Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 3273–3276

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS, DOPAMINE AND SEROTONIN TRANSPORTER BINDING AFFINITIES OF NOVEL ANALOGUES OF MEPERIDINE

Stacey A. Lomenzo,[a] Sari Izenwasser,[b] Robert M. Gerdes,[b] Jonathan L. Katz,[c] Theresa Kopajtic,[c] and Mark L. Trudell*[a]

[a]*Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA*
[b]*Department of Neurology, University of Miami School of Medicine, Miami, FL 33136, USA*
[c]*National Institute on Drug Abuse, Division of Intramural Research, P. O. Box 5180, Baltimore, MD 21224, USA*

Received 14 September 1999; accepted 5 October 1999

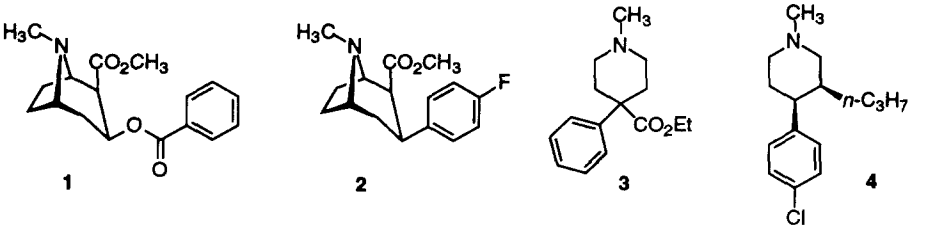
Abstract: A series of meperidine analogues was synthesized and the binding affinities for the dopamine and serotonin transporters were determined. The substituents on the phenyl ring greatly influenced the potency and selectivity of these compounds for the transporter binding sites. In general, meperidine (**3**) and its analogues were more selective for serotonin transporter binding sites and the esters **9** were more potent than the corresponding nitriles **8**. The 3,4-dichloro derivative **9e** was the most potent ligand of the series for dopamine transporter binding sites while the 2-naphthyl derivative **9g** exhibited the most potent binding affinity and was highly selective for serotonin transporter binding sites.

It has been reported that the binding of cocaine (**1**) and WIN 35,428 (**2**) to the dopamine transporter (DAT) is better described by a two-site model that consists of high- and low-affinity components.[1–3] Currently there are no known dopamine uptake inhibitors that discriminate between high- and low-affinity binding to the DAT. In a recent report, meperidine (**3**, an atypical opioid agonist with some stimulant effects) was described as exhibiting monophasic binding (K_i > 1 μM) at dopamine transporters labeled with [^{3}H]WIN 35,428 ([^{3}H]-**2**).[4] Furthermore, the meperidine mediated [^{3}H]dopamine uptake inhibition resembled the high affinity component of the cocaine dopamine uptake inhibition curve. The maximal inhibition of dopamine uptake by meperidine (20%) was also consistent with the high affinity component of cocaine dopamine uptake inhibition (~18%).[4] In addition, when the opioid effects of **3** were antagonized in vivo by the μ-opioid receptor antagonist, naltrexone, meperidine (**3**) completely substituted for cocaine in squirrel monkeys trained to discriminate cocaine from saline.[4] This effect was not observed for the μ-opioid receptor ligand, morphine.

From the in vitro data described above, it may be suggested that meperidine (**3**) mediates its activity via the high-affinity cocaine binding site on the DAT. The in vivo studies further suggest that the discriminative stimulus effects of meperidine (**3**) and therefore cocaine (**1**) are mediated by occupation of the high affinity cocaine binding component on the DAT.[3–5] It has been noted that the "high" and "low" affinity components of dopamine uptake are so named based on the affinity of cocaine (**1**). Therefore, it may be possible for different compounds to exhibit high affinity for the "low" affinity binding site or as in the case with meperidine (**3**) may be selective for the "high" affinity component, albeit with low binding affinity.[4,5]

