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THE SYNTHESIS OF BIPHENYL AMINO ACIDS AND RELATED 2,3 - DIHYDROIMIDAZO [1,2-a]DIBENZ [c,e] AZEPINES.

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Abstract The synthesis of biphenyl amino acids, designed as potential metabotropic glutamate receptor ligands, is described. Some unexpected tricyclic intermediates were characterised and one such intermediate was further transformed into the related 2,3-dihydroimidazo[1,2-a]dibenz[c,e] azepines.

Agents acting at metabotropic glutamate receptors in the central nervous system have therapeutic potential for the treatment of epilepsy, cerebral ischemia and Alzheimer's disease[1]. This has stimulated interest in the synthesis of compounds which act specifically at these receptors.

(1S,3R)-1-Aminocyclopentane 1,3- dicarboxylic acid ((1S,3R)-ACPD) (FIG.1) is a known selective metabotropic glutamate agonist[2] whose activity may depend on the proximity of the amino and distal carboxyl groups (fixed by their "cis" configuration). Molecular modelling[3] of biphenyl amino acids of type 1 (FIG.I) showed that, in the lowest energy conformation, in which the phenyl rings are aligned at an angle of

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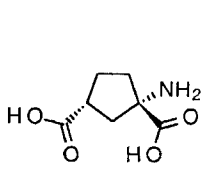

(1S,3R) - ACPD

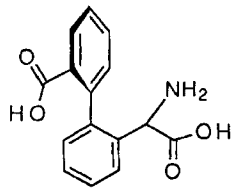

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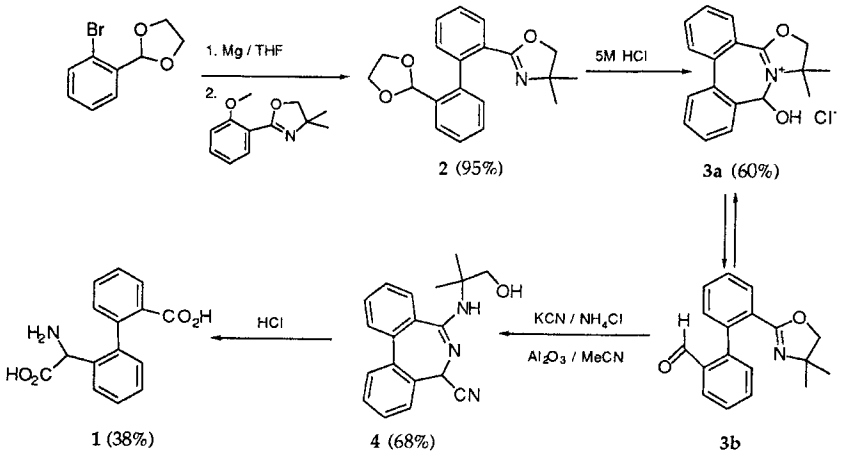
FIG. 1

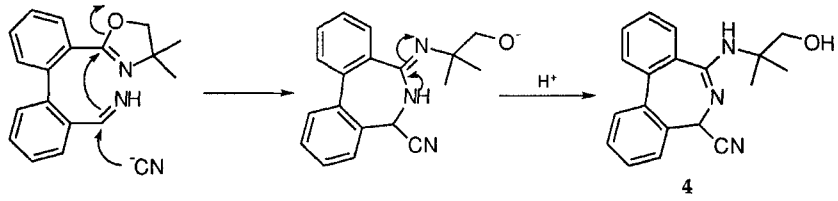


Scheme 1

between 60° and 90°, a similar proximity of functional groups occurs. They are thus potential metabotropic ligands.

