Journal of Fluorine Chemistry 134 (2012) 136–145

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis and evaluation of fluorinated analogues of monoamine reuptake inhibitors

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ARTICLE INFO

Article history:
Received 18 January 2011
Received in revised form 9 February 2011
Accepted 27 February 2011
Available online 15 March 2011

Key words:
Monoamine reuptake inhibition
Fluoroalkyl
Trifluoromethyl
Fluorine

ABSTRACT

The synthesis of two series of fluorinated analogues of monoamines reuptake inhibitors based on tertiary alcohols 2-substituted morpholines scaffold has been achieved through the incorporation of fluorinated substituent into 2-substituted morpholino ketones. Their binding affinities have been measured on different monoamine transporters.

The research pursued in our group focuses on new synthetic methodologies, involving organofluorine and peptide chemistry, devoted to medicinal chemistry and effort towards new processes respectful of environment. Due to the increasing importance of fluorinated compounds in a large number of domains (drugs, materials, surfactants, contrasting agents, etc.) the search for new fluorinated molecules is a permanent quest. The group has a long lasting experience in biologically active molecules where the introduction of fluoroalkyl substituents can improve the pharmacological profile of drugs. Typical examples are fluorinated analogues of natural products: artemisinin derivatives (anti-malaria and anti-cancer) and styryl lactone analogues (anti-tumor), and new fluorinated peptidomimetic units as inhibitors of protein-protein interactions (anti-infectious, anti-tumor drugs and inhibition of amyloide aggregation).

1. Introduction

In the central nervous system (CNS), monoamine neurotransmitters such as serotonin (SER), norepinephrine (NE), and dopamine (DA), are involved in many physiological and pathological processes. Their regulations are ensured by transporters, respectively SERT, NET, and DAT which are integral membrane proteins that uptake the monoamine neurotransmitter from the extracellular space into neurons [1,2]. The development of monoamines reuptake inhibitors has shown a significant therapeutic advance in many CNS diseases [3,4]. For example, selective serotonin reuptake inhibitors, such as fluoxetine (Prozac®), have been considered as a breakthrough in the antidepressant therapy [5–7]. Among these inhibitors, the 3-aryloxypropylamine scaffold has been shown to be a privileged motif in the selective (SER) or dual (SER/NE) monoamine transporter inhibition as exemplified by the marketed drugs: fluoxetine, reboxetine and duloxetine (Fig. 1) [8–15].

Although numerous monoamine transporter inhibitors are clinically available, little is known regarding the structural basis of inhibitor function [16]. Thus, there is still continuous interest in developing novel selective or mixed inhibitors with improved pharmacological and metabolic properties. Indeed, recently novel series of ketones or tertiary alcohols with expanded sets of aryl and heteroaryl moieties have been reported [17–19]. Among them, tertiary alcohol containing 2-substituted morpholines **1** has been discovered as potent and selective inhibitors of norepinephrine transporters with K_i values up to 4 nM [8]. These inhibitors are characterized by a high hydrophobicity due to the presence of aromatic rings, but the role of the hydroxyl function still remain

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doi:10.1016/j.jfluchem.2011.02.018

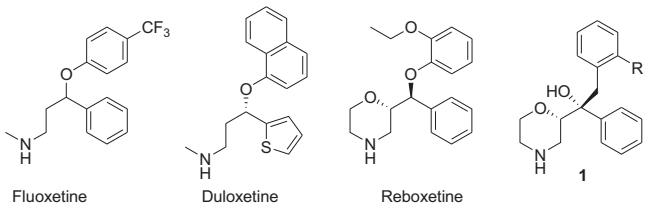


Fig. 1. Selective or dual monoamine reuptake inhibitors.

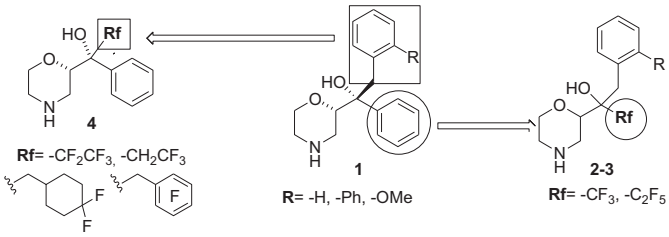


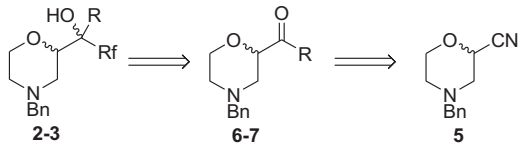
Fig. 2. Fluorinated analogues of monoamine reuptake inhibitors.

unclear (hydrogen bond acceptor or donor). The introduction of fluorinated tertiary alcohols into this series of molecules could provide a better understanding of the interaction with the receptor. The incorporation of fluorine into molecules has become a useful tool in medicinal chemistry for improving the pharmacological profile of bioactive compounds [20–27]. Indeed, the high electrowithdrawing effect of fluoroalkyl groups can modify the pKa of neighboring functions and their ability to form hydrogen bonds [28,29]. Furthermore, fluoroalkyl groups, at the same time highly hydrophobic, and sterically demanding, are able to mimic phenyl or benzyl groups with beneficial effects. In addition, a fluoroalkyl tertiary alcohol is expected to be more stable towards solvolysis or dehydration process. In order to explore the potential replacement of aromatic rings and study the effect of fluorinated groups in these series of compounds, we have synthesized two types of fluorinated analogues. In the first one the phenyl substituent is replaced by a trifluoromethyl or pentafluoroethyl group (molecules **2**–**3**). In the second one, the ortho-substituted benzyl group is replaced by a fluorinated substituent bearing a CH_2 or CF_2 spacer ($-C_2F_5$, $-CH_2CF_3$, pentafluorobenzyl and 1,1-difluoro-4-methylcyclohexyl), molecules **4** (Fig. 2).

Herein we report the synthesis and binding affinities of these two series of fluorinated tertiary alcohols containing the 2-substituted morpholine scaffold.

2. Chemistry

The first approach developed to synthesize molecules **2** and **3** was based on the previously reported synthesis of 2-substituted morpholines [8] starting from the 4-benzylmorpholine-2-carbonitrile **5**, prepared itself by the addition of the *N*-benzyl ethanolamine to the 2-chloroacrylonitrile (Scheme 1) [30]. Reaction of the nitrile **5** or the corresponding ester with a fluoroakylation reagent would provide fluoroalkyl ketones which would further react with an appropriate organometallic reagent in a diastereoselective manner to give alcohols **2** or **3** (Scheme 1).



Scheme 2.

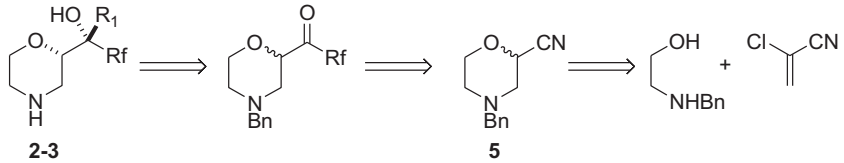
Unfortunately, whatever the reaction conditions (trifluoromethylation of the ester analogue of **5** using the trifluoromethyl trimethysilane (CF_3TMS) reagent or addition of fluoroalkyl organometallic reagents to the nitrile **5**), fluorinated ketones were obtained under highly stable hydrated forms which could not be dehydrated and neither further reacted to lead to the corresponding alcohols even with a large excess of organometallic reagent. We thus turned to an alternative strategy in which the different steps were inverted: a previous generation of a non-fluorinated ketone followed by the addition of a fluoroalkylation reagent (Scheme 2).

The reaction of the morpholinonitrile **5** with ortho-substituted benzyl Grignard reagents afforded the corresponding ketones **6a**–**c** in good yields (Scheme 3). The synthesis of trifluoromethyl alcohol containing 2-substituted morpholines **7a**–**c** was achieved by the addition of the CF_3TMS reagent to ketones **6a**–**c**, which afforded a 1/1 mixture of 2 diastereoisomers in moderate yields (40–52%). In the case of compounds **7c** each diastereoisomer **7c$_1$** and **7c$_2$** could be isolated separately by silica gel purification.

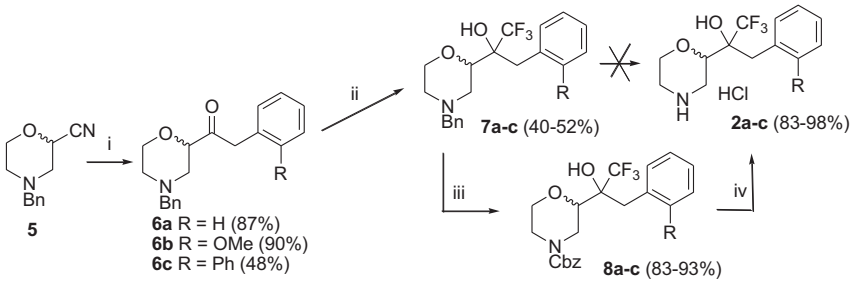
The *N*-debenzylation of compounds **7a**–**c** could not be achieved by standard hydrogenolysis. A two-step procedure has been applied: carbamate exchange with benzylchloroformate (compounds **8a**–**c**) [31] followed by hydrogenolysis using Pd/C 10%. Morpholino derivatives **2a**–**c** have been isolated in good yields as chloride salts. On the other hand, the pentafluoroethyl derivative **9** has been prepared only from **6a** (R=H) by addition of the pentafluoroethyllithium reagent (Scheme 4) and was obtained in a moderate yield (52%). The *N*-debenzylated compound **3** was obtained in good yield following the previously two-step procedure.

In this case, the reaction is highly diastereoselective leading to only one diastereoisomer like the closely related previously reported system by Cases-Thomas [8], and thus, the present isomer was strongly assumed to have a *cis* relative configuration due to the chelation-controlled attack of the organometallic reagent.

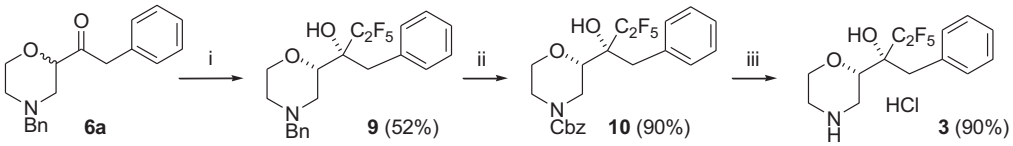
The same procedure was applied for the synthesis of fluorinated analogues **4a**–**d** (Scheme 5). The addition of phenylmagnesium bromide to the *N*-benzyl-2-cyanomorpholine **5** afforded the corresponding phenyl ketone **11** in good yield (79%). This latter was then submitted to various fluorinated organometallic reagents: lithium or magnesium reagents were prepared from commercially available halides ($CF_3CH_2CH_2I$, C_2F_5I, and $C_6F_5CH_2Br$) and from the iodomethyl-difluorocyclohexane prepared according to the literature [32]. The addition of these organometallic reagents to **11** was in all cases diastereoselective. Removal of the benzyl group as previously described, afforded compounds **4a**–**d** as single *cis* diastereoisomers in good yields (Scheme 5).



