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The effect of the pyridyl nitrogen position in pyridylpiperazine sigma ligands

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Abstract

A series of pyridylpiperazines was synthesized and analyzed for sigma receptor binding affinity to determine the optimal pyridyl nitrogen position and chain length for the σ_1 and σ_2 receptor recognition. The (3-pyridyl)piperazines and (4-pyridyl)piperazines favor σ_1 receptors, while previously studied (2-pyridyl)piperazines favor σ_2 receptors.

The continued growth in the abuse of methamphetamine necessitates the urgent development of pharmacotherapies. No pharmacotherapies for methamphetamine abuse currently exist and efforts have mainly focused on the development of therapies for the dopaminergic systems.[1–4] Our studies have utilized the fact that methamphetamine interacts with sigma receptors[5, 6] and sigma antagonists attenuate both the stimulant and neurotoxic effects of methamphetamine. Although sigma receptors were first thought to be a subtype of opioid receptors, they are now considered to be a unique class of receptors[7] comprised of two subtypes, σ_1 and σ_2.[8] σ_1 Receptors have been cloned[9, 10] and are involved in intracellular signaling, synaptic transmission, modulation of inositol phosphates, protein kinases, and calcium.[11–15] In addition, σ_1 antagonists reduce the convulsive, lethal, locomotor stimulatory and rewarding actions of cocaine in mice.[16–20] σ_2 Receptors have not yet been cloned; however they appear to be comprised of heterodimers and are smaller in size compared to σ_1.[21–23] Further studies have demonstrated that σ_1 selective antagonists reduce the stimulant effects of methamphetamine, while AC927 (*N*-phenethylpiperidine), a mixed σ_1 and σ_2 antagonist, attenuates the locomotor stimulant and neurotoxic effects of methamphetamine in mice.[6, 24] A selective σ_2 antagonist is therefore urgently required to further study the relationship between σ_2 antagonism and methamphetamine neurotoxicity.

Truly selective σ_2 antagonists continue to be the goal of several research groups.[25–27] One of the major disadvantages of the current σ_2 antagonists is their ability to bind to the dopamine receptors, opioid receptors, and N-methyl-D-aspartate (NMDA) receptors.[28] Recent studies showed that CM156 (3-(4-(4-cyclohexylpiperazin-1-yl)butyl)benzo[*d*]thiazole-2(3*H*)-thione) exhibits better affinity for the sigma receptor however, it has poor metabolic stability.[25] Studies performed previously by our laboratory have showed that *N*-(2-pyridyl)piperazines not only have the tendency to favor σ_2 receptors but they also favor sigma receptors over opioid and NMDA receptors with low affinity for the dopamine receptor.[29, 30] Specifically, compound **5**, 1-(2-Phenylethyl)-4-(2-pyridyl)piperazine, produced protective actions against cocaine induced convulsions which

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provides evidence that compound **5** is an antagonist.[29, 31] Moreover, 1-(3-phenylpropyl)-4-(2-pyridyl)piperazine, **6**, has 17-fold preference for the σ_2 receptor, over σ_1.[30] In an effort to design a pharmacophore for selective σ_2 antagonism in this series, we have investigated the effect of pyridyl nitrogen position and chain length in the phenylalkylpiperazinepyridine series.

Compounds **1–4** (Figure 1) were prepared by the alkylation of the corresponding halogenated alkyl phenyls with the appropriate pyridinylpiperazine in the presence of K_2CO_3 in DMF at room temperature. and purified as oxalate salts from methanol.[30] All salt targets were characterized using NMR and MS and all elemental analyses of salts were within ±0.4%.

