Bioorganic & Medicinal Chemistry Letters 23 (2013) 4404–4407

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

3-Aryl-3-arylmethoxyazetidines. A new class of high affinity ligands for monoamine transporters

Amber Thaxton [a], Sari Izenwasser [b], Dean Wade [b], Edwin D. Stevens [a], David L. Mobley [c], Vivian Jaber [a], Stacey A. Lomenzo [a], Mark L. Trudell [a,*]

[a] Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA
[b] Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[c] Department of Pharmaceutical Sciences, University of California-Irvine, Irvine, CA 92697, USA

ARTICLE INFO

Article history:
Received 3 April 2013
Revised 15 May 2013
Accepted 20 May 2013
Available online 29 May 2013

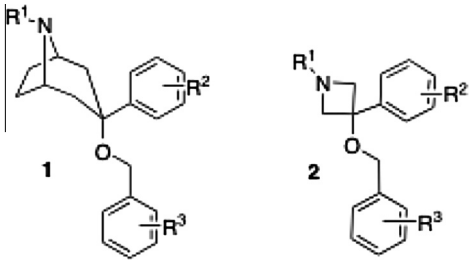
Keywords:
Azetidines
Serotonin transporters
Dopamine transporters

ABSTRACT

A series of 3-aryl-3-arylmethoxy-azetidines were synthesized and evaluated for binding affinities at dopamine and serotonin transporters. The 3-aryl-3-arylmethoxyazetidines were generally SERT selective with the dichloro substituted congener **7c** (K_i = 1.0 nM) and the tetrachloro substituted derivative **7i** (K_i = 1.3 nM) possessing low nanomolar affinity for the SERT. The 3-(3,4-dichlorophenyl-3-phenylmethoxyazetidine (**7g**) exhibited moderate affinity at both DAT and SERT transporters and suggests that substitution of the aryl rings can be used to tune the mononamine transporter affinity.

To date there are no pharmacological therapies for psychostimulant-dependence or the adverse side effects associated with craving and withdrawal. A variety of medications have been investigated as potential treatment strategies, however, none have been identified as having significant promise.[1] The failure of these drugs to be effective may be due to the limited scope of action, targeting single monoaminergic systems. To date there is mounting evidence that in addition to dopaminergic systems, brain serotonergic systems also modulate responses in psychostimulant-induced behaviors.[2–4] A single dopaminergic or serotonergic agent may not adequately attenuate the behavioral effects associated with psychostimulant abuse. It has been suggested by Rothman and co-workers that the development of an appropriately calibrated dual acting DAT/SERT agent may be more effective as a medication than an agent selective for a single transporter.[5] This model of psychostimulant addiction suggests that drug-induced dopamine and serotonin dysfunction contribute to the withdrawal symptoms, drug craving, and relapse. The model further postulates that decreased levels of synaptic dopamine during stimulant withdrawal are the source of anhedonia and psychomotor retardation. Moreover, decreased levels of synaptic serotonin results in depression, obsession, and lack of impulse control. Based upon this rationale, it should be possible to treat stimulant addicts that exhibit depleted synaptic levels of dopamine and serotonin with medications capable of restoring dopaminergic and serotonergic tone to disrupted neuronal systems. In this vein, both releaser-type drugs or uptake inhibitors could be developed.[5,6] To date, dopamine/norepinephrine uptake inhibitors (e.g., buproprion, methylphenidate), SSRIs (e.g., fluoxetine, paraoxetine) and SNRIs (e.g., duloxetine) and NRIs (e.g., reboxetine) have been widely prescribed for depression, ADHD and obesity and have good safety records.[7–11] This would suggest that a dual uptake inhibitor could be a promising pharmacological target for the treatment of psychostimulant addiction.

Our efforts to develop novel molecular scaffolds targeting monoamine transporter systems have led to the discovery of the 3α-arylmethoxy-3β-aryltropanes (**1**) as a unique class of monoamine transporter ligands that possess tunable affinity for dopamine and serotonin transporters.[12] This has prompted a broader examination of the structure-activity relationships of this molecular scaffold in



* Corresponding author. Tel.: +1 504 280 7337; fax: +1 504 280 6860.
E-mail address: mtrudell@uno.edu (M.L. Trudell).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.05.071

search of compounds with dual affinity for dopamine and serotonin transporters. It was of interest to explore condensed ring systems that would accommodate the pharmacophore requirements while reducing the overall molecular weight and lipophilicity inherent to the tropane derivatives. To this end, we identified the 3-arylmethoxy-3-arylazetidines (**2**) as viable targets for synthesis and biological evaluation at monoamine transporters.

