## Molecular recognition of xanthine alkaloids: First synthetic receptors for theobromine and a series of new receptors for caffeine

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Synthetic receptors (H3, H4, H5 and H6) are designed and synthesised for the first time for theobromine, a xanthine alkaloid used as a diuretic. The synthesis of the receptor H6 is achieved by  $Co(PPh_3)_3Cl$ -mediated homocoupling of 3-(ethoxycarbonyl)benzyl bromide 12 under mild conditions. New caffeine receptors (H7, H8 and H9) are designed and synthesised. The binding results of theobromine and caffeine (both by NMR and UV studies) are reported.

The design and synthesis of abiotic (*i.e.*, non-natural) receptors which undergo molecular recognition using weak non-covalent interactions is an emerging field <sup>1,2</sup> with many potential applications,<sup>3,4</sup> such as sensors,<sup>5</sup> carriers, and other molecular devices.<sup>5</sup> Such receptors can serve as models for the understanding of fundamental molecular recognition processes in biological systems.

Xanthine derivatives (G1, G2, G3) have several pharmacological actions, such as antibronchospastic, CNS-stimulation, and tachycardia activity,<sup>6</sup> etc. We report here for the first time the design and synthesis of receptors H3, H4, H5 and H6 (the numbering of receptors starts from H3) to recognise theobromine (G1, a difficult recognition substrate because of its very poor solubility in both chloroform and methanol) and their binding efficacy to solubilise it in a less polar solvent like chloroform. It is one of our goals in molecular recognition research to make the insoluble bio-substrate (e.g., urea<sup>7</sup>) soluble in chloroform (a common NMR solvent for binding studies) by hydrogen-bond complexation with the designed receptors quenching the individual self-polarity.



The other xanthine derivative, caffeine (G2) (a trimethylxanthine), which is present in tea and coffee seeds, has long been known to be responsible for the stimulating effect of tea, and plays important roles in determining the liquor characters,<sup>8</sup> *i.e.* tea creaming (strength and briskness), for the desirable attributes of the beverage. So it has interested chemists for its complexation studies.<sup>9</sup>

Previously, complexation studies of caffeine in aqueous solution have been performed with a number of known polyphenols<sup>10</sup> and cyclodextrins.<sup>10</sup> We report here the recognition of caffeine in chloroform with our new synthetic amidic and non-amidic receptors **H7**, **H8** and **H9**.

#### **Recognition of theobromine**

Our designs are based on the structural features of theobromine which suggest that the two lactam carbonyl groups

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are good proton acceptors and that one imide N–H proton is a good proton donor like thymine<sup>11</sup> in the six-membered pyrimidine ring of xanthines and so it is an ADA (A, D = hydrogen-bond acceptor and donor, respectively)-type hydrogen-bonding system along with an AA system of the imidazole ring. We have designed different host molecules H3, H4, H5 and H6 for consideration of binding (structures of receptors and their complexes are shown in Fig. 1) on the basis of hydrogen-bond donor and acceptor properties of the guest theobromine and the corresponding receptors. The fact is that a binuclear guest such as theobromine needs more spacious receptors compared with H4 and H5, therefore we designed the bigger receptor H6.

#### Synthesis of host molecules (H3, H4, H5 and H6)

The synthesis of the receptors H3, H4, H5 and H6 for theobromine is shown in Scheme 1. The synthesis of H4 is achieved by the synthesis of carbamate 10 from *m*-aminobenzoic acid followed by formation of the amide bond by the mixed anhydride method. The synthesis of H6, having a bigger spacer, is made by the important  $Co^{I}$  coupling reaction <sup>12</sup> of 12 where the ester functionality survives. Compound 12 was prepared by the reaction between 11 and *N*-bromosuccinimide in the presence of benzoyl peroxide in carbon tetrachloride.

### **Result and discussion**

Energy-minimised structures of theobromine complexes A, B, C and D with H3, H4, H5 and H6, respectively, are shown in Fig. 2 using MMX (Serena Software 1993) calculations. Molecular modelling was done using standard constants, and the relative permittivity was maintained at 1.5. Alternative complex structures (Complexes A', B', C' and D' respectively) were obtained by flipping over the structure of theobromine, and the comparative energy values are shown in Table 1.

We therefore examined the simple pyridine diamide H3 as the first candidate as a receptor for theobromine based on the triple hydrogen-bonding complementarity (DAD-ADA) between 2,6-diaminopyridines, but the six-membered ring containing the imide group of theobromine (Complex A) leaves the imidazole ring uncomplexed although H3 makes G1 soluble in chloro-form. The comparative binding<sup>13</sup> results of the other designed receptors (H4, H5 and H6) and the protons undergoing shifts

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Fig. 1 Assignment of hydrogen-bond donors and acceptors in H3, H4, H5 and H6 and their probable hydrogen-bonding patterns in complexes A, B, C and D with G1.

