



Synthesis of Biindolyis by the Reaction of Indoles with Indolin-2-ones and Phosphoryl Chloride or Trifluoromethanesulfonic Anhydride

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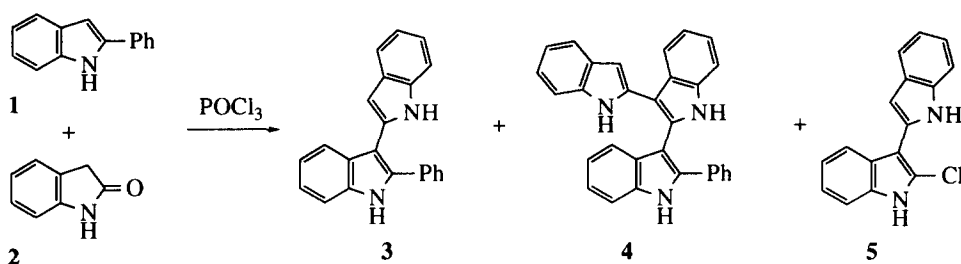
Abstract: Examples of 2,2'-, 2,3'-, and 2,7'-biindolyis have been prepared by the reaction of indoles with indolin-2-ones and phosphoryl chloride or trifluoromethanesulfonic anhydride. In certain conditions terindolyis can also be formed and those described contain combinations of the above linkages.

Considerable interest has been shown in the development of general methods for the synthesis of 2,2'-, 2,3'- and 2,7'-biindolyl systems.¹⁻⁶ In particular, the formation of 2,3'-biindolyis by combination of 1-methylindole and 1-methylindolin-2-one in the presence of phosphoryl chloride has been achieved by Bergman and Eklund.² Also, an electrophilic substitution involving 3-bromoindolinium cations has been reported.^{4,6} Interest in 2,7'- and some other biindolyl systems has been heightened by the observation of these structural fragments in a range of natural products. It has been shown that the oxidative polymerisation of 5,6-dihydroxyindole leads to a series of melanin oligomers, some of which contain 2,7'-biindolyl systems.⁷⁻⁹ Similar systems arise from the oxidative and biological chemistry of 5,6-dihydroxytryptamine.¹⁰⁻¹³

We have previously reported that suitably activated indoles undergo formation of a range of 7-imino derivatives on reaction with secondary amides and phosphoryl chloride.¹⁴ We now report details of such reactions incorporating indolin-2-ones, which not only participate in the normal way, but generate indolenines which isomerise to the related 2-indolyl derivatives.⁵ Thus, by this technique it is possible to synthesise a variety of 2-linked biindolyis, by judicious choice of the indole substrate.

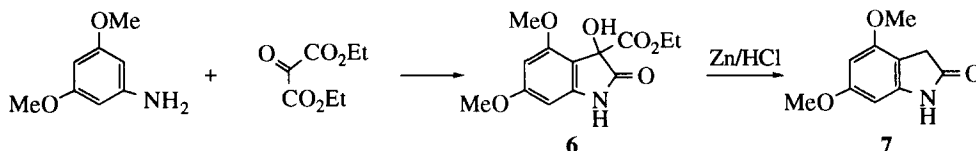
Reaction of simple indoles with indolin-2-ones

Reaction of 2-phenylindole **1** with indolin-2-one **2** and phosphoryl chloride gave the 2,3'-biindolyl **3** in 60% yield, together with the terindolyl **4** in 19% yield. Formation of the terindolyl is the result of reaction of the biindolyl at its 3-position with a further equivalent of the indolin-2-one. When excess reagent is used, the yield of terindolyl **4** can be increased to 60%, but traces of the chlorobiindolyl **5** are also formed. This latter by-product presumably arises from combination of 2-chloroindole (formed from reaction of indolin-2-one and phosphoryl chloride) with either itself or a precursor.¹⁵ The terindolyl **4** could also be obtained in 50% yield from further treatment of biindolyl **3** with the modified Vilsmeier reagent. All attempts to extend the reaction beyond the terindolyl stage were unsuccessful, as formation of chlorobiindolyl **5** and general decomposition intervened when more vigorous conditions were applied. Formation of a quaterindolyl has been reported from a similar reaction involving the more robust substrates 1-methylindole and 1-methylindolin-2-one.²

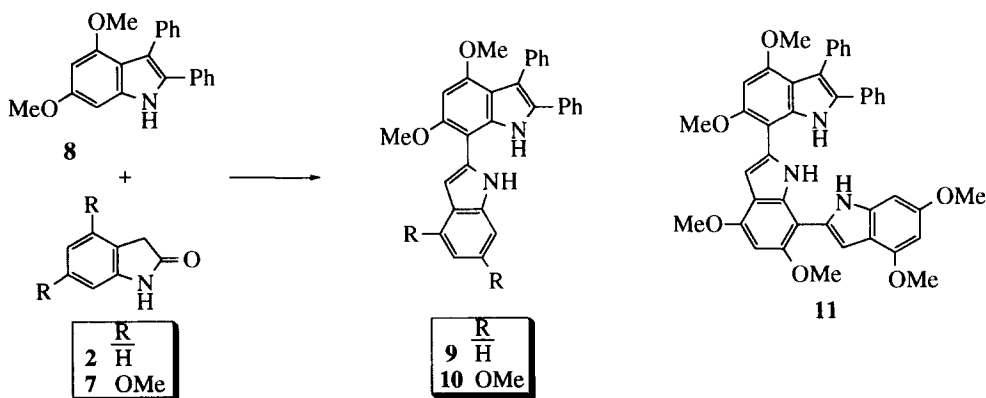


Reaction of 4,6-dimethoxyindoles with indolin-2-ones

In addition to indolin-2-one itself, the 4,6-dimethoxy analog **7** was also used in these reactions in an attempt to achieve subsequent reaction beyond the biindolyl product. Indolinone **7** has been prepared previously in 70% yield by the Wolff-Kishner reduction of the hydrazone of 4,6-dimethoxyisatin.⁵ Our preferred synthesis involves the Clemmensen reduction in 95% yield of the hydroxy-ester **6**, formed in 85% yield from 3,5-dimethoxyaniline and diethylmesoxalate.¹⁶

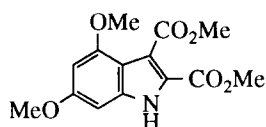
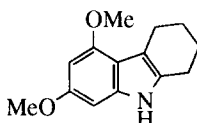
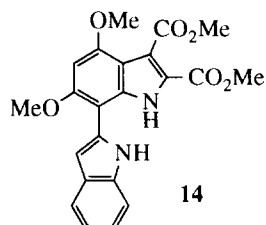


Reaction between 4,6-dimethoxy-2,3-diphenylindole **8** and indolinone **2** with phosphoryl chloride gave the 2,7'-biindolyl **9** in 75% yield, whilst the corresponding reaction with indolinone **7** gave the related 2,7'-biindolyl **10** in 55% yield together with the terindolyl **11** in 30% yield. Substitution at C7 is the only possibility in this indole **8** and should also be the case for other 2,3-disubstituted indoles.