The azetidine ring system has recently become an attractive molecular scaffold for the development of CNS active compounds.[13] Preliminary computational studies revealed that the replacement of the tropane ring system with an azetidine scaffold would lead to significant decrease in molecular weight and lipophilicity (*c*Log*P* values, Table 1).[14] In addition, superposition of the of predicted favorable solvated conformers of **1** and **2** (Fig. 1)[15] suggested that the azetidine scaffold would lead to a favorable alignment of the major structural elements of the two compounds.

As illustrated in Scheme 1, the syntheses of a series of chlorinated target compounds were achieved from commercially available *N*-Boc-3-azetidinone (**3**). The chlorinated derivatives were selected as initial targets since the corresponding tropane analogues (**1a**–**c**, Table 1) had demonstrated a broad range of DAT/SERT selectivity. Introduction of the substituted 3-aryl group was achieved by addition of a preformed aryl lithium reagent to the ketone moiety of **3**.[16] To minimize degradation the azetidine ring the work-up was performed under weakly acidic conditions [10% NH_4Cl (aq.)] at cold temperatures (5–10 °C). This afforded the alcohols **4** in high yields (86–94%).

To complete the synthesis of the initial series of target compounds, the alcohols **4** were alkylated with a variety of substituted benzyl bromides using phase-transfer conditions to furnish the *N*-Boc-3-arylmethoxy-3-aryl-azetidines (**5**). Typically the azetidines **5** were not isolated and purified but rather converted into the 3-arylmethoxy-3-arylazetidine hydrochloride salts **6** or the *N*-methyl-3-arylmethoxy-3-arylazetidine salts **7**. Treatment of **5** with 2 M HCl in EtOAc at room temperature afforded the corresponding hydrochloride salts **6** in 21–64% overall yield. Alternatively, the *N*-methyl derivatives **7** were prepared in 18–55% overall yield by heating **5** with 1 M lithium aluminum hydride in THF at 65 °C. After work-up with Glauber's salt the *N*-methyl derivatives were treated with 2 M HCl in EtOAc at room temperature to give the hydrochloride salts. In general, we found that direct conversion of the azetidine bases to the hydrochloride salts gave stable solid compounds. In the few exceptions that solid hydrochloride salts were not formed, the acidic oils were treated with sodium carbonate solution and the resulting azetidine free base was converted into the oxalate salt. Many of the salts gave crystalline compounds which allowed the structure to be confirmed unequivocally by X-ray crystallography (Fig. 2, **6a**).[17]

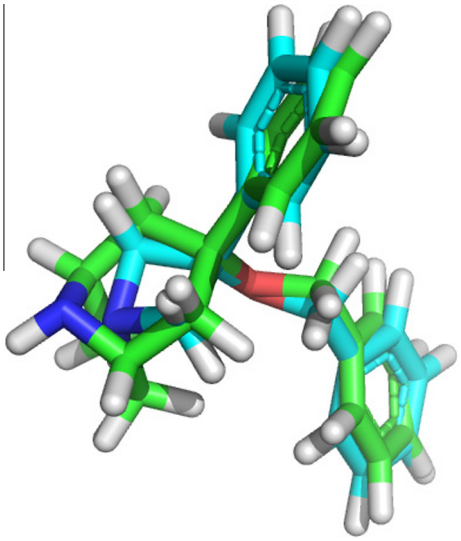


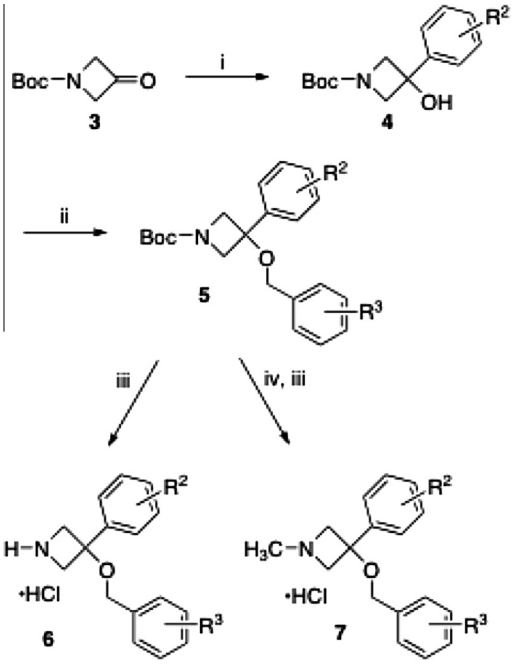
Figure 1. Superimposed predicted favorable solvated conformers of **1** (green) and **2** (cyan).

