

## Radiosynthesis of Carbon-11 Labelled N-Methyl-2-(arylothio)benzylamines: Potential Radiotracers for the Serotonin Reuptake Receptor.

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### Summary

The potent and selective serotonin reuptake inhibitor, N,N-dimethyl-2-(2-amino-4-trifluoromethylphenylthio)benzylamine (**1**), and a potential metabolite, N-methyl-2-(2-amino-4-trifluoromethylphenylthio)benzylamine (**2**) were radiolabelled with Carbon-11 as potential positron emission tomography (PET) radiotracers. Both [<sup>11</sup>C]-(**1**) and [<sup>11</sup>C]-(**2**) were obtained in good radiochemical yield by alkylation of their respective non-methyl precursors with [<sup>11</sup>C]-iodomethane in dimethylformamide. Upon HPLC purification and formulation radiochemically pure products were obtained in 25-30% yield (from [<sup>11</sup>C]-iodomethane, uncorrected) with specific activities of 25-40 GBq/mole. To further establish the site of labeling, [<sup>13</sup>C]-(**1**) and [<sup>13</sup>C]-(**2**) were also synthesised, using [<sup>13</sup>C]-iodomethane, for <sup>13</sup>C NMR analysis. Preliminary biodistribution studies in rats show that both [<sup>11</sup>C]-(**1**) and [<sup>11</sup>C]-(**2**) efficiently and rapidly cross the blood brain barrier.

**Key Words:** carbon-11, serotonin reuptake inhibitor, positron emission tomography, SSRI

## Introduction

Selective serotonin reuptake inhibitors (SSRIs) have played a dominant role in the treatment of depression, anxiety, and a variety of other affective psychiatric disorders for over ten years (1). Despite the clinical successes of SSRIs and in contrast to the plethora of dopamine transporter (DAT) positron emission tomography (PET) (2) and single photon emission computed tomography (SPECT) imaging agents (3), there is a scarcity of good radiotracers for *in vivo* imaging of serotonin reuptake or transporter sites (SERT) (4). The isoquinoline, [ $^{11}\text{C}$ ](+)-McN5662, is the most promising PET agent thus far reported with high affinity for SERT, high selectivity over DAT, and partial selectivity over norepinephrine transporter sites (NET) (5,6). However the McNeil compound presents problems regarding defining the nonspecific binding component of its signal in brain regions and has only moderate signal contrast in human PET studies (7,8). In addition its pharmacokinetics are not optimal for a radiotracer labelled with  $^{11}\text{C}$  (half-life 20.4 min).

Recently a new class of potent serotonin reuptake inhibitors has been described, namely N,N-dimethyl-2-(arylthio)benzylamines, with moxifetin (9), and later 403U76 (10), (Figure 1), emerging as lead structures. Some of these diphenylsulphides have been reported to possess very high selectivity for SERT over NET and DAT binding sites (11) (12).

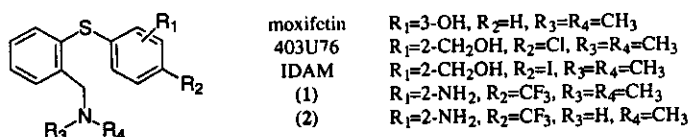


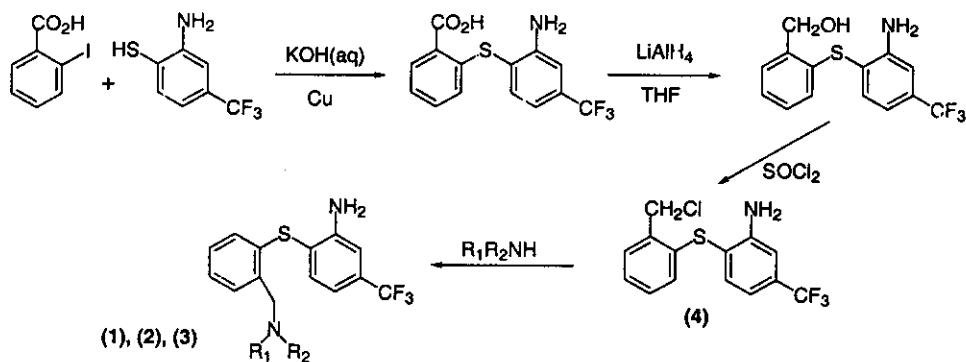
Figure 1. Structure of 2-(arylthio)benzylamines, potential SERT imaging agents.

