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Synthesis and in vitro evaluation of fluorinated diphenyloxide derivatives and sulfur analogs as serotonin transporter ligands

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ABSTRACT

As the serotonin transporter (SERT) is involved in several neurodegenerative and psychiatric disorders; radiopharmaceuticals to image the SERT by PET would be valuable in studying these diseases. To this end we synthesized diphenyloxide derivatives and sulfide analogs, as new tracers, incorporating a fluorine or oxyalkyl fluorinated group on 4′ or 5′-position on phenyl ring B. Three of these exhibited good to high in vitro affinity ($7 < K_i < 8$ nM) and selectivity for the SERT over the other monoamine transporters.

1. Introduction

The serotonin transporter (SERT) plays a pivotal role in the regulation of serotoninergic neurotransmission by clearance of serotonin from the synaptic cleft via reuptake into the presynaptic neuron.[1,2] Alteration of serotoninergic neurotransmission is associated with psychiatric disorders[3–5] such as depression and several neurodegenerative[6,7] such as Alzheimer's and Parkinson's diseases. In the brain the SERT is widely distributed in the thalamus and the raphe. In humans, SERT in vivo imaging to assess the transporter density or functionality by positron emission tomography (PET) would assist in the early diagnosis and follow-up of treatment of these diseases.[8,9] Different classes of compounds have been screened for their SERT affinity (for review see Ref. 10) such as the 3-amino-4-[2-(dimethylaminomethyl)phenylsulphanyl] benzonitrile (DASB)[11,12] or *N,N*-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine (MADAM).[13] These derivatives which are labeled with carbon-11 have to be used at the site of C-11 production and have to display an appropriate in vivo kinetics commensurate with the short half life of C-11 ($T_{1/2}$ = 20.4 min). Today, fluorine-18 (half-life: 109.8 min) represents one of the most attractive positron-emitting radioisotope. Its half time is long enough to do kinetic studies or plasma metabolite analysis. The radiolabeling could be performed by multi-step synthetic pathways, by aliphatic nucleophilic fluorination or aromatic electrophilic fluorination. For these reasons, several fluorinated diphenylsulfide analogs have been synthesized as PET tracers for imaging the SERT. These include: [^{18}F]AFM,[14] [^{18}F]AFA,[14,15] [^{18}F]AFC[16] or 5-[^{18}F]F-ADAM,[17] [^{18}F]AFE and [^{18}F]AFP[18] (Fig. 1).

Our contribution to this field has been the synthesis of several of these derivatives expanding the structure–activity profile of these classes.[13,19] As a results of these studies, we proposed that a *N,N*-dimethylaminomethyl group in position 1 on phenyl ring A and an amino function at position 2′ of ring B of the diphenyl sulfide structure yield compounds such as MADAM[13] (Fig. 1) with high in vitro and in vivo affinity in monkeys[20] and the good selectivity for the SERT that could be attributed to the methyl in 5′-position on ring B.

Several studies have been performed evaluating the impact of substituent on the 2′-, 4′- or 5′-position on ring B (Fig. 1) but very few studies have been achieved on ring A. Recently 5-position has been studied,[21–23] with a diphenylsulfide core, but to our knowledge, nothing has been performed at the 4-position.

In parallel, the substitution of the sulfur atom of IDAM by an oxygen (ODAM,[24] Fig. 1) results in a little effect on the in vitro SERT affinity (K_{iSERT} = 0.171 nM), increased brain uptake, slower kinetics and peripheral metabolism.[24,25] Vercouillie et al. have also observed this result in an in vitro study.[19,23] Furthermore, it has been shown in our previous study that for one derivative of these compounds, the sulfone analog (which could be an in vivo MADAM metabolite) does not possess any affinity for the SERT.[19] For these two reasons, it could be interestingly to investigate the diphenyloxide skeleton.

So, we hypothesized that a series of fluoro (on A ring) diphenyl oxide or sulfide derivatives built on the MADAM structure should provide insight into SERT binding properties. In this paper, we

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report the synthesis and in vitro evaluation of eight new fluoro derivatives.

2. Chemistry

All of the compounds tested for their in vitro binding properties (**7a–c** and **14–16**) were synthesized as shown in Schemes 1 and 2. 2-Amino-4-fluoro-benzoic acid **1a** was converted to a diazonium, displaced by sulfur. The intermediate disulfide was reduced with zinc in acetic acid to give the thiol **2** in 62% yield. All the carboxylic acids (**2**, **1b**,**c** and **8a**,**b**) were converted to the amides **3**, **4a**,**b**, and **9a**,**b**, respectively, by amidification with P_2O_5 in DMF, for 2 days under reflux (36%, 52%, 85%, 38% and 76% yield, respectively, not improved). The diphenyl compounds **5a–c** and **10a**,**b** were obtained by an Ullmann condensation performed via a copper-catalyzed coupling of 1-bromo-4-methyl-2-nitrobenzene using K_2CO_3 as a base, in DMF. Reduction of the amide function of compounds **5a–c** and **10a**,**b** was achieved using BH_3/THF complex to provide the benzylamino derivatives **6a–c**, and **11a**,**b** (42–95% yields, not improved). The nitro group of **6a–c**, and **11a**,**b** was reduced using tin(II) chloride in concentrated hydrochloric acid solution and methanol to give the corresponding amino derivatives **7a–c** and **12a**,**b** (62–73% yields, not improved). The phenolic derivatives **13a**,**b** were obtained by demethylation with BBr_3. This free hydroxyl OH was alkylated with 1-bromo-fluoro-ethane or -butane in DMF with Cs_2CO_3 as basic agent to give the target compounds **14a**,**b** and **16** (Scheme 2). For oxypropyl chain, the fluorotosylpropane ester was used as reactant, in presence of K_2CO_3 to give **15a**,**b** in 33% yields.