Binding affinities for the dopamine and serotonin transporters were determined by the ability of the drug to displace the radiolabeled ligands [^{3}H]WIN 35,428 and [^{3}H]citalopram, respectively, from the monoamine transporters in rat brain tissue using previously reported assays.[18] The monoamine transporter binding

Table 1
Monoamine transporter affinity and selectivity

Cmpd[a]	Code	R^1	R^2	R^3	*c*Log*P*[b]	DAT[c] (K_i, nM)	SERT[c] (K_i, nM)	DAT/SERT
1a[d]	HK2–151	H	H	H	3.67	117 ± 19	247 ± 27	0.47
1b[d]	HK3–77	H	H	4-Cl	4.27	22 ± 8.0	6.1 ± 0.50	3.6
1c[d]	HK3–45	H	H	3,4-Cl_2	4.87	16 ± 1.0	0.061 ± 0.024	258
6a	ANT-I-35	H	H	H	3.02	4860 ± 450	1230 ± 70	4.0
6b[e]	ANT-I-74	H	H	4-Cl	3.63	3610 ± 25	2590 ± 20	1.4
6c[e]	ANT-I-57	H	H	34-Cl_2	4.23	2820 ± 110	7.3 ± 0.70	390
6d	ANT-I-129	H	4-Cl	H	3.63	3180 ± 360	825 ± 8.0	3.9
6e	ANT-I-87	H	4-Cl	4-Cl	4.23	3830 ± 42	3.5 ± 0.20	1100
6f	ANT-I-92	H	4-Cl	3,4-Cl_2	4.83	3770 ± 320	8.1 ± 3.2	470
6g	ANT-I-110	H	3,4-Cl_2	H	4.23	1300 ± 86	208 ± 8.0	6.3
6h	ANT-I-126	H	3,4-Cl_2	4-Cl	4.83	3020 ± 340	2.9 ± 0.30	1000
6i	ANT-I-108	H	3,4-Cl_2	3,4-Cl_2	5.44	3670 ± 30	4.2 ± 0.30	870
7a	ANT-I-47	CH_3	H	H	3.40	1730 ± 320	73 ± 9.4	24
7b	ANT-I-73	CH_3	H	4-Cl	4.01	3910 ± 280	4.0 ± 0.3	980
7c	ANT-I-72	CH_3	H	3,4-Cl_2	4.61	1210 ± 69	1.0 ± 0.20	1210
7d	ANT-I-85	CH_3	4-Cl	H	4.01	1410 ± 107	39 ± 7.0	36
7e	ANT-I-84	CH_3	4-Cl	4-Cl	4.61	2030 ± 600	7.8 ± 3.3	490
7f	ANT-I-125	CH_3	4-Cl	3,4-Cl_2	5.22	976 ± 61	3.0 ± 1.1	330
7g	ANT-I-133	CH_3	3,4-Cl_2	H	4.61	620 ± 140	23 ± 1.6	27
7h	ANT-I-124	CH_3	3,4-Cl_2	4-Cl	5.22	2290 ± 513	4.8 ± 2.2	630
7i	ANT-I-106	CH_3	3,4-Cl_2	3,4-Cl_2	5.82	436 ± 66	1.3 ± 0.0	340

[a] Compounds were tested as the hydrochloride salts unless otherwise noted.
[b] See Ref. 13.
[c] All values are the mean ± SEM of three experiments preformed in triplicate.
[d] Data taken from Ref. 12.
[e] Compound was tested as the oxalate salt.



Scheme 1. Reagents and conditions: (i) R^2-C_6H_4Br, *n*-BuLi, THF, −78 °C. (ii) R^3-$C_6H_4CH_2Br$, Bu_4NBr, 4 N NaOH/CH_2Cl_2, reflux. (iii) 2 M HCl/EtOAc, rt. (iv) $LiAlH_4$, THF, 65 °C.