An analogue of 403U76, [ $^{123}\text{I}$ ]IDAM (5-iodo-2-((2-((dimethylamino)-methyl)phenyl)thio)benzyl alcohol, has lately shown some promise as a new SPECT agent for the SERT. IDAM (Figure 1) was shown to have sub-nanomolar affinity for SERT with high selectivity over DAT and NET binding sites both *in vitro* and *in vivo* (13).

As part of our programme on PET imaging in affective disorders (14,15), our laboratory was also interested in the N,N-dimethyl-2-(arylthio)benzylamines as potential ligands for PET imaging of SERT. We report here the radiosynthesis of N,N-dimethyl-2-(2-amino-4-trifluoromethylphenylthio) benzylamine (**1**), and also the radiosynthesis of its normethyl analogue, N-methyl-2-(2-amino-4-trifluoromethylphenylthio)benzylamine (**2**) (Figure 1), a potential confounding metabolite.

### Results and Discussion

Scheme 1 depicts the synthesis of (**1**), (**2**), and the primary amine 2-(2-amino-4-trifluoromethylphenylthio)benzylamine (**3**) required for the radiolabelling of (**2**).

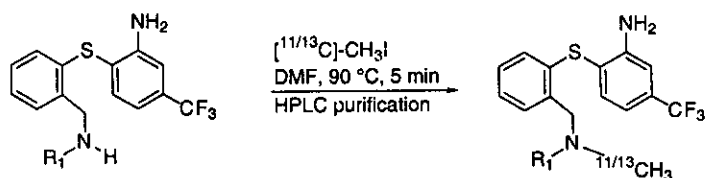


Scheme 1. Synthesis of 2-(arylthio)benzylamines.

The required benzyl chloride, 2-(2-amino-4-(trifluoromethyl)phenylthio)benzyl chloride (**4**), was prepared in three steps from commercially available 2-amino-4-trimethylbenzenethiol and 2-iodobenzoic acid by literature methods (12). The benzyl chloride (**4**) was then aminated by dimethylamine hydrochloride, methylamine hydrochloride and ammonia to give (**1**), (**2**), and (**3**) respectively. Isolated yields of (**1**) and (**2**) were surprisingly poor (23% and 19%) but were not optimised as the easily procured starting materials provided ample quantities of products for characterisation, radiolabelling, and *in vivo* testing.

Alkylation of the 2° benzylamine (**2**) with cyclotron produced [<sup>11</sup>C]-iodomethane in DMF at 90°C (Scheme 2) proceeded smoothly yielding two major radioactive peaks after 5 min reaction. The larger (75% of total injected radioactivity) had the same

retention time ( $k'$  8.6) as the anticipated product (1), while the lesser (15%) had a much shorter retention time ( $k'$  2.1) on the  $C_{18}$  reverse phase column. The balance of the remaining radioactivity was mainly unreacted [ $^{11}C$ ]-iodomethane (10%) with small amounts of by-products eluting with the solvent front. Unreacted precursor (2) ( $k'$  1.9) was easily resolved from the product (1) ( $k'$  8.6) under the HPLC purification conditions employed. After HPLC purification, evaporation, filtration, and formulation, isolated radiochemical yields of [ $^{11}C$ ]-**(1)** were typically 25-30% (uncorrected, from [ $^{11}C$ ]-iodomethane). The product was chemically and radiochemically pure (> 98%) by TLC and HPLC while syntheses times, including quality control, were 30 min from end-of-bombardment. Specific activities of 25-40 GBq/ $\mu$ mole at end-of-synthesis were obtained.



Scheme 2. Synthesis of [ $^{11/13}C$ ]-**(1)** [ $R_1=CH_3$ ] and [ $^{11/13}C$ ]-**(2)** [ $R_1=H$ ].

