Supplementary material for "3-Amido-3-aryl-piperidines: a Novel Class of Potent, Selective and Orally Active GlyT1 Inhibitors"

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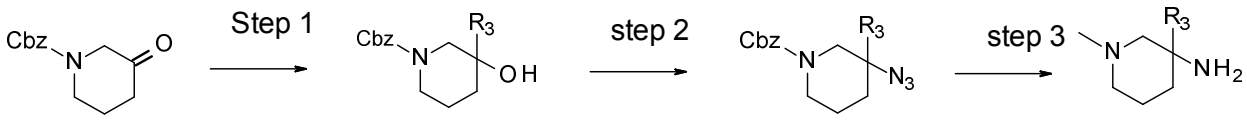
Chemistry experimental section.

General Experimental:

All solvents and reagents were obtained from commercial sources and were used as received. All reactions were followed by TLC (TLC plates F254, Merck) or LCMS (liquid chromatography-mass spectrometry) analysis. Proton NMR spectra were obtained on Bruker 300 or 600 MHz instrument with chemical shifts (δ in ppm) reported relative to tetramethylsilane as internal standard. NMR abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broadened. Elemental analyses were performed by Solvias AG (Mattenstrasse, Postfach, CH-4002 Basel, Switzerland). Column chromatography was carried out on silica gel 60 (32-60 mesh, 60 Å) or on prepacked columns (Isolute Flash Si). Mass spectra were recorded on an SSQ 7000 (Finnigan-MAT) spectrometer for electron impact ionization.

1) Preparation of intermediates

General procedure A: Preparation of N-methyl-3-amino-3-aryl-piperidines 44a-44d.

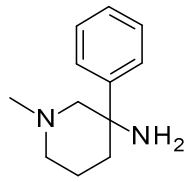


46a-d **47a-d** **44a-d**

R_3: **a**: Ph; **b**: 4-F-Ph; **c**: 4-Cl-Ph; **d**: 4-Me-Ph

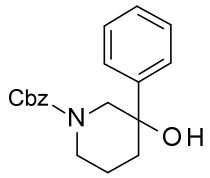
		Yield (%)		
intermediate	**R3:**	**step 1**	**step 2**	**step 3**
44a	**Ph**	71	92	47
44b	**4-F-Ph**	78	100	49
44c	**4-Cl-Ph**	66	87	32
44d	**4-Me-Ph**	84	98	63

***rac*-1-methyl-3-phenyl-piperidin-3-ylamine (44a)**



44a

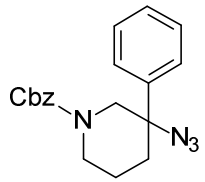
Step 1: *rac*-3-Hydroxy-3-phenyl-piperidine-1-carboxylic acid benzyl ester (46a)



46a

To a solution of 9 mL (9 mmol) phenylmagnesium bromide (1M solution in THF) in THF (13 mL) was added a solution of 1.5 g (6.00 mmol) 3-oxo-piperidine-1-carboxylic acid benzyl ester in THF (5 mL) at room temperature over a period of 15 minutes. The mixture was stirred for 30 minutes and then quenched under ice bath cooling with a 20 % ammonium chloride solution (4 ml). The organic layer was decanted and the residue was extracted once with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 50 %) to provide 1.3 g (71 %) of the desired compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.39-7.25 (m, 8H), 5.16 (m, 2H), 4.25-3.95 (m, 2H), 3.23 (d, J = 15 Hz, 1H), 2.92 (m, 1H), 2.40-1.87 (m, 4H), 1.70-1.50 (m, 1H). MS (EI) *m/e:* 312.0 $(M+H)^+$.

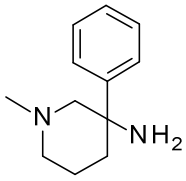
Step 2: *rac*-3-Azido-3-phenyl-piperidine-1-carboxylic acid benzyl ester (47a).



47a

1.0 g (3.212 mmol) *rac*-3-Hydroxy-3-phenyl-piperidine-1-carboxylic acid benzyl ester **46a** was dissolved in a cold mixture (10 °C) of trifluoroacetic acid (12.3 mL) and water (2.0 mL). The solution was cooled to 0 °C and 1.46 g (22.48 mmol) sodium azide was added portionwise. The temperature rose to 10 °C. The ice bath was removed and the mixture was stirred at room temperature for 3 hours. The mixture was cooled in an ice bath and basified by dropwise addition of a 25 % ammonium hydroxide solution (13.0 mL) maintaining the temperature below 20 °C. The mixture was diluted with water (45 mL) and extracted 3 times with dichloromethane. The combined extracts were washed once with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide 1g (92%) of the desired compound as a light yellow oil which was used in the next step without further purification.

Step 3: *rac*-1-Methyl-3-phenyl-piperidin-3-ylamine (44a).

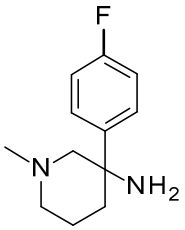


44a

To a suspension of 126 mg (3.15 mmol) $LiAlH_4$ in THF (2.7 mL) at temperature below 10 °C was added dropwise a solution of 530 mg (1.576 mmol) of *rac*-3-azido-3-phenyl-piperidine-1-carboxylic acid benzyl ester **47a** in THF (5.3 mL). The ice bath was removed. The temperature rose to 35 °C. The mixture was then heated in a 65 °C oil bath for 1 hour. The mixture was cooled to 0 °C. Water (125 uL), NaOH 5N (125 uL) and finally water (0.375 mL) were added dropwise maintaining the temperature below 10 °C. The mixture was diluted with ethyl acetate. Sodium sulfate was added. The mixture was filtered and the filtrate was concentrated in vacuo. The crude oil was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 0.14 g (47 %) of the desired compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.57

(m, 2H), 7.25-7.38 (m, 3H), 2.80-2.95 (m, 1H), 2.71 (d, J = 12 Hz, 1H), 2.30-2.40 (m, 1H), 2.31 (s, 3H), 1.51-2.10 (m, 7H). MS (EI) m/e: 191.5 (M+H)+

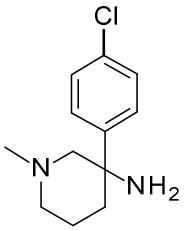
***rac*-3-(4-Fluoro-phenyl)-1-methyl-piperidin-3-ylamine (44b).**



44b

44b was prepared following the general procedure A (light yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.50 (m, 2H), 7.06-6.96 (m, 2H), 2.88-2.72 (m, 1H), 2.61 (d, J = 9 Hz, 1H), 2.35-2.25 (m, 1H), 2.34 (s, 3H), 1.51-2.10 (m, 7H). MS (EI) *m/e:* 209.2 $(M+H)^+$.

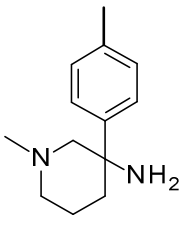
***rac*-3-(4-Chloro-phenyl)-1-methyl-piperidin-3-ylamine (44c).**



44c

44c was prepared following the general procedure A (light yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 9 Hz, 2H), 7.30 (d, J = 9 Hz, 2H), 2.85-2.75 (m, 1H), 2.67 (s, 2H), 2.59 (d, J = 12 Hz, 1H), 2.32-2.25 (m, 1H), 2.28 (s, 3H), 2.10-1.60 (m, 5H). MS (EI) *m/e:* 225.3 $(M+H)^+$.

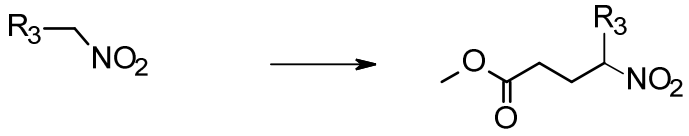
***rac*-1-Methyl-3-p-tolyl-piperidin-3-ylamine (44d).**



44d

44d was prepared following the general procedure A (light yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 9 Hz, 2H), 7.16 (d, J = 9 Hz, 2H), 2.85-2.72 (m, 1H), 2.61 (d, J = 9 Hz, 1H), 2.35-2.28 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.10-1.60 (m, 7H). MS (EI) *m/e:* 205.3 $(M+H)^+$.

General procedure B: Preparation of 4-aryl-4-nitro-butyric acid methyl esters 51e,g-i,k,o.

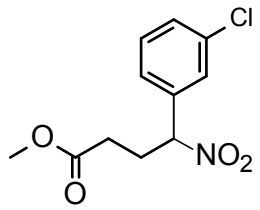


48 e,g-i, k, o **51 e,g-i, k, o**

R_3:
e: Ph;
g: 3-F-Ph;
h: 3-Cl-Ph;
i: 3-OMe-Ph
k: pyridin-4-yl;
o: pyrimidin-4-yl

intermediate	R3:	Yield (%)
51e	**Ph**	85
51g	**3-F-Ph**	84
51h	**3-Cl-Ph**	65
51i	**3-OMe-Ph**	67
51k	**Pyridine-4-yl**	57
51o	**Pyrimidin-4-yl**	41

***rac*-4-(3-Chloro-phenyl)-4-nitro-butyric acid methyl ester (51h)**

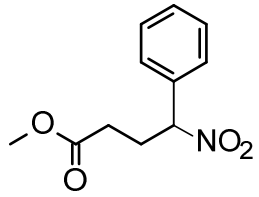


51 h

To a solution of 1g (5.828 mmol) 1-chloro-3-nitromethyl-benzene at 0 °C in 2 mL dioxane was added 0.512 g (5.828 mmol) methyl acrylate followed by 3.3 g Amberlyst
A-21. The reaction mixture was stirred overnight at room temperature, filtered and the filtrate was dried over sodium sulfate and concentrated in vacuo. The crude product was purified with flash column chromatography on silica gel (Eluent: Heptane/ethyl acetate 0 to 10 %) to provide 980 mg (65 %) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s,

1H), 7.43-7.38 (m, 1H), 7.38-7.34 (m, 2H), 5.59-5.54 (m, 1H), 3.70 (s, 3H), 2.81-2.68 (m, 1H), 2.47-2.35 (m, 3H). MS (EI) *m/e:* 275.1 ($M+NH_4^+$).