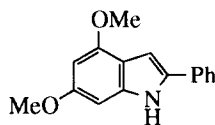
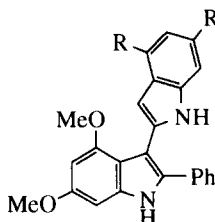
However, the 2,3-dicarboxylic ester **12**¹⁷ and the tetrahydrocarbazole **13**¹⁸ failed to react under the same conditions, prior to the onset of indiscriminate decomposition. As previously mentioned⁴, 2,3'-biindolyls have been formed by an electrophilic substitution involving 3-bromoindolinium cations. In an

attempt to obtain the 2,7'-biindolyl systems from indoles **12** and **13**, they were reacted with 3-bromoindole in the presence of one drop of trifluoroacetic acid, but only decomposition occurred after extended reflux. On the other hand, a similar reaction with the 2,3-diphenylindole **8** and 3-bromoindole yielded the 2,7'-biindolyl **9** in 80% after only five minutes at room temperature. It has been shown ¹⁹ that the use of trifluoromethanesulfonic anhydride (triflic anhydride) instead of phosphoryl chloride, on reaction with N,N-dimethylformamide leads to the formation of a very reactive iminium salt resulting in the formylation of relatively less activated aromatic compounds under mild conditions. Similar conditions using indolin-2-one **2** were found to convert the indole **8** into the biindolyl **9** in quantitative yield. This is clearly the synthetic method of choice, as it also results in the precipitation of the triflate salt, which on basification yields the product without requiring chromatographic purification. These conditions are so effective that they also enable formation of the 2,7'-biindolyl **14** from the previously unreactive diester **12** in 70% yield.

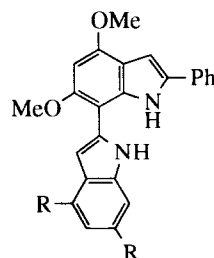
**12****13****14**

When indole **8** was reacted with the indolinone **7** and phosphoryl chloride the 2,7'-biindolyl **10** was obtained in 55% yield and the terindolyl **11** in 30%. This terindolyl has further potential for substitution, either at the terminal 7-position, or at the two unsubstituted 3-positions. Use of excess indolinone and phosphoryl chloride led to the isolation of terindolyl **11** in 75% yield, but no other polyindolyl products were observed. Use of triflic anhydride gave the biindolyl **10** in 100% yield without the need for chromatography. All attempts to obtain the terindolyl **11** from this reaction failed, even when a large excess of reagent was employed. However, if the biindolyl **10** was reacted with indolinone **7** and triflic anhydride, the terindolyl **11** was produced in 50% yield, but further substitution could not be achieved.

In the dimethoxyindole **8**, there is only one potential site for reaction, and it was of interest to see if there was any regioselectivity in reactions of 2- and 3-substituted-dimethoxyindoles, where there are two

