8.04 (1H, m), 7.86-7.85 (1H, dd, J = 1.1, 4.9 Hz), 7.25-7.22 (1H, dd, J = 3.9, 4.9 Hz), 2.67-2.68 (2H, m), 2.55-2.65 (2H, m).

**19F NMR** (CDCl₃, 471 MHz) δ: -102.5 (t, J = 16.0 Hz).

**13C NMR** (CDCl₃, 151 MHz) δ: 181.5 (C, t, J = 31.9 Hz), 137.32 (C, t, J = 3.3 Hz), 137.29 (CH, s), 136.4 (CH, t, J = 5.17 Hz), 129.1 (CH, s), 119.1-115.8 (CF₂, t, J = 255.3 Hz), 117.9 (C, s), 30.0-29.5 (CH₂, t, J = 23.1 Hz), 10.7-10.4 (CH₂, t, J = 5.94 Hz).

4,4-difluoro-5-oxo-5-(pyridin-3-yl)pentanenitrile (5g)

Using general procedure C: to a solution of 3-bromopyridine (134 mg, 847 µmol, 0.3 M) in Et₂O and THF (1:1) at -95°C added dropwise n-BuLi (600 µL, 960 µmol, 1.6 molar in hexane). After the generation of the organolithium reagent, to this a solution of 3 (100mg, 564 µmol, 1 M) in Et₂O was added. The crude residue was purified by flash column chromatography AcOEt: AcOEt/MeOH/Et₃N (85/10/5) from 100:0 to 80:20 to yield the desired product as a yellow oil (100mg, 0.564 mmol, 71% yield).

**1H NMR** (CDCl₃, 600 MHz) δ: 9.31-9.29 (1H, m), 8.88-8.86 (1H, dd, J = 1.1, 4.9 Hz), 8.40-8.35 (1H, m), 7.52-7.46 (1H, dd, J = 1.01, 4.90, 8.23 Hz), 2.74-2.69 (2H, m), 2.68-2.59 (2H, m).

**19F NMR** (CDCl₃, 471 MHz) δ: -102.5 (t, J = 16.5 Hz).

**13C NMR** (CDCl₃, 151 MHz) δ: 187.9-187.2 (C, t, J = 33.4 Hz), 155.2 (CH, s), 151.6-142.2 (CH, t, J = 4.4 Hz), 137.9-137.6 (CH, t, J = 2.8 Hz), 127.5-127.0 (C, t, J = 3.8 Hz), 123.8 (CH, s), 120.1-116.2 (CF₂, t, J = 254.6 Hz), 118.1 (CH, s), 30.0-29.0 (CH₂, t, J = 23.7 Hz), 11.0-10.6 (CH₂, t, J = 6.5 Hz).
General procedure reduction-reductive amination

General procedure D
The reactions were carried out using H-Cube Pro® (ThalesNano) continuous-flow hydrogenation system, which includes a H₂ generator and a cartridge, CartCart Raney Nickel THS01112, used as a fixed-bed reactor. This experimental set-up allows mixing the H₂ gas with the solution of the reactant and modifier under a system pressure set by a back pressure regulator, set to P= 5 bar. The compound was dissolved in Acetic Acid (0.01 M). The temperature T= 50°C and the flow rate 1mL/min. The reaction was followed by LC-MS. After full conversion of the starting material into the desired product, the solvent was removed in vacuo and the product was purified by flash column chromatography.

General procedure E
Milder condition were developed to avoid reduction of the heteroaromatics.
The reactions were carried out using H-Cube Pro® (ThalesNano) continuous-flow hydrogenation system, which includes a H₂ generator and a cartridge, CartCart Raney Nickel THS01112, used as a fixed-bed reactor. This experimental set-up allows mixing the H₂ gas with the solution of the reactant and modifier under a system pressure set by a back pressure regulator, set to P= 5 bar. The compound was dissolved in Acetic Acid (0.01 M). The temperature T= 25°C and the flow rate 1mL/min. After observed the conversion of the nitrile into the imine by LC-MS, the solvent was removed. The crude residue was dissolved in MeOH (0.2 M) and filtered on celite. The filtrate was cooled to 0°C and NaBH₄ (2eq) was added. Conversion was followed by LC-MS after conversion to the desired product the reaction was quenched with water. The inorganic phase extracted 3 times with AcOEt. The combined organic phases were dried over MgSO₄, filtered, concentrated in vacuo and purified using silica gel chromatography to provide the desired product.

3,3-difluoro-2-phenylpiperidine (7a)
Starting from 5a (100 mg, 0.478 mmol) and using general procedure D.
The desired product was purified by flash column chromatography AcOEt: AcOEt:MeOH/Et₃N (85/10/5) from 100:0 to 50:50 to yield a yellow oil (81 mg, 0.411 mmol, 86 % yield).

