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Competitive NMDA Receptor Antagonists:

(R)-4-Oxo-5-phosphononorvaline Structure-Activity Relationships

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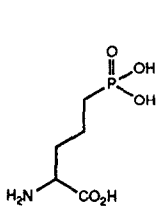
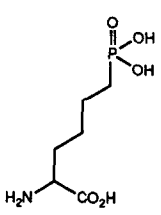
Abstract: *The synthesis of methylated analogs of (R)-4-oxo-5-phosphononorvaline (4) led to antagonists of reduced binding potency. In contrast, oxime derivatives, including the relatively bulky O-benzyloxime analog, proved to be essentially equipotent with the parent compound.*

N-Methyl D-aspartic acid (NMDA) antagonists are neuroprotective during abnormal physiological conditions, such as stroke and trauma, and offer potential treatment for long-term neurodegenerative diseases such as Huntington's chorea[1]. For these compounds to be truly effective in the clinic, in addition to being able to block the action of the endogenous excitatory amino acids (glutamic and aspartic acid), they must be able to cross membranes, such as the blood brain barrier, and preferably, for stroke and trauma, have a fast onset of action. Over the past decade, phosphonoamino acids have been fully evaluated in this regard and found to be effective in blocking the glutamate site of the NMDA receptor but, presumably due to their highly polar nature, the first generation compounds, such as AP5 (1), were poorly transported to the brain[2].

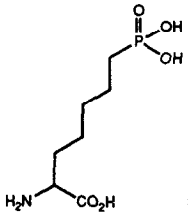
A number of approaches have been tried in order to design new, competitive NMDA antagonists with improved in vivo profiles. For example, the cyclic analogs CGS 19755[3] and CPPene[4], as well as the deceptively simple alicyclic analogue CGP 37849[5], all have been reported to be active in models of epilepsy and stroke[1]. On initial inspection, this would appear to be due to the increase in lipophilic character of these molecules which helps to offset the polar nature of the phosphonoamino acid and assists in their passage across various membranes. Other factors, though, may be important. For example, we have demonstrated that the less lipophilic β-ketophosphonates also have improved bioavailability. MDL 100,453 (4) was designed, in part, from a computer aided molecular modeling study in which we developed a pharmacophore for this class of competitive, NMDA receptor antagonist[6,7].



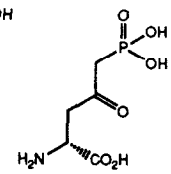
1, AP5



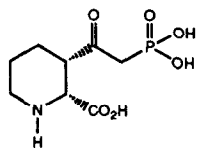
2, AP6



3, AP7

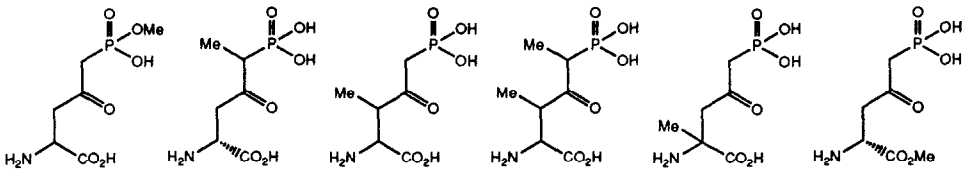


4, MDL 100,453



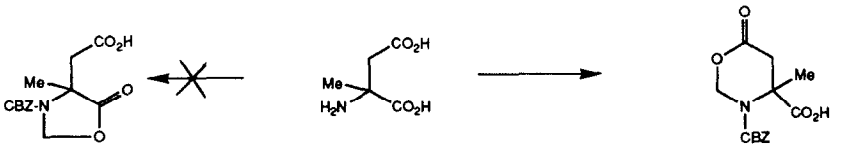
5, MDL 100,925

In order to more fully understand the topography of the glutamic acid binding site, we have systematically explored methylation of the basic MDL 100,453 (4) structure. Thus, methyl groups have been introduced into the positions shown in structures **6-11** with the hope of delineating sterically restricted sites and perhaps uncovering any lipophilic regions within the receptor pocket of which we might take advantage[14].

