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A new direct synthesis of ACPA and novel AMPA analogues

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Abstract—A novel synthesis of the potent glutamate neurotransmitter agonist (*RS*)-2-amino-3-(3-carboxy-5-methyl-4-isoxazolyl) propionic acid (ACPA) provides access to numerous analogues as drug candidates for neurological disorders. The one-pot synthesis of an alpha amino phosphonate from aldehyde **4** was successful using $ErCl_3$ as a catalyst. Molecular modeling of the new amino phosphonic acid with the (*RS*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid (AMPA) receptor crystal structure suggests this should be an effective receptor binder.

1. Introduction

The ionotropic glutamate receptors (iGluRs) are multimeric proteins which mediate excitatory neuronal transmission via ligand-induced cation channels within the central nervous system. The iGluRs play an important role in neurological processes such as memory, learning, and neural plasticity.[1] Excitatory imbalance of these receptors is thought to be the primary culprit in, or related to, a wide range of neurological disorders including epilepsy,[2] cerebral ischemia,[3] schizophrenia,[4] as well as neurodegenerative pathologies such as, Parkinson's[5] and Alzheimer's[6] diseases. Analogues of the (*RS*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid (AMPA) receptor subtype (GluR1-4) are a priority in light of initial findings, which suggest antagonists could mitigate the neurodegenerative effects of cerebral ischemia and agonists may be of use for the treatment of Alzheimer's disease.[1,6] The synthetic agonist (*RS*)-2-amino-3-(3-carboxy-5-methyl-4-isoxazolyl) propionic acid (ACPA) was shown to be more active than AMPA itself in binding the AMPA receptor.[7]

In previous studies a number of agonists and antagonists were developed, which allowed for the pharmacological characterization and structure–activity studies of iGluR subtypes; however, very few compounds have the requisite binding affinity and subunit specificity to make them viable drug candidates.[1,8]

2. Discussion

Using the crystal structure of an AMPA receptor binding domain (GluR2) occupied by kainate,[9] molecular docking analysis of ACPA was performed using the InsightII® software (Fig. 1). The initial orientation of ACPA was established from the then unpublished crystal structure data[10] of AMPA bound to the glutamate receptor. After energy minimization (900 iterations) and docking analysis, the modeling showed that ACPA can hydrogen bond with Arg 485, Ser 654, Thr 655, and Tyr 450, which is analogous to the hydrogen bonding

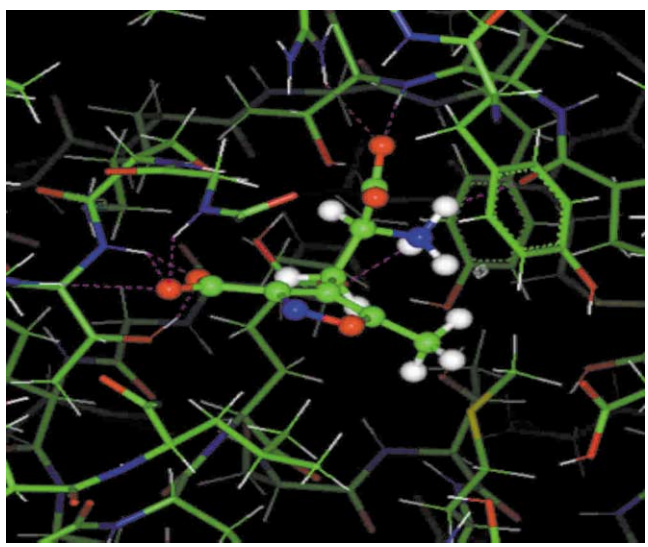

Figure 1. ACPA in the proposed binding domain of an AMPA type glutamate receptor. Hydrogen bonds to key residues are shown.

Keywords: isoxazole; AMPA; glutamate.

