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Bioorganic & Medicinal Chemistry Letters
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Bioorganic & Medicinal Chemistry Letters 14 (2004) 1213–1216

Subtype selective NMDA receptor antagonists: evaluation of some novel alkynyl analogues

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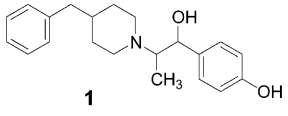
Received 22 September 2003; revised 9 December 2003; accepted 12 December 2003

Abstract—A benzylpiperidine analogue with an acetylenic linker, 5-{3-[4-(4-fluorobenzyl)-piperidin-1-yl]-prop-1-ynyl}-1,3-dihydrobenzimidazol-2-one (**3**), was identified as a chemical lead with excellent activity at the NR1A/2B receptor (IC_{50} = 3 nM). Efforts to optimize this activity led to focused modifications around the structural motif of **3**. The synthesis and SAR studies are discussed.

N-Methyl-D-aspartate (NMDA)-type ligand gated ion channel glutamate receptors mediate a number of physiological and pathophysiological processes in the mammalian central nervous system (CNS). The physiological receptor is a heteromer containing an NR1 subunit (which is present throughout the brain and spinal cord) with one or more of the different NR2 subunits (NR2A, NR2B, NR2C, and NR2D).[1] In contrast to the NR1 subunit, the NR2 subunits show a differential development and regional localization.[2] This presents the possibility that substances that are selective for an individual NR2 subunit may possess some of the therapeutic properties of the broad spectrum NMDA antagonists but lack their side-effect profile. In particular, antagonists of the NR1A/2B receptor have shown efficacy in neuroprotection, antihyperalgesic, and anti-Parkinson[3] animal models. Early work in this area has shown ifenprodil (**1**), to be a selective antagonist of NR1A/NR2B receptors with an improved side-effect profile versus other NMDA antagonists.[4] However, ifenprodil also has high affinity for other receptors such as the adrenergic alpha-1A receptor. Based on the ifenprodil structure, a search for selective NR1A/NR2B antagonists was initiated.



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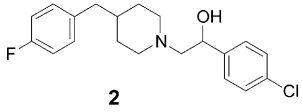

2

In our laboratories, the initial chemical leads such as ifenprodil and eliprodil (**2**) set the stage for discovering second generation NR2B antagonists. The common motif, or pharmacophore, shown in Figure 1 appeared to be a tertiary basic amine attached via linkers to aryl rings. The presence of both aryl rings, in which the A-ring was non-polar and the B-ring was polar with a

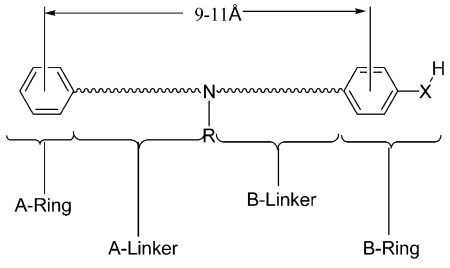

Figure 1.

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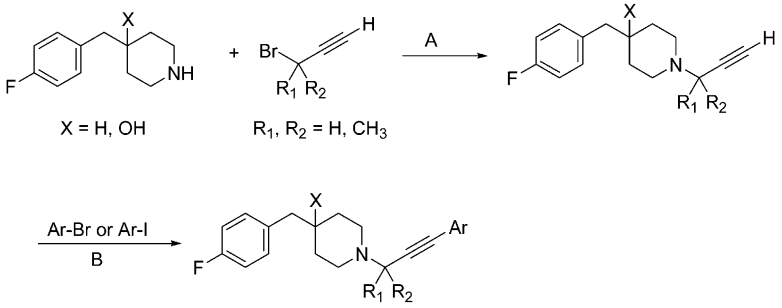
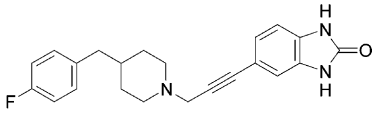
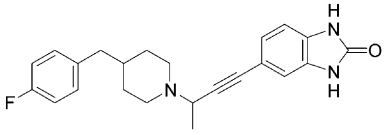
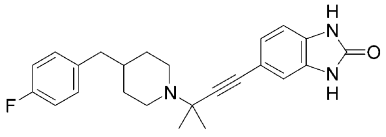
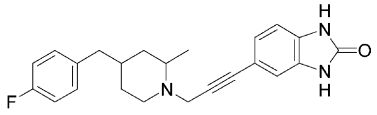
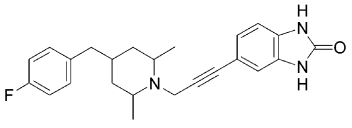
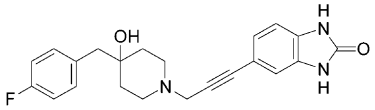
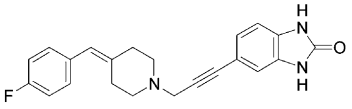
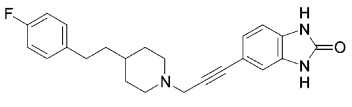
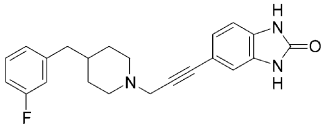
doi:10.1016/j.bmcl.2003.12.049



