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Formation of *C*-Amido-calix[3]indoles from 2′- and 7′-Indolylglyoxylamides

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Abstract—A range of 2′- and 7′-indolylglyoxylic amides **1** and **2**, derived from 3-(4′-chlorophenyl)-4,6-dimethoxyindole, have been reduced to the corresponding alcohols **3** and **4** respectively. On treatment with acid, these alcohols underwent trimerisation to give the calix[3]indoles **8**. The major conformer was generally the flattened partial cone, but in certain cases the cone conformers could be detected and even isolated. The related 2′-indolylglyoxylic amides **13**, derived from 4,6-dimethoxy-3-methylindole, were also converted into calix[3]indoles **15**.

Introduction

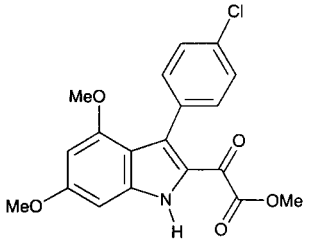
Calix[3]indoles are macrocyclic compounds which consist of three substituted indole units linked together by single carbon bridges. Those described so far have been linked through the 2- and 7-positions of the indoles.[1–3] These macrocyclic trimers can be linked symmetrically (i.e. 2,7; 2,7; 2,7) or unsymmetrically (i.e. 2,2; 7,2; 7,7). The symmetrically oriented calixindoles can be prepared either by the reaction of 3-substituted-4,6-dimethoxyindoles with aryl aldehydes in the presence of phosphoryl chloride[1,3] or by the acidic treatment of indolyl-2- or 7-methanols.[2] Two different conformations of calix[3]indoles are possible, namely the flattened partial cone and the cone conformations. So far, all examples of the calix[3]indoles appear to be in the flattened partial cone conformation, and routes to the cone conformers are being pursued. In the case of calix[4]-arenes, the cone conformation is stabilised by a cyclic network of hydrogen bonds between the four phenolic hydroxyl groups.[4,5] It was hoped that a similar application of hydrogen bonding phenomena might enable the formation of stable cone conformers of the calix[3]indoles. Thus the oxygen atom of a carbonyl substituent on the linking carbon atom might hydrogen bond with the adjacent indole NH, and thereby stabilise the cone conformer. To this end, *C*-amido-calix[3]indoles were sought by the acid-catalysed trimerisation of appropriate indolyl methanol derivatives. Some preliminary results of these studies have been reported.[6]

Results and Discussion

Formation of alcohol precursors

The reaction of oxalyl chloride with 3-aryl-4,6-dimethoxyindoles has been shown to generate mixtures of 2′- and 7′-glyoxylic acid chlorides, which could be converted into a wide range of glyoxylic esters and amides, and these could be separated readily and made available for further transformations.[7] The 2′- and 7′-indolylglyoxylic amides **1** and **2** respectively were reduced in high yield to the related 2′- and 7′-indolylmethanols **3** and **4** respectively, with sodium borohydride in methanol (Scheme 1).

Unlike the glyoxylamides **1** and **2**, the hydroxyethanamides **3** and **4** showed no sign of crystallinity and no significant hydrogen bonding. The indole NH protons for the alcohols **3** and **4** were observed around 8.5 and 9.3 ppm respectively in the ^{1}H NMR spectra in chloroform, compared with values around 11.5 and 10.5 respectively for ketones **1** and **2**. However, the absence of hydrogen bonding in these precursors of calixindoles cast some doubt about their ability to influence the formation of cone conformers. Most attempts to reduce the 2′- and 7′-indolylglyoxylic esters, **5**



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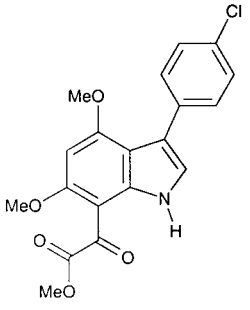

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Keywords: calixarenes; indoles; keto acids and derivatives; hydroxy acids and derivatives.

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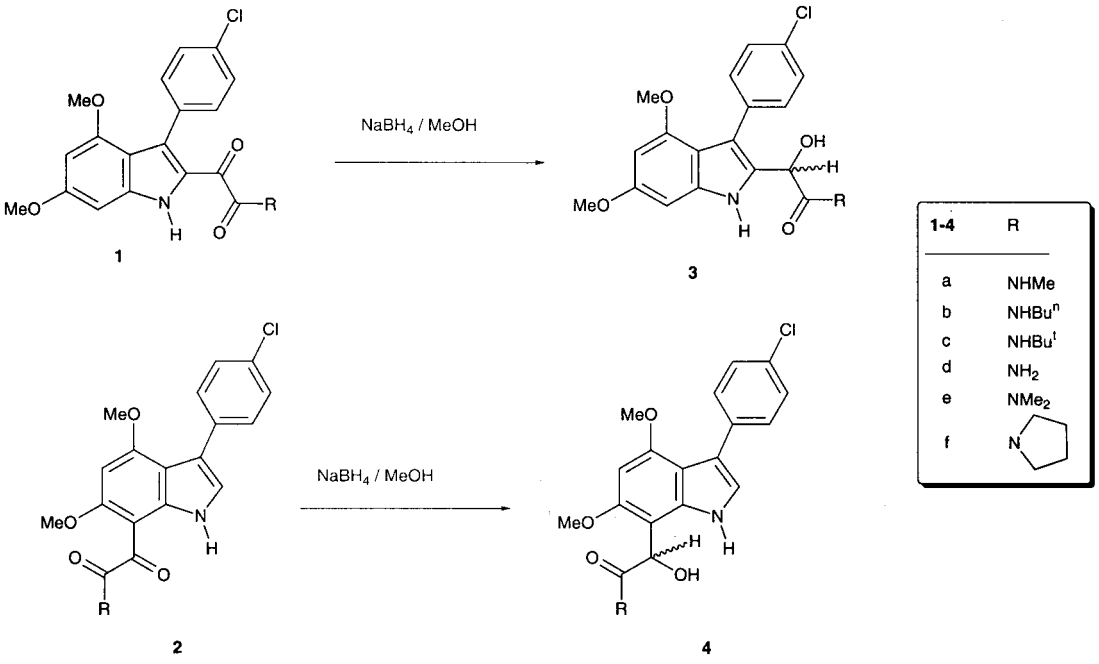
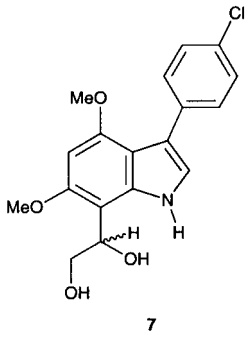


Scheme 1.



and **6** respectively, gave unsatisfactory yields, impure products and inconsistent results. However, when the 7′-glyoxylic ester **6** was treated with an excess of lithium aluminium hydride in tetrahydrofuran, the ethanediol **7** was obtained as a stable, crystalline, white solid.

Formation of calixindoles

A variety of acid-catalysed reactions were used for the formation of three new types of *C*-amidocalixindoles, namely primary, secondary and tertiary amidomethine bridged calixindoles. An attempt was made to ascertain the major factors which control these reactions, by variation of the type of amide, the temperature, the solvent and the substrate regioisomer (i.e. 2′- or 7′-hydroxyethanamide). To obtain ratios of the products formed, the indole NH peaks were integrated. These peaks were chosen as they were clear of any overlapping from other peaks and should all have approximately the same T_1 relaxation times so that the integration values should be relatively accurate. The primary diagnostic tool used to determine whether calixindoles had been formed was ^{1}H NMR spectroscopy. The disappearance of the two *meta* coupled doublets corresponding to H5′ and H7′ of the 2′-hydroxyethanamides **3** or the disappearance of the H2′ doublet in the case of the 7′-hydroxyethanamides **4** was used to identify substitution at the 2- or 7-position of the indole ring respectively. Accompanying this was the appearance of the bridging methine proton as a singlet resonance. The indole NH peaks were invaluable in identifying products from complex mixtures because of their separation downfield from other resonances.

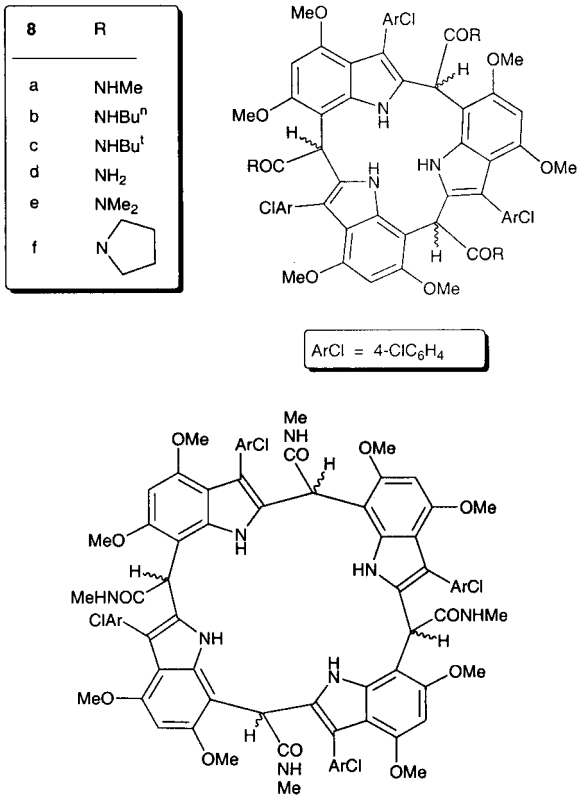
Calixindoles from 3-(4-chlorophenyl)-4,6-dimethoxyindole

