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Synthesis of indolo[2,3-*c*]quinolines from 3-arylindole-2-ketoximes

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Abstract—Treatment of the 2,4-dinitrophenyl ethers of some 3-arylindole-2-ketoximes with base results in a cyclisation reaction to yield indolo[2,3-*c*]quinolines.

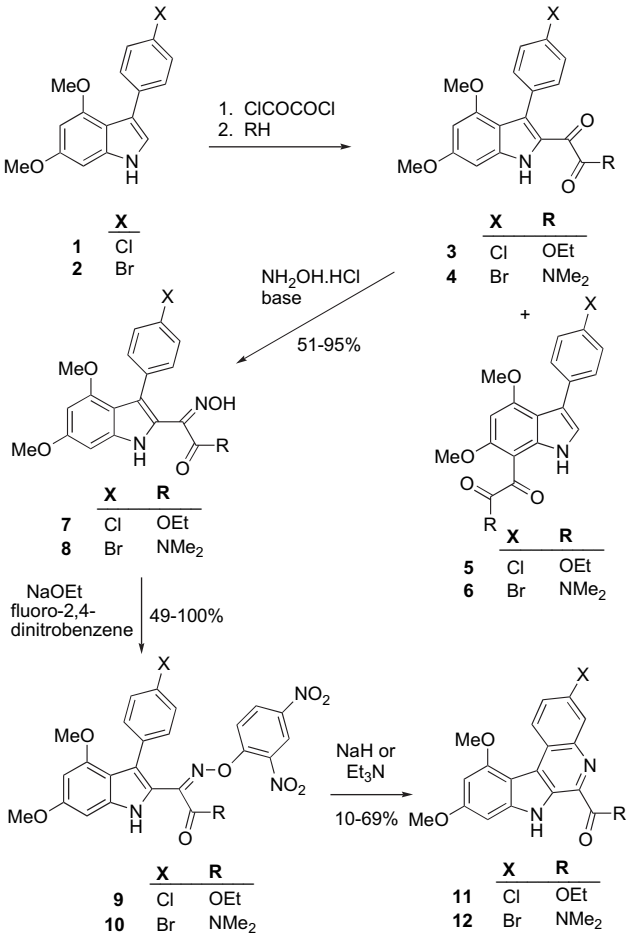
1. Introduction

We have previously reported that treatment of 2,4-dinitrophenyl ethers of a range of indole-7-ketoximes with base provides an effective method for the synthesis of the novel pyrrolo[3,2,1-*hi*]indazoles.[1] In view of this result, we decided to investigate the situation where the oxime ether was attached in a vicinal relationship to a benzene ring, and such a possibility arises in the case of the oxime ethers of 3-arylindole-2-ketoximes. Compounds of this type are available through the reaction of 3-aryl-4,6-dimethoxyindoles with oxalyl chloride, followed by quenching with alcohols or amines to give both 2- and 7-glyoxylic esters and amides, which can be readily separated and purified.[2]

2. Results and discussion

2.1. Formation of indole-2-ketoximes and ketoxime ethers

The two activated indoles **1** and **2** were converted to the corresponding 2-glyoxylic ester **3** and 2-glyoxylic amide **4**, respectively, by acylation with oxalyl chloride followed by addition of either ethanol or dimethylamine (Scheme 1). The isomeric 7-gloxylic ester **5** and the 7-glyoxylic amide **6** were also isolated as minor products. It has already been reported that the bromophenyl indole **2**, when treated with oxalyl chloride in diethyl ether followed by dimethylamine, gave a predominance of the 2-glyoxylamide **4** over the 7-glyoxylamide **6**.[2]



Scheme 1.

Reaction of the glyoxylic ester **3** with hydroxylamine hydrochloride in absolute ethanol containing sodium acetate yielded the indole-2-ketoxime **7** in 82%. The related glyoxylamide **4** required different conditions, namely heating in

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ethanol containing pyridine, to give the oxime **8** in 90% yield (Scheme 1). The observed spectroscopic data for the oximes **7** and **8** showed mixtures of *anti* and *syn* isomers in ratios of 10:1 and 1.2:1, respectively.

Treatment of the indole-2-ketoximes **7** and **8** with fluoro-2,4-dinitrobenzene in the presence of sodium ethoxide at 0 °C for 2 h yielded the respective oxime ethers **9** and **10**. Both compounds were characterised fully, with the exception of ^{13}C NMR spectra because of relative insolubility. Again mixtures of *anti* and *syn* isomers were observed, with the expectedly more stable *anti* isomer predominating.