1H NMR (CDCl₃, 600 MHz) δ: 7.46-7.43 (2H, m), 7.38-7.32 (3H, m), 3.89-3.84 (1H, d, J= 23.2 Hz); 3.25-3.19 (1H, m), 2.83-2.75 (1H, bs), 2.35-2.25 ( 1H, m), 1.95-1.80 ( 3H, m).

19F NMR (CDCl₃, 471 MHz) δ: -99.5 (d, J= 240.7 Hz), -117.5 (m).

13C NMR (CDCl₃, 151 MHz) δ: 135.9 (C, s), 128.8 (CH, s), 128.3 (CH, s), 121.1-117.8 (CF₂, dd, J= 244.9, 248.0 Hz), 66.0-65.4 (CH, dd, J= 26.5, 22.0 Hz), 45.9 (CH₂, s), 33.8-33.4 (CH₂, dd, J= 25.9, 21.7 Hz), 24.0-23.9 (CH₂, d, J= 9.9 Hz).

HRMS-ESI m/z for C₁₁H₁₃F₂N [MH⁺] calcd 198.1089; found: 198.1090.

3,3-difluoro-2-(4-fluorophenyl)piperidine (7b)
Starting from 5b (100 mg, 0.440 mmol) and using general procedure D.
The desired product was purified by flash column chromatography AcOEt: AcOEt:MeOH/Et₃N (85/10/5) from 100:0 to 50:50 to yield a yellow oil (64 mg, 0.299 mmol, 68% yield).

1H NMR (CDCl₃, 600 MHz) δ: 7.45-7.42 (2H, m), 7.06-7.02 (2H, m), 3.87-3.82 (1H, d, J= 22.7 Hz); 3.23-3.19 (1H, m), 2.82-2.76 (1H, m), 2.35-2.25 (1H, m), 1.94-1.79 (4H, m).

19F NMR (CDCl₃, 471 MHz) δ: -99.5 (d, J= 244.2 Hz), -114.6 (s), -117.2 (m).

13C NMR (CDCl₃, 151 MHz) δ: 163.7 (C, s), 132.8 (C, s), 130.7 (CH, s), 121.1 (CF₂, dd, J= 255.4, 256.5 Hz), 115.2 (CH, d, J= 20.9 Hz), 65.9-65.3 (CH, dd, J= 22.4, 27.4 Hz), 46.1 (CH₂, s), 34.4-33.9 (CH₂, dd, J= 22.5, 25.9 Hz), 24.4-24.1 (CH₂, d, J= 9.6 Hz).

HRMS-ESI m/z for C₁₁H₁₂F₃N [MH⁺] calcd 216.0995; found: 216.0994.
4-(3,3-difluoropiperidin-2-yl)phenol (7c)
Starting from **5c** (100 mg, 0.317 mmol) and using general procedure D. The desired product was purified by flash column chromatography AcOEt: AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50 to yield a colorless oil (53mg, 0.249mmol, 79% yield).

**1H NMR** (CDCl₃, 600 MHz) δ: 7.32-7.29 (2H, m), 6.81-6.77 (2H, m), 3.82-3.77 (1H, d, J = 23.1 Hz); 3.23-3.18 (1H, m), 2.82-2.75 (1H, m), 2.35-2.25 (1H, m), 1.91-1.79 (4H, m).

**19F NMR** (CDCl₃, 471 MHz) δ: -99.8 (d, J = 239.1 Hz), -118.1 (m).

**13C NMR** (CDCl₃, 151 MHz) δ: 155.9 (C, s), 130.5 (CH, s), 128.5 (C, s), 120.6-117.7 (CF₂, t, J = 248.5 Hz), 115.4 (CH, s), 65.7-65.2 (CH, dd, J = 22.1, 26.9 Hz), 46.4 (CH₂, s), 34.2-33.7 (CH₂, dd, J = 22.0, 25.9 Hz), 24.4-24.3 (CH₂, d, J = 9.8 Hz).

**HRMS-ESI** m/z for C₁₁H₁₃F₂NO [MH⁺] calcd 214.1038; found: 214.1040.

3,3-difluoro-2-(1-methyl-1H-pyrazol-4-yl)piperidine (7d)
Starting from **5d** (100 mg, 0.469 mmol) and using general procedure D. The desired product was purified by flash column chromatography AcOEt: AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50 to yield a yellow oil (100mg, 0.419 mmol, 89% yield).