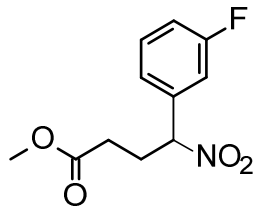
***rac*-4-Nitro-4-phenyl-butyric acid methyl ester (51e).**



51 e

51e was prepared following the general procedure B (colorless oil). ^1H NMR (300 MHz, $CDCl_3$) δ 7.47-7.40 (m, 5H), 5.58 (dd, J = 9 Hz, 6 Hz, 1H), 3.69 (s, 3H), 2.84-2.69 (m, 1H), 2.50-2.34 (m, 3H). MS (EI) *m/e:* 246.2 (M+Na).

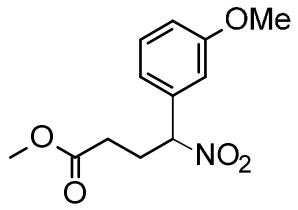
***rac*-4-(3-Fluoro-phenyl)-4-nitro-butyric acid methyl ester (51g).**



51 g

51g was prepared following the general procedure B (colorless oil). ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 1H), 7.26-7.07 (m, 3H), 5.63-5.56 (m, 1H), 3.70 (s, 3H), 2.83-2.63 (m, 1H), 2.48-2.33 (m, 3H).

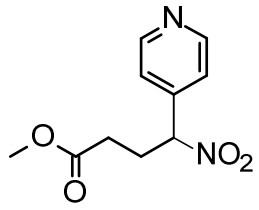
***rac*-4-(3-Methoxy-phenyl)-4-nitro-butyric acid methyl ester (51i).**



51 i

51i was prepared following the general procedure B (colorless oil). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, J = 9 Hz, 1H), 7.05-6.90 (m, 3H), 5.54 (dd, J = 9 Hz, J = 6 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 2.82-2.69 (m, 1H), 2.49-2.32 (m, 3H).

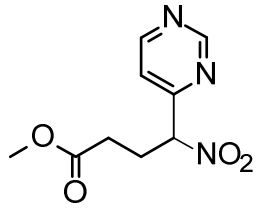
***rac*-4-Nitro-4-pyridin-4-yl-butyric acid methyl ester (51k).**



51 k

51k was prepared following the general procedure B (yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 6 Hz, 2H), 7.36 (d, J = 6 Hz, 2H), 5.62 (dd, J = 9 Hz, 3 Hz, 1H), 3.71 (s, 3H), 2.80-2.71 (m, 1H), 2.43-2.39 (m, 3H). MS (EI) *m/e:* 225.1 (M+H+).

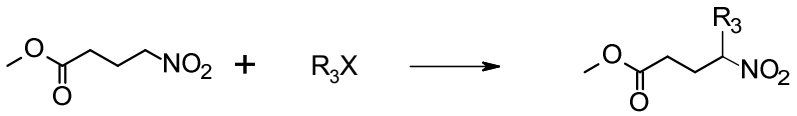
***rac*-4-Nitro-4-pyrimidin-4-yl-butyric acid methyl ester (51o).**



51 o

51o was prepared following the general procedure B (yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.85 (d, J = 6 Hz, 1H), 7.46 (d, J = 6 Hz, 1H), 5.77 (dd, J = 9 Hz, J = 3 Hz, 1H), 3.71 (s, 3H), 2.83-2.73 (m, 1H), 2.61-2.53 (m, 1H), 2.50-2.44 (m, 2H). MS (EI) *m/e:* 179 (M-NO_2)

General procedure C: Preparation of 4-aryl-4-nitro-butyric acid methyl esters 51 f,j,l-n.



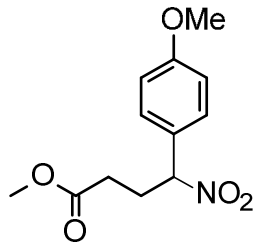
49 **50 f, j, l- n** **51 f, j, l-n**

R_3:
f: 4-OMe-Ph;
j: 5-F-pyridin-2-yl;
l: pyridin-3-yl;
m: pyrazinyl-2-yl;
n: pyrimidin-2-yl

intermediate	R3:	X:	Yield (%)
51f	**4-OMe-Ph**	Br	90
51j	**5-F-pyridin-3-yl**	Br	36
51l	**Pyridin-3-yl**	Br	10
51m	**Pyrazinyl-2-yl**	Cl	23

51n	**Pyrimidin-2-yl**	Br	12

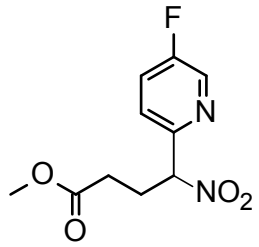
***rac*-4-(4-Methoxy-phenyl)-4-nitro-butyric acid methyl ester (51f)**



51f

As described by Buchwald *et al.* (J. Org. Chem. 2002, 106): in a flask was added successively: 187 mg (0.198 mmol) Pd_2dba_3, 247 mg (0.791 mmol) 2-(Di-t-butylphosphino)-2`-methybiphenyl, and 1.555 g (4.747 mmol) cesium carbonate. The mixture was put under argon and 740 mg (3.956 mmol) 4-bromoanisole, 15 mL of DME and finally 600 mg (3.956 mmol) of methyl 4-nitrobutyrate were successively added. The mixture was stirred vigorously for 1 minute at room temperature and the flask was placed in a preheated oil bath at 50 °C and stirred at this temperature overnight. The reaction mixture was cooled to room temperature, and a saturated NH_4Cl solution and ethyl acetate were added. Aqueous phase was extracted 3 times with ethyl acetate and combined organic phases were washed with brine, and concentrated in vacuo. The crude product was purified with flash column chromatography on silica gel (Eluent: heptane/ethyl acetate 0 to 20 %) to provide 897 mg (90 %) of the desired compound as a orange oil. δ 7.38 (d, J = 12 Hz, 2H), 6.92 (d, J = 12 Hz, 2H), 5.52 (dd, J = 9 Hz, 6 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 2.81-2.70 (m, 1H), 2.48-2.33 (m, 3H). MS (EI) *m/e:* 207 ($M-NO_2$)

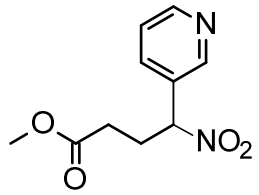
***rac*-4-(5-Fluoro-pyridin-2-yl)-4-nitro-butyric acid methyl ester (51j).**



51 j

51j was prepared following the general procedure C (orange oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (br, 1H), 7.50-7.44 (m, 2H), 5.77 (dd, J = 9 Hz, 6 Hz, 1H), 3.70 (s, 3H), 2.82 (m, 1H), 2.57 (m, 1H), 2.44-2.39 (m, 2H).

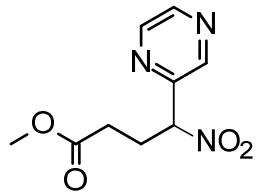
***rac*-4-Nitro-4-pyridin-3-yl-butyric acid methyl ester (51l).**



51 l

51l was prepared following the general procedure C (yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (br, 2H), 7.86 (d, J = 9 Hz, 1H), 7. 38 (dd, J = 9 Hz, 6 Hz, 1H), 5.65 (dd, J = 9 Hz, 6 Hz, 1H), 3.70 (s, 3H), 2.77 (m, 1H), 2.38-2.49 (m, 3H). MS (EI) *m/e:* 225.2 $(M+H)^+$

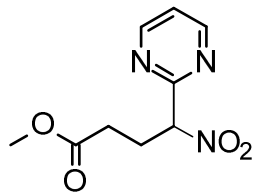
***rac*-4-Nitro-4-pyrazin-2-yl-butyric acid methyl ester (51m).**



51 m

51m was prepared following the general procedure C (orange oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.77-8.63 (m, 2H), 5.85 (dd, J = 9 Hz, 6 Hz, 1H), 3.71 (s, 3H), 2.86 (m, 1H), 2.55 (m, 1H), 2.52-2.38 (m, 2H). MS (EI) *m/e:* 226.3 $(M+H)^+$.

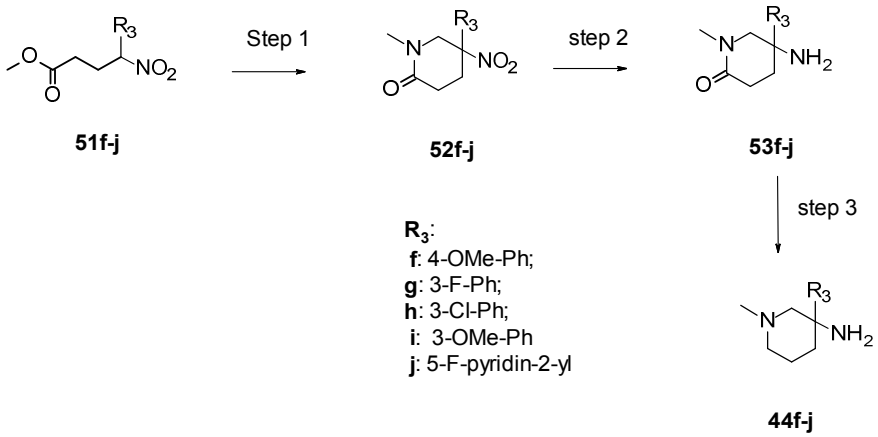
***rac*-4-Nitro-4-pyrimidin-2-yl-butyric acid methyl ester (51n).**



51 n

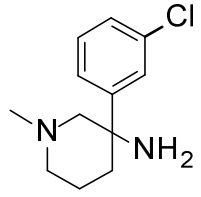
51n was prepared following the general procedure C (yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, J = 6 Hz, 2H), 7.34 (t, J = 6 Hz, 1H), 5.90 (dd, J = 9 Hz, 6 Hz, 1H), 3.70 (s, 3H), 2.77 (m, 2H), 2.53-2.48 (m, 2H). MS (EI) *m/e:* 226.3 $(M+H)^+$.

General procedure D: Preparation of N-methyl-3-amino-3-aryl-piperidines 44f-j.



