Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 5635–5639
Bioorganic & Medicinal Chemistry Letters

Synthesis and amine transporter affinities of novel phenyltropane derivatives as potential positron emission tomography (PET) imaging agents

Xuemei Peng,[a,c] Ao Zhang,[a] Nora S. Kula,[b] Ross J. Baldessarini[b] and John L. Neumeyer[a,c,*]

[a]*Medicinal Chemistry Laboratory, Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478-9106, USA*
[b]*Neuropharmacology Laboratory, Mailman Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA*
[c]*Natural Pharmacia International, 115 Mill Street, Belmont, MA 02478, USA*

Received 3 August 2004; revised 19 August 2004; accepted 19 August 2004
Available online 11 September 2004

Abstract—A series of novel fluoroalkyl-containing tropane derivatives (**6**–**8**, **10**–**14**, **17**, and **18**) were synthesized from cocaine. Novel compounds were evaluated for affinity and selectivity in competitive radioligand binding assays selective for cerebral serotonin (5-HT), dopamine (DA), and norepinephrine (NE) transporters (SERT, DAT, and NET). The nortropane-fluoroalkyl esters (**7**, **10**, **11**) were most potent for SERT (K_i: 0.18, 0.24, and 0.30 nM, respectively). Tosylate esters **17** and **18**, synthesized as precursors for [^{18}F]-labeled, Positron Emission Tomography (PET) imaging agents, also showed high affinity for DAT.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Cocaine blocks reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE) by transporter proteins specific to each neurotransmitter amine (DAT, SERT, and NET)[1] in a process that terminates the physiological action of each released monoamine neurotransmitter by reuptake into the corresponding presynaptic neurons.[2] Changes in the density and function of these amine transport processes contribute to the actions of drugs effective for the treatment of clinical major depression[3] and may contribute to the pathophysiology of Alzheimer's[4] and Parkinson's diseases,[5] as well as to the neurotoxic effects of some illicit drugs.[6,7] These synaptic amine-regulating neuronal transporter systems also play a prominent role in the behavioral effects of cocaine and other stimulants.[8–11]

The development of radioligands with which to characterize the in vivo distribution, density, and occupancy of specific monoamine transporters by the use of Positron Emission Tomography (PET) should advance efforts to define the function and pharmacology of these important proteins as highly specific molecular markers of their responsive neuron types in the living human brain. Clinical applications of such radioligands might include the diagnosis of major depression or other neurobehavioral disorders, monitoring the potency and actions of antidepressant drugs that interact with monoamine transmitters, and monitoring of responses to such treatment.[12–16]

PET is sensitive and specific neuroimaging technology for quantitative measurement of in vivo density of neurotransmitter transporters and receptors. For PET studies,[18] F is a particularly attractive radionuclide. Its 110-min half life allows sufficient time (3×110 min) for chemical incorporation into tracer molecules and purification of products suitable for administration. In addition, the relatively low energy of positrons emitted by ^{18}F (0.635 MeV, 2.4 mm positron range) affords particularly high-resolution images.[17–19]

Keywords: Dopamine transporter; PET imaging; Nortropane; Fluoroalkylesters.
* Corresponding author. Tel.: +1 6178553388; fax: +1 6178552519; e-mail: neumeyer@mclean.harvard.edu

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.08.049

Major efforts have focused on development of radiolabeled phenyltropane derivatives to study the physiology, pharmacology, and pathophysiology of cerebral monoamine transporters. Most PET radiotracers developed to target monoamine transporters have been radiocarbon [^{11}C]-labeled phenyltropanes.[20–27] There are a few available [^{18}F]-labeled tracers for amine transporters, but most of them require multi-step radiosynthesis.[28–37] Moreover, the selectivity of such compounds for specific monoamine transporters varies, and requires further improvement.

Given the circumstances just summarized, our objectives in this study were to synthesize and pharmacologically evaluate novel *N*- or *O*-fluoroalkyl tropane derivatives, aiming at simplified, one-step [^{18}F]-radiolabeling of novel radiopharmaceuticals for PET imaging.[28,38] We report the synthesis and monoamine transporter binding potencies and selectivities of a series of novel fluoroalkyl-substituted tropane derivatives, as well as the synthesis of two tosylate compounds, which were developed as precursors for the one-step radiolabeling to provide PET imaging agents. We found that several novel compounds of this type possess high affinity and selectivity for both DAT and SERT, and are attractive potential ligands for labeling these monoamine transporters in brain tissue, including compounds suitable for efficient conversion to [^{18}F]-labeled radiopharmaceuticals.