 Table 1
 Energy-minimised values of different complexes in different mode of binding

Complex	Energy <sup><i>a</i></sup> /kcal mol <sup>-1</sup>	Complex	Energy <sup><i>a</i></sup> /kcal mol <sup>-1</sup>
Ā	-20.620	Α'	-20.709
В	-7.056	$\mathbf{B}'$	-6.340
С	-9.749	<b>C</b> ′	-10.522
D	-7.601	$\mathbf{D}'$	-8.413
<sup><i>a</i></sup> 1 cal = 4.1	84 J.		

**Table 2** NH chemical shifts and association constants  $K_a$  for G1 withdifferent hosts (H3, H4, H5 and H6)

Host	Guest	Differen and am proton host (Δ	Different amide and amine proton shifts of host ( $\Delta\delta$ /ppm)		proton guest n)	$K_{a}/\mathrm{M}^{-1}$
Н3	G1	NHb	0.37	NHa	0.61	Complex A $1.94 \times 10^2$
H4	G1	NHb NHc NHd	0.13 0.52 0.15	NHa	0.78	Complex <b>B</b> $9.43 \times 10^2$
Н5	G1	NHb NHc NHd	0.18 0.34 0.39	NHa	0.68	Complex C $9.97 \times 10^2$
H6	G1	NHb NHc	0.28 0.36	NHa	1.79	Complex <b>D</b> $2.41 \times 10^3$

on complexation with theobromine are shown in Table 2. The assignments of amide and carbamate protons of H4 are suggested from the ROESY experiment (500 MHz, Fig. 3). The assignment of protons of H5 is connoted from a comparison of the downfield shifts of the corresponding protons due to acetylation of the pyridine amino group of H4. The different syn and anti forms of carbamates<sup>14</sup> H4 and H5 are shown in Fig. 4. With the incorporation of a carbamate moiety in the receptors H4 and H5, the respective binding constant with G1 is increased to some extent compared with that of H3. H4 shows a small downfield chemical-shift change for the carbamate proton ( $\Delta\delta$  0.13 ppm) on complexation with theobromine (G1). Being frustrated with the isophthaloyl spacer for this type of binuclear guest, we then designed the bigger receptor H6 (DADDD) having more space between the binding groups compared with the isophthaloyl spacer to accommodate freely the bicyclic theobromine to complex both the *N*-methylimidazole moiety as well as the pyrimidine ring. The receptor H6 more efficiently solubilises G1 by making one additional hydrogen bond with the most basic nitrogen [imidazole nitrogen (N-9) of purine ring] forming a total of four hydrogen bonds and leaving one amide NH in the host uncomplexed (NHa in Complex D). Interestingly these receptors do not bind theophylline, i.e. 1,3-dimethylxanthine G3, possibly due to the presence of the bulky N1-CH<sub>3</sub> group for which the adjacent two imide carbonyls cannot participate in hydrogen-bond formation with the amide protons of the receptors.



Scheme 1 Synthesis of the hosts H3, H4, H5 and H6.

### **Recognition of caffeine**

Previous receptors for caffeine's interaction with polyphenols<sup>15</sup> show the formation of 1 : 1 complexes between caffeine and known polyphenols in aqueous solution. In aqueous medium, caffeine forms a number of complexes of variable stoichiometry with polyphenols and aromatic hydroxy acids such as methyl gallate,<sup>16</sup> 3-nitrobenzoic acid,<sup>16</sup> 5-chlorosalicylic acid,<sup>17</sup> pyrogallol,<sup>9</sup> potassium chlorogenate<sup>18</sup> and cyclodextrins,<sup>19</sup> *etc*. For caffeine recognition, we designed first the tetraamide macrocyclic receptor **H7** containing the smaller isophthaloyl spacer which unfortunately failed to bind caffeine. We then designed polyphenolic receptors (**H8** and **H9**) which form 1 : 1 complexes with caffeine in chloroform.

#### Synthesis of caffeine receptors

The synthesis of the macrocyle **H7** is achieved by high-dilution coupling of **17** with the bis(acid chloride) of **16** (Scheme 2). The syntheses of other compounds are straightforward and the procedures are mentioned in the Experimental section.

In the complexes with caffeine, the phenolic protons of **H8** and **H9** underwent upfield shifts (maximum  $\Delta\delta$  of OH in **H8** = 0.015 ppm and that in **H9** = 0.84 ppm, respectively) as expected. Both **H8** and **H9** in organic solution may be intramolecularly hydrogen bonded, giving rise to two possible conformations in equilibrium as shown in Fig. 5. The intramolecularly hydrogen-bonded conformations have significant influence on the chemical shift of the imino C–H and also the complexation with caffeine.

In H9, the imine hydrogen appears at  $\delta$  8.67 (intramolecular hydrogen bonds of OH with the imino nitrogen may cause imino C–H to appear at such a downfield position). Interestingly the two different phenolic OH protons of both H8 and H9 appear at different chemical shifts. The phenolic OH group which makes a stronger intramolecular hydrogen bond [probably the OH group *ortho* to the imino group is more acidic than the other OH group due to electron-withdrawing resonance of the imino nitrogen and the formation of a sixmembered intramolecular hydrogen bond (Fig. 5)] appears more downfield. Surprisingly the most downfield OH proton of



Fig. 2 Energy-minimised structures in different modes of complexes A, B, C and D.