Secondary *C*-amidocalixindoles. *C-Methylamidocalixindoles.* The secondary *C*-methylamidocalix[3]indole **8a** was used initially to investigate thoroughly the reaction conditions and their effects on the products formed. This calixindole **8a** was formed when the 2′-alcohol **3a** was treated with concentrated hydrochloric acid in tetrahydrofuran. The ^{1}H NMR spectrum showed three sets of peaks and consequently indicated the flattened partial cone isomer. This compound will be referred to as calixindole **8a**(**fpcone**). Formed together with this isomer was a trace of the isomer **8a**(**cone**). Use of carbon tetrachloride as solvent led to a heterogeneous reaction and formation of a 65:35 mixture of isomer **8a**(**fpcone**) and isomer **8a**(**cone**), the latter showing a very deshielded ^{1}H NMR resonance at 11.8 ppm for the indole NH. The reaction of the 2′-alcohol **3a** with concentrated hydrochloric acid was also performed in toluene and gave rise to three products in the ratio 55:20:25 as shown by ^{1}H NMR spectroscopy. Two of these compounds corresponded to calix[3]indoles **8a**(**fpcone**) and **8a**(**cone**), and the third was assigned the calix[4]indole[8] structure **9** on the basis of a MALDI mass spectrum which showed a small peak at 1368 (M−56), consistent with a fragment ion for a tetramer which has lost one methylamide group. This new compound also showed a peak at 9.1 ppm in the ^{1}H NMR spectrum assigned to be the indole NH. The use of cyclohexane as solvent led

Table 1. Effect of solvent, catalyst and temperature on calixindole formation from alcohol **3a**

Solvent	Catalyst	Temperature (°C)	% Yield of **8a**(**fpcone**)	% Yield of **8a**(**cone**)	% Yield of **9**
THF	HCl (conc)	20	100	0	0
CCl_4	HCl (conc)	20	65	35	0
CCl_4	HCl (conc)	−5	60	40	0
CCl_4	HCl (conc)	77	70	30	0
Toluene	HCl (conc)	20	55	20	25
Cyclohexane	HCl (conc)	20	65	20	15
MeOH	HCl (conc)/$Ni(OAc)_2$	20	85	15	0
THF	$BF_3{\cdot}Et_2O$	20	85	15	0
CCl_4	$BF_3{\cdot}Et_2O$	20	0	0	0
Toluene	$BF_3{\cdot}Et_2O$	20	60	30	10
CH_2Cl_2	$BF_3{\cdot}Et_2O$	20	90	0	10
Et_2O	$BF_3{\cdot}Et_2O$	20	80	20	0
THF	*p*-TsOH/AcOH	20	75	25	0
CCl_4	*p*-TsOH	20	65	30	5
Toluene	*p*-TsOH	20	45	20	35
CH_2Cl_2	K10 clay	20	100	0	0
THF	$POCl_3$	20	95	5	0
Et_2O	$SnCl_2{\cdot}2H_2O$	20	70	0	30

to the formation of all three products. The change in solvent could affect the reactivity of the intermediate carbocation and also the degree of hydrogen bonding between the indole NH and amide carbonyl oxygen atom.



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Various acid catalysts and solvents were investigated for their effect on the reaction with alcohol **3a**, and the results are shown in Table 1.

A one pot synthesis was developed for *C*-amidocalixindoles: the 2′-glyoxylamide **1a** was reduced with sodium borohydride in methanol and then acidified directly using concentrated hydrochloric acid. A small amount of white precipitate was obtained from the reaction and identified as isomer **8a**(**cone**). The ^{1}H NMR spectrum showed a broad peak at 2.95 ppm corresponding to the amido methyl groups. Two singlet resonances corresponding to the two non-equivalent methoxy groups occurred at 3.34 and 3.54 ppm, and a further two singlets at 5.88 and 6.02 ppm were assigned to the bridging methine proton and the indole H5 respectively. Two broad peaks from 6.70 to 7.50 ppm corresponded to the *p*-chlorophenyl protons. The amide NH was seen as a broad peak at 8.50 ppm and the typically deshielded indole NH occurred at 11.75 ppm. The significant broadening in the spectrum of the *p*-chlorophenyl ring, amide NH and the amide methyl groups was resolved on heating. Presumably, restricted rotation caused by crowding is responsible for the broadening of these signals. Two peaks were observed in the MALDI mass spectrum. The higher mass peak at 1068 corresponded to the molecular weight of a protonated trimer, while the second peak at 1010 mass units corresponded to loss of one methyl amide group. All attempts to isolate and fully characterise isomer **8a**(**cone**) failed because of its poor solubility, and incompatibility with chromatography media.

A symmetrical calix[3]indole which cannot undergo inversion must exist in the cone conformation. The presence of three chiral centres in the molecule leads to two possible isomeric forms that would display the symmetry exhibited by isomer **8a**(**cone**), namely a 'tri-axial' isomer and a 'tri-equatorial' isomer (see Fig. 1). The 'tri-axial' calixindole is preferred as the most likely structure because the three amide groups would be in less sterically demanding positions and also capable of hydrogen bonding to the indole NH protons, thus explaining the deshielded NH peak. Molecular modelling of a related series of *C*-amidocalix[3]indoles which have no substituents on the indole ring also suggested that the 'tri-axial' diastereoisomer is the more energetically favourable.

When the 7′-alcohol **4a** was reacted with concentrated hydrochloric acid in tetrahydrofuran, the two products **8a**(**fpcone**) and **8a**(**cone**) were obtained in a ratio of 65:35. Extended reaction and extraction with ethyl acetate gave a product mixture corresponding to a trimer, a tetramer

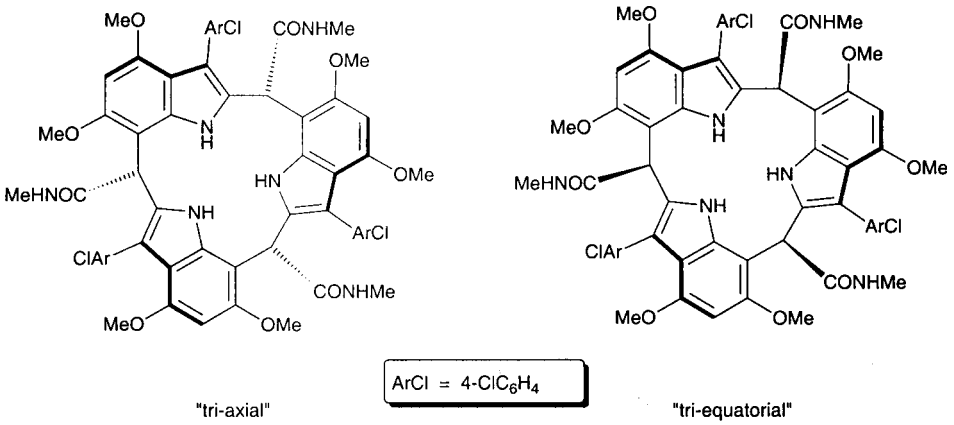


Figure 1. 'Tri-axial' and 'tri-equatorial' cone conformers of calix[3]indole **8a**.

and a pentamer, according to the MALDI mass spectrum. The ^{1}H NMR spectrum contained a broad peak at 8.8 ppm corresponding to the calix[5]indole NH. The larger size of the lower rim (25-membered ring) could allow the amide groups to pass through the annulus and invert, hence causing the broadening of the indole NH peak. The variation in product formation from the 2′-alcohol **3a** and the 7′-alcohol **4a** is likely to be caused by the different reactivities of the two resulting carbocations and the different nucleophilic strengths of the indole C2 and C7 sites. Experience indicates that C2 is generally a more powerful nucleophilic site than C7 and this would be consistent with the formation of more of the less thermodynamically stable cone conformer from alcohol **4a** than from **3a**.

C-n-Butylamidocalixindoles. As isomer **8a**(**cone**) was a minor product and could not be isolated, the amide groups were varied with the hope that a symmetrical cone conformer could be maximised and isolated. The use of long alkyl chains has been shown to favour the cone conformation in calix[4]resorcinarenes.[9–11] A similar approach was adopted by increasing the chain length of the amide so that aggregation of these alkyl chains might favour the cone conformation in calixindoles. The 2′-*n*-butylglyoxylamide **1b** was reduced to the corresponding alcohol, which without isolation was treated with concentrated hydrochloric acid in a number of solvents. Although the cone isomer **8b**(**cone**) was observed, this product could not be isolated.

C-t-Butylamidocalixindoles. After a series of preliminary experiments, it was found that reaction of alcohol **3c** with concentrated hydrochloric acid in refluxing chloroform gave the two calix[3]indoles **8c**(**fpcone**) and **8c**(**cone**), which could be separated by thin layer chromatography. The ^{1}H NMR spectrum of isomer **8c**(**fpcone**) displays three sets of peaks. The three indole NHs show chemical shifts of 11.30, 10.03 and 8.84 ppm in deuterated chloroform. The three *p*-chlorophenyl rings can be clearly seen in the range of 7.04–7.61 ppm with one aryl ring showing considerably broadened signals. The methine protons occur over a wide range at 5.29, 5.48 and 6.10 ppm, while the H5 protons occur over a narrower range at 6.14, 6.17 and 6.42 ppm. The amide NHs are also in this area and can be differentiated because of broadened signals at 5.26, 5.77 and 6.12 ppm. The MALDI mass spectrum of the isomer **8c**(**fpcone**) using α-cyano-4-hydroxycinnamic acid as the matrix gave rise to peaks at 1195, corresponding to the protonated molecular ion, and at 1095, corresponding to the removal of one *t*-butylamide group. The spectrum using sinapinic acid as the matrix showed essentially one peak corresponding to the protonated molecular ion.