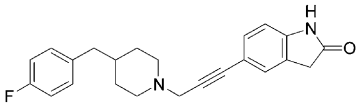
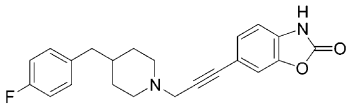
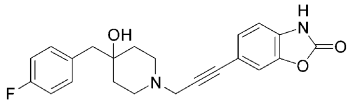
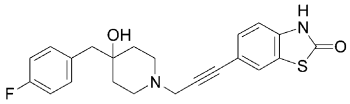
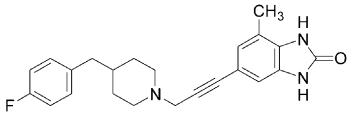
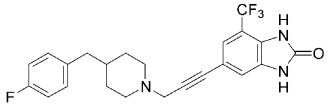
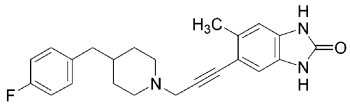
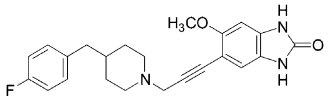
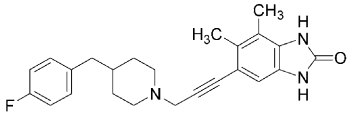
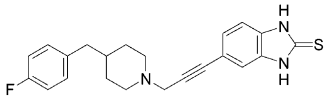
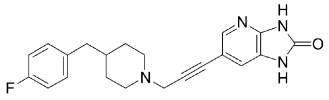
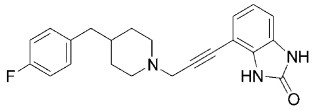
Scheme 1. (A) K_2CO_3, DMF, 60 °C; (B) $Pd(PPh)_3$, pyrrolidine, 60 °C; or $Pd(PPh)_2Cl_2$, CuI, Et3N, DMF, 80 °C.

Table 1. Planarity distortions and A-Ring modifications

No.	Structure	[^{3}H]-IFPNR IC_{50} (μM)[a]	6-OHDA, MED, mg/kg (PO)	FT, MED, mg/kg (PO)
3		0.003	Active at 10	Active at 10
4		0.100	NA	NA
5		>1	NA	NA
6		0.104	NA	NA
7		0.157	NA	NA
8		0.021	NA	NA
9		0.142	NA	NA
10		0.481	NA	NA
11		0.014	NA	NA

NA = Not active.
[a] IC_{50} Values reflect the average of 3 determinations.

Table 2. SAR of B-Ring analogues

No.	Structure	[^{3}H]-IFPNR IC_{50} (μM)[a]	6-OHDA, MED, mg/kg (PO)	FT, MED, mg/kg (PO)
12		0.056	NA	NA
13		0.015	NA	Active at 30
14		0.051	NA	Active at 30
15		0.024	NA	NA
16		0.020	Active at 30	NA
17		NA	NA	NA
18		0.004	NA	NA
19		0.009	NA	NA
20		0.031	NA	NA
21		0.019	NA	NA
22		0.002	NA	NA
23		0.284	NA	NA

NA = Not active.
[a] IC_{50} Values reflect the average of 3 determinations.

hydrogen bond donor, was necessary. In-house modeling studies suggested an optimal distance of 9-11 angstroms between the two rings and the distance of the basic nitrogen from either aryl ring was not well defined. Of the various classes of compounds examined, the focus of this paper will be specifically on NR1A/2B receptor antagonists containing an acetylenic linker between the A- and B-rings.