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Fig. 3 300 MHz NMR spectra of 1 : 1 complex of H4 and G1 (0.02 mmol  $mL^{-1}$ ) by gradual addition of CDCl<sub>3</sub> at 25 °C and the ROESY (500 MHz) spectrum of H4.



Fig. 4 *anti* and *syn* forms of H5.

**H8**, unlike **H9**, does not undergo any chemical-shift change on complexation with caffeine. The electron-withdrawing influence of a sulfonyl moiety, as well as it giving a wider spacing in **H9** compared with the bridging methylene group in **H8**, is more effective in increasing the binding affinity of **H9** with caffeine compared with **H8**. The values of association constants ( $K_a$ ) for the formation of 1 : 1 complexes between caffeine and polyphenolic receptors have been calculated using the up field chemical-shift changes observed for phenolic OH during

addition of increasing amounts of guest. The chemical-shift changes ( $\Delta\delta$ ) of the protons of the polyphenol were monitored as a function of guest (caffeine) concentration. It is clear that the phenolic hydroxy group is a good proton donor but poor acceptor in hydrogen bonding, but the amide carbonyl [CO(NMe)] groups in caffeine may be good proton acceptors. Thus complexation reactions of caffeine with polyphenols, with hydrogen bonding between the polyphenol (proton donor) and caffeine (proton acceptor), may ultimately make specific

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Scheme 2 Synthesis of the hosts H7, H8 and H9.

contributions to the stability of the complexes E (1 : 1 complex of H8 and G2,  $K_a = 0.56 \times 10^2 \text{ M}^{-1}$  at 25 °C) and F (1 : 1 complex of H9 and G2,  $K_a = 1.36 \times 10^2 \text{ M}^{-1}$  at 25 °C) (Fig. 6). and the substrate P,  $\Delta_0^{AP}$  = chemical-shift difference between the caffeine resonance in the unbound state and the state in which it is totally in the form of a 1 : 1 complex.

## Binding studies of H4, H5 and H6 with theobromine and H8 and H9 with caffeine

**NMR method.** The <sup>1</sup>H NMR binding studies were carried out in CDCl<sub>3</sub> and in a mixture of DMSO-d<sub>6</sub> (10%) in CDCl<sub>3</sub>. The NMR spectrum of the host (**H8** or **H9**) at known concentration was recorded to obtain chemical shifts of unbound host and then small aliquots of the guest stock solution in CDCl<sub>3</sub> were added to the NMR tube *via* a microsyringe. The chemical shifts of selected protons of the host were monitored as a function of guest concentration. Addition of guest was continued until no further shift of the selected protons was observed. The binding constants were measured by using equation (1)<sup>18</sup> where  $\Delta$  = chemical-shift change induced by substrate P at concentration [P<sub>0</sub>], [P<sub>0</sub>] = formal substrate concentration, *K* = equilibrium constant for the formation of 1 : 1 complex between caffeine  $\frac{1}{\Delta} = \frac{1}{K \cdot \Delta_0^{\text{AP}}} \cdot \frac{1}{[P_0]} + \frac{1}{\Delta_0^{\text{AP}}}$ (1)

In the case of theobromine, the titration with guests H3, H4, H5 and H6 was done by gradual dilution of the 1 : 1 complex of corresponding host and guest, and monitoring of the amide protons as a function of concentration. The binding constants were measured by using equation (2)<sup>13a</sup> where  $\alpha = (\delta - \delta_0)/(\delta_{max} - \delta_0)$ ,  $\delta_0$  is the initial chemical shift (host only),  $\delta$  is the chemical shift at each titration point,  $\delta_{max}$  is the chemical shift when the receptor is entirely bound, and [c] = concentration of the host and guest.

$$K_{\text{assoc}} = \frac{a}{(1-a)^2 [c]}$$
(2)

 Table 3
 Comparative binding study results for hosts H4, H5, H6, H8, H9 by UV method

Host	Guest	Concentration of host	Concentration of guest	$\lambda_{\rm max}$ /nm monitored	$K_{ m a}/{ m M}^{-1}$
H4 H5 H6 H8 H9	G1 G1 G1 G2 G2	$\begin{array}{l} 2.66\times10^{-5}\ mol\ dm^{-3}\\ 2.92\times10^{-5}\ mol\ dm^{-3}\\ 2.70\times10^{-5}\ mol\ dm^{-3}\\ 1.2\times10^{-5}\ mol\ dm^{-3}\\ 3.28\times10^{-5}\ mol\ dm^{-3} \end{array}$	$\begin{array}{c} 2.77\times 10^{-4}\ {\rm mol}\ dm^{-3}\\ 2.77\times 10^{-4}\ {\rm mol}\ dm^{-3}\\ 2.77\times 10^{-4}\ {\rm mol}\ dm^{-3}\\ 8.4\times 10^{-3}\ {\rm mol}\ dm^{-3}\\ 3.61\times 10^{-4}\ {\rm mol}\ dm^{-3}\\ \end{array}$	334 338 329 324 274	$\begin{array}{l} 5.51 \times 10^{3} \\ 4.40 \times 10^{3} \\ 3.72 \times 10^{4} \\ 5.78 \times 10^{2} \\ 7.96 \times 10^{3} \end{array}$