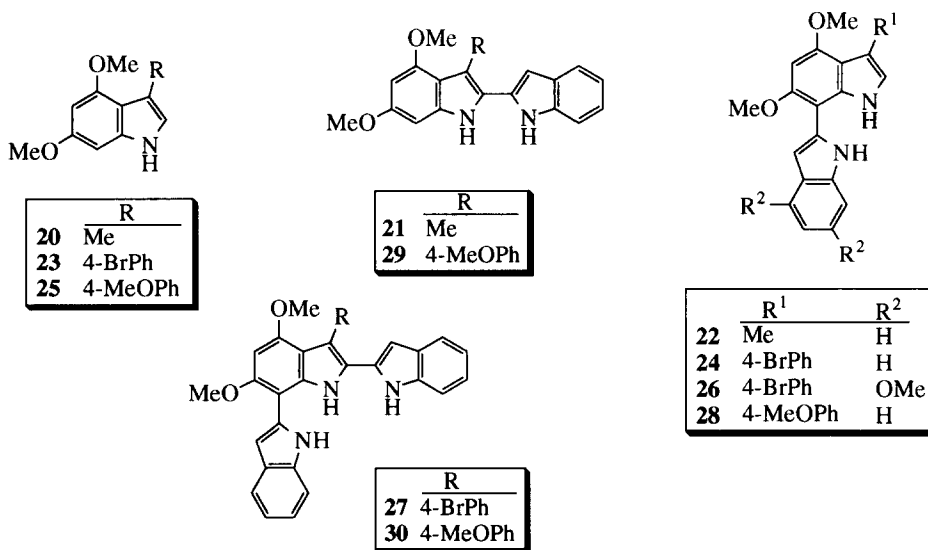
**15**

R
16 H
18 OMe



R
17 H
19 OMe

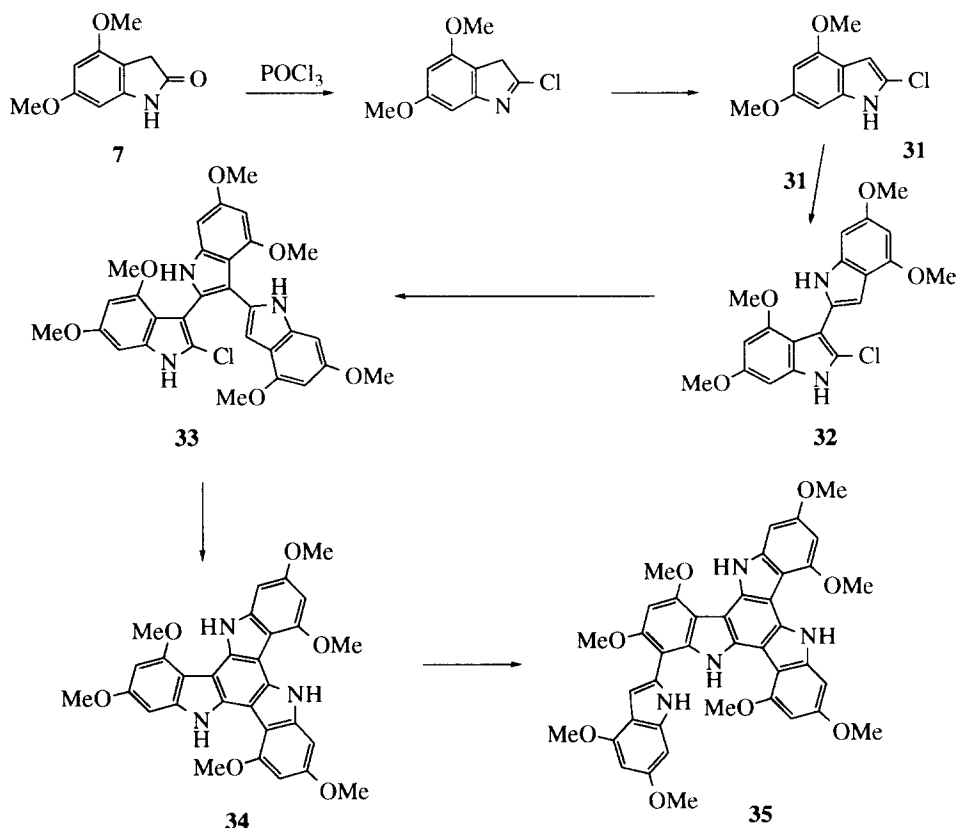
alternative reactive sites. Thus 4,6-dimethoxy-2-phenylindole **15** reacts with indolinone **2** and phosphoryl chloride to give the 2,3'-bi-indolyl **16** and the 2,7'-bi-indolyl **17** in 56% and 25% yields respectively. Furthermore, the reaction of indole **15** with indolinone **7** and phosphoryl chloride gave the corresponding 2,3'-bi-indolyl **18** in 30% yield and the 2,7'-bi-indolyl **19** in trace amounts only. Similarly, 4,6-dimethoxy-3-methylindole **20** undergoes reaction with indolinone **2** and phosphoryl chloride at C7 and C2 to give the 2,2'-bi-indolyl **21** and 2,7'-bi-indolyl **22** in 33% and 27% respectively. The corresponding reaction of indole **20** with the more activated indolinone **7** gave a complex mixture of products. The more stable 3-(4'-bromophenyl)-4,6-dimethoxyindole **23** failed to react with the indolinone **2** and phosphoryl chloride at room temperature, and reaction at reflux led to multiple products all in small yields. After exhaustive chromatography compound **24** was isolated in only 5% yield. Clearly under these conditions further reaction at the free 2- or 3-positions must occur. When the more reactive 3-arylindole **25** was reacted under these conditions the result was even less discriminating and no products could be isolated in a pure state. When the milder conditions utilising triflic anhydride were extended to the reactions of 3-aryl indoles with indolinones the desired products were formed. Quantitative conversion to the 2,7'-biindolyl compounds **24** and **26** occurred when 3-aryl indole **23** was reacted with indolinones **2** and **7** respectively. All attempts to react 2,7'-biindolyls **24** and **26** with further equivalents of indolinones **2** and **7** failed. The reaction mixtures were found to be unreactive and had to be refluxed for an extended period and this resulted in formation of multiple products, none of which could be isolated in a pure state.



¹H N.m.r. spectra of partially purified reaction mixtures resulting from the reaction of biindolyl **24** and indolinone **2** with triflic anhydride clearly showed the presence of three NH resonances between 8 and 10 ppm, each with the same integration. Thus the 2,7'; 2,2'-terindolyl **27** could have been formed. However, the reaction of indole **25** with indolinone **2** and triflic anhydride appeared to give the 2,7'-biindolyl **28**, the 2,2'-biindolyl **29** and the 2,7'; 2,2'-terindolyl **30** based on data from ¹H n.m.r. spectra of partially purified reaction mixtures. On the other hand, when excess indolinone **2** was reacted with 3-aryl indole **25** and triflic

anhydride, the terindolyl **30** could be isolated in 50% yield after chromatography. This clearly shows again the reactive nature of the 3-aryl indoles and in particular the directing ability of the 4'-methoxy substituent.

In reactions between the indolinone **7** and phosphoryl chloride it is conceivable that the generated intermediate, probably 2-chloro-4,6-dimethoxyindole **31**, is able to undergo reaction with itself, being both electrophilic at C2 and nucleophilic at C3 and C7. Although no products of such a process had been observed in any of the above reactions, it was relevant to investigate this possibility in the absence of a competing indole nucleophile. The indolinone **7** was found to be relatively unreactive and extended reflux with phosphoryl chloride in chloroform eventually gave very small yields of the very interesting diindolocarbazole **34** and its further indolyl-substituted product **35**. This result clearly shows again the reactivity of the 3-position. Presumably the 2-chloroindole **31** undergoes reaction with itself to give the 3,2-biindolyl **32**, which combines with a further equivalent of 2-chloroindole **31** to give the 3,2;3,2-terindolyl **33**, which then cyclises to the product **34**. Similar behaviour has been observed in reactions of benzimidazolone with phosphoryl chloride.^{20,21} The 1-methylindole trimer related to compound **34** has been prepared in good yield by reaction of 2-iodo-1-methylindole with activated copper bronze¹ and also by a stepwise route.²



EXPERIMENTAL

General Information

^1H n.m.r. spectra were recorded at 300 MHz with a Bruker CXP-300 or at 500 MHz with a Bruker AM-500 spectrometer, and refer to deuteriochloroform solutions with chloroform (7.26 ppm) as an internal standard. Signals due to exchangeable protons (NH) were identified by exchange with deuterium oxide. The usual notational conventions are used. ^{13}C n.m.r. spectra were recorded at 125.77 MHz with a Bruker AM-500 spectrometer, and refer to deuteriochloroform solutions with chloroform (77.0 ppm) as an internal standards. Low resolution mass spectra were obtained on an A.E.I. MS12 spectrometer at 70eV and 8000V accelerating potential at 210 °C ion source temperature. Infrared spectra were recorded with a Perkin Elmer 580B and refer to paraffin mulls or KBr disks of solids. Microanalyses were performed by Dr. H.P. Pham of the UNSW Microanalytical Unit.

