Synthesis of Potential Agonists and Antagonists for Central Glutamate Receptors by a Novel 'Ring Switching' Process

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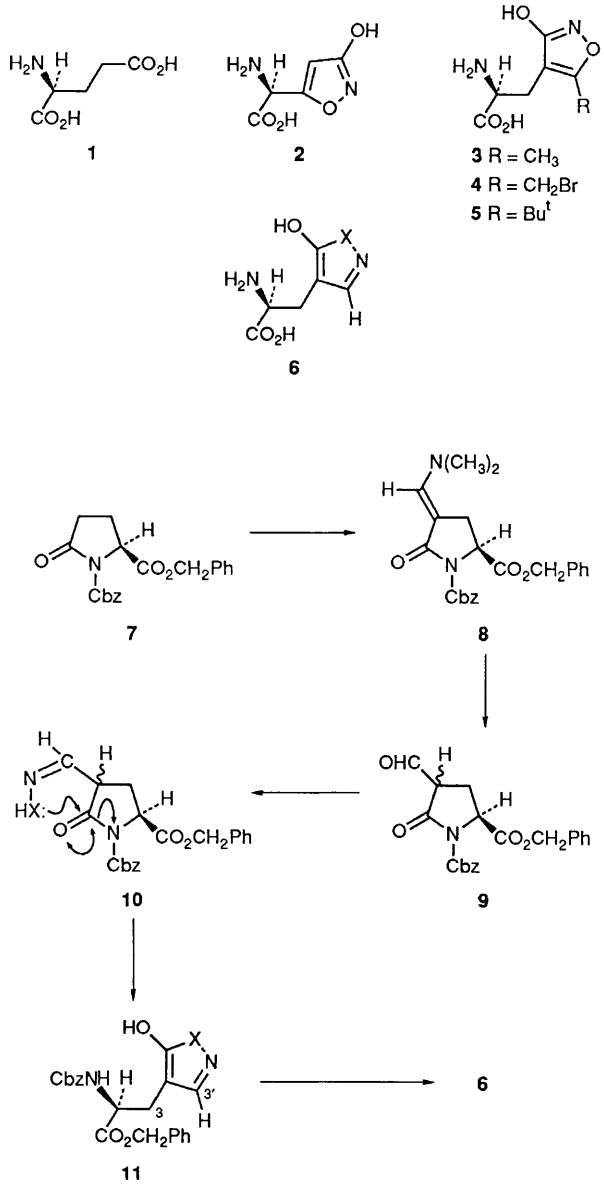
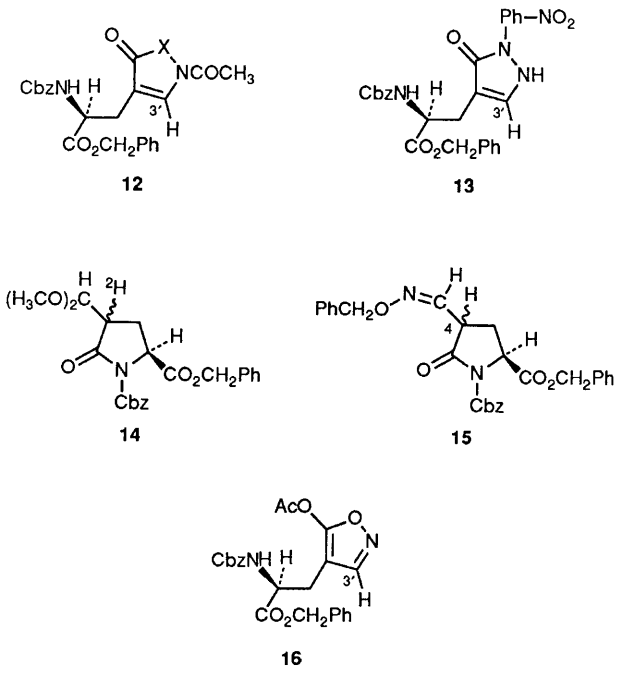
Heterocyclic derivatives **6** of (*S*)-glutamic acid, which are structurally related to key central nervous system (CNS) glutamate receptor agonists, are prepared from the aldehyde **9** using a novel reaction in which the pyroglutamate ring is cleaved in concert with formation of the new heterocyclic ring.