 $R = C_6H_4CH_2C_6H_4, C_6H_4SO_2C_6H_4$ 

**Fig. 5** Intramolecular hydrogen-bonded conformations of the imines **H8** and **H9**.







Complex F

Fig. 6 Hypothetical complexation mode of caffeine with receptors H8 and H9.

UV method. Stock solutions of different hosts were made in the order of  $10^{-5}$  mol dm<sup>-3</sup>. Aliquots of a solution of respective guest in the order of  $10^{-4}$  mol dm<sup>-3</sup> were added and the UV spectra were recorded for each addition for each host.

The concentrations of different hosts and the guest were calculated for Benesi–Hildebrand analyses.<sup>13*d*,13*e*</sup> The comparative binding results are shown in Table 3. The linear nature of the plot (Fig. 7) suggests a 1 : 1 stoichiometry for the different complexes.<sup>13*e*</sup>

#### Conclusions

In summary, we have developed a new class of biomimetic semirigid receptors for xanthine alkaloids that employs the



Fig. 7 (I) Benesi–Hildebrand plot of (a) H6 with G1, (b) H4 with G1, (c) H5 with G1. (II) Benesi–Hildebrand plot of (a) H9 with G2, (b) H8 with G2.

recognition strategy of substrate-induced organisation of the binding site (induced fit) and we report the first receptors for theobromine which effectively solubilise it in nonpolar solvents such as chloroform. Systematic binding studies of caffeine with a series of newly designed diverse receptors show the importance of optimum space requirements especially in a macrocyclic receptor such as **H7** that fails to bind caffeine due to its smaller-than-optimum cavity. This follows the creation of a bigger synthetic cavity in the functionalised receptors for theobromine and caffeine. The synthesis of functionalised and more highly-spaced receptor **H6** for theobromine has been achieved by an important Co<sup>1</sup> coupling reaction.<sup>12</sup>

#### Experimental

## General

The following solvents were freshly distilled prior to use: tetrahydrofuran (THF) from sodium and benzophenone, ethanol from calcium oxide, magnesium turnings and I<sub>2</sub>, methylene dichloride and triethylamine from calcium hydride. All other solvents and reagents were of reagent-grade quality and were used without further purification. Reactions were run under nitrogen unless otherwise noted. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker-AM-200 and AM-300 spectrometers. ROESY experiments were done on a Bruker-AM-500 spectrometer giving 300 ms mixing time. Chemical shifts are reported in  $\delta$  ppm, and coupling constants *J* are in Hz. IR spectra were recorded on a Perkin-Elmer MODEL No-883 spectrometer; absorptions are reported in cm<sup>-1</sup>. Melting points were recorded (uncorrected) in open capillaries with a hot-stage apparatus (Toshniwal). Elemental analyses were performed at IACS, Calcutta. NMR titrations were carried out in CDCl<sub>3</sub> except in the case of titration of **H9** with caffeine where d<sub>6</sub>-DMSO was added (5%) to solubilise **H9** at 25 °C. Error limits of binding constants are within ±10%. The water content in the NMR solutions was checked by integration of the water peak at  $\delta$  *ca.* 1.6 and was found to be 2–4 mM; in some cases where d<sub>6</sub>-DMSO was used along with CDCl<sub>3</sub>, water content was more likely to be 4–6 mM. Petroleum ether refers to the fraction with distillation range 60–80 °C.

### N-[6-(Butyrylamino)pyridin-2-yl]butyramide H3

To an ice-cooled solution of 2,6-diaminopyridine (1 g, 9.17 mmol) and triethylamine (1.85 g, 18.34 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added dropwise a solution of butyryl chloride (1.95 g, 18.34 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The mixture was stirred for 5 h at 0–10 °C and quenched with water (50 mL). The organic layer was separated, washed with 5% aq. sodium bicarbonate (20 mL), dried over sodium sulfate, and evaporated under reduced pressure. The crude solid was recrystallised from chloroform–hexane to afford H3 (2.14 g, 94%) as a white solid, mp 101–102 °C; IR  $\nu_{max}$  (KBr) 3320, 2950, 1669, 1531, 1455, 1304 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>)  $\delta$  8.52 (2H, br s), 7.92 (2H, d, *J* 8), 7.63 (1H, t, *J* 8), 2.40 (4H, t, *J* 7.6), 1.83–1.65 (4H, m), 1.00 (6H, t, *J* 6) (Calc. for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.54; H, 7.59; N, 16.82%).