We also set out to make the tetrazole analogue of the amino acid because this group has been widely reported as a carboxylic acid bioisostere.[4,5,6,7]

The synthetic strategy was to construct the biphenyl ring system using the methodology of Meyers[8] (Scheme1). The remote carboxyl group would be carried in masked form as its 4,4-dimethyloxazoline, and the



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Scheme 2

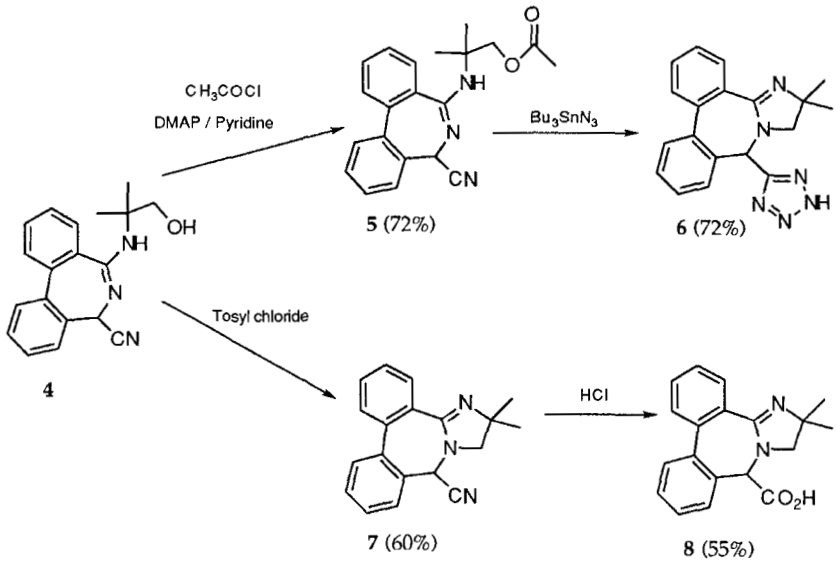
amino acid elaborated by a Strecker reaction of an unmasked aldehyde group.

Reaction of 2-(2-methoxyphenyl)-4,4-dimethyloxazoline with the Grignard of 2-(2-bromophenyl)-1,3-dioxolane proceeded in 95% yield to give biphenyl **2**. Selective hydrolysis of the acetal moiety using 5 molar hydrochloric acid at ambient temperature gave the unexpected tricyclic hydrochloride **3a** in 60% yield. This was characterised by its very low field (∂ = 6.58) methine signal in the proton NMR and by mass spectrometry. Proton NMR studies showed that an equilibrium is established with the free aldehyde **3b** in DMSO solution.

A modified Strecker reaction, employing basic alumina and accelerated by ultrasound[9], furnished the tricyclic amidine **4** in 68% yield. The proton NMR showed an NH singlet and coupling between the methylene and hydroxyl groups, indicating ring opening of the oxazoline moiety had occurred. This tricyclic intermediate presumably arises from ring opening of the oxazoline by the intermediate imine in the Strecker reaction. (Scheme 2).

Hydrolysis of tricyclic amidine **4** in refluxing 5 molar hydrochloric acid gave the target amino acid **1** in 38% yield.

In a first attempt to synthesise an aminotetrazole analogue of **1** (Scheme 3), the tricyclic amidine **4** was protected by acetylation. The loss of the CH_2/OH coupling in the proton NMR confirmed this to be the *O* - acetyl derivative **5**. However, on heating **5** with tributyl tin azide at 90° the tetracyclic tetrazole **6** was formed. This compound was subsequently found to be resistant to hydrolysis in refluxing concentrated hydrochloric