In vitro competition binding assays were preformed as follows. Preparation of rat brain membrane and binding assays for the σ_1 and σ_2 receptor were performed as previously described in detail.[32, 33] In brief, σ_1 receptors were labeled with 5 nM [^{3}H](+)-pentazocine. The σ_2 receptors were labeled with 3 nM [^{3}H]di-o-tolylguanidine (DTG) in the presence of 300 nM (+)-pentazocine to block σ_1 receptors. Nonspecific binding was determined in the presence of 10 μM haloperidol. Ten concentrations of each sigma compound (0.1–10,000 nM) were used in the assays. The compounds were incubated for 120 min at 25°C to measure their ability to displace the radioligands from their binding sites. Termination of the reaction was achieved through rapid vacuum filtration over glass fiber filters which were previously soaked in 1% polyethyleneimine for at least 45 min. K_i values were calculated using the Cheng-Prusoff equation.[34]

All compounds possessed affinity at both σ_1 and σ_2 receptors (Table 1). As shown previously, (2-pyridyl)piperazines (**5**,**6**) favored σ_2 receptors,[30] while (3-pyridyl)piperazines (**3**,**4**) and (4-pyridyl)piperazines (**1,2**) showed preference for σ_1 receptors. Similar binding affinities were achieved by the (4-pyridyl)piperazine compounds (**1**,**2**) independent of the chain length, whereas the phenylpropyl linker in both (3-pyridyl)piperazine and (2-pyridyl)piperazine resulted in higher affinity for both σ_1 and σ_2 receptors. All new compounds showed significantly lower affinity for σ_2 receptors than our lead compound **6**.

In summary, binding affinity studies showed that the (3-pyridyl)piperazines and (4-pyridyl)piperazines have lower affinity for σ_2 receptors, than the previously reported lead compound **6**. Moreover, both new series lost σ_2 selectivity, indicating that (2-pyridyl)piperazines are optimal for the development of highly selective σ_2 ligands.

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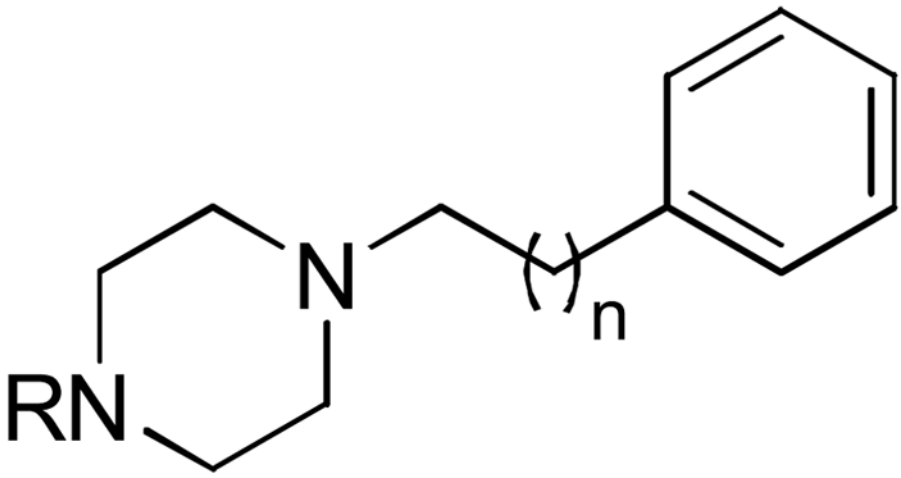

1 R = 4-pyridyl, n = 1
2 R = 4-pyridyl, n = 2
3 R = 3-pyridyl, n = 1
4 R = 3-pyridyl, n = 2
5* R = 2-pyridyl, n = 1
6* R = 2-pyridyl, n = 2

Figure 1.
Phenylalkylpiperazinepyridines
*Reported in reference ref. 30

Table 1

Binding affinities of phenylalkylpiperazinepyridines **1**–**6** at sigma receptors.

	K_i (nM)±SEM		Selectivity
Cmpds	σ_1[a]	σ_2[b]	σ_1/σ_2
1	41.8 ± 5.9	69.7 ± 6.3	0.60
2	34.2 ± 2.8	84.0 ± 5.9	0.41
3	97.2 ± 6.9	440 ± 20	0.22
4	21.2 ± 2.3	110.0 ± 8.6	0.19
5 *	326 ± 41.2	119 ± 3.8	2.7
6 *	82.9 ± 0.21	4.91 ± 0.77	16.9

*Citations reference previously known compounds and results ref. 30

[a]Displacement of [^{3}H](+)-pentazocine

[b]Displacement of [^{3}H]DTG in presence of (+)-pentazocine