The ^{1}H NMR spectrum of isomer **8c**(**cone**) shows one indole NH occurring significantly downfield at 11.38 ppm. This chemical shift in deuterated chloroform suggests a strongly hydrogen bonded indole NH as originally planned. Singlet resonances at 5.71, 5.77 and 6.03 ppm were assigned to the amide NH, the methine proton and H5 respectively. The only broadening in the spectrum occurs for the *p*-chlorophenyl ring protons occurring between 7.00 and 7.40 ppm. Each *p*-chlorophenyl ring is flanked by two methoxy groups at the upper rim, one at the 4-position of the indole containing the aryl ring and the other at the 7-position of the neighbouring indole. CPK models of a cone shaped calix[3]indole consistent with the structural features of isomer **8c**(**cone**) show that the 3-aryl moiety cannot rotate fully, mainly because of the 4-methoxy group. A MALDI mass spectrum of calixindole **8c**(**cone**) using α-cyano-4-hydroxycinnamic acid as the matrix showed only one peak at approximately 1096, corresponding to the M−100 peak. The spectrum using the matrix sinapinic acid gave a protonated molecular ion peak at 1195, and a peak at 1095 corresponding to M−100. X-Ray quality crystals of the isomer **8c**(**cone**) were obtained by recrystallization from absolute ethanol, and the subsequent crystal structure determination, details of which have been deposited,[6] proved the cone shape with a 'tri-axial' arrangement of substituents (Fig. 2). An exciting feature of the crystal structure is that the calix[3]indole **8c**(**cone**) contained an ethanol molecule inside the cup, with the alkyl portion deep within the cavity. There is presumably an interaction between the very electron rich cup and the relatively electron poor alkyl portion of ethanol which holds the ethanol molecule within the cup. The ethanol molecule also interacts with the side of another calix[3]indole molecule. The oxygen of the ethanol molecule hydrogen bonds to an amide NH and the alcoholic proton hydrogen bonds to a methoxy oxygen atom. The hydrogen bonding of the amide carbonyls to the indole NHs is not quite as expected. Instead of all three amide carbonyls pointing into the annulus of the macrocycle and

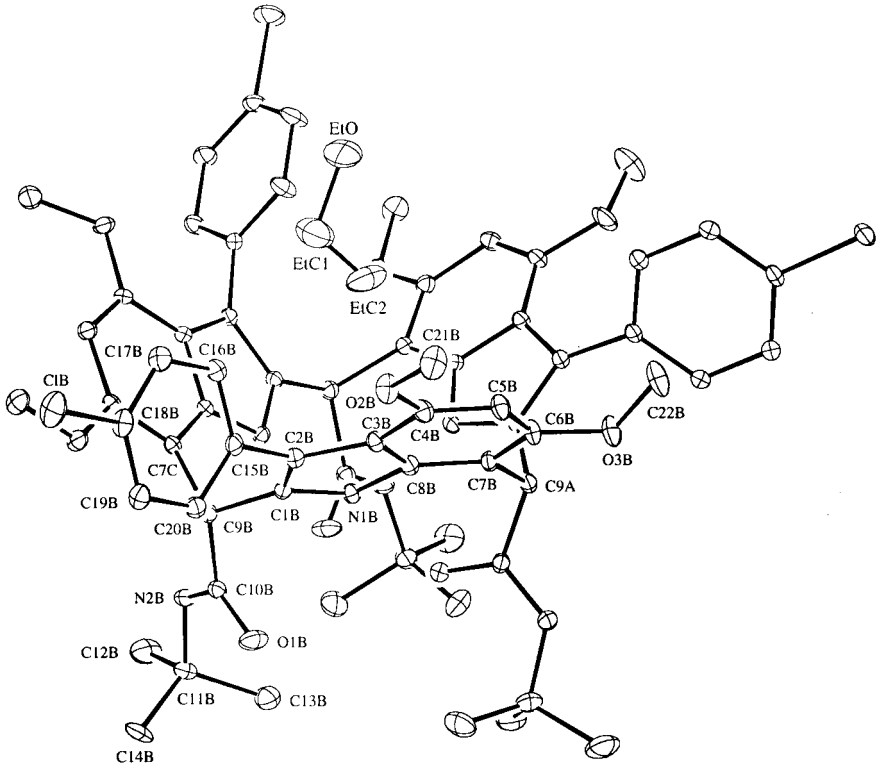


Figure 2. X-Ray crystal structure for calix[3]indole **8c**(**cone**).

forming a hydrogen bonded network around the base of the calix, only two carbonyls are in positions capable of hydrogen bonding to the indole NHs. However, all three indole molecules are hydrogen bonded in some way. One amide carbonyl oxygen atom is in a position capable of hydrogen bonding to one indole via a 6-membered ring (2.723 Å) and another indole via a 7-membered ring (2.746 Å). The second carbonyl oxygen atom is only capable of hydrogen bonding to one indole via a 6-membered ring (2.653 Å), and the third amide has the carbonyl oxygen atom pointing away from the centre of the annulus and thus is not capable of hydrogen bonding to an indole NH. The unsymmetrical nature of the three amide groups in the X-ray crystal structure is not reflected in the ^{1}H NMR spectrum. In solution the amide groups could be in a fluxional equilibrium with only two amides in hydrogen bonding positions at any one time, as is the case in the X-ray structure, or all three amide carbonyl oxygen atoms could be hydrogen bonding in solution but in the solid state one amide is forced to rotate out of the hydrogen bonded position.

The indole NH ^{1}H NMR chemical shift of calixindole **8a**(**cone**) is observed at 11.75 ppm (in both d_6-DMSO and $CDCl_3$), while that of calixindole **8c**(**cone**) is seen at 11.38 ppm (also in both d_6-DMSO and $CDCl_3$) showing that a greater degree of hydrogen bonding exists in the former. It is proposed that calixindole **8a**(**cone**) shows a hydrogen bonded network involving all indole NHs in solution as originally suggested. The broadening of the amide signals in the ^{1}H NMR spectrum of this compound would be caused by restricted rotation as the amides are fixed by the strong hydrogen bonded network. Calixindole **8c**(**cone**) is proposed to exhibit a time averaged signal for the indole NHs in the ^{1}H NMR spectrum which involves the hydrogen bonding shown in the X-ray crystal structure. The bulky *t*-butylamide groups do not allow all three amide carbonyls to point simultaneously into the centre of the annulus. Only two carbonyls can point in at any one time and the amides rotate rapidly on the NMR time scale. The lesser degree of hydrogen bonding is seen in the indole NH chemical shift and the increased solubility is a consequence of the greater flexibility of the system provided by the *t*-butyl groups. All three *t*-butyl groups are in an axial arrangement seemingly aggregating at the base of the cone. The X-ray crystal structure shows that the *t*-butyl groups are in such close proximity that the base of the cone is almost completely covered. The orientation of the *p*-chlorophenyl rings is also interesting. The rings have all rotated to a position where they are as far away as possible from the flanking methoxy groups. Again the crystal structure shows the high degree of steric hindrance around the *p*-chlorophenyl rings, which show a consequent degree of distortion.

When the calixindole **8c**(**cone**) was treated with methoxide ion an irreversible isomerisation to the conformer **8c**(**fpcone**) occurred. When this reaction was performed in deuterated methanol/deuterated methoxide, the indole NHs, amide NHs and the methine protons were all replaced by deuterium. The reaction presumably proceeds via a planar carbanion intermediate from the deprotonation of the methine group rather than a ring opening process from which polymeric material would be expected. The irreversible conversion shows that the isomer **8c**(**fpcone**) is indeed the thermodynamically more stable product. All attempts to form metal complexes of the calixindole **8c**(**cone**) failed, possibly because of prior interconversion

to isomer **8c**(**fpcone**), or because the bulky *t*-butyl groups at the base of the cone stop the metal ion from reaching the indole binding sites.

When the 7′-*t*-butylamidoalcohol **4c** was reacted with concentrated hydrochloric acid in dichloromethane the calix[3]indole **8c**(**fpcone**) was the major product and only a slight trace of the conformer **8c**(**cone**) was observed. This result was in contrast to that observed for the acid catalysis of the methylamides **3a** and **4a**. An additional minor product corresponded to an unsymmetrical tetramer. The crude reaction mixture showed a MALDI mass peak at 1593 consistent with the protonated molecular ion of a tetramer and the ^{1}H NMR spectrum showed four indole NH signals.

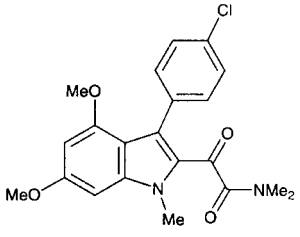
Primary *C*-amidocalixindoles. A number of problems were encountered with the isolation and characterisation of primary *C*-amidocalixindoles. The products from these macrocyclisation reactions were insoluble and very difficult to purify. Because of these undesirable qualities only a preliminary investigation was made. When the 7′-alcohol **4d** was reacted with concentrated hydrochloric acid in tetrahydrofuran the major product was an unsymmetrical calix[3]indole **8d**(**fpcone**), together with two symmetrical products, which decomposed on attempted purification.

Tertiary *C*-amidocalixindoles. *C-Dimethylamidocalixindoles.* The tertiary amidoalcohols were generally less reactive than the corresponding primary and secondary amidoalcohols, probably because of the increased steric hindrance around the carbocation centre. The reactions of the 2′-dimethylamidoalcohol **3e** and 7′-dimethylamidoalcohol **4e** generally gave polymers and a 42% yield of an unsymmetrical calixindole **8e**(**fpcone**). Traces of two symmetrical isomers showing strongly hydrogen bonded NH resonances at 12.0 and 11.1 ppm were observed in reactions of alcohols **3e** and **4e** respectively.

C-Pyrrolididocalixindoles. When the 2′-pyrrolididoalcohol **3f** was treated with concentrated hydrochloric acid in dichloromethane the sole product was the calixindole **8f**(**fpcone**). The ^{1}H NMR spectrum showed the three indole NH resonances at 9.09, 10.07 and 11.12 ppm as well as the six singlets occurring between 5.50 and 6.43 ppm arising from the methine and H5 protons. When the 7′-pyrrolididoalcohol **4f** was treated with concentrated hydrochloric acid in dichloromethane, calixindole **8f**(**fpcone**) remained the major product but was accompanied by a minor amount of a tetrameric compound which gave rise to four sets of peaks in the ^{1}H NMR spectrum. When the one pot synthesis was applied to this system considerably different results were obtained. Three products were obtained from the 2′-glyoxylpyrrolidide **1f**. The major product was the calixindole **8f**(**fpcone**) but it was accompanied by a significant amount of an unsymmetrical tetramer and a small amount of the calix[3]indole **8f**(**cone**).