3. In vitro evaluation

In vitro affinities of derivatives **7** and **14–16** were evaluated by competition studies using tritiated ligands of SERT ([^{3}H]citalopram), DAT ([^{3}H]GBR12935), and NET ([^{3}H]nisoxetine) (see Table 1). For each compound and each transporter, K_i values were only determined when 100 nM of a target compound inhibited at least 50% of tritiated ligand binding (IC_{50} <100 nM) in accordance with the published procedure.[26]

4. Results and discussion

Regarding the excellent affinity for the SERT and their good selectivity toward the two other monoamines transporters (DAT and NET), many diphenylsulfide analogs radiolabeled with carbon-11 have been described; however no suitable fluorine-18 ligand has been developed to date. Several chemical modulations have been reported on the 4- and 5-position on B ring, but A ring is not fully explored, especially the 5-position. As previously mentioned by Vercouillie et al.[23] the 5-position on A ring lead to suit-

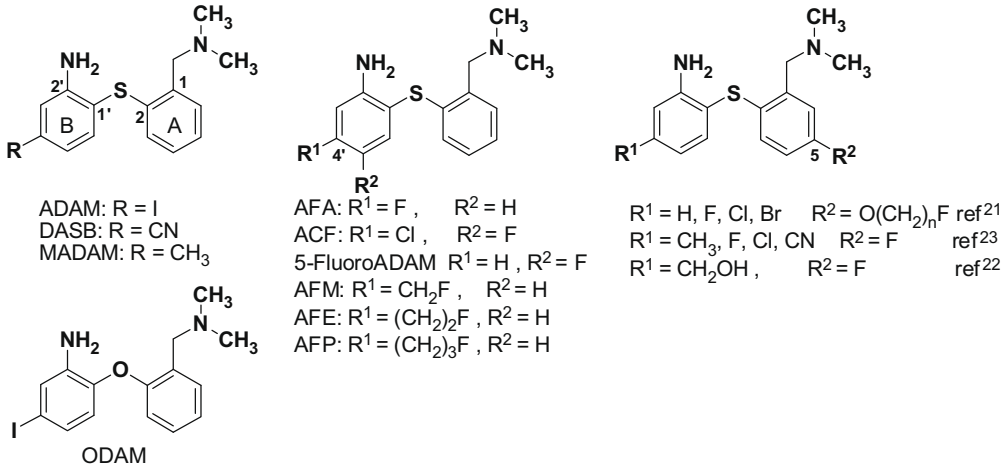
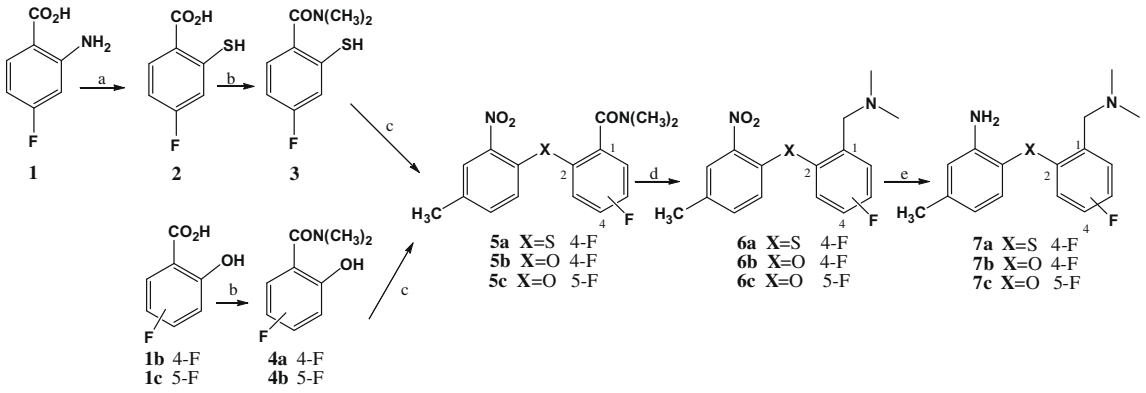
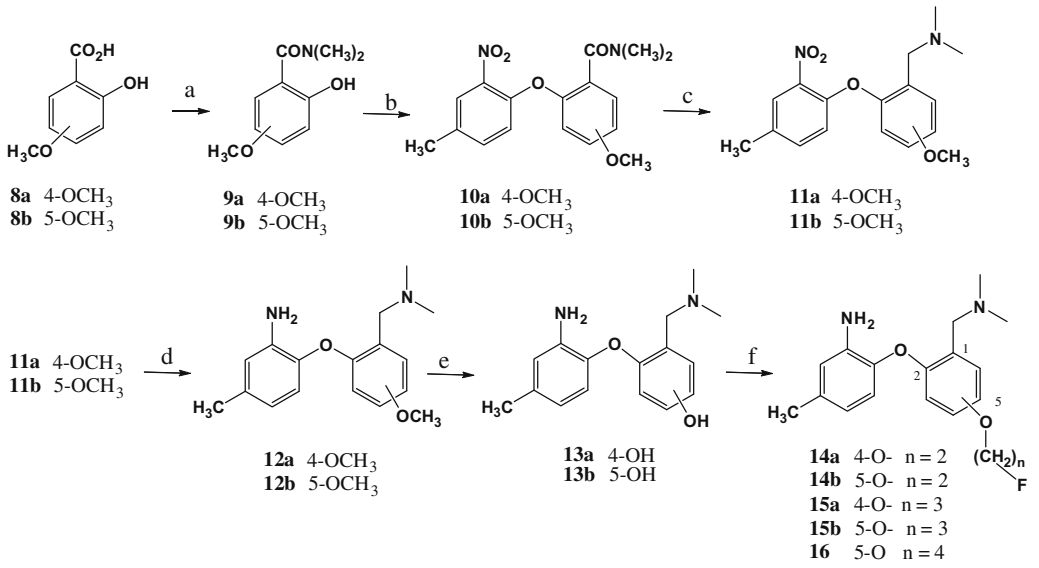


Figure 1. Structure of literature SERT ligands for potential PET imaging.



Scheme 1. Syntheses of target compounds **7a–c**. Reagents and conditions: (a) (1) $NaNO_2$, HCl, Na_2S_2, 5 °C, then rt 2 h; (2) CH_3COOH, Zn, reflux, 4 h; (3) NaOH diluted, reflux 30 min; (b) P_2O_5, DMF, 160 °C, 2 days; (c) 1-bromo-4-methyl-2-nitrobenzene, DMF, K_2CO_3, Cu, reflux, 17 h; (d) BH_3/THF, reflux 4 h, rt overnight, HCl/H_2O reflux 2 h; (e) $SnCl_2$/HCl/MeOH, 5 °C to rt overnight.