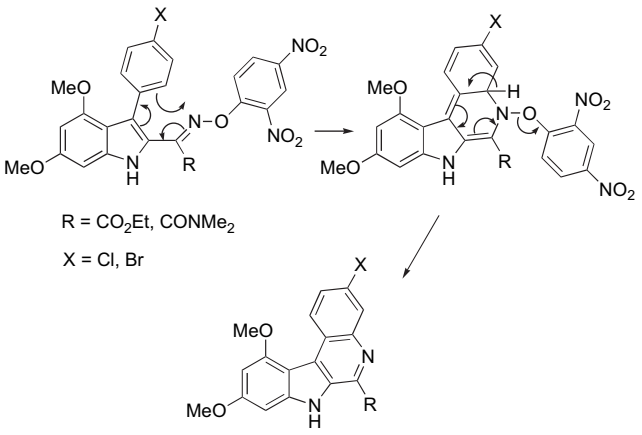
2.2. Formation of indolo[3,2-*c*]quinolines

On treatment with triethylamine in tetrahydrofuran, the oxime ethers **9** and **10** gave light yellow solid products. The ^1H NMR spectra of the products displayed an absence of the typical 1,4-disubstituted benzene pattern, with two doublets at δ 8.33 and 9.33 ppm and one doublet of doublets at 7.69 ppm, in total corresponding to three protons. This indicates the loss of one proton from the 3-aryl group, presumably resulting from linkage to the oxime nitrogen atom. The resulting structures **11** and **12**, which are indolo[3,2-*c*]quinolines are supported by all the spectroscopic and analytical evidence (Scheme 1).

Compounds **11** and **12** are benzo analogues of β-carboline, which is an important structural feature of alkaloids of the harman group.[3,4] Benzo-β-carbolines can be prepared by a variety of specialised methods involving indole formation via pyrolysis of a 3-azido-4-arylquinoline derivative,[4] intramolecular coupling of a 2-arylaminomethylindole,[5] or the application of a stepwise Bischler indole synthesis.[6]

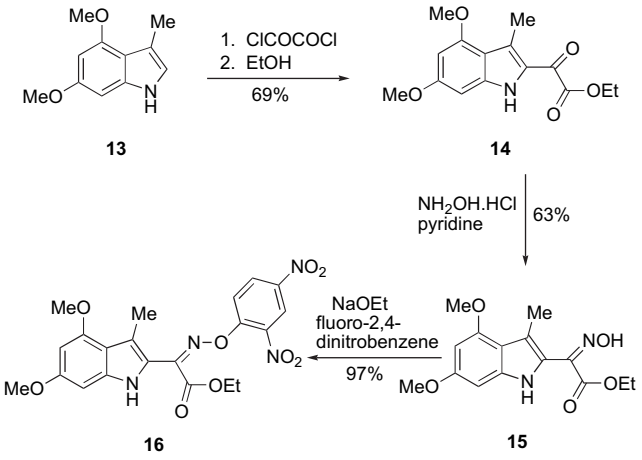
The cyclisation reactions leading to compounds **11** and **12** could possibly proceed via several different mechanisms. These broadly include the involvement of a nitrenium cation or nitrene, a base catalysed displacement, or an electrocyclic process. Nitrenes have been postulated in some photochemical and thermal transformations of *O*-acyl oximes.[7,8] On the other hand, cyclisation reactions of oximes to form the pyridine ring moiety of harman-like structures appear to involve electrocyclisation of an intermediate azatriene.[9,10] Compound **11** was formed in 25 and 55% yields by heating the oxime ether **9** in tetrahydrofuran and xylene, respectively, for 24 h, results were consistent with an electrocyclic mechanism (Scheme 2). Further studies will be carried out in order to attempt to clarify the mechanism of this interesting cyclisation reaction. The extent to which the reaction is affected by the stereochemistry of the oxime ether is also unclear, as pure isomers have not been obtainable.

