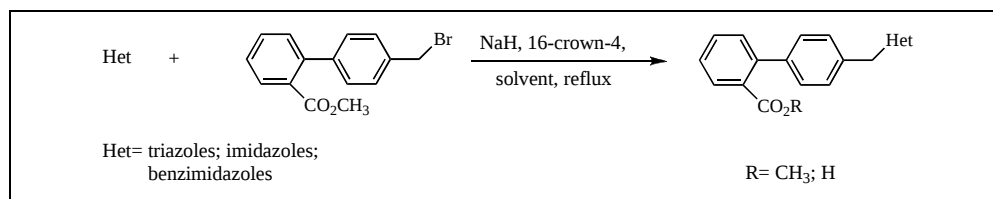


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Several novel analogues of Losartan **2** were synthesized as potential non-peptide angiotensin (II) receptor antagonists. In these non-peptide analogues, the tetrazole and the substituted imidazole rings of Losartan **2** were replaced, respectively, by a carboxylic acid function or its methyl ester and substituted triazole, imidazole or benzimidazole moieties. The biphenyl bromide precursor **3** (BPE) used to introduce the linker between the acid/ester function and the heterocyclic moiety was synthesized using Suzuki biphenyl coupling and then incorporated into the target molecule by simple nucleophilic substitution. The fixed N-aryl isomeric forms of several azole and benzimidazole tautomers were successfully separated by HPLC using 50% aqueous acetonitrile as eluent. Intermediate reaction products and final target compounds were fully characterized spectroscopically.

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INTRODUCTION

The renin-angiotensin system (RAS) cascade involves initial conversion of renin into angiotensin I (Ang I) followed by the formation of angiotensin II (Ang II) through the agency of angiotensin converting enzymes (ACE). The RAS cascade is essential in blood-pressure regulation and electrolyte fluid transport processes and consequently in antihypertensive therapy [1]. Hypertension is the most common cardiovascular malady afflicting as many as 50 million people in the USA alone [2].

RAS could be interrupted at the ACE stage with ACE blockers or by use of Ang II receptor antagonists. Both rennin and ACE inhibitors met with various difficulties in application or due to side effects, and hence more attention has been given to Ang II receptor antagonists. These include peptide and non-peptide antagonists, the first albeit weakly active non-selective, non-peptide

inhibitor being **1** (X = Cl, NO₂) [3-8]. The most successful among the non-peptide Ang II antagonists used in antihypertensive therapy is Losartan **2** (Figure I).

In the present work, we describe the different stages of the synthesis of new heterocyclic-based biphenyl Losartan analogues using substituted benzimidazoles and heterocycles derived from diaminomaleonitrile (DAMN) **4**, in addition to the techniques used to separate and identify the isomeric fixed forms obtained by the alkylation of tautomeric azoles with bromomethyl derivatives of biphenyl ester **3** (BPE), and their conversion into the corresponding carboxylic acid **3** (BPA) analogues by hydrolysis. It is envisaged that the present heterocyclic systems will induce and enhance the potential for possible synthesis and application of biologically active heterocyclic-based AT₁-non-peptide angiotensin (II) receptor antagonists.

