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Parallel Synthesis of a Series of Subtype-Selective NMDA Receptor Antagonists

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Abstract—A series of 1-(heteroarylthioalkyl)-4-benzylpiperidines was rapidly synthesized through the use of parallel synthesis to investigate the binding affinity for the NR1A/2B receptor subtype.

Parkinson's disease affects 1% of the population over 50 years of age.[1] It is a progressive degenerative central nervous system disorder, which has many debilitating effects such as muscle rigidity, resting tremors and slowness or poverty of movement. Parkinson's disease results from degeneration of dopaminergic neurons that lie within the substantia nigra. The treatment of choice has been dopamine replacement therapy, using L-dihydroxyphenylalanine (L-DOPA). However, long term treatment often results in adverse side effects such as dyskinesias. It has been shown that *N*-methyl-D-aspartate (NMDA) antagonists can potentiate the effects of L-DOPA in animal models of Parkinson's disease. The use of non-selective NMDA antagonists also results in several side effects, the most common being ataxia, sedation and cognitive impairments. The recent discovery of multiple subtypes of NMDA receptors, which are differentially expressed throughout the brain, may allow separation of therapeutic activity from adverse side effects.

We recently reported a novel series of acetylene-linked NMDA NR1A/2B subtype-selective antagonists,[2] in which compound **1** showed sub-micromolar potency at the NR1A/2B receptor subtype ($IC_{50} = 0.1$ μM) expressed in Xenopus oocytes and good selectivity (NR1A/2A and NR1A/2C IC_{50}s >100 μM). Compound **1** was also shown to potentiate the effects of L-DOPA when administered interperitoneally but not orally in the 6-hydroxydopamine-lesioned (6-OHDA) rat, a model of Parkinson's disease.[3] A direct analogue (**2**) was prepared and it maintained good binding activity and selectivity (NR1A/2A $IC_{50} = 35.0$ μM, NR1A/2B $IC_{50} = 0.17$ μM, NR1A/2C IC_{50} >100 μM). Due to the known high metabolism of the phenol moiety,[4] our objective was to identify phenol replacements that might show oral activity in vivo. The hydrogen bonding character of the phenol moiety was needed to maintain good binding activity: therefore, we focused our synthesis on heterocyclic replacements which contain similar H-bonding character.

Utilizing parallel synthesis, we were able to rapidly synthesize analogues of **2** to explore the binding affinity for the NMDA NR1A/2B receptor subtype. The general synthesis is shown in Scheme 1.[5]

A standard S_N2 reaction between the appropriate bromide and the 4-benzyl piperidine resulted in the alcohol. This alcohol was reacted with thionyl chloride to give the chlorides in 60~80% yield. Standard solutions (0.5 M) of the chlorides in acetonitrile were prepared and subsequently transferred (4 mL) to ten 28×95 mm vials. Solutions (0.5 M) of each thiol were prepared and 4 mL transferred to the appropriate vial. Potassium carbonate (303 mg) was added separately to each reaction vial.

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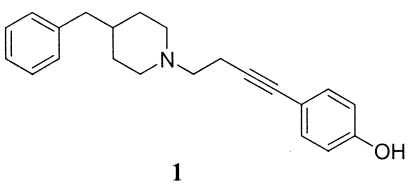
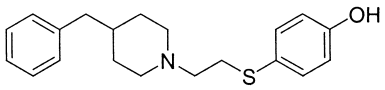


1



2

The vials were flushed with nitrogen, sealed and warmed with mixing to 100 °C on a J-Kem™ heater/shaker. After 18 h at 100 °C the reactions were cooled, filtered and concentrated. The crude mixtures were purified in parallel by MPLC on silica gel (10 g) resulting in the desired products in 50∼95% yield.

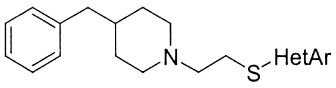
To initiate our SAR study, we explored the effects on NR1A/2B antagonist potency by replacing the phenol of **2** with heteroaryl groups. We identified several compounds that were potent at NR1A/2B receptors (Table 1). The best potency correlated with the presence of a H-bond donor, as in compound **4**. Lack of a hydrogen bond donor, as in compound **9**, resulted in a decrease in the binding potency. Larger heteroaryl groups that contain a H-bond donor (such as in **11**) also resulted in a reduction of receptor binding.

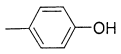
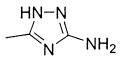
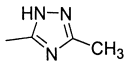
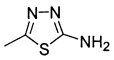
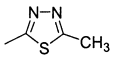
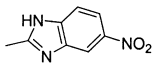
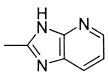
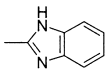
In Table 2 the NR1A/2B activity was examined for the higher chain homologues. This change was not well tolerated at NR1A/2B receptors, resulting in a reduction of potency by a factor of 4- to 8-fold (e.g. compound **4** versus **14**). However, exceptions in the reductions were seen, such as compound **20**, where an increase in binding potency was observed. This binding increase may be the result of additional rotational freedom in the molecule.