The radiosynthesis of [ $^{11}C$ ]-**(2)** from [ $^{11}C$ ]-iodomethane and the 1° amine precursor **(3)** was carried out under the same conditions as described above for [ $^{11}C$ ]-**(1)** with very similar results (Scheme 2). However in this case separation of the unreacted precursor **(3)** ( $k'$  6.4) from the desired product **(2)** ( $k'$  9.9) proved more onerous with some tailing of the precursor peak into the product. Consequently, the final formulated product was contaminated with substantial (5-20%, based on **(2)**) quantities of **(3)**, although the product was radiochemically pure. The lipophilicities (octanol/water partition) of both radiotracers were measured at pH 7.4 ( $\text{Log } P_{7.4}$ ) as this is one of the most important parameters for correlating structure with biological activity (16). Compound **(1)** had  $\text{Log } P_{7.4}$  of 3.4 while **(2)** had  $\text{Log } P_{7.4}$  of 2.9. Both radiolabelling precursors, **(2)** and **(3)**, contain two nucleophilic sites — the target aliphatic amine nitrogen and the aromatic amine nitrogen. While aromatic

amines are generally less reactive towards alkylating agents, unanticipated effects such as steric hindrance could reverse this order. As further evidence of the site of radiolabelling, the synthetic procedures described above were repeated, substituting [ $^{13}\text{C}$ ]-iodomethane for [ $^{11}\text{C}$ ]-iodomethane (Scheme 2) (17,18). [ $^{13}\text{C}$ ]-**(1)** and [ $^{13}\text{C}$ ]-**(2)** were isolated in 53% and 28% labelling yields respectively and analysed by  $^{13}\text{C}$  NMR. The observed chemical shifts for [ $^{13}\text{C}$ ]-**(1)** and [ $^{13}\text{C}$ ]-**(2)** were 45.2 and 35.9 ppm respectively, in good agreement (cf. 45.1 and 36.1 ppm) with the  $^{13}\text{C}$  chemical shifts obtained for **(1)** and **(2)** as synthesised in Scheme 1.

Animal studies were carried out to determine the permeability of [ $^{11}\text{C}$ ]-**(1)** or [ $^{11}\text{C}$ ]-**(2)** across the BBB. Rats were injected (tail vein) with the radiotracer and sacrificed at various time points whence the brain was removed for counting the accumulated radioactivity. As shown in Table 1, uptake of radioactivity in the brain for both radiotracers was high with a slow washout while levels in whole blood were considerably less.

Table 1. Whole brain and blood levels of radioactivity upon injection of [ $^{11}\text{C}$ ]-**(1)** and [ $^{11}\text{C}$ ]-**(2)** in rats (% injected dose /g wet tissue  $\pm$  SD)

		5 min	15 min	30 min	60 min
Brain	[ $^{11}\text{C}$ ]- <b>(1)</b>	1.02 $\pm$ 0.07	1.00 $\pm$ 0.02	0.91 $\pm$ 0.02	0.67 $\pm$ 0.10
	[ $^{11}\text{C}$ ]- <b>(2)</b>	1.24 $\pm$ 0.18	1.22 $\pm$ 0.03	1.21 $\pm$ 0.01	0.95 $\pm$ 0.05
Blood	[ $^{11}\text{C}$ ]- <b>(1)</b>	0.35 $\pm$ 0.05	0.21 $\pm$ 0.04	0.21 $\pm$ 0.02	0.12 $\pm$ 0.02
	[ $^{11}\text{C}$ ]- <b>(2)</b>	0.17 $\pm$ 0.02	0.14 $\pm$ 0.02	0.14 $\pm$ 0.01	0.12 $\pm$ 0.01

In a recent patent (12), the diphenylsulphide **(1)**, an analogue of moxefetin, was one of a series of N,N-dimethyl-2-(arylthio)benzylamines synthesised and reported to have very high affinity and selectivity for SERT. Compound **(1)**, with a reported  $\text{IC}_{50}$  of 0.02 nM for inhibition of serotonin uptake in rat synaptosome preparations, was chosen as a candidate for radiolabelling based on its high affinity and the suitability of its N-methyl groups as a site for the facile introduction of a Carbon-11

label. The current work of Oya et al (13), which demonstrates that an iodinated N,N-dimethyl-2-(arylthio)benzylamine binds to SERT *in vivo* in rats, supports the idea that this class of compounds has potential as imaging agents for PET and SPECT.

At least two different reports suggest that a significant metabolic pathway for N,N-dimethyl-2-(arylthio)benzylamines in animals is demethylation of one of the N-methyl groups (19,20). If this holds true in humans, and if the desmethyl metabolite crosses the blood-brain-barrier (BBB), then *in vivo* imaging of SERT could be confounded by the presence of radiolabelled metabolites. An additional complication could arise from receptor binding of the desmethyl radiolabeled metabolite as one report also indicated that the desmethyl metabolite of 403U76 was "potent" but provided no further details (20).