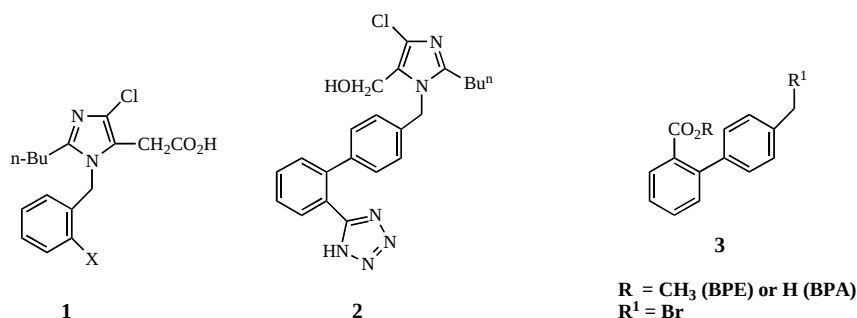


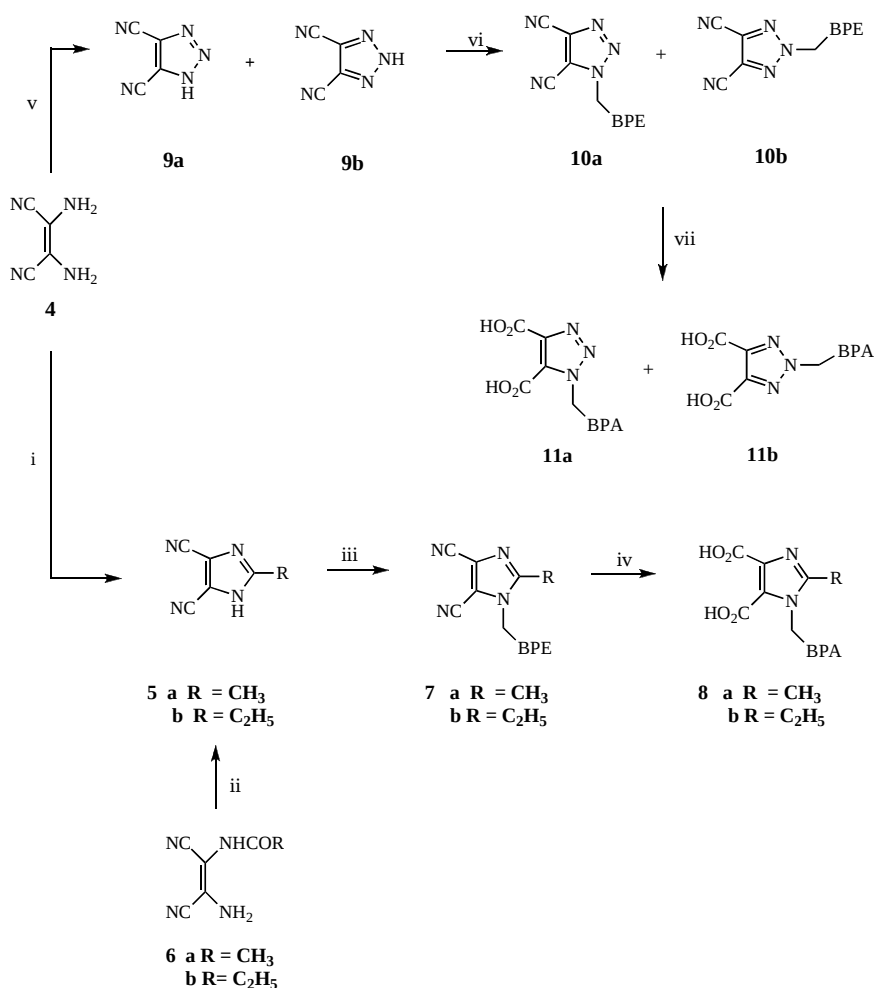
Figure I

RESULTS AND DISCUSSION

Diaminomaleonitrile (DAMN) **4** is a well known precursor in the preparation of many heterocyclic compounds [9]. The synthesis of imidazole derivatives, for example **5a,b** from **4** has been reported by several authors [10-11]. We have prepared these imidazoles in pure forms following the procedure reported by Rapoport *et al.* [11]; (route i, Scheme I). Alternatively, imidazoles **5** were obtained when amides **6** (route ii, Scheme I) were refluxed in the presence of NaH/DMF, the imidazoles **5a,b** were then decolorized by charcoal, and the yields were comparable to those reported [11]. *N*-[2-Amino-1,2-dicyanovinyl]acetamide or propanamide **6a,b** were readily prepared by direct reaction of **4** and the appropriate anhydrides [8-12], or by dissolving the hydrochloride salts of the corresponding amides in deionized water to furnish **6a,b** in just a few minutes [12]. The imidazoles **5a,b** were

then reacted with the biphenyl ester (BPE) **3** to yield the alkylated derivatives **7a,b** and the latter were hydrolyzed with aqueous KOH into **8a,b**, respectively (routes iii, iv, Scheme I). The formation of **8a,b** proceeded by concomitant hydrolysis of the ester group and the two cyano functions of **7a,b** as indicated by $^1\text{H}/^{13}\text{C}$ NMR spectra and elemental analyses. The ^1H NMR of **7a,b** showed the appearance of methylene protons as singlets at δ 5.30 ppm **7a** and δ 5.31 ppm **7b**, respectively. The hydrolysed derivatives **8a,b** showed also the presence of carboxylic acid protons as broad singlets at δ 7.5-13 ppm. The salts of the alkylated imidazole derivatives **8a,b** offered the advantage of use in aqueous preparations.

1,2,3-Triazole-4,5-dicarbonitrile **9** was obtained *via* diazotization of DAMN **4** following literature procedure [13]. Two high intensity ^{13}C NMR signals were observed at 113.6 and 123.2 ppm, and a third very low intensity peak at 128.4 ppm. Assuming that the highest intensity



i) triethyl orthoacetate/propionate (1.2-1.4 equiv.), NaOCH₃, anisole, 2 hrs; ii) NaH (1 equiv.), DMF, reflux, 10-18 hrs; iii) NaH (1 equiv.), **3** (BPE, R¹ = Br) (1 equiv.), cat. 16-crown-4ether, 1,4-dioxane, reflux, 18 hrs; iv) KOH (10%), reflux, 18 hrs; v) HCl/NaNO₂, 0 °C, 1 hr; vi) NaH (1 equiv.), **3** (BPE, R¹ = Br) (1 equiv.), cat. 16-crown-4ether, toluene, reflux, 5 hrs; vii) KOH (10%), reflux, 18 hrs.

