Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 497–500

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

N-Arylalkylpiperidines as High-Affinity Sigma-1 and Sigma-2 Receptor Ligands: Phenylpropylamines as Potential Leads for Selective Sigma-2 Agents

Dean Y. Maeda,[a] Wanda Williams,[b] Wes E. Kim,[a] Linn N. Thatcher,[a] Wayne D. Bowen[b] and Andrew Coop[a,*]

[a]*Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 North Pine Street, Baltimore, MD 21201, USA*

[b]*Laboratory of Medicinal Chemistry National Institute of Diabetes, Digestive, and Kidney Diseases Building 8, Room B1-23, Bethesda, MD 20892, USA*

Received 24 September 2001; accepted 19 November 2001

Abstract—To delineate the differences between the structural requirements necessary for recognition at sigma-1 and sigma-2 receptors, a range of phenethyl- and phenylpropylpiperidines were evaluated in binding assays. Phenethylpiperidines were found to favor sigma-1 receptors, whereas phenylpropylpiperidines tend to favor sigma-2 receptors. It appears that phenylpropylamine is a potential pharmacophore for selective sigma-2 ligands.

Sigma receptors were first described by Martin as a subtype of opioid receptor.[1] It is now known that sigma receptors are a distinct class, comprising sigma-1 and sigma-2 subtypes[2] that are unrelated to the sites described in earlier studies. The sigma-1 receptor has recently been cloned and represents a unique protein,[3] but sigma-1 pharmacology has been notoriously complicated to understand due to the ligands employed interacting with other systems.[4] However, through the use of a series of arylethylenediamines, which are selective for sigma receptors over other systems,[5,6] and other selective ligands, it is known that sigma-1 receptors modulate many physiological systems (Fig. 1).[7–11]

Sigma-2 receptor pharmacology has been similarly complicated and suffers from the fact that the receptor has not yet been cloned. Sigma-2 receptors have been implicated in the side effects of typical antipsychotic

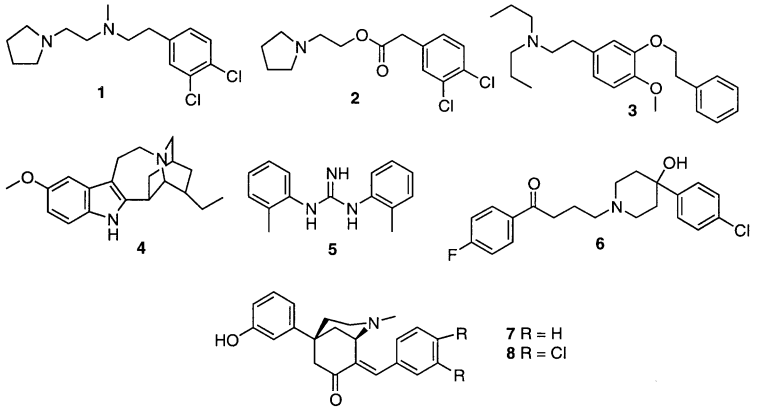


Figure 1. Arylalkylamine-based sigma receptor ligands.

*Corresponding author. Tel.: +1-410-706-2029; fax: +1-410-706-0346; e-mail: acoop@rx.umaryland.edu

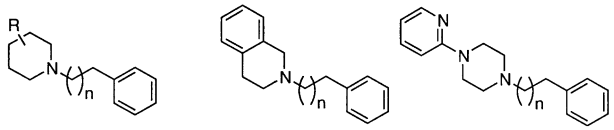
0960-894X/02/$ - see front matter
PII: S0960-894X(01)00788-0

drugs,[12,13] but recent studies have suggested that the sigma-2 receptor system potentially offers a pharmacological system capable of modulating apoptosis,[14–19] and it is essential that selective agonists and antagonists are developed to allow full characterization of their role in apoptosis. However, a wide variety of structural classes are recognized by sigma receptors and it has been difficult to determine definitive structure–activity relationships for the system. In addition, the fact that many early studies only investigated affinity at sigma-1 receptors,[2,6] underscores the necessity for further studies of simple compounds to determine the structural features necessary for preferential recognition at sigma-2 receptors over sigma-1 (Table 1).

We have recently shown that the central amine of the high-affinity, subtype nonselective, sigma receptor ligand BD1008 (**1**)[5] is important for sigma-2 affinity. This is indicated by the observation that the ester **2** showed sigma-1 selectivity over sigma-2, due to much reduced affinity at sigma-2.[20] We now present our studies into the removal of the terminal amine of **1**.