#### 3-(Ethoxycarbonylamino)benzoic acid 10

Ethyl chloroformate (1.98 g, 17.5 mmol) was added dropwise to a solution of 3-aminobenzoic acid (2 g, 14.6 mmol) and 1 M NaOH (50 mL) solution over a period of 30 min at room temperature. After stirring for an additional 3 h at room temperature, the mixture was neutralised by dil. phosphoric acid. The precipitate was filtered off, washed with cold water, and dried to afford **10** (2.6 g, 82%) as a white solid, mp 234– 236 °C; IR  $\nu_{max}$  (KBr) 3338, 2922, 1635, 1558,1238 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>)  $\delta$  8.87 (1H, br s), 8.02 (1H, s), 7.66–7.54 (2H, m), 7.20 (1H, d, J 8), 4.09 (2H, q, J 6), 1.22 (3H, t, J 6) (Calc. for C<sub>10</sub>H<sub>11</sub>NO<sub>4</sub>: C, 57.74; H, 5.29; N, 6.69. Found: C, 57.65; H, 5.24; N, 6.61%).

## {[3-(6-Aminopyridin-2-yl)carbamoyl]phenyl}carbamic acid ethyl ester H4

A mixture of 10 (0.5 g 2.39 mmol), ethyl chloroformate (0.26 g, 2.39 mmol), dry THF (50 mL), and triethylamine (0.4 mL) was stirred under argon at room temperature for 3 h. 2,6-Diaminopyridine (0.26 g, 2.39 mmol) was added to the mixture, which was then refluxed for an additional 3 h before being cooled to room temperature and the solvent was removed under reduced pressure. The residue was chromatographed (5% petroleum ether in chloroform) to afford H4 (0.49 g, 64%) as grey solid, mp 199–200 °C (dec.); IR v<sub>max</sub> (KBr) 3401, 3279, 1732, 1617, 1454, 1309, 1234 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; 10% d<sub>6</sub>-DMSO in CDCl<sub>3</sub>)  $\delta$  8.75 (1H, br s, carbamate NH), 8.35 (1H, br s, pyr. amide), 7.78 (1H, s), 7.47 (1H, d, J 8), 7.30 (2H, t, J 8), 7.22-7.07 (2H, m), 6.02 (1H, d, J 8), 4.62 (2H, s), 3.97 (2H, q, J 6), 1.09 (3H, t, J 6); <sup>1</sup>H NMR (500 MHz; 10% d<sub>6</sub>-DMSO in CDCl<sub>3</sub>)  $\delta$  8.85 (1H, br s, carbamate NH), 8.58 (1H, br s, pyr. amide), 7.76 (1H, s), 7.35 (1H, d, J 7.75), 7.19 (1H, d, J 8), 7.16 (1H, d, J 8), 7.06 (1H, t, J 8), 7.00 (1H, t, J 8), 5.94 (1H, d, J 8), 4.74 (2H, br s), 3.85 (2H, q, J 7), 0.97 (3H, t, J 7); <sup>13</sup>C NMR (50 MHz; d<sub>6</sub>-DMSO)  $\delta_{\rm C}$  165.42, 158.25, 153.90, 149.99, 139.48, 139.19, 135.07, 128.82, 121.72, 121.35, 117.58, 104.32, 102.04,

60.47, 14.52; MS (EI) m/z (relative intensity) 300.1 (M<sup>+</sup>, 56%), 254.1, 192.1, 145.6, 91.1 (Calc. for  $C_{15}H_{16}N_4O_3$ : C, 59.99; H, 5.37; N, 18.66. Found: C, 60.01; H, 5.20; N, 18.56%).

## (3-{[6-(Acetylamino)pyridin-2-yl]carbamoyl}phenyl)carbamic acid ethyl ester H5

A mixture of H4 (200 mg, 0.66 mmol) and distilled acetic anhydride (2 mL) was heated to 120 °C for 2 h. The reaction mixture was evaporated to dryness and the solid residue was dissolved in ethyl acetate. The organic layer was washed successively several times with 5% aq. sodium bicarbonate and water. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to afford H5 (0.21 g, 94%) as a grayish white solid, mp 220-223 °C (dec.); IR v<sub>max</sub> (KBr) 3265, 1729, 1620, 1445, 1312, 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; CDCl<sub>2</sub>)  $\delta$  8.34 (1H, br s, carbamate NH), 8.11 (1H, br s, pyr. aromatic amide), 8.04-8.01 (2H, m), 7.92 (1H, d, J 8), 7.75 (1H, d, J 8), 7.56 (2H, t, J 8), 7.42 (1H, d, J 6), 7.00 (1H, br s, pyr. NHCOCH<sub>3</sub>), 4.25 (2H, q, J 5), 2.23 (3H, s), 1.32 (3H, t, J 6); <sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>)  $\delta_{\rm C}$  166.21, 160.34, 158.42, 154.45, 150.78, 139.32, 139.19, 135.98, 129.61, 121.36, 121.19, 117.62, 104.98, 103.07, 60.47, 28.56, 14.39; MS (EI) m/z 342.3 (M<sup>+</sup>) (Calc. for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>: C, 59.65; H, 5.26; N, 16.37. Found: C, 59.42; H, 5.19; N, 16.13%).