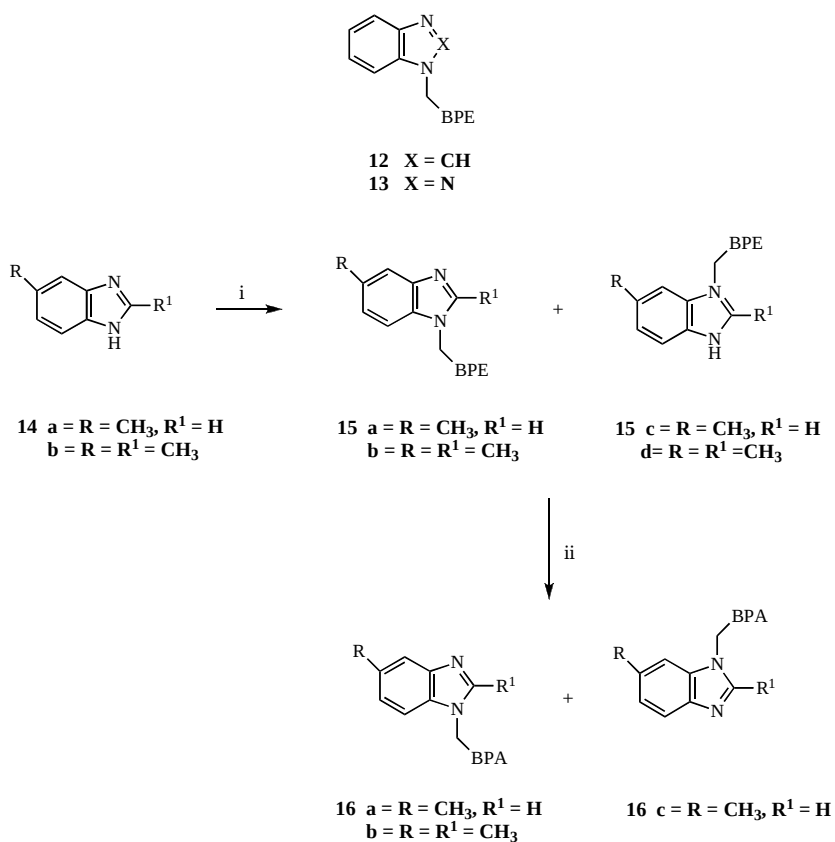
Scheme I

peak at 113.6 is the result of an overlap of two signals, **9a** would be considered the predominant tautomer. However, taken on their own, the two high intensity peaks would be indicative of tautomer **9b**. This tautomer is symmetric, with its lone pair of electrons on (N) effectively delocalized in the ring and partitioned over the two cyano groups. Many studies showed that the tautomer relative ratio depends on temperature, solvent used in ¹H NMR, and concentration, ¹⁵N studies also supported the previous study that 1*H*-1,2,3-triazole exists in 66% in CDCl₃, on the other hand, the 2*H* tautomer is favoured by 55% in d₆-DMSO. Another study in aqueous solution, showed that the 2*H* isomer predominates by a factor of two lone pair repulsion is the most probable cause. The study also revealed that the tautomerism ratio is solvent dependant [14-15]. Alkylation of 1,2,3-triazole-4,5-dicarbonitrile **9** gave a pale yellow oil, the ¹H NMR spectrum of which revealed the presence of two fixed isomeric forms of the ester **10** in approximately 1:2 ratio. The ¹H NMR spectrum of the mixture showed two methylene groups at δ 5.75 ppm and δ 5.80 ppm for the major and the minor isomers, respectively. The same ratio has been observed on hydrolysis of the mixture on reflux in aqueous KOH solution to the corresponding acid forms **11**.

In an attempt to assign the major and the minor isomers of **10**, the isomers were successfully separated using preparative HPLC with 50% aqueous acetonitrile as eluent. One of the HPLC fractions obtained as a pale yellow oil showed 15 carbons in its ¹³C NMR spectrum corresponding to the structure of the fixed isomer **10b** derived from the symmetric tautomer **9b**. Based on this result and the analysis of both ¹H and ¹³C NMR spectral data of the isomeric mixture, isomer **10b** is the major.

Alkylation of benzimidazole and benzotriazole with **3** (BPE, R¹= Br) to prepare, respectively, the ester **12** and **13** analogues has already been reported [16]. Here, we now present the results of the reaction of both 5-methylbenzimidazole **14a** and 2,5-dimethylbenzimidazole **14b** with methyl 4'-(bromomethyl)biphenyl-2-carboxylate **3**, first to prepare the esters **15** and then hydrolyse these into the acids **16**.

The precursors **14a** and **b** were prepared *via* reacting 4-methyl-1,2-phenylenediamine with, respectively, formic acid and acetic acid. The benzimidazole derivative **14a** reacted with **3** (route i, Scheme II) to yield a mixture of the isomers **15a** and **15c** in a ratio of 9:1. HPLC was also performed on the mixture to separate the two isomers.



i) NaH (1 equiv.), **3** (BPE, R¹= Br) (1 equiv.), toluene, reflux, 5 hrs; ii) KOH (10%), reflux, 18 hrs.

Scheme II

The fact that **15a** is the major isomer can be attributed to a steric effect favouring formation of the less bulky isomer. Further, the influence of steric effects on the isomer ratios of the reaction of **14** is clearly evident from the outcome of the reaction of **14b** with **3** (BPE, R¹ = Br) (route i, Scheme II). Analysis of the product of this reaction indicated the formation of only **15b**, with no trace of its bulkier isomeric form **15d**. Hydrolysis of **15a,c** mixture and **15b** (route ii, Scheme II) afforded **16a** with no trace of **16c** as shown by ¹H NMR spectrum, and **16b** in good yields.

CONCLUSION

A library of non-peptide angiotensin (II) receptor antagonists is built for screening as potential agents in antihypertensive therapy. The library now includes several promising candidates. Formation of isomers can be easily solved by separating them using highly advanced techniques such as preparative HPLC.

Acknowledgements. The financial support of Kuwait University received through research grant SC 04/02 and SAF facilities through Projects GS 01/01 and GS 03/01 are gratefully acknowledged.

EXPERIMENTAL

General. Diaminomaleonitrile (DAMN) **4**, 16-crown-4-ether, 4-tolylboronic acid and sodium hydride are from Aldrich, and 5-methylbenzimidazole **14a**, 2,5-dimethylbenzimidazole **14b**, and methyl 4'-(bromomethyl)biphenyl-2-carboxylate **3** (BPE, R¹ = Br) used in this work were prepared according to literature procedures [8,17-18]. ¹H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz, and ¹³C NMR spectra were obtained using a Bruker DPX 400 spectrometer at 100 MHz; TMS was used as a reference. Mass spectra were from a VG Autospec Q spectrometer with digital data output. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on KBr disc using Perkin Elmer 2000 FT Spectrophotometer. TLC was performed on 0.25 mm pre-coated silica gel plates (Merck). Substrates were separated in pure form using Waters Preparative HPLC Delta Prep 4000 combining PrepLC Controller, PrepCL 4000 Series solvent delivery unit, and an integral injector panel assembly within a simple, three-level shelf. The detector used was a Water 2996 Photodiode Array and variable path length flow cell for both analytical and preparative work. HPLC columns used for the analysis and separation were Supelco (25 cm length, 4.6 mm ID) and (25 cm length, 21.2 mm ID) ABZ⁺, respectively. The mobile phase composition used in the separation was 50:50 v/v [CH₃CN:H₂O].