General procedure for the reaction of indoles with indolones and phosphoryl chloride

To a stirred solution of the indole (1.52mmol) and the indolin-2-one (1.52mmol) in anhydrous chloroform (30ml) was added phosphoryl chloride (3.04mmol). After refluxing for 4-12h, the mixture was cooled and made strongly basic with sodium hydroxide solution (10%). The mixture was then extracted with chloroform, dried, concentrated and chromatographed on silica gel using dichloromethane as the eluent to yield the product.

General procedure for the reaction of indoles with indolones and triflic anhydride

To an ice cold solution of the indole (1.52mmol) and indolin-2-one (1.52mmol) in anhydrous chloroform was added triflic anhydride (3.04mmol). After stirring for 30 min at room temperature the mixture was made strongly basic with sodium hydroxide (10%). The mixture was then extracted with chloroform, dried, concentrated and recrystallised from dichloromethane and petroleum ether to give the product.

Reaction of 2-phenylindole (1) and indolin-2-one (2) with phosphoryl chloride

Indole **1** (0.5g, 2.59mmol) and indolin-2-one **2** (0.35g, 2.63mmol) gave two products.

(i) 3-(Indol-2'-yl)-2-phenylindole (3)

(0.48g, 60%), R_f 0.85, mp 208-209°C (from dichloromethane and petroleum ether). (Found: C, 85.5; H, 5.0; N, 9.2. $\text{C}_{22}\text{H}_{16}\text{N}_2$ requires C, 85.7; H, 5.2; N, 9.1%). λ_{max} 218nm(ϵ 18140), 245(16130), 275(10120), 294(13500), 301(13740). ν_{max} 3400, 2924, 1456, 1377, 1340, 794, 746, 700 cm^{-1} . ^1H n.m.r. (CDCl_3): δ 6.78, d, J2.0Hz, H3'; 7.14-7.33, m, 5H, ArH; 7.39-7.45, m, 4H, ArH; 7.52-7.56, m, 2H, ArH; 7.66-7.69, m, 1H, ArH; 7.90, d, J8.0Hz, 1H, ArH; 7.91, bs, NH; 8.25, bs, NH. ^{13}C n.m.r. (CDCl_3): δ 101.86, 110.59, 111.03, 119.76, 120.09, 120.96, 121.41, 123.17, 128.19, 128.49 and 129.07, ArCH; 106.57, 128.32, 129.21, 132.06, 132.19, 134.71, 135.99 and 136.04, ArC. Mass spectrum: m/z 308(M, 100%), 307(62), 306(42), 204(10), 153(20).

(ii) 3-[3'-(Indol-2''-yl)indol-2'-yl]-2-phenylindole (4)

(0.16g, 19%), R_f 0.60, mp 264-265°C (from dichloromethane and petroleum ether). (Found: C, 84.9; H, 4.7; N, 9.6. $\text{C}_{30}\text{H}_{21}\text{N}_3$ requires C, 85.1; H, 5.0; N, 9.9%). λ_{max} 244nm(ϵ 12500), 272(12250), 281(12120), 319(3370), 341(2670), 356(3650). ν_{max} 3429, 3223, 2929, 1612, 1469, 1373, 1329, 1261, 1136, 738 cm^{-1} .

^1H n.m.r. (CDCl_3): δ 6.70, t, J7.1Hz, 1H, ArH; 6.72, d, J7.9Hz, 1H, ArH; 6.91-7.14, m, 4H, ArH; 7.29-7.48, m, 11H, ArH and NH; 7.58, d, J8.1Hz, 1H, ArH; 8.14, s, NH; 8.22, d, J7.5Hz, 1H, ArH; 8.75, s, NH. ^{13}C n.m.r. (CDCl_3): δ 110.55, 111.06, 115.21, 118.34, 119.68, 119.86, 120.51, 121.35, 123.92, 124.75, 127.18, 127.85, 128.13, 128.71, 129.16, 130.69 and 132.76, ArCH; 106.04, 113.85, 122.13, 122.32, 124.35, 133.86, 135.26, 138.05, 138.88, 139.25, 139.45 and 144.99, ArC. Mass spectrum: m/z 423(M, 100%), 324(28), 345(12).

Reaction of 2-phenylindole (1) and excess indolin-2-one (2) with phosphoryl chloride

Indole **1** (0.5g, 2.59mmol) and indolin-2-one **2** (0.70g, 5.26mmol) gave three products.

(i) **3-(Indol-2'-yl)-2-phenylindole (3)** (0.24g, 30%), R_f 0.85, mp 208-209°C.

(ii) **3-[3'-(Indol-2''-yl)indol-2'-yl]-2-phenylindole (4)** (0.49g, 60%), R_f 0.60, mp 264-265°C.

(iii) **2-Chloro-3-(indol-2'-yl)indole (5)**

(0.01g, 1.4%), R_f 0.70, mp 136-138°C (from dichloromethane and petroleum ether). (Found: C, 72.3; H, 4.1; N, 10.3. $\text{C}_{16}\text{H}_{11}\text{ClN}_2$ requires C, 72.1; H, 4.2; N, 10.5%). λ_{max} 226nm(ϵ 122510), 249(69760), 292(26730), 306(85330). ν_{max} 3474, 3342, 1458, 1369, 1306, 1246, 995 cm^{-1} . ^1H n.m.r. (CDCl_3): δ 6.92, d, J2.3Hz, 1H, H3'; 7.12, m, 5H, ArH; 7.44, d, J7.9Hz, 1H, ArH; 7.69, d, J7.6Hz, 1H, ArH; 7.93, d, J6.7Hz, 1H, ArH; 8.23, bs, NH; 8.62, bs, NH. ^{13}C n.m.r. (CDCl_3): δ 101.48, C2'; 110.70, 119.51, 120.07, 120.27, 121.41, 121.91 and 123.33, ArCH; 106.50, 126.17, 128.77, 130.44, 134.54 and 135.91, ArC. Mass spectrum: m/z 268(M, ^{37}Cl , 37%), 267(25), 266(M, ^{35}Cl , 100%), 231(56), 229(22), 204(22).