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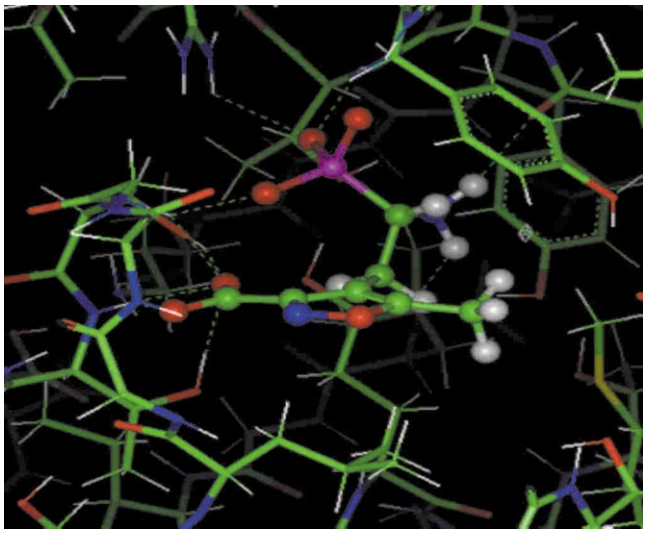
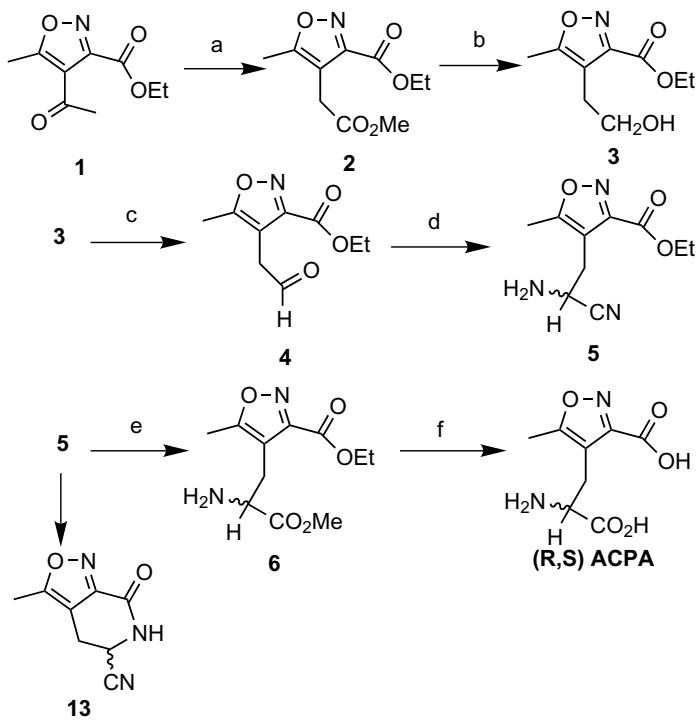


Figure 2. Modeling of an amino phosphonic acid predicts additional H-bonding interactions which may improve binding affinity.

observed in the kainate bound crystal structure. The carboxyl group of the amino acid forms a crucial interaction with Arg 485, which site directed mutagenesis studies indicate is essential for receptor function.[11] The docking data agree very well with the recent X-ray crystal data of AMPA bound to the GluR2 ligand binding core.[12] Modeling also shows enough space such that groups slightly larger than the amino acid may also bind to the receptor. An amino phosphonic acid is a non-classical bioisostere of an amino acid, and further modeling using the same energy minimization and docking modules suggested that such an analogue of ACPA may bind very well with the AMPA receptor (Fig. 2). The docking model indicates that the phosphonic acid forms hydrogen bonds with the same essential amino acids as ACPA and the second hydroxy group of the acid also establishes an additional hydrogen bond with Thr 480. This added hydrogen bond may translate into a higher affinity for the AMPA receptor.

In pursuit of therapeutic candidates, the starting material **1** (Scheme 1) was chosen since it already possesses the C-5 methyl group and C-3 ethyl carboxylate directly analogous to ACPA, which is known to be a potent agonist of the AMPA receptor. Compound **1**[13] was readily homologated to methyl ester **2** via the modified Willgerodt–Kindler conditions of Ila and Junjappa.[14] Borane–THF selectively reduced the methyl ester of **2** to give alcohol **3** in good yield, followed by Dess–Martin[15] oxidation to produce aldehyde **4**. To our knowledge, this is the first example of a Dess–Martin oxidation bearing an isoxazole ring. Aldehyde **4**, which can be produced in multigram quantities, presents a myriad of synthetic opportunities for the pursuit of ACPA bioisosteres. It also contains the essential carbon framework for AMPA receptor specificity.[16]

