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SYNTHESIS OF A PYRIMIDINE ISOSTERE OF THE N-METHYL-D-ASPARTATE ANTAGONIST SDZ EAB 515

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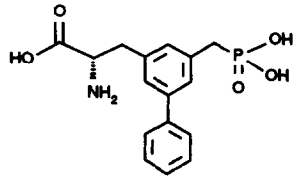
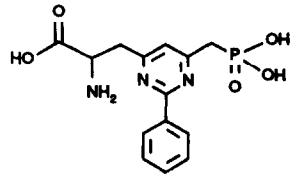
Abstract: The synthesis of a pyrimidine isostere 2 of the potent N-methyl-D-aspartate (NMDA) receptor antagonist SDZ EAB 515, 1, has been achieved. Surprisingly, isostere 2 is more than two orders of magnitude less active than 1.

The importance of excitatory amino acids and their corresponding glutamate receptors in central nervous system neurotransmission is now well accepted.[1] N-methyl-D-aspartate receptor antagonists have been proposed to have therapeutic potential and are under clinical investigation.[2] Recently, the synthesis and receptor binding of the potent NMDA antagonist biphenyl amino acid (S)-1 (SDZ EAB 515) has been described.[3] One of the drawbacks of the phosphonic acid amino acid NMDA antagonists is their highly polar nature which may detract from their resorption and CNS penetrability. As part of our ongoing interest in exploring the effects of isosteric replacements[4] on bioactive molecules, we set out to synthesize the pyrimidine isostere, 2, and investigate its NMDA receptor activity and physical properties relative to 1.



1 SDZ EAB 515

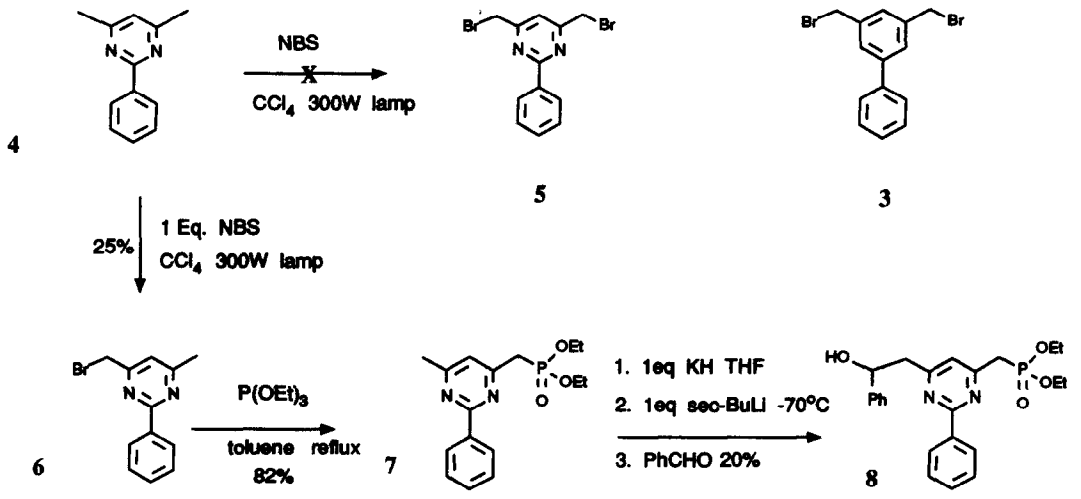


2

The synthesis of 1 was performed via the bis-bromomethyl intermediate 3 (derived from the corresponding diol) using a mono Arbuzov reaction followed by the introduction of a glycine equivalent.[5] Attempts to prepare (Scheme 1) the bis-bromomethylpyrimidine 5 via photolytic bromination of 2-phenyl-4,6-dimethylpyrimidine, 4,[6] with two equivalents of N-bromosuccinimide (NBS) were unsatisfactory due to facile formation of the bis-dibromomethyl derivative.[7,8] The monobromination product 6 could be isolated in 25% yield using one equivalent of NBS. Arbuzov reaction of 6 with triethylphosphite gave the corresponding diethylphosphonate 7 in good yield. NBS bromination of 7 proceeded α- to phosphorus and so was not of use. The dianion of 7 could be prepared at least to some extent by treatment first with one equivalent of potassium hydride at room temperature followed by treatment with