Removing the terminal amine of **1** gives phenethylamines, a sigma pharmacophore as proposed by Glennon,[21,22] but the assays employed by Glennon in the early 1990's are now known to predominantly measure sigma-1 affinity, and little can be concluded about the necessity of this pharmacophore for sigma-2 receptors. Such a phenethylamine is present in the sigma-1-selective (+)-benzomorphans[1,6] and in NE-100 (**3**)[23] a selective sigma-1 antagonist. Ibogaine (**4**), a low-affinity selective sigma-2 agonist,[24] also contains an arylethylamine. The sigma subtype non-selective DTG (**5**)[2] can also be considered to contain an amine two atoms away from an aromatic ring. However, other monoamines that bind to sigma receptors do not contain such a pharmacophore: nonselective haloperidol (**6**)[2] contains an amine three carbons from one aromatic group, and four carbons from another, and the high-affinity sigma-2 selective benzylidene-5-phenylmorphans, CB-64D (**7**) and CB-184 (**8**)[25] contain an amine three carbons from both aromatic rings.

The high sigma-2 affinity and selectivity of the phenylpropylamine-containing **7** and **8**, together with the low sigma-2 affinity of the phenethyl containing (+)-benzomorphans and **3**, led to our current hypothesis that phenylpropylamines may provide a lead for selective sigma-2 ligands. That **4** is somewhat sigma-2 preferring is also consistent with the hypothesis, if the phenyl group alone is viewed as the aryl group. Indeed, the fact



9 n = 1, R = H
10 n = 2, R = H
11 n = 1, R = 3-Methyl
12 n = 2, R = 3-Methyl
13 n = 1, R = 4-Methyl
14 n = 2, R = 4-Methyl

15 n = 1
16 n = 2

17 n = 1
18 n = 2

Figure 2. Target phenylalkylpiperines.

that the aromatic group is actually an indole two carbons distant from the amine, may account for the relatively low sigma-2 affinity, compared to **7** and **8**. **6** contains the necessary phenylpropylamine, but also contains a phenylbutylamine, a functional group known to interact preferentially with sigma-1 receptors.[26] It is therefore consistent with the current hypothesis that **6** would be a high-affinity nonselective sigma ligand.

Since few systematic studies have investigated the sigma receptor binding differences between phenethylamines and phenylpropylamines without the complication of elaborate functionality[23] or conformational restraint as is seen in the above examples, we decided to prepare simple phenylalkylamine-based ligands to study the sigma receptor system and test our hypothesis. Glennon has previously investigated phenethylpiperidine (**9**) and phenylpropylpiperidine (**10**),[27] and shown that they have moderate affinity for sigma-1 receptors. We therefore decided to initially focus on simple phenylalkyl piperidines, compare the effects of phenethyl versus phenylpropyl, and investigate the effect of simple substitution on the piperidine ring. Only simple substitution (e.g., methyl, phenyl) was investigated in order to be able to draw meaningful conclusions, and to determine potential positions for additional functionalization in future studies.

The piperidines **10**–**16** and piperazines **17** and **18** (Fig. 2) were prepared by simple alkylation of the appropriate secondary amine with the corresponding phenyl alkyl halide in DMF in the presence of $NaHCO_3$. After addition of water, the products were extracted into Et_2O, concentrated under reduced pressure, and then converted to water soluble oxalate salts. Commercially available *N*-phenethylpiperidine (**9**) was converted directly to the oxalate salt. All products displayed NMR and mass spectra consistent with their structure and gave acceptable CHN analyses (±0.4%).[28] The ligands were evaluated in competition assays at sigma-1 and sigma-2 receptors as described previously.[24,25,29]

All amines possessed affinity at both sigma-1 and sigma-2 sites, suggesting that the terminal amine does not contribute to subtype selectivity. In contrast to the removal of the central amine **2**, affinity was observed at both receptors. *N*-Phenethylpiperidine (**9**) showed similar affinity at both sigma-1 and sigma-2, $K_i = 88$ and 112 nM, respectively: these data are in accord with the previous findings of Glennon.[27] The corresponding *N*-phenylpropyl analogue[27] demonstrated 4-fold greater affinity at sigma-2 sites and slightly lower affinity at sigma-1. Interestingly, the affinity of these simple compounds at sigma-2 is equal to the affinity of the arylethylenediamine **1**,[5,6] and greater than that of the phenylmorphans **7** and **8**.[25] Thus, phenylpropylpiperidine (**10**) is 6-fold selective for sigma-2 over sigma-1, and this implies that three carbons between the aromatic ring and the basic amine is better tolerated by the sigma-2 receptor than the sigma-1. In general, the *N*-phenylpropyl analogues had higher affinity at sigma-2 than the corresponding *N*-phenethyl analogues, and the *N*-phenethyl analogues possessed higher affinity for