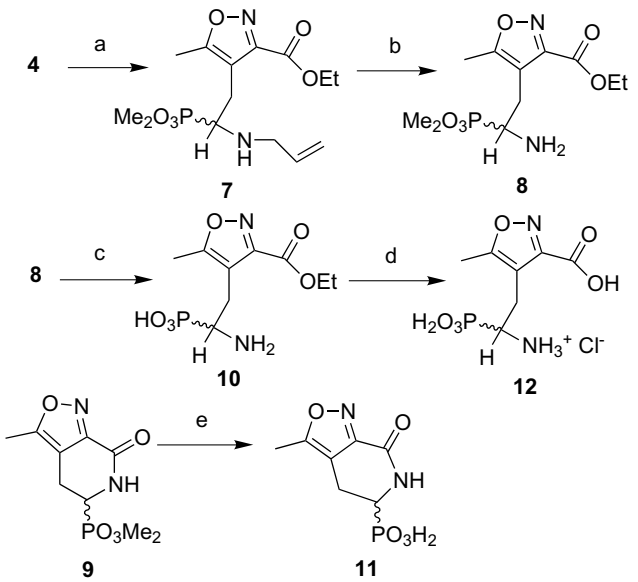
Under classic Strecker[17] conditions amino nitrile **5** was produced and directly hydrolyzed to ACPA, but in low yield (6%). Attempts varying base conditions (1–3 M NaOH, and NaOH/6% HOOH) and temperature (rt −50°C) failed to improve the yield. The Pinner[14] synthesis of amino ester **6** provided the best solution, followed



Scheme 1. Synthesis of ACPA. *Reagents and conditions*: (a) BF_3·etherate, MeOH, lead(IV) acetate, benzene, 96%; (b) borane–THF, THF, reflux, 72%; (c) Dess–Martin, CH_2Cl_2, 81%; (d) NH_4Br, KCN, MeOH, 37%; (e) MeOH, HCl, 78%; (f) 1 M HCl, 63%; (g) MeOH, 18%.

by HCl hydrolysis at 60°C to give ACPA, which was identical in all spectroscopic respects to the material reported by Madsen, but had a sharper melting point (212–213 versus 204–214).[7]

The synthesis of alpha amino phosphonate **7** was achieved in a one-pot fashion with $ErCl_3$ as a catalyst (Scheme 2). Initial attempts with $TiCl_4$ resulted in an ether byproduct so the more mild lanthanide catalyst was chosen. Deprotection was achieved by Pd(0)-catalyzed deallylation[18] using dimethylbarbituric acid as an allyl scavenger giving the free amine **8** in good yield. Upon standing in $CHCl_3$, a sample of **8** readily cyclized to lactam **9** in quantitative yield (Fig. 3). The amine group of compound **5** was also found to readily cyclize to lactam **13** upon standing in MeOH (Fig. 4).



Scheme 2. Amino phosphonate synthesis. *Reagents and conditions*: (a) allyl amine, 10 mol% $ErCl_3$, $HPO(OCH_3)_2$, MeOH, 12 h, 63%; (b) 10 mol% $Pd(PPh_3)_4$, dimethylbarbituric acid, CH_2Cl_2, 2 h, 91%; (c) 4 equiv. Br-TMS, CH_3CN, 1 h, 96%; (d) 1 M HCl, 60°C, 17 h, 89%; (e) 3 equiv. Br-TMS, CH_3CN, 1 h, 97%.

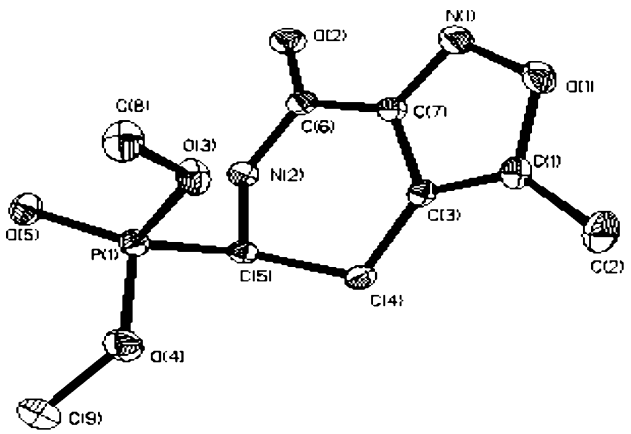


Figure 3. ORTEP plot of phosphonate lactam **9** (30% probability, H atoms omitted for clarity).