7-(Indol-2'-yl)-4,6-dimethoxy-2,3-diphenylindole (9)

Method A: Indole **8** (0.5g, 1.52mmol), indolin-2-one **2** (0.2g, 1.52mmol) and phosphoryl chloride (0.28ml, 3.04mmol) gave the corresponding biindolyl **9** (0.51g, 75%), mp 222-223°C (from dichloromethane and petroleum ether). (Found: C, 81.0; H, 5.2; N, 6.2. $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_2$ requires C, 81.1; H, 5.4; N, 6.3%). λ_{max} 267nm(ϵ 13111), 339(15712). ν_{max} 3442, 1716, 1603, 1317, 1222, 1137, 995, 752 cm^{-1} . ^1H n.m.r. (CDCl_3): δ 3.76 and 3.95, 2s, OCH_3 ; 6.39, s, H5; 6.85, s, H3'; 7.05-7.72, m, ArH; 8.84, s, NH; 9.25, s, NH. ^{13}C n.m.r. (CDCl_3): δ 55.50 and 57.37, OMe; 89.98, C5; 99.85, C3'; 110.78, 119.88, 119.95, 121.81, 126.10, 127.28, 127.40, 128.06, 128.57 and 131.47, ArCH; 98.15, 113.95, 115.22, 127.97, 128.49, 132.68, 133.01, 133.06, 135.71 and 135.75, ArC; 153.76 and 154.99, COMe . Mass spectrum: m/z 445(M+1, 30%), 444(M, 100%), 429(35).

Method B: One drop of trifluoroacetic acid was added to a stirred solution of indole **8** (0.5g, 1.52mmol) and 3-bromoindole (0.3g, 1.52mmol) in dichloromethane at room temperature. After 15 min stirring the reaction mixture was washed thoroughly with sodium hydroxide (10%). The resulting dichloromethane layer was then separated, dried, concentrated and column chromatographed with dichloromethane to yield the product **9** after recrystallisation from dichloromethane and petroleum ether as a fluffy white solid (0.54g, 80%) mp 222-223°C.

Method C: To an ice cold solution of indole **8** (0.5g, 1.52mmol) and indolin-2-one **2** (0.2g, 1.52mmol) in anhydrous chloroform was added triflic anhydride (0.86g, 0.51ml, 3.04mmol). After stirring for 30 min at room temperature the mixture was made strongly basic with sodium hydroxide (10%). The mixture was then extracted with chloroform, dried, concentrated and recrystallised from dichloromethane and petroleum ether to give the product **9** as a fluffy white solid (0.676g, 100%).

Reaction of indole (8) and indolin-2-one (7). with phosphoryl chloride

Indole **8** (0.5g, 1.52mmol) and indolin-2-one **7** (0.27g, 1.52mmol) gave two products.

(i) 4,6-Dimethoxy-7-(4'-6'-dimethoxyindol-2'-yl)-2,3-diphenylindole (10)

(0.42g, 55%), R_f 0.75, mp 219-220°C (from dichloromethane and petroleum ether). (Found: C, 76.0; H, 5.7; N, 5.3. $C_{32}H_{28}N_2O_4$ requires C, 76.2; H, 5.4; N 5.6%). λ_{max} 238nm(ϵ 18260), 265(15000), 323(13200). ν_{max} 3481, 3459, 1619, 1604, 1329, 1222, 1141, 998, 702 cm^{-1} . 1H n.m.r. ($CDCl_3$): δ 3.76, 3.89, 3.94 and 3.98, 4s, OMe; 6.30, d, J1.93Hz, H5'; 6.40, s, H5; 6.59, d, J1.82Hz, H3'; 6.88, d, J2.31Hz, H7'; 7.26-7.47, m, ArH; 8.89, s, NH; 9.20, s, NH. ^{13}C n.m.r. ($CDCl_3$): δ 55.30, 55.44, 55.70 and 57.43, OMe; 86.79, 90.23, 91.63, 96.99, C5, C3', C5' and C7'; 126.00, 127.22, 127.32, 128.22, 128.50 and 131.47, ArCH; 98.60, 113.68, 113.90, 115.11, 129.94, 132.68, 133.14, 135.47, 135.77 and 137.00, ArC; 153.22, 153.38, 154.45 and 157.52, \underline{COCH}_3 . Mass spectrum: m/z 504(M, 100%), 489(80), 475(18).

(ii) 4,6-Dimethoxy-7-[4',6'-dimethoxy-7'-(4'',6''-dimethoxyindol-2''-yl)indol-2'-yl]-2,3-diphenylindole (11)

(0.77g, 30%), R_f 0.40, mp 255°C (from dichloromethane and petroleum ether). (Found: C, 74.1; H, 5.4; N, 6.0. $C_{42}H_{36}N_3O_6$ requires C, 74.3; H, 5.4; N, 6.2%). λ_{max} 247nm(ϵ 37500), 300(31600), 320(28060), 335(24390), 384(3880). ν_{max} 3337, 3316, 1627, 1606, 1565, 1518, 1340, 1152, 790 cm^{-1} . 1H n.m.r. ($CDCl_3$): δ 3.77, 3.79, 3.82, 3.84, 3.86 and 3.95, 6s, OMe; 6.14, d, J1.54Hz, 1H, ArH; 6.33, d, J 2.05Hz, 1H, ArH; 6.38, s, 1H, ArH; 6.45, d, J1.78Hz, 1H, ArH; 6.46, bs, 1H, ArH; 6.50, d, J1.87Hz, 1H, ArH; 6.66-6.68, m, 2H, ArH; 7.01-7.07, m, 3H, ArH; 7.22-7.30, 5H, ArH; 7.94, s, NH; 9.67, s, NH; 9.10, s, NH. ^{13}C n.m.r. ($CDCl_3$): δ 55.31, 55.37, 55.60, 55.71 and 57.51, OMe; 86.89, 87.06, 90.07, 91.79, 92.56 and 99.75, C3', C3'', C5, C5', C5'' and C7''; 125.75, 126.68, 127.65, 127.96, 128.01 and 131.47, ArCH; 98.06, 106.68, 110.85, 113.49, 113.91, 114.55, 129.72, 132.48, 133.05, 135.30, 135.91, 137.61 and 137.99, ArC; 153.28, 153.77, 154.67, 155.27, 156.98 and 157.55, \underline{COMe} . Mass spectrum: m/z 679(M, 100%), 664(20), 649(80), 617(25).

Reaction of indole (8) and excess indolin-2-one (7). with phosphoryl chloride

Indole **8** (0.5g, 1.52mmol) and indolin-2-one **7** (0.54g, 3.04mmol) gave two products.