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00606-X

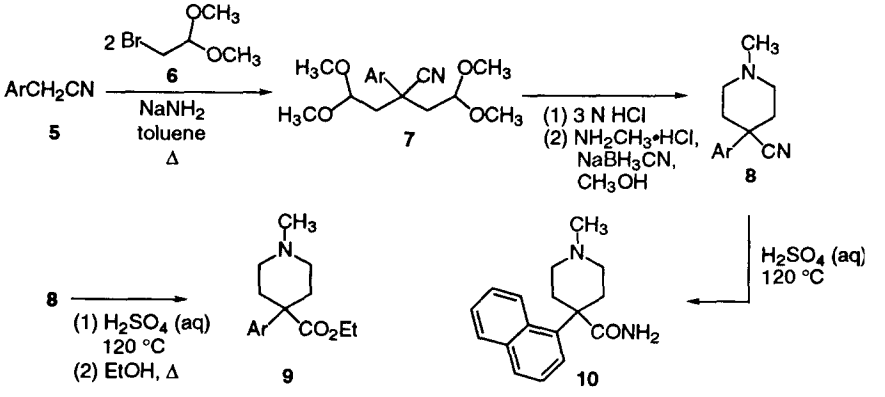
It was recently reported that the piperidine derivative **4** was a potent dopamine uptake inhibitor but did not exhibit heterogeneous binding at DAT.[6] Based upon the similarity in structure between meperidine (**3**), cocaine (**1**), WIN 35,428 (**2**), and **4** it was of interest to develop high affinity analogues of **3** for pharmacological comparison. It was envisaged that high affinity analogues of **3** could be prepared to further elucidate the heterogeneous binding sites on the DAT and provide a greater understanding of the stimulant and behavioral effects mediated by cocaine binding to the DAT. Herein we wish to describe recent progress directed toward the development of potent meperidine-based DAT ligands.[7]



Chemical Synthesis

There are several methods available for the synthesis of meperidine (**3**).[8] However, it was of interest to develop a general approach that was amenable to the future incorporation of a variety of substituents and functional groups as well as to avoid highly toxic starting materials and intermediates. To this end, a synthetic sequence was designed which could be easily adapted to explore a broad SAR of **3**. As illustrated in Scheme 1, the dialkylation of the 2-aryl acetonitriles **5** with bromoacetaldehyde dimethyl acetal (**6**) afforded the diacetals **7** in good yields (75–90%). Hydrolysis of the acetals and concomitant reductive amination gave the *N*-methyl-4-aryl-4-cyanopiperidines **8** in moderate overall yields (30–50%). The nitriles were then converted into the corresponding ethyl esters via a two-step sequence. First, the nitriles were hydrolyzed into the corresponding carboxylic acids; then without isolation of the carboxylic acid, excess ethanol was added to the reaction mixture. Removal of water by azeotropic distillation then furnished the ethyl esters **9** in good overall yields (50–80%). Surprisingly, the nitrile **8f** was resistant to conversion into the carboxylic acid and only the corresponding amide **10** was obtained.

Scheme 1



Pharmacology

The in vitro binding affinities of the meperidine analogues **8** and **9** are summarized in Table 1. Binding affinities for the DAT were measured by competition against bound [^{3}H]WIN 35,428 ([^{3}H]-**2**).[9] In addition, the binding affinities of the meperidine analogues for serotonin transporter (SERT) sites were determined by competition against [^{3}H]paroxetine.[10]

Table 1. In Vitro Binding Affinities of Meperidine Analogues **8** and **9** for Dopamine Transporters (DAT) and Serotonin Transporters (SERT).