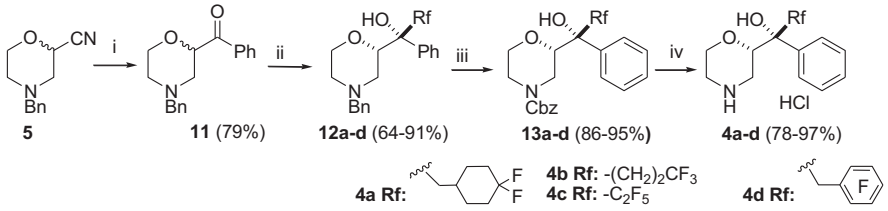
Scheme 1.



Scheme 3. Reagents and conditions: (i) ortho-substituted benzyl bromide, Mg, Et_2O 0 °C to rt, then HCl aq. 1 M 48–90%. (ii) CF_3TMS, CsF, toluene 0 °C to rt, then TBAF·$3H_2O$, THF 0 °C to rt, 40–52%. (iii) $PhCH_2OCOCl$ 5 equiv., THF 0 °C to rt, 1 day 83–93%. (iv) H_2, Pd/C 10%, MeOH at rt, then HCl/EtOH 6 M, EtOH 0 °C 30 min 83–98%.



Scheme 4. Reagents and conditions: (i) IC_2F_5, MeLi, Et_2O −78 °C, 45 min, then H_2O, 52%. (ii) $PhCH_2OCOCl$ 5 equiv., THF 0 °C to rt, 1 day 90%. (iii) H_2, Pd/C 10%, MeOH at rt, then HCl/EtOH 6 M, EtOH 0 °C 30 min 90%.



Scheme 5. Reagents and conditions: (i) phenyl bromide, Mg, Et_2O 0 °C to rt, then HCl aq. 1 M, 79%. (ii) R_fLi or R_fMgBr, Et_2O −78 °C or 0 °C to rt, 64–91%. (iii) $PhCH_2OCOCl$ 5 equiv., THF 0 °C to rt, 1 day 86–95%. (iv) H_2, Pd/C 10%, MeOH at rt, then HCl/EtOH 6 M, EtOH 0 °C 30 min 78–97%.

The *in vitro* binding affinities of fluorinated analogues **2**–**4** were measured on 5-HT, NE and DA transporters by competition assays using specific radioligands. Compounds **4a**–**d** in which the benzyl group have been replaced by a fluorinated substituent did not show any binding affinity to the transporters. In the same line the replacement of the phenyl group by a pentafluoroethyl substituent (compound **3**) did not afford any binding to the transporters. This loss of binding activity cannot be ascribed to the configuration of compounds **2**–**4** since, for the reference non fluorinated compounds (with benzyl and phenyl substituents) all 4 stereoisomers are active towards NE transporters with K_i values ranging from 3.2 to 160 nM [8]. These data seem to show that the benzyl substituent does not bring only hydrophobic interactions but more likely interactions through the aromatic group, such as π–stacking interactions. These assumptions could be supported by the loss of activity of the compound **4d**. Indeed the substitution of the aromatic protons by fluorine atoms modifies the electron density of the aromatic ring which could lead to a disruption of the π–stacking interactions. In contrast, the replacement of the phenyl substituent by a trifluoromethyl one resulted in a quite good binding activity to the norepinephrine transporter, with K_i = 240 nM for **2b** and 95 nM for the stereoisomer **2c$_2$** (Table 1). Considering they are mixture of diastereoisomers, it can be assumed that CF_3 well mimics the phenyl substituent.

This suggests that in this site: (i) π–π interactions are of less importance and (ii) both H-bond donor and acceptor ability of the alcohol function is not the main factor for binding affinity. Indeed a trifluoromethyl ethanol structure is more acidic than a benzyl one (pKa ∼ 12 vs 14–15) and conversely β-values are respectively 0 and 0.5 for CF_3CH_2OH and benzylic alcohol [33,34].

Table 1
NET, SERT and DAT binding affinities of fluorinated analogues.

Entry	Compound	*n*	R^1	R^2	K_i (μM)		
					SERT	NET	DAT
1	**2a**	1	CF_3	H	>10	>3	>10
2	**2b**	1	CF_3	OMe	>10	0.24	>10
3	**2c$_1$**	1	CF_3	Ph isomer 1	>10	1.7	>32
4	**2c$_2$**	1	CF_3	Ph isomer 2	>10	0.095	12
5	**3**	1	C_2F_5	H	>10	>10	>10
6	**4a**	0	$CH_2(C_6H_9F_2)$	H	>10	>10	>10
7	**4b**	0	$(CH_2)_2CF_3$	H	>10	>10	>10
8	**4c**	0	C_2F_5	H	>10	>10	>10
9	**4d**	0	$CH_2C_6F_5$	H	>10	>10	>10
10	**4a**	0	$CH_2(C_6H_9F_2)$	H	>10	>10	>10
11[a]	–	1	Ph	Ph	0.003	0.0037	0.0029

[a] Binding affinities of non-fluorinated reference compound [8].

3. Conclusions

In summary, we have designed and synthesized new fluorinated analogues of monoamines transporters inhibitors. Most of the fluorinated compounds exhibit low activity, only one exhibits a binding affinity to the transporters in the nanomolar range. Moreover, the half-life of non-fluorinated tertiary alcohols is usually very short and a possible advantage of replacing the phenyl group by a CF_3 could be the increase of the tertiary alcohol metabolic stability.

4. Experimental

4.1. General experimental procedures

Melting points were measured on a Stuart® SMP10 apparatus. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker® ARX 200 apparatus at respectively 300, 75 and 188 MHz (unless precised) in deutered solvent ($CDCl_3$, MeOD or DMSO) with TMS as internal standard for ^1H and ^{13}C and $CFCl_3$ for ^{19}F NMR. Mass spectra were performed on a Bruker® Esquire-LC apparatus. IR spectra were recorded on a Bruker® Vector 22 apparatus. Elemental analyses were carried out on an Ankersmit CAHN® 25 apparatus. TLC monitoring was performed with Merk® silica gel aluminium sheets (type 60 F_{254}). Visualization were performed under a SVL Bioblock Scientific lamp at 254 nm and/or by developing the plates with $KMnO_4$ solution followed by heating. Purifications were done by column chromatography at atmospheric pressure with Merk® silica gel (60 μm).

4.2. 4-Benzylmorpholine-2-carbonitrile 5

2-Chloroacrylonitrile (2.1 mL, 26.4 mmol) was added dropwise at 0 °C to a cooled solution of *N*-benzylethanolamine (3.8 mL) to 0 °C. The mixture was allowed to warm to room temperature and after 20 h of stirring, it was dissolved in 13 mL of anhydrous THF. The resulting solution was cooled to 0 °C for the addition of several portions of *t*-BuOK (4.40 g, 39.6 mmol). After 1 h of stirring, an aqueous solution of $NaHCO_3$ was added. The product was extracted several times with Et_2O and the organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. Purification of the resulting oil by chromatography on silica gel (cyclohexane/AcOEt: 9/1) provided 3.58 g (74%) of a yellow light oil, **5** as a racemic mixture. ^1H NMR ($CDCl_3$) δ ppm: 7.26–7.38 (m, 5H), 4.59 (t, 1H, *J* = 3.9 Hz), 4.02 (ddd, 1H, *J* = 11.7, 8.7, 2.7 Hz), 3.77 (dt, 1H, *J* = 11.7, 3.9 Hz), 3.61 (d, 1H, *J* = 13.2 Hz), 3.54 (d, 1H, *J* = 13.2 Hz), 2.76 (ddd, 1H, *J* = 12.0, 3.9, 1.2 Hz), 2.64 (dddd, 1H, *J* = 12.0, 3.9, 2.7, 1.2 Hz), 2.56 (dd, 1H, *J* = 12.0, 3.3 Hz), 2.42 (ddd, 1H, *J* = 12.0, 8.7, 3.3 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 136.7, 128.7, 128.3, 127.3, 117.0, 65.0, 64.3, 62.2, 54.4, 52.1. IR (cm^{-1}): 2817, 1454, 1114, 1094, 1022, 862, 742, 699. MS (APCI) *m/z:* 203 $(MH)^+$. Anal. Calcd for $C_{12}H_{14}N_2O$ (%): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.78; H, 7.05; N, 14.06.

4.3. General procedure and characterization for ketones 6a–c

I_2 or 1,2-dibromoethane was added to an anhydrous etheral solution (few mL) of magnesium in a three-neck round bottom flask fitted with a refluxing condenser. The flask was placed in an ice bath and an ethereal solution of the halogenated compound was introduced dropwise with a dropping funnel. After total addition of the halogenated compound solution, the mixture was allowed to warm to room temperature and was stirred for 30 min. The flask was cooled to 0 °C and an ethereal solution of compound **5** was added dropwise. The mixture was then allowed to warm to room temperature and was stirred for 2 h. Then, the mixture was cooled to 0 °C for the addition of a 1 M HCl aqueous solution. After 5 min of stirring, a 10 M NaOH aqueous solution was added and the product was extracted with Et_2O. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel to afford products as a racemic mixture.

4.3.1. 1-(4-Benzylmorpholin-2-yl)-2-phenylethanone 6a

Magnesium (972 mg, 40.0 mmol, I_2 (several crystals), benzyl chloride (5.06 g, 40.0 mmol in 20 mL of anhydrous Et_2O) and compound **5** (2.32 g, 11.5 mmol in 19 mL of anhydrous Et_2O) gave after purification (cyclohexane/AcOEt: 17/3) product **6a** (2.94 g, 87%) as a colourless oil. ^1H NMR ($CDCl_3$) δ ppm: 7.05–7.24 (m, 10H, HAr), 3.98 (dd, 1H, *J* = 10.1, 2.7 Hz, OCH), 3.86 (ddd, 1H, *J* = 11.1, 3.3, 2.1 Hz, OCH_2), 3.80 (d, 1H, *J* = 15.9 Hz, NCH_2Ph), 3.71 (d, 1H, *J* = 15.9 Hz, NCH_2Ph), 3.58 (td, 1H, *J* = 11.1, 2.1 Hz, OCH_2), 3.42 (d, 1H, *J* = 13.1 Hz, $COCH_2$), 3.35 (d, 1H, *J* = 13.1 Hz, $COCH_2$), 2.88 (ddd, 1H, *J* = 11.1, 2.7, 2.1 Hz, NCH_2CH), 2.53 (dq, 1H, *J* = 11.1, 2.1 Hz, NCH_2CH_2), 2.09 (td, 1H, *J* = 11.1, 3.3 Hz, NCH_2CH_2), 1.94 (dd, 1H, *J* = 11.1, 10.1 Hz, NCH_2CH). ^{13}C NMR ($CDCl_3$) δ ppm: 206.7 (CO), 137.4(Cq), 133.7 (Cq), 129.8, 129.2, 128.6, 128.4, 127.4, 126.9, 80.3 (OCH), 66.8 (CH_2), 63.2 (CH_2), 54.4 (CH_2), 52.6(CH_2), 45.3 (CH_2). IR (cm^{-1}): 2810, 1720, 1494, 1453, 1122, 1028, 738, 697. MS (APCI) *m/z:* 296 $(MH)^+$. Anal. Calcd for $C_{19}H_{21}NO_2$ (%): C, 77.26; H, 7.17; N, 4.74. Found: C, 76.90; H, 6.98; N, 4.50.