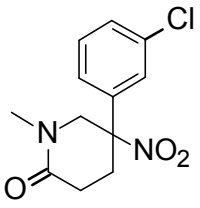
		Yield (%)		
intermediate	**R3:**	**step 1**	**step 2**	**step 3**
44f	**4-OMe-Ph**	72	73	86
44g	**3-F-Ph**	84	61	84
44h	**3-Cl-Ph**	76	86	86
44i	**3-OMe-Ph**	94	40	84
44j	**5-F-pyridin-2-yl**	59	13	71

***rac*-3-(3-Chloro-phenyl)-1-methyl-piperidin-3-ylamine (44h)**



44h

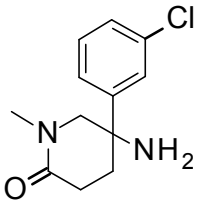
Step 1: *rac*-5-(3-Chloro-phenyl)-1-methyl-5-nitro-piperidin-2-one (52h)



52h

To a stirred room temperature solution of 164 ul (1.940 mmol) methylamine (41 % in water) in 1 mL dioxane was added 141 uL (1.940 mmol) formaldehyde (37 % in water) dropwise (exothermic reaction). The mixture was stirred for 5 min and then a solution of 0.5 g (1.940 mmol) *rac*-4-(3-chloro-phenyl)-4-nitro-butyric acid methyl ester **51h** in 1.5 mL dioxane was added at once. The mixture was stirred at 65 °C for 6 h. The mixture was cooled to room temperature, ethyl acetate and a saturated NaCl solution were added. Aqueous phase was extracted 2 times with ethyl acetate. Combined organic phases were washed with a saturated NaCl solution, dried over sodium sulfate and concentrated in vacuo. The crude product was purified with flash column chromatography on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 395 mg (76 %) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.26 (m, 4H), 4.44 (dd, J = 15 Hz, J = 3 Hz, 1H), 3.81 (d, J = 15 Hz, 1H), 3.14-3.10 (m, 1H), 3.04 (s, 3H), 2.64-2.43 (m, 3H). MS (EI) *m/e:* 269.2 $(M+H)^+$.

Step 2: *rac*-5-Amino-5-(3-chloro-phenyl)-1-methyl-piperidin-2-one (53h)

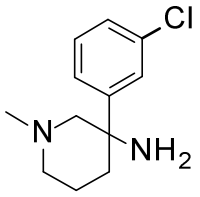


53h

To a solution of 115mg (0.428 mmol) *rac*-5-(3-chloro-phenyl)-1-methyl-5-nitro-piperidin-2-one **52h** in 0.5mL dioxane was added 2 mL 3N HCl and 280 mg (4.28 mmol) zinc dust. The mixture was stirred at room temperature for 30 minutes. The mixture was filtered and the filtrate was basified with a 5N NaOH solution. Ethyl acetate was added. The mixture was filtered through a pad of decalite. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in

vacuo to provide 88 mg (86 %) of the desired compound as light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.38-7.27 (m, 3H), 3.64 (d, J = 12 Hz, 1H), 3.28 (dd, J = 12 Hz, J = 3 Hz, 1H), 3.00 (s, 3H), 2.66-2.55 (m, 1H), 2.39-2.27 (m, 2 H), 2.04-1.94 (m, 1H), 1.62 (br, 2H). MS (EI) *m/e:* 239.0 $(M+H)^+$.

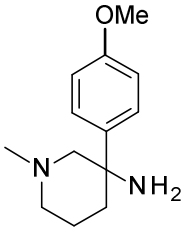
Step 3: *rac*- 3-(3-Chloro-phenyl)-1-methyl-piperidin-3-ylamine (44h)



44h

To a slurry of 20 mg (0.494 mmol) $LiAlH_4$ in 0.5mL THF was added dropwise a solution of 59 mg (0.247 mmol) *rac*-5-amino-5-(3-chloro-phenyl)-1-methyl-piperidin-2-one **53h** in 0.6 mL THF at room temperature. The mixture was refluxed for 30 minutes. The mixture was cooled in an ice bath and quenched carefully with 20 uL water, 20 uL 5N NaOH and finally 60uL water. Ethyl acetate was added. The mixture was filtered and the filtrate was concentrated in vacuo to provide 48 mg (86 %) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.46 (d, J = 9 Hz, 1H), 7.35-7.20 (m, 2H), 2.75 (m, 1H), 2.57 (d, J = 9 Hz, 1H), 2.30-2.20 (m, 1H), 2.24 (s, 3H), 2.10-1.55 (m, 7H). MS (EI) *m/e:* 225.2 $(M+H)^+$.

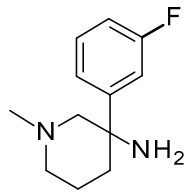
***rac*-3-(4-Methoxy-phenyl)-1-methyl-piperidin-3-ylamine (44f).**



44f

44f was prepared following the general procedure D (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 12 Hz, 2H), 6.88 (d, J = 12 Hz, 2H), 3.79 (s, 3H), 2.75 (m, 1H), 2.57 (d, J = 9 Hz, 1H), 2.30-2.20 (m, 1H), 2.24 (s, 3H), 2.10-1.55 (m, 7H). MS (EI) *m/e:* 221.2$(M+H)^+$.

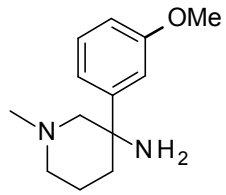
***rac*-3-(3-Fluoro-phenyl)-1-methyl-piperidin-3-ylamine (44g).**



44g

44g was prepared following the general procedure D (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 3H), 6.93 (m, 1H), 2.76 (m, 1H), 2.57 (d, J = 9 Hz, 1H), 2.30-2.26 (m, 1H), 2.28 (s, 3H), 2.10-1.58 (m, 7H). MS (EI) *m/e:* 209.1 $(M+H)^+$.

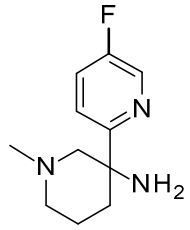
***rac*-3-(3-Methoxy-phenyl)-1-methyl-piperidin-3-ylamine (44i).**



44i

44i was prepared following the general procedure D (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.20-7.11 (m, 2H), 6.79 (d, J = 9 Hz, 1H), 3.82 (s, 3H), 2.77 (m, 1H), 2.59 (d, J = 12 Hz, 1H), 2.30-2.25 (m, 1H), 2.27 (s, 3H), 2.10-1.60 (m, 7H).

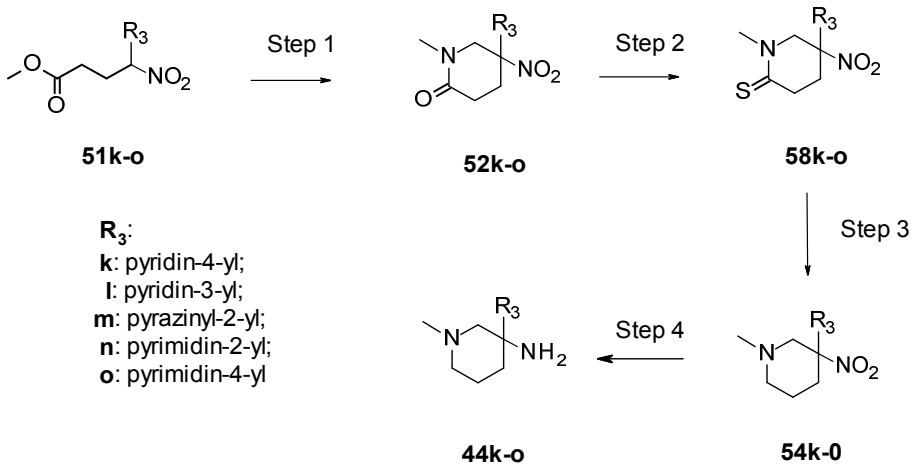
***rac*-5-Fluoro-1'-methyl-1',4',5',6'-tetrahydro-2'H-[2,3']bipyridinyl-3'-ylamine (44j).**



44j

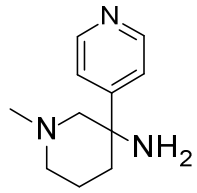
44j was prepared following the general procedure D (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (br, 1H), 7.68-7.63 (m, 1H), 7.40-7.34 (m, 1H), 2.75 (m, 1H), 2.57 (d, J = 9 Hz, 1H), 2.30-2.20 (m, 1H), 2.28 (s, 3H), 2.10-1.55 (m, 7H). MS (EI) *m/e:* 210.2 $(M+H)^+$.

General procedure E: Preparation of N-methyl-3-amino-3-aryl-piperidines 44k-o.



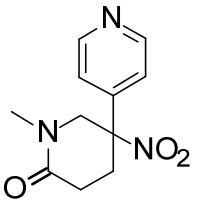
		Yield (%)			
intermediate	**R3:**	**step 1**	**step 2**	**step 3**	**step 4**
44k	**Pyridin-4-yl**	84	79	57	88
44l	**Pyridin-3-yl**	61	77	58	98
44m	**Pyrazinyl-2-yl**	54	83	49	100
44n	**Pyrimidin-2-yl**	54	94	76	91
44o	**Pyrimidin-4-yl**	49	100	71	87

***rac*-1-Methyl-1,4,5,6-tetrahydro-2H-[3,4']bipyridinyl-3-ylamine (44k)**



44k

Step 1: *rac*-1-Methyl-3-nitro-2,3,4,5-tetrahydro-1H-[3,4']bipyridinyl-6-one (52k)

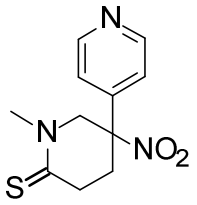


52k

52k was prepared following the general procedure D, step 1 (yellow solid).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 6 Hz, 2H), 7.32 (d, J = 6 Hz, 2H), 4.42 (dd, J = 15 Hz, J = 3 Hz, 1H), 3.83

(d, J = 15 Hz, 1H), 3.14-3.10 (m, 1H), 3.05 (s, 3H), 2.66-2.47 (m, 3 H). MS (EI) *m/e:* 236.2 $(M+H)^+$.