Excitatory amino acid receptor agonists and antagonists are of major interest as tools for investigating central nervous mechanisms and as potential drugs for CNS disorders.[1] The amino acid (*S*)-glutamic acid **1** is a major excitatory neurotransmitter in the CNS and its structural analogues can act as agonists and antagonists at a variety of CNS receptor sites.[2] The discovery that ibotenic acid **2**, the active component of the psychotropic fly agaric mushroom *Amanita muscaria Fr.*, had potent neuroexcitatory properties led to the synthesis of a variety of heterocyclic analogues of glutamic acid. Many of these compounds had specific CNS properties and investigation of their neurophysiological properties allowed a classification of central excitatory amino acid receptors to be made. Whereas ibotenic acid **2** seems to activate aspartate receptors, the synthetic glutamate analogue α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA, **3**) is a potent and specific glutamate agonist[2b,3] as are its derivatives **4** and **5**.[4]

Synthesis of heterocyclic glutamate agonists has become a field of great importance and yet to date the methods used have invariably involved simple, routine amino acid syntheses based on a heterocyclic building block and resulting in racemic products.[3–10] The resolution of these racemates[11,12] showed, not unexpectedly, that it is the (*S*)-isomer that is the more potent agonist. A synthesis of enantiomerically pure material





would, therefore, seem appropriate. We now report a synthesis that allows easy access to a series of enantiomerically pure heterocyclic glutamate derivatives of general formula **6** and which involves a novel and interesting 'ring switching' reaction.

Pyroglutamic acid was used to provide the (*S*)-stereochemistry of the glutamate analogues and benzyl *N*-benzyloxycarbonylpyroglutamate **7**[13] was converted to the enamine **8** using *tert*-butoxy-bis(dimethylamino)methane following the method of Danishefsky.[14] We had shown[15] that this enamine could be hydrolysed to the aldehyde **9** under very carefully controlled acidic conditions and so this aldehyde was prepared *in situ* in methanol and treated either directly at pH 1 or buffered at pH 5 with a variety of α-nucleophiles at room temperature.

When the reaction was conducted at pH 5 with methylhydrazine, TLC initially showed the presence of two new compounds but one was converted to the other within 15 h. The final product was obtained in 80% yield and was further purified by chromatography to give a gum, $[\alpha]_D^{24}$ −8.3° (*c* 0.35, $CHCl_3$), $C_{22}H_{23}N_3O_5$.† Loss of the absorption due to the imide in the IR spectrum at ν_{max} 1791 cm^{-1} indicated that the pyroglutamate ring had opened and the structure **11**, X = NMe was assigned to the compound. This was confirmed by the other spectra. The ^1H NMR spectrum in $[^2H_6]DMSO$ showed the $-NHCHCH_2-$ system to be a two proton AB system centred at δ 2.68 coupled to the amino acid α-proton multiplet at δ 4.17. This latter multiplet was coupled to an NH doublet at δ 7.9, which disappeared on addition of ^2H_2O. The 3′-H proton of the pyrazole ring appeared as a singlet at δ 7.07 and ^{13}C NMR, UV and IR spectra were in keeping with the compound being the enol tautomer **11**.

Acetylation of the enol **11**, X = NMe using acetic anhydride and dimethylaminopyridine in acetonitrile at room temperature gave an acetamide $C_{24}H_{25}N_3O_6$.† The spectra of the product indicated that it was the acetamide **12**, X = NMe. The longer chromophore in the UV spectrum at λ_{max} 332 nm (**11**, X = NMe had λ_{max} = 254 nm) and the 13% NOE observed in the singlet at δ 8.17 for H-3′ in the ^1H NMR spectrum when the acetamide methyl at δ 2.31 was irradiated were particularly convincing evidence of this point.