2. Chemistry

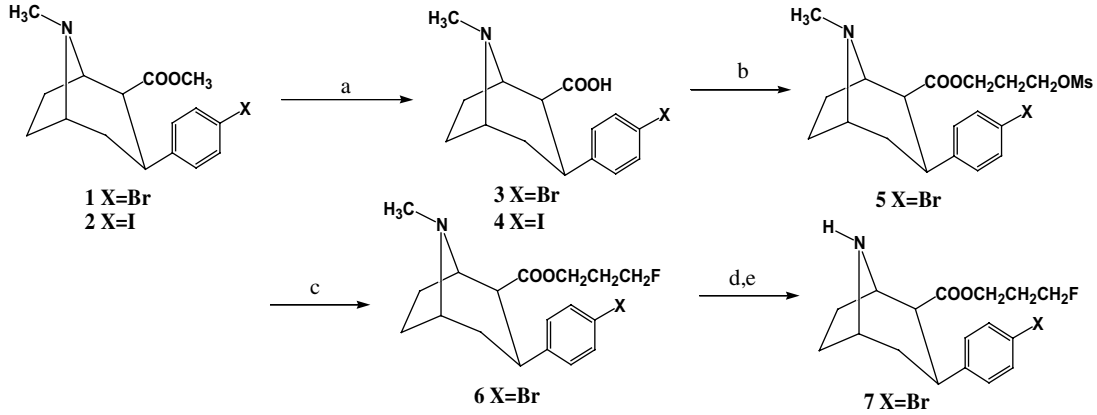
We first hydrolyzed cocaine with 6 N HCl, followed by treatment with $POCl_3$ and MeOH to obtain anhydroecgonine-methyl ester in 97% overall yield after bulb-to-bulb distillation. Grignard addition with 4-trimethylsilyl-phenylmagnesium bromide yielded a series of 2-β-carbomethoxy-3β-(4-trimethylsilylphenyl)-tropanes after quenching the reaction with trifluoroacetic acid at low temperature. The halogen-substituted phenyltropanes, 2-β-carbomethoxy-3-β-(4-bromophenyl)-tropane (β-CBT; **1**) and its 4-iodo congener (β-CIT; **2**) were prepared by previously reported procedures.[38] Hydrolysis of **1** and **2** in aqueous dioxane gave the corresponding acids **3** and **4** in ⩾90% yields. Treatment of **3** with $POCl_3$ yielded the acid chloride; without further purification, this material was treated with 1,3-propane-diol monomesylate to produce compound **5**. Treatment of the mesylate ester **5** with tetrabutylammonium fluoride (TBAF) in refluxing THF provided the 3-fluoropropyl ester **6** in ⩾90% yield. N-demethylation of compound **6** with α-chloroethyl-chloroformate (ACE-Cl)[39] in ethylene dichloride, followed by treatment with MeOH, provided the nortropane **7** (see Scheme 1).

The fluoroalkyl-containing ester and amide analogs of the tropanes **8**, **9**, **13**, and **14** were prepared by treatment of the corresponding acid chloride with 2-fluoroethanols and 2-fluoroethylamines (see Scheme 2). N-demethylation of **8** and **9** provided the nortropanes **10** and **11**. *N*-(fluoroalkyl)Phenyltropane **12** was prepared by alkylation of **10** with fluoropropyl bromide according to previously reported procedures.[40,41]