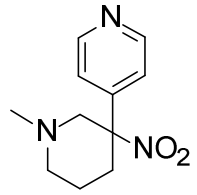
Step 2: *rac*-1-Methyl-3-nitro-2,3,4,5-tetrahydro-1H-[3,4']bipyridinyl-6-thione (58k)



58k

To a solution of 125 mg (0.531 mmol) *rac*-1-Methyl-3-nitro-2,3,4,5-tetrahydro-1H-[3,4']bipyridinyl-6-one **52k** in 2.5 mL toluene were added 240 mg (0.584 mmol) Lawesson reagent. The suspension was heated in a 80°C oil bath for 30 minutes. The mixture was concentrated in vacuo. The crude oil was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 105 mg (79 %) of the desired compound as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (br, 2H), 7.29 (br, 2H), 4.65 (d, J = 15 Hz, 1H), 3.87 (d, J = 15 Hz, 1H), 3.56 (s, 3H), 3.32-3.25 (m, 1H), 3.11-3.03 (m, 2 H), 2.58 (m, 1H). MS (EI) *m/e:* 252.1 $(M+H)^+$.

Step 3: *rac*-1-Methyl-3-nitro-1,2,3,4,5,6-hexahydro-[3,4']bipyridinyl (54k)

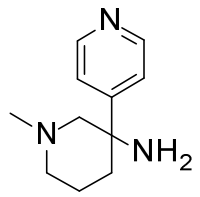


54k

To a solution of 105 mg (0.418mmol) *rac*-1-Methyl-3-nitro-2,3,4,5-tetrahydro-1H-[3,4']bipyridinyl-6-thione **58k** in 2.1 mL methanol was added 144 mg (3.8 mmol) $NaBH_4$. The mixture was stirred at room temperature for 20 minutes. Water (1.0 ml) was added. The mixture was stirred for 1 hour. The methanol was removed in vacuo. The residue was diluted with water and extracted 3 times with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 53 mg (57 %) of the desired compound as a yellow

oil. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 6 Hz, 2H), 7.35 (d, J = 6 Hz, 2H), 3.65 (d, J = 12 Hz, 1H), 2.83-2.70 (m, 3H), 2.37 (s, 3H), 2.20-2.14 (m, 1H), 1.96-1.60 (m, 3H). MS (EI) *m/e:* 222.3 $(M+H)^+$.

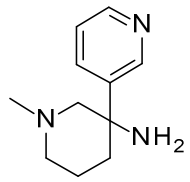
Step 4: *rac*-1-Methyl-1,4,5,6-tetrahydro-2H-[3,4']bipyridinyl-3-ylamine (44k)



44k

To a 0°C cooled solution of 52 mg (0.235 mmol) *rac*-1-Methyl-3-nitro-1,2,3,4,5,6-hexahydro-[3,4']bipyridinyl **54k** in 2.0 mL THF were added 150 uL of Raney Nickel (50% in water). The mixture was stirred at 0°C under a hydrogen atmosphere for 7 hours. The catalyst was filtered and the filtrate was concentrated in vacuo to provide 45 mg (88 %) of the desired compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 6 Hz, 2H), 7.49 (d, J = 6 Hz, 2H), 2.85-2.52 (m, 1H), 2.54 (d, J = 12 Hz, 1H), 2.30-2.26 (m, 1H), 2.28 (s, 3H), 2.05-1.50 (m, 7H). MS (EI) *m/e:* 192.4 $(M+H)^+$.

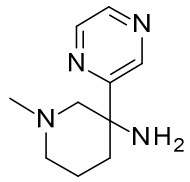
***rac*-1-Methyl-1,4,5,6-tetrahydro-2H-[3,3']bipyridinyl-3-ylamine (44l).**



44l

44l was prepared following the general procedure E (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (br, 1H), 8.49 (d, J = 6 Hz, 2H), 7.92 (d, J = 9 Hz, 1H), 7.26 (br, 1H), 2.85-2.70 (m, 1H), 2.53 (d, J = 12 Hz, 1H), 2.35-2.25 (m, 1H), 2.28 (s, 3H), 2.10-1.50 (m, 7H). MS (EI) *m/e:* 192.4 $(M+H)^+$.

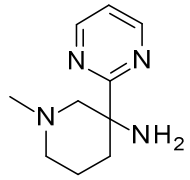
***rac*-1-Methyl-3-pyrazin-2-yl-piperidin-3-ylamine (44m).**



44m

44m was prepared following the general procedure E (colorless oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.52 (s, 1H), 8.45 (s, 1H), 2.80-2.65 (m, 1H), 2.58 (d, J = 12 Hz, 1H), 2.30 (s, 3H), 2.20-1.50 (m, 8H). MS (EI) *m/e:* 193.4 $(M+H)^+$.

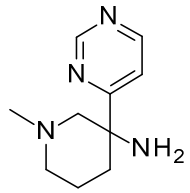
***rac*-1-Methyl-3-pyrimidin-2-yl-piperidin-3-ylamine (44n).**



44n

44n was prepared following the general procedure E (yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (d, J = 6 Hz, 2H), 7.15 (t, J = 6 Hz, 1H), 2.80-2.60 (m, 3H), 2.29 (s, 3H), 2.25-1.70 (m, 7H). MS (EI) *m/e:* 193.3 $(M+H)^+$.

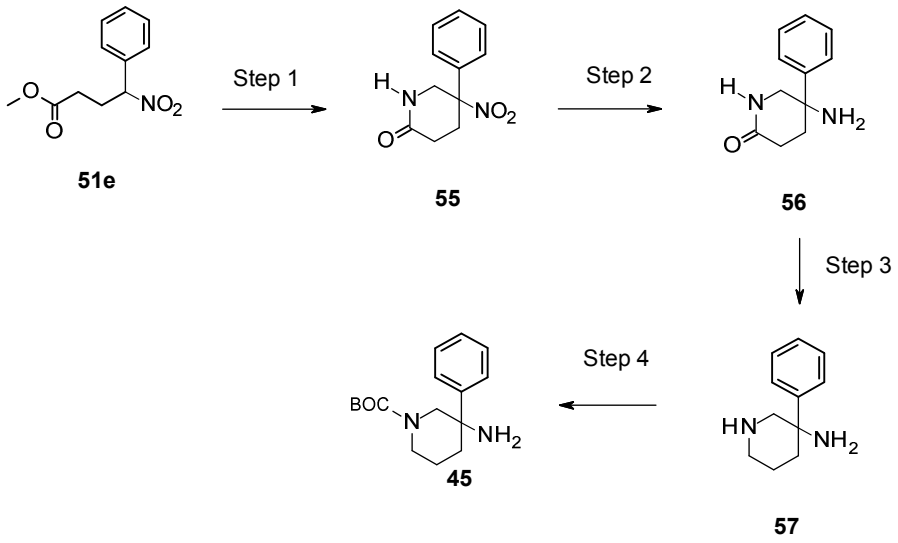
***rac*-1-Methyl-3-pyrimidin-4-yl-piperidin-3-ylamine (44o).**



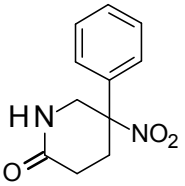
44o

44o was prepared following the general procedure E (yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.69 (d, J = 6 Hz, 1H), 7.69 (d, J = 6 Hz, 1H), 2.86 (m, 1H), 2.52 (m, 1H), 2.30-2.25 (m, 1H), 2.29 (s, 3H), 2.25-1.70 (m, 7H). MS (EI) *m/e:* 175 $(M-NH_3)$.

Preparation of *rac*-3-Amino-3-phenyl-piperidine-1-carboxylic acid -tert-butyl ester 45.



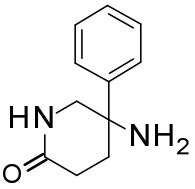
Step 1: *rac*-5-Nitro-5-phenyl-piperidin-2-one (55)



55

To a stirred solution of 2.11 g (26.88 mmol) ammonium acetate in 15 ml ethanol under nitrogen at room temperature, was added 980 uL (13.44 mmol) formaldehyde (37% in water), followed by a solution of 3 g (13.44 mmol) *rac*-4-Nitro-4-phenyl-butyric acid methyl ester **51e** in 7.5 mL ethanol. The mixture was refluxed for 26 hours then cooled to room temperature and the solvent was evaporated. Water was added. The resulting suspension was stirred for 15 minutes, filtered, rinsed with water, then with diethyl ether and dried in vacuo to provide 2.49 g (yield: 84.1 %) of the desired compound as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 5H), 6.26 (br, 1H), 4.54 (d, J = 15 Hz, 1H), 3.86 (d, J = 15 Hz, 1H), 3.25-3.15 (m, 1H), 2.70-2.50 (m, 3 H). MS (EI) *m/e:* 221.2 $(M+H)^+$.

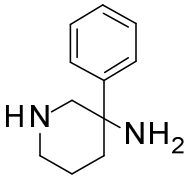
Step 2: *rac*-5-Amino-5-phenyl-piperidin-2-one (56)



56

56 was prepared following the general procedure E, step 4 (89% yield, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.51 (m, 2H), 7.42-7.26 (m, 3H), 6.09 (br, 1H), 3.71 (d, 9 Hz, 1H), 3.33 (d, 9 Hz, 1H), 2.70-2.53 (m, 1H), 2.40-2.25 (m, 2H), 2.10-1.95 (m, 1H), 1.63 (br, 2H). MS (EI) *m/e:* 191.4 $(M+H)^+$.

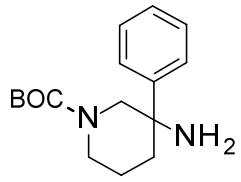
Step 3: *rac*- 3-Phenyl-piperidin-3-yl-amine (57)



57

57 was prepared following the general procedure D, step 3 (97% yield, yellow oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.40-7.33 (m, 2H), 7.30-7.15 (m, 1H), 3.10-2.95 (m, 2H), 2.82 (d, J = 12 Hz, 1H), 2.70-2.60 (m, 1H), 2.10-1.52 (m, 7H). MS (EI) *m/e:* 177.3 $(M+H)^+$.