Scheme 2. Syntheses of target compounds **14**–**16**. Reagents and conditions: (a) P_2O_5, DMF, 160 °C, 2 days; (b) 1-bromo-4-methyl-2-nitrobenzene, DMF, K_2CO_3, Cu, reflux, 17 h; (c) BH_3/THF, reflux 4 h, rt overnight, HCl/H_2O reflux 2 h; (d) $SnCl_2$/HCl/MeOH, 5 °C to rt overnight; (e) (1) BBr_3, CH_2Cl_2, −40 °C to rt overnight; (2) MeOH, 1 h, rt; (f) for **14a**,**b** and **16**: bromo-fluoro-ethane or -butane, DMF, Cs_2CO_3, reflux, 4 h; for **15a**,**b**: fluoro-*O*-tosylate-propanol, DMF, K_2CO_3, 70 °C, overnight.

Table 1
Binding affinities of the new derivatives for monoamine transporters

Compd	hSERT [^{3}H]Citalopram K_i[a] (nM)	hNET [^{3}H]Nisoxetine K_i[a] (nM)	hDAT [^{3}H]WIN35428 K_i[a] (nM)
1b (MADAM)	1.65 ± 0.10		
7a	13 ± 1.4	1203 ± 78	1220 ± 219
7b	7 ± 0.2	503 ± 17	960 ± 18
7c	8 ± 0.2	1245 ± 43	503 ± 28
14a	519 ± 25	8854 ± 365	726 ± 55
14b	401 ± 75	667 ± 23	4186 ± 412
15a	445 ± 24	>500	>1000
15b	7 ± 0.5	632 ± 25	6976 ± 564
16	12 ± 1.3	406 ± 299	3604 ± 162

[a] Inhibition constants (K_i) were obtained from the mean ± SD of four separate determination each in triplicate.

able in vitro affinity for the SERT, but we have showed (see Table 1) here that the 4-position is also a suitable site to host a fluorine atom (derivatives **7a** and **7b**, K_i = 13 and 7 nM, respectively). Furthermore, an oxygen or a sulfur atom as the linking atom between the two phenyl groups gave compounds with similar SERT affinities.

However in vitro evaluation shows that the 4-position on A phenyl ring seems to tolerate a bulky *O*-alkyl group such as fluoroethoxy or propoxy group. On the other hand the SERT binding site seems to be more able to accept fluoro alkoxy group at the 5-position on the A ring, **15b** and **16**, prove good affinity (K_i = 7 and 12 nM, respectively) and selectivity for the SERT over the other monoamine transporters [dopamine (DAT), and norepinephrine (NET)] (K_i >500 nM). Surprisingly, the substitution with a 5-(2-fluoroethoxy) (**14b**) dramatically changed the affinity for the SERT (K_i = 401 nM) conversely from an analog (a diphenyl sulfide derivative) describing by Parhi et al.[21] (their fluoroethoxy derivative at the 5-position displayed a slightly better affinity for the SERT than the fluoropropoxy derivative).

5. Conclusion

Eight novel fluoro diphenyloxide and sulfur analog were synthesized and tested as serotonin transporter ligands for potential use as PET imaging agents. Fluorophenyl derivatives on 4- or 5-position showed good in vitro affinity and selectivity for the SERT. The position of the substitution by an *O*-alkyl chain influenced the affinity for the SERT. Only for the 5-position, a 3-fluoropropoxy or 4-fluoro-butoxy lead to compounds with high affinities for the SERT.

Thus, the corresponding tosylate precursors with a propyl or a butyl chain, substituted on the 5-position for [^{18}F]-radiolabeling are in progress. The derivatives will be soon evaluated in vivo as PET imaging agents for mapping SERT in brain.

6. Experimental part

6.1. Chemistry

NMR spectra were recorded on a Brüker DPX Avance 200 spectrometer (200 MHz for ^{1}H, 50.3 MHz for ^{13}C). $CDCl_3$ or DMSO-d_6 was used as solvent; chemical shifts are expressed in ppm relative to TMS as an internal standard. Mass spectra were obtained on a CG–MS Hewlett Packard 5989A spectrometer (electronic impact at 70 eV). The thin-layer chromatographic (TLC) analyses were performed using Merck 60-F_{254} silica gel plates. Flash chromatography was used for routine purification of reaction products using silica gel (230–400 Mesh). Visualization was accomplished under UV or in an iodine chamber. All chemicals and solvents were of commercial quality and were purified following standard procedures. Elemental analyses of new compounds were within ±0.4% of theoretical values.

6.1.1. 4-Fluoro-2-mercapto-benzoic acid (2)

2-Amino-5-fluoro-benzoic acid (0.93 g, 6 mmol) in water (3 mL) with HCl_{aq} (1.2 mL) was cooled to 5 °C. A cold solution of $NaNO_2$ (0.41 g, 6 mmol in 2 mL of water) was added drop by drop. The mixture was stirred at 5 °C. A cold solution of Na_2S_2, prepared with 2 mL of boiled water, Na_2S, $9H_2O$ (1.57 g, 6.66 mmol), sulfur S (0.20 g, 6.6 mmol) and NaOH 10 N (0.6 mL), cooled to 5 °C, was added drop by drop at 5 °C max. Then, the mixture was stirred at room temperature for 2 h. The mixture was acidified with HCl_{aq}, the precipitate corresponding to the disulfide derivative was filtered and washed with water. In a flask, this disulfide was dis-

solved in acetic acid (1.8 mL) with Zn (0.18 g, 2.76 mmol). The mixture was stirred under reflux for 4 h, then cooled, and filtered. The precipitate was boiled in basified water (1.2 mL with 0.3 mL of NaOH 33%) for 30 min. After cooling, the mixture was made acid with HCl_{aq}, and the precipitate obtained was filtered, and washed with water. The thiosalicylic acid was obtained as a white crystal in 62% yield.