Table 1. Binding affinity at sigma receptors

Amine moiety	*N*-Phenethyl	K_i (nM) Sigma-1[a]	K_i (nM) Sigma-2[b]	*N*-Phenyl-propyl	K_i (nM) Sigma-1[a]	K_i (nM) Sigma-2[b]
Piperidine	**9**[c]	88.5±13.6	112±3.3	**10**[c]	143±16	25±3.0
3-Methylpiperidine	**11**[d]	4.15±0.11	84.4±0.66	**12**	5.25±3.02	6.61±0.16
4-Methylpiperidine	**13**[e]	20.9±1.85	33.3±0.13	**14**	3.35±0.58	12.1±0.35
Tetrahydroisoquinoline	**15**[f]	5.90±0.11	57.3±1.3	**16**	13.9±0.03	14.2±1.1
(2-Pyridyl)piperazine	**17**[g]	326±41.2	119±3.78	**18**	82.9±0.21	4.91±0.77

[a]Displacement of [^{3}H]-(+)-pentazocine.
[b]Displacement of [^{3}H]-DTG in the presence of dextrallorphan.
[c]Previously prepared in ref 27.
[d]Previously prepared in ref 30.
[e]Previously prepared in ref 31.
[f]Previously prepared in ref 32.
[g]Previously prepared in ref 33.

sigma-1 than the *N*-phenylpropyl analogues. One exception to this general trend were the 4-methyl analogues in which the *N*-phenylpropyl (**14**) displayed higher affinity than the *N*-phenethyl (**13**) at both receptors.

Simple changes in the methyl substitution pattern on the piperidine ring gave rise to major changes in receptor affinity and selectivity, underscoring the need to study compounds without elaborate functionality. In the *N*-phenethyl series, the greatest affinity at sigma-1 was observed with the 3-methyl substituent (**11**), and the greatest affinity at sigma-2 with the 4-methyl substituent (**13**). Whereas, in the phenylpropyl series, the greatest affinity for sigma-2 was observed with the 3-methyl analogue (**12**), and the 3- and 4-methyl substituted derivatives both demonstrated very high affinity for sigma-1.

The higher affinity of the 3- and 4-methyl substituted analogues compared to the unsubstituted analogues, prompted us to study the tetrahydroisoquinoline and (2-pyridyl)piperazine analogues. As can be seen, in the tetrahydroisoquinoline series, the phenethyl (**15**) displayed high affinity at sigma-1 receptors, but lower affinity at sigma-2, whereas the phenylpropyl (**16**) displayed high affinity at both receptors, due to a 3-fold increase in sigma-2 affinity. The (2-pyridyl)piperazines showed most clearly the tendency for phenylpropylamines to favor sigma-2 sites: the phenethyl derivative (**17**) displayed only moderate affinity at both receptors, whereas the phenylpropyl (**18**) possessed high sigma-2 affinity (K_i = 4.9 nM) and selectivity (17-fold) over sigma-1 sites. The increase in sigma-2 selectivity when phenylpropyl is compared to phenethyl is due largely to a 24-fold increase in sigma-2 affinity. Sigma-1 affinity increased only 4-fold. Although the degree of sigma-2 selectivity of **10** (6-fold) and **18** (17-fold) does not approach that of the benzylidene-5-phenylmorphans **7** and **8** (200- to 500-fold), it is remarkable that a simple amine with little functionality and no conformational constraint, possesses sigma-2 affinity and selectivity to this degree.

This preliminary systematic investigation of the phenylalkylpiperidines has yielded valuable information into the structural features tolerated by the two different sigma receptors, and underscores the fact that even small changes in structure can result in dramatic changes in pharmacological profiles. Indeed, it appears that a phenylpropylamine based structure would be more likely to result in a high-affinity, sigma-2 selective ligand than the traditional phenethylamine-based sigma ligands.