Step 4: *rac*-3-Amino-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester (45)



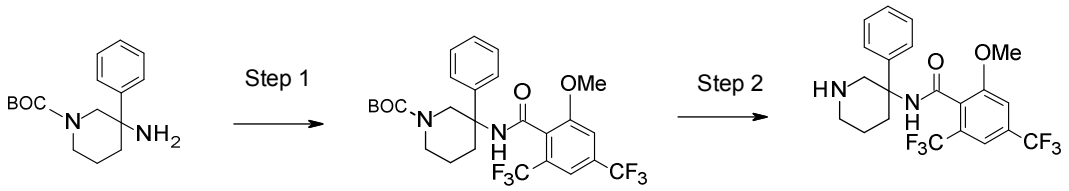
45

To a solution of 20 mg (0.113 mmol) *rac*- 3-Phenyl-piperidin-3-yl-amine **57** in 100 uL dichloromethane under nitrogen at room temperature, was added 18.9 uL (0.136 mmol) triethylamine. The reaction mixture was cooled to 0°C and a solution of 24.9 mg (0.113 mmol) di-tert-butyl dicarbonate in 100 uL dichloromethane was added dropwise. The reaction mixture was stirred at room temperature for 2.5 hours. The mixture was quenched with a saturated

solution of sodium bicarbonate. The organic layer was washed twice with water, dried over sodium sulfate, filtered and concentrated in vacuo. The crude compound was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide to provide 22 mg (70 %) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.54 (m, 2H), 7.38-7.33 (m, 2H), 7.28-7.23 (m, 1H), 3.90-3.65 (m, 2H), 3.45 (d, J = 12 Hz, 1H), 3.03 (dt, J = 9 Hz, 3 Hz, 1H), 2.10-1.95 (m, 1H), 1.90-1.70 (m, 2H), 1.56 (br, 3H), 1.47 (s, 9H). MS (EI) *m/e:* 277.2 $(M+H)^+$.

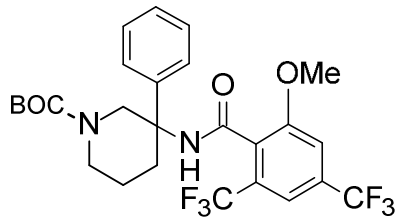
2) Preparation of 3-amido-3-aryl-piperidines 8-43

Preparation of *rac*-2-Methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide 9.



45 **59** **9**

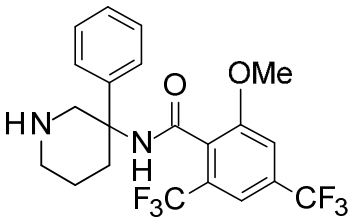
Step 1: *rac*- 3-(2-Methoxy-4-methyl-6-trifluoromethyl-benzoylamino)-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester (59)



59

59 was prepared following the general procedure F, (white foam, 86% yield) from *rac*-3-amino-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester **45**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 6 Hz, 2H), 7.50 (s, 1H), 7.42 (m, 2H), 7.30 (m, 2H), 4.13 (m, 1H) 3.92 (s, 3H), 3.30 (m, 1H), 2.87 (m, 2H), 3.20-1.95 (m, 3H), 1.70 (m, 2H), 1.34 (s, 9H). MS (EI) *m/e:* 569.2 (M+Na).

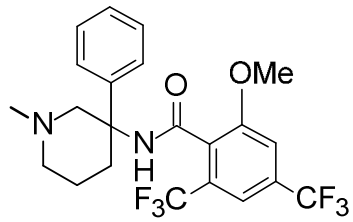
Step 2: *rac*-2-Methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide (9)



9

To a solution of *rac*-3-(2-Methoxy-4-methyl-6-trifluoromethyl-benzoylamino)-3-phenyl-piperidine-1-carboxylic acid tert-butyl ester **59** (30 mg, 54.9 µmol) in dioxane (450 µl) at room temperature was added dropwise HCl 4M in dioxane (137 µl, 549 µmol). The mixture was stirred for 5 hours at room temperature then the solvent was removed in vacuo. The residue was basified with sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to provide 12 mg (86 %) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.52 (m, 3H), 7.39-7.26 (m, 4H), 6.73 (br, 1H), 3.96 (s, 3H), 3.22 (d, J = 12 Hz, 1H), 3.04 (m, 1H), 2.81 (m, 1H), 2.70-2.60 (m, 2H), 2.17-1.90 (m, 2H), 1.75-1.55 (m, 2H). MS (EI) *m/e:* 247.2 $(M+H)^+$.

General procedure F: Preparation of *rac*-2-Methoxy-N-(1-methyl-3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide

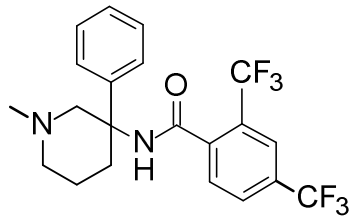


8

To a solution of 205 mg (1.077 mmol) *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a** and 369 uL (2.154 mmol) N-ethyldiisopropylamine in dichloromethane (2.5 mL) was added dropwise a solution of 430 mg (1.4 mmol) 2-methoxy-4,6-bis-trifluoromethyl-benzoyl chloride in dichloromethane (2.0 mL) at room temperature. The mixture was stirred at room temperature for 16 hours. The solvent was removed in vacuo. The crude product was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 340 mg (69 %) of the desired compound as

a light yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.52 (m, 3H), 7.39-7.26 (m, 4H), 6.82 (br, 1H), 3.96 (s, 3H), 2.87-2.77 (m, 3H), 2.21 (s, 3H), 2.10-1.65 (m, 5H). MS (EI) *m/e:* 461.4 $(M+H)^+$.

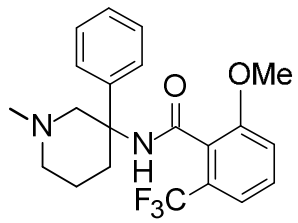
General procedure G: Preparation of *rac*-N-(1-Methyl-3-phenyl-piperidin-3-yl)-2,4-bis-trifluoromethyl-benzamide (20)



20

To a solution of 30.11 mg (0.116 mmol) 2,4-bis(trifluoromethyl)benzoic acid, 60.24 mg (0.158 mmol) HATU and 71.90 uL (0.420 mmol) of N-ethyldiisopropylamine in DMF (1 mL) was added a solution of 20 mg (0.105 mmol) of *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a** in DMF (0.25mL). The mixture was stirred at room temperature for 20 hours. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate. The solution was washed once with water and twice with a saturated solution of sodium bicarbonate. The aqueous layer was extracted once with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 40 %) to provide 30.9 mg (68 %) of the desired compound as a light yellow gum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86 (d, J = 9 Hz, 1H), 7.75 (d, J = 6 Hz, 1H), 7.51 (d, J = 9 Hz, 2H), 7.38 (t, J = 6 Hz, 2H), 7.28 (d, J = 9 Hz, 1H), 6.97 (br, 1H), 2.84-2.80 (m, 3H), 2.25 (s, 3H), 2.10-1.70 (m, 5H). MS (EI) *m/e:* 431.3 $(M+H)^+$.

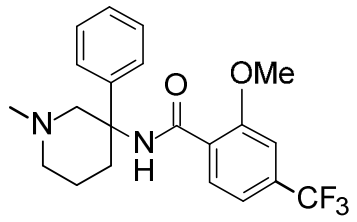
***rac*-2-Methoxy-N-(1-methyl-3-phenyl-piperidin-3-yl)-6-trifluoromethyl-benzamide (18)**



18

18 was prepared following the general procedure F, (colorless oil, 57% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 9 Hz, 2H), 7.45-7.33 (m, 3H), 7.26-7.22 (m, 2H), 7.11 (d, J = 9 Hz, 1H), 6.78 (br, 1H), 3.90 (s, 3H), 2.88-2.76 (m, 3H), 2.20 (s, 3H), 2.15-1.65 (m, 5H). MS (EI) *m/e:* 293.3 $(M+H)^+$.

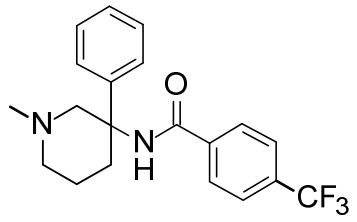
***rac*-2-Methoxy-N-(1-methyl-3-phenyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (19)**



19

19 was prepared following the general procedure F, (colorless oil, 38% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (br, 1H), 8.14 (d, J = 6 Hz, 1H), 7.46 (d, J = 9 Hz, 2H), 7.36-7.20 (m, 5H), 4.06 (s, 3H), 2.90-2.78 (m, 3H), 2.32 (s, 3H), 2.05-1.60 (m, 5H). MS (EI) *m/e:* 393.2 $(M+H)^+$.

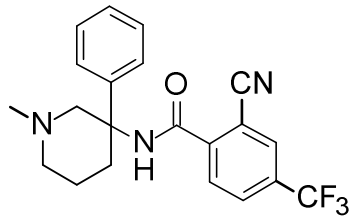
***rac*-N-(1-Methyl-3-phenyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (21)**



21

21 was prepared following the general procedure G, (yellow oil, 18% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 6 Hz, 2H), 7.71 (d, J = 9 Hz, 2H), 7.53-7.45 (m, 3H), 7.35 (t, J = 6 Hz, 2H), 7.26 (br, 1H), 2.90-2.80 (m, 3H), 2.31 (s, 3H), 2.05-1.65 (m, 5H). MS (EI) *m/e:* 363.2 $(M+H)^+$.

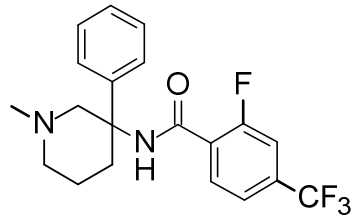
***rac*-2-Cyano-N-(1-methyl-3-phenyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (22)**



22

22 was prepared following the general procedure G, (yellow foam, 30% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (br, 1H), 7.98 (d, J = 12 Hz, 1H), 7.81 (m, 2H), 7.52 (d, J = 12 Hz, 1H), 7.45-7.20 (m, 4H), 2.90-2.80 (m, 3H), 2.38 (s, 3H), 2.05-1.65 (m, 5H). MS (EI) *m/e:* 288.2 $(M+H)^+$.