affinities of the 3-arylmethoxy-3-aryl-azetidines (**6**) were generally selective for the SERT over the DAT exhibiting nanomolar affinity for the SERT and micromolar affinity for the DAT. The dichloro substituted congeners **6e** (K_i = 3.5 nM) and **6h** (K_i = 2.9 nM) were the most potent of the azetidines at SERT. The binding affinities of *N*-methyl 3-arylmethoxy-3-aryl-azetidines **7** also exhibited high affinity for the SERT. The *N*-methyl analogues typically exhibited higher affinity at the SERT than the corresponding unsubstituted analogues **6**. The dichloro substituted congener **7c** (K_i = 1.0 nM) and the tetrachloro substituted derivative **7i** (K_i = 1.3 nM) were the most potent analogues of the entire series. However, the NH analogues **6e** and **6h** exhibited similar SERT affinity to the corresponding *N*-methyl analogues **7e** and **7h**, while the DAT affinities of **6e** and **6h** were not similarly affected. Overall, *N*-methyl, 3,4-dichloro analogue **7c** exhibited the greatest selectivity for SERT (DAT/SERT = 1210) of all the azetidine derivatives.

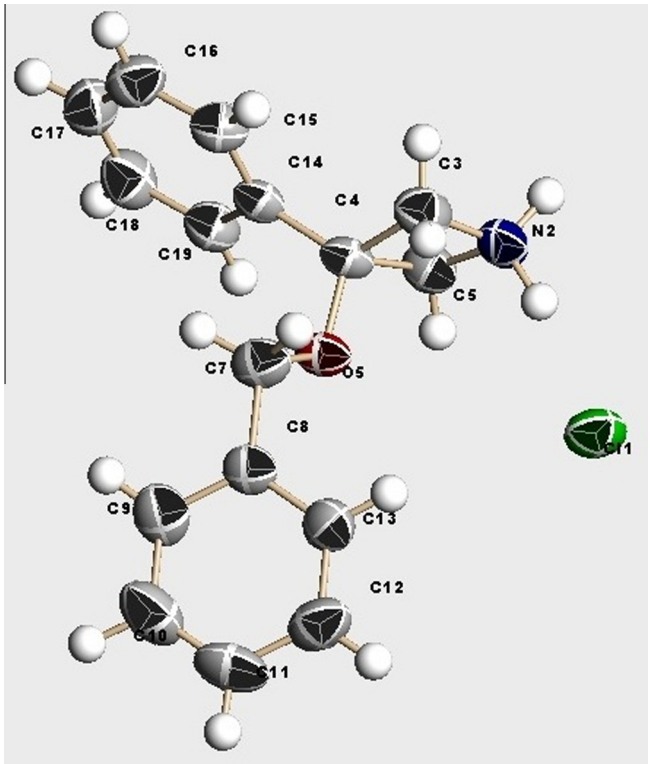


Figure 2. X-ray crystal structure of **6a**.

Inspection of the SAR of the azetidines **6** and **7**, revealed that for compounds with the 3,4-dichlorophenyl group attached as the 3-aryl substituent (e.g., **6g** and **7g**) the relative DAT affinity was improved and the DAT/SERT selectivity was decreased. A similar effect had been observed for a series of meperidine derivatives.[19] However, if the 3-arylmethoxy moiety possessed a chloro substituent (e.g., **6h** and **7h**) then the DAT affinity decreased and the SERT selectivity dominated. Alternatively, if the 3-arylmethoxy moiety possessed the 3,4-dichloro substituent pattern (e.g., **6c** and **7c**) then the ligand exhibited high SERT affinity. However, when both aryl groups possessed the 3,4-dichlorophenyl moiety there was little improvement in affinity or selectivity. The effect of the 3-(3,4-chlorophenyl-methoxy) moiety on SERT affinity and selectivity is consistent with the SAR observed for the 3α-arylmethoxy-3β-aryltropanes.[12] Among the tropane congeners, the 3β-(3,4-chlorophenylmethoxy) derivatives (e.g., **1c**) typically exhibited some of the highest SERT affinity and selectivity for the class of ligands.

Of the azetidine derivatives, **7g** exhibited a binding profile which most closely approached that of a dual DAT/SERT uptake inhibitor (DAT/SERT = 27) while maintaining nanomolar affinity at both transporters. Although SERT selective, the moderate affinity for the DAT observed for **7g** (K_i = 620 nM) was encouraging. While the SAR of the azetidines did not mirror the SAR of the tropanes, it was clear that substitution of the aryl rings can be used to tune the monoamine transporter affinity and suggests that the proper substitution of the aryl rings might lead to a potent DAT/SERT dual inhibitor.

