Published in final edited form as:

Bioorg Med Chem Lett. 2009 December 15; 19(24): 6865–6868. doi:10.1016/j.bmcl.2009.10.087.

Synthesis and Monoamine Transporter Affinity of 3 α -Arylmethoxy-3 β -aryl nortropans

Harneet Kaur^a, Sari Izenwasser^b, Abha Verma^a, Dean Wade^b, Amy Housman^b, Edwin D. Stevens^a, David L. Mobley^a, and Mark L. Trudell^{a,*}

^aDepartment of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

^bDepartment of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami FL 33136, USA

Abstract

A series of 3-aryl nortrop-2-enes and 3 α -arylmethoxy-3 β -aryl nortropans were synthesized and evaluated for binding affinity at monoamine transporters. The 3-(3,4-dichlorophenyl) nortrop-2-ene (**6e**) exhibited high affinity for the SERT (K_i = 0.3 nM). The 3 α -arylmethoxy-3 β -aryl nortropans were generally SERT selective with the 3 α -(3,4-dichlorophenylmethoxy)-3 β -phenyl nortrop-2-ene (**7c**) possessing subnanomolar potency (K_i = 0.061 nM). However, 3 α -(3,4-dichlorophenylmethoxy)-3 β -phenyl nortrop-2-ene (**7b**) exhibited high affinity at all three transporters [(DAT K_i = 22 nM), (SERT K_i = 6 nM) and (NET K_i = 101 nM)].

Monoamine transporters have been therapeutic targets for a variety of neurological diseases and disorders. Drug development strategies have focused upon central nervous system (CNS) monoamine transporter selective agents. This approach has been highly successful for the development of medications for the treatment of depression.^{1,2} Selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine and paroxetine)³ as well as selective norepinephrine reuptake inhibitors (SNRIs, e.g. reboxetine)^{4,5} have been widely prescribed for patients suffering from this common psychiatric disorder. In addition, dopamine selective uptake inhibitors have been targets for the development of therapeutics for cocaine addiction.^{6–8}

Over the past decade, the rationale for the development of new pharmacotherapies has expanded to target compounds that exhibit efficacy at multiple monoamine transporter systems. The dual serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g. venlafaxine and duloxetine) have been widely accepted as more efficacious than SSRIs for the treatment of depression with reduced side effects.^{9,10} More recently, pharmacological evidence suggests that triple monoamine uptake inhibitors (TUIs), targeting dopamine transporters (DAT) as well as serotonin transporters (SERT) and norepinephrine transporters (NET) may be even more efficacious and exhibit improved safety profiles as antidepressants.¹¹ The prototypical TUI, DOV 216,303 was found to be both safe and effective in Phase II clinical studies on depression.^{12,13} In addition to therapeutics for depression, there is increasing evidence that the reinforcing

© 2009 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: +1 504-280-7337. mtrudell@uno.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:xxxx

effects of cocaine may in part be mediated by the SERT.^{14–16} In lieu of these findings, dual DAT/SERT uptake inhibitors have become viable pharmacological targets for cocaine addiction.^{17,18}

Our efforts to develop novel molecular scaffolds targeting monoamine transporter systems have led to the development of several classes of selective DAT ligands and selective SERT ligands. There have been numerous studies that have shown that 3-aryltropane derivatives exhibit high affinity and selectivity for the DAT.^{7,8} More recently, we have reported on a series of piperidine derivatives that exhibit potent and selective affinity for the SERT.^{19,20} Given the somewhat similar structural characteristics of these two classes of molecules it was of interest to explore the possibility of merging the two pharmacophores to develop a class of monoamine transporter ligands that would have unique profile of multiple transporter affinity. To this end, the 3 α -arylmethoxy-3 β -aryltropane pharmacophore (**1**) was envisaged. The pharmacophore **1** was designed not only to incorporate the main skeletal features of the DAT selective tropanes and the SERT selective piperidines, but the arylmethoxy moiety common to many of the prototypical SSRIs and SNRIs also was envisaged to be an important structural feature for molecular recognition at monoamine transporters. Herein we describe the synthesis and monoamine transporter affinities of a series 3 α -arylmethoxy-3 β -aryl-tropane derivatives.