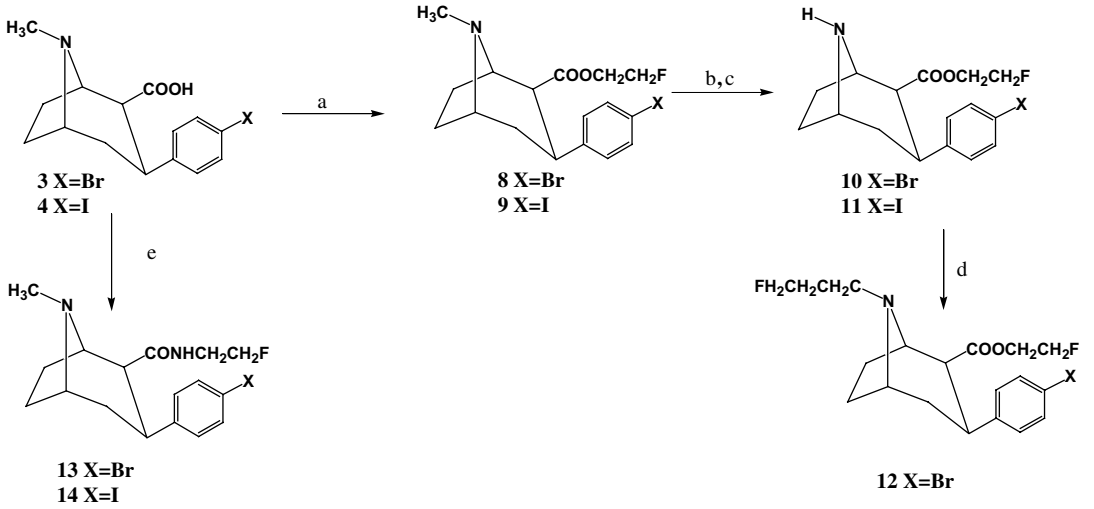
Attempts to treat the acid chlorides of **3** or **4** with 2-(*p*-toluylsulfonyl)ethanol failed to yield desired tosylates **17** and **18**. However, **17** and **18** were readily prepared by treatment of alcohols **15** and **16** with *p*-toluenesulfonyl chloride and *N*,*N*,*N*′,*N*′-tetramethyl-1,6-hexanediamine in acetonitrile at 0–5 °C for 3 h (see Scheme 3). The tosylates **17** and **18** can be readily converted to the fluoro-compounds **8** and **MCL 301** using microwave technology. A CEM explorer microwave discover system was used for this conversion, which required 15 min at 100 °C in 80% yield. This conversion to the ^{18}F compounds was subsequently reported by Baldwin et al.[44]

3. Structure–activity relationships

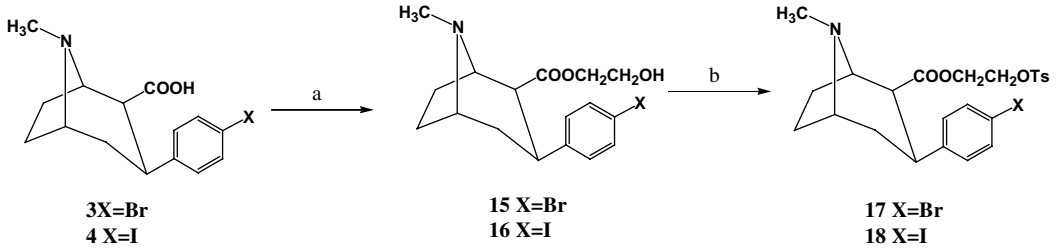
In vitro transporter-binding potencies of test compounds were evaluated by radioligand competition assays based on tritiated radioligands that are highly selective for DAT, SERT, and NET sites in rat forebrain tissue preparations, as detailed previously.[42,43] Potencies are expressed as affinity constants (K_i) in nanomolar (nM), and selectivities for specific transporter-types are



Scheme 1. Reagents and conditions: (a) dioxane/H_2O (1:1, v/v), reflux 1 day; (b) $POCl_3$, $HOCH_2CH_2CH_2OMs$, Et_3N, CH_2Cl_2; (c) TBAF, THF, reflux 2 h; (d) ACE-Cl, $ClCH_2CH_2Cl$, reflux 2 days; (e) MeOH, rt.



Scheme 2. Reagents and conditions: (a) $POCl_3$, $HOCH_2CH_2F$, Et_3N, CH_2Cl_2; (b) ACE-Cl, $ClCH_2CH_2Cl$, reflux 2 days; (c) MeOH, rt; (d) $FCH_2CH_2CH_2Br$, KI, Et_3N, EtOH, reflux 2 h; (e) $POCl_3$, $NH_2CH_2CH_2F$, Et_3N, CH_2Cl_2.