(i) 4,6-Dimethoxy-7-(4'-6'-dimethoxyindol-2'-yl)-2,3-diphenylindole (10) (0.17g, 20%), R_f 0.75, mp 219-220°C.**(ii) 4,6-Dimethoxy-7-[4',6'-dimethoxy-7'-(4'',6''-dimethoxyindol-2''-yl)indol-2'-yl]-2,3-diphenylindole (11)** (0.77g, 75%), R_f 0.40, mp 255°C**4,6-Dimethoxy-7-(4'-6'-dimethoxyindol-2'-yl)-2,3-diphenylindole (10)**

Indole **8** (0.5g, 1.52mmol), indolin-2-one **7** (0.27g, 1.52mmol) and triflic anhydride (0.26ml, 1.52mmol) gave the product **10** (0.776g, 100%), mp 219-220°C.

Similar reaction with excess indolin-2-one gave the same result.

Reaction of 2,7'-bi-indolyl (10) and indolin-2-one (7) with triflic anhydride

2,7'-Bi-indolyl **10** (0.2g, 0.04mmol), indolin-2-one **7** (0.01g, 0.50mmol) and triflic anhydride (0.10ml, 0.60mmol) gave the terindolyl **11** (0.14g, 50%), mp 255°C.

Dimethyl 4,6-dimethoxy-7-(indol-2'-yl)indole-2,3-dicarboxylate (14)

Triflic anhydride (0.3ml, 1.78mmol) was added to a stirred and ice cooled solution of indole **12** (0.5g, 1.71mmol) and indolin-2-one **2** (0.23g, 1.73mmol) in anhydrous chloroform (20ml). The solution was allowed to come to room temperature for 0.5h then made strongly basic with a sodium hydroxide solution (20%). The mixture was then extracted with chloroform and column chromatographed on silica gel using

chloroform as the eluent to give the biindolyl **14** as a pale green solid (0.51g, 70%), mp 198-200°C (from dichloromethane and petroleum ether). (Found: C, 64.4; H, 5.2; N, 6.6. $C_{22}H_{20}N_2O_6$ requires C, 64.7; H, 4.9; N, 6.9). λ_{\max} 254nm(ϵ 20057), 280(12127), 309(23701), 341(11685). ν_{\max} 3460, 3302, 1731, 1710, 1600, 1557, 1539, 1441, 1419, 1339, 1259, 1204, 1164, 1142, 1070, 990, 792 cm^{-1} . 1H n.m.r. [(CD_3) $_2$ SO]: δ 3.81, 3.86, 3.90 and 3.96, 4s, OMe; 6.63, s, H3'; 6.64, s, H5; 7.05, t, J8.00Hz, 1H, ArH; 7.11, t, J6.86Hz, 1H, ArH; 7.44, d, J8.00Hz, 1H, ArH; 7.58, d, J7.71Hz, 1H, ArH; 11.11, s, NH; 11.12, s, NH. Mass spectrum: m/z 408(M, 50%), 377(35), 376(100), 361(40).

Reaction of indole (15) and indolin-2-one (2), with phosphoryl chloride

Indole **15** (0.5g, 1.98mmol) and indolin-2-one **2** (0.27g, 2.03mmol) gave two products.

(i) **4,6-Dimethoxy-3-(indol-2'-yl)-2-phenylindole (16)**

(0.41g, 56%), R_f 0.75, mp 113-114°C (from dichloromethane and petroleum ether). (Found: C, 76.1; H, 5.5; N, 7.3. $C_{24}H_{20}N_2O_2(0.5H_2O)$ requires C, 76.4; H, 5.6; N, 7.4%). λ_{\max} 253nm(ϵ 43170), 278(36760), 290(44860), 300(53700), 336(17500), 369(6300). ν_{\max} 3435, 3398, 1585, 1512, 1458, 1350, 1224, 1122, 981, 688 cm^{-1} . 1H n.m.r. ($CDCl_3$): δ 3.87 and 3.91, 2s, OMe; 6.25, d, J1.8Hz, H3'; 6.34, d, J2.0Hz, H5; 6.51, d, J2.0Hz, H7; 7.04, t, J7.1Hz, 1H, ArH; 7.13, t, J6.8Hz, 1H, ArH; 7.35-7.50, m, 7H, ArH; 8.14, bs, NH; 9.31, bs, NH. ^{13}C n.m.r. ($CDCl_3$): δ 55.71 and 55.79, OMe; 87.19, C5; 93.18, C7; 102.02, C3'; 110.50, 119.27, 119.98 120.76, 128.08 and 128.78, ArCH; 106.05, 119.10, 133.02, 133.23, 134.23, 136.05 and 137.83, ArC; 153.94 and 157.77, C-OMe. Mass spectrum: m/z 369(M+1, 26%), 368(M, 100%), 367(22), 353(24), 351(15).

(ii) **4,6-Dimethoxy-7-(indol-2'-yl)-2-phenylindole (17)**

(0.18g, 25%), R_f 0.90, mp 144-146°C (from dichloromethane and petroleum ether). (Found: C, 78.1; H, 5.3; N, 7.4. $C_{24}H_{20}N_2O_2$ requires C, 78.3; H, 5.4; N, 7.6%). 1H n.m.r. (100MHz, $CDCl_3$): δ 3.95 and 4.02, 2s, OMe; 6.34, s, H5; 6.84, bs, H3; 6.89-7.75, m, 10H, ArH and H3'; 8.82, bs, NH; 9.28, bs, NH. Mass spectrum: m/z 369(M+1, 22%), 368(M, 100), 353(82), 325(14), 310(18).

Reaction of indole (15) and indolin-2-one (7) with phosphoryl chloride

Indole **15** (0.5g, 1.98mmol) and indolin-2-one **7** (0.39g, 2.02mmol) gave two products.

(i) **4,6-Dimethoxy-3-(4',6'-dimethoxyindol-2'-yl)-2-phenylindole (18)**

(0.25g, 30%), R_f 0.70, mp 228°C (from dichloromethane and petroleum ether). (Found: C, 72.8; H, 5.5; N, 6.2. $C_{26}H_{24}N_2O_4$ requires C, 72.9; H, 5.7; N, 6.5%). 1H n.m.r. (100MHz, $CDCl_3$): δ 3.35 3.62, 3.75 and 3.79, 4s, OMe; 6.05, d, J2.0Hz, 1H, ArH; 6.12, d, J1.7Hz, 1H, ArH; 6.18, d, J2.0Hz, 1H, ArH; 6.47, bd, J1.6Hz, 1H, H3'; 6.54, d, J1.7Hz, 1H, ArH; 7.17-7.40, m, 5H, ArH; 10.72, bs, NH; 11.42, s, NH. Mass spectrum: m/z 428(M, 100%), 429(32), 414(20), 413(50), 398(14), 397(18).

