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Synthesis of Glutamate Agonists and Antagonists by a Ring Switching Strategy

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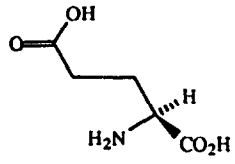
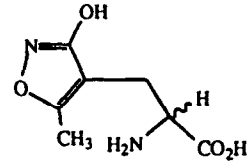
Abstract : Our ring switching strategy for synthesis of compounds with structural features consistent with activity at glutamate receptors has been modified to prepare L-alanine derivatives substituted at the β-carbon atom with six-membered heteroaromatic rings. The pyrimidinone (**11**, R = R^1 = R^2 = H) has been shown to be a glutamate agonist and the compound (**13**) to be an antagonist.

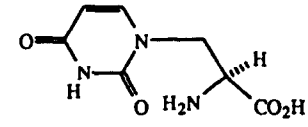
Since the excitatory action of L-glutamic acid (**1**) on single neurones in the CNS was first demonstrated by Curtis in 1959,[2] a number of structurally related amino acids have been tested as agonists and antagonists. This led to the realisation that there were several different sub-types of glutamate receptors. The implication of these receptors in memory processes and Alzheimer's disease[3] and the potential of excitatory amino acid antagonists in anti-epileptic therapy[4] and stroke prevention[5] has initiated a great interest in the field. The AMPA receptor was first identified when the parent compound (RS)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid [AMPA, (**2**)] was prepared.[6] The 3-hydroxyisoxazole moiety acts as a bioisostere of the γ-carboxyl group of (S)-glutamic acid (**1**) in this compound, and this led to the synthesis[6-12] of a variety of heterocyclic analogues of glutamic acid. These syntheses were lengthy and led to racemic products. When the enantiomers were separated, it was found that there was pronounced receptor stereoselectivity with compounds of the L-configuration often being the more active.[13-15] Synthesis of conformationally restricted analogues has led to some understanding of the spatial requirements of the receptors.[16] The naturally occurring heterocyclic amino acid willardiine (**3**) also appears to exert its excitatory effects *via* activation of AMPA receptors.[17,18]



(**1**)



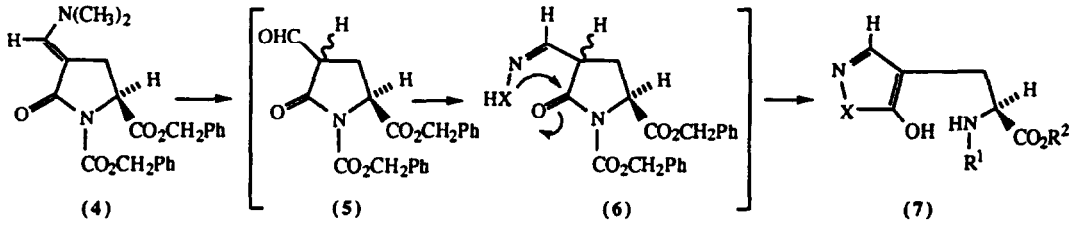
(**2**)



(**3**)

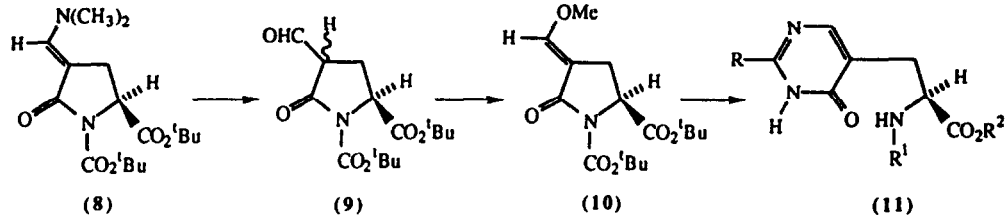
Because of the lack of versatility and large number of steps in the existing syntheses of AMPA agonists and antagonists, and the fact that these syntheses led to racemates, we devised the more versatile synthesis shown in Scheme 1, using the protected 4-formyl-(2S)-pyroglutamic acid ester (**5**), formed *in situ* from the corresponding enaminone (**4**), as starting material.[19] This involved developing a novel "ring switching" approach in which reaction of the aldehyde (**5**) with an *alpha*-nucleophile such as hydroxylamine or a substituted hydrazine gave rise to the protected hydroxyisoxazole (**7**, R^1 = Cbz, R^2 = CH_2Ph, X = O) or to the protected hydroxypyrazoles (**7**, R^1 = Cbz, R^2 = CH_2Ph, X = NR), *via* the unstable intermediate oxime or hydrazones (**6**). On deprotection, the optically pure (2S)-amino acids (**7**, R^1 = R^2 = H, X = NH) and (**7**, R^1 = R^2 = H, X = NMe) were tested for activity and found to demonstrate an inhibitory effect on ibotenate stimulated phosphoinositide response.[20] Subsequent to our synthesis of these compounds, the anti-fungal antibiotic TAN-