4.3.2. 1-(4-Benzylmorpholin-2-yl)-2-(2-methoxyphenyl)-ethanone 6b

Magnesium (2.64 g, 108.6 mmol), 1,2-dibromoethane (three drops), 2-methoxybenzyl chloride (5.00 g, 32.0 mmol in solution in 15 mL of anhydrous Et_2O) and compound **5** (1.74 g, 8.6 mmol in 14 mL of anhydrous Et_2O) gave, after purification (cyclohexane/AcOEt: 8/2), product **6b** (2.50 g, 90%) as a colourless oil. ^1H NMR ($CDCl_3$) δ ppm: 7.13–7.25 (m, 6H, HAr), 6.98 (dd, 1H, *J* = 7.5, 1.8 Hz, HAr), 6.82 (td, 1H, *J* = 7.5, 0.9 Hz, HAr), 6.76 (d, 1H, *J* = 8.4 Hz, HAr), 4.08 (dd, 1H, *J* = 10.0, 2.7 Hz, OCH), 3.90 (ddd, 1H, *J* = 11.1, 3.3, 2.1 Hz, OCH_2), 3.65 (s, 3H, OCH_3), 3.74 (s, 2H, $COCH_2$), 3.62 (td, 1H, *J* = 11.1, 2.1 Hz, OCH_2), 3.48 (d, 1H, *J* = 12.9 Hz, NCH_2Ph), 3.42 (d, 1H, *J* = 12.9 Hz, NCH_2Ph), 2.95 (ddd, 1H, *J* = 11.1, 2.7, 2.1 Hz, NCH_2CH), 2.57 (dq, 1H, *J* = 11.1, 2.1 Hz, NCH_2CH_2), 2.17 (td, 1H, *J* = 11.1, 3.3 Hz, NCH_2CH_2), 2.07 (dd, 1H, *J* = 11.1, 10.0 Hz, NCH_2CH). ^{13}C NMR ($CDCl_3$) δ ppm: 206.1 (CO), 157.2 (Cq), 137.2 (Cq), 131.3, 129.1, 128.3, 128.2, 127.2, 122.9 (Cq), 120.5, 110.3, 80.5 (OCH), 66.5 (CH_2), 63.1 (CH_2), 55.2(CH_3), 54.2 (CH_2), 52.5 (CH_2), 40.4 (CH_2). IR (cm^{-1}): 2811, 1723, 1495, 1456, 1246, 1115, 1029. MS (ESI) *m/z:* 348.2 $(MNa)^+$. Anal. Calcd for $C_{20}H_{23}NO_3$ (%): C, 73.82; H, 7.12; N, 4.30. Found: C, 74.31; H, 7.05; N, 4.14.

4.3.3. 1-(4-Benzylmorpholin-2-yl)-2-(2-phenylphenyl)-ethanone 6c

Magnesium (2.64 g, 108.6 mmol, 7.3 equiv.), 1,2-dibromoethane (three drops), 2-phenylbenzyl bromide (5.00 g, 20.2 mmol in solution in 15 mL of anhydrous Et_2O) and compound **5** (2.99 g, 14.8 mmol, 1 equiv. in 15 mL of anhydrous Et_2O) gave, after purification (cyclohexane/AcOEt: 9/1) product **6c** (2.64 g, 48%) as a colourless oil. ^1H NMR ($CDCl_3$) δ ppm: 7.16–7.40 (m, 14H, HAr), 3.90 (dd, 1H, *J* = 10.1, 2.7 Hz, OCH), 3.89 (d, 1H, *J* = 18.3 Hz, $COCH_2$), 3.80–3.86 (m, 1H, OCH_2), 3.81 (d, 1H, *J* = 18.3 Hz, $COCH_2$), 3.57 (td, 1H, *J* = 11.1, 2.1 Hz, OCH_2), 3.47 (d, 1H, *J* = 13.1 Hz, NCH_2Ph), 3.40 (d, 1H, *J* = 13.1 Hz, NCH_2Ph), 2.78 (ddd, 1H, *J* = 11.1, 2.7, 2.1 Hz, NCH_2CH), 2.48 (dq, 1H, *J* = 11.1, 2.1 Hz, NCH_2CH_2), 2.09 (td, 1H, *J* = 11.1, 3.3 Hz, NCH_2CH_2), 1.78 (dd, 1H, *J* = 11.1, 10.1 Hz, NCH_2CH). ^{13}C NMR ($CDCl_3$) δ ppm: 206.9(CO), 142.6 (Cq), 141.4 (Cq), 137.2 (Cq), 131.6 (Cq), 130.8, 130.0, 129.1, 129.1, 128.3, 128.1, 127.4, 127.3, 127.0, 127.0, 80.6 (OCH), 66.4 (CH_2), 63.1 (CH_2), 54.1 (CH_2), 52.4 (CH_2), 43.3 (CH_2). IR (cm^{-1}): 2923, 1721, 1126, 748, 703. MS (ESI) *m/z:* 372.2 $(MH)^+$, 394.1 $(MNa)^+$, 765.4 $(2MNa)^+$. Anal.

Calcd for $C_{25}H_{25}NO_2$ (%): C, 80.83; H, 6.78; N, 3.77. Found: C, 80.74; H, 6.64; N, 3.47.

4.4. General procedure and characterization for fluorinated alcohols 7a, 7b, $7c_1$ and $7c_2$

Dry $TMSCF_3$ and CsF were successively added to a 0 °C solution of carbonylated product **6** in anhydrous toluene under inert atmosphere. The mixture was allowed to warm to room temperature and stirred for 2 days. After removal of toluene under reduced pressure, the crude product was dissolved in Et_2O and the organic layer was washed with an aqueous solution of $NaHCO_3$. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was dissolved in THF, cooled to 0 °C, a 1 M solution of TBAF·$3H_2O$ in THF was added and the mixture was stirred for 1 h at room temperature. The solution was then washed with an aqueous solution of $NaHCO_3$ and with brine. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel to afford products as 2 racemic mixtures (1/1) of diastereoisomers.

4.4.1. 2-(4-Benzyl-morpholin-2-yl)-1,1,1-trifluoro-3-phenylpropan-2-ol 7a

Product **6a** (0.50 g, 1.7 mmol), $TMSCF_3$ (1.3 mL, 8.5 mmol), CsF (approximately 0.5 equiv.) and TBAF·$3H_2O$ (2.0 mL) gave after purification (cyclohexane/AcOEt: 9/1), product **7a** (322 mg, 52%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ ppm: 7.38–7.53 (m, 20H, HAr), 4.08–4.14 (m, 2H, OCH), 3.60–3.84 (m, 8H), 3.34–3.41 (m, 2H),), 3.00–3.11 (m, 4H), 2.71–2.78 (m, 2H), 2.32–2.55 (m, 4H). ^{13}C NMR ($CDCl_3$) δ ppm: 137.1, 137.1, 134.1, 134.0, 130.8, 130.7, 129.0, 128.9, 128.2, 128.2, 128.1, 128.0, 127.3, 127.2, 126.9, 126.9, 125.5 (q, J = 286.5 Hz), 125.5 (q, J = 285.9 Hz), 77.2 (q, J = 31.5 Hz), 76.4 (q, J = 26.2 Hz), 75.9, 66.7, 66.5, 63.1, 62.8, 52.9, 52.9, 52.7, 52.5, 37.4, 37.3. ^{19}F NMR ($CDCl_3$) δ ppm: −74.64, −74.84. IR (cm^{-1}): 2817, 1454, 1165, 1112, 741, 698. MS (ESI) m/z: 366 $(MH)^+$, 388 $(MNa)^+$. Anal. Calcd for $C_{20}H_{22}F_3NO_2$ + 0.33 H_2O (%): C, 64.68; H, 6.15; N, 3.77. Found: C, 64.46; H, 5.93; N, 3.52.

4.4.2. 2-(4-Benzyl-morpholin-2-yl)-1,1,1-trifluoro-3-(2-methoxyphenyl)-propan-2-ol 7b

Product **6b** (100 mg, 0.31 mmol), $TMSCF_3$ (230 μL, 1.5 mmol), CsF (approximately 0.5 equiv.) and 370 μL of TBAF·$3H_2O$ gave, after purification (cyclohexane/AcOEt: 9/1) 49 mg of product **7b** (40%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ ppm: 7.25–7.35 (m, 14H, HAr), 6.88–7.03 (m, 4H, HAr), 3.89–3.97 (m, 2H, OCH), 3.85 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.03–3.63 (m, 14H), 2.60–2.64 (m, 2H), 2.25–2.32 (m, 1H), 2.10–2.19 (m, 3H). ^{13}C NMR ($CDCl_3$) δ ppm: 157.2, 157.1, 137.6, 137.4, 133.5, 133.1, 129.1, 129.0, 128.7, 128.4, 128.2, 128.1, 127.1, 127.0, 125.9 (q, J = 286.0 Hz), 125.7 (q, J = 286.5 Hz), 123.4, 122.9, 121.5, 120.9, 110.6, 110.3, 77.2, 76.7 (q, J = 26.5 Hz), 76.6 (q, J = 25.8 Hz), 76.5, 67.2, 67.1, 63.3, 63.3, 55.5, 55.3, 53.3, 53.1, 52.6, 52.5, 32.6, 31.4. ^{19}F NMR ($CDCl_3$) δ ppm: −75.62, −76.89. IR (cm^{-1}): 2927, 1493, 1455, 1241, 1172, 1117, 1027, 751, 699. MS (ESI) m/z: 395.8 $(MH)^+$, 417.6 $(MNa)^+$. Anal. Calcd for $C_{21}H_{24}F_3NO_4$ + 0.33H_2O (%): C, 61.91; H, 6.27; N, 3.44. Found: C, 61.83; H, 6.08; N, 3.18.

4.4.3. 2-(4-Benzyl-morpholin-2-yl)-3-biphenyl-2-yl-1,1,1-trifluoropropan-2-ol $7c_1$ and $7c_2$

Product **6c** (100 mg, 0.270 mmol), $TMSCF_3$ (200 μL, 1.54 mmol), CsF (approximately 0.5 equiv.) and 320 μL of TBAF·$3H_2O$ gave after purification eluting with cyclohexane/AcOEt: 9/1, product **7c** (50 mg, 42%) as a colourless oil containing a mixture of 2 diastereoisomers. They could be separated after a tedious chromatography (cyclohexane/AcOEt: 9/1) to give $\mathbf{7c_1}$ (16 mg, 13%) and $\mathbf{7c_2}$ (20 mg, 17%).