^{1}H NMR (DMSO-d_6): δ 7.19–7.37 (m, 2Har); 8.11–8.18 (m, 1Har). ^{13}C NMR (DMSO-d_6): δ 111.5 ($^2J_{C-F}$ = 27 Hz), 113.5 ($^2J_{C-F}$ = 22 Hz), 124.9, 134.8 ($^3J_{C-F}$ = 9 Hz), 142.3 ($^3J_{C-F}$ = 8 Hz), 164.9 ($^1J_{C-F}$ = 253 Hz); 167.4.

6.1.2. Synthesis of compounds (3) and (4a,b) and (9a,b)

General procedure: A mixture of benzoic acid derivative **2** or 4-(or 5-)-fluoro(or hydroxy)-2-hydroxy-benzoic acid (3 mmol) and P_2O_5 (206 mg, 1.45 mmol) in DMF (1,4 mL) was heated at 160 °C for 2 days. After cooling, DMF was evaporated under reduced pressure. Water was added to the residue, the solution was basified with 2 N NaOH to pH 10 and extracted with ether. The water layer was acidified with 0.1 N HCl to pH 1 and extracted with chloroform. The organic layers were dried over $MgSO_4$ and evaporated in vacuo. The product obtained was used for the next step without purification.

6.1.2.1. 4-Fluoro-2-mercapto-*N*,*N*-dimethyl-benzamide (3). Yellow solid, (36% yield). ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 3.17 (br s, 1H, SH), 7.01 (td, 1Har, J = 8 Hz, J = 2 Hz), 7.24 (dd, 1Har, J = 8 Hz, J = 2 Hz), 7.45 (dd, 1Har, J = 9 Hz, J = 2 Hz). ^{13}C NMR ($CDCl_3$): δ 39.0, 40.7, 112.2 ($^2J_{C-F}$ = 27 Hz), 114.2 ($^2J_{C-F}$ = 22 Hz), 125.6 ($^3J_{C-F}$ = 8 Hz), 129.4, 135.5 ($^3J_{C-F}$ = 9 Hz), 163.1 ($^1J_{C-F}$ = 228 Hz), 168.2.

6.1.2.2. 4-Fluoro-2-hydroxy-*N*,*N*-dimethyl-benzamide (4a). Orange powder, (52% yield). ^{1}H NMR ($CDCl_3$): δ 3.20 (br s, 6H, NCH_3), 6.60 (dd, 1Har, J = 8 Hz, J = 2 Hz), 7.63 (dd, 1Har, ^FJ = 10 Hz, J = 3 Hz), 7.30–7.36 (m, 1Har). ^{13}C NMR ($CDCl_3$): δ 38.9 (2C), 105.5 ($^2J_{C-F}$ = 24 Hz), 106.4 ($^2J_{C-F}$ = 22 Hz), 113.4 ($^3J_{C-F}$ = 8 Hz), 129.3, 131.4 ($^3J_{C-F}$ = 8 Hz), 163.2 ($^1J_{C-F}$ = 252 Hz), 168.0.

6.1.2.3. 5-Fluoro-2-hydroxy-*N*,*N*-dimethyl-benzamide (4b). Compound **4b** (85% yield). ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 3H, NCH_3), 3.11 (s, 3H, NCH_3), 5.31 (s, OH), 6.68–7.03 (m, 3Har). ^{13}C NMR ($CDCl_3$): δ 38.6 (2C), 105.1 ($^2J_{C-F}$ = 24 Hz), 106.0 ($^2J_{C-F}$ = 22 Hz), 113.0 ($^3J_{C-F}$ = 9 Hz), 128.8, 130.4 ($^3J_{C-F}$ = 11 Hz), 165.1 ($^1J_{C-F}$ = 251 Hz), 172.0.

6.1.2.4. 2-Hydroxy-4-methoxy-*N*,*N*-dimethyl-benzamide (9a). Compound **9a** (38% yield). ^{1}H NMR ($CDCl_3$): δ 3.20 (s, 6H, $N(CH_3)_2$), 3.85 (s, 3H, OCH_3), 6.44 (dd, 1Har, J = 8.7 Hz, J = 2.5 Hz), 6.54 (d, 1Har, J = 2.5 Hz), 7.31 (d, 1Har, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$): δ 38.5, 55.2, 101.6, 105.5, 109.1, 130.0, 161.9, 162.9, 172.1.

6.1.2.5. 2-Hydroxy-5-methoxy-*N*,*N*-dimethyl-benzamide (9b). Compound **9b** (76% yield). ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 6H, $N(CH_3)_2$), 3.80 (s, 3H, OCH_3), 6.85–6.95 (m, 3Har). ^{13}C NMR ($CDCl_3$): δ 37.9, 54.3, 113.1, 118.1, 118.2, 118.8, 151.3, 151.6, 171.1

6.1.3. Synthesis of compounds (5a–c) and (10a,b)

General procedure: To a solution of the amide derivative **3**, **4a**,**b** or **9a**,**b**, 1-bromo-4-methyl-2-nitrobenzene (2.60 g, 12 mmol) and potassium carbonate (2.48 g, 18 mmol) in DMF (22 mL) heated to reflux was added over 15 min Cu (0.25 g, 4 mmol). The mixture was refluxed overnight, and then cooled to rt. The solvent was eliminated under reduce pressure. Water (80 mL) is added, and the crude product was extracted with ethyl acetate and purified by flash chromatography (EtOAc/hexane 8/2).

6.1.3.1. 4-Fluoro-*N*,*N*-dimethyl-2-(4-methyl-2-nitrophenylthio)-benzamide (5a). Compound **5a** (54% yield). ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.89 (s, 3H, NCH_3), 3.07 (s, 3H, NCH_3), 6.95 (d, 1Har, J = 8.3 Hz), 7.25–7.46 (m, 4Har), 8.00 (s, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.4, 34.6, 38.2, 115.4 ($^2J_{C-F}$ = 24 Hz), 117.2 ($^2J_{C-F}$ = 22 Hz), 119.8, 120.8 ($^3J_{C-F}$ = 8 Hz), 125.5, 130.9 ($^3J_{C-F}$ = 8 Hz), 133.8, 135.1, 140.1, 147.2, 148.0, 159.5 ($^1J_{C-F}$ = 247 Hz), 166.3.