When the aldehyde **9** was treated *in situ* with hydrazine hydrate or phenylhydrazine at pH 5 similar reactions were observed, intermediate compounds being converted to **11**, X = NH† and **11**, X = NPh† respectively in good yields and with spectra in keeping with those found for **11**, X = NMe. In view of the greater scope for tautomerism of **11**, X = NH, it was not possible to be so certain of the precise tautomer obtained and the product of monoacetylation,† although evidently an amide from the IR spectrum, did not show the NOE exhibited by the acetamide **12**, X = NMe.

Use of *p*-nitrophenylhydrazine at pH 5 gave the analogous heterocyclic compound **11**, X = $N–C_6H_4–NO_2$† in good yield. The UV spectrum of the pyrazole, λ_{max} 327 nm, was more in keeping with it being the amide tautomer **13** than the enol found in the other cases and amide bands at ν_{max} 1683 and 1637 cm^{-1} in the IR spectrum were in keeping with this assignment. Acetylation gave the acetamide **12**, X = $NC_6H_4NO_2$† which showed an NOE between the pyrazole H-3′ absorption and the acetamide methyl absorption in the ^1H NMR spectrum. The intermediate compound observed on TLC in the course of preparation of **11**, X = $N–C_6H_4–NO_2$ was the only product when the reaction

† The compounds had satisfactory analytical and spectroscopic data.

was conducted at pH 1 and the spectra indicated that it was the *p*-nitrophenylhydrazone **10**, X = N–C_6H_4–NO_2† obtained as a mixture of stereoisomers. Reaction of the aldehyde **9** with 2,4-dinitrophenylhydrazine at either pH 1 or 5 gave only the 2,4-dinitrophenylhydrazone **10**, X = $NC_6H_3(NO_2)_2$† as a 2 : 1 mixture of stereoisomers and it proved impossible to convert this to the 'ring switched' product **11**.

It is evident from the above results that substituted hydrazines react with aldehyde **9** to yield intermediate hydrazones **10**, which may then undergo a concerted ring opening/closure reaction to yield the heterocyclic glutamate derivatives. Although all products exhibited optical rotations, we checked that the chiral centre remained intact in the process by repeating the reaction with hydrazine hydrate using ^{2}HCl and MeO^{2}H. Although in this case the major product appeared to be the acetal **14**, the pyrazole **11**, X = NH obtained showed no incorporation of deuterium by mass spectrometry, and ^{2}H and ^{1}H NMR spectroscopy.

Reaction of the aldehyde **9** with hydroxylamine at pH 5 gave a product that proved to be rather unstable but had spectra consistent with its having the structure **11**, X = O. There was no sign of the intermediate oxime **10**, X = O on TLC, although reaction with *O*-benzylhydroxylamine gave the corresponding *O*-benzyl derivative **15**† as a mixture of 4*R*, 4*S*, and *syn* and *anti* isomers. When the isoxazole **11**, X = O was acetylated immediately after formation, the corresponding acetate **16** proved to be considerably more stable and, unlike the acetamide **12** of the pyrazole series, appeared to be an enol acetate with ν_{max} 1771 cm^{-1} and no amide absorption in the IR spectrum.

Having developed a route to heterocyclic derivatives of glutamic acid, we now deprotected **11**, X = NH and **11**, X = NMe by hydrogenation in glacial acetic acid using Adams catalyst. The products **6**, X = NH,† $[\alpha]_D^{24}$ −37.7° (*c* 0.48, H_2O), and **6**, X = NMe,† $[\alpha]_D^{24}$ −55.5° (*c* 0.51, H_2O), had the expected spectra.

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