**1H NMR** (CDCl₃, 600 MHz) δ: 7.52 (1H, s), 7.43 (1H, s), 3.92-3.86 (4H, m), 3.16-3.10 (CH, m), 2.68-2.60 (1H, m), 2.31-2.22 (1H, m), 1.91-1.76 (4H, m).

**19F NMR** (CDCl₃, 471 MHz) δ: -99.6 (d, J = 242.3 Hz), -117.6 (m).

**13C NMR** (CDCl₃, 151 MHz) δ: 138.9 (CH, s), 129.4 (CH, s), 121.3 (C, s), 121.1-117.8 (CF₂, t, J = 248.8 Hz), 116.7 (C, s), 57.7-57.3 (CH, dd, J = 23.9, 26.8 Hz), 45.3 (CH₂, s), 39.0 (CH₃, s), 33.2-32.8 (CH₂, dd, J = 25.3, 22.0 Hz), 24.6-24.5 (CH₂, d, J = 8.4 Hz).

**HRMS-ESI** m/z for C₉H₁₃F₂N₃ [MH⁺] calcd 202.1150; found: 202.1150.

3,3-difluoro-2-methylpiperidine HCl salt (7e)
Starting from crude **5g** (0.680 mmol) and using general procedure D. The AcOH was partially gently removed in vacuo. The solid intermediate was dissolved in dichloroethane (1ml). To the solution was added di-t-butyldicarbonate (0.178 g, 0.816 mmol) and triethylamine (190 µL, 1.360 µmol) at room temperature and the reaction stirred for 16 h. The volatiles were removed in vacuo. The solid was purified by flash column chromatography using as eluent a solution (heptane:AcOEt) from 100:0 to 70:30. To the purified product was added 2 mL of MeOH and 2 mL of a solution HCl-Et₂O (2M) and the solution stirred at room temperature for 1h. The volatiles were removed in vacuo, to yield the desired product as a yellow oil (37 mg, 0.274 mmol, 40% yield for 2 steps).

**1H NMR** (DMSO, 600 MHz) δ: 10.59 (1H, bs), 9.31 (1H, bs), 3.75-3.64 (1H, m), 3.20-3.12 (1H, m), 3.00-2.90 (1H, m), 2.24-2.15 (1H, m), 2.11-1.99 (1H, m), 1.95-1.88 (1H, m), 1.79-1.69 (1H, m), 1.31-1.29 (3H, d, J = 6.8 Hz).

**19F NMR** (DMSO, 471 MHz) δ: -102.5 (d, J = 246.8 Hz), -114.2 (m).

**13C NMR** (DMSO, 151 MHz) δ: 122.0-117.0 (CF₂, t, J = 244.7 Hz), 53.2-52.7 (CH, dd, J = 25.8, 33.5 Hz), 41.6 (CH₃, s), 30.2-29.8 (CH₂, t, J = 23.0 Hz), 19.4-19.2 (CH₂, d, J = 9.8 Hz), 9.88-9.76 (CH₂, d, J = 3.5 Hz).

**HRMS-ESI** m/z for C₆H₁₂ClF₂N [MH⁺-HCl] calcd 136.0932; found: 136.0930.

3,3-difluoro-2-(thiophen-2-yl)piperidine (7f)
Starting from **5f** (100 mg, 0.465 mmol) and using general procedure E. The desired product was purified by flash column chromatography AcOEt: AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50, to yield a yellow oil (29 mg, 0.143 mmol, 30% yield).

**1H NMR** (CDCl₃, 600 MHz) δ: 7.31-7.29 (1H, dd, J = 1.1, 5.1 Hz), 7.14-7.12 (1H, d, J = 3.5 Hz), 7.02-7.00 (1H, dd, J = 3.5, 5.1 Hz), 4.23-4.18 (1H, dd, J = 1.7, 21.0 Hz), 3.20-3.14 (1H, m), 2.81-2.75 (1H, m), 2.35-2.26 (1H, m), 1.95-1.77 (4H, m).

**19F NMR** (CDCl₃, 471 MHz) δ: -99.4 (d, J = 242.7 Hz), -117.3 (m).
13C NMR (CDCl3, 151 MHz) δ: 137.6 (C, s), 129.0 (CH, s), 128.0 (CH, s), 126.9 (CH, s), 123.2-119.6 (CF2, t, J = 250.3 Hz), 58.6-57.9 (CH, t, J = 31.0 Hz), 42.5 (CH2, s), 30.5-30.1 (CH2, t, J = 25.7 Hz), 22.6-22.5 (CH2, t, J = 4.1 Hz).

HRMS-ESI m/z for C9H11F2NS [MH+] calcd 204.0653; found: 204.0653.