6.1.3.2. 4-Fluoro-*N*,*N*-dimethyl-2-(4-methyl-2-nitrophenoxy)-benzamide (5b). Compound **5b** (51% yield). ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 2.98 (s, 6H, $N(CH_3)_2$), 6.55 (dd, 1Har, J = 9 Hz, J = 2 Hz), 6.94–7.06 (m, 2Har), 7.38–7.43 (m, 2Har), 7.81 (s, 1Har) ^{13}C NMR ($CDCl_3$): δ 20.6, 34.9, 38.5, 105.7 ($^2J_{C-F}$ = 25 Hz), 111.6 ($^2J_{C-F}$ = 21 Hz), 121.7, 124.7, 125.8, 129.9 ($^3J_{C-F}$ = 9 Hz), 135.2, 135.4, 141.1, 146.7, 153.3 ($^3J_{C-F}$ = 10 Hz), 163.4 ($^1J_{C-F}$ = 250 Hz), 167.3.

6.1.3.3. 5-Fluoro-*N*,*N*-dimethyl-2-(4-methyl-2-nitrophenoxy)-benzamide (5c). Compound **5c** (52% yield). ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.99 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3), 6.89–6.99 (m, 2Har), 7.06–7.17 (m, 2Har), 7.30 (d, J = 2 Hz, 1Har), 7.76 (s, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.4, 34.8, 38.3, 115.1 ($^2J_{C-F}$ = 24 Hz), 116.9 ($^2J_{C-F}$ = 23 Hz), 119.8, 120.7 ($^3J_{C-F}$ = 8 Hz), 125.5, 127.3 ($^3J_{C-F}$ = 9 Hz), 133.8, 135.0, 140.8 146.7, 151.5 159.3 ($^1J_{C-F}$ = 246 Hz), 167.8.

6.1.3.4. 4-Methoxy-*N*,*N*-dimethyl-2-(4-methyl-2-nitrophenoxy) benzamide (10a). Compound **10a** (74% yield). ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.99 (s, 3H, NCH_3), 3.03 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.47 (d, J = 2 Hz, 1Har), 6.80 (dd, J = 8.5 Hz, J = 2 Hz, 1Har), 6.95 (d, J = 8.5 Hz, 1Har), 7.29–7.39 (m, 2Har), 7.76 (d, J = 2 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.4, 34.7, 38.5, 55.5, 104.9, 110.2, 120.4, 121.6, 125.4, 129.7, 133.8, 135.1, 140.5, 147.7, 152.5, 161.4, 167.9.

6.1.3.5. 5-Methoxy-*N*,*N*-dimethyl-2-(4-methyl-2-nitrophenoxy) benzamide (10b). Compound **10b** (30% yield). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 2.97 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 6.83 (d, J = 8.5 Hz, 1Har), 6.93–6.96 (m, 3Har), 7.25 (dd, J = 8.5 Hz, J = 2.1 Hz, 1Har), 7.70 (d, J = 2.1 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.3, 34.7, 38.3, 55.7, 112.9, 116.6, 118.7, 121.6, 125.4, 130.8, 132.7, 134.9, 143.8, 149.0, 156.9, 167.5.

6.1.4. Synthesis of compounds (6a–c) and (11a,b)

General procedure: To a solution of the diphenyl compound **5a–c** or **10a**,**b** (2.6 mmol) in THF (6.5 mL) under nitrogen atmosphere was added drop wise BH_3/THF (1*M*, 6.5 mL) at 0 °C. The mixture was heated to reflux for 4 h, stirred at room temperature overnight and quenched with HCl solution (10 N, 0.35 mL). The solvent was eliminated under reduce pressure and the residue was then dissolved in MeOH (20 mL). The mixture was heated to reflux during 2 h. The MeOH was eliminated under reduce pressure. After cooling, water was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (EtOAc).

6.1.4.1. 4-Fluoro-*N*,*N*-dimethyl-2-(4-methyl-2-nitrophenylthio) benzylamine (6a). Compound **6a** (55% yield). ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 6H, NCH_3), 2.41 (s, 3H, CH_3), 3.53 (s, 2H, CH_2), 6.70 (d, 1Har, J = 8.2 Hz), 7.18–7.30 (m, 3Har), 7.64 (dd, 1Har, J = 8.2 Hz, J = 2,9 Hz), 8.06 (s, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.5, 47.2 (2C), 60.4, 117.0 ($^2J_{C-F}$ = 21 Hz), 122.6, 125.9 ($^2J_{C-F}$ = 22 Hz), 128.8, 131.9 ($^3J_{C-F}$ = 8 Hz), 133.1, 133.8, 134.5, 136.7 ($^3J_{C-F}$ = 8 Hz), 138.2, 143.8, 162.7 ($^1J_{C-F}$ = 251 Hz).

6.1.4.2. 4-Fluoro-*N*,*N*-dimethyl-2-(2-nitro-4-toloxy)benzylamine (6b). Compound **6b** (42% yield). ^{1}H NMR ($CDCl_3$): δ 2.30 (br s, 9H, CH_3,

$N(CH_3)_2$), 3.54 (s, 2H, CH_2); 6.52 (dd, 1Har, J = 9 Hz, J = 2 Hz), 6.89–6.95 (m, 2Har), 7.30–7.55 (m, 2Har), 7.83 (s, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.4, 45.0 (2C), 56.5, 105.3 ($^2J_{C-F}$ = 24 Hz), 111.0 ($^2J_{C-F}$ = 20 Hz), 120.7, 125.1, 125.9, 132.3 ($^3J_{C-F}$ = 9 Hz), 134.1, 134.9, 140.8, 147.4, 155.0 ($^3J_{C-F}$ = 10 Hz), 162.1 ($^1J_{C-F}$ = 247 Hz).