Compound[a]	Ar	[^{3}H]WIN 35,428 Binding (DAT), K_i (μM)[b]	[^{3}H]Paroxetine Binding (SERT), K_i (μM)[b]	DAT/SERT
meperidine	C_6H_5	17.8 ± 2.67	0.412 ± 0.043	43.3
8a	4-FC_6H_4	45% @ 100 μM[c]	10.1 ± 0.43	
8b	4-ClC_6H_4	22.0 ± 10.1[d]	5.11 ± 0.53	4.31
8c	4-IC_6H_4	8.34 ± 0.67	0.43 ± 0.034	19.4
8d	4-CH_3 C_6H_4	41.8 ± 6.10[e]	13.7 ± 0.36	3.06
8e	3,4-Cl_2 C_6H_3	2.67 ± 0.24	0.805 ± 0.12	3.32
8f	1-naphthyl	16.0 ± 1.60	1.02 ± 0.17	16.7
8g	2-naphthyl	2.36 ± 0.66	0.125 ± 0.022	18.9
9a	4-FC_6H_4	10.7 ± 2.25	0.308 ± 0.026	34.7
9b	4-ClC_6H_4	4.10 ± 1.27[d]	0.277 ± 0.040	14.8
9c	4-IC_6H_4	3.25 ± 0.195	0.021 ± 0.0024	155
9d	4-$CH_3C_6H_4$	12.4 ± 5.21[e]	1.61 ± 0.106	7.69
9e	3,4-$Cl_2C_6H_4$	0.125± 0.015	0.019 ± 0.0026	6.68
9g	2-naphthyl	1.14 ± 0.38	0.0072± 0.00053	158

[a]All compounds were tested as the hydrochloride salts. [b]All values are the mean ± SEM of three experiments performed in triplicate using protocols previously established in references 9 and 10. [c]45% inhibition of [^{3}H]-**2** @ 100 μM. [d]79% inhibition of [^{3}H]-**2** @ 100 μM. [e]68% inhibition of [^{3}H]-**2** @ 100 μM.

In general, the esters **9** were more potent than the nitriles **8** at both the DAT and SERT. However, like meperidine (**3**) all of the meperidine analogues exhibited a greater affinity for the SERT than the DAT. The DAT/SERT ratios illustrate that the meperidine analogues had 3– to 158-times greater affinity for SERT than for DAT. The increased affinities of the 4-iodo derivative **9c** (K_i = 21 nM, 20-fold) and the 2-naphthyl congener **9g** (K_i = 7 nM, 60-fold) relative to **3** for the SERT were not surprising based on previous SAR described in other tropane systems.[11,12] However, the high selectivity of **9c** and **9g** for the SERT over the DAT was extraordinary (>150-fold) and these compounds are among some of the most selective agents for the SERT reported to date.

At the DAT, the nitrile derivatives, **8a**, **8b**, and **8d** as well as the ester derivatives, **9b** and **9d** did not completely inhibit the binding of [^{3}H]-**2** at the highest concentration tested (100 μM). However, it is noteworthy that although the meperidine analogues were less potent, their SAR was similar to that which has been reported for the 2β-carbomethoxy-3β-phenyltropanes (WIN series) and related bicyclo[3.2.1]octane congeners.[11–14] The substituent on the phenyl ring significantly influenced the binding affinities of the analogues **8** and **9** for the DAT (K_i for DAT: 3,4-Cl_2<< 4-I < 4-Cl <4-CH_3 ≈ 4-F < H). The 3,4-dichloro derivative **9e** (K_i = 125 nM) was

found to be the most potent ligand of the series for DAT and was 142-fold more potent than meperidine (**3**). Moreover, **9e** was the least selective of the ester analogues for the SERT. From the SAR of the meperidine derivatives **9** and the WIN analogues, it is clear the 3,4-dichlorophenyl group is an important moiety for molecular recognition at the DAT. Although, the 3,4-dichlorophenyl group also increased the binding affinity of **9e** for SERT, the overall effect was only 15% of that observed for the DAT. Alternatively, the 2-naphthyl group increased the binding affinity of **9g** relative to **3**, at both DAT and SERT but was much more selective for SERT.