Synthesis of *N*-[2-Amino-1,2-dicyanovinyl]acetamide (**6a**).

Method A. DAMN **4** (1.00 g, 9.26 mmol) was gently warmed with acetic anhydride (2.0 mL) in which it dissolved readily. On cooling, pale violet crystals were obtained. The crystals were collected by filtration and washed with chloroform. The product was refluxed with charcoal in ethanol, for 15 min, and crystallised to give on cooling colourless needles **6a** (1.37 g, 9.13 mmol, 99% yield).

Method B. In a 50 mL round-bottomed flask a suspension of **4** (1.00 g, 9.26 mmol), and ethyl acetate (15.0 mL) was stirred at room temperature. Acetyl chloride (0.73 g, 9.26 mmol) was then added. An exothermic reaction took place with formation of white fumes. TLC (9:1 v/v, CHCl₃:EtOH) showed the reaction to be complete within one hour. The reaction mixture was then filtered and the solid so obtained washed with diethyl ether, and the resultant yellow powder was then stirred in deionised water to furnish **6a** (1.2 g, 8.0 mmol, 86% yield). M.p. 164 °C [Found: C, 48.2; H, 4.0; N, 37.1; m/z (EI) M⁺ 108 (M-COCH₃), 100%, 151 (M+1), 50% C₆H₆N₄O requires: C, 48.0; H, 4.0; N, 37.3; M 150]; δ_H 400 MHz (d₆-DMSO, Me₄Si) 1.93 (s, 3H, CH₃), 7.19 (s, 2H, NH₂), 9.14 (s, 1H, NH); δ_C 100 MHz (d₆-DMSO, Me₄Si) 169.4, 127.35, 117.7, 114.7, 90.2, 23.4; ν_{max}: (KBr) 3524, 3316, 3200, 2999, 2251, 2212, 1695, 1530, 1395, 1367, 1303, 992 cm⁻¹.

Synthesis of *N*-[2-Amino-1,2-dicyanovinyl]propanamide (6b**).** A mixture of **4** (1.00 g, 9.26 mmol) and propanoic anhydride (1.21 g, 9.3 mmol) was heated gently in a water bath at 50 °C for 10 minutes. The precipitate formed was collected by filtration and washed with petroleum ether to afford **6b** as a white powder (1.30 g, 7.93 mmol, 86% yield). M.p. 165 °C [Found: C, 51.0; H, 4.9; N, 34.2; m/z (EI) (COCH₂CH₃), 57 100%, 164 M⁺, 15% C₇H₈N₄O requires: C, 51.2; H, 4.8; N, 34.1; M 164]; δ_H 400 MHz (d₆-DMSO, Me₄Si) 1.00 (t, 3H, J 7.5 Hz, CH₃), 2.21 (q, 2H, J 7.5 Hz, CH₂), 7.16 (s, 2H, NH₂), 9.06 (s, 1H, NH); δ_C 100 MHz (d₆-DMSO, Me₄Si) 173.1, 127.3, 117.9, 115, 90.6, 29.0, 10.0; ν_{max}: (KBr) 3410, 3319, 3217, 2978, 2879, 2251, 2212, 1669, 1638, 1523, 1383, 1292, 1072 cm⁻¹.

Synthesis of 2-Methyl-1*H*-imidazole-4,5-dicarbonitrile (**5a**) and 2-Ethyl-1*H*-imidazole-4,5-dicarbonitrile (**5b**).

Method A. A mixture of **4** (5.0 g, 46.3 mmol) and, respectively, triethyl orthoacetate (9.75 g, 60.2 mmol) for **5a** and triethyl orthopropionate (9.79 g, 55.6 mmol) for **5b** in anisole (60 mL) was heated in a water bath at 100 °C, with distillation of ethanol over a period of 2 hours. Sodium metal (0.18 g, 7.87 mmol) in methanol (5 mL) was then added, and heating was continued until no more ethanol distillate was obtained. The reaction mixture was filtered while hot, and then cooled to afford **5a** (4.3 g, 32.6 mmol, 70% yield) and **5b** (4.5 g, 30.8 mmol, 67% yield).

Method B. A mixture of either **6a** (0.5 g, 3.3 mmol) or **6b** (0.5 g, 3.0 mmol) with an equimolar amount of NaH in DMF (15 mL) was refluxed for 10-18 hours. The mixture was then cooled and poured into water. The pH was adjusted to 7 and the resulting mixture was extracted with diethyl ether to yield **5a** (0.21 g, 1.6 mmol, 48% yield) and **5b** (0.12 g, 0.82 mmol, 27% yield). **5a**: M.p. 228 °C [Found accurate mass: 132.0436; m/z (EI) M⁺ 132, 100%, C₆H₄N₄ requires: 132.0431; M 132]; δ_H 400 MHz (d₇-DMF, Me₄Si) 2.49 (s, 3H, CH₃), 12.8 (brs, 1H, NH); δ_C 100 MHz (d₇-DMF, Me₄Si) 152.1, 115.9, 111.9, 79.8, 14.1; ν_{max}: (KBr) 3414, 3162, 3006, 2893, 2750, 2641, 2536, 2236, 1581, 1520, 1394, 1299, 1145, 1039, 920, 770 cm⁻¹. **5b**: M.p. 184 °C [Found: C, 57.5; H, 4.1; N, 38.4; m/z (EI) M⁺ 147 (M+1), 100%, C₇H₆N₄ requires: C, 57.5; H, 4.1; N, 38.4; M 146]; δ_H 400 MHz (d₇-DMF, Me₄Si) 1.28 (t, 3H, J 7.7 Hz, CH₃), 2.80 (q, 4H, J 7.6 Hz, CH₂), 14.1 (brs, 1H, NH); δ_C 100 MHz (d₇-DMF, Me₄Si) 157.0, 115.9, 112.1, 79.9, 22.3, 12.0; ν_{max}: (KBr) 3129, 2985, 2237, 1569, 1521, 1414, 1322, 1301, 1211, 1064, 1038 cm⁻¹.