The general procedure used to synthesize the compounds shown in the accompanying tables is depicted in Scheme 1. Based on the overall metabolic profile of the compounds described in this communication it was important to have a fluoro group in the *para* position of the A-ring. Shifting the fluorine to the *meta* position (i.e., **11**) resulted in weaker NR2B activity. As indicated in Scheme 1, a variety of 4-(4-fluorobenzyl)-piperidine analogues[5] were alkylated with propargyl bromides to give the corresponding terminal alkynes. Palladium cross-coupling reactions with a variety of aryl bromides or iodides gave the desired products in moderate to good yields.[6]

The affinity of target compounds for the NR1A/2B receptor was determined by a ^{3}H-ifenprodil radioligand binding assay using native rat brains. Those compounds with desirable affinity were further tested for in vivo activity (PO or IP) in the unilaterally 6-hydroxy-dopamine (6-OHDA) lesioned rat model (a measure of anti-Parkinson's activity), and the formalin test (FT, a model of neuropathic pain).

It was interesting to note that compound **3** was the only compound that displayed efficacy in both the 6-OHDA and FT assays with nanomolar affinity in the ifenprodil binding assay. However, the in vivo activity in this compound could be limited due to its poor solubility. To optimize the in vivo activity and improve overall pK properties, extensive SAR studies were undertaken. The rationale here was to improve aqueous solubility by reducing the planarity as well as incorporating heteroatoms in the structural motif. The results are listed in Tables 1 and 2.

The non-planar compounds with conformationally constrained amines (**4**–**7**, Table 1) had significantly weaker NR2B binding than compound **3** indicating a preference for unconstrained amine. The branching away from the amine was better tolerated as demonstrated by the tertiary carbinol[7] (**8**) which had improved binding affinity in comparison to analogues **4**–**7**. However compound **8** was inactive in vivo. The benzylpiperidine motif for the A-ring and A-linker in compound **3** appears to be optimum since modifications with regard to unsaturation (**9**),[8] chain length (**10**),[9] and positioning of the fluorine atom (**11**) all resulted in reduced NR2B binding affinity.

SAR studies in the B-ring primarily focused on replacing the benzimidazolone moiety with other H-bond donor heterocycles. While the oxindole analogue (**12**) reduced binding affinity, the benzisoxazolone analogues (**13** and **14**) retained better binding affinity and were active in FT at 30 mg/kg PO.

Substitutions *ortho* to the B-linker in the phenyl B-ring (**18** and **19**) were well tolerated and resulted in highly active compounds whereas reduced activity was observed in compounds with substitutions *meta* to the linker (**16** and **17**). The 7-azabenzimidazolone analogue, **22**, had similar NR2B affinity as **3** but was inactive in all the in vivo models similar to **18** and **19**. We believe the poor in vivo activity of **18**, **19**, and **22** is due to their relative insolubility, resulting in poor absorption. Further B-ring modifications such as the thiourea analogue (**21**) and attachment of the linker at the 4-position of the benzimidazolone (**23**)[10] showed no advantage indicating the preference for a linear motif.

Compound **3** was identified as a highly selective NR1A/2B receptor antagonist with good efficacy in models of Parkinson's disease and neuropathic pain. SAR studies around the structural motif of **3** indicated that conformationally constrained A- and B- linkers offered no significant advantages over **3** in vitro and in vivo. Alterations within the B-ring resulted in compounds with excellent potency in vitro, however, in vivo activity remains elusive. Further work is in progress to optimize the in vivo activity.

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10. Prepared from coupling with 4-bromo-1,3-dihydrobenzimidazol-2-one, which was made via nitration of 2-bromoacetanilide and separation of the desired 2-bromo-6-nitroacetanilide according to the procedure described in *J. Chem. Soc.* **1928**, 3092.