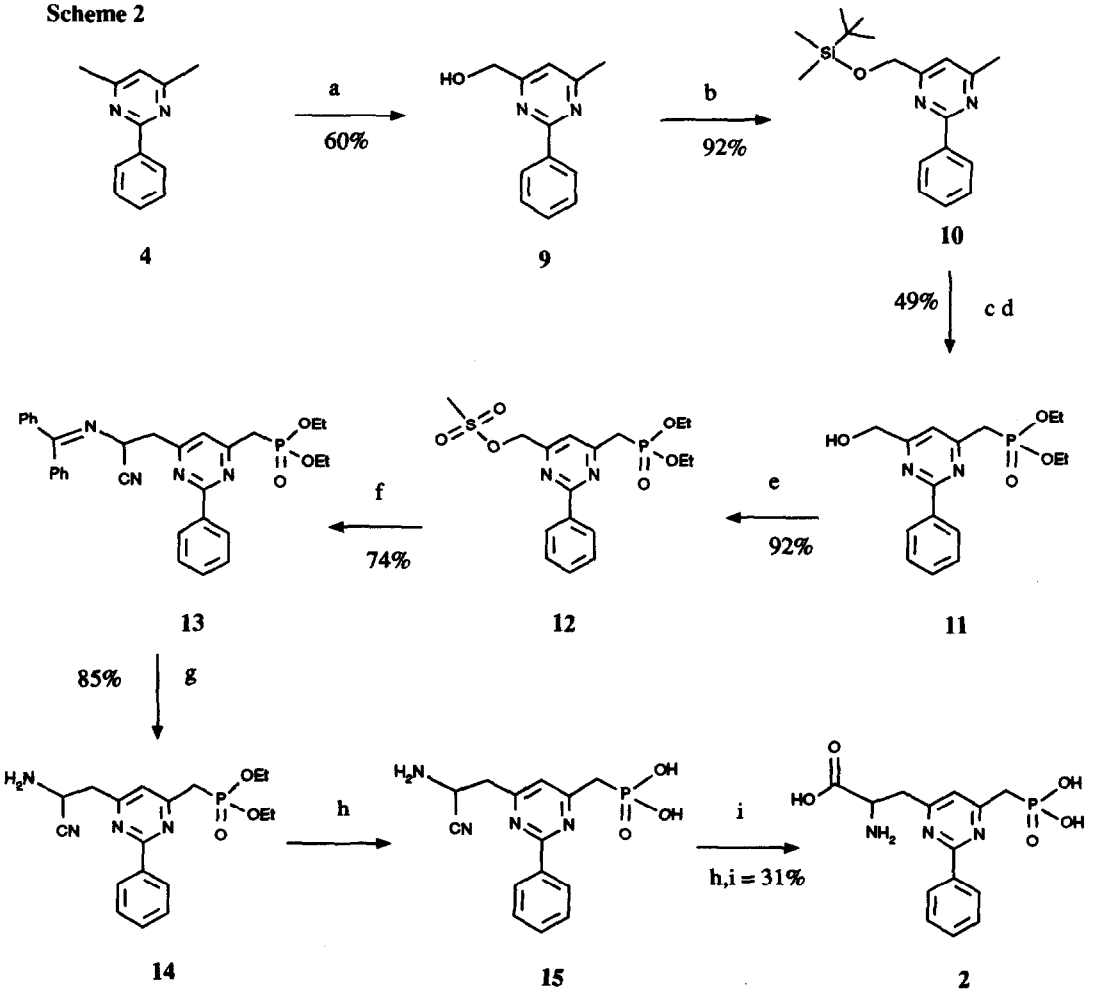
sec-butyllithium at -70°C in THF. However, when the dianion was trapped with one equivalent of benzaldehyde the monoaddition product 8 was isolated in only 15-20% yield. As a result it was necessary to