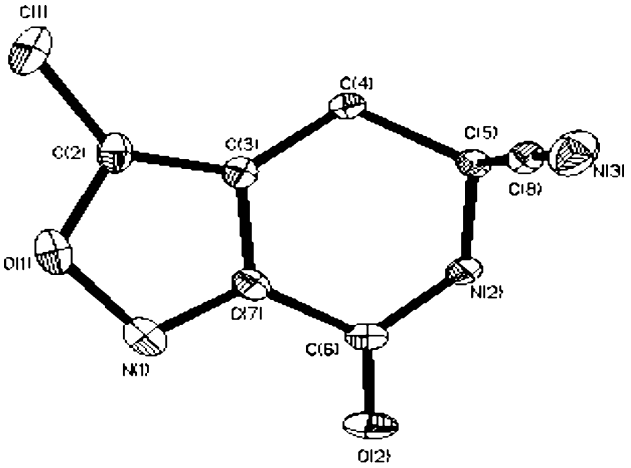


Figure 4. ORTEP plot of cyano lactam **13** (30% probability, H atoms omitted for clarity).

Bromo–TMS[19] selectively hydrolyzed compounds **8** and **9** to their corresponding amino acids in high yield. The final compound **12**[20] was obtained by hydrolysis in 1 M HCl. Analogue **11** is of particular interest since it places the amino acid in a locked conformation. Although not as promising as **12**, molecular modeling of **13** indicates that it may also bind to the Glu receptor site.

3. Conclusion

In summary, Schemes 1 and 2 provide a good synthetic route to a wide array of ACPA analogues and represents a more efficient method of the title compound than the original synthesis.[7] An efficient synthesis of the alpha amino phosphonic acid analogue of ACPA was achieved by this pathway and molecular modeling with a Glu receptor crystal structure predicts a promising hydrogen bonding framework. Compounds **11** and **12** are currently under evaluation in a biological assay to determine their receptor affinity. Work on enantioselective amino acid and phosphonate synthesis using asymmetric catalysis is underway.

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20. All intermediates were characterized by ^{1}H and ^{13}C NMR spectrometry. All final compounds were characterized by ^{1}H, ^{13}C NMR, and mass spectrometry. Selected spectral data: Compound **11**: ^{1}H NMR (acetone-d_6) 2.41 (s, 3H), 3.03 (dd, 1H, $J=14.3$ Hz, 5.76 Hz), 3.12 (dd, 1H, 14.3 Hz, 5.76 Hz), 3.99 (m, 1H, $J=5.76$ Hz) ^{31}P NMR 24.9; ^{13}C NMR 10.5, 18.9, 49.8, 111.6, 155.0, 161.3, 166.0; HRMS: (EI), $C_7H_9N_2O_5P$, calcd 232.0249, found (M+) 232.0244 151 (loss of $PO(OH)_2$), 111.0. Compound **12**: ^{1}H NMR (D_2O) 2.50 (s, 3H), 2.87 (ddd, 1H, $J_{H-P}=10.0$ Hz, $J=15.4$ Hz, 10.4 Hz), 3.14 (ddd, 1H, $J_{H-P}=6.4$ Hz, $J=15.4$, 4.62), 3.49 (ddd, 1H, $J_{H-P}=13.5$ Hz, $J=10.4$ Hz, 4.62 Hz); ^{31}P NMR 16.3; ^{13}C NMR 11.39, 22.52, 50.13, 111.04, 155.29, 163.47, 172.74; MS-MS: (ES+), (M+) 250.96, 169.02 (loss of PO_3H_3), 125.08 (loss of CO_2), 83.03 (loss of CH_2CO). Compound **13**: ^{1}H NMR (MeOH-d_4) 2.50 (s, 3H), 3.13 (dd, 1H, $J=0.9$, 4.5 Hz), 3.15 (dd, $J=0.9$, 4.5 Hz) 4.95 (t, $J=4.5$ Hz) ^{13}C NMR 13.8, 26.6, 47.0, 113.9, 122.3, 157.8, 163.7, 171.6; HRMS: (EI), $C_8H_7N_3O_2$, calcd 177.0538, found (M+) 177.0531, 123.0 (loss of NHCHCN), 96.1, 54.0.