Characterization of $\mathbf{7c_1}$: ^{1}H NMR ($CDCl_3$) δ ppm: 7.13–7.48 (m, 14H), 3.77 (dt, 1H, J = 11.4, 4.5 Hz), 3.35–3.46 (m, 3H), 3.11–3.25 (m, 3H), 2.56 (d, 1H, J = 11.9 Hz), 2.41 (d, 1H, J = 11.9 Hz), 2.03 (td, 1H, J = 10.5, 3.3 Hz), 1.92 (t, 1H, J = 10.5 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 143.4, 141.7, 138.1, 132.1, 131.8, 130.6, 130.1, 129.7, 129.3, 129.2, 128.6, 128.4, 128.3, 127.8, 127.4, 127.3, 127.3, 127.2, 125.5 (q, J = 286.9 Hz), 76.5 (q, J = 26.2 Hz), 75.6, 66.6, 63.2, 53.2, 52.3, 33.1. ^{19}F NMR ($CDCl_3$) δ ppm: −75.81. IR (cm^{-1}): 3493, 2963, 1252, 1163, 1096, 1043, 800, 755, 741, 698. MS (ESI) m/z: 442.4 $(MH)^+$, 464.3 $(MNa)^+$. Anal. Calcd for $C_{26}H_{26}F_3NO_2$ + 0.25H_2O (%): C, 69.32; H, 6.04; N, 3.11. Found: C, 69.24; H, 5.82; N, 2.49.

Characterization of $\mathbf{7c_2}$: ^{1}H NMR ($CDCl_3$) δ ppm: 7.52–7.57 (m, 1H), 7.15–7.32 (m, 13H), 3.67 (ddd, 1H, J = 1.1, 2.0, 11.1 Hz), 3.00–3.38 (m, 6H), 2.34 (d, 1H, J = 11.4 Hz), 1.97 (d, 1H, J = 11.4 Hz), 1.84 (td, 2H, J = 11.1 3.0 Hz), ^{13}C NMR ($CDCl_3$) δ ppm: 143.4, 141.6, 137.7, 132.6, 131.4, 130.4, 129.7, 128.7, 128.3, 128.2, 127.2, 127.0, 127.0, 127.0, 125.6 (q, J = 286.9 Hz), 75.9 (q, J = 26.2 Hz), 75.6, 67.3, 62.6, 53.4, 51.7, 31.8. ^{19}F NMR ($CDCl_3$) δ ppm: −76.42. IR (cm^{-1}): 3495, 2961, 1255, 1160, 1098, 1043, 801, 757, 740, 699. MS (ESI) m/z: 442.4 $(MH)^+$, 464.4 $(MNa)^+$. Anal. Calcd for $C_{26}H_{26}F_3NO_2$ + 1H_2O (%): C, 67.96; H, 6.14; N, 3.05. Found: C, 67.55; H, 5.81; N, 2.52.

4.5. General procedure and characterization for compounds 8a, 8b, $8c_1$ and $8c_2$

Benzyl chloroformate was added dropwise to a 0 °C solution of product **7** in anhydrous THF under inert atmosphere. The resulting mixture was allowed to warm to room temperature and was stirred for one day. An aqueous solution of $NaHCO_3$ was added and product **8** was extracted with Et_2O. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel.

4.5.1. Benzyl 2-(1-benzyl-2,2,2-trifluoro-1-hydroxyethyl)morpholine-4-carboxylate 8a

Product **7a** (1.50 g, 4.1 mmol) and benzyl chloroformate (2.9 mL, 20.6 mmol) gave, after purification eluting with cyclohexane/AcOEt: 9/1, 1.39 g (83%) of product **8a** (colourless oil) as 2 racemic mixtures (1/1) of diastereoisomers. ^{1}H NMR ($CDCl_3$) δ ppm: 7.17–7.28 (m, 20H), 5.07 (s, 2H), 5.03 (s, 2H), 4.13–4.24 (br s, 2H), 3.81–3.91 (m, 4H), 3.26–3.41 (m, 4H), 3.16 (d, 1H, J = 14.4 Hz), 3.11 (d, 1H, J = 14.4 Hz), 2.86–3.00 (m, 6H). ^{13}C NMR ($CDCl_3$) δ ppm: 155.1, 140.8, 136.3, 130.8, 129.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 127.3, 127.2, 126.9, 126.0 (q, J = 285.0 Hz), 76.3, 75.9, 75.9 (q, J = 26.2 Hz), 67.5, 67.4, 43.8, 37.0, 36.9. ^{19}F NMR ($CDCl_3$) δ ppm: −74.87, −75.66. IR (cm^{-1}): 3317, 2861, 1674, 1437, 1239, 1170, 1105, 732, 695. MS (ESI) m/z: 432.5 $(MNa)^+$. Anal. Calcd for $C_{21}H_{22}F_3NO_4$ (%): C, 62.61; H, 5.42; N, 3.42. Found: C, 62.74; H, 5.30; N, 3.21.

4.5.2. (2-Methoxyphenyl)methyl 2-(1-benzyl-2,2,2-trifluoro-1-hydroxyethyl)morpholine-4-carboxylate 8b

Product **7b** (450 mg, 1.2 mmol) and benzyl chloroformate (0.82 mL, 5.7 mmol) gave, after purification eluting with cyclohexane/AcOEt: 9/1, 0.47 g (93%) of product **8b** (colourless oil) as 2 racemic mixtures (1/1) of diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ ppm: 7.20–7.37 (m, 14H), 6.88–7.00 (m, 4H), 5.06–5.19 (m, 4H), 4.53–4.70 (m, 2H), 4.22–4.25 (m, 2H), 3.93–3.39 (m, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.62 (dd, 1H, J = 10.9, 1.9 Hz), 3.49 (td, 1H, J = 11.6, 1.8 Hz), 2.92–3.39 (m, 8H), 2.82 (t, 1H, J = 12.1 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 157.1, 157.0, 155.1, 155.0, 136.4, 136.4, 133.4, 132.8, 128.9, 128.6, 128.4, 128.3, 128.3, 128.0, 127.8, 127.7, 125.7 (q, J = 285.8 Hz), 125.5 (q, J = 286.3 Hz), 123.0, 122.5, 121.5, 121.1,

110.7, 110.4, 77.1, 76.4 (q, J = 26.7 Hz), 67.2, 67.0, 66.9, 66.8, 55.5, 55.4, 44.0, 43.7, 43.3, 43.3, 32.5, 31.3. ^{19}F NMR (376 MHz, $CDCl_3$, 323 K) δ ppm: −75.48, −77.58. MS (ESI) *m/z:* 462.0 $(MNa)^+$. Anal. Calcd for $C_{22}H_{24}F_3NO_5$ (%): C, 60.13; H, 5.51; N, 3.19. Found: C, 60.31; H, 5.62; N, 2.95.

4.5.3. Benzyl 2-[2,2,2-trifluoro-1-hydroxy-1-[(2-phenylphenyl)methyl]ethyl]morpholine-4-carboxylate **8c$_1$**, **8c$_2$**

8c$_1$: Product **7c$_1$** (510 mg, 1.2 mmol) and benzyl chloroformate (0.83 mL, 5.8 mmol) gave, after purification (cyclohexane/AcOEt: 9/1) product **8c$_1$** (470 mg, 84%) as a yellow oil as one racemic mixture. ^{1}H NMR ($CDCl_3$) δ ppm: 7.30–7.54 (m, 14H), 5.20 (s, 2H), 3.90–4.23 (m, 3H), 3.45–3.50 (m, 3H), 2.88–3.03 (m, 2H), 2.45–2.58 (m, 1H). ^{13}C NMR ($CDCl_3$) δ ppm: 155.0, 143.4, 141.4, 136.3, 131.7, 131.1, 130.6, 129.8, 129.5, 128.9, 128.5, 128.4, 128.4, 128.1, 128.1, 127.9, 127.2, 127.2, 127.0, 125.4 (q, J = 292.2 Hz), 76.2, 76.1 (q, J = 26.7 Hz), 67.3, 67.2, 43.4, 43.4, 32.5. ^{19}F NMR ($CDCl_3$) δ ppm: −75.70. MS (ESI) *m/z:* 508.4 $(MNa)^+$. IR (cm^{-1}): 2923, 1700, 1432, 1235, 1169, 1109, 748, 699. Anal. Calcd for $C_{27}H_{26}F_3NO_4 + 0.25H_2O$ (%): C, 66.18; H, 5.45; N, 2.86. Found: C, 66.13; H, 5.12; N, 2.66.

8c$_2$: Product **7c$_2$** (358 mg, 0.8 mmol) and benzyl chloroformate (0.58 mL, 4.1 mmol) gave, after purification eluting with cyclohexane/AcOEt: 9/1, product **8c$_2$** (335 mg, 85%) as a yellow oil as one racemic mixture. ^{1}H NMR ($CDCl_3$) δ ppm: 7.39–7.42 (m, 1H), 7.11–7.30 (m, 13H), 5.07 (d, 1H, J = 12.3 Hz), 4.99 (d, 1H, J = 12.3 Hz), 3.70–3.82 (m, 3H), 3.15–3.33 (m, 3H), 2.68–2.96 (m, 2H), 2.47 (t, 1H, J = 12.2 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 155.1, 143.7, 141.4, 136.4, 132.0, 131.2, 130.6, 129.5, 128.5, 128.3, 128.1, 127.9, 127.2, 127.1, 126.9, 125.2 (q, J = 287.4 Hz), 76.0, 75.6 (q, J = 26.8 Hz), 67.3, 66.9, 43.4, 43.3, 32.5. ^{19}F NMR ($CDCl_3$) δ ppm: −76.68. IR (cm^{-1}): 2929, 1700, 1431, 1236, 1173, 1106, 750, 699. MS (ESI) *m/z:* 508.4 $(MNa)^+$. Anal. Calcd for $C_{27}H_{26}F_3NO_4 + 0.5H_2O$ (%): C, 65.58; H, 5.50; N, 2.83. Found: C, 65.40; H, 5.50; N, 2.65.

4.6. General procedure and characterization for hydrochloride compounds **2a**, **2b**, **2c$_1$** and **2c$_2$**

Pd/C (30% in mass) was added to a solution of carbamate **9** in MeOH. The mixture was vigorously stirred for one night under H_2 atmosphere and after four filtrations on celite and concentration under reduced pressure; the crude product was dissolved in absolute ethanol. The resulting solution was cooled to 0 °C and a few drops of a 7 M ethanolic solution of HCl were added. After 30 min of stirring, EtOH and HCl were removed under reduced pressure. Few drops of $CDCl_3$ were added to the crude product and addition of cyclohexane provided precipitation of the product. The solid was then washed several times with distilled cyclohexane and distilled Et_2O.