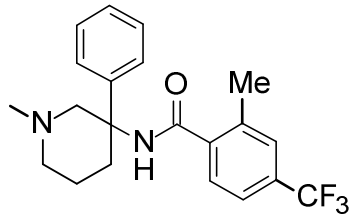
***rac*-2-Fluoro-N-(1-methyl-3-phenyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (23)**



23

23 was prepared following the general procedure F, (yellow oil, 89 % yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (m, 1H), 7.82 (m, 1H), 7.53-7.29 (m, 7H), 2.95-2.76 (m, 3H), 2.30 (s, 3H), 2.05-1.79 (m, 5H). MS (EI) *m/e:* 381.2 $(M+H)^+$.

***rac*-2-Methyl-N-(1-methyl-3-phenyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (24)**

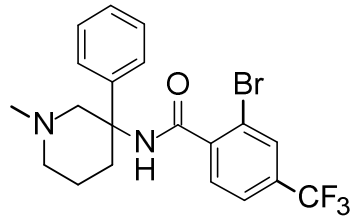


24

24 was prepared following the general procedure F, (light yellow gum, 58% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.25 (m, 8H),

6.90 (br, 1H), 2.87-2.75 (m, 3H), 2.48 (s, 3H), 2.23 (s, 3H), 2.05-1.60 (m, 5H). MS (EI) *m/e:* 377.3 $(M+H)^+$.

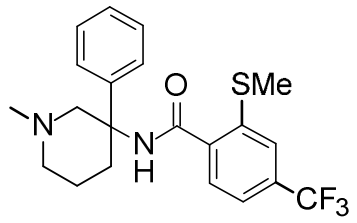
***rac*-2-Bromo-N-(1-methyl-3-phenyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (25)**



25

25 was prepared following the general procedure G, (light yellow oil, 56% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.63 (m, 2H), 7.54 (d, J = 6 Hz, 2 H), 7.38 (t, J = 6 Hz, 2H), 7.26 (m, 1H), 7.07 (br, 1H), 2.87-2.75 (m, 3H), 2.23 (s, 3H), 2.05-1.70 (m, 5H). MS (EI) *m/e:* 441.2 $(M+H)^+$.

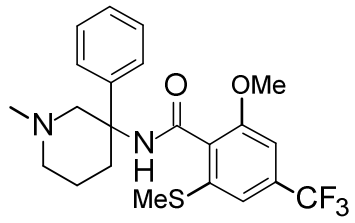
***rac*-N-(1-Methyl-3-phenyl-piperidin-3-yl)-2-methylsulfanyl-4-trifluoromethyl-benzamide (26)**



26

26 was prepared following the general procedure F, (light yellow oil, 72% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 9 Hz, 1 H), 7.56-7.26 (m, 7H), 7.18 (br, 1H), 2.95-2.75 (m, 3H), 2.51 (s, 3H), 2.24 (s, 3H), 2.10-1.70 (m, 5H). MS (EI) *m/e:* 409.3 $(M+H)^+$.

***rac*-2-Methoxy-N-(1-methyl-3-phenyl-piperidin-3-yl)-6-methylsulfanyl-4-trifluoromethyl benzamide (27)**



27

27 was prepared following the general procedure F, (light yellow oil, 68% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 9 Hz, 2 H), 7.36 (t, J = 6 Hz, 2H), 7.26 (m, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.89 (br, 1H), 3.91 (s, 3H), 2.86 (m, 2H), 2.71 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.30-2.15 (m, 1H), 2.20 (s, 3H), 2.00-1.85 (m, 3H), 1.71 (m, 1H). MS (EI) *m/e:* 439.4 $(M+H)^+$.

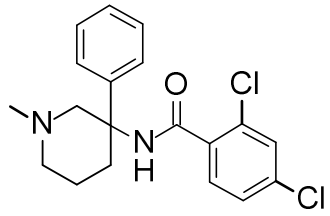
(*S*)-2-Methoxy-N-(1-methyl-3-phenyl-piperidin-3-yl)-6-methylsulfanyl-4-trifluoromethyl benzamide (28) and (*R*)-2-Methoxy-N-(1-methyl-3-phenyl-piperidin-3-yl)-6-methylsulfanyl-4-trifluoromethyl benzamide (29). 27 (270 mg, 0.616 mmol) was separated on a preparative Chiralpack AD® column (flow 35 ml / min, pressure: 15 bar, detection at 220 nm) using heptane: isopropanol 75:15 as eluant to afford (*S*)-enantiomer **28** (100 mg, 37% yield, 1st eluting product, retention time: 50 min) and (*R*)-enantiomer **29** (95 mg, 35% yield, 2nd eluting product, retention time: 101 min).

28: white solid, $[\alpha]_D^{20}$ -23.7° (*c*1.0, MeOH) of HCl salt. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 9 Hz, 2 H), 7.36 (t, J = 6 Hz, 2H), 7.26 (m, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.89 (br, 1H), 3.91 (s, 3H), 2.86 (m, 2H), 2.71 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.30-2.15 (m, 1H), 2.20 (s, 3H), 2.00-1.85 (m, 3H), 1.71 (m, 1H). MS (EI) *m/e:* 439.4 $(M+H)^+$. HPLC, analytical Chiralpack AD® column (flow 1 ml / min, pressure: 25 bar, detection at 220 nm) using heptane: isopropanol 75:25 as eluant, retention time: 7.3 min. ee > 99%.

29: white solid, $[\alpha]_D^{20}$ +24.2° (*c*1.0, MeOH) of HCl salt. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 9 Hz, 2 H), 7.36 (t, J = 6 Hz, 2H), 7.26 (m, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.89 (br, 1H), 3.91

(s, 3H), 2.86 (m, 2H), 2.71 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.30-2.15 (m, 1H), 2.20 (s, 3H), 2.00-1.85 (m, 3H), 1.71 (m, 1H). MS (EI) *m/e:* 439.4 $(M+H)^+$. Anal. Calcd. for $C_{22}H_{25}F_3N_2O_2S$(1:1 H_2O) C, 57.88; H, 5.96; N, 6.14; S, 7.02; F, 12.48. Found: C, 57.96; H, 6.18; N, 6.25; S, 7.11; F, 12.52. HPLC, analytical Chiralpack AD® column (flow 1 ml / min, pressure: 25 bar, detection at 220 nm) using heptane: isopropanol 75:25 as eluant, retention time: 14.1 min. ee > 99%.

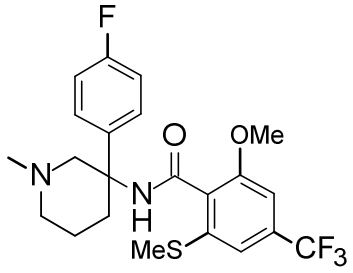
***rac*- 2,4-Dichloro-N-(1-methyl-3-phenyl-piperidin-3-yl)-benzamide (30)**



30

30 was prepared following the general procedure F, (light yellow gum, 54% yield) from *rac*-1-methyl-3-phenyl-piperidin-3-ylamine **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.23 (m, 9H), 2.87-2.75 (m, 3H), 2.24 (s, 3H), 2.05-1.80 (m, 4H), 1.73 (br, 1H). MS (EI) *m/e:* 363.1 $(M+H)^+$.

***rac*-N-[3-(4-Fluoro-phenyl)-1-methyl-piperidin-3-yl]-2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzamide (31)**

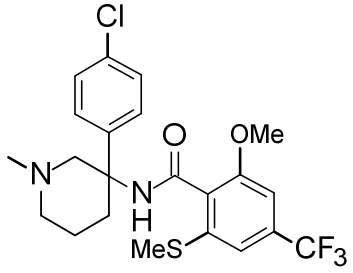


31

31 was prepared following the general procedure F, (white foam, 15% yield) from *rac*-3-(4-fluoro-phenyl)-1-methyl-piperidin-3-ylamine **44b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 9

Hz, J = 6 Hz, 2 H), 7.12 (s, 1H), 7.03 (t, J = 6 Hz, 2H), 6.84 (s, 1H), 6.91 (br, 1H), 3.90 (s, 3H), 2.88 (m, 2H), 2.68 (d, J = 12 Hz, 1H), 2.46 (s, 3H), 2.25-2.15 (m, 1H), 2.20 (s, 3H), 2.00-1.80 (m, 3H), 1.65 (m, 1H). MS (EI) *m/e:* 457.2$(M+H)^+$.

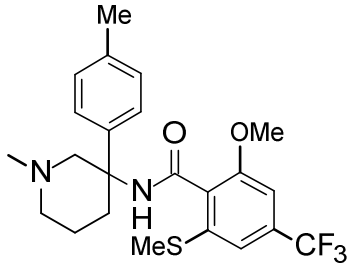
***rac*-N-[3-(4-Chloro-phenyl)-1-methyl-piperidin-3-yl]-2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzamide (32)**



32

32 was prepared following the general procedure G, (light yellow oil, 23% yield) from *rac*-3-(4-chloro-phenyl)-1-methyl-piperidin-3-ylamine **44c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 9 Hz, 2 H), 7.32 (d, J = 9 Hz, 2H), 7.12 (s, 1H), 6.94 (s, 2H), 6.91 (br, 1H), 3.91 (s, 3H), 2.83 (m, 2H), 2.67 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.25-2.15 (m, 1H), 2.21 (s, 3H), 2.00-1.80 (m, 3H), 1.68 (m, 1H). MS (EI) *m/e:* 473.3$(M+H)^+$.

