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SYNTHESIS AND CHARACTERIZATION OF PHOSPHONIC ACID-SUBSTITUTED AMINO ACIDS AS EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

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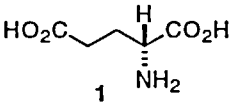
Abstract Decahydroisoquinoline-3-carboxylic acids, substituted at C-6 with an acidic moiety such as a phosphonic, sulfonic or carboxylic acid or tetrazole, were prepared as antagonists of excitatory amino acid (EAA) receptors.

Glutamic acid (1) is the major excitatory neurotransmitter in the central nervous system, acting at a number of subclasses of excitatory amino acid (EAA) receptors. *N*-methyl-D-aspartic acid (NMDA) and 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propanoic acid (AMPA) EAA receptors are coupled to ion channels, and signals are transduced through depolarizations resulting from changes in calcium and sodium ion concentrations.[1] It has been postulated that antagonists of NMDA and AMPA receptors may be useful therapeutic agents in the treatment of epilepsy,[2] cerebral ischemia,[3] head[4] and spinal cord trauma,[5] and chronic neurodegenerative disorders such as Alzheimer's[6] and Parkinson's disease.[7]



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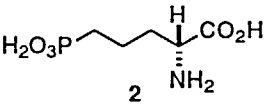

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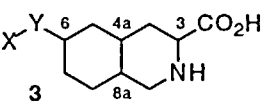

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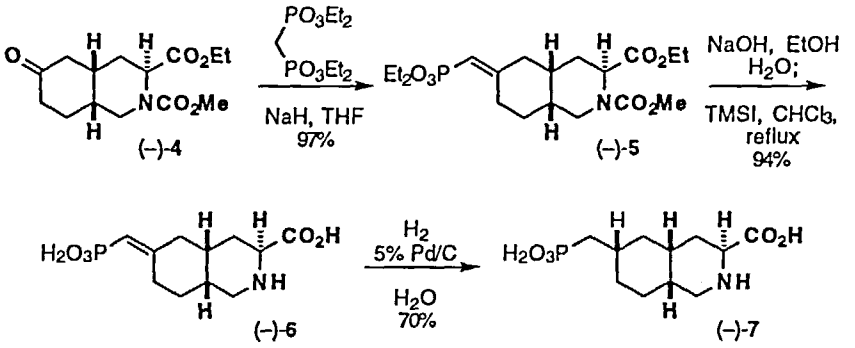
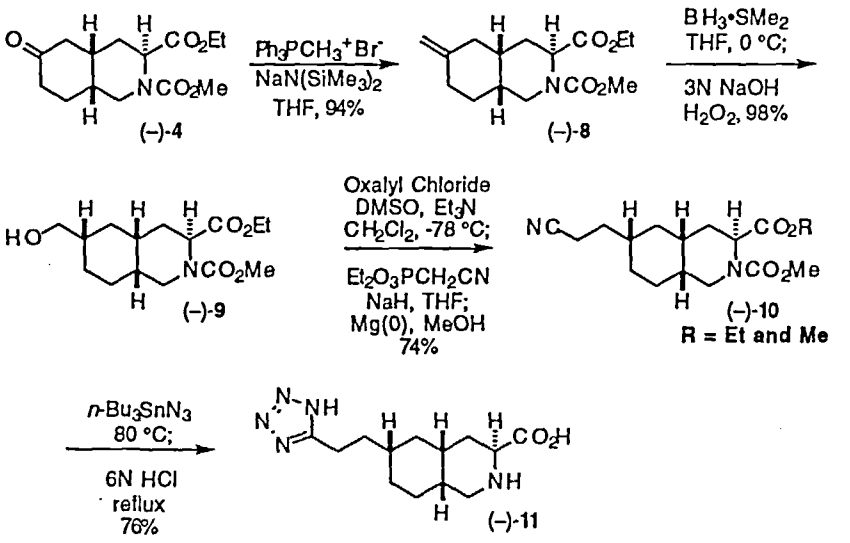
Elongation of the chain connecting the two acidic moieties, conversion of the distal acid to the bioisosteric phosphonic acid, and inversion of the amino acid from *S* to *R* yielded the potent, selective and competitive NMDA antagonist 2*R*-2-amino-5-phosphonopentanoic acid (2, 2*R*-AP5).[8] A significant limitation of this compound and its congeners, however, was their lack of potency following systemic administration. It was therefore the goal of our medicinal chemistry research to identify novel structures that were more potent and afforded better bioavailability. We incorporated the AP5 substructure, which identified the minimum structural

requirements for NMDA antagonist activity, into a variety of cyclic systems. It was our hope that the conformational constraint of a cyclic system would provide a structure whose potency increased because the bioactive conformation was more readily attained. In the distal acid position, we incorporated the phosphonic acid, which provided a significant increase in potency and selectivity in the SAR of **2**. We also examined other acid bioisosteres (e.g., sulfonic acid and tetrazole) which we hoped would be as beneficial as a phosphonic acid. Of the cyclic systems that we investigated, a series of 6-substituted decahydroisoquinoline-3-carboxylic acids (**3**) were the most fruitful in providing potent, subclass selective EAA antagonists.