4.6.1. 1,1,1-Trifluoro-2-morpholin-2-yl-3-phenylpropan-2-ol hydrochloride **2a**

Product **8a** (139 mg, 0.34 mmol) and Pd/C (42 mg) gave product **2a** (100 mg, 95%) as a yellow light solid containing 2 racemic mixtures (1/1) of diastereoisomers. M.p. = 178–182 °C; ^{1}H NMR (MeOD) δ ppm: 7.29–7.40 (m, 10H), 4.27 (dd, 1H, J = 13.4, 4.1 Hz), 4.19 (dd, 1H, J = 11.7, 3.5 Hz), 3.97 (dd, 1H, J = 11.7, 2.1 Hz), 3.85 (td, 1H, J = 12.6, 2.1 Hz), 3.39–3.60 (m, 4H), 3.12–3.27 (m, 8H), 3.01–3.09 (m, 2H). ^{13}C NMR (75 MHz, MeOD) δ ppm: 135.9, 135.4, 132.3, 132.2, 129.4, 129.3, 128.4, 125.6 (q, J = 285.0 Hz), 125.5 (q, J = 285.9 Hz), 76.7 (q, J = 26.3 Hz), 76.1 (q, J = 26.1 Hz), 75.5, 74.1, 65.6, 65.1, 44.7 (q, J = 4.0 Hz), 44.1, 43.9 (q, J = 2.3 Hz), 43.7, 38.4 (q, J = 2.1 Hz), 37.9 (q, J = 1.0 Hz). ^{19}F NMR (188 MHz, $CDCl_3$) δ ppm: −74.74, −76.31. MS (ESI) *m/z:* 276.3 $(M)^+$. IR (cm^{-1}): 3123, 2262, 2480, 1603, 1456, 1183, 1154, 1132, 1080, 755, 700. Anal. Calcd for $C_{13}H_{17}F_3ClNO_2 + 0.6H_2O$ (%): C, 48.41; H, 5.69; N, 4.34. Found: C, 48.32; H, 5.23; N, 3.96.

4.6.2. 1,1,1-Trifluoro-3-(2-methoxyphenyl)-2-(morpholin-2-yl)-propan-2-ol hydrochloride **2b**

Product **8b** (200 mg, 0.46 mmol) and Pd/C (60 mg) gave product **2b** (129 mg, 83%) as a yellow sticky oil containing 2 racemic mixtures (1/1) of diastereoisomers. ^{1}H NMR (MeOD) δ ppm: 7.27–7.37 (m, 4H), 6.93–7.08 (m, 4H), 4.14–4.26 (m, 2H), 4.04 (d, 1H, J = 10.8 Hz), 3.91 (s, 3H), 3.90 (s, 3H), 3.65–3.75 (m, 2H), 2.89–3.47 (m, 13H). ^{13}C NMR (75 MHz, MeOD) δ ppm: 159.3, 159.2, 134.2, 134.1, 130.3, 130.0, 127.3 (q, J = 286.0 Hz), 126.9 (q, J = 285.5 Hz), 124.1, 123.3, 122.1, 121.9, 112.2, 112.1, 77.7 (q, J = 26.8 Hz), 77.4 (q, J = 26.3 Hz), 75.9, 75.2, 65.7, 65.2, 56.4, 56.3, 44.7 (q, J = 3.1 Hz), 44.2 (q, J = 2.5 Hz), 44.1, 43.9, 32.6, 31.6. ^{19}F NMR (188 MHz, MeOD) δ ppm: −78.58, −76.74. MS (ESI) *m/z:* 306.3 $(M)^+$. IR (cm^{-1}): 3355, 2263, 2454, 1587, 1492, 1441, 1271, 1235, 1216, 1172, 1144, 1125, 1094, 1013, 761. Anal. Calcd for $C_{22}H_{24}F_3NO_5 + 0.75H_2O$ (%): C, 47.33; H, 5.83; N, 3.94. Found: C, 47.45; H, 5.61; N, 3.72.

4.6.3. 1,1,1-Trifluoro-2-(morpholin-2-yl)-3-(2-phenylphenyl)-propan-2-ol hydrochloride **2c$_1$**, **2c$_2$**

2c$_1$: Product **8c$_1$** (135 mg, 0.28 mmol) and Pd/C (41 mg) gave product **2c$_1$** (100 mg, 93%) as a yellow sticky oil as one racemic mixture. ^{1}H NMR (MeOD) δ ppm: 7.56–7.62 (m, 1H), 7.07–7.35 (m, 8H), 3.66 (dd, 1H, J = 12.8, 3.5 Hz), 3.36–3.44 (m, 2H), 3.13–3.23 (m, 2H), 2.85–3.03 (m, 4H). ^{13}C NMR (MeOD) δ ppm: 145.1, 143.0, 132.7, 132.6, 131.8, 130.8, 129.3, 128.2, 128.2, 128.2, 127.2 (q, J = 286.4 Hz), 77.4 (q, J = 26.2 Hz), 75.3, 65.6, 44.6 (q, J = 3.8 Hz), 43.9, 33,9 (q, J = 2.3 Hz). ^{19}F NMR (MeOD) δ ppm: −76.90. MS (ESI) *m/z:* 352.3 $(M)^+$. IR (cm^{-1}): 3365, 2930, 1650, 1480, 1453, 1255, 1171, 1126, 1104, 752, 705. Anal. Calcd for $C_{19}H_{21}ClF_3NO_2$ (%): C, 58.84; H, 5.46; N, 3.61. Found: C, 59.03; H, 5.59; N, 3.73.

2c$_2$: Product **8c$_2$** (194 mg, 0.40 mmol) and Pd/C (58 mg) gave product **2c$_2$** (152 mg, 98%) as a yellow sticky oil as one racemic mixture. ^{1}H NMR (MeOD) δ ppm: 7.52–7.55 (m, 1H), 7.12–7.36 (m, 8H), 3.72–3.85 (m, 2H), 3.55 (t, 1H, J = 13.6 Hz), 3.30 (d, 1H, J = 14.4 Hz), 3.09 (d, 1H, J = 14.4 Hz), 3.03–3.12 (m, 1H), 2.91 (d, 1H, J = 13.6 Hz), 2.81 (td, 1H, J = 12.0, 3.6 Hz), 2.38 (t, 1H, J = 12.0 Hz). ^{13}C NMR (MeOD) δ ppm: 145.0, 143.3, 133.1, 133.0, 131.7, 130.9, 129.3, 128.2, 128.1, 128.1, 126.9 (q, J = 286.4 Hz), 77.4 (q, J = 26.2 Hz), 75.1, 64.9, 44.1 (q, J = 2.5 Hz), 43.7, 32.7. ^{19}F NMR (MeOD) δ ppm: −78.91. MS (ESI) *m/z:* 352.4 $(M)^+$. IR (cm^{-1}): 3387, 2925, 1655, 1453, 1176, 1102, 750, 704. Anal. Calcd for $C_{19}H_{21}ClF_3NO_2 + 0.4H_2O$ (%): C, 57.77; H, 5.57; N, 3.55. Found: C, 57.71; H, 5.59; N, 3.17.

4.7. 2-(4-Benzyl-morpholin-2-yl)-3,3,4,4,4-pentafluoro-1-phenylbutan-2-ol **9**

An anhydrous ethereal solution (20 mL) of **6a** (917 mg, 3.1 mmol) was cooled to −78 °C. Under anhydrous conditions, CF_3CF_2I (2.5 g, 10.1 mmol) was bubbling into the mixture and a 1.6 M ethereal solution of methyl lithium was added (4.8 mL, 7.7 mmol). After 45 min of stirring at −78 °C, an aqueous solution of HCl 1 M was added. The mixture was basified with a 10 M aqueous solution of NaOH and the product was extracted with Et_2O. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica (cyclohexane/AcOEt: 8/2) to afford product **9** (664 mg, 1 racemic mixture) as a colourless oil with the yield of 52%. ^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ ppm: 7.26–7.38 (m, 10H, HAr), 3.92 (dd, 1H, J = 11.1, 1.8 Hz), 3.70 (d, 1H, J = 10.0 Hz), 3.62 (td, 1H, J = 11.3, 2.3 Hz), 3.44–3.55 (m, 2H), 3.17 (d, 1H, J = 14.8 Hz), 3.04 (d, 1H, J = 14.8 Hz), 2.89 (d, 1H, J = 11.3 Hz), 2.64 (d, 1H, J = 11.1 Hz), 2.16–2.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$,

323 K) δ ppm: 137.5, 134.7, 131.2, 129.2, 128.4, 128.2, 127.4, 127.0, 111.8–121.0 (m, CF_2, CF_3), 76.9, 76.7, 67.2, 63.4, 53.2, 52.7, 36.9. ^{19}F NMR (376 MHz, $CDCl_3$, 300 K): δ ppm: −78.66 (s, 3F, CF_3), −118.49 (d, 1F, J = 285.8 Hz, CF_2), −119.41 (d, 1F, J = 285.8 Hz, CF_2). IR (cm^{-1}): 3529, 3477, 3032, 1496, 1455, 1331, 1214, 1177, 1108, 1027, 744, 698. MS (APCI) *m/z:* 416.3 $(MH)^+$. Anal. Calcd for $C_{21}H_{22}F_5NO_2$ (%): C, 60.72; H, 5.34; N, 3.37. Found: C, 61.01; H, 5.42; N, 3.16.

4.8. [2-(1-Benzyl-2,2,3,3,3-pentafluoro-1-hydroxy-propyl)morpholin-4-yl] 2-phenylacetate 10

See protocol used for synthesis of products **9a**–**c**. Product **8** (580 mg, 1.4 mmol) and benzyl chloroformate (0.99 mL, 6.9 mmol) gave, after purification eluting with cyclohexane/AcOEt: 9/1, product **10** (570 mg, 90%, 1 racemic mixture) as a colourless oil. ^{1}H NMR (400 MHz, DMSO, 333 K) δ ppm: 7.27–7.35 (m, 10H), 5.06 (d, 1H, J = 12.0 Hz), 5.02 (d, 1H, J = 12.0 Hz), 4.09 (d, 1H, J = 12.0 Hz), 3.92 (dd, 1H, J = 12.0, 4.0 Hz), 3.77 (d, 1H, J = 12.0 Hz), 2.87–3.19 (m, 6H). ^{13}C NMR (100 MHz, DMSO, 333 K) δ ppm: 154.2, 136.6, 134.3, 130.9, 128.2, 127.6, 127.2, 126.5, 112.9–121.7 (m, CF_2, CF_3), 76.7, 76.7 (t, J = 19.0 Hz), 66.3, 66.2, 43.3, 43.1, 37.3. ^{19}F NMR (376 MHz, DMSO, 353 K) δ ppm: −77.04 (s, 3F, CF_3), −116.38 (d, 1F, J = 282.0 Hz, CF_2), −117.86 (d, 1F, J = 282.0 Hz, CF_2). IR (cm^{-1}): 3380, 1681, 1435, 1213, 1177, 1106, 1004, 988, 753, 697. MS (APCI) *m/z:* 460.2 $(MH)^+$. Anal. Calcd for $C_{22}H_{22}F_5NO_4 + H_2O$ (%): C, 57.07; H, 4.88; N, 3.03. Found: C, 56.71; H, 5.29; N, 2.87.