950, isolated from culture filtrates of *Streptomyces platensis* A-136 was shown to be the isoxazole (**7**, R^1 = R^2 = H, X = O) which exhibited affinity for excitatory amino acid receptors in the rat brain.[21]



Scheme 1

Because of the reported activity of willardiine (**3**) at glutamate receptors,[17,18] synthesis of isomers of this compound was of interest. We therefore attempted to extend our methodology to six-membered heteroaromatic compounds by reacting the poorer nucleophiles urea, thiourea and guanidine directly with the aldehyde (**5**), prepared *in situ*. This method proved ineffective and so an alternative approach was sought. Acid hydrolysis of the enaminone (**8**)[22] gave the aldehyde (**9**) which, on treatment with diazomethane, gave the enol ether (**10**),† m.p. 98 - 99 °C, $[\alpha]_D$ -17. 7 ° (*c* 1.1, $CHCl_3$), λ_{max} 263 nm, in 60 % overall yield. Attempts to form useful "ring-switched" products by reacting this with urea, thiourea or guanidine failed but, on heating the enol ether (**10**) with acetamidine hydrochloride and K_2CO_3 in ethanol at reflux, the 2-methylpyrimidin-4-one (**11**, R = Me, R^1 = Boc, R^2 = ^{t}Bu),† m.p. 128 - 130 °C, $[\alpha]_D$ -39. 5 ° (*c* 0.5, $CHCl_3$), was obtained in 87 % yield. The ^{1}H NMR spectrum showed the expected exchangeable NH absorption coupled to the α-amino acid proton, a feature which was not present in the spectrum of the starting material and the imide absorption at 1759 cm^{-1} in the IR spectrum of the starting material was no longer present. The UV spectrum exhibited λ_{max} 276 nm, reversibly shifting to λ_{max} 263 nm on addition of acid, which was consistent with the behaviour expected of a 2,5-dialkylpyrimidin-4-one.[23] The ^{1}H NMR spectrum showed the presence of a second compound (*ca.* 20% by integration) in spite of its sharp melting point, analytical purity and apparent chromatographic homogeneity. The spectrum associated with the minor component at room temperature in [$^2H_6$]-DMSO coalesced with that of the major component at 80 °C in this solvent, suggesting the presence of two conformational isomers. When either the aldehyde (**9**) or the enaminone (**8**) was used in this synthesis, the pyrimidinone (**11**, R = Me, R^1 = Boc, R^2 = ^{t}Bu) was obtained but in lesser yield than in the reaction with the enol ether (**10**).

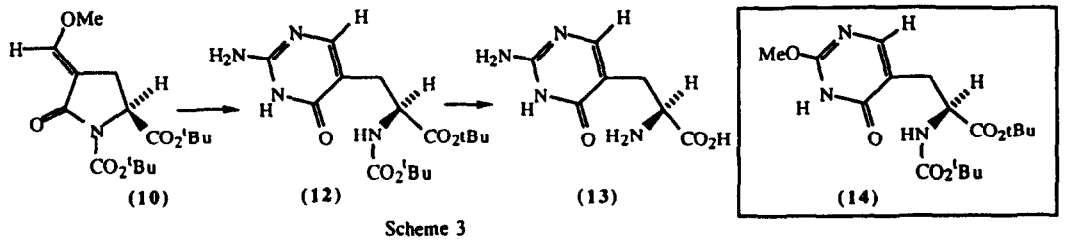


Scheme 2

Reaction of the enol ether (**10**) with benzamidine hydrochloride and with formamidine acetate under the conditions used in the reaction of the enol ether with acetamidine hydrochloride above, gave the pyrimidinones (**11**, R = Ph, R^1 = Boc, R^2 = ^{t}Bu),† m.p. 188 - 189 °C, $[\alpha]_D$ +14. 5 ° (*c* 1.3, $CHCl_3$), and (**11**, R = H, R^1 = Boc, R^2 = ^{t}Bu),† $[\alpha]_D$ -19. 7 ° (*c* 2.6, $CHCl_3$), in 55 % and 76 % yields respectively. Both compounds had spectra in keeping with those of the methyl analogue (**11**, R = Me, R^1 = Boc, R^2 = ^{t}Bu), including the variable temperature ^{1}H NMR spectral effect ascribed to conformational isomerism. All three pyrimidinones were cleanly deprotected by treatment with concentrated HCl at room temperature, giving the hygroscopic amino acid hydrochlorides (**11**, R^1 = R^2 = H, R = Me),† (**11**, R^1 = R^2 = H, R = Ph)† and (**11**, R^1 = R^2 = R = H).† The compound (**11**, R = H) was tested[24,25] for activity and found to be a