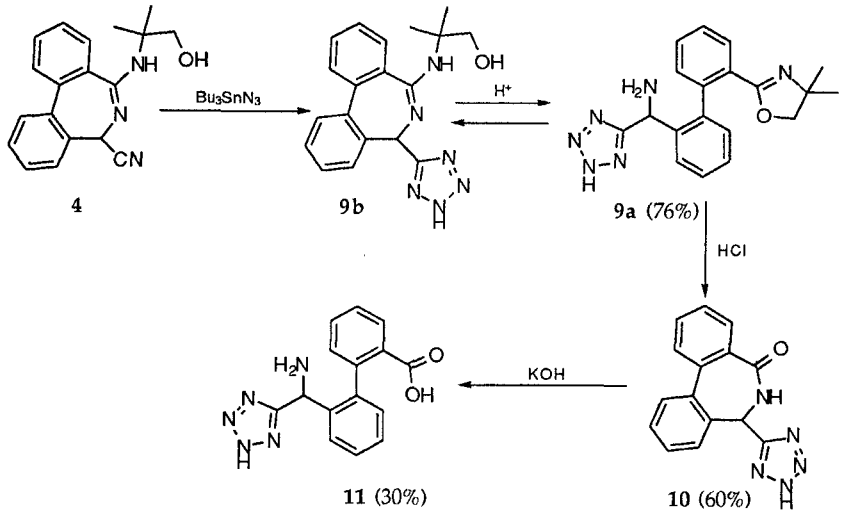
Scheme 3

acid. The tetracyclic structure of **6** was confirmed by nuclear Overhauser effect experiments which demonstrated the proximity of the methine and imidazole ring protons.

We postulated that the tetracyclic **6** is a result of internal nucleophilic displacement of the *O*-acetyl function by the ring amidine nitrogen. To confirm this, and at the same time synthesise a carboxylic acid analogue of **6**, we prepared an *O*-tosyl derivative of tricyclic amidine **4**. Consistent with tosyl being a better leaving group, we found that this compound spontaneously cyclised at ambient temperature to give the tetracyclic nitrile **7** in 60% yield. Subsequent treatment with concentrated hydrochloric acid at 90° in a sealed vessel furnished the carboxylic acid **8** in 55% yield.

The dibenzazepines **6** and **8** are themselves potential amino acid bioisosteres.

In our second attempt to synthesise an aminotetrazole analogue of **1** (Scheme 4), the unacylated tricyclic amidine **4** was heated with tributyl



Scheme 4

tin azide at 90° to furnish the tetrazole oxazoline **9a**. This compound was characterised by the relatively shielded (∂=6.55) signal in the NMR of the proton *ortho-* to the oxazoline ring. Proton NMR studies show that an equilibrium is established with the amidine **9b** in DMSO/DCl solution. Refluxing with concentrated hydrochloric acid gave predominantly the cyclic amide **10**. (Proton NMR in D_2O shows a singlet at ∂ = 5.9 for the amide methine). The stability of this seven membered ring was demonstrated by the harsh hydrolysis conditions (*i.e.* 2 molar potassium hydroxide at 100°C in a sealed vessel for 24 hours) needed to form the aminotetrazole **11**. (Proton NMR in D_2O shows a singlet at ∂ = 5.8 for the aminotetrazole methine.)

In conclusion, the target biphenyl amino acids were successfully synthesised and some unexpected tri- and tetra-cyclic ring systems characterised. With hindsight, the facile formation of these intermediates can be viewed as a natural consequence of the proximity of the phenyl substituents, as predicted by the molecular modelling.

The target biphenyl amino acids and the dibenzazepines were found to be inactive in a metabotropic [^{3}H] glutamate binding assay[10]. It is

hypothesised that the steric bulk of the biphenyl system precludes their binding to these receptors.

EXPERIMENTAL

Proton and carbon-13 NMR spectra were recorded on a Bruker AM or AC 300 MHz spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Bruker IFS 48 instrument (as KBr disc). Ultraviolet spectra were recorded on a Pye Unicam 8725 spectrometer. Mass spectra were recorded on a VG 7070E double focusing spectrometer using chemical ionisation (100eV) with ammonia as reagent gas. Melting points (uncorrected) were measured on a Kofler hot stage. Thin layer chromatography was carried out on Merck 60 F254 silica gel-coated glass plates. High performance liquid chromatography was carried out using a Waters 600E/484 instrument.