Scheme 3. Reagents and conditions: (a) $POCl_3$, $HOCH_2CH_2OH$, Et_3N, CH_2Cl_2; (b) TsCl, $Me_2N(CH_2)_6NMe_2$, CH_3CN.

expressed as K_i ratios; our previously reported[38] K_i values for CBT, nor-CBT, FP-CBT, MCL 301 are included for comparison (Table 1).

In general, the novel fluoroalkyl esters of halophenyltropanes showed higher affinity than fluoroalkyl amides at both DAT and SERT (compare: **8** vs **13**, and MCL301 vs **14**; Table 1). The fluoroethyl ester of nor-CIT (**11**) showed highest SERT potency (K_i = 0.18 nM), and moderate selectivity for SERT over DAT (4.7-fold). The fluoroethyl ester of nor-CBT (**10**; K_i = 0.57 nM), as well as the tosyl-ethyl ester **18** (K_i = 0.52 nM)) showed the highest DAT potencies, and the fluoroethyl ester of FP-CBT (**12**) showed relatively high affinity at NET sites (K_i = 2.03 nM).

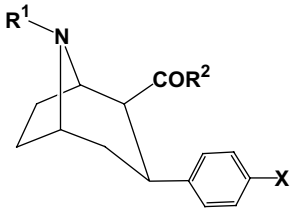
The fluoroethyl (**8**) and fluoropropyl (**6**) esters of CBT had lower affinity at DAT and NET sites than did CBT itself, but similar affinity for SERT, resulting in greater selectivity for SERT compared to CBT. The fluoroethyl ester *N*-fluoropropyl derivative **12** showed 3.2-fold less affinity at DAT than did the *N*-fluoropropyl methyl ester,[38] as well as greater potency at both SERT (2-fold) and NET (over 200-fold), resulting in decreased selectivity for DAT versus SERT and NET.

The potency of the nortropane esters **7**, **10**, and **11**, relative to their *N*-methyl analogs **6** and **8** indicated that replacement of the *N*-methyl group by hydrogen enhanced potency at all three monoamine transporters and led to greater selectivity for SERT (9.5–22 fold) and NET (18.4–27.6 fold) than at DAT (1.1–3.4 fold). Compared to nor-CBT, the nortropane fluoroalkyl esters **7**, **10**, and **11** showed little change in DAT affinity, but lower potency at SERT or NET, so as to yield 3.2–5.3 fold selectivity for DAT over SERT, and 8.7–14.9 fold selectivity for DAT over NET (Table 1).

The fluoroethyl amide derivatives (**13** and **14**) showed lower affinity for DAT and SERT, and are expected to have a longer pharmacological action. The tosylate ester analogs **17** and **18** were designed as precursors for the preparation of [^{18}F]-labeled PET agents. Compared to fluoroethyl ester analogs, the tosylates (**20** and **21**) showed relatively high affinity at both DAT and SERT (K_i = 0.5–1.6 nM), suggesting that DAT and SERT can accommodate sterically demanding functional groups at the 2-β position of phenyltropanes (compare: **7** vs **17**, and **18** vs MCL 301; Table 1).

In conclusion, a series of fluoroalkyl derivatives of halophenyltropanes and two tosylate precursors for the preparation of [^{18}F] radiolabeled derivatives (**17** and **18**) were synthesized and evaluated for potency and selectivity at monoamine transporters for DA, NE, and 5-HT in rat forebrain tissue. Novel halophenyltropanes **6**, **7**, **8**, **10**, and **11** are especially attractive

Table 1. Transporter binding affinity and SAR of fluoroalkyl derivatives of halophenyltropanes