## 1,2-Bis(3-carboxyphenyl)ethane 14

3-(Ethoxycarbonyl)benzyl bromide **12** (1.0 g, 4.1 mmol) was treated with Co(PPh<sub>3</sub>)<sub>3</sub>Cl (4.34 g, 4.9 mmol) in degassed dry benzene (70 mL) at 5–10 °C for 20 min under argon atmosphere. The reaction mixture was filtered and the filtrate was washed with water and concentrated to dryness. The crude residue **13** was hydrolysed by addition 3 M NaOH (60 mL) and boiling for 3–4 h. The reaction mixture was cooled to room temperature and neutralised with dil. H<sub>2</sub>SO<sub>4</sub>. The precipitate was filtered off and the solid was washed several times with petroleum ether. Finally it was purified by chromatography on a silica gel column (3 : 1 ethyl acetate–methanol) to afford **14** (0.69 g, 78%) as a white solid, mp 225–228 °C; <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>)  $\delta$  8.19 (2H, s), 7.92 (2H, dd, *J* 2, *J* 8), 7.69 (2H, d, *J* 8), 7.43 (2H, t, *J* 8), 2.97 (4H, s) (Calc. for C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>: C, 71.10; H, 5.22. Found: C, 71.21; H, 5.19%).

## 1,2-Bis{3-[(6-amino-2-pyridyl)carbamoyl]phenyl}ethane 15

A slurry of 14 (0.2 g, 0.74 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), oxalyl dichloride (0.8 mL) and a drop of DMF was stirred under an inert atmosphere for 3 h, resulting in a clear orange solution. The reaction mixture was evaporated to dryness under vacuum and the resulting light orange solid was re-dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The dissolved acid chloride solution was added slowly via cannula to a vigorously stirred solution of 2,6diaminopyridine (0.49 g, 4.44 mmol) in triethylamine (0.3 mL) and dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at 0 °C. The reaction mixture was allowed to attain room temperature and was then stirred for 24 h. The reaction mixture was concentrated, and washed with water to remove excess of 2,6-diaminopyridine and triethylamine hydrochloride. The crude product was purified by crystallisation from THF-hexane to afford 15 (0.24 g, 72%) as a light yellow powder; IR  $v_{max}$  (KBr) 3398, 3282, 1617 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>) δ 8.58 (2H, br s), 8.20 (2H, s), 7.92 (2H, d, J 8), 7.69-7.65 (4H, m), 7.50 (2H, t, J 8), 7.43 (2H, t, J 8), 6.29 (2H, d, J 8), 4.40 (4H, br s), 2.97 (4H, s) (Calc. for C<sub>26</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>: C, 69.01; H, 5.35; N, 18.57. Found: C, 69.11; H, 5.28; N, 18.42%).

## 1,2-Bis(3-{[6-(butyrylamino)-2-pyridyl]carbamoyl}phenyl)ethane H6

To a solution of 15 (0.2 g, 0.44 mmol) and triethylamine (0.13 mL, 0.88 mmol) in anhydrous THF (50 mL) was added

butyryl chloride (0.094 g, 0.88 mmol). After stirring at room temperature overnight, the reaction mixture was concentrated to give a sticky light yellow solid. Chromatography on silica gel using ethyl acetate–chloroform (1 : 3) as eluant yielded **H6** (0.16 g, 62%), mp 60–62 °C; <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>)  $\delta$  8.20 (2H, br s), 7.99 (2H, br s), 7.98–7.87 (4H, m), 7.83–7.64 (4H, m), 7.48–7.28 (6H, m), 3.03 (4H, s), 2.46 (4H, t, *J* 6), 1.53–151 (4H, m), 1.07 (6H, t, *J* 6); <sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>)  $\delta_{\rm c}$  171.53, 165.72, 149.58, 140.85, 138.73, 134.07, 133.00, 128.64, 127.84, 124.08, 109.63, 109.56, 39.57, 21.27, 18.72, 13.63; MS (EI) *m/z* 592 (M<sup>+</sup>, 15%), 549, 521, 479, 370, 344 (Calc. for C<sub>34</sub>H<sub>36</sub>N<sub>6</sub>O<sub>4</sub>: C, 68.90; H, 6.12; N, 14.18. Found: C, 68.47; H, 6.34; N, 13.99%).