6.1.4.3. 5-Fluoro-*N*,*N*-dimethyl-2-(2-nitro-4-toloxy)benzylamine (6c). Compound **6c** (57% yield). ^1H NMR ($CDCl_3$): δ 2.35 (br s, 9H, CH_3, $N(CH_3)_2$), 4.09 (s, 2H, CH_2), 6.60–7.41 (m, 6Har). ^{13}C NMR ($CDCl_3$): δ 20.2, 50.2 (2C), 60.4, 117.1 ($^2J_{C-F}$ = 24 Hz), 118.7 ($^2J_{C-F}$ = 23 Hz), 120.2 ($^3J_{C-F}$ = 8 Hz), 121.3, 123.8 ($^3J_{C-F}$ = 7 Hz), 125.8, 134.6, 135.1, 140.8, 146.9, 151.5, 157.9 ($^1J_{C-F}$ = 244 Hz).

6.1.4.4. 4-Methoxy-*N*,*N*-dimethyl-2-(2-nitro-4-toloxy)benzylamine (11a). Compound **11a** (95% yield). ^1H NMR ($CDCl_3$): δ 2.23 (s, 6H, $N(CH_3)_2$), 2.40 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 6.44 (d, J = 2.5 Hz, 1Har), 6.75 (dd, J = 8.5 Hz, J = 2.5 Hz, 1Har), 6.85 (d, J = 8.5 Hz, 1Har), 7.29 (dd, J = 8.5 Hz, J = 2 Hz, 1Har), 7.77 (d, J = 2 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.4, 34.8, 38,5, 55,5, 62,5, 105.0, 110.2, 120.5, 121.5, 125.4, 129.7, 133.8, 135.1, 147.6, 152.5, 161.4, 167.9.

6.1.4.5. 5-Methoxy-*N*,*N*-dimethyl-2-(2-nitro-4-toloxy)benzylamine (11b). Compound **11b** (93% yield). ^1H NMR ($CDCl_3$): δ 2.24 (s, 6H, $N(CH_3)_2$), 2.38 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.70 (d, J = 8.5 Hz, 1Har), 6.81 (dd, J = 8.5 Hz, J = 3 Hz, 1Har), 6.91 (d, J = 8.5 Hz, 1Har), 7.12 (d, J = 3 Hz, 1Har), 7.25 (dd, J = 8.5 Hz, J = 2.3 Hz, 1Har), 7.75 (d, J = 2.3 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.2, 45.4 (2C), 55.6, 57.3, 114.0, 115.5, 117.7, 121.2, 125.6, 131.8, 132.0, 134.5, 139.7, 146.5, 149.8, 156.9.

6.1.5. Synthesis of compounds (7a–c) and (12a,b)

General procedure: To a solution of compound **6a**–**c** or **11a**,**b** (0.11 mmol), 10 N HCl (1 mL) and MeOH (3.5 mL) was added by portion below 5 °C $SnCl_2$ (0.71 g, 0.38 mmol). The reaction mixture was stirred at rt overnight. MeOH was eliminated under reduce pressure and the crude product was treated with H_2O (1 mL), basified with 10 N NaOH solution to pH 10 and extracted with EtOAc (3 × 3 mL). The organic phase was dried and removed under vacuo and flash chromatography on silica gel (EtOAc/MeOH 100/0 to 90/10).

6.1.5.1. 4-Fluoro-*N*,*N*-dimethyl-2-(2-amino-4-methylphenylthio)benzylamine (7a). Compound **7a** (62% yield). ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 2.36 (s, 6H, $N(CH_3)_2$), 3.59 (s, CH_2), 4.20 (br s, 2H, NH_2), 6.65 (d, 1Har, J = 7.8 Hz), 6.73 (s, 1Har), 6.93–7.27 (m, 3Har), 6.78 (dd, 1Har, J = 8.6 Hz, J = 2 Hz). ^{13}C NMR ($CDCl_3$): δ 21.3, 45.2 (2C), 53.4, 114.7 ($^2J_{CF}$ = 22 Hz), 115.9, 116.7 ($^2J_{CF}$ = 22 Hz), 117.6, 118.5, 119.6, 129.1 ($^3J_{CF}$ = 8 Hz), 132.1, 137.1, 137.4, 141.3, 148.5 ($^3J_{CF}$ = 12 Hz), 160.9 ($^1J_{CF}$ = 244 Hz). MS: m/z = 290 (12), 243 (30), 183 (100), 168 (42), 152 (31), 58 (34), 44 (58).

6.1.5.2. 4-Fluoro-*N*,*N*-dimethyl-2-(2-amino-4-methylphenoxy)benzylamine (7b). Compound **7b** (70% yield). ^1H NMR ($CDCl_3$): δ 2.31 (br s, 9H, CH_3, $N(CH_3)_2$), 3.58 (s, 2H, CH_2), 4.52 (s, 2H, NH_2), 6.53–6.70 (m, 4Har), 6.90 (d, 1Har, J = 8 Hz), 7.25 (dd, 1Har, J = 8 Hz, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 21.1, 45.0 (2C), 58.2, 102.9 ($^2J_{CF}$ = 25 Hz), 108.3 ($^2J_{CF}$ = 21 Hz), 117.2, 118.3, 121.7, 123.2, 132.0 ($^3J_{CF}$ = 9 Hz), 135.6, 139.6, 139.6, 157.8 ($^3J_{CF}$ = 10 Hz), 162.9 ($^1J_{CF}$ = 246 Hz). MS: m/z = 274 (42), 228 (74), 216 (3), 166 (82), 150 (23), 107 (35), 58 (36), 44 (100).

6.1.5.3. 5-Fluoro-*N*,*N*-dimethyl-2-(2-amino-4-methylphenoxy)benzylamine (7c). Compound **7c** (68% yield). ^1H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.36 (s, 6H, $N(CH_3)_2$), 3.61 (s, 2H, CH_2), 4.13 (br s, 2H, NH_2), 6.54 (dd, 1Har, J = 3 Hz, J = 1.4 Hz), 6.64 (d, 1Har, J = 1.8 Hz), 6.72–6.91 (m, 3Har), 7.12 (dd, 1Har, J = 8.8 Hz, J = 3 Hz). ^{13}C NMR ($CDCl_3$): δ 20.9, 45.1 (2C), 58.0, 114.7 ($^2J_{CF}$ = 23 Hz), 117.0, 117.2 ($^3J_{CF}$ = 7 Hz), 117.5 ($^2J_{CF}$ = 23 Hz), 118.5, 120.1, 129.7 ($^3J_{CF}$ = 7 Hz), 134.6, 138.8, 141.0, 152.0, 157.5 ($^1J_{CF}$ = 240 Hz). MS: m/z = 274 (24), 228 (63), 166 (58), 152 (34), 58 (44), 44 (100).