Attempted synthesis of *C*-amido-*N*-methylcalixindoles

The appearance of tetrameric calixindoles in trace amounts in some of these reactions prompted an attempt to promote their formation. As there seemed to be a high level of steric interaction between the indole NHs in the calix[3]indole structure it was proposed to replace the indole NH with a larger group to encourage the system to form larger macrocycles. The glyoxylamide **1e** was treated with an excess of potassium hydroxide in dimethyl sulfoxide followed by methyl iodide to obtain the *N*-methyl-dimethylglyoxylamide **10**, which was then reduced to the corresponding alcohol **11** using sodium borohydride in methanol. When the *N*-methyl alcohol **11** was reacted with concentrated hydrochloric acid in tetrahydrofuran at room temperature no reaction occurred.



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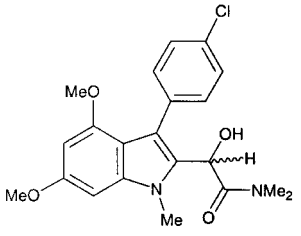

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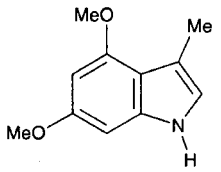
Calixindoles from 4,6-dimethoxy-3-methylindole

It was considered that the steric hindrance around the 3-aryl rings of the 3-arylcalix[3]indole **8c**(**cone**) was a significant factor inhibiting its formation. The synthesis of 3-methylcalix[3]indoles was undertaken to discover whether the smaller methyl group at the upper rim would lead to an increase in the cone conformer. CPK models of cone calix[3]indoles showed that a 3-methyl group could rotate freely.

***C*-Pyrrolididocalixindoles.** 3-Methylindole **12** was converted regiospecifically into the 2′-indolylglyoxylpyrrolidide **13a**, presumably as the result of the electron donating influence of the 3-methyl group. Consequently, reactions of the 7′-indolyl series could not be investigated. The 2′-indolylglyoxylamide **13a** was reduced to the corresponding alcohol **14a** which was treated with concentrated hydrochloric acid to yield two macrocyclic products, which were shown to be the unsymmetrical calixindole **15a**(**fpcone**) and the symmetrical isomer **15a**(**cone**) in the ratio of 55:45. This latter product was again characterised by the significantly downfield indole NH resonance (11.57 ppm) in the ^{1}H NMR spectrum. The H5 and methine proton resonances occurred at 6.25 and 6.19 ppm but were not differentiated. The two methoxy group resonances occurred at 3.95 and 3.83 ppm while that for the 3-methyl group was seen at 2.42 ppm. A MALDI mass spectrum using α-cyano-4-hydroxycinnamic acid as the matrix showed a large cluster of peaks centred about 933 mass units. When the one pot synthesis using the 3-methylglyoxylamide **13a** is compared with that of the 3-arylglyoxylamide **1f** a great difference in products is observed. Only a trace of symmetrical 3-arylcalixindole was observed but the symmetrical 3-methylcalixindole was almost the major product. The 3-aryl series also yielded a minor amount of an unsymmetrical tetramer and no related product was formed from the 3-methyl precursor.



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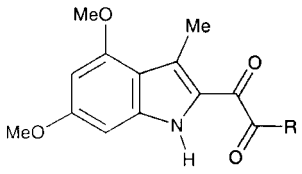

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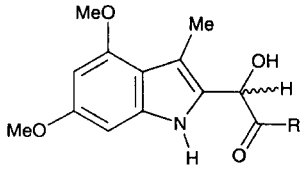

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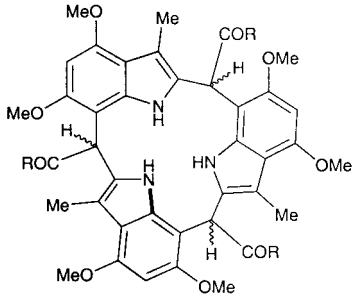

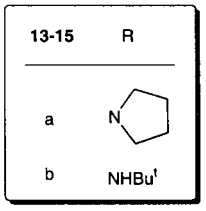

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***C*-*t*-Butylamidocalix[3]indoles.** On the basis of previous experiments it was decided to target calixindoles from the *t*-butylglyoxylamide **13b**, which could provide the best chance of obtaining cone conformers. The *t*-butylglyoxylamide **13b** was reduced with sodium borohydride in methanol, and the alcohol **14b** was extracted into dichloromethane and treated with concentrated hydrochloric acid. The only product observed was the unsymmetrical calixindole **15b**(**fpcone**). On the other hand, when the glyoxylamide **13b** was reduced with sodium borohydride in methanol, extracted into dichloromethane and treated with concentrated hydrochloric acid, a 50:50 mixture of calixindoles **15b**(**fpcone**) and **15b**(**cone**) was observed in the ^{1}H NMR spectrum. This striking difference in product distribution brought about by a change in solvent was much larger than experienced in the 3-aryl series and represents the highest proportion of calix[3]indole cone conformer achieved. The ^{1}H NMR spectrum of **15b**(**fpcone**) showed methine proton resonances at 5.35, 5.55 and 5.60 ppm and H5 resonances at 6.25, 6.30 and 6.35 ppm. The indole NH resonances occurred at 8.2, 8.7 and 10.4 ppm. The spectrum of the cone conformer **15b**(**cone**) displayed the indole NH resonance at 11.0 ppm, showing less deshielding relative to the pyrrolididocalix[3]indole **13f**(**cone**), and again suggesting that the *t*-butyl groups do not allow maximum hydrogen bonding. The methine and H5 resonances appeared at 5.8 and 6.2 ppm, respectively, and the amide protons showed a broad singlet resonance at 5.75 ppm.

Clearly the size of the group at the 3-position of the indole ring considerably affects the formation of the cone isomer, with the 3-methyl group providing less steric inhibition. The 3-methyl series also appears to be affected by solvent changes to a greater extent than the 3-aryl series. So far no substrates or reaction conditions have been found to afford the cone isomers specifically.

Conclusion

The following general conclusions about *C*-amidocalix[3]-indoles can be made. It seems that a carbonyl function is required at the lower rim to allow the cone conformer to be formed. However, this factor cannot be isolated from the reactivity of the alcohols. All the cone calix[3]indoles observed except the *t*-butylamide macrocycle **8c**(**cone**) exhibit a cyclic array of hydrogen bonds at the base of the cone. This results in very rigid and insoluble molecules. Generally the 2′-alcohols **3** give only trimeric compounds while the 7′-alcohols **4** give rise to traces of tetramers and pentamers as well. The size of the group at the 3-position of the indole ring appears to affect the formation of the cone conformation. The larger aryl ring could give rise to unfavourable interactions with the neighbouring methoxy groups and hence reduce the formation of this conformer. The 3-methyl group on the other hand is smaller and would interact to a lesser extent with the flanking methoxy groups and thus allow the cone conformation to form more readily. Reactions of the 3-methyl alcohols **14** appear to be affected by solvent to a greater extent than the 3-aryl alcohols **3**.

Experimental

General information

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz on a Bruker AC300F spectrometer and at 500 MHz on a Bruker AM500 spectrometer. Chemical shifts were measured on the δ scale internally referenced to the solvent peaks: $CDCl_3$ (7.30 ppm, 77.7 ppm) and d_6-DMSO (2.30 ppm, 39.0 ppm). EI mass spectral analyses were performed on a VG Quattro mass spectrometer at 70 eV ionisation voltage and 200°C ion source temperature. Microanalyses were performed by Dr H. P. Pham of the UNSW Microanalytical Unit. Infrared spectra were obtained on a Perkin–Elmer 298 IR spectrometer and a Mattson Sirius FTIR using KBr discs while ultraviolet spectra were carried out on a Hitachi U-3200 and Carey 5 spectrophotometers. Electrospray (ES) mass spectra were recorded on a VG Quattro mass spectrometer at 4000 V probe voltage, 1000 V counter electrode, 65 V cone voltage using a mixture of acetonitrile and water (1.10 containing 1% acetic acid as the solvent and at 5 μl/min flow rate). High molecular weight compounds were measured using a matrix assisted laser desorption (MALDI) mass spectrometer Finnigan MAT or Lasermat 2000.

***N*-Methyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-2′-yl)-2-hydroxyethanamide (3a).** The 2′-indolylglyoxylamide[7] **1a** (1.66 g, 4.45 mmol) was partially dissolved in methanol (40 ml) and excess sodium borohydride was added. The solution was stirred under nitrogen for 20 min. Water was then added dropwise until the solution just began

to turn cloudy. The volume was then immediately reduced to approximately one third under reduced pressure until a white precipitate formed. The resulting precipitate was filtered off, washed with water, dried and column chromatographed (5% methanol/chloroform) to yield the 2′-hydroxyethanamide **3a** (1.44 g, 86%) as a white solid, mp 112°C; [Found: C, 60.7; H, 5.4; N, 7.0. $C_{19}H_{19}ClN_2O_4$ requires C, 60.9; H, 5.1; N, 7.5%]; ν_{max} 3300br, 1625s, 1595s, 1550s, 1150s, 1045m, 810w cm^{-1}; λ_{max} 223 (ϵ 30,800), 275 nm (15,000); δ_H (d_6-DMSO) 2.76 (3H, d, J=4.0 Hz, NMe), 3.74, 3.85 (6H, 2s, OMe), 5.0 (^{1}H s, C*H*OH), 6.25, 6.61 (2H, 2s, H5′, H7′), 6.46 (1H, br, CHO*H*), 7.48, 7.67 (4H, 2d, J=8.2 Hz, aryl), 7.67 (1H, d, J=8.1 Hz, CONH), 11.10 (1H, br, NH); δ_C (d_6-DMSO) 25.6 (NMe), 54.9, 55.2 (OM), 66.1 (CHO), 87.2 (C5′), 91.5 (C7′), 126.8, 132.5 (aryl CH), 110.1, 113.5, 130.3, 132.4, 134.2, 137.3, 154.0, 156.8 (aryl C), 171.5 (carbonyl C); *m/z* 376 ($M^{37}Cl$, 5%), 374 ($M^{35}Cl$, 20%), 318 (30), 316 (100).