Synthesis of methyl 4'-(4,5-dicyano-2-methylimidazol-1-ylmethyl)-biphenyl-2-carboxylate (7a**) and methyl 4'-(4,5-dicyano-2-ethylimidazol-1-ylmethyl)-biphenyl-2-carboxylate**

(**7b**). A mixture of either **5a** (1.0 g, 7.6 mmol) or **5b** (1.0 g, 6.8 mmol) with an equimolar amount of sodium hydride in 1,4-dioxane (30 mL) was warmed for 5 minutes. After cooling, a catalytic amount of 16-crown-4ether was added followed by addition of an equimolar amount of **3** (BPE, R¹ = Br). After refluxing the reaction mixture for 18 hours, the mixture was cooled and then poured into water and extracted with dichloromethane. Evaporation of dichloromethane gave the crude **7a** and **7b** as brown oils. Column chromatography (1:1, v/v, EtOAc:CHCl₃) furnished **7a** (1.7 g, 4.8 mmol, 63% yield), and **7b** (1.5 g, 4.0 mmol, 60% yield). **7a**: M.p. 124 °C [Found: C, 70.5; H, 4.7; N, 15.8; m/z (EI) M⁺ 356, 60%, (M-C₆H₃N₄) 225, 100%, C₂₁H₁₆N₄O₂ requires: C, 70.8; H, 4.5; N, 15.7; M 356]; δ_H 400 MHz (CDCl₃, Me₄Si) 2.52 (s, 3H, CH₃), 3.69 (s, 3H, OCH₃), 5.30 (s, 2H, CH₂), 7.18 (d, 2H, J 8 Hz, ArH), 7.33 (m, 3H, ArH), 7.45 (dt, 1H, J 0.88 Hz, J 7.5 Hz, ArH), 7.56 (dt, 1H, J 1 Hz, J 7.5 Hz, ArH), 7.90 (d, 1H, J 8 Hz, ArH); δ_C 100 MHz (CDCl₃, Me₄Si) 168.9, 151.4, 143.2, 142.0, 132.2, 132.1, 131.3, 131.2, 130.7, 130.2, 128.4, 127.3, 128.2, 113.3, 112.3, 109.1, 52.7, 50.6, 14.5; ν_{max}: (KBr) 3438, 3001, 2839, 2231, 1724, 1516, 1416, 1256, 1087, 747 cm⁻¹. **7b**: M.p. 96 °C [Found: C, 71.3; H, 4.9; N, 15.2; m/z (EI) M⁺ 370, 10%, (M-C₆H₃N₄) 225, 100%, C₂₂H₁₈N₄O₂ requires: C, 71.3; H, 4.8; N, 15.1; M 370]; δ_H 400 MHz (CDCl₃, Me₄Si) 1.36 (t, 3H, J 7.4 Hz, CH₃), 2.74 (q, 2H, J 7.5 Hz, CH₂), 3.68 (s, 3H, OCH₃), 5.31 (s, 2H, CH₂), 7.17 (d, 2H, J 8 Hz, ArH), 7.33 (m, 3H, ArH), 7.44 (dt, 1H, J 0.9 Hz, J 7.6 Hz, ArH), 7.55 (dt, 1H, J 1.0 Hz, J 7.6 Hz, ArH), 7.89 (d, 1H, J 7.4 Hz, ArH); δ_C 100 MHz (CDCl₃, Me₄Si) 169.0, 155.9, 143.2, 142.0, 132.3, 132.2, 131.3, 130.7, 130.6, 130.1, 128.4, 127.1, 122.5, 113.2, 112.5, 109.1, 52.7, 50.9, 21.6, 11.7; ν_{max}: (KBr) 3027, 2988, 2946, 2232, 1720, 1508, 1449, 1417, 1280, 1243, 1123, 1050, 818, 758 cm⁻¹.