6.1.5.4. 4-Methoxy-*N*,*N*-dimethyl-2-(2-amino-4-methylphenoxy)benzylamine (12a). Compound **12a** (73% yield). ^1H NMR ($CDCl_3$): δ 2.30 (s, 9H, CH_3, $N(CH_3)_2$), 3.55 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 4.25 (br s, NH_2), 6.44 (d, J = 2.5 Hz, 1Har), 6.50–6.62 (m, 3Har), 6.86 (d, J = 8 Hz, 1Har), 7.21 (d, J = 8.3 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.9, 44.9 (2C), 55.2, 58.1, 102.1, 106.7, 116.9, 118.2, 119.9, 121.1, 131.8, 134.8, 139.3, 140.2, 157.4, 160.1.

6.1.5.5. 5-Methoxy-*N*,*N*-dimethyl-2-(2-amino-4-methylphenoxy)benzylamine (12b). Compound **12b** (71% yield). ^1H NMR ($CDCl_3$): δ 2.28 (s, 9H, $N(CH_3)_2$, CH_3), 3.53 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.30 (br s, NH_2), 6.40 (dd, J = 8 Hz, J = 1.8 Hz, 1Har), 6.50 (d, J = 1.8 Hz, 1Har), 6.70–6.84 (m, 3Har), 6.95 (d, J = 2.8 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.9, 45.4 (2C), 55.6, 58.4, 113.3, 116.3, 116.8, 117.6, 118.3, 119.4, 129.6, 133.8, 138.5, 141.8, 149.6, 154.9.

6.1.6. Synthesis of compounds (13a,b)

General procedure: To a solution of **12a**,**b** (0.35 mmol) in CH_2Cl_2 freshly distilled (50 mL), at −40 °C, was added BBr_3 (0.306 g, 1.23 mmol). The reaction mixture was stirred at rt overnight. The residue was then dissolved in MeOH and stirred during 1 h at rt. The CH_2Cl_2 and MeOH were removed under vacuo and the crude product was treated with H_2O, basified with a solution of $NaHCO_3$. The mixture was extracted with EtOAc. The crude compound is purified on aluminium oxide (CH_2Cl_2/MeOH: 90/10).

6.1.6.1. 3-(2-Amino-4-methylphenoxy)-4-[(dimethylamino)methyl]phenol (13a). Compound **13a** (71% yield). ^1H NMR ($CDCl_3$): δ 2.25 (s, 9H, CH_3, $N(CH_3)_2$), 3.47 (s, 2H, CH_2), 4.99 (br s, 3H, NH_2, OH), 6.10 (d, 1H, J = 2.0 Hz), 6.30 (dd, 1Har, J = 8.2 Hz, J = 2.0 Hz), 6.47 (d, 1Har, J = 8 Hz), 6.57(s, 1Har), 6.66 (d, 1Har, J = 8.2 Hz), 7.00 (d, 1Har, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$): δ 20.8, 43.9 (2C), 56.6, 103.8, 110, 115.23, 117.2, 119.1, 120.2, 132.8, 134.5, 138.5, 140.5, 157.2, 158.6.

6.1.6.2. 4-(2-Amino-4-methylphenoxy)-3-[(dimethylamino)methyl]phenol (13b). Compound **13b** (57% yield). ^1H NMR ($CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.40 (s, 6H, $N(CH_3)_2$), 3.60 (s, 2H, CH_2), 4.18 (br s, 3H, NH_2, OH), 6.48 (dd, 1Har, J = 8.1 Hz, J = 1.5 Hz), 6.59 (d, 1Har, J = 8.1 Hz), 6.66–6.80 (m, 3Har), 6.83 (s, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.9, 44.5 (2C), 57.1, 116.9, 117.0, 118.0, 118.6, 118.9 (2C), 126.6, 133.6, 137.7, 142.4, 148.6, 152.5.

6.1.7. Synthesis of compounds (14a,b), and (16)

General procedure: Compound **12** (60 mg, 0.2 mmol) was dissolved in 5 mL of DMF in presence of Cs_2CO_3 (143 mg, 0.4 mmol). The mixture was stirred at room temperature for 10 min and then was added 1-bromo-2-fluoroethane or 1-bromo-4-fluorobutane (0.4 mmol). The mixture was stirred at reflux for 4 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layers were washed with water, dried and concentrated under reduced pressure to give the crude derivative.

6.1.7.1. *N*,*N*-Dimethyl-4-(2-fluoroethoxy)-2-(2-amino-4-methylphenoxy)benzylamine (14a). The crude product was purified by flash chromatography on silica gel (EtOAc/Hex: 4/6) to give **14a** as a white solid (10% yield). ^1H NMR ($CDCl_3$): δ 2.31 (br s, 9H, $N(CH_3)_2$, CH_3), 3.60 (s, CH_2), 4.10 (td, J = 28 Hz, J = 4 Hz, OCH_2), 4.68 (dt, J = 47 Hz, J = 4 Hz, CH_2F), 6.48 (d, J = 2.5 Hz, 1Har), 6.45 (d,

J = 8.5 Hz, 1Har), 6.53 (dd, J = 2.5 Hz, J = 8.5 Hz, 1Har), 6.70 (s, 1H), 6.73 (d, J = 8 Hz, 1Har), 7.20 (d, J = 8 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 21.4, 45.4 (2C), 58.0, 67.4 ($^2J_{CF}$ = 20 Hz), 81.7 ($^1J_{CF}$ = 169.5 Hz), 103.8, 107.5, 114.3, 117.8, 119.3, 120.8, 131.8, 134.8, 138.3, 139.8, 156.7.1, 159.1. MS: m/z = 318 (37), 302 (15), 274 (100), 254 (26), 210 (8), 58 (20).