***N*-Methyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-7′-yl)-2-hydroxyethanamide (4a).** The 7′-indolylglyoxylamide[7] **2a** (1.34 g, 3.59 mmol) was partially dissolved in methanol (20 ml) and excess sodium borohydride was added. The solution was stirred under nitrogen for 20 min. Water was then added dropwise until the solution just began to turn cloudy. The volume was then immediately reduced to approximately one third under reduced pressure until a white precipitate was formed. The resulting precipitate was filtered off, washed with water, dried and column chromatographed (5% methanol/chloroform) to yield the 7′-hydroxyethanamide **4a** (1.28 g, 95%) as a white solid, mp 221–222°C; [Found: C, 59.1; H, 5.4; N, 7.1. $C_{19}H_{19}ClN_2O_4{\cdot}0.5H_20$ requires C, 59.5; H, 5.0; N, 7.3%)]; ν_{max} 3420m, 3390s, 3230br, 1645s, 1615m, 1600m, 1540m, 1210m, 1130s, 1020s, 790s cm^{-1}; λ_{max} 230 (ϵ 27,700), 280 (16,100), 300 nm (12,400); δ_H ($CDCl_3$) 2.84 (3H, d, J= 5.1 Hz, Nme), 3.87, 4.02 (6H, 2s, OMe), 4.41 (1H, s, OH), 5.77 (1H, s, CH), 6.31 (1H, br, CONH), 6.38 (1H, s, H5′), 7.05 (1H, s, H2′), 7.34, 7.52 (4H, 2d, J=8.2 Hz, aryl), 9.34 (1H, br, NH); δ_C (d_6-DMSO) 25.8 (NMe), 55.4, 57.9 (OMe), 66.7 (alkyl CH), 90.2 (C5′), 123.1 (C2′), 127.7, 130.9 (aryl CH), 106.0, 110.6, 115.5, 130.0, 135.5, 136.7, 153.7, 153.7 (aryl C), 172.8 (carbonyl C); *m/z* 376 ($M^{37}Cl$, 5%), 374 ($M^{35}Cl$, 20%); 318 (30), 316 (100).

1-(3′-(4″-Chlorophenyl)-4′,6′-dimethoxyindol-7′-yl)-1,2-ethanediol (7). Lithium aluminium hydride (0.04 g, 1.1 mmol) was dissolved in anhydrous tetrahydrofuran (30 ml) and cooled to 0°C with an ice bath. A solution of 7′-indolylglyoxylic ester[7] **6** (0.20 g, 0.54 mmol) in anhydrous tetrahydofuran (10 ml) was added in portions, and the solution was allowed to warm to room temperature and stirred for a further 30 min. Water was added slowly until all the lithium aluminium hydride was destroyed and the resulting mixture was filtered through a pad of celite. The resulting solution was extracted with dichloromethane, washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the diol **7** (0.12 g, 62%) as colourless rods, mp 198°C (from dichloromethane); [Found: C, 62.1; H, 5.4; N, 4.0. $C_{18}H_{18}ClNO_4$ requires C, 62.2; H, 5.2; N, 4.0%]; ν_{max} 3437m, 3341br, 1599w, 1331w, 1211w, 1086w, 812w cm^{-1}; λ_{max} 226 (ϵ 27,300), 278 nm (17,700); δ_H (d_6-DMSO) 3.58–3.71 (2H, m, CH_2OH), 3.88, 3.93 (6H, 2s, OMe), 4.82 (1H, t, J=5.3 Hz, CH_2O*H*), 5.27–5.30 (1H, m, C*H*OH), 5.53 (1H, d, J=3.1 Hz, CHO*H*), 6.49 (1H, s, H5′), 7.24 (1H, d, J=1.8 Hz, H2′), 7.45, 7.61 (4H, 2d, J=8.5 Hz, aryl), 10.62 (1H, br, NH); δ_C (d_6-DMSO) 55.1, 57.0 (OMe), 65.3 (alkyl CH_2), 68.6 (alkyl CH), 89.3 (C5′), 122.8 (C2′), 127.3, 130.4 (aryl CH), 106.0, 110.4, 114.6, 129.5, 135.4, 136.8, 152.0, 152.8 (aryl C); *m/z* 349 ($M^{37}Cl$, 10%), 347 ($M^{35}Cl$, 35%), 329 (24), 318 (30), 316 (100), 300 (50).

***N*-*t*-Butyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-2′-yl)-2-hydroxyethanamide (3c).** The hydroxyethanamide **3c** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **1c** (2.18 g, 5.25 mmol), methanol (15 ml) and excess sodium borohydride. This yielded a cream solid, which after gravity column chromatography (2.5% methanol/chloroform) gave the hydroxyethanamide **3c** (2.16 g, 99%) as a white solid, mp 109–110°C; [Found: C, 63.3; H, 6.3; N, 6.5. $C_{22}H_{25}ClN_2O_4$ requires C, 63.4; H, 6.0; N, 6.7%]; ν_{max} 3350br, 1655m, 1625m, 1210m, 1150m cm^{-1}; λ_{max} 224 (ϵ 28,200), 242 (19,200), 275 (11,400), 300 nm (7,600); δ_H ($CDCl_3$) 1.22 (9H, s, CMe_3), 3.74, 3.87 (6H, 2s, OMe), 4.18 (1H, br, OH), 5.17 (1H, s, CH), 5.39 (1H, br, CONH), 6.25, 6.50 (2H, 2d, J=1.6 Hz, H5′, H7′), 7.42, 7.51 (4H, 2d, J=8.4 Hz, aryl), 8.55 (1H, br, NH); δ_C ($CDCl_3$) 29.1 (C*Me*$_3$), 52.6 (*C*Me$_3$), 55.7, 56.2 (OMe), 67.1 (CH), 87.4 (C5′), 93.0 (C7′), 128.8, 132.8 (aryl CH), 112.1, 115.5, 130.1, 133.2, 134.0, 137.9, 155.4, 158.7 (aryl C), 170.9 (carbonyl C); *m/z* 418 ($M^{37}Cl$, 5%), 416 ($M^{35}Cl$, 10%), 318 (30), 316 (100).

***N*-*t*-Butyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-7′-yl)-2-hydroxyethanamide (4c).** The hydroxyethanamide **4c** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **2c** (0.15 g, 0.36 mmol), methanol (15 ml) and excess sodium borohydride. After column chromatography (2.5% methanol/chloroform) this yielded the hydroxyethanamide **4c** (0.12 g, 80 %) as a white solid, mp 186°C; [Found: C, 61.5; H, 6.4; N, 6.3. $C_{22}H_{25}ClN_2O_4{\cdot}0.5H_2O$ requires C, 62.0; H, 6.2; N, 6.6%)]; ν_{max} 3530br, 3400br, 3180br, 1660m, 1620m, 1525m, 1210m cm^{-1}; λ_{max} 230 (ϵ 28,000), 285 (13,200), 302 nm (11,500);: δ_H ($CDCl_3$) 1.35 (9H, s, CMe_3), 3.88, 4.02 (6H, 2s, OMe), 5.65 (1H, s, CH), 6.37 (1H, s, H5′), 6.39 (1H, br, CONH), 7.06 (1H, d, J=2.6 Hz, H2′), 7.35, 7.54 (4H, 2d, J=8.7 Hz, aryl), 9.37 (1H, br, NH); δ_C ($CDCl_3$) 29.3 (C*Me*$_3$), 52.17 (*C*Me$_3$), 55.9, 57.9 (OMe), 68.4 (CH), 89.3 (C5′), 122.7 (C2′), 128.3, 131.4 (aryl CH), 103.7, 112.4, 117.4, 132.1, 135.2, 137.2, 153.6, 155.1 (aryl C), 173.2 (carbonyl C); *m/z* 418 ($M^{37}Cl$, 5%), 416 ($M^{35}Cl$, 20%), 318 (70), 316 (100), 251 (50), 121 (70).

2-(3′-(4″-Chlorophenyl)-4′,6′-dimethoxyindol-2′-yl)-2-hydroxyethanamide (3d). The hydroxyethanamide **3d** was synthesised according to the method for compound **3a** using glyoxylamide **1d** (0.58 g, 1.62 mmol), methanol (25 ml) and excess sodium borohydride. After column chromatography (5% methanol/chloroform) this yielded the hydroxyethanamide **3d** (0.47 g, 80%) as a white solid, mp 118–120°C; [Found: C, 59.9; H, 5.2; N, 7.3. $C_{18}H_{17}ClN_2O_4$ requires C, 59.9; H, 4.8; N, 7.8%]; ν_{max} 3441w, 3341w, 1694m, 1215w,

1154m, 1047w cm^{-1}; λ_{max} 223 (ϵ 28,300), 273 (17,500), 364 nm (750); δ_H (d_6-DMSO) 3.75, 3.86 (6H, 2s, OMe), 4.95 (1H, s, C*H*OH), 6.26, 6.62 (2H, 2d, *J*=2.0 Hz, H5′, H7′), 6.35, 7.47, 7.62 (3H, 3br, $CONH_2$, OH), 7.49, 7.68 (4H, 2d, *J*=8.2 Hz, aryl), 11.14 (1H, br, NH); δ_C (d_6-DMSO) 54.4, 54.7 (OMe), 65.8 (alkyl CH), 86.8 (C5′), 91.0 (C7′), 126.3, 132.0 (aryl CH), 109.6, 112.9, 129.8, 130.1, 133.8, 137.0, 153.5, 156.3 (aryl C), 173.3 (carbonyl C); *m/z* 360 (M, 10%), 316 (10), 236 (20).