Compd[a,b]	R^1	R^2	X	Potency (K_i ± SE, nM)[c]			Selectivity[d]	
				DAT	SERT	NET	DAT/SERT	DAT/NET
6	CH_3	$OCH_2CH_2CH_2$ F	Br	1.91 ± 0.10	2.86 ± 0.14	244 ± 28	1.50	128
7	H	$OCH_2CH_2CH_2F$	Br	0.72 ± 0.10	0.30 ± 0.10	8.85 ± 0.66	0.42	12.3
8 (MCL322)	CH_3	OCH_2CH_2 F	Br	2.33 ± 0.19	5.10 ± 0.22	280 ± 37	2.19	120
10	H	OCH_2CH_2F	Br	0.57 ± 0.05	0.24 ± 0.01	15.2 ± 1.1	0.42	26.7
11	H	OCH_2CH_2F	I	0.85 ± 0.07	0.18 ± 0.02	—	0.21	—
12	$CH_2CH_2CH_2F$	OCH_2CH_2F	Br	10.6 ± 0.55	18.3 ± 1.5	2.03 ± 2.48	1.72	0.19
13	CH_3	$NHCH_2CH_2$ F	Br	25.7 ± 3.1	38.7 ± 2.6	ca. 3000	1.51	ca. 117
14	CH_3	$NHCH_2CH_2F$	I	44.5 ± 2.3	30.8 ± 2.2	>10,000	0.69	>225
17	CH_3	OCH_2CH_2OTs	Br	1.23 ± 0.07	1.65 ± 0.09	225 ± 25	1.34	183
18	CH_3	OCH_2CH_2OTs	I	0.52 ± 0.10	0.62 ± 0.02	413 ± 59	1.19	794
Nor-CBT	H	OCH_3	Br	0.52 ± 0.10	0.95 ± 0.10	1.02 ± 0.15	0.55	0.51
CBT	CH_3	OCH_3	Br	0.30 ± 0.05	4.95 ± 0.50	15.3 ± 1.0	0.06	0.02
MCL301[e]	CH_3	OCH_2CH_2F	I	0.93 ± 0.10	4.02 ± 0.48	116 ± 12	4.30	125
FP-CBT[e]	$CH_2CH_2CH_2F$	OCH_3	Br	3.33 ± 0.99	36.4 ± 2.2	196 ± 14	10.9	58.9

[a] All compounds exhibited 1H NMR spectra consistent with their assigned structures.
[b] CHN analyses were within 0.4% of theoretical values.
[c] Transporter binding affinity assays were detailed previously.[42,43] For DAT, rat striatal homogenates incubated with 0.3 nM [^{3}H] CIT (Tocris-Cookson); for SERT, rat cerebral cortical homogenates incubated with 0.71 nM [^{3}H]cyanoimiprimine (NEN); for NET, rat cerebral cortical homogenates incubated with 0.35 nM [^{3}H]nisoxetine (NEN).
[d] Selectivity = ratios of K_i for SERT or NET versus for DAT (ratios >1.0 indicate preference for DAT over SERT or NET).
[e] Reported previously,[38] and included for comparison with novel agents.

candidates for the development of [^{18}F]-labeled PET radiotracers for clinical imaging DAT in human brain in that they all showed high affinity (K_i < 5 nM) for DAT sites. We recently prepared both [^{18}F]-labeled **8** (MCL322) and [^{18}F]-labeled MCL301 in one step from the respective tosylate precursors **17** and **18**, and reported on their assessment by PET imaging of baboon and rodent brains.[44] These preliminary findings indicated high selectivity for both novel [^{18}F]-radioligands for DAT over SERT or NET, are in keeping with the in vitro affinity data shown in Table 1.

Finally, the fluoroethyl ester of nor-CBT (**10**) showed the highest potency and selectivity for SERT versus DAT. Since inhibition of serotonin reuptake may modulate the reinforcing properties of cocaine,[45] compounds such as **10** may be of interest as therapeutic agents for the clinical management of stimulant abuse disorders.

Acknowledgements

This work was supported, in part, by grants from the National Institute of Neurological Disorders and Stroke (NS-40587, to J.L.N.), the Bruce J. Anderson Foundation and the McLean Hospital Private Donors Neuropharmacology Research Fund (to R.J.B.). Cocaine was generously donated by Mallinkrodt Corporation.