4,4-Dimethyl-2-{2-(2-[1,3-dioxolan-2-yl]phenyl)phenyl}oxazoline (2)

To magnesium turnings (1.52g, 63mmol) covered with dry tetrahydrofuran (THF) (200mls) under a nitrogen atmosphere were added a few drops of methyl iodide. The mixture was briefly refluxed to initiate reaction. A solution of 2-(2-bromophenyl)-1,3-dioxolane (11.45g, 50mmol) in dry THF (50mls) was then added dropwise at such a rate as to maintain gentle reflux. After addition was complete the reaction was refluxed for a further 20 minutes and then allowed to cool.

The solution of Grignard reagent was decanted from unreacted magnesium, added to a solution of 2-(2-methoxyphenyl)-4,4-dimethyl oxazoline (5.13g, 25mmol) in dry THF (100mls), and the mixture was stirred at room temperature.

After 16 hours the reaction mixture was poured into saturated ammonium chloride solution (400mls) and extracted with diethyl ether (3X100mls).The combined extracts were dried over magnesium sulphate, filtered and evaporated *in vacuo* to give an amber oil (11.10g). The crude oil was purified by flash chromatography on silica (eluant 3:1 diethyl ether: hexane) to yield a light-yellow oil (7.68g, 95%). ^{1}H NMR ($CDCl_3$) ∂: 7.8 (dd, 1H), 7.64 (dd, 1H), 7.3-7.5 (m, 5H), 7.2 (dd, 1H), 5.55 (s, 1H, CH),

4.0-4.1 (m, 2H), 3.8-3.9 (m, 2H), 3.75 (d, 1H), 3.6 (d, 1H), 1.24 (s, 3H, Me), 1.20 (s, 3H, Me).

3,3-Dimethyl-5-hydroxy-2,3-dihydro-5*H*-oxazolo[3,2-a]-dibenz[c,e]-azepinium chloride (3a/3b)

The biphenyl **2** (7.60g, 24mmol) was dissolved in 5 molar hydrochloric acid (25mls) and stirred at room temperature for 2 hours. The precipitated solid was collected by filtration, washed with diethyl ether on the sinter funnel and dried *in vacuo* at 50°C to give a white solid (4.67g, 59%). Mpt. 146-50°C. IR (KBr disc): 3296 (OH), 1626cm^{-1}(CHO). MS: 315/17(M^+), 280 (M^+-Cl). ^{1}H NMR (DMSO-d_6) (a) Tricyclic **3a** ∂: 8.08-8.14 (m, 2H), 8.0 (dd, 1H), 7.8-7.9 (m, 2H), 7.75 (dd, 1H), 7.58-7.64 (m, 2H), 6.58 (s, 1H, CH), 5.0 (d, 1H, CH_2), 4.85 (d, 1H, CH_2), 1.85 (s, 3H, Me), 1.50 (s, 3H, Me); (b) Aldehyde **3b** ∂: 9.7 (s, 1H, CHO), 8.3 (dd, 1H), 7.36 (dd, 1H), 7.3 (dd, 1H), 4,05 (d, 2H, CH_2), 1.1 (d, 6H, Me's). (Other aromatics overlain by tricyclic aromatics in equilibrium mixture).

5-Cyano-7-([2-methyl-3-hydroxy-prop-2-yl]amino)-5-*H*-dibenz[c,e]-azepine (4)

A suspension of potassium cyanide (2.28g, 37mmol), ammonium chloride (2.06g, 40mmol) and basic alumina (ICN grade1) (22.8g) in acetonitrile (100mls) was immersed in a ultrasonic bath for 1 hour. The tricyclic hydrochloride **3a/3b** (2.34g, 7.4mmol) was then added and ultrasonification continued overnight (the bath temperature rising to 40°C).