For these reasons we also radiolabeled with  $^{11}\text{C}$  compound (2), the N-normethyl derivative of compound (1) to investigate whether or not [ $^{11}\text{C}$ ]-2 crosses the BBB. As shown in Table 1, while [ $^{11}\text{C}$ ]-1 demonstrates facile penetration of the BBB, so too does [ $^{11}\text{C}$ ]-2. In fact uptake of [ $^{11}\text{C}$ ]-2 is slightly higher and more enduring than that observed for [ $^{11}\text{C}$ ]-1. It has been argued that the ideal  $\text{LogP}_{7.4}$  of a radiotracer for brain receptors is around 2-2.5 (21), reflecting a balance between brain penetration and non-specific binding. The  $\text{LogP}_{7.4}$  of (1) at 3.4 significantly greater than this ideal; nevertheless brain penetration is excellent and it remains to be seen if less lipophilic analogues exhibit faster brain washout.

We have demonstrated that N,N-dimethyl-2-(arylthio)benzylamines can be efficiently radiolabelled with  $^{11}\text{C}$  in the N-methyl position, providing a route to a potentially new class of SERT imaging ligands for PET. In addition, [ $^{11}\text{C}$ ]-1 crosses the BBB well with a high brain to blood ratios (5 to 1) 15 min post injection. However the high brain uptake of the potential metabolite [ $^{11}\text{C}$ ]-2 suggests that any research program devoted towards the development of this class of compounds as potential PET or SPECT ligands must be circumspect regarding the issue of brain penetration of radiolabelled metabolites. Further work on the regional and pharmacological specificity of brain radioactivity uptake of [ $^{11}\text{C}$ ]-1 and its metabolic profile is in progress.

## Experimental

Purification and analyses of radioactive mixtures by HPLC were performed with an in-line UV (254 nm) detector in series with a NaI crystal radioactivity detector. HPLC columns used were: A, Phenomenex Prodigy C<sub>18</sub> (250 mm x 10 mm, 10 $\mu$ ); and B, Phenomenex Prodigy C<sub>18</sub> (250 mm x 4.6 mm, 10 $\mu$ ). Peak areas were measured using Hewlett-Packard 3396 and Waters 746 recording integrators. Isolated radiochemical yields were determined with a dose-calibrator (Capintec CRC-712M). THF was freshly (same day) distilled under nitrogen from LiAlH<sub>4</sub> and DMF was distilled from BaO and stored over 4 Å molecular sieves. All other chemicals were obtained from commercial sources. NMR were run on a Varian Unity 500 at 500 MHz (<sup>1</sup>H) or 127.5 MHz (<sup>13</sup>C) in CDCl<sub>3</sub> with TMS as internal standard. High resolution mass spectrometry (electron impact 70 ev) were carried out on a Micromass 70-250-S. Radio-TLC of radioactive solutions were performed on a Berthold Tracemaster 20 Linear analyzer.

***N,N*-Dimethyl-2-(2-amino-4-trifluoromethyl)phenylthio)benzylamine (1).** A mixture of 2-(2-amino-4-(trifluoromethyl)phenylthio)benzyl chloride hydrochloride (12) (1.5 g, 4.23 mmol), dimethylamine hydrochloride (2.0g, 24.5 mmol), and K<sub>2</sub>CO<sub>3</sub> (2.5g, 18.1 mmol) in DMSO (10 mL) and water (1 mL) was stirred at 50 °C for 2 hr. The mixture was quenched with water (50 mL) and extracted with EtOAc (2 x 30 mL). The combined organic fractions were washed with aqueous HCl (1N, 3 x 10 mL) and the aqueous washings neutralised with conc. NH<sub>4</sub>OH. Upon back extraction with ether (2 x 15 mL), the ethereal solution was dried (K<sub>2</sub>CO<sub>3</sub>), filtered, and evaporated to give a clear oil (0.29 g, 23.3%); <sup>1</sup>HNMR  $\delta$  2.40 (s, 6H), 3.65 (s, 2H), 5.07 (br s, 2H), 6.84-6.91 (m, 2H), 6.93-6.97 (m, 1H), 7.07-7.17 (m, 2H), 7.20-7.22 (m, 1H), 7.51-7.54 (m, 1H); <sup>13</sup>CNMR  $\delta$  148.8, 137.4, 137.2, 135.7, 132.2 (q, J=29 Hz), 130.5, 129.1, 128.2, 126.1, 124.0 (q, J=276 Hz), 119.9, 113.9, 111.3, 62.5, 45.2; C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>F<sub>3</sub>S calc. mass 326.10646; found 326.10669.