6.1.7.2. *N,N*-Dimethyl-5-(2-fluoroethoxy)-2-(2-amino-4-methylphenoxy)benzylamine (14b). The crude product was purified by flash chromatography on silica gel (EtOAc/Hex: 4/6) to give **14b** as a white solid (13% yield). ^{1}H NMR ($CDCl_3$): δ 2.25 (s, CH_3), 2.34 (s, $N(CH_3)_2$), 3.60 (s, CH_2), 4.20 (td, J = 28 Hz, J = 4 Hz, OCH_2), 4.73 (dt, J = 50 Hz, J = 4 Hz, CH_2F), 6.48 (d, J = 9 Hz, 1Har), 6.60 (s, 1Har), 6.67 (d, J = 9 Hz, 1Har), 6.76–6.78 (m, 2Har), 7.02 (s, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.9, 45.0 (2C), 58.0, 67.6 ($^2J_{CF}$ = 20 Hz), 81.8 ($^1J_{CF}$ = 170.5 Hz), 113.9, 116.8, 117.1, 117.5, 118.3, 119.4, 128.8, 134.1, 138.9, 141.5, 150.1, 153.6. MS: m/z = 318 (100), 272 (76), 210 (38), 164 (59), 58 (79), 44 (87).

6.1.7.3. *N,N*-Dimethyl-5-(4-fluorobutoxy)-2-(2-amino-4-methylphenoxy)benzylamine (16). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 8/2) to give **16** as an oil (26% yield). ^{1}H NMR ($CDCl_3$): δ 1.95 (m, $2CH_2$), 2.28 (s, CH_3), 2.36 (s, $N(CH_3)_2$), 3.59 (s, CH_2), 4.01 (t, J = 6 Hz, CH_2), 4.57 (td, J = 5 Hz, J = 50 Hz, CH_2F), 6.50 (d, J = 8 Hz, 1Har), 6.63–6.78 (m, 4Har), 6.99(d, J = 4 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.9, 25.3 ($^3J_{CF}$ = 5 Hz), 27.2 ($^2J_{CF}$ = 20 Hz), 45.1 (2C), 58.1, 67.7, 83.8 ($^1J_{CF}$ = 164 Hz), 114.4, 116.9, 117.0, 117.7, 118.4, 119.2, 134.0, 138.4, 141.8, 149.6, 154.1, 158.2. MS: m/z = 346 (100), 300 (74), 224 (40), 164 (73), 58 (74), 44 (87).

6.1.7.4. *N,N*-Dimethyl-4-(3-fluoropropoxy)-2-(2-amino-4-methylphenoxy)benzylamine (15a). Compound **13a** (80 mg, 0.294 mmol) was dissolved in DMF (8 mL) with K_2CO_3 (88 mg, 0.63 mmol). The mixture was stirred at room temperature for 10 min and then toluene-4-sulfonic acid 3-fluoro-propyl ester (136 mg, 0.59 mmol) was added. The mixture was stirred at 70 °C for 16 h. The DMF was removed under vacuo and the crude product was poured into water and extracted with chloroform. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) to give **15a** as an oil (21 mg, 22% yield). ^{1}H NMR ($CDCl_3$): δ 2.10 (td, J = 4 Hz, J = 26 Hz, 2H, CH_2), 2.25 (s, CH_3), 2.27 (s, 6H, $N(CH_3)_2$), 3.49 (s, CH_2), 3.97 (t, J = 6 Hz, CH_2), 4.59 (td, 2H, J = 6 Hz, J = 47 Hz, CH_2F), 6.38 (s, 1Har), 6.47–6.52 (m, 2Har), 6.59 (s, 1Har), 6.85 (d, J = 8 Hz, 1Har), 7.15 (d, J = 8 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 21.0, 30.3 ($^2J_{CF}$ = 20 Hz), 45.1 (2C), 58.3, 64.0 ($^3J_{CF}$ = 5 Hz), 80.7 ($^1J_{CF}$ = 164 Hz), 102.5, 106.9, 117.0, 118.2, 119.9, 121.5, 131.8, 134.8, 139.3, 140.2, 157.4, 160.1. MS: m/z = 332 (7.5), 285 (100), 210 (15), 196 (62), 168 (15), 77 (61), 44 (86).

6.1.7.5. *N,N*-Dimethyl-5-(3-fluoropropoxy)-2-(2-amino-4-methylphenoxy)benzylamine (15b). Same procedure as above from **13b** (80 mg, 0.294 mmol) to give **15b** as an oil (33 mg, 33% yield). ^{1}H NMR ($CDCl_3$): δ 2.16 (m, CH_2), 2.30 (br s, 9H, $3CH_3$), 3.51 (s, CH_2), 4.09 (t, J = 6 Hz, CH_2), 4.66 (td, 2H, J = 6 Hz, J = 47 Hz, CH_2F), 6.47 (d, J = 8 Hz, 1Har), 6.60 (s, 1Har), 6.68 (d, J = 8 Hz, 1Har), 6.71 (dd, J = 9 Hz, J = 3 Hz, 1Har), 6.77 (d, J = 9 Hz, 1Har), 6.94 (d, J = 3 Hz, 1Har). ^{13}C NMR ($CDCl_3$): δ 20.9, 30.5 ($^2J_{CF}$ = 20 Hz), 45.2 (2C), 58.2, 64.0, 80.8 ($^1J_{CF}$ = 164 Hz), 114.1, 116.8, 117.0, 117.6, 118.3, 119.3, 129.5, 133.9, 138.4, 142.0, 149.7, 154.1. MS: m/z = 332 (100), 287 (70), 210 (72), 164 (78), 58 (61), 44 (77).

6.2. In vitro binding studies

Candidate compounds were assayed for their affinities to the monoamine transporters (SERT, NET and DAT) in competitive binding experiments in vitro using cloned human receptors (hSERT, hNET, and hDAT) expressed on HEK-293 cells and the radioligands [^{3}H]citalopram (SERT), [^{3}H]nisoxetine (NET), and [^{3}H]GBR12935 (DAT), in accordance with the published procedures.[26] For experimental details please refer to the PDSP web site http://pdsp.med.unc.edu/.

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