Scheme 1



devise a new synthetic route to 2. We decided to take advantage of the acidity of the methyl group(s) of pyrimidine 4. The new strategy was to introduce oxygen functionality onto one of the methyl groups of 4. Due to the mesomeric effect it should then be possible to selectively deprotonate the other methyl group and perform a phosphonylation after which the amino acid could be elaborated from the oxygen functionality. The successful realization of this strategy is depicted in Scheme 2. The dark red anion of 4 was easily formed with n-butyllithium at -70°C in THF. This anion could be hydroxylated in moderate yield with bis-trimethylsilyl peroxide;[9] however, better yields were obtained using N-benzenesulfonyl-phenyloxaziridine.[10] The hydroxymethylpyrimidine 9 was isolated in 60% yield after quenching at -70°C with acetic acid, followed by aqueous work-up and chromatographic purification. This material was converted to its t-butyldimethylsilyl ether 10 in standard fashion. Treatment of 10 with n-BuLi followed by quenching the resulting anion with D_2O demonstrated that deprotonation occurred exclusively at the pyrimidine methyl group as expected. Due to the acidity of the phosphonylation product two equivalents of a non-nucleophilic base are necessary for its preparation. Treatment of 10 with two equivalents of LDA at -70°C in THF for one hour followed by the addition of diethylphosphochloridate, warming to room temperature and quenching with ammonium chloride gave the desired phosphonate in moderate yield. The silylether of this crude phosphonate was directly cleaved under acidic conditions to give the hydroxy phosphonate 11. Conversion of the hydroxyl function to the corresponding mesylate via the sulfene method yielded 12 in almost quantitative yield requiring no purification. It remained to introduce a glycine equivalent for which the benzophenone-imine of glycine nitrile was chosen.[11] Reaction of the sodium salt of the benzophenone-imine of glycine nitrile with 12 in THF gave alkylation product 13 in moderate yield after chromatography. Acid hydrolysis of the benzophenone-imine proceeded smoothly to give the aminonitrile 14. The phosphonate ethylester groups were then cleaved with excess trimethylsilyl bromide[12] in dichloromethane to give 15. Direct hydrolysis of 15

Scheme 2



a)1.1eq. n-BuLi, THF, -70°C, 1.2eq. N-benzenesulfonyl-phenyloxaziridine b)1.1eq $Me_2Si(tBu)Cl$, Et_3N,. DMAP, CH_2Cl_2
c) 2.0 eq. LDA, THF -70°C, 1.0eq. $(EtO)_2POCl$ d) THF, 1N HCl, 1:1 RT e) 1.5eq. Et_3N, THF, -35°C, 1.1eq. MsCl
f)glycinenitrile benzophenoneimine, 1.1eq NaH, THF 45°C g) 3N HCl-Ethanol
h) Me_3SiBr:CH_2Cl_2 1:1 vv RT I) 12N HCl reflux

was performed by heating at reflux in 12N HCl for 4h. Concentration *in vacuo* followed by reverse phase semipreparative HPLC purification gave 2 in 31% yield over the two steps. Interestingly, the ^{1}H-NMR analysis of 2 in 1N DCl (2 has poor solubility in D_2O) at room temperature showed that the methylene protons α-to the phosphonic acid moiety are rapidly exchanged (minute time scale). The other methylene protons β-to the amino acid function are exchanged on a time scale of hours while the α-amino acid proton is stable to exchange under these conditions.

In NMDA receptor binding studies, the pyrimidine isostere 2 displayed a pK_i of 4.3 and in the cortical

wedge test for functional NMDA activity a pA_2 value of 4.6 was measured.[3] For (S)-1 these values were 6.7 and 6.94 respectively.[3] Thus, the pyrimidine isostere 2 was more than two orders of magnitude less active than the potent NMDA antagonist 1. These results are quite astonishing in light of the seemingly small structural differences and await explanation.

Experimental

General: TLC: Merck silica gel 60 F_{254} anal. plates, detection either by UV, or spraying with iodine solution (25 g I_2/ 20 g KI/ 200 ml EtOH/ 800 ml H_2O) or Dragendorff's reagent. Medium Pressure Liquid Chromatography (MPLC); Merck silica gel 60 (230-400 mesh), ^{1}H-NMR spectra (δ, ppm): (^{1}H=200 MHz) Varian Gemini 200, (^{1}H=360 MHz) Bruker AM 360 , chemical shifts in ppm relative to TMS as internal reference MS, m/z(%) EI: VG TS 250 spectrometer, 70 eV and FAB: Varian MAT 212 spectrometer, 8 keV. Solvents were purchased from Merck, n-BuLi from Aldrich, and the other reagents from Fluka.