References and notes

1. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 970.
2. Boja, J. W.; Vaughan, R.; Patel, A.; Shaya, E. K.; Kuhar, M. J. In *Doapmine Receptors and Transporters: Pharmacology, Structure, and Function*; Niznik, H. B., Ed.; Marcel Dekker: New York, 1994; p 611.
3. Kapur, S.; Mann, J. J. *Biol. Psychiatry* **1992**, *32*, 1.
4. Rinne, J. O.; Bergman, J.; Ruottinenm, H.; Haaparanta, M.; Eronen, E.; Oikonen, V.; Sonninen, P.; Solin, O. *Synapse* **1999**, *31*, 119.
5. Niznik, H. B.; Fogel, E. F.; Fassos, E. F.; Seeman, P. *J. Neurochem.* **1991**, *56*, 192.
6. Doughtery, D. D.; Bonab, A. A.; Spencer, T. J.; Rauch, S. L.; Madras, B. K.; Fishman, A. J. *Lancet* **1999**, *354*, 2132.
7. Dresel, S.; Krause, J.; Krause, K. H.; La Fougere, C.; Brinkbaumer, K.; Kung, H. F.; Hahn, K.; Tatsch, K. *Eur. J. Nucl. Med.* **2000**, *27*, 1518.
8. Giros, B.; Jaber, M.; Jones, S. R.; Wightman, R. M.; Caron, M. G. *Nature* **1996**, *379*, 606.
9. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.
10. Volkow, N. D.; Wang, G. J.; Fischman, M. W.; Foltin, R. W.; Fowler, J. S.; Abumrad, N. N.; Vitkun, S.; Logan, J.; Gatley, S. J.; Pappas, N.; Hitzemann, R.; Shea, C. E. *Nature* **1997**, *386*, 827.
11. Volkow, N. D.; Wang, G. J.; Fowler, J. S.; Logan, J.; Gatley, S. J.; Hitzemann, R.; Chen, A. D.; Dewey, S. L.; Pappas, N. *Nature* **1997**, *386*, 830.
12. Farde, L. *Trends Neurosci.* **1996**, *19*, 211.