Synthesis of 1-(2'-carboxybiphenyl-4-ylmethyl)-2-methyl-1H-imidazole-4,5-dicarboxylic acid (8a) and 1-(2'-carboxybiphenyl-4-ylmethyl)-2-ethyl-1H-imidazole-4,5-dicarboxylic acid (8b). A solution of either **7a** (0.50 g, 1.4 mmol) or **7b** (0.50 g, 1.35 mmol) with KOH 10% was refluxed for 18 hours. After cooling the mixture was neutralised with aqueous HCl. The precipitate that formed was collected by filtration and dried to give **8a** (0.32 g, 0.84 mmol, 60% yield), and **8b** (0.34 g, 0.86 mmol, 64 % yield). **8a**: M.p. 225 °C [Found: C, 62.8; H, 4.2; N, 7.5; m/z (EI) M⁺ 380, 10%, (M-C₆H₅N₂O₄) 211, 100%, C₂₀H₁₆N₂O₆ requires: C, 63.1; H, 4.2; N, 7.4; M 380]; δ_H 400 MHz (d₆-DMSO, Me₄Si) 2.50 (s, 3H, CH₃), 5.94 (s, 2H, CH₂), 7.22 (d, 2H, J 8.1 Hz, ArH), 7.30 (d, 2H, J 8.1 Hz, ArH), 7.35 (d, 1H, J 7.5 Hz, ArH), 7.44 (t, 1H, J 7.4 Hz, ArH), 7.55 (m, 2H, CO₂H, ArH), 7.71 (d, 1H, J 7.0 Hz, ArH), 8.30 (s < 1H, CO₂H), 12.8 (brs, 1H, CO₂H); δ_C 100 MHz (d₆-DMSO, Me₄Si) 170.6, 160.3, 160.2, 148.5, 141.4, 141.3, 135.0, 133.3, 132.0, 131.4, 130.5, 130.1, 129.7, 128.4, 127.9, 127.6, 49.3, 12.2; ν_{max}: (KBr) 3477, 3024, 1725, 1700, 1592, 1547, 1514, 1444, 1381, 1322, 1233, 1131, 1005, 764 cm⁻¹. **8b**: M.p. 215 °C [Found: C, 63.8; H, 4.9; N, 7.3; m/z (EI) (M-C₄H₅O₄) 277, 100%, C₂₁H₁₈N₂O₆ requires: C, 63.9; H, 4.6; N, 7.1; M 394]; δ_H 400 MHz (d₆-DMSO, Me₄Si) 1.05 (t, 3H, J 7.6 Hz, CH₃), 2.90 (q, 2H, J 7.6 Hz, CH₂), 6.98 (s, 1H, CH₂), 7.20 (d, 2H, J 8.1 Hz, ArH), 7.30 (d, 2H, J 8.1 Hz, ArH), 7.35 (d, 1H, J 7.6 Hz, ArH), 7.44 (t, 1H, J 7.6 Hz, ArH), 7.55 (dt, 1H, J 7.5 Hz, J 1.2 Hz, ArH), 7.71 (d, 1H, J 7.6 Hz, ArH), 12.8 (brs, 1H, CO₂H); δ_C 100 MHz (d₆-DMSO, Me₄Si) 170.5, 160.4, 160.2, 152.5, 141.4, 141.2, 135.7, 133.2, 132.0, 131.5, 131.0, 130.2, 129.7, 128.4, 127.8, 127.3, 49.1, 19.3, 12.6; ν_{max}: (KBr) 3446, 3024, 2794, 1696, 1592, 1540, 1511, 1374, 1283, 1188, 1005, 767 cm⁻¹.

Synthesis of 1,2,3-triazole-4,5-dicarbonitrile (9). Compound **4** (1.0 g, 9.26 mmol) was stirred in aqueous HCl (37%, 10 mL). The reaction mixture was cooled to 0 °C and a solution of sodium nitrite (0.7 g, 10 mmol) in water (2 mL) was added while stirring. After one hour, a clear solution was formed which was extracted with diethyl ether to furnish **9** (0.77 g, 6.5 mmol, 70% yield). M.p. 145 °C [Found: C, 40.3; H, 0.81; N, 59.2; m/z (EI) M⁺ 119, 100%, C₄H₃N₅ requires: C, 40.3; H, 0.84; N, 58.8; M 119]; δ_H 400 MHz (d₆-DMSO, Me₄Si) 10.10 (s, 1H, NH); δ_C 100 MHz (d₆-DMSO, Me₄Si) 128.4, 123.2, 113.6; ν_{max}: (KBr) 3260, 2261, 1479, 1382, 1129, 791 cm⁻¹.

Synthesis of isomeric methyl 4'-(4,5-dicyano-[1,2,3]triazol-1-ylmethyl)biphenyl-2-carboxylate (10a) and methyl 4'-(4,5-dicyano-[1,2,3]triazol-2-ylmethyl)biphenyl-2-carboxylate (10b). A mixture of **9** (1.0 g, 8.4 mmol) and NaH (0.2 g, 8.3 mmol) in toluene was heated gently for five minutes and allowed to cool to room temperature. A catalytic amount of 16-crown-4ether and an equimolar amount of methyl 4'-(bromomethyl)biphenyl-2-carboxylate **3** were then added and the mixture was refluxed for five hours. After cooling to room temperature, the reaction mixture was poured into water and extracted with toluene to afford a brown oil. Column chromatography (65:35, v/v, hexane : ethyl acetate) as an eluent yielded a mixture of **10a** and **10b** (1.53 g, 4.5 mmol, 53% yield). [Found: C, 66.0; H, 3.9; N, 20.3; m/z (EI) M⁺ 343, 100%, C₁₉H₁₃N₅O₂ requires: C, 66.4; H, 3.8; N, 20.4; M 343]; δ_H 400 MHz (CDCl₃, Me₄Si): **Mixture**: 3.69 (s, 3H, OCH₃), 5.75 (s, 2H, CH₂), 5.80 (s, 2H, CH₂), 7.32 (m, 3H, ArH), 7.45 (m, 3H, ArH), 7.55 (tt, 1H, J 7.6 Hz, J 1.5 Hz, ArH), 7.90 (td, 1H, J 8.5 Hz, J 1.4 Hz, ArH). **10b (Major Isomer)**: 3.70 (s, 3H, OCH₃), 5.75 (s, 2H, CH₂), 7.32 (m, 3H, ArH), 7.44 (m, 3H, ArH), 7.55 (tt, 1H, J 1.5 Hz, J 7.6 Hz, ArH), 7.90 (d, 1H, J 7.7 Hz, ArH); δ_C 100 MHz (CDCl₃, Me₄Si): **Mixture**: 168.90, 144.11, 143.70, 142.21, 142.00, 132.24, 132.22, 131.36, 131.34, 131.04, 130.80, 130.74, 130.65, 130.27, 130.21, 129.96, 129.92, 129.12, 128.99, 128.94, 128.44, 128.34, 126.39, 109.04, 108.88, 106.07, 61.73, 61.58, 55.98, 52.67. **10b (Major Isomer)**: 168.92, 143.72, 142.20, 132.20, 131.36, 131.07, 130.74, 130.29, 129.92, 129.11, 128.34, 126.41, 108.87, 61.73, 52.65; ν_{max}: (KBr): **Mixture**: 3064, 2952, 2254, 1724, 1435, 1287, 1192, 1129, 1091, 911, 762 cm⁻¹. **10b (Major Isomer)**: 3029, 2961, 2255, 1723, 1599, 1481, 1440, 1283, 1261, 1190, 1125, 1092, 1019, 912, 797 cm⁻¹.