As illustrated in Scheme 1, the syntheses of the target compounds were envisaged to proceed from commercially available tropinone (**2**). Conversion of **2** into the carbamate **3** was achieved in a traditional fashion using ethyl chloroformate.^{21,22} The preparation of **3** was necessary to reduce the basicity and nucleophilicity of the nitrogen atom. This served to facilitate subsequent chromatography as well as provide a chemical handle for manipulation of potential nitrogen substituents. Introduction of the substituted 3-aryl group was achieved by addition of a preformed aryl lithium reagent to the ketone moiety of **3**. Initially, a mixture of the desired alcohol **4** along with the alkene **5** was obtained in low yields. The formation of the alkene **5** was the result of the dehydration of **4** that occurred during the acidic work-up. To minimize this dehydration side-reaction, the work-up was performed under weakly acidic conditions [10 % NH₄Cl (aq.)] at cold temperatures (5–10 °C). This afforded the alcohols **4** in good yields (40–65%). Although we were confident that the addition the aryl ring occurred from the less hindered β -face of the tropinone skeleton,²² the relative stereochemistry was confirmed unequivocally by X-ray crystallography.²³ As illustrated in Figure 3 for **4a**, the 3-phenyl moiety was shown to occupy the 3 β -pseudo equatorial position and the hydroxy group was in the 3 α -pseudo axial position.

The ease in which the alcohols **4** were dehydrated prompted us to divert our attention toward the synthesis of a series of 3-arylnortrop-2-ene derivatives **6**. It was envisaged that these rigid alkenes might have a similar binding motif at monoamine transporters to that of the DOV 216,303. The alkenes **5** could be prepared directly from the crude reaction mixtures containing **4**, by stirring the concentrated residues in dichloromethane containing one equivalent of trifluoroacetic acid. This furnished the alkenes **5** in good overall yields ranging from 35–60%. Since many of the potent monoamine uptake inhibitors (SSRIs, SNRIs and TUIs) possess a NH moiety, it was determined that the tropane nitrogen atom would be converted into a secondary amine as well. Hydrazine mediated removal of the carbamate moiety gave the ($\pm$)-3-arylnortrop-2-enes **6** in 85–95% yield.

To complete the synthesis of an initial series of target compounds for biological evaluation, the alcohols **4** were alkylated with a variety of substituted benzyl bromides to afford the corresponding 3 α -arylmethoxy derivatives. Subsequent removal of the carbamate protecting group gave the target secondary amines **7**.

Binding affinities for the dopamine, serotonin and norepinephrine transporters were determined by the ability of the drug to displace the radiolabeled ligands [³H]WIN 35,428, [³H]citalopram, and [³H]nisoxetine, respectively, from the monoamine transporters in rat brain tissue using previously reported assays.^{19,20,24} The binding affinities of all compounds listed in Table 1 were initially determined for the DAT and SERT. The compounds that exhibited either DAT or SERT binding affinities with K_i values < 100 nM were then evaluated at norepinephrine transporters to determine a monoamine transporter selectivity profile. The monoamine transporter binding affinities of the 3-arylnortrop-2-enes **6** were consistent with a previous report that described the SERT selectivity of a series of 3-aryltrop-2-ene derivatives.²⁵ The nortropenes **6** exhibited selectivity for SERT over both DAT and NET. The 3,4-dichloro congener **6e** (SERT K_i = 0.3 nM) was the most potent of the nortropenes at SERT. However, **6e** was not the most SERT selective nortropene of the series (e.g. **6d**). In fact, **6e** exhibited high affinity at all three monoamine transporters with DAT and NET affinities nearly equipotent (NET/DAT = 1.3).

The 3 α -arylmethoxy-3 β -arylnortropanes **7** were found to exhibit some similar trends in transporter affinity to those of the nortropenes **6**. As expected the congeners **7** were generally SERT selective and exhibited high affinity for SERT. The most potent SERT ligand of the series was **7c** (SERT K_i = 0.061 nM), which also exhibited the highest affinity for the DAT (DAT K_i = 16 nM) of the series. However, despite the high DAT and SERT affinity of **7c**, the dichloro derivative **7f** was the most SERT selective ligand with DAT/SERT = 630 and NET/SERT = 23,700. It is noteworthy that the mono chloro derivative **7b** exhibited good affinity for all three monoamine transporters. Despite being somewhat SERT selective, **7b** exhibited transporter selectivity that is similar to other reported monoamine TUIs.^{11,12}

In comparing the two classes of compounds **6** and **7**, it is interesting to note that the structure-activity relationships of the aryl group of the rigid tropene **6** are more closely aligned with the 3 α -arylmethoxy group of **7** than the 3 β -aryl group. This is most evident when comparing the effects of the 3,4-dichlorophenyl moiety on SERT affinity of **6e** with that of **7c** and **7i**. When the 3,4-dichlorophenyl moiety occupies the 3 α -position (**7c**), the SERT affinity is high but when the 3,4-dichlorophenyl moiety occupies the 3 β -position (**7i**), SERT affinity is significantly reduced. This trend is also evident for the mono chloro derivatives **6c**, **7b** and **7e**. For predicted favorable solvated conformers of **6c**, **7c** and **7i** (Figure 4)²⁷ the alignment of the 3 α -arylmethoxy group of **7c** with the aryl group of **6c** is similar for the *boat* conformer, while there is no overlap between these two aryl moieties for the *chair* conformer. This suggests that it is the *boat* conformer of **7c** that exhibits high affinity for the SERT.