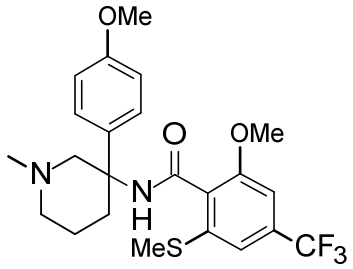
***rac*-2-Methoxy-6-methylsulfanyl-N-(1-methyl-3-p-tolyl-piperidin-3-yl)-4-trifluoromethyl-benzamide (33)**



33

33 was prepared following the general procedure G, (colorless oil, 32% yield) from *rac*-1-methyl-3-p-tolyl-piperidin-3-ylamine **44d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 9 Hz, 2 H), 7.16 (d, J = 9 Hz, 2H), 7.11 (s, 1H), 6.93 (s, 1H), 6.87 (br, 1H), 3.86 (s, 3H), 2.85 (m, 2H), 2.70 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.33 (s, 3H), 2.25-2.15 (m, 1H), 2.19 (s, 3H), 2.00-1.80 (m, 3H), 1.67 (m, 1H). MS (EI) *m/e:* 453.3$(M+H)^+$.

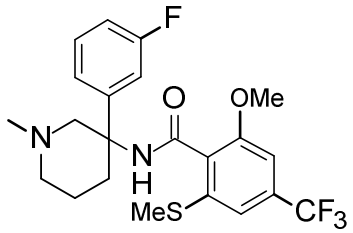
***rac*-2-Methoxy-N-[3-(4-methoxy-phenyl)-1-methyl-piperidin-3-yl]-6-methylsulfanyl-4-trifluoromethyl-benzamide (34)**



34

34 was prepared following the general procedure F, (white foam, 89% yield) from *rac*-3-(4-methoxy-phenyl)-1-methyl-piperidin-3-ylamine **44f**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 9 Hz, 2 H), 7.12 (br, 1H), 6.93-6.85 (m, 4H), 3.90 (s, 3H), 3.80 (s, 3H), 2.81 (m, 2H), 2.70 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.25-2.15 (m, 1H), 2.19 (s, 3H), 2.00-1.80 (m, 3H), 1.67 (m, 1H). MS (EI) *m/e:* 469.2 $(M+H)^+$.

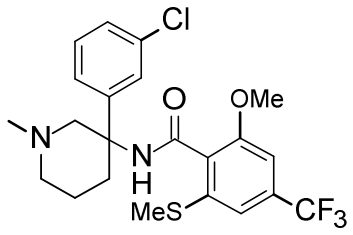
***rac*-N-[3-(3-Fluoro-phenyl)-1-methyl-piperidin-3-yl]-2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzamide formiate (35)**



35

35 as formic acid salt was prepared following the general procedure F, (white foam, 41% yield) from *rac*-3-(3-fluoro-phenyl)-1-methyl-piperidin-3-ylamine **44g**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.49 (d, J = 12 Hz, 1H), 7.43-7.30 (m, 2H), 7.13 (s, 1H), 7.01 (m, 1H), 6.93 (s, 1H), 5.24 (br, 2H), 3.91 (s, 3H), 3.52-3.33 (m, 3H), 2.54 (s, 3H), 2.49 (s, 3H), 2.39 (d, J = 9 Hz, 1H), 2.06-1.85 (m, 2H). MS (EI) *m/e:* 457.3 $(M+H)^+$.

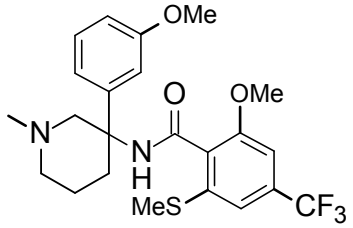
***rac*-N-[3-(3-Chloro-phenyl)-1-methyl-piperidin-3-yl]-2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzamide (36)**



36

36 was prepared following the general procedure F, (colorless oil, 67% yield) from *rac*- 3-(3-chloro-phenyl)-1-methyl-piperidin-3-ylamine **44h**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.46 (d, J = 9 Hz, 1 H), 7.35-7.30 (m, 2H), 7.14 (s, 1H), 6.95 (s, 1H), 6.86 (br, 1H), 3.91 (s, 3H), 2.83 (m, 2H), 2.67 (d, J = 12 Hz, 1H), 2.49 (s, 3H), 2.25-2.15 (m, 1H), 2.20 (s, 3H), 2.00-1.80 (m, 3H), 1.71 (m, 1H). MS (EI) *m/e:* 437.2 $(M+H)^+$.

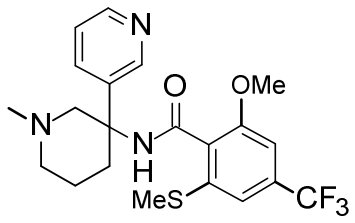
***rac*-2-Methoxy-N-[3-(3-methoxy-phenyl)-1-methyl-piperidin-3-yl]-6-methylsulfanyl-4-trifluoromethyl-benzamide (37)**



37

37 was prepared following the general procedure F, (white foam, 73% yield) from *rac*-3-(3-Methoxy-phenyl)-1-methyl-piperidin-3-ylamine **44i**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 3H); 7.12 (s, 1H), 6.94 (s, 1H), 6.87 (br, 1H), 6.80 (d, J = 6 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 2.85 (m, 2H), 2.70 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 2.23-2.16 (m, 1H), 2.19 (s, 3H), 2.00-1.48 (m, 4H). MS (EI) *m/e:* 469.2 $(M+H)^+$.

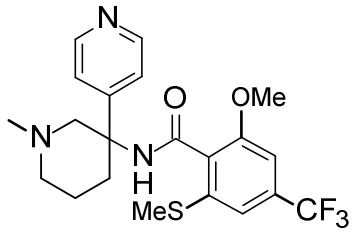
***rac*- 2-Methoxy-6-methylsulfanyl-N-(1-methyl-1,4,5,6-tetrahydro-2H-[3,3']bipyridinyl-3-yl)-4-trifluoromethyl-benzamide (38)**



38

38 was prepared following the general procedure G, (yellow solid, 46% yield) from *rac*-1-Methyl-1,4,5,6-tetrahydro-2H-[3,3']bipyridinyl-3-ylamine **44l**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.50 (d, J = 3 Hz, 1 H), 7.94 (d, J = 9 Hz, 1H), 7.29 (m, 1H), 7.12 (s, 1H), 6.98 (br, 1H), 6.94 (s, 1H), 3.92 (s, 3H), 2.87 (m, 2H), 2.76 (d, J = 12 Hz, 1H), 2.48 (s, 3H), 2.25-2.15 (m, 1H), 2.25 (s, 3H), 2.05-1.80 (m, 3H), 1.74 (m, 1H). MS (EI) *m/e:* 440.2 $(M+H)^+$.

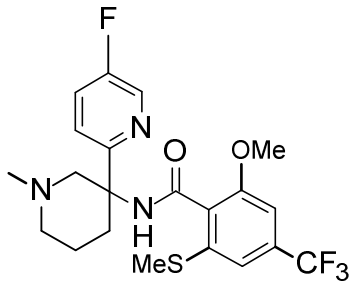
***rac*-2-Methoxy-6-methylsulfanyl-N-(1-methyl-1,4,5,6-tetrahydro-2H-[3,4']bipyridinyl-3-yl)-4-trifluoromethyl-benzamide (39)**



39

39 was prepared following the general procedure G, (yellow solid, 36% yield) from *rac*-1-methyl-1,4,5,6-tetrahydro-2H-[3,4']bipyridinyl-3-ylamine **44k**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 3 Hz, 2H), 7.53 (d, J = 6 Hz, 2 H), 7.13 (s, 1H), 6.98 (br, 1H), 6.95 (s, 1H), 3.93 (s, 3H), 2.80 (m, 2H), 2.68 (d, J = 12 Hz, 1H), 2.49 (s, 3H), 2.25-2.15 (m, 1H), 2.24 (s, 3H), 2.05-1.80 (m, 3H), 1.76 (m, 1H). MS (EI) *m/e:* 440.2 $(M+H)^+$.

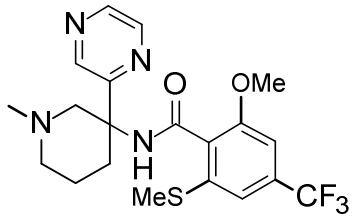
***rac*-N-(5-Fluoro-1'-methyl-1',4',5',6'-tetrahydro-2'H-[2,3']bipyridinyl-3'-yl)-2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzamide (40)**



40

40 was prepared following the general procedure F, (light yellow oil, 19% yield) from *rac*-5-fluoro-1'-methyl-1',4',5',6'-tetrahydro-2'H-[2,3']bipyridinyl-3'-ylamine **44j**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 3 Hz, 1H), 7.84 (dd, J = 9 Hz, J = 3 Hz, 1 H), 7.38 (td, J = 9 Hz, J = 3 Hz, 1H), 7.12 (br, 2H), 6.94 (s, 1H), 3.91 (s, 3H), 2.80 (m, 3H), 2.48 (s, 3H), 2.25-2.15 (m, 1H), 2.23 (s, 3H), 2.05-1.80 (m, 3H), 1.76 (m, 1H). MS (EI) *m/e:* 458.2 $(M+H)^+$.

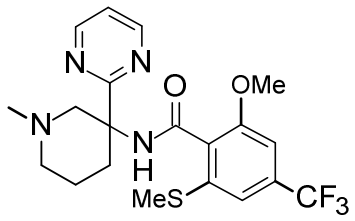
***Rac*-2-Methoxy-N-(1-methyl-3-pyrazin-2-yl-piperidin-3-yl)-6-methylsulfanyl-4-trifluoromethyl-benzamide (41)**



41

41 was prepared following the general procedure F, (light yellow solid, 35% yield) from *rac*-1-methyl-3-pyrazin-2-yl-piperidin-3-ylamine **44m**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.52 (s, 1H), 8.45 (s, 1H), 7.13 (s, 1H), 7.06 (br, 1H), 6.95 (s, 1H), 3.94 (s, 3H), 2.95-2.65 (m, 3H), 2.49 (s, 3H), 2.35-1.95 (m, 4H), 2.24 (s, 3H), 1.76 (m, 1H). MS (EI) *m/e:* 441.2 $(M+H)^+$.