## Bis{4-[(2,3-dihydroxyphenyl)methylideneamino]phenyl}methane H8

Bis(4-aminophenyl)methane (0.2 g, 1.01 mmol) was added gradually to a methanolic (60 mL) solution of 2,3-dihydroxybenzaldehyde (0.28 g, 2.02 mmol) and the solution was stirred for 1 h at 50 °C. The orange solid precipitate was collected by filtration; mp 183 °C; IR  $v_{max}$  (KBr) 3420, 1624, 1461, 1369, 1275, 1228 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  8.59 (2H, br s), 7.24–7.21 (6H, m), 7.03 (4H, d, *J* 7.5), 6.94 (4H, d, *J* 8), 6.82 (2H, t, *J* 8), 4.08 (2H, s); <sup>1</sup>H NMR (500 MHz; CDCl<sub>3</sub>)  $\delta$  13.87 (2H, br s) (at 300 MHz it had broadened), 8.60 (2H, s), 7.28–7.24 (8H, m), 7.03 (2H, d, *J* 7.5), 6.94 (2H, d, *J* 8), 6.82 (2H, t, *J* 8), 5.79 (2H, br s), 4.05 (2H, s); MS (EI) *m/z* 438.3 (M<sup>+</sup>, 81%) (Calc. for C<sub>27</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.96; H, 5.06; N, 6.38. Found: C, 73.89; H, 5.26; N, 6.23%).

# Bis{[(2,3-dihydroxyphenyl)methylideneamino]phenyl} sulfone H9

Bis(4-aminophenyl) sulfone (0.2 g, 0.81 mmol) was added gradually to a methanolic (60 mL) solution of 2,3-dihydroxybenzaldehyde (0.22 g, 1.61 mmol), the solution was stirred for 1 h at 50 °C and the orange solid precipitate was collected by filtration; mp 250 °C (dec.); IR  $v_{max}$  (KBr) 3432, 1622, 1577, 1466, 1368, 1316, 1279, 1206; <sup>1</sup>H NMR (300 MHz; d<sub>6</sub>-DMSO)  $\delta$  8.67 (4H, br s), 8.01 (4H, d, *J* 8), 7.64 (2H, s), 7.43 (4H, d, *J* 8), 7.05–6.98 (4H, m), 6.81 (2H, t, *J* 7.5); MS (EI) *mlz* 487.9 (M<sup>+</sup>, 18%) (Calc. for C<sub>26</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>S: C, 63.93; H, 4.13; N, 5.73. Found: C, 63.86; H, 4.25; N, 5.52%).

#### 2,7-Bis{3-[(3-aminophenyl)carbamoyl]propoxy}naphthalene 17

2,7-Bis(3-carboxypropoxy)naphthalene **16** (0.36 g, 1 mmol) was suspended in dry  $CH_2Cl_2$  and oxalyl dichloride (0.5 mL) and DMF (1 drop) were added; the reaction mixture was stirred at room temperature for 2 h. After some time all the starting material had dissolved. The solvent was removed on a rotary evaporator and the residue was kept under high vacuum for 3 h. The diiacid dichloride was used without purification.

To a solution of 1,3-diaminobenzene (0.702 g, 6.50 mmol) and triethylamine (0.25 mL) in dry THF (50 mL) was added dropwise a solution of the above diacid dichloride (0.300 g, 0.81 mmol) in dry THF (10 mL). After 3 h the reaction mixture was evaporated to dryness and the solid residue was washed several times with water. Purification by column chromatography (THF-CH<sub>2</sub>Cl<sub>2</sub> eluant 20 : 80) gave diamine 17 (0.29 g, 52%) which was directly used for further reaction, mp 165 °C; IR v<sub>max</sub> (KBr) 3440, 3281, 1654, 1618, 1532 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; d<sub>6</sub>-DMSO) δ 9.00 (2H, br s), 7.36 (2H, d, J 10), 7.04 (2H, s), 6.90-6.67 (8H, m), 6.26 (2H, d, J 8), 3.88 (4H, t, J 6), 3.12 (4H, br s), 2.33 (4H, t, J 6), 1.99–1.91 (4H, m); <sup>13</sup>C NMR (50 MHz; d<sub>6</sub>-DMSO) δ<sub>c</sub> 171.01, 157.19, 144.38, 139.72, 135.67, 129.18, 128.75, 123.91, 116.01, 115.30, 111.04, 107.69, 106.04, 66.96, 33.40, 24.92 (Calc. for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>4</sub>: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.21; H, 6.18; N, 10.79%).