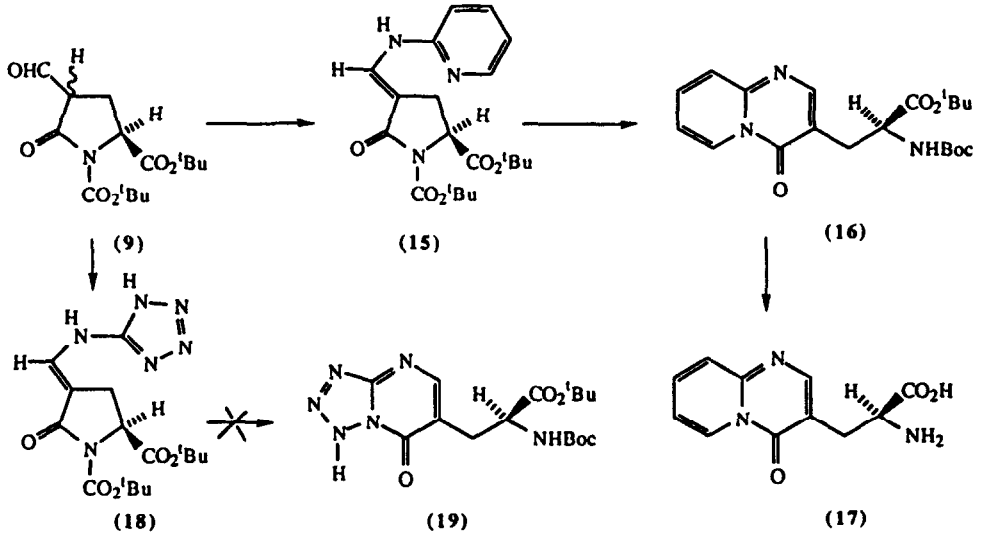
glutamate agonist, and a single crystal X-ray structure analysis[26] confirmed the structure as that of the dihydrochloride monohydrate, with the pyrimidinone protonated on N_1.

The enol ether (**10**) did not react with guanidine hydrochloride and potassium carbonate at reflux in ethanol but, on heating it with guanidine carbonate at reflux in ethanol, a mixture of two compounds could be obtained. One of these proved to be the desired 2-aminopyrimidinone (**12**),† $[\alpha]_D$ -74 ° (*c* 2.4, $CHCl_3$), in 39 % yield. This showed the variable temperature ^1H NMR spectral effects exhibited by the related compounds in the series, and it was deprotected using concentrated HCl at room temperature to yield the amino acid hydrochloride (**13**),† m.p. 210 °C (decomp.), $[\alpha]_D$ -2. 9 ° (*c* 1.8, H_2O), which was a weak antagonist to ACPD at the metabotropic receptor.[24, 25] Attempts to prepare the 2-methoxypyrimidinone (**14**) by reacting the enol ether (**10**) with O-methylisourea seemed to be partly successful from the ^1H NMR spectrum of the crude product but this could not be purified.



Scheme 3

In an attempt to extend the synthesis to polycyclic aromatic analogues of glutamate agonists and antagonists, the enol ether (**10**) was heated with 2-aminopyridine at reflux in ethanol but no reaction was observed. On reacting the aldehyde (**9**) with 2-aminopyridine in dioxane at reflux, however, a product was obtained in 68 % yield. This still retained the imide absorption due to the N-*tert*-butoxycarbonylpyroglutamate system in the IR spectrum and microanalytical and spectral data indicated that it was the enaminone (**15**),† m.p. 186 - 188 °C (decomp.), $[\alpha]_D$ +0. 5 ° (*c* 0.7, $CHCl_3$), λ_{max} 287 and 335 nm. This compound was heated at reflux with potassium carbonate in ethanol to yield the desired pyrido[1, 2-a]pyrimidine (**16**),† m.p. 78 - 79 °C, $[\alpha]_D$ -39.2° (c 0.5, $CHCl_3$), λ_{max} 242 and 339 nm, in 55 % yield. Deprotection with concentrated HCl at room temperature gave the hydrochloride of the amino acid (**17**),† $[\alpha]_D$ -3. 9 ° (*c* 1, H_2O), in quantitative yield.



Scheme 4

In an attempt to obtain the fused ring system (**19**), we first heated the 4-formylpyroglutamate (**9**) with aminotetrazole at reflux in dioxane and obtained the enaminone (**18**),† m.p. 183 °C (decomp.), λ_{max} 297 nm, in 70 % yield. A number of attempts were made to convert this compound to the pyridotetrazole (**19**) by the ring switching reaction but none was successful.

Acknowledgements

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† These compounds had the expected analytical and spectroscopic properties.

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