4.9. 3,3,4,4,4-Pentafluoro-2-morpholin-2-yl-1-phenylbutan-2-ol hydrochloride 3

See protocol used for synthesis of products **2a**–**c**. Product **10** (230 mg, 0.5 mmol) and Pd/C (66 mg) gave 156 mg of product **3** (90%, 1 racemic mixture) as a yellow oil. ^{1}H NMR (300 MHz, MeOD) δ ppm: 7.28–7.38 (m, 5H, HAr),), 4.15 (dd, 1H, J = 12.9, 3.6 Hz, OCH_2), 3.37–3.52 (m, 3H), 3.03–3.31 (m, 5H). ^{13}C NMR (75 MHz, MeOD) δ ppm: 135.4 (CqAr), 132.3 (CHAr), 129.3 (CHAr), 128.4 (CHAr), 114.8–133.1 (m, CF_2, CF_3), 78.3 (t, J = 20.6 Hz, $COHCF_2$), 76.2 (OCH), 65.5 (OCH_2), 44.5 (t, J = 5.3 Hz, NCH_2CH), 44.0 (NCH_2CH_2), 38.8 (CH_2Ph). ^{19}F NMR (188 MHz, MeOD) δ ppm: −79.85 (s, 3F, CF_3), −119.34 (d, 1F, J = 283.0 Hz, CF_2), −121.59 (d, 1F, J = 283.0 Hz, CF_2). MS (APCI) *m/z:* 326.2 $(M)^+$. IR (cm^{-1}): 3254, 2741, 2431, 2116, 1449, 1335, 1212, 1181, 1141, 1094, 1004, 715. Anal. Calcd for $C_{14}H_{17}ClF_5NO_2 + 0.5H_2O$ (%): C, 45.35; H, 4.89; N, 3.78. Found: C, 45.16; H, 4.94; N, 4.03.

4.10. (4-Benzyl-morpholin-2-yl)-phenylmethanone 11

Several crystals of I_2 and 1 mL of phenyl bromide were added to an anhydrous etheral solution (few mL) of magnesium (8.56 g, 352 mmol) in a three-neck round bottom flask fitted with a refluxing condenser. The flask was placed in an ice bath and a solution of phenyl bromide (14.8 mL, 140.8 mmol in 75 mL of anhydrous Et_2O) was introduced dropwise. After total addition of the halogenated compound solution, the mixture was allowed to warm to room temperature and was stirred for 15 min. The flask was cooled to 0 °C and the solution of product **5** (7.09 g, 35.2 mmol, in solution in 75 mL of anhydrous Et_2O) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 1.5 h. The mixture was cooled to 0 °C for the addition of a 1 M HCl aqueous solution. After 5 min of stirring, a 10 M NaOH aqueous solution was added and product **11** was extracted with Et_2O and CH_2Cl_2. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel eluting with cyclohexane/AcOEt: 8/2 to give product **11** (7.79 g, 79% mmol, 1 racemic mixture) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.86–7.89 (m, 2H), 7.43–7.49 (m, 1H), 7.32–7.38 (m, 2H), 7.14–7.26 (m, 5H), 4.83 (dd, 1H, J = 9.9, 2.7, Hz), 3.94 (ddd, 1H, J = 11.1, 3.3, 2.1 Hz), 3.74 (td, 1H, J = 11.1, 2.7 Hz), 3.51 (d, 1H, J = 13.2 Hz), 3.41 (d, 1H, J = 13.2 Hz), 2.98 (dt, 1H, J = 11.4, 2.1 Hz), 2.61 (dq, 1H, J = 11.4, 2.1 Hz), 2.16–2.28 (m, 2H).^{13}C NMR ($CDCl_3$) δ ppm: 196.7, 137.3, 135.0, 133.3, 129.0, 128.8, 128.4, 128.2, 127.2, 78.0, 67.0, 63.1, 55.0, 52.5. MS (APCI) *m/z*: 282 $(MH)^+$. IR (cm^{-1}): 2806, 1689, 1449, 1204, 1119, 1027, 739, 693. Anal. Calcd for $C_{18}H_{19}NO_2$ (%): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.54; H, 6.68; N, 4.99.

4.11. General procedure and characterization for compounds 12a and 12b

Under inert atmosphere, a solution of *tert*-butyl lithium (1.6 M in pentane) was added to an anhydrous ethereal solution of iodide compound cooled to −85 °C. After 5 min of stirring, an ethereal solution of methanone **11** was added and the resulting mixture was stirred at −85 °C for 2 h. The mixture was allowed to warm to room temperature after addition of an aqueous solution of $NaHCO_3$. The product was extracted with Et_2O; the organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was purified by chromatography on silica gel. Products were obtained in the form of 1 racemic mixture.

4.11.1. 1-(4-Benzyl-morpholin-2-yl)-2-(4,4-difluoro-cyclohexyl)-1-phenylethanol 12a

1,1-Difluoro-4-iodomethyl-cyclohexane (613 mg, 2.4 mmol, in 15 mL of anhydrous ether), *tert*-butyl lithium (1.5 mL, 2.4 mmol), product **11** (335 mg, 1.2 mmol) in 15 mL of anhydrous Et_2O, gave, after purification eluting with cyclohexane/AcOEt: 8/2, product **12a** (311 mg, 64%) as a yellow solid. M.p. = 106–108 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 7.09–7.27 (m, 10H), 3.97 (dt, 1H, J = 11.1, 3.6 Hz), 3.56–3.66 (m, 2H), 3.37 (d, 1H, J = 12.6 Hz), 3.08 (d, 1H, J = 12.6), 2.42 (dt, 1H, J = 3.3, 11.4 Hz), 2.01–2.11 (m, 4H), 0.96–1.92 (m, 10H). ^{13}C NMR ($CDCl_3$) δ ppm: 142.5, 137.2, 129.2, 128.2, 128.1, 127.2, 126.7, 125.5, 123.6 (dd, J = 237.8, 240.7 Hz), 80.4, 78.4, 66.2, 63.2, 53.1, 52.3, 44.7, 33.4 (dd, J = 22.3, 23.4 Hz), 31.2, 30.3 (d, J = 9.9 Hz). ^{19}F NMR ($CDCl_3$) δ ppm: −91.19 to −92.68 (m, 1F), −101.25 to −103.09 (m, 1F). IR (cm^{-1}): 3554, 2937, 2874, 1447, 1359, 1111, 1030, 963, 939, 914, 859, 743, 699. MS (APCI) *m/z:* 416 $(MH)^+$. Anal. Calcd for $C_{25}H_{31}F_2NO_2 + 0.33H_2O$ (%): C, 71.23; H, 7.57; N, 3.32. Found: C, 71.16; H, 7.21; N, 3.36.

4.11.2. 1-(4-Benzyl-morpholin-2-yl)-4,4,4-trifluoro-1-phenylbutan-1-ol 12b

1,1,1-Trifluoro-3-iodopropane (2.87 g, 12.8 mmol, in 22 mL of anhydrous Et_2O), *tert*-butyl lithium (8 mL, 12.8 mmol), product **11** (1.2 g, 4.3 mmol, in 22 mL of anhydrous Et_2O), gave, after purification (cyclohexane/AcOEt: 8.5/1.5), product **12b** (1.38 g, 85%) as a yellow light solid. M.p. = 71–72 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 7.09–7.23 (m, 10H), 3.97 (dt, 1H, J = 11.4, 3.6 Hz), 3.60–3.67 (m, 2H), 3.38 (d, 1H, J = 12.9 Hz), 3.08 (d, 1H, J = 12.9 Hz), 2.43 (dt, 1H, J = 12.3, 3.6 Hz), 2.34 (dd, 1H, J = 13.2, 3.6 Hz), 2.04–2.09 (m, 4H), 1.90–1.95 (m, 1H), 1.39–1.60 (m, 1H). ^{13}C NMR ($CDCl_3$) δ ppm: 141.1, 137.2, 129.2, 128.4, 128.3, 127.8 (q, J = 274.4 Hz), 127.2, 127.1, 125.3, 79.7, 77.2, 66.2, 63.2, 53.1, 52.3, 31.9 (q, J = 2.3 Hz), 28.3 (q, J = 28.35 Hz). ^{19}F NMR ($CDCl_3$) δ ppm: −66.55 (t, J = 11.1 Hz). IR (cm^{-1}): 3541, 3029, 2949, 2862, 1451, 1385, 1316, 1254, 1231, 1129, 1069, 1042, 993, 913, 872, 739, 700. MS (APCI) *m/z:* 380 $(MH)^+$. Anal. Calcd for $C_{21}H_{24}F_3NO_2$ (%): C, 66.48; H, 6.38; N, 3.69. Found: C, 66.34; H, 6.11; N, 3.63.

4.12. 1-(4-Benzylmorpholin-2-yl)-3,3,3,3,3-pentafluoro-1-phenylprop-2-yn-1-ol 12c

Under inert atmosphere, CF_3CF_2I (4.0 g, 16.3 mmol) was added to an anhydrous etheral solution (20 mL) of **11** (1.50 g, 5.3 mmol) cooled to −78 °C. A solution of methyl lithium (1.6 M in Et_2O, 4.7 mL, 7.5 mmol) was added and after 45 min of stirring at −78 °C, the reaction mixture was treated with an aqueous solution of HCl, basified with a 10 M aqueous solution of NaOH and the product was extracted with Et_2O. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel (cyclohexane/AcOEt: 8/2). Product **12c** (1.94 g, 91%, 1 racemic mixture) was obtained as a white pinkish solid. M.p. = 59–60 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 7.59–7.61 (m, 2H), 7.25–7.40 (m, 8H), 5.14–5.20 (br s, 1H, OH), 4.50–4.53 (m, 1H), 4.19 (dt, 1H, J = 11.7, 3.6 Hz), 3.89 (ddd, 1H, J = 11.7, 9.3, 3.0 Hz), 3.50 (d, 1H, J = 13.1 Hz), 3.27 (d, 1H, J = 13.1 Hz), 2.62 (dt, 1H, J = 3.0, 11.7), 2.24–2.33 (m, 2H), 2.11 (dd, 1H, J = 8.3, 11.7 Hz). ^{13}C NMR ($CDCl_3$) δ ppm: 136.7, 134.7, 129.1, 128.5, 128.2, 128.1, 127.2, 126.1, 110.3–121.5 (m, CF_2, CF_3), 77.9 (t, J = 21.9 Hz), 75.1, 66.0, 62.9, 52.5, 51.9. ^{19}F NMR ($CDCl_3$) δ ppm: −78.79 (s, 3F, CF_3), −119.44 (d, 1F, J = 277.3 Hz, CF_2), −122.03 (d, 1F, J = 277.3 Hz, CF_2). IR (cm^{-1}): 2817, 1453, 1221, 1175, 1136, 1111, 1069, 1029, 870, 745, 716, 699. MS (APCI) *m/z:* 402 $(MH)^+$. Anal. Calcd for $C_{20}H_{20}F_5NO_2$ (%): C, 59.85; H, 5.02; N, 3.49. Found: C, 59.65; H, 4.96; N, 3.55.