The solid material was removed by filtration and washed with more acetonitrile on the sinter. The combined filtrates were evaporated *in vacuo* to give a white solid, which was purified by flash chromatography on silica (eluant diethyl ether). (1.65g, 69%). MS: 306 (M+H), 289 (M+H-OH), 279 (M-CN), 274 (M-CH_2OH). ^{1}H NMR ($CDCl_3$) ∂: 7.8 (dd, 1H), 7.6 (m, 4H), 7.5 (m, 3H), 6.5 (t, 1H, OH), 4.8 (s, 1H, CH), 4.5 (s, 1H, NH), 3.5-3.6 (m, 2H, CH_2), 1.4 (s, 3H, Me), 1.2 (s, 3H, Me). ^{13}C NMR (DMSO-d_6) ∂: 157.9 (amidine), 137.6, 137.1, 135.6, 131.4 (4 quaternary aromatics), 130.2, 130.0, 128.5, 128.3, 128.1, 127.9, 127.7, 126.7 (8 aromatics), 119.5 (CN), 67.8 (CH_2OH), 55.1 ($\underline{C}Me_2$), 51.6 (CH), 23.0 (Me), 22.6 (Me).

2-Amino-[2-(2-carboxyphenyl)phenyl]acetic acid (1)

The tricyclic amidine **4** (100mgs, 0.33mmols) was refluxed in 5 molar hydrochloric acid (25mls) for 16 hours. The solution was then

evaporated to dryness and the solid residue washed with acetone, redissolved in water and purified by ion exchange chromatography. (Dowex 50x8-100; column washed with a) H_2O b) 1:1 H_2O:THF c) H_2O; compound eluted with 9:1 H_2O:pyridine). The pyridine was removed azeotropically, the residual solid redissolved in water and freeze dried to give a fluffy white solid (39mgs, 38%). Mpt. >250°C. MS: 272 (M+H), 226 (M-CO_2). ^{1}H NMR (D_2O) ∂: 7.75 (d, 1H), 7.55-7.60 (m, 2H), 7.4-7.53 (m, 4H), 7.25 (s, 1H), 4.75 (s, 1H, CH).

5-Cyano-7-([2-methyl-3-acetoxy-prop-2-yl]amino)dibenz-5*H*-[c,e]azepine (5)

A solution of tricyclic amidine **4** (342mgs, 0.1mmol) and 4-dimethylaminopyridine (5mgs) in pyridine (5mls) was cooled to 5°C in an ice bath, and acetyl chloride (142µl, 2mmol) added with a syringe. The mixture was allowed to warm to room temperature and stirred for 2 hours.

The reaction mixture was poured into water and extracted with diethyl ether (3x). The combined extracts were washed with a) H_2O (2x) b) saturated brine , dried over magnesium sulphate, filtered and evaporated *in vacuo* to give a viscous yellow oil. The crude oil was purified by flash chromatography on silica (eluant 1:1 hexane:diethyl ether) to yield a white solid (250mgs, 72%). IR (KBr disc): 3373(sharp) (NH), 1728 (C=O), 1617, 1530cm^{-1}. MS: 348 (M+H), 321 (M-CN), 288 (M-$OCOCH_3$). ^{1}H NMR ($CDCl_3$) ∂: 7.82 (dd, 1H), 7.58-7.0 (m, 4H), 7.45-7.55 (m, 3H), 4.75 (s, 1H, CH), 4.38 (d, 1H, CH_2), 4.20 (d, 1H, CH_2), 1.90 (s, 3H, CH_3CO), 1.18 (s, 3H, Me), 1.16 (s, 3H, Me).

2,2-Dimethyl-5-(1*H*-tetrazol-5-yl)-2,3-dihydro-5*H*-imidazo[1,2-a]dibenz-[c,e]azepine (6)

A mixture of **5** (250mgs, 0.72mmol) and tributyltin azide (0.72g, 2.1mmol) was stirred at 90°C for 16 hours.