2-Phenyl-4-hydroxymethyl-6-methylpyrimidine (9)

To a stirred solution of 4[6] (15.6g, 85 mmol) in 400ml THF was added BuLi (34ml, 2.5M hexane, 85 mmol) at -78°C under argon. The resulting dark red solution was stirred for 45min -78°C and 2-sulfonyl-3-phenyl-oxaziridine (28.8g, 110mmol) in 400ml THF was added slowly, maintaining the temperature below -70°C. After the addition was complete, the mixture was stirred for 30min, 12ml HOAc were added and the mixture was concentrated under reduced pressure. Dichloromethane and water were added, the organic layer was washed with water dried over sodium sulfate and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10-20% ethyl acetate - hexane) to yield 10.2g (60%) of 9 as a clear oil. ^{1}H-NMR ($CDCl_3$, 360MHz) 8.40-8.52 (m, 2H), 7.44-7.53 (m, 3H), 7.00 (s, 1H), 4.73 (s, 2H), 3.62 (broad singlet, OH), 2.57 (s, 3H). MS (EI) M^+ 200 (90), 199 (100), 104 (65).

2-Phenyl-4-*t*-butyldimethylsilyloxymethyl-6-methylpyrimidine (10)

A mixture of 9 (11.0g, 55mmol), t-butyldimethylsilyl chloride (9.0g, 60mmol) triethylamine (6.6g, 65mmol) and 5mol% of dimethylaminopyridine in 500mL of dichloromethane was stirred at room temperature for 20h. The solvent was removed under reduced pressure and the residue was diluted with water and extracted with hexane. The combined organic layers were dried over sodium sulfate and concentrated to give a yellow oil which was eluted through a short colum of silica gel with hexane to afford 15.8g (92%) of 10 as a clear oil. ^{1}H-NMR (200MHz, $CDCl_3$) 8.36-8.48 (m, 2H), 7.41-7.51 (m, 3H), 7.27 (s, 1H), 4.82 (s, 2H), 2.59 (s, 3H), 0.98 (s, 9H), 0.18 (s, 6H).

Diethyl[(-2-phenyl-6-hydroxymethyl)-pyrimidine-4yl]-methylphosphonate (11)

A solution of 10 (9.6g, 31mmol) in 75mL THF was added dropwise at -78°C to a solution of lithium diisopropylamide (62mmol) in 50mL THF under argon. The mixture was stirred for 1h at -78°C and diethyl-phosphochloridate (5.2g, 31mmol) in 10mL THF was added dropwise. The mixture was allowed to warm to room temperature and quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate and the combined organic phases were dried over sodium sulfate and concentrated to give 8.3g of product as a colorless oil. The above product (8.3g) was stirred at room temperature overnight in 500 mL THF containing 75mL 1N HCL. MPLC (ethyl acetate-[10% methanol-ethylacetate] gradient) purification gave 5.1g (49%) of 11 as a clear viscous oil. ^{1}H-NMR (200MHz, $CDCl_3$) δ 8.41-8.51 (m, 2H), 7.42-7.52 (m, 3H), 7.28 (s, 1H), 4.79 (d, 2H, J= 3.0Hz), 4.13 (quintet, 4H, J = 6.8Hz), 3.92 (broad singlet, OH), 3.45 (d, 2H, J = 21Hz), 1.29 (t, 6H, J = 6.8Hz) MS(FAB) MH^+= 337.

6-Methanesulfonyloxymethyl-2-phenyl-pyrimidin-4ylmethyl-phosphonic-acid-diethylester (12)

To a solution of 11 (2.0g, 6.0mmol) in 50mL of THF at -35°C was added triethylamine (1.4mLg, 10mmol) followed by methanesulfonyl chloride (4.8mL, 6.3mmol). The solution was allowed to warm to room temperature and saturated ammonium chloride solution and ethyl acetate were added. The aqueous phase was extracted with ethylacetate and the combined organic layers were dried over sodium sulfate and concentrated to give 2.3g of 12 92% which did not require further purification. ^{1}H-NMR (200MHz, $CDCl_3$) δ 8.41-8.51 (m, 2H), 7.46-7.54 (m, 3H), 7.41 (d, 1H, J = 1.3Hz), 5.36 (s, 2H), 4.13 (quintet, 4H, J = 6.8Hz), 3.48 (d, 2H, J = 21Hz), 3.17 (s, 3H), 1.29 (t, 6H, J = 6.8Hz).