The binding affinities of **7** at the DAT were also significantly affected by the substituents on the aryl moieties. Within the series, the unsubstituted 3 β -phenyl derivatives **7a** – **7c**, exhibited good to high affinity for DAT. However, substitution of the 3 β -aryl moiety afforded compounds with diminished affinity at the DAT. Finally, only the monochloro congener **7b** exhibited good NET binding affinity suggesting that the target pharmacophore **1** may be predisposed toward the development of dual DAT/SERT selective ligands.

In conclusion, we have synthesized a novel class of monoamine transporter ligands. In general, the 3 α -arylmethoxy-3 β -arylnortropanes **7** exhibited potent affinity and high selectivity for the SERT. However, several derivatives were found to have good affinity for the DAT as well, and the chloro congener **7b** exhibited high affinity at all three transporters. Based upon this preliminary study, the 3 α -arylmethoxy-3 β -arylnortropane scaffold seems to be well suited for the development of new compounds that display a broad spectrum of monoamine transporter selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Dr. Amy Hauck Newman at the NIDA Intramural Research Program, Baltimore, Maryland for the assistance provided to Harneet Kaur in the aftermath of Hurricane Katrina. 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.

References and notes

1. Evrard DA, Harrison BL. *Ann. Rep. Med. Chem* 1999;34:1.
2. Spinks D, Spinks G. *Curr. Med. Chem* 2002;9:799. [PubMed: 11966445]
3. Boyer, W.; Feighner, JP. *SSRIs Depression and Anxiety*. Montgomery, SA.; den Boer, JA., editors. Chichester: John Wiley & Sons, Inc.; 2001. p. 107-118.
4. Montgomery SA. *J. Psychopharmacol* 1997;11:9.
5. Kasper S, el Giamal N, Hilger E. *Exp. Opin. Pharmacother* 2000;1:771.
6. Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. *Science* 1987;237:1219. [PubMed: 2820058]
7. Runyon SP, Carroll FI. *Curr. Top. Med. Chem* 2006;6:1825. [PubMed: 17017960]
8. Runyon, SP.; Carroll, FI. *Dopamine Transporters: Chemistry Biology and Pharmacology*. Trudell, ML.; Izenwasser, S., editors. Hoboken: John Wiley & Sons, Inc.; 2008. p. 125-170.
9. Nemeroff CB, Entsuah R, Benattiab I, Demitrack M, Sloan DM, Thase ME. *Biol. Psychiatry* 2008;83:424. [PubMed: 17888885]
10. Carter NJ, McCormack PL. *CNS Drugs* 2009;23:523. [PubMed: 19480470]
11. Marks DM, Pae CU, Patkar AA. *Curr. Neuropharmacol* 2009;6:338. [PubMed: 19587855]
12. Chen Z, Skolnick P. *Exp. Opin. Invest. Drugs* 2007;16:1365.
13. Skolnick P, Kreiter P, Tizzano J, Popik P, Czobor P, Lippa A. *CNS Drug Rev* 2006;12:123. [PubMed: 16958986]
14. Sora I, Hall FS, Andrews AM, Itokawa M, Li XF, Wei HB, Wichems C, Lesch KP, Murphy DL. *Proc. Nat. Acad. Sci. U.S.A* 2001;98:5300.
15. Walsh SL, Cunningham KA. *Psychopharmacology* 1997;130-141. [PubMed: 9201800]
16. Howell LL, Carroll FI, Votaw JR, Goodman MM, Kimmel HL. *J. Pharmacol. Exp. Ther* 2007;320:757. [PubMed: 17105829]
17. Greiner E, Boos TL, Prisinzano T, De Martino MG, Zeglis B, Dersch CM, Marcus J, Partilla JS, Rothman RB, Jacobson AE, Rice KC. *J. Med. Chem* 2006;49:1766. [PubMed: 16509591]
18. Jin C, Navarro HA, Carroll FI. *J. Med. Chem* 2008;51:8048. [PubMed: 19053748]
19. Lomenzo SA, Rhoden J, Izenwasser S, Wade D, Kopajtic T, Katz' JL, Trudell ML. *J. Med. Chem* 2005;48:1336. [PubMed: 15743177]
20. Rhoden J, Bouvet M, Izenwasser S, Wade D, Lomenzo SA, Trudell ML. *Bioorg. Med. Chem* 2005;13:5623. [PubMed: 15993612]
21. Bradley AL, Izenwasser S, Wade D, Klein-Stevens C, Zhu N, Trudell ML. *Bioorg. Med. Chem. Lett* 2002;12:2387. [PubMed: 12161139]
22. Paul NM, Taylor M, Kumar R, Deschamps JR, Luedtke RR, Newman AH. *J. Med. Chem* 2008;51:6095. [PubMed: 18774793]
23. CCDC 748234 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
24. Zhang S, Izenwasser S, Wade D, Xu L, Trudell ML. *Bioorg. Med. Chem* 2006;14:7943. [PubMed: 16905323]
25. Kronic A, Mariappan S, Reith MEA, Dunn WJ. *Bioorg. Med. Chem. Lett* 2005;15:5488. [PubMed: 16202585]