## Trisphenyl macrocycle H7

A solution of diamine 17 (0.1 g, 0.195 mmol) in THF (50 mL) and triethylamine (54 µL) was added simultaneously with a solution of 5-octyloxyisophthaloyl dichloride (0.065 g, 0.195 mmol) in THF (30 mL) to stirred THF (30 mL) at room temperature over a period of 3 h. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography on silica gel (6% MeOH in CHCl<sub>3</sub> eluant). Crystallisation from CHCl<sub>3</sub>-MeOH (1 : 1) afforded the product macrocycle H7 (0.042 g, 28%); mp 310-311 °C (dec.); IR v<sub>max</sub> (KBr) 3309, 3055, 1978, 1820, 1721, 1649 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>) δ 9.42 (1H, br s), 9.10 (1H, br s), 8.00 (2H, br s), 7.87 (3H, m), 7.68 (2H, d, J 8), 7.55 (2H, s), 7.46 (2H, d, J 8), 7.13 (2H, t, J 8), 6.95 (2H, d, J 8), 6.80 (2H, d, J 8), 4.07 (4H, m), 3.81 (2H, t, J 6), 2.09-2.02 (4H, m), 1.61-1.63 (4H, m), 1.28–1.11 (12H, m), 0.78–0.73 (5H, m); <sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>)  $\delta_{\rm C}$  179.71, 170.92, 164.72, 159.26, 156.86, 138.78, 138.41, 135.68, 135.29, 128.44, 124.54, 123.83, 117.22, 116.89, 116.12, 114.94, 111.88, 105.40, 71.04, 66.24, 38.23, 32.12, 29.01, 28.41, 24.21, 23.23, 22.39, 22.02, 13.51; HRMS (FAB) 771 (MH<sup>+</sup>, 100%), 705, 453, 435, 307 (Calc. for C<sub>46</sub>H<sub>50</sub>N<sub>4</sub>O<sub>7</sub>: C, 71.66; H, 6.54; N, 7.27. Found: C, 71.53; H, 6.78; N, 7.32%).

## Complex of H3-G1

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>)  $\delta$  11.37 (1H<sub>G1</sub>, br s), 8.95 (2H, br s), 7.96 (2H, d, *J* 8), 7.69 (1H, t, *J* 8), 7.59 (1H<sub>G1</sub>, s), 4.00 (3H<sub>G1</sub>, s, NCH<sub>3</sub>), 3.59 (3H<sub>G1</sub>, s, NCH<sub>3</sub>), 2.43 (4H, t, *J* 7.6), 1.84–1.66 (4H, m), 1.00 (6H, t, *J* 6).

#### Complex of H4-G1

<sup>1</sup>H NMR (300 MHz; 2% d<sub>6</sub>-DMSO in CDCl<sub>3</sub>)  $\delta$  9.85 (1H<sub>G1</sub>, br s), 8.61 (1H, br s), 8.39 (1H, br s), 7.99 (1H, s), 7.72 (1H, d, *J* 8), 7.63 (1H, d, *J* 7.5), 7.55 (1H<sub>G1</sub>, s), 7.50–7.41 (2H, m), 7.37 (1H, d, *J* 7.4), 6.34 (1H, d, *J* 7.8), 4.70 (2H, br s), 4.23 (2H, q, *J* 6.6), 3.96 (3H<sub>G1</sub>, s, NCH<sub>3</sub>), 3.52 (3H<sub>G1</sub>, s, NCH<sub>3</sub>), 0.86 (3H, t, *J* 6).

### Complex of H5-G1

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  9.84 (1H<sub>G1</sub>, br s), 9.29 (1H, br s), 9.24 (1H, br s), 8.55 (1H, br s), 7.93 (1H, br s, *peri*), 7.90 (1H, d, J 8.6), 7.76 (1H, d, J 8), 7.62 (1H, d, J 8), 7.56–7.49 (2H, m), 7.45 (1H<sub>G1</sub>, s), 7.29 (1H, t, J 7.9), 4.11 (2H, q, J 7.2), 3.84 (3H<sub>G1</sub>, s), 3.39 (3H<sub>G1</sub>, s), 2.16 (3H, s), 1.22 (3H, t, J 7.2).

#### Complex of H6-G1

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>)  $\delta$  10.58 (1H<sub>G1</sub>, br s), 8.38 (3H, br s), 8.24 (1H, br s), 7.99–7.86 (4H, m), 7.82–7.67 (4H, m), 7.52 (1H<sub>G1</sub>, s), 7.49–7.23 (6H, m), 3.9 (3H<sub>G1</sub>, s), 3.50 (3H<sub>G1</sub>, s), 3.02 (s, 4H), 2.44 (4H, t, *J* 7.2), 1.87–1.69 (4H, m), 1.02 (6H, t, *J* 6).

#### Complex of H8–G2

<sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>)  $\delta$  8.59 (4H, br s), 7.50 (1H<sub>G2</sub>, s), 7.25 (6H, br s), 7.03 (4H, d, *J* 7.8), 6.95 (4H, d, *J* 7.2), 6.82 (2H, t, *J* 7.8), 4.04 (2H, s), 3.99 (3H<sub>G2</sub>, s), 3.58 (3H<sub>G2</sub>, s), 3.41 (3H<sub>G2</sub>, s).

## Complex of H9–G2

<sup>1</sup>H NMR (300 MHz; 10% d<sub>6</sub>-DMSO in CDCl<sub>3</sub>)  $\delta$  8.66 (4H, br s), 8.0 (4H, d, *J* 8.4), 7.69 (1H<sub>G2</sub>, s), 7.61 (2H, br s), 7.43 (4H, d, *J* 8.4), 7.05–6.98 (4H, m), 6.82 (2H, t, *J* 7.8), 3.99 (3H<sub>G2</sub>, s), 3.56 (3H<sub>G2</sub>, s), 3.31 (3H<sub>G2</sub>, s).

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