Scheme 1 Synthesis of the phosphonic acid-substituted NMDA antagonist (–)-7



Scheme 2 Synthesis of the tetrazole-substituted AMPA antagonist (–)-11

The structure activity studies of 3[9,10,11] looked at a number of different features. We varied stereochemistry, preparing six of the eight possible diastereomeric pairs; examined the effects of varying the distal acid isostere X; and varied the chain Y that connects the acid X to the bicyclic nucleus, both in terms of length of the tether (one to four atoms) and substitution along the chain with heteroatoms (N, O and S). The syntheses of these amino acids were reported,[9-13] and the stereoselective syntheses of (–)-7 (LY235959) and (–)-**11** (LY293558) are shown in Schemes 1 and 2, respectively, as representative examples from this series. The novel amino acids prepared were evaluated for affinity at NMDA and AMPA receptors using selective radioligand binding assays;[9,10,11] for antagonist potency in a cortical slice preparation;[9,10,11] and in vivo in mice versus NMDA-induced lethality and maximal electroshock induced convulsions.[9,10,11]

Of the different diastereomers prepared, compounds whose relative stereochemistry corresponded to 7 and **11** were the most potent.[9,10] When these amino acids were resolved, activity was found to reside in the isomer whose absolute stereochemistry corresponds to the isomer shown in Schemes 1 and 2 for (–)-7[11] and (–)-**11**,[10] respectively. With a single methylene spacer between the distal acid moiety and the bicyclic nucleus, compounds were selective NMDA antagonists.[9] With an ethylene spacer, compounds were AMPA antagonists.[10] One of the more interesting aspects of this SAR was evident when one examined the nature of the distal acid group relative to potency at either NMDA or AMPA receptors. Figure 1 shows a number of compounds from this SAR that are identical except for their distal acid substitution. For compounds with a methylene spacer, substitution with a phosphonic acid (7) at the distal acid position imparted high affinity and antagonist potency at NMDA receptors; the tetrazole (**13**) was nearly as potent an NMDA antagonist as its phosphonic acid substituted counterpart. Interestingly, the analogous compounds substituted with either a sulfonic acid (**14**, P.L. Ornstein, unpublished results) or a carboxylic acid (**16**) were significantly less potent as NMDA antagonists. We were surprised by this finding, considering that a sulfonic acid is similar in structure and acidity to a phosphonic acid, and a carboxylic acid is similar in structure and acidity to a tetrazole. For compounds with an ethylene spacer, the most potent AMPA antagonist activity was observed for the tetrazole-substituted compound **11**. The sulfonic acid-substituted compound **14** was less potent, the carboxylic acid compound **17** significantly less potent, and the phosphonic acid-substituted compound **12** was inactive (P.L. Ornstein, unpublished results). As in the NMDA SAR, no logical connection exists between activity and the nature of the distal acid moiety.

The phosphonic acid substituted amino acid **7** is a potent, selective NMDA antagonist that is active in animals following systemic and oral administration.[14] This compound also protects against excitatory amino acid-induced neuronal degeneration in animals,[14] and thus has the therapeutic potential to serve as a neuroprotective agent.

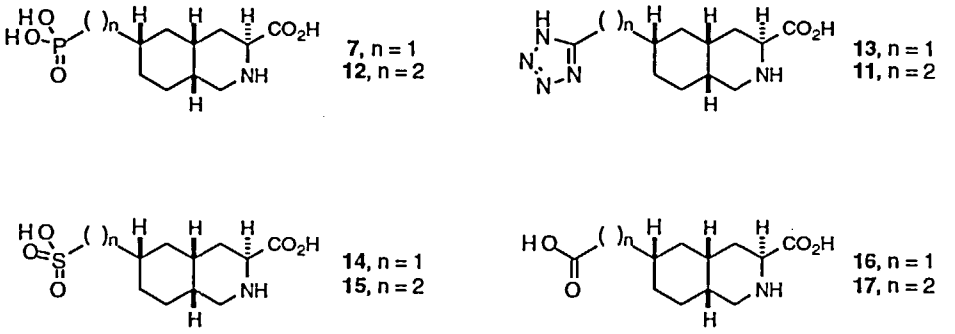


Figure 1 6-Substituted decahydroisoquinoline-3-carboxylic acid SAR

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