4.13. (4-Benzylmorpholin-2-yl)-2-(2,3,4,5,6-pentafluorophenyl)-1-phenylethanol 12d

Anhydrous Et_2O (2 mL), several crystals of I_2 and a piece of 2,3,4,5,6-pentafluorobenzyl bromide were introduced under inert atmosphere, in a three-neck round bottom flask fitted with a refluxing condenser, containing Magnesium (1.04 g, 42.7 mmol). The flask was immediately placed in an ice bath, an ethereal solution of 2,3,4,5,6-pentafluorobenzyl bromide (4.40 g, 17.0 mmol, in 22 mL of anhydrous Et_2O) was introduced dropwise at 0 °C and the mixture was stirred for 15 min. An ethereal solution of product **11** (1.2 g, 4.3 mmol, in 11 mL of anhydrous Et_2O) was then added dropwise at 0 °C. The mixture was allowed to warm to room temperature, was stirred for 1.5 h and was cooled to 0 °C for the addition of an aqueous solution of $NaHCO_3$. Product **12d** was extracted with Et_2O. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was purified by chromatography on silica gel (cyclohexane/AcOEt: 8/2) to give product **12d** (1.47 g, 74%, racemic mixture) as a yellow light solid. M.p. = 91–92 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 7.05–7.17 (m, 10H), 3.90–3.95 (m, 2H), 3.66 (td, 1H, J = 10.5, 2.4 Hz), 3.54 (d, 1H, J = 13.6), 3.33 (d, 1H, J = 12.9 Hz), 3.03 (d, 1H, J = 12.9 Hz), 2.96 (d, 1H, J = 13.6 Hz), 2.42 (d, 1H, J = 11.4 Hz), 2.17 (d, 1H, J = 11.4 Hz), 1.94–2.03 (m, 2H). ^{13}C NMR ($CDCl_3$) δ ppm: 140.4, 137.2, 129.0, 128.1, 127.8, 127.2, 127.0, 125.2, 110.7–147.4 (m, CF), 79.1, 77.5, 66.5, 63.0, 53.1, 52.0, 33.6. ^{19}F NMR ($CDCl_3$) δ ppm: −140.5 (d, J = 7.7 Hz, 1F), −140.6 (d, J = 7.7 Hz, 1F), −157.8 (t, J = 20.9 Hz, 1F), −164.1 to −164.4 (m, 2F). IR (cm^{-1}): 3585, 2881, 1522, 1498, 1449, 1172, 1126, 1070, 1008, 955, 867, 747, 702. MS (APCI) *m/z:* 464 $(MH)^+$. Anal. Calcd for $C_{25}H_{22}F_5NO_2$ (%): C, 64.79; H, 4.78; N, 3.02. Found: C, 64.63; H, 4.70; N, 2.97.

4.14. General procedure and characterization for benzylcarboxylate compounds 13a–d

Benzyl chloroformate was added dropwise to a 0 °C solution of product **12** in anhydrous THF under inert atmosphere. The resulting mixture was allowed to warm to room temperature and was stirred for one day. An aqueous solution of $NaHCO_3$ was added and product **13** was extracted with Et_2O. The organic layer was dried over magnesium sulphate, filtrated and concentrated under reduced pressure. The resulting oil was then purified by chromatography on silica gel to obtain products as a racemic mixture.

4.14.1. Benzyl-2-[2-(4,4-difluorocyclohexyl)-1-hydroxy-1-phenylethyl]morpholine-4-carboxylate 13a

Product **12a** (239 mg, 0.58 mmol), THF (4.5 mL) and benzyl chloroformate (0.4 mL, 2.9 mmol) gave, after purification (cyclohexane/AcOEt: 8/2), product **13a** (228 mg, 86%) as a colourless oil. ^{1}H NMR (400 MHz, 328 K, $CDCl_3$) δ ppm: 7.18–7.39 (m, 10H), 5.09 (d, 1H, J = 12.6 Hz), 4.99 (d, 1H, J = 12.6 Hz), 3.92–4.00 (m, 2H), 3.62 (td, 1H, J = 11.6, 2.5 Hz), 3.48 (dd, 1H, J = 10.7, 1.7 Hz), 3.38 (d, 1H, J = 13.2 Hz), 2.92 (td, 1H, J = 12.8, 3.4, Hz), 2.75 (dd, 1H, J = 13.2, 11.6 Hz), 2.12 (dd, 1H, J = 14.8, 6.0 Hz), 1.77 (dd, 1H, J = 14.8, 4.0 Hz), 1.08–2.04 (m, 9H). ^{13}C NMR (100 MHz, 323 K, $CDCl_3$) δ ppm: 155.3, 141.2, 136.7, 128.5, 128.0, 127.6, 127.3, 125.5, 123.5 (dd, J = 239.0, 240.0 Hz), 81.4, 77.2, 67.2, 67.0, 45.0, 43.9, 43.8, 33.6 (t, J = 24.0 Hz), 31.3, 30.4 (dd, J = 9.0, 2.0 Hz). ^{19}F NMR (376 MHz, 300 K, $CDCl_3$) δ ppm: −91.65 (d, 1F, J = 235.7 Hz), −101.81 (d, 1F, J = 235.7 Hz). IR (cm^{-1}): 3526, 2933, 2862, 1699, 1429, 1359, 1272, 1233, 1106, 1029, 964, 941, 868, 760, 735, 700. MS (ESI) *m/z:* 483 $(MNa)^+$.

4.14.2. Benzyl-2-(4,4,4-trifluoro-1-hydroxy-1-phenylbutyl)morpholine-4-carboxylate 13b

Product **12b** (1.11 g, 2.9 mmol), THF (22 mL) and benzyl chloroformate (2.1 mL, 14.7 mmol) gave, after purification on silica gel eluting with cyclohexane/AcOEt: 8/2, product **13b** (1.16 g, 94%) as a white solid. M.p. = 118 °C. ^{1}H NMR (400 MHz, 328 K, $CDCl_3$) δ ppm: 7.20–7.39 (m, 10H), 5.12 (d, 1H, J = 12.5 Hz), 5.02 (d, 1H, J = 12.5 Hz), 3.95–4.02 (m, 2H), 3.65 (td, 1H, J = 11.8, 2.8 Hz), 3.59 (dd, 1H, J = 10.8, 2.1 Hz), 3.45 (d, 1H, J = 13.2 Hz), 2.94 (td, 1H, J = 13.2, 3.6 Hz), 2.80 (dd, 1H, J = 13.2, 11.2 Hz), 2.46 (td, 1H, J = 13.2, 3.6 Hz), 2.13–2.30 (m, 1H), 2.02 (td, 1H, J = 13.2, 4.4 Hz), 1.63–1.75 (m, 1H). ^{13}C NMR (75 MHz, 300 K, $CDCl_3$) δ ppm: 154.9, 139.5, 136.2, 128.4, 128.2, 127.7, 127.5 (q, J = 274.5 Hz), 127.3, 126.6, 124.9, 80.3, 75.5, 66.8, 66.5, 43.6, 31.6, 28.6 (q, J = 28.6 Hz). ^{19}F NMR (188 MHz, 300 K, $CDCl_3$) δ ppm: −66.34 (t, J = 10.7 Hz). IR (cm^{-1}): 3495, 1683, 1434, 1370, 1294, 1253, 1232, 1117, 1069, 983, 875, 764, 738, 709, 698, 654. MS (ESI) *m/z:* 446 $(MNa)^+$. Anal. Calcd for $C_{22}H_{24}F_3NO_4$ (%): C, 62.40; H, 5.71; N, 3.31. Found: C, 62.25; H, 5.69; N, 3.24.

4.14.3. Benzyl-2-(-3,3,3,3,3-pentafluoro-1-hydroxy-1-phenyl-prop-2-ynyl)morpholine-4-carboxylate 13c

Product **12c** (1.62 g, 4.0 mmol), THF (20 mL) and benzyl chloroformate (2.8 mL, 20.2 mmol) gave, after purification on silica gel (cyclohexane/AcOEt: 8/2), product **13c** (1.71 g, 95%) as a white solid. M.p. = 92 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 328 K) δ ppm: 7.59–7.60 (m, 2H), 7.26–7.40 (m, 8H), 5.19 (d, 1H, J = 12.4 Hz), 5.06 (d, 1H, J = 12.4 Hz), 4.29 (d, 1H, J = 10.3 Hz), 3.97–4.02 (m, 1H), 3.99 (dd, 1H, J = 11.5, 3.2 Hz), 3.71 (td, 1H, J = 11.5, 2.6 Hz), 3.53 (d, 1H, J = 13.2 Hz), 2.94 (td, 1H, J = 13.2, 3.2 Hz), 2.69 (dd, 1H, J = 13.2, 11.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ ppm: 155.0, 136.2, 133.1, 128.9, 128.4, 128.0, 127.3, 126.8, 126.0, 119.0 (qt, J = 287.0, 36.0 Hz, CF_3), 114.4 (qt, J = 265.0, 34.0 Hz, CF_2), 76.5 (t, J = 21.5 Hz), 75.6, 67.2, 66.5, 43.5, 43.2. ^{19}F NMR (188 MHz, $CDCl_3$, 300 K) δ ppm: −78.84 (s, 3F, CF_3), −119.28 (d, 1F, J = 277.6 Hz, CF_2), −121.70 (d, 1F, J = 277.6 Hz, CF_2). IR (cm^{-1}): 3507, 1704, 1429, 1219, 1176, 1136, 1070, 866, 717. MS (ESI) *m/z:* 468.0 $(MNa)^+$. Anal. Calcd for $C_{21}H_{20}F_5NO_4$ (%): C, 56.63; H, 4.53; N, 3.14. Found: C, 56.65; H, 4.45; N, 3.10.

4.14.4. Benzyl-2-[1-hydroxy-2-(2,3,4,5,6-pentafluorophenyl)-1-phenyl-ethyl]morpholine-4-carboxylate **13d**

Product **12d** (899 mg, 1.9 mmol), THF (14 mL) and benzyl chloroformate (1.4 mL, 9.7 mmol) gave, after purification on silica gel (cyclohexane/AcOEt: 8/2), product **13d** (920 mg, 93%) as a translucent solid. M.p. = 112–115 °C. ^{1}H NMR (400 MHz, 328 K, $CDCl_3$) δ ppm: 7.20–7.34 (m, 10H), 5.12 (d, 1H, J = 12.5 Hz), 5.00 (d, 1H, J = 12.5 Hz), 3.96–4.04 (m, 2H), 3.84 (dd, 1H, J = 10.8, 1.8 Hz), 3.71 (td, 1H, J = 11.8, 2.7 Hz), 3.53–3.60 (m, 2H), 3.10 (d, 1H, J = 13.6 Hz), 2.95 (td, 1H, J = 13.1, 3.4, Hz), 2.75 (dd, 1H, J = 13.6, 10.8, Hz). ^{13}C NMR (75 MHz, 300 K, $CDCl_3$) δ ppm: 155.0, 139.0, 136.3, 128.2, 128.0, 127.7, 127.5, 126.7, 125.0, 110.2–147.3 (m, CF), 79.3, 76.5, 66.9, 66.7, 43.6, 43.3, 33.6. ^{19}F NMR (188 MHz, 300 K, $CDCl_3$) δ ppm: −140.77 (d, J = 7.7 Hz, 1F), −140.89 (d, J = 7.7 Hz, 1F), −157.34 (t, J = 19.7 Hz, 1F), −164.00 (d, J = 19.7 Hz, 1F), −164.11 (d, J = 19.7 Hz, 1F). IR (cm^{-1}): 3513, 2930, 1698, 1520, 1500, 1428, 1272, 1235, 1177, 1124, 1013, 957, 910, 887, 733, 701. MS (ESI) m/z: 530 $(MNa)^+$. Anal. Calcd for $C_{26}H_{22}F_5NO_4$ (%): C, 61.54; H, 4.37; N, 2.76. Found: C, 61.33; H, 4.33; N, 2.68.