The reaction mixture was cooled, dissolved in acetonitrile:water (1:1), acidified with glacial acetic acid and stirred at room temperature for 2 hours. The mixture was then washed with diethyl ether:hexane (1:1) and evaporated *in vacuo* to give a white solid (175mgs). The crude material was recrystallised from dioxan:water (9:1) to give white crystals (102mgs, 42%). Mpt. >260°C. MS : 331 (M+H). ^{1}H NMR (DMSO-d_6 + DCl) ∂: 7.81-

7.87 (m, 2H), 7.73-7.78 (m, 2H), 7.67-7.70 (m, 3H), 7.55 (t, 1H), 6.9 (s, 1H, CH), 4.4 (d, 1H, CH_2), 4.2 (d, 1H, CH_2), 1.7 (s, 3H, Me), 1.4 (s, 3H, Me). (nOe data show proximity of CH and CH_2 protons, consistent with a ring structure). ^{13}C NMR (d_6DMSO+DCl) ∂: 161.0 (amidine), 155.1 (tetrazole), 137.9, 135.3, 135.2, 119.5 (4 quaternary aromatics), 133.9, 130.7, 129.8, 129.7, 129.1, 129.0, 128.8, 127.9 (8 aromatics), 63.0 (CH_2), 60.6 ($\underline{C}Me_2$), 54.1 (CH), 26.6 (Me), 26.1 (Me). UV : λ_{max} = 233nm. Reverse phase HPLC (Nucleosil 120-5C18-1383; 1:1 H_2O:methanol; pH = 4.65 [NH_4OAc]), single peak.

2,2-Dimethyl-2,3-dihydro-5*H*-imidazo[1,2-a]dibenz[c,e]azepine-5-carbonitrile (7)

To a solution of tricyclic amidine **4** (300mgs, 1mmol) in pyridine (5mls), cooled in an ice bath, was added tosyl chloride (381mgs, 2mmols) and the mixture stirred at room temperature overnight.

The pyridine was evaporated *in vacuo* and the residual yellow gum triturated with diethyl ether until a white solid resulted. The crude product was dissolved in water (any insoluble material filtered off) and the filtrates basified with 2 molar potassium hydroxide. The white flocculent precipitate was collected by filtration, washed with more water on the sinter and dried *in vacuo* at 60°C to give a white solid (140mgs, 60%). ^1H NMR (DMSO-d_6) ∂: 8.1 (d, 1H), 7.98-8.06 (m, 2H), 7.74-7.90 (m, 4H), 7.64 (t, 1H), 6.95 (s, 1H, CH), 4.30 (d, 1H, CH_2), 4.0 (d, 1H, CH_2), 1.55 (s, 3H, Me), 1.35 (s, 3H, Me).

2,2-Dimethyl-2,3-dihydro-5*H*-imidazo[1,2-a]dibenz[c,e]azepine-5-carboxylic acid (8)

The tetracyclic nitrile **7** (140mgs, 0.488mmol) was dissolved in concentrated hydrochloric acid (2mls) and heated in a sealed vessel at 90°C for 16 hours.

The precipitated white solid was collected by filtration (80mgs, 55%). Mpt. >260°C. IR (KBr disc): 1737cm^{-1} (C=O). MS : 307 (M+H), 263 (M-CO_2). ^1H NMR (DMSO-d_6) ∂: 7.94 (d,1H), 7.88 (m, 2H), 7.54-7.76n (m, 5H), 5.97 (s, 1H, CH), 4.07 (d,1H, CH_2), 4.03 (d, 1H, CH_2), 1.54 (s, 3H, Me), 1.38 (s, 3H, Me). (nOe's show proximity of CH and CH_2 protons, confirming ring structure). ^{13}C NMR (DMSO-d_6) ∂: 167.8 (CO_2H), 161.3 (amidine), 138.2, 136.0, 134.8, 120.3 (4 quaternary aromatics), 134.0, 130.5, 130.2, 129.6, 129.5, 129.1, 128.7, 128.3 (8 aromatics), 63.2 (CH_2), 60.6 (CH),

60.3 (CMe_2), 27.2 (Me), 25.6 (Me). UV : λ_{max} = 260nm. Reverse phase HPLC (Nucleosil 120-5C18-1383; 1:1 H_2O:methanol; pH=4.65 [NH_4OAc]), single peak.

5-{Amino(2-[2-(4,4-dimethyloxazolin-2-yl)phenyl]phenyl)methyl}-1*H*-tetrazole (9a/9b)

A mixture of tricyclic amidine **4** (343mgs, 1.1mmol) and tributyl tin azide (1.00g, 3mmol) was stirred at 90°C for 48 hours.