2-(3′-(4″-Chlorophenyl)-4′,6′-dimethoxyindol-7′-yl)-2-hydroxyethanamide (4d). The hydroxyethanamide **4d** was synthesised according to the method for compound **3a** using glyoxylamide **2d** (0.46 g, 1.28 mmol), methanol (20 ml) and excess sodium borohydride. After column chromatography (5% methanol/chloroform) this yielded the hydroxyethanamide **4d** (0.38 g, 82%) as a white solid, mp 231°C; [Found: C, 59.6; H, 4.9; N, 7.5. $C_{18}H_{17}ClN_2O_4$ requires C, 59.9; H, 4.8; N, 7.8%)]; ν_{max} 3430m, 3200br, 1670s, 1620m, 1075m, 790m cm^{-1}; λ_{max} 230 (ϵ26,100), 278 nm (18,100); δ_H ($CDCl_3$) 3.87, 4.05 (6H, 2s, OMe), 4.21 (1H, d, *J*=2.0 Hz, OH), 5.44, 6.42 (2H, 2br, $CONH_2$), 5.84 (1H, d, *J*=2.0 Hz, CH), 6.38 (1H, s, H5′), 7.07 (1H, d, *J*=2.6 Hz, H2′), 7.35, 7.53 (2H, 2d, *J*=5.1 Hz, aryl), 9.32 (1H, br, NH); δ_C (d_6-DMSO) 54.7, 57.1 (OMe), 65.9 (alkyl CH), 89.4 (C5′), 122.3 (C2′), 126.9, 130.1 (aryl CH), 105.2, 109.9, 114.7, 129.2, 134.8, 135.9, 152.9, 152.9 (aryl C), 174.1 (carbonyl C); *m/z* 362 ($M^{37}Cl$, 5%), 360 ($M^{35}Cl$, 20%), 318 (15), 316 (40), 251 (25), 178 (25).

***N,N*-Dimethyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-2′-yl)-2-hydroxyethanamide (3e).** The hydroxyethanamide **3e** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **1e** (0.60 g, 1.55 mmol), methanol (20 ml) and excess sodium borohydride. After column chromatography (2.5% methanol/chloroform) this yielded the hydroxyethanamide **3e** (0.53 g, 88%) as colourless crystals, mp 210–212°C; [Found: C, 61.8; H, 5.7; N, 6.7. $C_{20}H_{21}ClN_2O_4$ requires C, 61.8; H, 5.4; N, 7.2%]; ν_{max} 3432br, 3191br, 1645s, 1206m, 1154m, 1071m, 835w cm^{-1}; δ_H (d_6-DMSO) 2.57, 2.87 (6H, 2s, NMe), 3.73, 3.84 (6H, 2s, OMe), 5.25 (1H, s, C*H*OH), 5.5 (1H, br, O*H*), 6.25, 6.66 (2H, 2d, *J*=1.9 Hz, H5′, H7′), 7.53–7.46 (4H, m, aryl), 10.8 (1H, br, NH); δ_C (d_6-DMSO) 35.5 (NMe), 54.9, 55.2 (OMe), 63.2 (CH), 87.4 (C5′), 91.7 (C7′), 127.1, 132.2 (aryl CH), 110.0, 113.3, 130.5, 130.8, 134.0, 137.6, 154.1, 156.9 (aryl C), 170.3 (carbonyl C); *m/z* 390 ($M^{37}Cl$, 5%) 388 ($M^{35}Cl$, 15%), 318 (30), 316 (100), 281 (15).

2-(3′-(4″-Chlorophenyl)-4′,6′-dimethoxyindol-2′-yl)-2-hydroxyethano-1-pyrrolidide (3f). The hydroxyethanamide **3f** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **1f** (0.64 g, 1.55 mmol), methanol (15 ml) and excess sodium borohydride. After column chromatography (2.5% methanol/chloroform) this yielded the hydroxyethanamide **3f** (0.59 g, 91%) as a white solid, mp 198–199°C; [Found: C, 63.3; H, 5.9; N, 6.4. $C_{22}H_{23}ClN_2O_4$ requires C, 63.7; H, 5.6; N, 6.8%]; ν_{max} 3280br, 1630s, 1590m, 1150m cm^{-1}; λ_{max} 223 (ϵ 27,100), 241 (19,500), 276 (11,700), 300 nm (7,800); δ_H ($CDCl_3$) 1.72–1.82, 2.68–2.73, 2.85–2.92, 3.38–3.45, 3.50–3.58 (8H, 5m, CH_2), 3.75, 3.85 (6H, 2s, OMe), 4.61 (1H, br, OH), 5.12 (1H, br, CH), 6.23, 6.46 (2H, 2d, *J*=1.7 Hz, H5′, H7′), 7.41, 7.53 (4H, 2d, *J*=8.4 Hz, aryl), 8.54 (1H, br, NH); δ_C ($CDCl_3$) 23.7, 25.7 (CH_2), 45.3, 46.6 (NCH_2), 55.0, 55.5 (OMe), 64.7 (alkyl CH), 86.7 (C5′), 92.3 (C7′), 127.7, 132.2 (aryl CH), 110.6, 116.7, 128.6, 130.7, 133.4, 137.8, 154.9, 158.1 (aryl C), 170.0 (carbonyl C); *m/z* 416 ($M^{37}Cl$, 10%), 414 ($M^{35}Cl$, 35%), 318 (80), 316 (100), 301 (20), 281 (30).

***N,N*-Dimethyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-7′-yl)-2-hydroxyethanamide (4e).** The hydroxyethanamide **4e** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **2e** (1.21 g, 3.13 mmol), methanol (25 ml) and excess sodium borohydride. After column chromatography (2.5% methanol/chloroform) this yielded the hydroxyethanamide **4e** (1.06 g, 87%) as a white solid, mp 213–214°C, which could not be obtained analytically pure; ν_{max} 3440br, 3370br, 1635, 1590s, 1100m, 840m, 800m cm^{-1}; λ_{max} 231 (ϵ 24,500), 284 (13,300), 302 nm (11,100); δ_H ($CDCl_3$) 2.93, 3.03 (6H, 2s, NMe), 3.86, 4.00 (6H, 2s, OMe), 4.40 (1H, d, *J*=5.1 Hz, OH), 6.10 (1H, d, *J*=5.1 Hz, CH), 6.34 (1H, s, H5′), 7.02 (1H, d, *J*=2.0 Hz, H2′), 7.34, 7.52 (4H, 2d, *J*=8.2 Hz, aryl), 9.21 (1H, br, Na); δ_C ($CDCl_3$) 36.6, 37.0 (NMe), 55.8, 58.1 (OMe), 64.0 (alkyl CH), 89.1 (C5′), 122.6 (C2′), 128.3, 131.3 (aryl CH), 102.5, 112.1, 117.7, 132.1, 135.2, 137.3, 154.3, 155.8 (aryl C), 174.9 (carbonyl C); *m/z* 390 ($M^{37}Cl$, 5%), 388 ($M^{35}Cl$, 10%), 318 (40), 316 (100), 251 (30); HRMS (ES): $(M+Na)^+$, found 411.1063. $C_{20}H_{21}ClN_2O_4$+Na requires 411.1087.

2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxyindol-7′-yl)-2-hydroxyethano-1-pyrrolidide (4f). The hydroxyethanamide **4f** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **2f** (0.77 g, 1.86 mmol), methanol (20 ml) and excess sodium borohydride. After column chromatography (2.5% methanol/chloroform) this yielded the hydroxyethanamide **4f** (0.66 g, 85%) as a white solid, mp 201–202°C, which could not be obtained analytically pure; ν_{max} 3430m, 3270br, 1740w, 1635s, 1600s, 1150m, 990m cm^{-1}; λ_{max} 228 (ϵ 78,900), 280 nm (45,100); δ_H ($CDCl_3$) 1.64–1.70, 2.95–3.16, 3.42–3.65 (8H, 3m, CH_2), 3.91, 4.04 (6H, 2s, OMe), 4.91 (1H, d, *J*=6.2 Hz, C*H*OH), 5.99 (1H, d, *J*=4.6 Hz, CHO*H*), 6.34 (1H, s, H5′), 7.02 (1H, d, *J*=2.0 Hz, H2′), 7.32–7.42 (4H, m, aryl), 9.36 (1H, br, N); *m/z* 416 ($M^{37}Cl$, 5%); 414 ($M^{35}Cl$, 15%), 318 (40), 316 (100); HRMS (ES): $(M+Na)^+$, found 437.1220. $C_{22}H_{23}ClN_2O_4$+Na requires 437.1238.

3-(4′-Chlorophenyl)-*C*-methylcarboxamidocalix[3]indole [8a(fpcone)]. The 2′-indolylalcohol **3a** (1.44 g, 3.84 mmol) was dissolved in tetrahydrofuran (70 ml) and concentrated hydrochloric acid (approximately 1 ml) was added dropwise. The solution was allowed to stir for 1.5 h at room temperature. Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting solid was purified using gravity column chromatography (2.5% methanol/dichloromethane) to yield the calix[3]-indole **8a(fpcone)** (0.62 g, 45%) as colourless crystals, mp 245°C (from acetone); [Found: C, 64.1; H, 5.1; N, 7.5.