4.15. General procedure and characterization for hydrochloride compounds 4a–d

Pd/C (30% in mass) was added to a solution of carboxylate **13** in MeOH. The mixture was vigorously stirred for one night under H_2 atmosphere and after four filtrations on celite and concentration under reduced pressure; the crude product was dissolved in absolute ethanol. The resulting solution was cooled to 0 °C and a few drops of a 7 M ethanolic solution of HCl were added. After 30 min of stirring, EtOH and HCl were removed under reduced pressure. Few drops of $CDCl_3$ were added to the crude product and addition of cyclohexane provided precipitation of the compound **4**. The solid was then washed several times with distilled cyclohexane and distilled Et_2O. Products **4** were obtained as a racemic mixture.

4.15.1. 2-(4,4-Difluorocyclohexyl)-1-(morpholin-2-yl)-1-phenylethanol hydrochloride 4a

Product **13a** (172 mg, 0.38 mmol) and Pd/C (52 mg) gave product **4a** (131 mg, 97%) as a white solid. M.p. = 170–176 °C ^{1}H NMR (MeOD) δ ppm: 7.51 (d, 2H, J = 7.2 Hz), 7.40 (t, 2H, J = 7.2 Hz), 7.30 (t, 1H, J = 7.2 Hz), 4.21 (d, 1H, J = 13.2 Hz), 3.91–4.00 (m, 2H), 3.24 (d, 1H, J = 12.6 Hz), 2.96–3.14 (m, 2H), 2.54 (d, 1H, J = 12.6 Hz), 2.18–2.23 (m, 1H), 0.98–1.95 (m, 10H). ^{13}C NMR (MeOD) δ ppm: 142.9, 129.5, 128.4, 126.8, 124.5 (dd, J = 236.9, 239.9 Hz, CF_2), 80.8, 77.8, 64.8, 44.5, 44.0, 43.8, 34.4 (dd, J = 24.0, 26.3 Hz, CH_2CF_2), 32.3, 31.3 (dd, J = 14.3, 9.3 Hz, $CH_2CH_2CF_2$). ^{19}F NMR (MeOD) δ ppm: −93.26 (d, 1F, J = 234.8 Hz), −103.59 (br d, 1F, J = 234.8 Hz). IR (cm^{-1}): 3563, 3334, 2938, 1448, 1360, 1212, 1099, 963, 941, 915, 865, 701. MS (APCI) m/z: 326 $(M)^+$. Anal. Calcd for $C_{18}H_{26}ClF_2NO_2 + 2H_2O$ (%): C, 54.34; H, 7.60; N, 3.52. Found: C, 54.35; H, 6.83; N, 3.08.

4.15.2. 4,4,4-Trifluoro-1-(morpholin-2-yl)-1-phenylbutan-1-ol hydrochloride 4b

Product **13b** (300 mg, 0.70 mmol) and Pd/C (90 mg) gave product **4b** (216 mg, 94%) as a white solid. M.p. = 206–208 °C ^{1}H NMR (MeOD) δ ppm: 7.51 (d, 2H, J = 7.2 Hz), 7.43 (t, 2H, J = 7.2 Hz), 7.33 (t, 1H, J = 7.2 Hz), 4.23 (d, 1H, J = 12.6 Hz), 4.08 (d, 1H, J = 11.4 Hz), 4.00 (t, 1H, J = 12.6 Hz), 3.27 (d, 1H, J = 12.6 Hz), 3.10–3.17 (m, 1H), 3.06 (t, 1H, J = 11.4 Hz), 2.60 (d, 1H, J = 12.6 Hz), 2.51 (t, 1H, J = 12.6 Hz), 2.04–2.29 (m, 2H), 1.55 (q, 1H, J = 12.6 Hz). ^{13}C NMR (MeOD) δ ppm: 141.6, 129.9, 129.1 (q, J = 273.3 Hz, CF_3), 128.8, 126.6, 80.1, 76.6, 64.9, 44.0, 43.9, 31.7 (q, J = 2.7 Hz, CH_2CH_2CF3), 29.2 (q, J = 28.4 Hz, CH_2CF_3). ^{19}F NMR (MeOD) δ ppm: −68.22 (t, J = 11.1 Hz). IR (cm^{-1}): 3390, 2957, 1449, 1391, 1315, 1257, 1134, 1095, 1075, 1000, 762, 700. MS (APCI) m/z: 290 $(M)^+$. Anal. Calcd for $C_{14}H_{19}ClF_3NO_2 + 0.75H_2O$ (%): C, 49.56; H, 6.09; N, 4.13. Found: C, 49.46; H, 5.91; N, 4.05.

4.15.3. 3,3,3,3,3-Pentafluoro-1-(morpholin-2-yl)-1-phenylprop-2-yn-1-ol hydrochloride 4c

Product **13c** (300 mg, 0.67 mmol) and Pd/C (90 mg) gave product **4c** (190 mg, 81%) as a white solid. M.p. = 240–248 °C ^{1}H NMR (MeOD) δ ppm: 7.63–7.65 (m, 2H), 7.41–7.48 (m, 3H), 4.76 (d, 1H, J = 12.6 Hz), 4.25 (dd, 1H, J = 12.6, 3.6 Hz), 4.04 (t, 1H, J = 12.6 Hz), 3.30 (d, 1H, J = 12.6 Hz), 3.16 (td, 1H, J = 12.6, 3.6 Hz), 2.95 (t, 1H, J = 12.6 Hz), 2.52 (d, 1H, J = 12.6 Hz). ^{13}C NMR (MeOD) δ ppm: 135.0, 130.4, 129.8, 127.4, 112.3–122.2 (m, CF_2, CF_3), 77.7 (t, J = 21.6 Hz), 76.4, 64.7, 43.6, 43.2. ^{19}F NMR (MeOD) δ ppm: −80.26 (s, 3F, CF_3), −119.05 (d, 1F, J = 277.7 Hz, CF_2), −123.01 (d, 1F, J = 277.7 Hz, CF_2). IR (cm^{-1}): 3324, 1213, 1182, 1142, 835, 716, 648. MS (ESI) m/z: 312 $(M)^+$. Anal. Calcd for $C_{13}H_{15}ClF_5NO_2 + 2/3H_2O$ (%): C, 44.06; H, 4.65; N, 3.95. Found: C, 44.13; H, 4.31; N, 3.80.

4.15.4. 1-(Morpholin-2-yl)-2-(2,3,4,5,6-pentafluorophenyl)-1-phenylethanol hydrochloride 4d

Product **13d** (300 mg, 0.59 mmol) and Pd/C (90 mg) gave product **4d** (189 mg, 78%) as a white solid. M.p. = 242–244 °C ^{1}H NMR (MeOD) δ ppm: 7.39–7.42 (m, 2H), 7.25–7.35 (m, 3H), 4.45 (dd, 1H, J = 11.1, 2.1 Hz), 4.30 (dd, 1H, J = 12.6, 3.9 Hz), 4.11 (td, 1H, J = 12.6, 2.1 Hz), 3.61 (d, 1H, J = 14.1 Hz), 3.31–3.36 (m, 2H), 3.19 (td, 1H, J = 12.6, 3.9 Hz), 3.02 (t, 1H, J = 12.6 Hz), 2.70 (d, 1H, J = 12.6 Hz). ^{13}C NMR (MeOD) δ ppm: 141.0, 129.3, 128.9, 126.7, 112.2–148.9 (m, CF), 79.0, 77.8, 65.0, 43.9, 43.8, 33.9. ^{19}F NMR (MeOD) δ ppm: −141.39 (d, J = 7.7 Hz, 1F), −141.50 (d, J = 7.7 Hz, 1F), −160.80 (t, J = 19.9 Hz, 1F), −167.26 to −167.56 (m, 2F). IR (cm^{-1}): 3570, 2779, 1525, 1502, 1446, 1178, 1126, 1098, 1014, 963, 950, 872, 748, 704, 621, 581. MS (APCI) m/z: 374 $(M)^+$. Anal. Calcd for $C_{18}H_{17}ClF_5NO_2 + 0.5H_2O$ (%): C, 51.62; H, 4.33; N, 3.34. Found: C, 51.78; H, 4.16; N, 3.37.

4.16. Monoamine transporter binding assays

4.16.1. Binding at hSERT, hNET and hDAT

Binding affinity was determined by competition using [^{3}H]citalopram (2 nM, PerkinElmer Life Sciences), [^{3}H]nisoxetine (2 nM, Amersham) and [^{3}H]GBR12909 (1 nM, PerkinElmer Life Sciences) as radioligands for hSERT, hNET and hDAT, respectively. Membranes prepared from HEK293 cells, Madin–Darby canine kidney cells and CHO cells stably expressing hSERT, hNET and hDAT, respectively, and purchased from PerkinElmer Life Sciences (Beltsville, MD) were incubated in a buffer containing HEPES (20 mM), NaCl (120 mM) and KCl (5 mM) with the radioligand and competing ligand in a final volume of 250 μL for 2 h at 22 °C. Non-specific binding was defined with paroxetine (1 μM) for hSERT, desipramine (10 μM) for hNET and GBR12909 (10 μMp) for hDAT.

4.16.2. Data analysis for binding studies

At the end of the incubation period, membranes were filtered through Whatman (Packard, Meriden, CT) GF/B filters pretreated with 0.1% polyethylenimine. Radioactivity retained on the filters was determined by scintillation counting. Binding isotherms were analyzed by nonlinear regression using Prism software (GraphPad Software Inc., San Diego, CA) to determine IC_{50} values. These were converted to inhibition constants (K_i) by use of the Cheng–Prusoff equation: $K_i = IC_{50}/\{(L/K_D) - 1\}$, where L is the concentration of ^{3}H-labeled ligand and K_D is its dissociation constant determined in saturation binding experiments. The K_D values were as follows: 2 nM for [^{3}H]citalopram at hSERTs; 2.2 nM for [^{3}H]nisoxetine at hNETs and 1 nM for [^{3}H]GBR12909 at hDATs.

Acknowledgements

We thank the French MENRT for awarding a research fellowship to C. Philippe and the Research Institute of Servier for the monoamine transporter binding assays.

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