(ii) **4,6-Dimethoxy-7-(4',6'-dimethoxyindol-2'-yl)-2-phenylindole (19)**

(0.008g, 1%), R_f 0.85, mp 243-245°C (from dichloromethane and petroleum ether). 1H n.m.r. (100MHz, $CDCl_3$): δ 3.86 and 3.89, 2s, OMe; 6.19, m, 2H, ArH; 6.24, s, H5; 6.49-6.51, m, 2H, ArH; 7.32-7.49, m, 5H, ArH; 8.15, bs, NH; 9.03, bs, NH. Mass spectrum: m/z 428(M, 30%), 356(100), 355(32), 268(21), 219(18), 193(25), 160(20), 149(20).

Reaction of indole (20) and indolin-2-one (2).

Indole **20** (0.5g, 2.78mmol) and indolin-2-one **2** (0.4g, 3.01mmol) gave two products.

(i) **2-(Indol-2'-yl)-4,6-dimethoxy-3-methylindole (21)**

(0.28g, 33%), R_f 0.75, mp 134-135°C (from dichloromethane and petroleum ether). (Found: C, 74.2, H, 6.0; N, 8.9. $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.2%). 1H n.m.r. (100MHz, $CDCl_3$): δ 3.65, s, Me; 3.87 and

3.93, 2s, OMe; 6.18, d, J2.0Hz, H5; 6.28, d, J2.0Hz, H7; 6.55, bs, H3'; 7.12-7.82, m, ArH; 7.82, bs, NH'; 8.16, bs, NH. Mass spectrum: m/z 306(M,100%), 301(78), 248(18), 191(20), 176(18), 153(17).

(ii) **7-(Indol-2'-yl)-4,6-dimethoxy-3-methylindole (22)**

(0.23g, 27%), R_f 0.90, mp 153°C (from dichloromethane and petroleum ether). (Found: C, 74.2, H, 5.7; N, 9.0. $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.2%). λ_{\max} 236nm(ϵ 99430), 327(59800). ν_{\max} 3453, 1608, 1464, 1319, 1213, 1138, 1095, 787, 760 cm^{-1} . 1H n.m.r. ($CDCl_3$): δ 2.47, s, Me; 3.94 and 3.98, 2s, OMe; 6.35, s, H5; 6.77, bd, J2.0Hz, H3'; 6.81, s, H2; 7.13, t, J7.0Hz, 1H, ArH; 7.20, t, J7.1Hz, 1H, ArH; 7.43, d, J7.9Hz, 1H, ArH; 7.64, d, J7.6Hz, 1H, ArH; 8.42, bs, NH; 9.35, bs, NH. ^{13}C n.m.r. ($CDCl_3$): δ 12.12, Me; 55.40 and 57.58, OMe; 88.92, 99.62 and 110.67, C2, C5 and C3'; 119.72, 119.81, 120.04 and 121.63, ArCH; 98.05, 112.63, 114.05, 128.53, 133.37, 135.63 and 136.05, ArC; 153.61 and 155.32, C-OMe. Mass spectrum: m/z 306(M, 100%), 301(75), 263(24), 248(16), 153(14).

3-(4''-Bromophenyl)-7-(indol-2'-yl)-4,6-dimethoxyindole (24)

Method A: Phosphoryl chloride (0.28ml, 3.0mmol) was added to a stirred and ice cooled solution of 3-(4'-bromophenyl)-4,6-dimethoxyindole **23** (0.5g, 1.5mmol) and indolin-2-one **2** (0.2g, 1.5mmol) in chloroform (20ml). The solution was then refluxed for 1h and on cooling the reaction mixture made strongly basic with sodium hydroxide solution (20%). The mixture was then extracted with dichloromethane, dried, concentrated, column chromatographed using dichloromethane as the eluent and the product with R_f 0.85 was isolated to give the biindolyl **24** as a white powder (0.03g, 5%), mp 229-231°C. (Found: C, 64.2; H, 4.3; N, 6.0. $C_{24}H_{19}BrN_2O_2$ requires C, 64.4; H, 4.3; N, 6.3%). λ_{\max} 242nm (ϵ 32260), 325(20160). ν_{\max} 3456, 3434, 1590, 1542, 1415, 1653, 1339, 1214, 1109, 798, 743 cm^{-1} . 1H n.m.r. ($CDCl_3$): δ 3.89 and 3.97, 2s, OMe; 6.44, s, H5; 6.80, bd, J 1.5Hz, H3'; 7.11, d, J2.5Hz, H2; 7.15, m, 1H, ArH; 7.22, m, 1H, ArH; 7.45, d, J7.6Hz, 1H, ArH; 7.49, s, 4H, ArH; 7.66, d, J7.6Hz, 1H, ArH; 8.87, bs, NH; 9.22, bs, NH'. ^{13}C n.m.r. [$(CD_3)_2SO$]: δ 55.51 and 57.06, OMe; 89.72, C5; 101.19, C3'; 111.50, 118.59, 119.64, 120.79, 123.63, 130.62 and 131.28, ArCH and C2; 98.97, 110.37, 116.09, 118.94, 128.47, 132.03, 135.71, 136.46 and 137.02, ArC; 153.77 and 154.13, C-OMe. Mass spectrum: m/z 448(M, ^{81}Br , 100%), 446(M, ^{79}Br , 100%), 433(24), 431(25).

Method B: Triflic anhydride (0.252ml, 1.5mmol) was added to a stirred and ice-cooled solution of 3-(4'-bromophenyl)-4,6-dimethoxyindole **23** (0.5g, 1.5mmol) and indolin-2-one **2** (0.2g, 1.5mmol) in chloroform (20ml). The solution was allowed to come to room temperature for 0.5h then made strongly basic with sodium hydroxide solution (20%). The mixture was then extracted with dichloromethane and the product recrystallised from dichloromethane and petroleum ether to give the biindolyl **24** as a white powder (0.67g, 99%), mp 229-231°C.