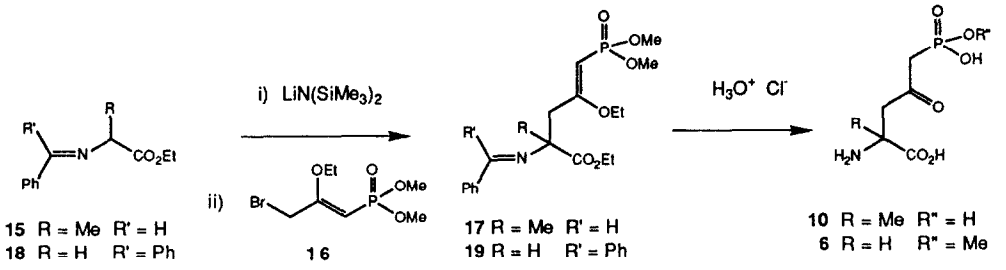


6 **7** **8** **9** **10** **11**

The syntheses of **7**, **8**, and **9** were accomplished in straightforward manner by adopting our published procedure of **4**[7]. Thus, the appropriate aspartic acid derivative was protected as the oxazilidone, then converted to the acid chloride which was coupled to dimethyl lithium alkylphosponate via a cuprate-catalyzed reaction. Problems were encountered when attempting to protect **12** on route to the α-methyl-substituted analog **10**, Rather than form the desired oxazilidone **13**, the formaldehyde in the reaction medium preferentially reacted with the distal carboxylic acid group to form the non-productive six-membered ring **14**[8]. This problem was avoided by selecting different protective groups. Thus, the Schiff base (**15**), formed from alanine and benzaldehyde, was deprotonated with lithium *bis*(trimethylsilyl)amide and alkylated with dimethyl 3-bromo-2-ethoxy-propenyl phosphonate (**16**)[9] to yield **17** in good yield; deprotection readily afforded **10**. Similarly, the monomethyl phosphonate **6** was synthesized by alkylation of the anion derived from the Schiff base (**18**) with **16**, followed by acid catalyzed, selective deprotection (1M aq. HCl, reflux). Finally, the methyl ester **11** was prepared in straightfoward manner from MDL 100,453 (4) using refluxing methanolic HCl[13] .



13 **12** **14**

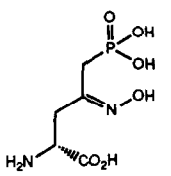


15 R = Me R' = H
18 R = H R' = Ph

16

17 R = Me R' = H
19 R = H R' = Ph

10 R = Me R" = H
6 R = H R" = Me



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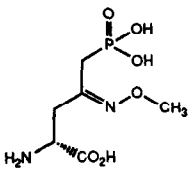
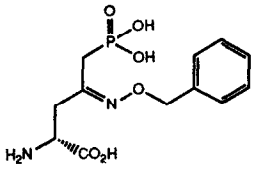


21



22

When the binding potencies of analogs 7-10 for the NMDA site of the glutamate receptor complex were evaluated using rat brain cortical membranes in a competitive assay with [^{3}H]-CPP as the radioligand[10], it was clear that α, β and δ methyl substitution all led to decreased binding affinity (Table). Consistent with observations from other laboratories, the methyl esters 6 and 11 were also less active than the parent compound. The fact that the β-substituted derivative 8 had a relatively low binding affinity compared to the cyclic analog MDL 100,925 (5)[11] no doubt reflects the fact that the β-substituent in the flexible acyclic molecule prefers to occupy a sterically forbidden region of the receptor pocket.

Since it appeared that the binding potency and relatively good bioavailability of MDL 100,453 (4) could be related to the β-keto functionality and, possibly, to one of the possible tautomeric forms[7], we sought to modify the ketone with similar, less readily enolizable groups[12]. Thus we targeted the oximes 20-22 which were synthesized by standard procedures[15]. Surprisingly, competitive binding assays revealed that the simplest oxime (20) was only slightly less active than the parent β-ketophosphonate 4. Furthermore, the substituted oximes (21, 22) were similar in potency to 20 which is in distinct contrast to the effect of methyl group substituion on 4.

This limited structure-activity study, which was intended to explore a few obvious substitutions of the lead compound 4, has led instead to a number of new questions. The results clearly show that the NMDA receptor is sensitive to many steric restraints. However, the data which shows that the oximes 20 and 22 are equipotent with 4 in a binding assay would appear to rule out the importance of tautomerism to binding potency. We are currently evaluating the in vivo activity of these analogs. A surprising observation from this study is that the large benzyl oxime functionality (22) is tolerated in the receptor binding pocket in contrast to the severe restraints imposed at other positions of the backbone. We are continuing to explore other groups in this regard.

TABLE

Compound	IC_{50} Values[a] µM	Compound	µM
4	0.11	10	20.0
6	5.0	11	1.7
7	1.8	20	0.2
8	7.0	21	0.6
9	< 100.0	22	0.5

[a]. IC_{50} values determined from competitive binding assays[10].

References and Notes

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8) Shown by NMR comparison with the oxazilidones from the rest of the series.
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13) Yields: 12-14, 87%; 15-17 53%; 17-10, 78%: 18-19, 47%; 19-6, 32%.
14) Stereochemistry of the compounds are as indicated in the diagrams.
15) Prepared from (*R*)-4-oxo-5-phosphononorvaline to give a mixture of the syn and anti oxime.