To our knowledge, there are no previous reports of the binding of meperidine to the serotonin transporter. However, there are multiple reports of a serotonin syndrome observed in patients treated with meperidine.[15,16] A serotonin syndrome, which is characterized by rigidity, confusion, nausea, diarrhea and coma, is caused by compounds that act as serotonin agonists and has been described in both humans[16] and animals.[17] It has been shown that meperidine inhibits serotonin uptake,[18] a finding consistent with our data showing that meperidine binds to the SERT, and this could explain the reports of a serotonin syndrome following meperidine administration.

In summary, we have demonstrated that the binding affinity of meperidine can be increased for the DAT or the SERT by incorporation of appropriate substituents on the phenyl ring. These new potent meperidine analogues, **9c**, **9e** and **9g**, should prove to be useful pharmacological probes for exploring the high- and low-affinity binding sites on the DAT. Dopamine and serotonin uptake inhibition and the corresponding behavioral effects of the potent meperidine analogues are currently under investigation and will be reported in due course.

Acknowledgment: We are grateful to the National Institute on Drug Abuse (NIDA) for the financial support of this research.

References

1. Madras, B. K.; Fahey, M. A.; Bergman, J.; Canfield, D. R.; Spealman, R. D. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 131-141.
2. Madras, B. K.; Spealman, R. D.; Fahey, M. A.; Neumeyer, J. L.; Saha, J. K.; Milius, R. A. *Mol. Pharmacol.* **1989**, *36*, 518-524.
3. Izenwasser, S.; Newman, A. H.; Katz, J. L. *Eur. J. Pharmacol.* **1993**, *243*, 201-205.
4. Izenwasser, S.; Newman, A. H.; Cox, B. M.; Katz, J. L. *Eur. J. Pharmacol.* **1996**, *287*, 9-17.
5. Katz, J. L.; Newman, A. H.; Izenwasser, S. *Pharmacol. Biochem. Behav.* **1997**, *57*, 505-512.
6. Kozikowski, A. P.; Araldi, G. L.; Boja, J.; Meil, W. M.; Johnson, K. M.; Flippen-Anderson, J. L.; George, C.; Saiah, E. *J. Med. Chem.* **1998**, *41*, 1962-1969.
7. Lomenzo, S. A.; Izenwasser, S.; Gerdes, R. M.; Trudell, M. L. *Abstract of Papers,* 217th National Meeting of the American Chemical Society, Anaheim, CA; ACS, Washington DC, 1999; MEDI 105.
8. (a) Smissman, E. E.; Hite, G. *J. Am. Chem. Soc.* **1959**, *81*, 1201-1203. (b) Eisleb, O. U. S. Patent 2 167 351, 1939; *Chem. Abstr.* **1939**, *33*, 8923
9. Izenwasser, S.; Terry, P. Heller, B.; Witkin, J. M.; Katz, J. L. *Eur. J. Pharmacol.* **1994**, *263*, 277-283.
10. Dutta, A. K.; Xu, C.; Reith, M. E. A. *J. Med. Chem.* **1996**, *39* 749-756.
11. Carroll, F. I. Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1994**, *37*, 2865-2873.
12. Davies, H. M. L.; Kuhn, L. A.; Thornley, C.; Matasi, J.; Sexton, Childers, S. R. *J. Med. Chem.* **1996**, *39*, 2554-2558.
13. Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M.; Chen, Z.; George, C.; Madras, B. K. *J. Med. Chem.* **1997**, *40*, 2661-2673.
14. Meltzer, P. C.; Blundell, P.; Chen, Z.; Yong, Y. F.; Madras, B. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 857-862.
15. Gillman, P. K. *Med. J. Aust.* **1995**, *162*, 554.
16. Bodner, R. A.; Lynch, T.; Lewis, L.; Kahn D. *Neurology* **1995**, *45*, 219-223.
17. Hwang, E. C.; Van Woert, M. H. *Res. Commun. Chem. Pathol. Pharmacol.* **1979**, *23*, 419-431.
18. Larsen, J. J.; Hyttel, J. *Acta Pharmacol. Toxicol.* **1985**, *57*, 214-218.