6-(2-benzophenoneimino-2-cyano-ethyl)-2-phenyl-pyrimidin-4ylmethyl-phosphonic-acid-diethylester (13)

To a stirred suspension of sodium hydride (0.13g, 80% oil dispersion, 4.9mmol) in 10mL of THF was added glycinenitrile benzophenonimine (1.1g, 4.9mmol) in 10mL THF under argon. The mixture was stirred at 45°C for 2h after which hydrogen evolution ceased and a clear solution was obtained. After cooling the solution to 0°C compound 12 (2.0g, 4.8mmol) was added in 10mL THF and the solution was allowed to warm to room temperature. After 2h saturated ammonium chloride solution was added. The mixture was extracted with ethylacetate and the combined organic phases were dried over sodium sulfate and concentrated to give the crude product. MPLC (ethyl acetate) purification gave 1.4g (74%) of 13 as a colorless oil. ^{1}H-NMR (200MHz, $CDCl_3$) δ 8.21-8.31 (m, 2H), 7.24-7.60 (m, 11H), 7.18 (d, 1H, J= 2.0Hz), 6.92-7.03 (m, 2H), 5.05 (t, 1H, J= 6.5Hz), 3.98-4.17 (m, 4H), 3.43 (d, 2H, J= 6.5Hz), 3.39 (d, 2H, J = 21Hz), 1.18-1.30 (6 lines overlapping triplets, 6H, J = 6.8Hz)

6-(2-amino-2-cyano-ethyl)-2-phenyl-pyrimidin-4ylmethyl-phosphonic-acid-diethylester (14)

Compound 13 (240mg, 0.45mmol) was stirred in 6mL ethanol containing 1.5mL 3N HCl for 18h at room temperature. The pH of the solution was adjusted to 7, toluene was added and the solvent was removed under reduced pressure. Flash chromatography of the residue (CH_2Cl_2, MeOH, NH_3(aq), 90:10:1) gave 150mg (85%) of 14 as a clear viscous oil. 14 ^{1}H-NMR (200MHz, $CDCl_3$) δ 8.43-8.53 (m, 2H), 7.44-7.54 (m, 3H), 7.21 (d, 1H, J= 2.0Hz), 4.45 (t, 1H, J= 7.0Hz.), 4.12 (quintet, 4H, J= 7.0Hz), 3.43 (d, 2H, J = 21Hz), 3.23 (dd, 2H, J = 2.0, 7.0Hz), 1.71 (broad singlet, NH_2), 1.29 (t, 6H, J= 7.0Hz).

2-Amino-3-(2-phenyl-6-phosphonomethyl-pyrimidin-4-yl)-propionic acid (2)

Compound 14 (100mg, 0.23mmol) was dissolved in 1.5mL CH_2Cl_2, 1.5mL of trimethylsilyl bromide were added and the mixture stirred at room temperature for 2h. The solvent was removed under reduced pressure to give an oily residue which was heated in 5mL of 12N HCl for 4h under reflux. The mixture was concentrated under high vacuum to give an amorphous white solid. This material was subjected to semipreparative HPLC on a Stachroma RP-18 (20X250mm, 10μ) column to give 24mg (31%) of lyophilized 2 after ion exchange (Biorad AG 4X-4, 100-200 mesh, 2NAcOH eluent). Analytical HPLC was performed on a 5μ Merck RP-18 column isocratic mixture 70% H_2O: 30% B [B= 900 H_2O: 100 CH_3CN: 2 H_3PO_4: 20 (10% NMe_4OH)] retetention time for 2= 5.9 min, flow 1.5ml/min (UV 254nm). Compound 2 displayed poor water solubility.
^{1}H-NMR (DMSO-d_6,360MHz, 120°C) δ= 8.32-8.40 (m, 2H), 7.37-7.50 (m, 4H), 5.40-6.0 (broad singlet, exchangable H), 3.89-3.96 (broad singlet, 1H), 3.30 (dd, part of AB system, 1H, J= 15Hz, 3.0Hz), 3.09 (d, 2H, J= 21.0Hz) 3.01-3.13 (second part of AB system buried under doublet at 3.09, 2H).
^{1}H-NMR (1N DCl, 360MHz) δ= 8.18 (d, 2H, J= 7.5Hz), 7.96 (s, 1H), 7.80-7.83 (3 line multiplet, 2H), 7.69-7.72 (3 line multiplet, 2H), 4.87-4.90 (3 line multiplet, α-proton=1H), 3.89-4.02 (m, partially exchanged ca, 1.5 H at time of measurement), 3.82 (d, J= 21.5Hz, exchanged to 90%).
FAB-MS; MH^+= 338

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