References and Notes

1. Martin, W. R.; Eades, C. E.; Thompson, J. A.; Huppler, R. E. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517.
2. Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. A. *Trends Pharmacol. Sci.* **1992**, *13*, 85.
3. Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H. G.; Striessnig, J.; Kempner, E.; Glossman, H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8072.
4. Izhak, Y. *Sigma Receptors*; Academic: San Diego, 1994.
5. de Costa, B. R.; Radesca, L.; Di Paolo, L.; Bowen, W. D. *J. Med. Chem.* **1992**, *35*, 38.
6. de Costa, B. R., He, X.-S. In *The Sigma Receptors, Neuroscience Perspectives Series*; Itzhak, Y., Ed., Academic: London, 1994; p 45.
7. Monnet, F. P.; Debonnel, G.; de Montigny, C. J. *Pharmacol. Exp. Ther.* **1992**, *261*, 123.
8. Gonzalez-Alvear, G. M.; Werling, L. L. *Brain Res.* **1995**, *673*, 61.
9. Matsumoto, R. R.; McCracken, K. A.; Pouw, B.; Miller, J.; Bowen, W. D.; Williams, W.; de Costa, B. R. *Eur. J. Pharmacol.* **2001**, *411*, 261.
10. McCracken, K. A.; Bowen, W. D.; de Costa, B. R.; Matsumoto, R. R. *Eur. J. Pharmacol.* **1999**, *370*, 225.
11. Maurice, T.; Lockhart, B. P. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1997**, *21*, 69.
12. Walker, J. M.; Matsumoto, R. R.; Bowen, W. D.; Gans, D. L.; Jones, K. D.; Walker, F. O. *Neurology* **1988**, *38*, 961.
13. Matsumoto, R. R.; Hemstreet, M. K.; Lai, N. L.; Thurkauf, A.; de Costa, B. R.; Rice, K. C.; Hellewell, S. B.; Bowen, W. D.; Walker, J. M. *Pharmacol. Biochem. Behav.* **1990**, *36*, 151.
14. Vilner, B. J.; de Costa, B. R.; Bowen, W. D. *J. Neurosci.* **1995**, *15*, 117.
15. Vilner, B. J.; Bowen, W. D. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 900.
16. Vilner, B. J.; Bowen, W. D. *Abstr. Soc. Neurosci.* **1997**, *23*, #905.6.
17. Crawford, K. W.; Vilner, B. J.; Bowen, W. D. *Proc. Am. Assoc. Cancer Res.* **1999**, *40*, 166.
18. Kinloch, R. A.; Treherne, J. M.; Furness, L. M.; Hajimohamadreza, I. *Trends Pharmacol. Sci.* **1999**, *20*, 35.
19. Deigner, H. P.; Kinscherf, R. *Curr. Med. Chem.* **1999**, *6*, 399.
20. Maeda, D. Y.; Williams, W.; Bowen, W. D.; Coop, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 17.

21. Glennon, R. A.; Smith, J. D.; Ismaiel, A. M.; El-Ashmawy, M.; Battaglia, G.; Fischer, J. B. *J. Med. Chem.* **1991**, *34*, 1094.
22. Glennon, R. A.; Ismaiel, A. M.; Smith, J. D.; Yousif, M.; El-Ashmawy, M.; Herndon, J. L.; Fischer, J. B.; Burke Howie, K. J.; Server, A. C. *J. Med. Chem.* **1991**, *34*, 1855.
23. Nakazato, A.; Ohta, K.; Sekiguchi, Y.; Okuyama, S.; Chaki, S.; Kawashima, Y.; Hatayama, K. *J. Med. Chem.* **1999**, *42*, 1076.
24. Bowen, W. D.; Vilner, B. J.; Williams, W.; Bertha, C. M.; Kuehne, M. E.; Jacobson, A. E. *Eur. J. Pharmacol.* **1995**, *279*, R1.
25. Bowen, W. D.; Bertha, C. M.; Vilner, B. J.; Rice, K. C. *Eur. J. Pharmacol.* **1995**, *278*, 257.
26. Ablordeppey, S. Y.; Fischer, J. B.; Glennon, R. A. *Bioorg. Med. Chem.* **2000**, *8*, 2105.
27. Ablordeppey, S. Y.; Fischer, J. B.; Burke Howie, K. J.; Glennon, R. A. *Med. Chem. Res.* **1992**, *2*, 368.
28. Melting points: **9**·oxalate 149–150 °C; **10**·oxalate 141–142 °C; **11**·oxalate 172–173 °C; **12**·oxalate 142–143 °C; **13**·oxalate. $0.33H_2O$ 160–161 °C; **14**·oxalate 149–151 °C; **15**·oxalate 177–178 °C; **16**·oxalate·$0.25H_2O$ 131–132 °C; **17**·2oxalate 193–193.5 °C; **18**·2oxalate 189–190 °C.
29. Hellewell, S. B.; Bruce, A.; Feinstein, G.; Orringer, J.; Williams, W.; Bowen, W. D. *Eur. J. Pharmacol.* **1994**, *268*, 9.
30. Ganellin, C. R.; Spickett, R. G. W. *J. Med. Chem.* **1965**, *8*, 619.
31. Cardonzo, M. G.; Kawai, T.; Iimura, Y.; Sugimoto, H.; Yamanishi, Y.; Hopfinger, A. J. *J. Med. Chem.* **1992**, *35*, 590.
32. Perrio-Huard, C.; Aubert, C.; Lasne, M.-C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 311.
33. Ratouis, R.; Boissier, J. R.; Dumont, C. *J. Med. Chem.* **1965**, *8*, 104.