3-(4''-Bromophenyl)-4,6-dimethoxy-7-(4',6'-dimethoxyindol-2'-yl)indole (26)

Triflic anhydride (0.252ml, 1.5mmol) was added to a stirred and ice-cooled solution of 3-(4'-bromophenyl)-4,6-dimethoxy indole **23** (0.5g 1.5mmol) and indolin-2-one **7** (0.29g, 1.5mmol) in chloroform (20 ml). The solution was allowed to come to room temperature for 0.5h and the product then made strongly basic with sodium hydroxide solution (20%). The mixture was then extracted with dichloromethane and chromatographed to give the bi-indolyl (0.76g, 99%), mp 189-204°C (from dichloromethane and petroleum ether). (Found: C, 61.9; H, 4.7; N, 5.3. $C_{26}H_{23}BrN_2O_4$ requires C, 61.6; H, 4.6; N, 5.5%). λ_{\max} 245nm (ϵ 22000), 328(13000). ν_{\max} 3476, 3397, 1590, 1543, 1378, 1216, 1150, 1127, 797 cm^{-1} . 1H n.m.r. ($CDCl_3$): δ 3.88, s, OMe; 4.00 and 4.06, 2s, OMe; 6.27, d, J1.9Hz, H5'; 6.42, s, H5; 6.58, d, J2.0Hz, H7'; 6.79, d, J2.3Hz, H3'; 7.09, d, J2.5Hz, H2; 7.49, s, ArH; 8.93, bs, NH'; 9.19, bs, NH. ^{13}C n.m.r. [$(CD_3)_2SO$]: δ 55.15 and

57.07, OMe; 55.50, 2xOMe; 87.53, 89.85, 91.14, 98.33, 123.66, 130.60 and 131.28, ArCH; 99.26, 110.41, 113.49, 116.03, 116.57, 128.84, 135.76, 136.77 and 137.65, ArC; 152.87, 153.47, 153.73 and 156.60, COMe. Mass spectrum : m/z 508(M, ^{81}Br , 100%), 506(M, ^{79}Br , 98), 493(60), 491(60), 333(18), 331(17).

3-(4'-Methoxyphenyl)-2,7-bi-(indol-2''-yl)-4,6-dimethoxyindole (30)

Triflic anhydride (1.13g, 4.0mmol) was added dropwise to an ice cooled solution of indole **25** (0.5g, 1.77mmol) and indolin-2-one **2** (0.5g, 3.76mmol) in chloroform (25ml). The solution was then allowed to come to room temperature resulting in the formation of a bright yellow precipitate which was neutralised with 10% sodium hydroxide followed by extraction with dichloromethane. This was then concentrated and column chromatographed to yield the product **30** as a white solid (0.45g, 50%), mp 240°C (from dichloromethane and petroleum ether). (Found: C, 75.8; H, 5.6; N, 7.7. $\text{C}_{33}\text{H}_{27}\text{N}_3\text{O}_3(0.5\text{H}_2\text{O})$ requires C, 75.8; H, 5.4; N, 8.0%). λ_{max} 258nm(ϵ 27550), 281(29550), 300(28100), 329(25800), 357(25050), 373(18300). ν_{max} 3450, 2924, 1576, 1464, 1319, 1134, 787 cm^{-1} . ^1H n.m.r. [$(\text{CD}_3)_2\text{SO}$]: δ 3.71, 3.85 and 3.89, 3s, OMe; 5.95, d, J2.0Hz, H3'; 6.52, s, H5; 6.76, d, J2.1Hz, H3'; 6.92, t, J7.5Hz, 1H, ArH; 7.00, d, J8.7Hz, 2H, ArH; 7.06, t, J7.4Hz, 2H, ArH; 7.14, t, J7.1Hz, 1H, ArH; 7.33, m, 2H, ArH; 7.35, d, J8.5Hz, 2H, ArH; 7.50, d, J7.9Hz, 1H, ArH; 7.63, d, J7.7Hz, 1H, ArH; 10.52, s, NH; 11.19, d, J2.0Hz, NH; 11.51, d, J1.7Hz, NH. ^{13}C n.m.r. [$(\text{CD}_3)_2\text{SO}$]: δ 55.23, 55.69 and 57.09, OMe; 90.09, C5; 100.17, 101.90, 111.10, 111.59, 113.39, 118.96, 119.58, 119.88, 119.92, 120.83, 121.45 and 132.28, ArCH; 98.79, 113.79, 115.20, 126.11, 128.45, 128.67, 130.71, 131.76, 135.92, 136.39 and 136.67, ArC; 154.30, 154.50 and 158.28, C-OMe. Mass spectrum: m/z 514(M+1, 40%), 513(M, 100), 497(25), 482(15), 466(20).

Reaction of indolin-2-one (7) with phosphoryl chloride

To a stirred solution of indolin-2-one **7** (0.5g, 2.62mmol) in anhydrous chloroform (30ml) was added phosphoryl chloride (0.5ml, 5.38mmol). After refluxing for 12 h the mixture was cooled and made strongly alkaline with sodium hydroxide solution (10%). The mixture was then extracted with chloroform, the extract dried, concentrated and column chromatographed using chloroform / methanol 95 : 5 as the eluent to yield two products.

(i) **1,3,6,8,11,13-Hexamethoxy-5,10,15-trihydrodiindolo[2,1-b][4,3-b]carbazole (34)**

(0.008g, 1.7%), mp > 300°C. ^1H n.m.r. [$(\text{CD}_3)_2\text{SO}$]: δ 3.89 and 4.23, 2s, OMe; 6.45, d, J2.1Hz, H2, H7 and H12; 7.14, d, J2.1Hz, 3H, H4, H9 and H14; 10.25, s, NH. Mass spectrum: m/z 526(M+1, 35%), 525(M, 95), 511(10), 510(40), 495(20).

(ii) **4-(4',6'-Dimethoxyindol-2'-yl)-1,3,6,8,11,13-hexamethoxy-5,10,15-trihydrodiindolo[2,1-b][4,3-b]carbazole (35)**

(0.005g, 1.1%), mp > 300°C. ^1H n.m.r. [$(\text{CD}_3)_2\text{SO}$]: δ 3.82, 3.88, 3.90, 4.01, 4.03, 4.24 and 4.36, 7s, 24H, OMe; 6.27, d, J2.1Hz, 1H, ArH; 6.44, d, J2.1Hz, 1H, ArH; 6.47, d, J2.1Hz, 1H, ArH; 6.67, d, J1.7Hz, 1H, ArH; 6.76, d, J2.3Hz, H3'; 6.78, s, H2; 7.16, d, J2.0Hz, 1H, ArH; 7.17, d, J2.1Hz, 1H, ArH; 10.27, 10.30 and 10.56, 3s, NH; 11.10, d, J2.2Hz, NH. Mass spectrum: m/z 702(M+1, 15%), 701(M, 80), 524(25).

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