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4-ARYLTETRAHYDROPYRIDINES AS SELECTIVE σ LIGANDS

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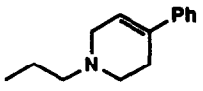
Abstract: 4-Aryltetrahydropyridines were prepared and evaluated in dopamine (DA) D2 and σ binding assays. Introduction of substituents into the 4 position of the aryl group on the tetrahydropyridine was found to both greatly decrease the affinity for the DA D2 receptor and increase the affinity for the brain σ binding sites.

Many clinically efficacious antipsychotics including haloperidol and remoxipride have been shown to have significant affinity for brain σ binding sites.[1] The σ binding site was first postulated by Martin to explain the psychotomimetic effects of the benzomorphan opioid (+/-) SKF 10,047.[2] There is ample evidence suggesting the σ binding sites to be distinct from opioid, dopaminergic and PCP receptors.[3] Although the exact physiological role of the σ binding sites remains unclear,[4] many potential antipsychotic compounds, in addition to being dopamine (DA) D2 receptor antagonists, have affinity for σ sites making this an intriguing area for antipsychotic drug discovery. Recently a diverse array of structures has been shown to have potent affinity for σ binding site.[5]



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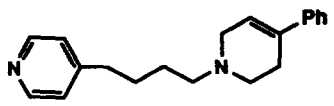
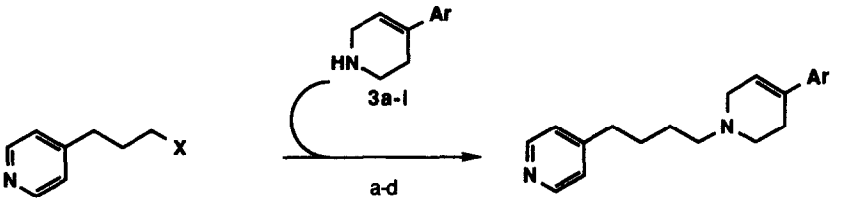


2a

For example N-propyl-4-phenyltetrahydropyridine (**1**) possesses good affinity for σ sites.[6] Compounds of this type are known to interact with a variety of monoaminergic receptors including DA receptors. As part of our program to identify novel antipsychotic agents we found that in addition to potent DA D_2 agonist activity, aryltetrahydropyridine **2a** also has potent affinity for σ sites. A variety of analogs were then prepared with the aim of exploring the effect of modifying the aryl group of the tetrahydropyridine on σ and DA ligand binding.

Chemistry

Substituted phenyl tetrahydropyridines **3b-f**[7a] (Table 1) as well as heteroaryl tetrahydropyridines **3g**[7b], **3h**[7c], and **3i**[7d] were prepared using published procedures. Nitrile **4**[8] was converted to the methyl ester **5** in 95% yield. LAH reduction of **5** proceeded in 99% yield and reaction of the resulting alcohol **6** with thionyl chloride gave chloride **7** in 89% yield. Chloride **7** was then used to alkylate tetrahydropyridines **3a-i**, to give the desired targets **2a-i**.



4 X = CN
5 X = CO_2Me
6 X = CH_2OH
7 X = CH_2Cl

2a-l

(a) HCl, MeOH; (b) $LiAlH_4$; (c) $SOCl_2$;
(d)3a-i, $KHCO_3$, CH_3CN, reflux

TABLE 1
ARYL SUBSTITUENT

2,3	Ar
a	Phenyl
b	4-Chlorophenyl
c	4-Methoxyphenyl
d	4-Fluorophenyl
e	4-Methylphenyl
f	2-Naphthyl
g	2-pyridyl
h	3-indolyl
i	2-thienyl

TABLE 2 PHYSICAL AND BIOCHEMICAL DATA[9]

No	MP (°C)	Sigma Ki (nM)	DA D_2 Ki (nM)
2a	89-90	2.72	69.1
2b	88-90	1.04	456
2c	72-73	0.45	1639
2d	64-66	1.75	5305
2e	80-82	5.86	957
2f	85-87	3.07	660
2g	98-99	44.5	322
2h	177-178	10.3	286
2i	86-87	2.13	496

Results and Discussion

Compounds **2a-i** were screened *in vitro* for DA D2 binding affinity ([^{3}H]spiperone[10]) and for σ binding affinity ([^{3}H]3-PPP[11]) in rat striatum and guinea pig brain preparations respectively. Comparison of Ki values for compounds **2a-2i** (Table 2) in the D2 DA and σ receptor binding assays revealed that it was possible to decrease DA receptor affinity of tetrahydropyridines while maintaining or even increasing σ affinity. Substitution in the 4 position of the aromatic

ring (**2b-e**) resulted in a significant loss of affinity for the DA D2 receptor . However σ binding affinity in these compounds was unaffected by the substituents examined. The methoxy analog **2c** had an increased affinity for σ sites, resulting in over 3000 fold selectivity for the σ binding sites over the DA D2 receptor. Interestingly the naphthalene and thiophene ring systems found in compounds **2f** and **2i** were tolerated by the σ sites while the pyridine and indole ring systems found in compounds **2g** and **2h** respectively had a deleterious effect on affinity for these sites.

TABLE 3
Behavioral and Mechanistic Tests

Test	2a	2c	2d
Inhibn. Mouse Locomotor Activity ED_{50} (mg/kg) IP	0.6	7.4	3.8
%Inhib Dopamine Synthesis @ 10 mg/kg IP	87	18	0
%Inhib Dopamine Firing @ 2.5 mg/kg IP	80	6	9

Because of their selectivity for σ binding sites, **2c** and **2d** were compared to **2a** in more detailed testing (Table 3). While less potent than **2a**, **2c** and **2d** inhibited spontaneous locomotor activity in mice, a behavioral measure of potential antipsychotic activity.[12] **2c** and **2d** neither inhibited the spontaneous firing of DA neurons in the substantia nigra of rats[13] nor inhibited DA synthesis in rat corpus striatum[14] measures of DA agonist or antagonist activity. This suggests that the behavioral effects of **2c** and **2d** are not due to interactions with DA D2 receptors.

As the search for the physiological significance of the σ binding sites continues, compounds such as **2c** and **2d** may represent important tools in unraveling the function of these sites. Furthermore, since the DA D2 receptor appears to be much more sensitive than the σ sites to substitution in the aryl ring on the tetrahydropyridine, this might be a good general strategy for the preparation of other selective σ ligands from various aryl amine containing structures.

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