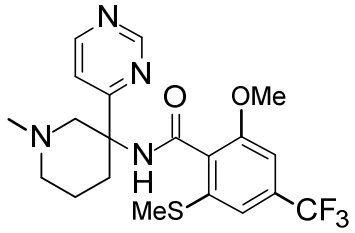
***Rac*-2-Methoxy-N-(1-methyl-3-pyrimidin-2-yl-piperidin-3-yl)-6-methylsulfanyl-4-trifluoromethyl-benzamide (42)**



42

42 was prepared following the general procedure F, (yellow oil, 45% yield) from *rac*-1-methyl-3-pyrimidin-2-yl-piperidin-3-ylamine **44n**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J = 6 Hz, 2H), 7.31 (br, 1H), 7.17 (t, J = 6 Hz, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 3.90 (s, 3H), 3.12 (d, J = 12 Hz, 1H), 2.80 (m, 2H), 2.43 (s, 3H), 2.25-2.20 (m, 1H), 2.23 (s, 3H), 2.20-1.90 (m, 3H), 1.76 (m, 1H). MS (EI) *m/e:* 441.2 $(M+H)^+$.

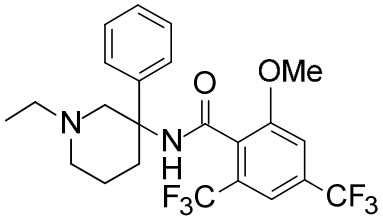
***Rac*-2-Methoxy-N-(1-methyl-3-pyrimidin-4-yl-piperidin-3-yl)-6-methylsulfanyl-4-trifluoromethyl-benzamide (43)**



43

43 was prepared following the general procedure F, (yellow oil, 4% yield) from *rac*-1-methyl-3-pyrimidin-4-yl-piperidin-3-ylamine **44o**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.70 (d, J = 6 Hz, 1H), 7.85 (d, J = 6 Hz, 1H), 7.14 (s, 2H), 6.96 (s, 1H), 3.93 (s, 3H), 2.92-2.65 (m, 3H), 2.50 (s, 3H), 2.24 (s, 3H), 2.22-2.14 (m, 1H), 1.90-1.80 (m, 4H). MS (EI) *m/e:* 441.2 $(M+H)^+$.

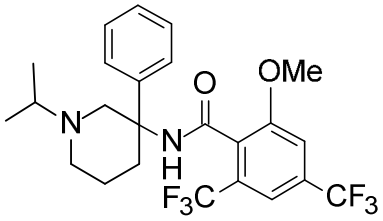
General procedure H: Preparation of *rac*-N-(1-Ethyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (10).



10

To a solution of 25.mg (0.056 mmol) *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9** in 0.25 mL dichloromethane were added 19.7 ul (0.112mmol) N-ethyldiisopropylamine and finally 6.0 uL (0.0728 mmol) iodoethane. The solution was stirred at room temperature for 20 hours. The solvent was removed in vacuo. The crude product was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 15 mg (58 %) of the desired compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.53 (m, 3H), 7.39-7.21 (m, 4H), 6.87 (br, 1H), 3.96 (s, 3H), 2.85-2.75 (m, 3H), 2.38 (q, J = 6 Hz, 2H), 2.10-1.90 (m, 4H), 1.73 (m, 1H), 1.01 (t, J = 6 Hz, 3H). MS (EI) *m/e:* 475.2 $(M+H)^+$.

General procedure I: Preparation of *rac*- N-(1-Isopropyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (11).

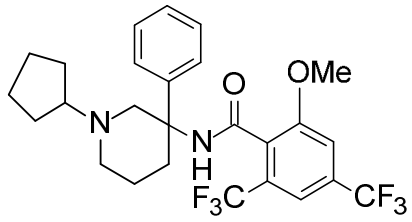


11

To a solution of 35.7 mg (0.08 mmol) *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9** in methanol were added 28 uL (0.48 mmol) acetic acid, 59 uL (0.8 mmol) acetone and finally 30 mg (0.4 mmol) sodium cyanoborohydride. The mixture was stirred at room temperature for 4 hours. The solvent was removed in vacuo. The residue was taken in ethyl acetate. The mixture was washed once with a 1N NaOH solution, once with water and once with brine. The aqueous layer was extracted once with ethyl acetate. The combined organic

layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 33 mg (85 %) of the desired compound as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.53 (m, 3H), 7.40-7.25 (m, 4H), 6.93 (br, 1H), 3.96 (s, 3H), 2.84-2.75 (m, 4H), 2.22 (m, 1H), 2.13 (d, J = 12 Hz, 1H), 2.01-1.90 (m, 2H), 1.71 (m, 1H), 0.96 (m, 6H). MS (EI) *m/e:* 489.4 $(M+H)^+$.

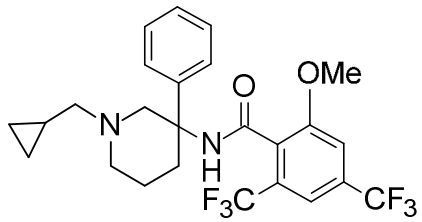
***Rac*-N-(1-Cyclopentyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (12)**



12

12 was prepared following the general procedure I, (white foam, 83% yield) from *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.54 (m, 3H), 7.39-7.25 (m, 4H), 6.91 (br, 1H), 3.96 (s, 3H), 3.00-2.75 (m, 3H), 2.57 (m, 1H), 2.05-1.90 (m, 4H), 1.85-1.70 (m, 3H), 1.70-1.20 (m, 6H). MS (EI) *m/e:* 515.5 $(M+H)^+$.

***Rac*-N-(1-Cyclopropylmethyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (13)**

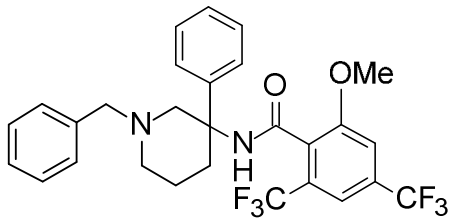


13

13 was prepared following the general procedure I, (colorless oil, 89% yield) from *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.53 (m, 3H), 7.39-7.25 (m, 4H), 6.92 (br, 1H), 3.97 (s, 3H), 3.00 (d, J = 9 Hz,

2H), 2.86 (d, J = 12 Hz, 1H), 2.24 (m, 2H), 2.15-1.90 (m, 4H), 1.72 (m, 1H), 0.86 (m, 1H), 0.47 (m, 2H), 0.02 (m, 2H). MS (EI) *m/e:* 501.3 $(M+H)^+$.

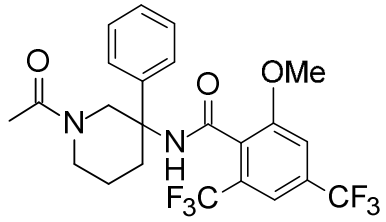
Rac-N-(1-Benzyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (14)



14

14 was prepared following the general procedure I, (colorless oil, 63% yield) from *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.45 (m, 3H), 7.39-7.25 (m, 9H), 6.85 (br, 1H), 3.92 (s, 3H), 3.52 (d, J = 12 Hz, 1H), 3.48 (d, J = 12 Hz, 1H), 2.90-2.80 (m, 3H), 2.15-1.90 (m, 4H), 1.72 (m, 1H). MS (EI) *m/e:* 537.3 $(M+H)^+$.

General procedure J: _Rac_-N-(1-Acetyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (15)

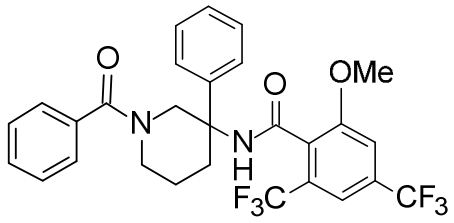


15

To a solution of 25 mg (0.056mmol) *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9** in 0.25mL dichloromethane were added 19.7uL (0.112mmol) N-ethyldiisopropylamine and finally 5.2uL (0.0728 mmol) acetyl chloride. The solution was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The crude product was purified on silica gel (Eluent: Heptane/ethyl acetate 0 to 100 %) to provide 27 mg (99 %) of the desired compound as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 6 Hz, 2H), 7.52-

7.25 (m, 5H), 6.75 (br, 1H), 4.81 (d, J = 15 Hz, 1H), 3.95 (m, 1H), 3.87 (s, 3H), 3.46 (d, J = 12 Hz, 1H), 3.17 (t, J = 12 Hz, 1H), 2.65 (d, J = 15 Hz, 1H), 2.12 (s, 3H), 2.10-1.60 (m, 3H). MS (EI) *m/e:* 489.4 $(M+H)^+$.

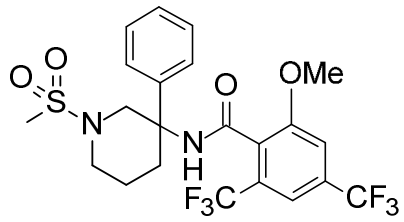
***Rac*-N-(1-Benzoyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (16)**



16

16 was prepared following the general procedure J, (white foam, 91% yield) from *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 9 Hz, 2H), 7.52-7.27 (m, 11H), 4.86 (d, J = 12 Hz, 1H), 3.96 (m, 1H), 3.87 (s, 3H), 3.46 (d, J = 15 Hz, 1H), 3.23 (t, J = 12 Hz, 1H), 2.89 (d, J = 15 Hz, 1H), 2.22 (dt, J = 15 Hz, J = 6 Hz, 1H), 2.04 (m, 1H), 1.70 (m, 1H). MS (EI) *m/e:* 551.3 $(M+H)^+$.

***Rac*-N-(1-Methanesulfonyl-3-phenyl-piperidin-3-yl)-2-methoxy-4,6-bis-trifluoromethyl-benzamide (17)**



17

17 was prepared following the general procedure J, (white foam, 65% yield) from *rac*-2-methoxy-N-(3-phenyl-piperidin-3-yl)-4,6-bis-trifluoromethyl-benzamide **9**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.45-7.27 (m, 4H), 6.59 (br, 1H), 3.97 (s, 3H), 3.83 (m, 2H), 3.23 (d, J = 12 Hz, 1H), 3.85-3.75 (m, 2H), 2.76 (s, 3H), 2.21-2.04 (m, 2H), 1.85 (m, 1H). MS (EI) *m/e:* 525.3 $(M+H)^+$.