***N*-Methyl-2-(2-amino-4-trifluoromethyl)phenylthio)benzylamine (2).** The procedure described above for compound (1) was followed using methylamine hydrochloride. The resultant product (a red oil) which was further purified by column chromatography (silica gel, EtOAc/Et<sub>3</sub>N (95/5)) yielding a light brown oil (0.22 g, 18.6 %); <sup>1</sup>HNMR  $\delta$  2.48 (s, 3H), 3.92 (s, 2H), 4.3-5.0 (br s, 2H), 6.88-6.96

(m, 3H), 7.08-7.18 (m, 2H), 7.29-7.33 (m, 1H), 7.41-7.46 (m, 1H);  $^{13}\text{C}$ NMR  $\delta$  148.4, 138.0, 136.5, 134.3, 132.3 (q,  $J=33$  Hz), 129.7, 128.6, 128.2, 126.4, 124.0 (q,  $J=264$  Hz), 119.1, 114.4, 111.5, 53.8, 35.9;  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{F}_3\text{S}$  calc. mass 312.09081; found 312.09125.

**2-(2-Amino-4-trifluoromethyl)phenylthio)benzylamine (3).** A solution of 2-(2-amino-4-(trifluoromethyl)phenylthio)benzyl chloride hydrochloride (12) (0.18 g, 0.51 mmol), in ammoniacal methanol (4N, 10 mL) was stirred at room temperature for 3 days. The mixture was evaporated to dryness and worked up as described for (1) above to give a faintly yellow oil (88.5 mg, 64.8%);  $^1\text{H}$ NMR  $\delta$  1.62 (br s, 2H), 4.01 (s, 2H), 4.52 (br s, 2H), 6.92-6.98 (m, 3H), 7.11-7.24 (m, 2H), 7.34-7.43 (m, 2H);  $^{13}\text{C}$ NMR  $\delta$  148.1, 141.7, 136.2, 133.2, 132.3 (q,  $J=32$  Hz), 129.5, 128.7, 128.5, 127.9, 123.9 (q,  $J=272$  Hz), 119.4, 114.9, 111.7, 44.7;  $\text{C}_{14}\text{H}_{13}\text{N}_2\text{F}_3\text{S}$  calc. mass 298.07516; found 298.07575.

$[^{11}\text{C}]$ -(1).  $[^{11}\text{C}]$ -iodomethane, produced from  $^{11}\text{CO}_2$  as described previously (22), was swept by a flow of  $\text{N}_2$  gas (15 mL/min) into a solution of (2) (1.0 mg) in DMF (200  $\mu\text{L}$ ) at  $-20$   $^\circ\text{C}$ . When radioactivity had peaked the solution was heated to  $90$   $^\circ\text{C}$  for 5 min and quenched with HPLC buffer (0.5 mL). The mixture was purified by semi-prep HPLC; Column A, 50%  $\text{CH}_3\text{CN}$ :50%  $\text{H}_2\text{O}$  + 0.1N  $\text{NH}_4\text{HCO}_2$ , 10 mL/min (Rt. of (1) — 8.3 min, Rt. of (2) — 2.5 min). The desired fraction was collected, evaporated to dryness, and the residue taken up in 10 mL of sterile saline. The saline solution of  $[^{11}\text{C}]$ -(1) was passed through a sterile 0.22  $\mu\text{m}$  filter into a sterile, pyrogen-free bottle containing aqueous sodium bicarbonate (1 mL, 8.4%). An aliquot (100  $\mu\text{L}$ ) of the formulated solution was used to establish the chemical and radiochemical purity and specific activity of the final solution by analytical HPLC; Column B, 50%  $\text{CH}_3\text{CN}$ :50%  $\text{H}_2\text{O}$  + 0.1N  $\text{NH}_4\text{HCO}_2$ , 4 mL/min (Rt. of (1) — 3.3 min).

$[^{11}\text{C}]$ -(2) was synthesized in an identical manner to  $[^{11}\text{C}]$ -(1) using 1.0 mg of (3) as precursor. HPLC conditions: Purification — Column A, 35%  $\text{CH}_3\text{CN}$ :65%  $\text{H}_2\text{O}$  + 0.1N  $\text{NH}_4\text{HCO}_2$ , 9 mL/min (Rt. of (2) - 10.5 min, Rt. of (3) - 7.1 min); Quality control — Column B, 40%  $\text{CH}_3\text{CN}$ :60%  $\text{H}_2\text{O}$  + 0.1N  $\text{NH}_4\text{HCO}_2$ , 4 mL/min (Rt. of (2) - 3.1 min). Radiochemical yields were comparable to  $[^{11}\text{C}]$ -(1).