The reaction mixture was then allowed to cool, diluted with acetonitrile, acidified with glacial acetic acid and stirred at room temperature for two hours. The acetonitrile solution was washed with hexane (5X) and evaporated *in vacuo* to give a white solid (300mgs, 76%). MS : 349 (M+H). ^{1}H NMR (DMSO-d_6) (a) Oxazoline form **9a** ∂: 7.9-8.1 (m, 4H), 7.8 (t, 1H), 7.65 (t, 1H), 7.5 (t, 1H), 6.55 (d, 1H), 6.0 (s, 1H, CH), 3.45-3.55 (2 doublets, 2H, CH_2), 1.5 (s, 3H, Me), 1.35 (s, 3H, Me); (b) Amidine form **9b** (+DCl) ∂: 6.75 (s, 1H, CH), 3.70 (d, 1H, CH_2), 3.58 (d, 1H, CH_2), 1.53 (s, 3H, Me), 1.38 (s, 3H, Me). (N.B. Aromatics are overlain by those from **9a** in an equilibrium mixture). ^{13}C NMR (DMSO-d_6) Oxazoline form **9a** ∂: 159.8 (oxazoline C=N), 153.4 (tetrazole), 125.6, 135.2, 138.4, 138.6, (4 quaternary aromatics), 123.0, 128.0, 128.7, 129.2(2C), 129.6, 131.2, 133.4 (8 aromatics), 68.4 (CH_2), 59.0 (CMe_2), 49.8 (CH), 24.2 (Me), 19.6 (Me).

7-(1*H*-Tetrazol-5-yl)-5*H*-dibenz[c,e]azepin-5-one (10)

A solution of **9** (300mgs, 0.86mmol) in concentrated hydrochloric acid (2mls) was refluxed for 16 hours.

The reaction was allowed to cool and then evaporated *in vacuo* to give a light-yellow solid (144mgs, 60%). MS: 278 (M+H). ^{1}H NMR (methanol-d_4) ∂: 7.3-7.75 (m, 8H, aromatics), 5.9 (s, 1H, CH). ^{13}C NMR (methanol-d_4) ∂: 172.1 (-CONH), 158.3 (tetrazole), 132.8, 131.7, 131.1, 130.7, 130.1, 129.8, 129.6, 129.1 (8 aromatics), 52.8 (CH).

5-{Amino-(2-[2-carboxyphenyl]phenyl)methyl}-1*H*-tetrazole (11)

The cyclic amide **10** (200mgs, 0.72mmol) was dissolved in 2 molar sodium hydroxide (5mls) and heated at 100°C in a sealed vessel for 16 hours.

The reaction mixture was allowed to cool and then acidified (pH4) with glacial acetic acid. The crude product was purified by: 1) Preparative reverse phase HPLC (AQ-323 S-5 120A ODS column; eluant 1:1

H_2O:methanol pH=4.65 [NH_4OAc buffer]); 2) Ion-exchange chromatography (Dowex 50X8-100; column washed with a) H_2O b) 1:1 H_2O:THF c) H_2O; compound eluted with 9:1 H_2O:pyridine. The pyridine was removed azeotropically, the residual solid redissolved in water and freeze-dried to give a fluffy white solid (45mgs, 30%). Mpt. 225-8°C. MS: 296 (M+H), 278 (M+H-H_2O). ^1H NMR (D_2O) ∂: 7.70 (dd, 1H), 7.48-7.60 (m, 4H), 7.30 (dd, 1H), 7.22-7.28 (m, 2H), 5.8 (s, 1H, CH). ^{13}C NMR (D_2O) ∂: 178.0 (CO_2H), 160.0 (tetrazole), 144.5, 141.0, 139.3, 135.2 (4 quaternary aromatics), 133.0, 132.5 (3P), 131.6, 131.3, 130.6, 130.0 (8 aromatics), 51.3 (CH).

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