Synthesis of 4'-(2'-carboxy-[1,2,3]triazol-1-ylmethyl)biphenyl-4,5-dicarboxylic acid (11a) and 4'-(2'-carboxy-[1,2,3]triazol-2-ylmethyl)biphenyl-5-dicarboxylic acid (11b). An isomeric mixture of **10a** and **10b** (1.0, 2.9 mmol) in KOH 10% was refluxed for 18 hours. After cooling, the mixture was neutralised with aqueous HCl, and an off-white solid started to form. The solid was recrystallized from ethanol to give an isomeric mixture of **11a** and **11b** (0.80 g, 2.0 mmol, 68% yield). M.p. > 250 °C [Found: C, 53.2; H, 3.0; N, 10.6; m/z (EI) 135, 100%; (M-C₄H₂N₃O₄) 211, 80%, C₁₈H₁₃N₃O₆.HCl requires: C, 53.5; H, 3.4; N, 10.4; (M-HCl) 367]; δ_H 400 MHz (CDCl₃, Me₄Si) 5.75 (s, 2H, CH₂, major isomer), 6.10 (s, 2H, CH₂, minor isomer), 7.27 (d, 1H, J 5 Hz, ArH), 7.33 (m, 4H, ArH), 7.44 (dt, 1H, J 1.22 Hz, J 7.5 Hz, ArH), 7.54 (m, 1H, ArH), 7.71 (dt, 1H, J 1.2 Hz, J 6 Hz, ArH), 12.8 (s, 1H, COOH); δ_C 100 MHz (CDCl₃, Me₄Si) 170.52, 162.20 (major isomer), 161.93 (minor isomer), 160.12, 143.73, 141.93, 144.45, 141.34, 136.44, 134.889, 133.51, 133.24, 131.94, 131.50, 130.57, 130.13, 129.71, 129.53, 128.99, 128.46, 128.39, 80.2, 59.3, 52.9; ν_{max}: (KBr) 3024, 2889, 2788, 1706, 1592, 1505, 1405, 1288, 1259, 1150, 1003, 861, 761 cm⁻¹.

Synthesis of methyl 4'-(5-methyl-benzimidazol-1-yl-methyl)biphenyl-2-carboxylate (15a) and methyl 4'-(5-methyl-benzimidazol-3-ylmethyl)biphenyl-2-carboxylate (15c) and methyl 4'-(2,5-dimethyl-benzimidazol-1-ylmethyl)-biphenyl-2-carboxylate (15b). On mixing equimolar amounts of NaH and **14a** (0.55 g, 4.2 mmol) or **14b** (0.50 g, 3.4 mmol) in toluene, a solid started to form after five minutes. This solution was warmed up and kept warm for five minutes more, and then allowed to cool to room temperature. Catalytic amount of 16-crown-4-ether and equimolar amount of biphenyl bromide **3** were added and the mixture was refluxed for five hours. The resultant reaction mixture was cooled to room temperature, then cold water was added, and the mixture was extracted with toluene. The solvent was evaporated to afford a mixture of **15a** and **15c** (0.97 g, 2.7 mmol, 65% yield), and **15b** (0.75 g, 2.0 mmol, 58% yield). **Mixture 15a, c**: M. p. 105 °C [Found: C, 77.3; H, 5.7; N, 8.0; m/z (EI) M⁺ 356, 100%, C₂₃H₂₀N₂O₂ requires: C, 77.5; H, 5.6; N, 7.9; M 356].