2-(3,3-difluoropiperidin-2-yl)pyridine (7g)
Starting from 5e (100 mg, 0.476 mmol) and using general procedure E. The desired product was purified by flash column chromatography AcOEt: AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50 to yield a yellow oil (49 mg, 0.250 mmol, 52% yield).

1H NMR (CDCl3, 600 MHz) δ: 8.65 (1H, s), 8.59-8.56 (1H, m), 7.84-7.80 (1H, m), 7.36 (1H, s), 7.31-7.28 (1H, dd, J = 4.8, 7.9Hz), 3.94-3.86 (1H, d, J = 22.5 Hz), 3.25-3.20 (1H, m), 2.83-2.76 (1H, m), 2.35-2.29 (1H, m), 1.99-1.83 (4H, m).

19F NMR (CDCl3, 471 MHz) δ: -99.3 (d, J = 241.9 Hz); -117.1 (m).

13C NMR (CDCl3, 151 MHz) δ: 150.3 (CH, s), 149.6 (CH, s), 136.4 (CH, s), 131.8 (C, s), 123.2 (CH, s), 121.1-117.8 (CF2, dd, J = 248.4, 244.2 Hz), δ: 64.0-63.4 (CH, dd, J = 27.3, 22.1 Hz), 46.0 (CH2, s), 33.6-33.2 (CH2, dd, J = 25.2, 21.7 Hz), 23.9-23.8 (CH2, d, J = 9.4 Hz).

HRMS-ESI m/z for C10H12F2N2 [MH+] calcd 199.1041; found: 199.1040.

6-chloro-3-(2-chlorophenyl)-[1,2,4]triazolo[3,4-a]phthalazine (10)
2-chlorobenzoyl chloride (6.3 mL, 50.0 mmol) was added to a suspension of 1-chloro-4-hydrazinophthalazine (9.73 g, 50.0 mmol) and pyridine (4 mL, 50.0 mmol) in dry MeCN (500 mL) and refluxed for 1 hour. All the volatiles were evaporated and water (250 mL) was added to the residue. The yellow precipitate was filtered and dried overnight at 60°C. The product was purified by flash column chromatography, and isolated (14.1 g, 90% yield) as yellow solid and used without further purification.

1H NMR (CDCl3, 600 MHz) δ: 8.83-8.79 (1H, dd, J = 8.1, 0.5 Hz), 8.32-8.29 (1H, dd, J = 8.1,0.5 Hz), 8.08-7.99 (1H, m), 7.90-7.85 (1H, dt, J = 7.7,1.1 Hz), 7.60-7.55 (1H, dd, J = 7.7,1.5 Hz), 7.49-7.45 (2H, m), 7.45-7.42 (1H, dd, J = 8.1,1.1 Hz), 7.39-7.35 (1H, dt, J = 7.7,1.5 Hz), 7.32-7.27 (3H, m), 3.92-3.85 (1H, d, J = 22.6 Hz), 3.26-3.20 (1H, m), 2.85-2.79 (1H, m), 2.36-2.28 (1H, m), 1.95-1.82 (4H, m).

The compound was already reported in the literature.

3-(2-chlorophenyl)-6-(4-(3,3-difluoropiperidin-2-yl)phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine (11)
Product 7c (50 mg, 0.234 mmol) and product 10 (73.9 mg, 0.234 mmol) were dissolve in DMSO (1.5mL), then K2CO3 (32.4 mg, 0.234 mmol) was added and the solution was stirred for 1 h at 120°C. The reaction was cooled to room temperature and then water was added and the mixture was extracted with DCM, collected the organic layers and dried with MgSO4. The product was purified by chromatography column using as eluent: AcOEt: AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50 to yield the desired product as a white solid (54 mg, 0.110 mmol, 47% yield).

1H NMR (CDCl3, 600 MHz) δ: 8.77-8.73 (1H, d, J = 8.1 Hz), 8.40-8.37 (1H, d, J = 8.1 Hz), 8.03-7.99 (1H, dt, J = 7.7,1.1 Hz), 7.90-7.85 (1H, dt, J = 7.7,1.1 Hz), 7.60-7.55 (1H, dd, J = 7.7,1.5 Hz), 7.49-7.45 (2H, m), 7.45-7.42 (1H, dd, J = 8.1,1.1 Hz), 7.39-7.35 (1H, dt, J = 7.7,1.5 Hz), 7.32-7.27 (3H, m), 3.92-3.85 (1H, d, J = 22.6 Hz), 3.26-3.20 (1H, m), 2.85-2.79 (1H, m), 2.36-2.28 (1H, m), 1.95-1.82 (4H, m).