13. Campbell, A.; Comar, D. *Drug Inform. J.* **1997**, *31*, 989.
14. Jones, T. *Eur. J. Nucl. Med.* **1996**, *23*, 807.
15. Burns, H. D.; Hamill, T. G.; Eng, W.; Francis, B.; Fioravanti, C.; Gibson, R. E. *Curr. Opin. Chem. Biol.* **1999**, *3*, 388.
16. Aboagye, E. O.; Price, P. M.; Jones, T. *Drug Discov. Today* **2001**, *6*, 293.
17. Fowler, J. S.; Volkow, N. D.; Wang, G. J.; Ding, Y. S.; Dewey, S. L. *J. Nucl. Med.* **1999**, *40*, 1154.
18. Brooks, D. J.; Frey, K. A.; Marek, K. L.; Oakes, D.; Paty, D.; Prentice, R.; Shults, C. W.; Stoessl, A. J. *Exp. Neurol.* **2003**, *184*, S68.
19. Phelps, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226.
20. Frost, J. J.; Rosier, A. J.; Reich, S. G.; Smith, J. S.; Ehlers, M. D.; Snyder, S. H.; Ravert, H. T.; Dannals, R. F. *Ann. Neurol.* **1993**, *34*, 423.
21. Meltzer, P. C.; Liang, A. Y.; Brownell, A. L.; Elmaleh, D. R.; Madras, B. K. *J. Med. Chem.* **1993**, *36*, 855.
22. Dannals, R. F.; Neumeyer, J. L.; Milius, R. A.; Ravert, H. T.; Wilson, A. A.; Wagner, H. N. *J. Labelled Compd. Radiopharm.* **1993**, *33*, 147.
23. Muller, L.; Halldin, C.; Farde, L.; Karlson, P.; Hall, H.; Swahnm, C. G.; Neumeyer, J. L.; Wang, S.; Milius, R. A. *Nucl. Med. Biol.* **1993**, *20*, 249.
24. Lundkvist, C.; Halldin, C.; Swahn, C. G.; Hall, H.; Karlson, P.; Nakashima, Y.; Wang, S.; Milius, R. A.; Neumeyer, J. L.; Farde, L. *Nucl. Med. Biol.* **1995**, *22*, 905.
25. Halldin, C.; Farde, L.; Lundkvist, C.; Ginovart, N.; Nakashima, Y.; Karlson, P.; Swahn, C. G. *Synapse* **1996**, *22*, 386.
26. Fishman, A. J.; Bonab, A. A.; Babich, J. W.; Livni, E.; Alpert, N. M.; Meltzer, P. C.; Madras, B. K. *Synapse* **2001**, *39*, 332.
27. Kämäräinen, E. L.; Kyllönen, T.; Airaksinen, A.; Lundkvist, C.; Yu, M.; Någren, K.; Sandell, J.; Langer, O.; Vepsäläinen, J.; Hiltunen, J.; Bergström, K.; Lötjönen, S.; Jaakkola, T.; Halldin, C. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 1235.
28. (a) Chaly, T.; Dhawan, V.; Kazumata, K.; Antonini, A.; Margouleff, C.; Dahl, R.; Belakhlef, A.; Margoulef, D.; Yee, A.; Wang, S.; Tamagnan, G.; Neumeyer, J. L. *Nucl. Med. Biol.* **1996**, *23*, 999; (b) Kazumata, K.; Dhawan, V.; Chaly, T.; Antonini, A.; Matgouleff, C.; Belakhlef, A.; Neumeyer, J. L.; Eidelberg, D. *J. Nucl. Med.* **1998**, *39*, 1521.
29. Lundkvist, C.; Halldin, C.; Ginovart, N.; Swahn, C. G.; Farde, L. *Nucl. Med. Biol.* **1997**, *24*, 621.
30. Goodman, M. M.; Keil, R.; Shoup, T. M.; Eshima, D.; Eshima, L.; Kilts, C. D.; Votaw, J.; Camp, V. M.; Votaw, D.; Smith, E.; Kung, M. P.; Malveaux, E.; Watts, R.; Huerkamp, M.; Wu, D.; Garcia, E.; Hoffman, J. M. *J. Nucl. Med.* **1997**, *38*, 119.
31. Petric, A.; Barrio, J. R.; Namavari, M.; Huang, S. C.; Satyamurthy, N. *Nucl. Med. Biol.* **1999**, *26*, 529–535.
32. Mach, R. H.; Nader, M. A.; Ehrenkaufer, R. L. *Synapse* **2000**, *37*, 109.
33. Wilson, A. A.; DaSilva, J. N.; Houle, S. *Nucl. Med. Biol.* **1996**, *23*, 141.
34. Xing, D.; Chen, P.; Keil, R.; Kilts, C. D.; Shi, B.; Camp, V. M.; Malveaux, G.; Ely, T.; Owens, M. J.; Votaw, J.; Davis, M.; Hoffman, J. M.; BaKay, R. A.; Subramanian, T.; Watts, R. L.; Goodman, M. M. *J. Med. Chem.* **2000**, *43*, 639.
35. Goodman, M. M.; Kilts, C. D.; Keil, R.; Dhi, B.; Martarello, L.; Xing, D.; Votaw, J.; Ely, T. D.; Lambert, P.; Owens, M. J.; Camp, V. M.; Malveaux, E.; Hoffman, J. M. *Nucl. Med. Biol.* **2000**, *27*, 1.
36. Davis, M. R.; Votaw, J. R.; Bremner, J. D.; Goodman, M. M. *J. Nucl. Med.* **2003**, *44*, 855.
37. Chaly, T.; Baldwin, R. M.; Neumeyer, J. L. *Nucl. Med. Biol.* **2004**, *31*, 125.
38. Gu, X. H.; Zong, R. S.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3049.
39. Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.
40. Neumeyer, J. L.; Wang, S.; Gao, Y.; Millius, R. A.; Kula, N. S.; Campbell, A.; Baldessarini, R. J.; Zea-Ponce, Y.; Baldwin, R.; Innis, R. B. *J. Med. Chem.* **1994**, *37*, 1558.
41. Neumeyer, J. L.; Tamagnan, G.; Wang, S.; Gao, Y.; Milius, R. A.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1996**, *39*, 543.
42. Kula, N. S.; Baldessarini, R. J. *Neuropharmacology* **1995**, *30*, 89.
43. Kula, N. S.; Baldessarini, R. J.; Fisser, R.; Wang, S.; Trometer, J.; Neumeyer, J. L. *Eur. J. Pharmacol.* **1999**, *385*, 291.
44. Baldwin, R. M.; Cosgrove, K.; Staley, J. K.; Vogel, R. S.; Amici, L.; Brenner, E.; Tian, H.; Peng, X.; Zhang, A.; Neumeyer, J. L.; Tamagnan, G. D. *Abstracts 5th Int. Symp. on Radiohalogens*, Vancouver B.C. 2004, 09.
45. Ritz, M. C.; Lamb, R. J.; Goldbery, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.