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1,4-Dibenzylpiperazines Possess Anticocaine Activity

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Abstract—*N,N*-Dibenzylpiperazines have high affinity for sigma receptors, and we aimed to increase their anticocaine activity by introducing substituents known to enhance such activity in other sigma ligands. Ligands with high affinity for sigma-1 receptors resulted, but their activity in attenuating cocaine-induced convulsions did not correlate with sigma-1 binding affinity, and may be more closely related to their sigma-2 binding affinities.

Cocaine abuse continues as a major problem, and development of efficacious treatment agents is urgently required.[1] The development of a potential maintenance therapy has been the focus of numerous research groups,[1,2] but fewer have focused on the development of medications for the treatment of acute cocaine overdose. The stimulant effects of cocaine on the cardiovascular system are well documented, and are usually the cause of death from cocaine overdose.[2] The dopamine hypothesis of cocaine[1] has been an important model for explaining the rewarding properties of the drug, but this hypothesis is incomplete. As it is now widely recognized that the actions of cocaine are due to its interactions with numerous biological systems,[1,2] we have focused on targeting other systems in order to attenuate the toxicity of cocaine.[3–5] One such system is the sigma receptor system, and the affinity of cocaine for sigma receptors makes this system physiologically relevant.[6]

The sigma receptor system was first described by Martin as a subtype of opioid receptors,[7] but it is now known that the sigma system is a unique receptor system, comprised of sigma-1 and sigma-2 sites.[8] Previous work has shown that sigma-1 antagonists attenuate the lethality, convulsions, and increased locomotor effects caused by cocaine.[3–5,9] The phenylethylenediamines [such as BD1008 (**1**)] are a class of sigma-1 antagonists which are selective for sigma sites over other systems,[10] and the potency of these agents at attenuating cocaine-induced convulsions is quite good.[3–5,9,11]

It was recently shown that a simple piperazine [1-benzyl-4-(2-naphthyl)piperazine (**2**)] demonstrated good affinity for sigma-1 receptors, and weak antagonism of the locomotor effects of stimulants (methamphetamine) was reported.[12] We considered that the introduction of the optimum substituents for anti-cocaine activity from the phenylethylenediamine system into this dibenzylpiperazine system may yield more potent compounds for attenuating the convulsive effects of cocaine. Substituents chosen included the substituents which yield the greatest activity in the phenylethylene diamine system; mono- and di-substituted chlorinated, and methoxyl substituted rings.[3–5,9,11]

The desired products (**3**–**10**, Fig. 1) were all prepared by reaction of 1-benzylpiperazine with the relevant benzyl halides in DMF in the presence of $NaHCO_3$ at room temperature for 24 h. The reaction mixture was partitioned between water and Et_2O, and the organic layer collected. After removal of the solvent, all amines were converted to water soluble salts. Table 1 summarizes the

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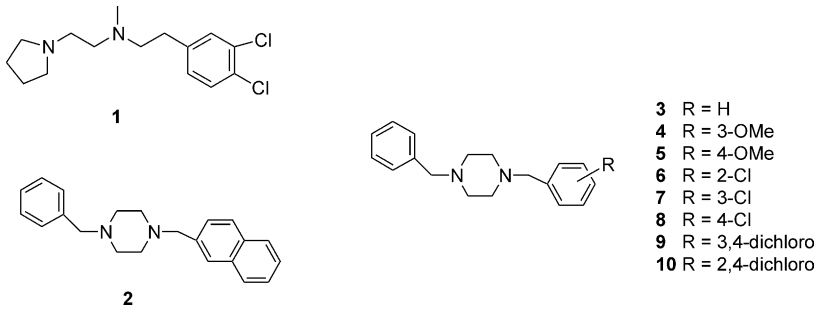

Figure 1. Structures of the sigma ligands.

Table 1. Pharmacological and physical data for sigma ligands

Compd	K_i (nM) ±SEM Sigma-1	K_i (nM) ±SEM Sigma-2	AD_{50}, mg/kg Attenuation of cocaine induced convulsions, mice	Salt form	Melting point (°C)
1[a]	2.0±1.0	8.0±2.0	2	—	—
3[b]	5.81±0.48	1274±24.4	23	Oxalate	233–235
4	0.39±0.01	107.8±1.7	17	2HCl	267–268
5[c]	0.47±0.04	161±18.6	27	2HCl	235–238
6	5.3±1.49	527±120	15	Oxalate	207–209
7	0.46±0.14	56.4±9.21	8	2HCl	285–286
8	1.40±0.16	187±16.7	29	2HCl	287–288
9	0.58±0.15	7.54±1.17	[d]	2HCl	289–290.5
10	7.6±3.7	123±11.0	16	2HCl	254–256

[a]Data from ref 5.
[b]Previously prepared in ref 13.
[c]Previously prepared in ref 14.
[d]Agonist activity, exacerbated the convulsive effects of cocaine.

salt form, the solvent, and the melting point of the salts. All free bases displayed NMR and mass spectral data consistent with the assigned structures, and combustion analysis of all salts were ±0.4% of theory (Atlantic Microlabs, Norcross, GA, USA).

The compounds were assayed for affinity to sigma-1 and sigma-2 sites through competition assays as previously described,[8] and the results are shown in Table 1. Anticocaine activity in mice was assessed through the attenuation of convulsions caused by the administration of cocaine (60 mg/kg, ip) as previously described,[3] and the results are also shown in Table 1.

All compounds were shown to possess high affinity for sigma-1 receptors, with four compounds (**4**, **5**, **7**, and **9**) possessing subnanomolar affinity. Interestingly, the potency in in vivo assays did not appear to mirror the sigma-1 affinities. For example, the 4-methoxy substituted analogue (**5**) was far less potent than the 3-chloro analogue (**7**), even though they possessed the same high sigma-1 affinity. Affinity at sigma-2 receptors was more variable within the group, with 3-chloro analogue (**7**) possessing the greatest sigma-2 affinity of the antagonist compounds. The fact that **7** also possesses the greatest potency in in vivo assays, as discussed above, tends to imply that sigma-2 is more important for attenuating the convulsive effects of cocaine in this series.[15,16]

The most surprising compound, however, was the 3,4-dichloro substituted analogue (**9**). This substitution pattern is seen in many of the antagonist phenylethylene diamines, yet **9** acts as an agonist in the cocaine assays and actually exacerbates the convulsions caused by cocaine. Since some of the phenethylene diamines with 3,4-dichloro substitutions also have agonist activity (e.g., BD1031 and BD1052);[5,9] it appears that this substitution conveys improved affinity for sigma receptors, but it is not a critical determinant of agonist versus antagonist actions.

In summary, the potent anticocaine activity of **7** makes this compound a useful lead for the development of future anticocaine medications. Further studies aimed at determining which additional biological systems these compounds interact with are currently underway.

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