*Identification and stability of radiotracers.* Formulated solutions of [ $^{11}\text{C}$ ]-**(1)** and [ $^{11}\text{C}$ ]-**(2)** showed no radiolysis products over a 45 min period as determined by analytical HPLC. Further evidence for the identity of both radiolabelled products were achieved by co-injection with authentic "cold" material using a further two different HPLC columns (Alltech  $\text{C}_8$  Econosil, Waters  $\text{C}_{18}$  Novapak). In addition, radio-scanning TLC showed one radioactive peak with the same retention factor as authentic material (Rf of **(1)**-0.60 and Rf of **(2)**-0.46, silica gel, EtOAc:Et $_3$ N 95:5 (v/v)).

[ $^{13}\text{C}$ ]-**(1)** and [ $^{13}\text{C}$ ]-**(2)** were synthesised and purified in an almost identical manner to their [ $^{11}\text{C}$ ]-labelled counterparts except that solutions of [ $^{13}\text{C}$ ]-iodomethane (1.0  $\mu\text{L}$  in 10  $\mu\text{L}$  DMF) were introduced to the precursor solutions (4.0 mg in 200  $\mu\text{L}$  DMF) by syringe rather than trapping [ $^{11}\text{C}$ ]-iodomethane. After HPLC purification, the  $\text{CH}_3\text{CN}$  was removed by evaporation under vacuum, the aqueous remains neutralised with KOH, and extracted with dichloromethane (2 x 2 mL). The combined organics were dried ( $\text{K}_2\text{CO}_3$ ), filtered and solvent removed. The residues were taken up in  $\text{CDCl}_3$  for NMR analysis. Isolated yields of [ $^{13}\text{C}$ ]-**(1)** and [ $^{13}\text{C}$ ]-**(2)** were 53% and 28% respectively (based on [ $^{13}\text{C}$ ]-iodomethane).  $^{13}\text{C}$ NMR  $\delta$  45.1 for [ $^{13}\text{C}$ ]-**(1)** and  $\delta$  36.1 for [ $^{13}\text{C}$ ]-**(2)**.

*Log P measurements* The determination of partition coefficients of radioactive compounds are performed in 1-octanol and 0.02 M phosphate buffer at pH 7.4. The two phases were pre-saturated with each other. To a 30 mL separatory funnel (30 mL containing 1-octanol (10 mL) and phosphate buffer (5 mL), 20 - 40  $\mu\text{L}$  of the formulated [ $^{11}\text{C}$ ]-labelled radiotracer was added. After shaking for about 3 min, the bottom aqueous layer was discarded (23). Four aliquots (2 mL) of the octanol layer were pipetted into four 12 mL test tubes containing phosphate buffer (2 mL). The test tubes were mechanically shaken for 10 min and centrifuged for 5 min at 1000 g. From each test tube approximately 0.5 mL of organic phase was pipetted into a pre-weighed small test tube for radioactive counting, the remaining octanol phase was removed carefully and discarded. Approximate 0.5 mL of buffer phase was also transferred into a separate pre-weighed small test tube. The amount of radioactivity in each tube was measured, back correcting for decay, by a gamma counter.

Accurate volumes of the counted buffer and octanol phases were determined by weight differences and known densities. LogP of a substance A is defined as:

$$\text{Log}_{10} \left\{ \frac{[A]_{\text{organic}}}{[A]_{\text{aqueous}}} \right\}. \text{ In the present case this becomes :}$$

$$\text{Log}_{10} \{ (\text{counts / mL in octanol}) / (\text{counts / mL in buffer}) \}.$$

*Animal Studies* All animal experiments were carried out under humane conditions, with approval from the Animal Care Committee at the Clarke Institute and in accordance with the guidelines set forth by the Canadian Council on Animal Care. Animals received 3-30 MBq of high specific activity radiotracer (350-450 ng) in 0.3 mL of buffered saline via the tail vein, vasodilated in a warm water bath. A previously described method was used to determine the brain uptake of radioactivity (24). Experiments were conducted on groups of three rats per time point.