$C_{57}H_{51}Cl_3N_6O_9$ requires C, 63.8; H, 4.8; N, 7.8%]; ν_{max} 3420w, 3287w, 1657m, 1597m, 1215w, 1092w cm^{-1}; λ_{max} 228 (ϵ 88,600), 282 nm (39,800); δ_H (d_6-DMSO) 2.40, 2.45, 2.64 (9H, 3d, J=4.1 Hz, NMe), 3.43, 3.69, 3.73, 3.84, 3.86, 3.95 (18H, 6s, OMe), 5.31, 5.65, 5.82 (3H, 3s, CH), 6.31, 6.49, 6.68 (3H, 3s, H5), 7.14–7.55 (12H, m, aryl), 7.93, 8.13, 8.45 (3H, 3d, J=4.4 Hz, CONH), 8.99, 10.61, 11.09 (3H, 3br, NH); δ_H ($CDCl_3$) 2.41, 2.57, 2.73 (9H, 3d, J=4.7 Hz, NMe), 3.43, 3.67, 3.68, 3.75, 3.78, 3.90 (18H, 6s, OMe), 5.35, 5.57, 5.90 (3H, 3s, CH), 5.52, 5.88, 6.06 (3H, 3d, J=4.7 Hz; CONH), 6.12, 6.21, 6.42 (3H, 3s, H5), 7.02–7.51 (12H, m, aryl), 8.93, 9.64, 11.07 (3H, 3br, NH); δ_C (d_6-DMSO) 25.1, 25.3, 25.5 (NMe), 37.5, 40.4, 41.2 (alkyl CH), 54.6, 54.6, 55.0, 55.6, 56.4, 57.1 (OMe), 88.4, 89.0, 90.3 (C5), 99.7, 100.8, 103.5 (C7), 126.2, 126.3, 126.3, 131.5, 131.9, 132.2br (aryl CH), 110.9, 111.3, 111.7, 112.6, 112.7, 113.5, 129.7, 129.8, 129.8, 130.3, 130.5, 130.8, 133.7, 133.7, 134.2, 134.3, 134.9, 135.9, 151.5, 151.5, 152.2, 152.3, 153.4, 153.5 (aryl C), 170.3, 171.0, 171.2 (carbonyl C); m/z 1069 (M+H ^{35}Cl, 55%), 1011 (50).

3-(4′-Chlorophenyl)-*C*-methylcarboxamidocalix[3]indole [8a(cone)]. The 2′-glyoxylamide **1a** (0.14 g, 0.38 mmol) was dissolved in methanol and excess sodium borohydride was added and the mixture allowed to stir for 30 min. Concentrated hydrochloric acid was added cautiously until hydrogen evolution ceased and then excess hydrochloric acid was added (approx. 1 ml) and the solution was allowed to stir for 1 h. The resulting precipitate was filtered off and water was added to the filtrate, which was extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a precipitate, which was dried and partially characterised as the calix[3]indole **8a**(**cone**) (0.03 g, 22%) as a cream solid, mp>285°C; δ_H ($CDCl_3$) 2.95 (9H, br, NMe), 3.34, 3.54 (18H, 2s, OMe), 5.88 (3H, s, CH), 6.02 (3H, s, H5), 6.70–7.50 (12H, br, aryl), 8.50 (3H, bs, CONH), 11.75 (3H, s, NH); m/z 1091 (M+Na, 60%), 1069 (M+H,), 1012 (55); HRMS (ES): $(M+K)^+$, found 1107.2404. $C_{57}H_{51}Cl_3N_6O_9$+K requires 1107.2414;); HRMS (ES): $(M+K)^+$, found 1107.2404. $C_{57}H_{51}Cl_3N_6O_9$+K requires 1107.2414.

***C-n*-Butylcarboxamido-3-(4′-chlorophenyl)calix[3]indole [8b(fpcone)].** The 2′-glyoxylamide **1b** (0.20 g, 0.48 mmol) was dissolved in methanol and excess sodium borohydride was added and the mixture allowed to stir for 30 min. Concentrated hydrochloric acid was added cautiously until hydrogen evolution ceased and then excess hydrochloric acid was added (approx. 1 ml) and the solution was allowed to stir for 1 h. Water was then added and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield crude calix[3]indole **8b**(**fpcone**) (0.18 g, 33%) as a green solid; δ_H ($CDCl_3$) 0.72–1.35 (21H, m, CH_2, Me), 2.72–3.27 (6H, m, CH_2), 3.50, 3.68, 3.68, 3.72, 3.79, 3.91 (18H, 6s, OMe), 5.36, 5.55, 5.94 (3H, 3s, CH), 5.42, 5.79, 6.04 (3H, 3t, J=5.04 Hz, CONH), 6.13, 6.18, 6.40 (3H, 3s, H5), 7.04–7.55 (12H, m, aryl), 8.94, 9.70, 11.06 (3H, 3s, NH).

***C-t*-Butylcarboxamido-3-(4′-chlorophenyl)calix[3]indole [8c(fpcone)] and *C-t*-butylcarboxamido-3-(4′-chlorophenyl)calix[3]indole [8c(cone)].** The 2′-*t*-butylhydroxyethanamide **3c** (1.86 g, 4.46 mmol) was dissolved in chloroform (100 ml) and brought to reflux. Concentrated hydrochloric acid (1 ml) was added rapidly to the refluxing solution. The solution was immediately cooled and water was added and the mixture was extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resulting solid was purified using gravity column chromatography (40% ethyl acetate/*n*-hexane) to give an overall yield of macrocyclic compounds of 71%. The second band obtained from the column yielded calix[3]indole **8c**(**fpcone**) (0.80 g, 45%) (which contained an approximately 8% contamination of tetrameric macrocycle) as a white solid, mp 220–221°C; [Found: C, 66.3; H, 6.1; N, 6.8. $C_{66}H_{69}Cl_3N_6O_9$ requires C, 66.3; H, 5.8; N, 7.0%)]; ν_{max} 3400br, 1670m, 1590m, 1205m, 1145m cm^{-1}; λ_{max} 228 (ϵ 90,000), 289 nm (33,600); δ_H ($CDCl_3$) 0.99, 1.07, 1.23 (9H, 3s, Me), 3.50, 3.67, 3.70, 3.71, 3.77, 3.89 (18H, 6s, OMe), 5.29, 5.48, 6.10 (3H, 3s, CH), 5.26, 5.77, 6.12 (3H, 3s, CONH), 6.14, 6.17, 6.42 (3H, 3s, H5), 7.04–7.61 (12H, m, aryl), 8.84, 10.03, 11.30 (3H, 3s, NH); δ_C ($CDCl_3$) 28.6, 28.8, 29.4 (CMe_3), 40.2, 42.9, 43.2 (CMe_3), 51.8, 52.1, 52.1, 55.9, 55.9, 55.9, 56.9, 57.2, 58.5 (OMe), 89.1, 89.1, 90.9 (C5), 127.4, 127.8, 128.4, 132.5, 132.8, 132.8 (aryl CH), 101.7, 101.9, 104.3, 113.2, 113.5, 113.8, 114.6, 115.3, 116.7, 131.4, 131.5, 131.8, 133.2, 133.2, 135.2, 135.5, 135.7, 136.0, 136.3, 137.1, 153.2, 153.5, 154.2, 154.3, 155.0, 155.2 (aryl C), 169.9, 171.5, 171.8 (carbonyl C); m/z 1195 (M+1, 80%).

The first band obtained from the column of the above reaction product yielded calix[3]indole **8c**(**cone**) (0.30 g, 17%) as a white solid, mp 215°C; [Found: C, 66.1; H, 6.0; N, 6.8. $C_{66}H_{69}Cl_3N_6O_9$ requires C, 66.3; H, 5.8; N, 7.0%]; ν_{max} 3420br, 3320br, 1670m, 1615m, 1595m, 1510m, 1210m cm^{-1}; λ_{max} 229 (ϵ 99,500), 277 (44,400), 309 nm (28,300); δ_H ($CDCl_3$) 1.14 (9H, s, Me), 3.35, 3.56 (18H, 2s, OMe), 5.71 (3H, s, CONH), 5.77 (3H, s, CH), 6.03 (3H, s, H5), 7.00–7.40 (12H, br, aryl), 11.38 (3H, s, NH); δ_C ($CDCl_3$) 29.4 (CMe_3), 40.2 (alkyl CH), 52.5 (CMe_3), 56.0, 56.4 (OMe), 88.5 (C5), 127.6, 133.2 (aryl CH), 103.5, 114.1, 114.8, 132.0, 132.8, 136.0, 136.7, 152.7, 153.9 (aryl C), 172.0 (carbonyl C); m/z 1195 (M+1, 70%), 1126 (30), 1095 (40).

Conversion of the calix[3]indole 8c(cone) to the calix[3]indole [8c(fpcone)]. The calix[3]indole **8c**(**cone**) (0.20 g, 0.17 mmol) (90) was dissolved in a mixture of methanol and sodium methoxide. The solution was brought to reflux and allowed to stir for 1 h. Water was then added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield calix[3]indole **8c**(**fpcone**) (0.17 g, 86%).

3-(4′-Chlorophenyl)-*C*-carboxamidocalix[3]indole [8d-(fpcone)]. The 7′-hydroxyethanamide **4d** (0.34 g, 0.95 mmol) was partially dissolved in tetrahydrofuran and concentrated hydrochloric acid (6 drops) was added. The solution was allowed to stir at room temperature for 1 h.

Water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield calix[3]indole **8d**(**fpcone**) (0.05 g, 16%); δ_H (d_6-DMSO) 3.38, 3.69, 3.74, 3.84, 3.86, 3.99 (18H, 6s, OMe), 5.32, 5.65, 5.94 (3H, 3s, CH), 6.31, 6.48, 6.64 (3H, 3s, H5), 6.86, 6.97, 7.97 (3H, 3br, CONH), 7.09, 7.12, 8.41 (3H, 3s, CONH), 9.09, 10.80, 11.10 (3H, 3s, NH).