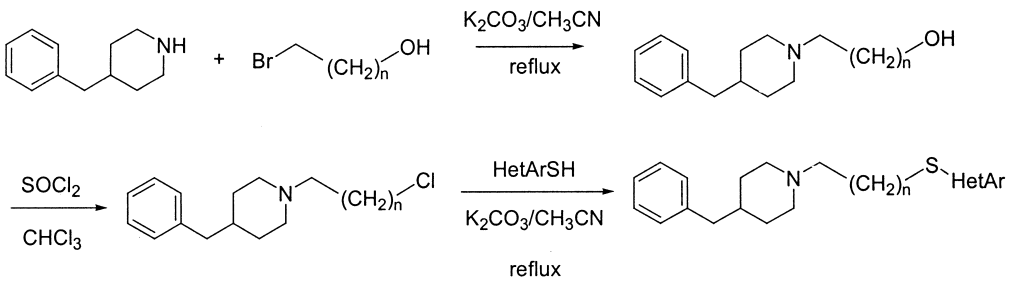
Compound **4** is a potent NR1A/2B antagonist and was subjected to further testing in the 6-hydroxydopamine-lesioned rat. Like many other compounds in this series, **4** showed no activity when administered at 10 mg/kg PO in the 6-OHDA rat model. The lack of oral activity may be due to first pass metabolism of the sulfur linkage or the inability of the compounds to cross the blood brain barrier.

In conclusion, through the use of parallel synthesis we rapidly investigated the thio ether linked heteraryl

Table 1. NR1A/2B receptor potency for analogues of **2**

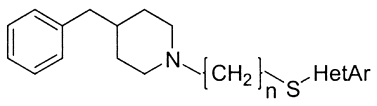


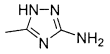
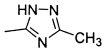
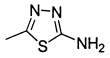
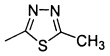
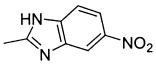
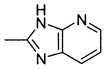
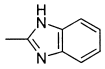
Compound	HetAr	NR1A/2A[2] IC_{50} (μM)	NR1A/2B[2] IC_{50} (μM)	NR1A/2C[2] IC_{50} (μM)
2		35.0 (1)	0.10 ± 0.02 (4)	>100 (1)
3		>100 (1)	0.93 ± 0.3 (3)	>100 (1)
4		>100 (1)	0.035 ± 0.01	>100 (1)
5		>100 (1)	0.07 ± 0.03 (3)	>100 (1)
6		>100 (1)	0.13 ± 0.01 (3)	>100 (1)
7		70.0 (1)	0.15 ± 0.02 (3)	>100 (1)
8		>100 (1)	0.21 ± 0.02 (3)	>100 (1)
9		>100 (1)	4.8 ± 0.7 (3)	>100 (1)
10		>100 (1)	7.4 ± 1.0 (3)	>100 (1)
11		>100 (1)	0.24 ± 0.03 (3)	>100 (1)
12		75 (1)	0.38 ± 0.03 (3)	>100 (1)



Scheme 1.

Table 2. NR1A/2B activity for analogues of **2**



Compound	*n*	HetAr	NR1A/2A[2] IC_{50} (μM)	NR1A/2B[2] IC_{50} (μM)	NR1A/2C[2] IC_{50} (μM)
3	2		>100 (1)	0.93 ± 0.3 (3)	>100 (1)
13	3		85.0 (1)	4.3 ± 1.0 (3)	>100 (1)
14	3		77.0 (1)	0.63 ± 0.1 (3)	>100 (1)
15	3		77.0 (1)	0.61 ± 0.04 (3)	>100 (1)
16	3		51.0 (1)	0.63 ± 0.04 (3)	>100 (1)
17	3		>100 (1)	1.0 ± 0.2 (4)	>100 (1)
18	3		73.0 (1)	0.56 ± 0.03 (3)	>100 (1)
19	3		>100 (1)	6.4 ± 1.0 (3)	>100 (1)
20	3		61.0 (1)	0.91 ± 0.2 (4)	>100 (1)
21	3		>100 (1)	1.6 ± 0.2 (3)	>100 (1)
22	3		64.0 (1)	1.0 ± 0.2 (4)	51.0 (1)

groups and identified several potent and selective NMDA NR1A/2B receptor antagonists. As with the previous acetylene-linked series, a hydrogen bond donor was required for potent NR1A/2B activity.[2] An ethylene link ($n = 2$) between the piperidine and the thio aryl system was preferred. While we found replacements for the phenol moiety of **2** that maintained in vitro activity, oral activity in vivo was not achieved.

References and Notes

1. Cooper, A. J.; Carroll, C. B.; Mitchell, I. J. *CNS Drugs* **1998**, *9*, 421.

2. All compounds were tested for inhibitory activity at NR1A/2A, NR1A/2B and NR1A/2C receptors in frog oocytes as previously described. Values are mean SEM taken from 1 to 4 experiments, as noted in parentheses: Wright, J. L.; Gregory, T. F.; Bigge, C. F.; Boxer, P. A.; Serpa, K.; Meltzer, L. T.; Wise, L. D.; Cai, S. X.; Hawkinson, J.; Whittemore, E.; Woodward, R.; Zhou, Z. *J. Med. Chem.* **1999**, *42*, 2469.

3. 6-OHDA rat model: rats were lesioned by injection of 6-hydroxydopamine into the right medial forebrain bundle rostral to the substantia nigra. After lesioning, rats are conditioned with L-DOPA methyl ester (10 mg/kg SC, mixed with s-carbidopa 1 mg/kg to prevent peripheral decarboxylation) to establish a stable response. Vehicle or the test compound was administered orally at the same time as L-DOPA in a randomized, crossover manner, with 1 week between treatments. The total number of contraversive rotations observed following dosing with the test compound + L-DOPA was compared with the response in the same rats to vehicle + L-DOPA, using a paired *t*-test.

4. Mistry, M.; Houston, J. B. *Drug Metab. Dispos.* **1985**, *13*, 740.

5. All new compounds had satisfactory ^{1}H NMR, IR, MS and microanalysis.