δ_{H} 400 MHz (CDCl₃, Me₄Si): **Mixture**: 2.48 (s, 3H, CH₃), 3.65 (s, 3H, OCH₃), 5.30 (s, 2H, CH₂), 5.39 (s, 2H, CH₂), 7.10 (m, 3H, ArH), 7.28 (m, 3H, ArH), 7.40 (t, 1H, *J* 7.5 Hz, ArH), 7.52 (t, 1H, *J* 7.5 Hz, ArH), 7.65 (s, 1H, ArH), 7.72 (d < 1H, *J* 8.7 Hz, ArH), 7.85 (d, 1H, *J* 7.7 Hz, ArH), 7.96 (s < 1H, ArH), 7.99 (s < 1H, ArH). **15a (Major Isomer)**: 2.49 (s, 3H, CH₃), 3.65 (s, 3H, OCH₃), 5.40 (s, 2H, CH₂), 7.10 (m, 2H, ArH), 7.21 (m, 2H, ArH), 7.28 (m, 3H, ArH), 7.34 (t, 1H, *J* 7.6 Hz, ArH), 7.53 (t, 1H, *J* 7.5 Hz, ArH), 7.65 (s < 1H, ArH), 7.73 (s < 1H, ArH), 7.85 (d, 1H, *J* 7.7 Hz, ArH), 7.96 (s, 1H, ArH). δ_{C} 100 MHz (CDCl₃, Me₄Si): **Mixture**: 169.27, 144.17, 143.59, 143.26, 143.29, 142.40, 142.05, 142.01, 134.90, 134.67, 133.92, 132.47, 132.5, 132.03, 131.86, 131.48, 131.29, 131.09, 130.56, 129.60, 128.04, 127.40, 127.34, 125.39, 124.75, 120.49, 120.33, 110.51, 110.30, 52.56, 52.53, 49.36, 49.12, 22.42, 22.12. **15a (Major Isomer)**: 169.28, 142.44, 141.19, 135.10, 133.75, 132.60, 132.03, 131.20, 130.57, 129.58, 128.03, 127.32, 125.20, 124.56, 120.78, 120.53, 110.45, 110.18, 52.54, 49.18, 22.26. **Mixture**: ν_{max} : (KBr) 3028, 2949, 1724, 1496, 1445, 1330, 1286, 1259, 1189, 1128, 1090, 911, 762, 731 cm⁻¹. **15b**: [Found: C, 76.0; H, 6.2; N, 7.3; m/z (EI) M⁺ 370, 90%; (M-C₉H₉N₂) 225, 100%, C₂₄H₂₂N₂O₂·0.5H₂O requires: C, 75.9; H, 6.0; N, 7.3; M 370]; δ_{H} 400 MHz (CDCl₃, Me₄Si) 2.48 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 3.66 (s, 3H, OCH₃), 5.37 (s, 2H, CH₂), 7.07 (m, 4H, ArH), 7.17 (d < 1H, *J* 8.2 Hz, ArH), 7.26 (m > 1H, ArH), 7.31 (m, 1H, ArH), 7.41 (t, 1H, *J* 7.5 Hz, ArH), 7.52 (m > 1H, ArH), 7.64 (d < 1H, *J* 8.0 Hz, ArH), 7.85 (d, 1H, *J* 7.7 Hz, ArH); δ_{C} 100 MHz (CDCl₃, Me₄Si) 169.3, 152.2, 151.9, 142.4, 135.2, 133.0, 132.6, 132.0, 131.2, 130.5, 129.6, 128.0, 126.5, 124.5, 119.3, 119.0, 110.0, 109.7, 52.6, 47.5, 22.4, 22.1; ν_{max} : (KBr) 3392, 2948, 2922, 1723, 1622, 1519, 1446, 1401, 1284, 1250, 1189, 1127, 1089, 1048, 1005, 758 cm⁻¹.

Synthesis of 4'-(5-methyl-benzimidazol-1-ylmethyl)biphenyl-2-carboxylic acid (16a) and 4'-(2,5-dimethyl-benzimidazol-1-ylmethyl)biphenyl-2-carboxylic acid (16b). A mixture of **15a** and **15c** (0.50 g, 1.40 mmol) or **15b** (0.5 g, 1.32 mmol) in aqueous KOH (10%, 10 mL) was refluxed for 18 hours. After cooling, the mixture was neutralized with aqueous HCl. A white precipitate was formed, which was filtered washed and dried to afford **16a** (0.36 g, 1.05 mmol, 75% yield), and **16b** (0.33 g, 0.93 mmol, 70% yield). **16a**: M.p. 233 °C [Found: C, 77.0; H, 5.3; N, 8.3; m/z (EI) M⁺ 342, 100%, C₂₂H₁₈N₂O₂ requires: C, 77.1; H, 5.2; N, 8.1; M 342]; δ_{H} 400 MHz (d₆-DMSO, Me₄Si) 2.41 (s, 3H, CH₃), 5.56 (s, 2H, CH₂), 7.09 (m, 1H, ArH), 7.29 (m, 5H, ArH), 7.42 (t, 1H, *J* 7.4 Hz, ArH), 7.51

(m, 3H, ArH), 7.70 (d, 1H, *J* 7.6 Hz, ArH), 8.59 (s < 1H, ArH), 8.68 (s < 1H, ArH), 12.73 (brs, 1H, COOH); δ_{C} 100 MHz (d₆-DMSO, Me₄Si) 170.7, 145.2, 144.8, 137.0, 132.9, 131.7, 131.4, 130.0, 129.7, 129.6, 128.3, 128.1, 128.0, 124.9, 124.2, 120.1, 111.4, 80.2, 48.1, 22.3; ν_{max} : (KBr) 3343, 2920, 1705, 1501, 1446, 1256, 1083, 804, 762 cm⁻¹. **16b**: M.p. > 250 °C [Found: C, 77.3; H, 5.8; N, 7.8; m/z (EI) M⁺ 356, 40%, 211, 100%, C₂₃H₂₀N₂O₂ requires: C, 77.5; H, 5.6; N, 7.8; M 356]; δ_{H} 400 MHz (d₆-DMSO, Me₄Si) 2.39 (s, 3H, CH₃), 2.51 (s, 3H, CH₃), 5.48 (s, 2H, CH₂), 6.97 (m, 1H, ArH), 7.12 (d, 2H, *J* 7.6 Hz ArH), 7.27 (m, 4H, ArH), 7.38 (m, 2H, ArH), 7.52 (t, 1H, *J* 7.5 Hz, ArH), 7.69 (d, 1H, *J* 7.6 Hz, ArH), 12.71 (brs, 1H, COOH); δ_{C} 100 MHz (CDCl₃, Me₄Si) 172.2, 151.6, 151.4, 142.6, 141.2, 134.2, 133.7, 132.3, 131.9, 131.0, 130.8, 128.0, 126.8, 125.9, 125.7, 117.8, 110.4, 110.2, 47.7, 22.4, 22.0; ν_{max} : (KBr) 3423, 3027, 2920, 1681, 1517, 1411, 1302, 1243, 1136, 1005, 807, 747 cm⁻¹.

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