In conclusion, we have synthesized a novel class of azetidine-based monoamine transporter ligands. In general, the 3-aryl-3-arylmethoxyazetidines **6** and **7** exhibited high affinity for the SERT and were generally selective for the SERT over the DAT. However, it is clear that DAT affinity can be improved with the proper substitution of the 3-aryl ring. Based upon these preliminary studies, the azetidine scaffold seems to be suitable replacement for the tropane scaffold and the 3-aryl-3-arylmethoxy-azetidines are well suited for the development of new compounds that display a broad spectrum of multi-targeted monoamine transporter affinity and selectivity.

Acknowledgments

This research was supported by the National Institute on Drug Abuse (DA11528) and the Louisiana Optical Network Initiative Institute (DLM), supported by the Louisiana Board of Regents Post-Katrina Support Fund Initiative Grant LEQSF(2007-12)-ENH-PKSFI-PRS-01.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.05.071. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Karila, L.; Weinstein, A.; Aubin, H. J.; Benyamina, A.; Reynaud, M.; Batki, S. L. *Br. J. Clin. Pharmacol.* **2010**, *69*, 578.
2. Rothman, R. B.; Partilla, J. S.; Baumann, M. H.; Dersch, C. M.; Carroll, F. I.; Rice, K. C. *Synapse* **2000**, *35*, 222.
3. Vocci, F. J.; Appel, N. M. *Addiction* **2007**, *102*(Suppl. 1), 96.
4. Baumann, M. H.; Clark, R. D.; Woolverton, W. L.; Wee, S.; Blough, B. E.; Rothman, R. B. *J. Pharmacol. Exp. Ther.* **2011**, *337*, 218.
5. Rothman, R. B.; Blough, B. E.; Baumann, M. H. *Exp. Clin. Psychopharmacol.* **2008**, *16*, 458.
6. Blough, B. E. In *Dopamine Transporters: Chemistry, Biology and Pharmacology*; Trudell, M. L., Izenwasser, S., Eds.; John Wiley & Sons: Hoboken, NJ, 2008; p 305.
7. Evrard, D. A.; Harrison, B. L. *Annu. Rep. Med. Chem.* **1999**, *34*, 1.
8. Spinks, D.; Spinks, G. *Curr. Med. Chem.* **2002**, *9*, 799.
9. Boyer, W.; Feighner, J. P. In *SSRIs in Depression and Anxiety*; Montgomery, S. A., den Boer, J. A., Eds.; John Wiley & Sons: Chichester, 2001; p 107.
10. Montgomery, S. A. *J. Psychopharmacol.* **1997**, *11*, 9.
11. Kasper, S.; el Giamal, N.; Hilger, E. *Expert Opin. Pharmacother.* **2000**, *1*, 771.
12. Kaur, H.; Izenwasser, S.; Verma, A.; Wade, D.; Housman, A.; Stevens, E. D.; Mobley, D. L.; Trudell, M. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6865.
13. Lowe, J. T.; Lee, M. D., IV; Akella, L. B.; Davoine, E.; Donckele, E. J.; Durak, L.; Duvall, J. R.; Gerard, B.; Holson, E. B.; Joliton, A.; Kesavan, S.; Lemercier, B. C.; Liu, H.; Marié, J.-C.; Mulrooney, C. A.; Muncipinto, G.; Welzel-O'Shea, M.; Panko, L. M.; Rowley, A.; Suh, B.-C.; Thomas, M.; Wagner, F. F.; Wei, J.; Foley, M. A.; Marcaurelle, L. A. *J. Org. Chem.* **2012**, *77*, 7187.
14. *c*Log*P* values were calculated for the free base using software from Collaborative Drug Discovery, Inc. at www.collaborativedrug.com.
15. Structures in Figure 1 were generated using OpenEye Scientific Software's Omega for conformers and OEChem for shape overlays, and the images were generated with PyMol (Delano Scientific LLC).
16. Sonesson, C.; Swanson, L.; Pettersson, F. WO 2,010,058,017A1, 2010; *Chem. Abstr*. **2010**, 152, 591844. Sonesson, C.; Swanson, L.; Pettersson, F. WO 2,010,058,020 A1, 2010; *Chem. Abstr*. **2010**, 152, 591843.
17. CCDC 930712 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
18. Cararas, S. A.; Izenwasser, S.; Wade, D.; Housman, A.; Verma, A.; Lomenzo, S. A.; Trudell, M. L. *Bioorg. Med. Chem.* **2011**, *19*, 7551.
19. Lomenzo, S. A.; Rhoden, J. B.; Izenwasser, S.; Wade, D.; Kopajtic, T.; Katz, J. L.; Trudell, M. L. *J. Med. Chem.* **2005**, *48*, 1336.