19F NMR (CDCl3, 471 MHz) δ: -99.6 (d, J = 236.9 Hz), -117.9 (m).
General procedure E
Hydrogenation using Asynt autoclave

A solution of compound 5 (0.5 mmol) was dissolved in AcOH (0.1 M) then 1.5mL of a solution of Raney-Nickel W.R. Grace and Co. Raney 3202, slurry, in H2O, active catalyst, was added. The hydrogenation made using Asynt autoclave, pressure P = 5 bar, temperature T = 25°C. After 30 minutes the catalyst was filtered and the solvent removed. The products purified by flash column chromatography.

3,3-difluoro-2-phenylpiperidine (7a)
Starting from 5a (100 mg, 0.478 mmol) and using general procedure E. The desired product was purified by flash column chromatography using AcOEt:AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50 to yield the desired product as a yellow oil (43 mg, 0.218 mmol, 45% yield).

2-(4-(benzyloxy)phenyl)-3,3-difluoropiperidine (7h)
Starting from 5c (200 mg, 0.634 mmol) and using general procedure E. The desired product was purified by flash column chromatography using AcOEt:AcOEt/MeOH/Et3N (85/10/5) from 100:0 to 50:50 to yield the desired product as a white solid (81 mg, 0.267 mmol, 42% yield).

Notes and references
Figure S1. $^1$H NMR spectrum of 7a data was acquired at 600 MHz in CDCl$_3$.

Figure S2. $^{13}$C NMR spectrum of 7a data was acquired at 151 MHz in CDCl$_3$. 
Figure S3. $^{19}$F NMR spectrum of 7a data was acquired at 471 MHz in CDCl$_3$.

Figure S4. $^1$H NMR spectrum of 7b data was acquired at 600 MHz in CDCl$_3$. 
Figure S5. $^{13}$C NMR spectrum of 7b data was acquired at 151 MHz in CDCl₃.

Figure S6. $^{19}$F NMR spectrum of 7b data was acquired at 471 MHz in CDCl₃.
Figure S7. $^1$H NMR spectrum of 7c data was acquired at 600 MHz in CDCl$_3$.

Figure S8. $^{13}$C NMR spectrum of 7c data was acquired at 151 MHz in CDCl$_3$. 
Figure S9. $^{19}$F NMR spectrum of 7c data was acquired at 471 MHz in CDCl$_3$.

Figure S10. $^1$H NMR spectrum of 7d data was acquired at 600 MHz in CDCl$_3$. 
Figure S11. $^{13}$C NMR spectrum of 7d data was acquired at 151 MHz in CDCl$_3$.

Figure S12. $^{19}$F NMR spectrum of 7d data was acquired at 471 MHz in CDCl$_3$. 
Figure S13. $^1$H NMR spectrum of 7f data was acquired at 600 MHz in CDCl$_3$.

Figure S14. $^{13}$C NMR spectrum of 7f data was acquired at 151 MHz in CDCl$_3$. 
Figure S15. $^{19}$F NMR spectrum of 7f data was acquired at 471 MHz in CDCl$_3$.

Figure S16. $^1$H NMR spectrum of 7g data was acquired at 600 MHz in CDCl$_3$. 
Figure S17. $^{13}$C NMR spectrum of 7g data was acquired at 151 MHz in CDCl$_3$.

Figure S18. $^{19}$F NMR spectrum of 7g data was acquired at 471 MHz in CDCl$_3$. 

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Figure S19. $^1$H NMR spectrum of $7e$ data was acquired at 600 MHz in (CD$_3$)$_2$SO.

Figure S20. $^{13}$C NMR spectrum of $7e$ data was acquired at 151 MHz in (CD$_3$)$_2$SO.
Figure S21. $^{19}\text{F}$ NMR spectrum of $7e$ data was acquired at 471 MHz in (CD$_3$)$_2$SO.

Figure S22. $^1\text{H}$ NMR spectrum of $7h$ data was acquired at 600 MHz in CDCl$_3$. 
Figure S23. $^{13}\text{C}$ NMR spectrum of $7\text{h}$ data was acquired at 151 MHz in CDCl$_3$.

Figure S24. $^{19}\text{F}$ NMR spectrum of $7\text{h}$ data was acquired at 471 MHz in CDCl$_3$. 
Figure S25. $^1$H NMR spectrum of 11 data was acquired at 600 MHz in CDCl$_3$.

Figure S26. $^{13}$C NMR spectrum of 11 data was acquired at 151 MHz in CDCl$_3$. 
Figure S27. $^{19}$F NMR spectrum of 11 data was acquired at 471 MHz in CDCl$_3$. 