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#### References

- (1) Rickels K., and Schweizer E. -*J Clin Psychiatry* **51 Suppl B**: 9 (1990).
- (2) Mazière B., Coenen H., Halldin C., Nagren K., and Pike V. -*Nuc. Med. Biol.* **19**: 497 (1992).
- (3) Innis R.B. -*Eur J Nucl Med* **21**: 1 (1994).
- (4) Crouzel C., Guillaume M., Barre L., Lemaire C., and Pike V. -*Nucl. Med. Biol.* **19**: 857 (1992).
- (5) Suehiro M., Scheffel U., Ravert H.T., Dannals R.F., and Wagner H.N., Jr. -*Life Sci* **53**: 883 (1993).
- (6) Suehiro M., Scheffel U., Dannals R.F., Ravert H.T., Ricaurte G.A., and Wagner H.N., Jr. -*J Nucl Med* **34**: 120 (1993).
- (7) Szabo Z., Scheffel U., Suehiro M., Dannals R.F., Kim S.E., Ravert H.T., Ricaurte G.A., and Wagner H.N. -*J Cereb Blood Flow Metab* **15**: 798 (1995).

- (8) Szabo Z., Kao P.F., Scheffel U., Suehiro M., Mathews W.B., Ravert H.T., Musachio J.L., Marenco S., Kim S.E., Ricaurte G.A., Wong D.F., Wagner H.N., and Dannals R.F. -*Synapse* **20**: 37 (1995).
- (9) Jilek J., Sindelar K., Pomykacek J., Kmonicek V., Sedivy Z., Hrubantova M., Holubek J., Svatek E., Ryska M., Koruna I., Valchar M., Dlabac A., Metysova J., Dlohozkova N., and Protiva M. -*Coll. Czech. Chem. Commun.* **54**: 3294 (1989).
- (10) Ferris R.M., Brieady L., Mehta N., Hollingsworth E., Rigdon G., Wang C., Soroko F., Wastila W., and Cooper B. -*J Pharm Pharmacol* **47**: 775 (1995).
- (11) Brieady L.E. -Patent application WO 93/12080 (1993).
- (12) Polivka Z., Zborovsketha P., Dobrovsky K., Silhankova A., Sindelar K., Mickova R., Valenta V., and Kreici I. -Patent application WO 97/17325 (1996).
- (13) Oya S., Kung M.P., Acton P.D., Mu M., Hou C., and Kung H.F. -*J Med Chem* **42**: 333 (1999).
- (14) Meyer J.H., Cho R., Kennedy S.H., and Kapur S. - *Psychopharm.* in press: (1999).
- (15) Meyer J.H., Kapur S., Houle S., DaSilva J., Owczarek B., Brown G.M., Wilson A.A., and Kennedy S.H. -*Amer. J. Psychiatry* in press: (1999).
- (16) Hansch C., Leo A., and Hoekman D.H. *Exploring QSAR. Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995.
- (17) Luthra S.K., Brady F., Turton D.R., Brown D.J., Dowsett K., Waters S.L., Jones A., Matthews R.W., and Crowder J.C. -*Appl Radiat Isotopes* **45**: 857 (1994).
- (18) Pretsch E., Seibel J., Simon W., and Clerc T. -*Tables of Spectral Data for Structure Determination of Organic Compounds 2nd Edition*, Springer-Verlag (Berlin) (1989).
- (19) Protiva M. -*Drugs Future* **16**: 911 (1991).
- (20) Silver I.S., Wurm R.M., Welch R.M., and Harrelson J.C. -*J. Liq. Chrom. & Rel. Technol.* **19**: 1117 (1996).
- (21) Kessler R.M., Ansari M.S., de Paulis T., Schmidt D.E., Clanton J.A., Smith H.E., Manning R.G., Gillespie D., and Ebert M.H. -*J. Nucl. Med.* **32**: 1593 (1991).
- (22) Wilson A.A., DaSilva J.N., and Houle S. -*J. Labelled Compd. Radiopharm.* **34**: 759 (1994).

- (23) Wilson A.A., Jin L., Garcia A., DaSilva J.N., and Houle S. -"Problems associated with Measuring the Lipophilicity of Radiotracers" 11th International Symposium on Radiopharmaceutical Chemistry, St Louis, Missouri. T7 (1999).
- (24) Wilson A.A., DaSilva J.N., and Houle S. -Nucl. Med. Biol. 23: 141 (1996).