26. Kulkarni SS, Grundt P, Kopajtic T, Katz JL, Newman AH. J. Med. Chem 2004;47:3388. [PubMed: 15189035]
27. Structures in Figure 4 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).

Figure 1.
Monoamine transporter reuptake inhibitors.

Figure 2.
Proposed pharmacophore of novel monoamine uptake inhibitors.

Figure 3.
X-ray crystal structure of **4a**.

Figure 4.
Superimposed predicted favorable solvated conformers of **6e** (red), **7c** (blue) and **7i** (yellow).

Scheme 1.

Reagents and conditions: (i) ClCO₂Et, K₂CO₃, toluene, reflux. (ii) X-C₆H₄Br, *n*-BuLi, THF, -78 °C. (iii) TFA, CH₂Cl₂. (iv) KOH, NH₂NH₂•H₂O, HOCH₂CH₂OH, reflux. (v) NaH, DMF, Y-C₆H₄CH₂Br, r.t.

Table 1

Monoamine Transporter Affinity and Selectivity

Cmpd ^a	Code	X	Y	DAT (K _i , nM) ^b	SERT (K _i , nM) ^b	NET (K _i , nM) ^b	DAT/SERT	NET/DAT	NET/SERT
6a	HK3-203	H		1,222 ± 87	176 ± 26	1,289 ± 54	6.9	1.1	7.3
6b	HK3-245	F		1,056 ± 201	129 ± 22	1,989 ± 268	8.2	1.9	1.5
6c	HK3-241	Cl		231 ± 14	2.8 ± 1.0	120 ± 41	83	0.52	43
6d	HK3-267	CF ₃		1,494 ± 246	1.8 ± 0.3	777 ± 96	830	1.9	432
6e	HK3-263	3,4-Cl ₂		16 ± 1.7	0.30 ± 0.10	20 ± 4.6	53	1.3	67
7a	HK2-151	H	H	117 ± 19	247 ± 27	NT	0.47		
7b	HK3-77	H	Cl	22 ± 8	6.1 ± 0.5	101 ± 0	3.6	4.6	17
7c	HK3-45	H	3,4-Cl ₂	16 ± 1	0.061 ± 0.024	996 ± 53	258	62	16,300
7e	HK3-87	Cl	H	172 ± 70	65 ± 25	1,718 ± 18	2.7	10	26
7f	HK3-35	Cl	Cl	63 ± 7	0.10 ± 0.02	2,370 ± 367	630	38	23,700
7g	HK3-135	Cl	3,4-Cl ₂	390 ± 28	8.5 ± 1.8	2,093 ± 1210	46	5.4	246
7h	HK3-105	CF ₃	H	1,390 ± 141	534 ± 34	5435 ± 2570	2.6	3.9	10
7i	HK3-119	3,4-Cl ₂	H	716 ± 52	62 ± 15	1,232 ± 438	11	1.7	20
7j	HK3-49	3,4-Cl ₂	3,4-Cl ₂	2,930 ± 70	4.7 ± 0.3	2,552 ± 326	601	0.87	543
	Cocaine			237 ± 33	286 ± 38 ^c	3,192 ± 877	0.83	12	11

^a All compounds were tested as the oxalate salts. NT: Not tested.

^b All values are the mean ± SEM of three experiments performed in triplicate.

^c Value taken from ref. 26.