3-(4′-Chlorophenyl)-*C*-dimethylcarboxamidocalix[3]indole [8e(fpcone)]. The 2′-indolyldimethylhydroxyethanamide **3e** (0.50 g, 1.29 mmol) was partially dissolved in methanol and concentrated hydrochloric acid (6 drops) was added. The solution was allowed to stir at room temperature for 1 h. The precipitate was filtered off and water was added to the filtrate and the mixture was extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield calix[3]indole **8e**(**fpcone**) (0.20 g, 42%) as colourless needles, mp 248°C (from ethanol/light petroleum); [Found: C, 63.9; H, 5.4; N, 7.0. $C_{60}H_{57}Cl_3N_6O_9{\cdot}H_2O$ requires C, 63.8; H, 5.3; N, 7.4%]; ν_{max} 3420br, 3200br, 1630m, 1610m, 1590m, 1205m, 990w cm^{-1}; λ_{max} 227 (ϵ 108,900), 291 nm (38,600); δ_H ($CDCl_3$) 2.62, 2.71, 2.75, 2.78, 2.85 (18H, 6s, NMe), 3.37, 3.64, 3.67, 3.73, 3.77, 3.90 (18H, 6s, OMe), 5.69, 6.06, 6.08 (3H, 3s, CH), 6.19, 6.27, 6.45 (3H, 3s, H5), 7.10–7.45 (12H, m, aryl), 9.10, 9.90, 10.94 (3H, 3br, NH); *m/z* 1111 (M+1, 45%), 1040 (M, 100).

***C*-Carboxypyrrolidido-3-(4′-chlorophenyl)calix[3]indole [8f(fpcone)].** The 2′-indolylhydroxypyrrolidide **3f** (1.05 g, 2.54 mmol) was dissolved in dichloromethane (30 ml) and concentrated hydrochloric acid (1 ml) was added dropwise and stirred at room temperature for 15 min. Water was added and the mixture was extracted with dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified using a plug of silica gel and eluting with chloroform to yield calix[3]indole **8f**(**fpcone**) (0.59 g, 58 %) as a cream solid, mp>290°C; [Found: C, 65.7; H, 5.6; N, 6.8. $C_{66}H_{63}Cl_3N_6O_9{\cdot}H_2O$ requires C, 65.6; H, 5.4; N, 7.0%]; ν_{max} 3420br, 3250br, 1645m, 1595m, 1340m, 1210m, 1150m cm^{-1}; λ_{max} 228 (ϵ 83,200), 286 nm (34,300); δ_H ($CDCl_3$) 1.65–1.80 (12H, m, CH_2), 2.92–3.47 (12H, m, CH_2), 3.32, 3.59, 3.61, 3.67, 3.73, 3.86 (18H, 6s, OMe), 5.50, 5.89, 6.02 (3H, 3s, CH), 6.08, 6.15, 6.43 (3H, 3s, H5), 7.09, 7.37 (12H, 2dd, *J*=8.2 Hz, aryl), 9.09, 10.07, 11.12 (3H, 3s, NH); δ_C ($CDCl_3$) 24.8, 24.8, 25.0, 26.5, 26.6, 26.7 (CH_2), 37.0, 39.4, 41.6 (alkyl CH), 46.3, 46.7, 46.9, 46.9, 47.0, 47.4 (NCH_2), 56.0, 56.1, 56.7, 57.1, 57.8, 58.4 (OMe), 89.3, 89.8, 91.2 (C5), 127.5, 127.7, 132.8, 133.1 (aryl CH), 99.8, 100.9, 105.2, 112.6, 113.5, 113.7, 114.9, 115.2, 116.3, 131.1, 131.9, 132.0, 132.2, 132.5, 132.8, 134.7, 135.6, 136.3, 136.4, 136.9, 138.1, 152.9, 153.2, 154.0, 154.7, 155.3 (aryl C), 170.4, 170.6, 171.2 (carbonyl C); *m/z* 1189 (M+H, 80%), 1122 (30), 1092 (45).

***N*,*N*-Dimethyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxy-1′-methylindol-2′-yl)glyoxylamide (10).** The 2′-indolylglyoxylamide **1e** (0.50 g, 1.34 mmol) was dissolved in dimethylsulfoxide (20 ml) and excess crushed potassium hydroxide was added until a strong red colour was evident. Iodomethane (0.20 ml, 2.96 mmol) was added and the mixture was stirred for 1 h. Water was then added and the resulting precipitate filtered, washed with water and dried under reduced pressure to yield the glyoxylamide **10** (0.40 g, 75%), as a yellow solid, mp 193°C, which could not be obtained analytically pure; δ_H ($CDCl_3$) 2.43, 2.75 (6H, 2s, CONMe), 3.60 (3H, s, NMe), 3.95, 4.10 (6H, 2s, OMe), 6.13, 6.37 (2H, 2d, *J*=1.8 Hz, H5′, H7′), 7.34 (4H, s, aryl); δ_C (d_6-DMSO) 32.1, 32.2 (CONMe), 36.0 (NMe), 54.8, 55.1 (OMe), 84.3 (C5′), 93.0 (C7′), 125.7, 132.0 (aryl CH), 110.8, 126.8, 127.1, 131.6, 131.6, 141.1, 155.7, 160.8 (aryl C), 164.9, 183.2 (carbonyl C); *m/z* 402 ($M^{37}Cl$, 5%), 400 ($M^{35}Cl$, 20%), 330 (10), 328 (40), 293 (60);); HRMS (ES): $(M+Na)^+$, found 423.1031. $C_{21}H_{21}ClN_2O_4$+Na requires 423.1082.

***N*,*N*-Dimethyl-2-(3′-(4″-chlorophenyl)-4′,6′-dimethoxy-1′-methylndol-2′-yl)-2-hydroxyethanamide (11).** The hydroxyethanamide **11** was synthesised according to the method for compound **3a** using the following quantities: glyoxylamide **10** (0.30 g, 0.75 mmol), methanol (20 ml) and excess sodium borohydride. After column chromatography (5% methanol/chloroform) this yielded the hydroxyethanamide **11** (0.21 g, 70%) as a white solid, which could not be obtained analytically pure; δ_H ($CDCl_3$) 2.44, 2.93 (6H, 2s, CONMe), 3.68, 3.73 (6H, 2s, OMe), 3.92 (3H, s, NMe), 4.85 (1H, d, *J*=3.1 Hz, OH), 5.19 (1H, d, *J*=3.6 Hz, CH), 6.25, 6.41 (2H, 2d, *J*=2.1 Hz, H5′, H7′), 7.40, 7.47 (4H, 2d, *J*=8.7 Hz, aryl); *m/z* 404 ($M^{37}Cl$, 5%), 402 ($M^{35}Cl$, 15%), 332 (30), 330 (100), 295 (20);); HRMS (ES): $(M+Na)^+$, found 425.1211. $C_{21}H_{23}ClN_2O_4$+Na requires 425.1238.

***C*-Carboxypyrrolidido-3-methylcalix[3]indole [15a(cone)].** The glyoxylpyrrolidide **13a** (40 mg, 0.13 mmol) was partially dissolved in methanol (15 ml) and excess sodium borohydride was added. The solution was allowed to stir at room temperature for 30 min. Concentrated hydrochloric acid was then added until hydrogen evolution ceased and additional acid (5 drops) was added. The solution was then allowed to stir for an additional 30 min. Water was added and the solution was extracted with ethyl acetate. The organic layer was washed with water, saturated brine solution and dried ($MgSO_4$). The resulting crude solid was purified using radial chromatography (chloroform, then 0.5% methanol/chloroform). The first band yielded the calix[3]indole **15a**(**cone**) (12 mg, 10%) which could not be obtained analytically pure; δ_H ($CDCl_3$) 1.70–2.00 (12H, m, CH_2), 2.42, (9H s, Me), 3.40–3.90 (12H, m, CH_2), 3.83, 3.95 (18H, 2s, OMe), 6.19 (3H, s, CH), 6.25 (3H, s, H5), 11.57 (3H, s, NH); *m/z* 934 (M+1, 70%).

***C*-*t*-Butylcarboxamido-3-methylcalix[3]indole [15b(cone)] and *C*-*t*-butylcarboxamido-3-methylcalix[3]indole [15b-(fpcone)].** The *t*-butylglyoxylamide **13b** (0.50 g, 1.57 mmol) was partially dissolved in methanol and excess sodium borohydride was added and the mixture was stirred at room temperature for 15 min. Concentrated hydrochloric acid was added until hydrogen evolution ceased and then a slight excess of acid was added (4 drops). The solution was allowed to stir at room temperature for 30 min. Water was then added and the mixture was extracted with

dichloromethane. The organic layer was washed with water and dried ($MgSO_4$). The crude material was purified using gravity column chromatography (40% ethyl acetate/light petroleum). The faster moving band yielded the calix[3]-indole **15b**(**cone**) (0.34 g, 24%) as a white solid, mp 198°C; [Found: C, 66.8; H, 7.6; N, 8.7. $C_{51}H_{66}N_6O_9{\cdot}H_2O$ requires C, 66.2; H, 7.2; N, 9.1%]; δ_H ($CDCl_3$) 1.42 (27H, s, CMe_3), 3.83, 3.96 (18H, 2s, OMe), 5.74 (3H, br, CONH), 5.80 (3H, s, CH), 6.19 (3H, s, H5), 10.94 (3H, br, NH); δ_C ($CDCl_3$) 11.2 (Me), 29.3 (CMe_3), 40.4 (CMe_3), 52.1 (alkyl CH), 6.1, 57.9 (OMe), 88.7 (C5), 108.9, 131.7, 136.6, 152.3, 154.5 (aryl C), 172.1 (carbonyl C); *m/z* 908 (M+1, 65%), 838 (60), 808 (100).

The second band from the column yielded the calix[3]indole **15b**(**fpcone**) (0.35 g, 25%) as a white solid, mp 176–177°C; [Found: C, 67.2; H, 7.5; N, 8.9. $C_{51}H_{66}N_6O_9$ requires C, 67.5; H, 7.3; N, 9.3%]; δ_H ($CDCl_3$) 0.95, 1.14, 1.40 (27H, 3s, CMe_3), 3.85, 3.86, 3.88, 3.90, 3.93, 4.00 (18H, 6s, OMe), 5.17, 6.11, 6.25 (3H, 3br, CONH), 5.51, 5.56, 5.70 (3H, 3s, CH), 6.22, 6.27, 6.35 (3H, 3s, H5; 8.18, 8.66, 10.37 (3H, 3s, NH); *m/z* 906 (M+1, 95%), 807 (100).

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