As the 3-aryl group is essential for the observed cyclisation reaction, it was of interest to investigate the effect of replacing it with a 3-methyl group. The 3-methylindole-2-glyoxylic ester **14** was prepared[11] in 69% yield by reaction of 4,6-dimethoxy-3-methylindole **13** with oxalyl chloride in diethyl ether, followed by the addition of ethanol (Scheme 3). Reaction of the glyoxylic ester **14** with hydroxylamine hydrochloride in the presence of pyridine gave the indole oxime **15** in 63% yield, as a mixture of *syn* and *anti* isomers in a ratio of 1:0.6. Subsequent treatment of the oxime **15**



Scheme 2.

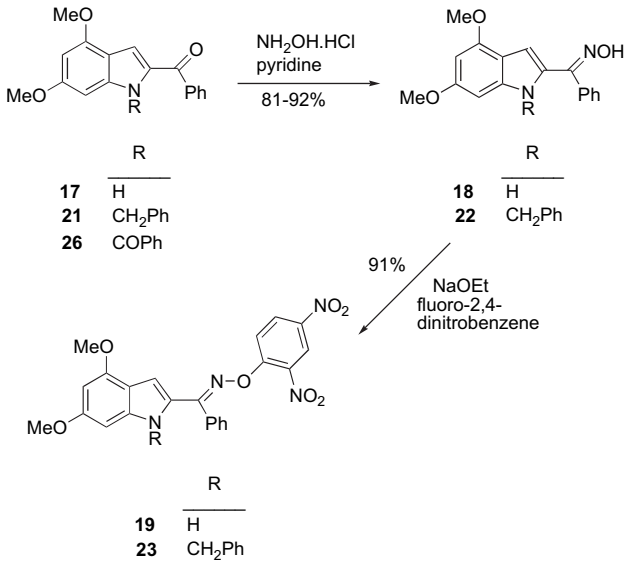
with fluoro-2,4-dinitrobenzene and sodium ethoxide gave the crude oxime ether **16** in 97% yield, as a single isomer; the absence of any significant hydrogen bonding of the indole NH proton suggests the assignment of the *anti* configuration (Scheme 3). Base treatment of the oxime ether **16** was carried out by heating it with triethylamine in dry tetrahydrofuran. The starting material remained intact after 12 h, a result that further supports the electrocyclic mechanism.



Scheme 3.

Furthermore, similar reaction of the 3-unsubstituted oxime ether **19** was investigated. The 2-benzoyl indole **17**[12] was converted to the oxime **18** (as a mixture of *syn* and *anti* isomers) in 92% yield by reaction with hydroxylamine hydrochloride and pyridine. Treatment of the oxime **18** with fluoro-2,4-dinitrobenzene gave the oxime ether **19** (as the single *anti* isomer) in 91% yield. Once again, no reaction was observed when this compound was heated with triethylamine at reflux in tetrahydrofuran for 12 h (Scheme 4).

It was also of interest to investigate the possible cyclisation of an indole-2-oxime ether on to a substituent on the nitrogen atom. In this context, cyclisation on to an *N*-benzyl or *N*-benzoyl group would be synthetically useful, as benzodiazepine derivatives would be formed. Such benzodiazepine derivatives are generally biologically active,[13] and in particular, the indolobenzodiazepines **20** show antihistamine and serotonin activities, as well as an ability to inhibit mediator

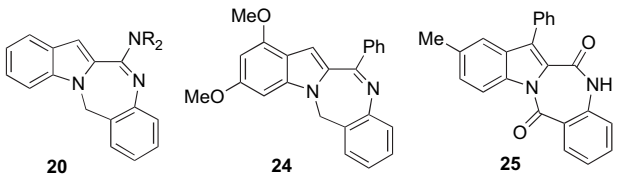


Scheme 4.

release and thus have potential for treatment of allergic reactions.[14]

The 2-benzoyl indole **17** was benzylated using benzyl bromide and potassium hydroxide in dry dimethyl sulfoxide to give the *N*-benzyl indole **21** in 76% yield. Treatment of this compound with hydroxylamine hydrochloride and pyridine gave the oxime **22** in 90% yield, as a mixture of *syn* and *anti* isomers. In this case, it is not possible to identify the individual isomers because there is no possibility of hydrogen bonding to distinguish between them. Treatment of the oxime **22** with fluoro-2,4-dinitrobenzene and sodium ethoxide gave the oxime ether **23** as a mixture of isomers (Scheme 4).

Cyclisation of oxime ether **23** was attempted by treatment under a variety of basic conditions. Heating the oxime ether **23** and triethylamine in tetrahydrofuran gave only unreacted starting material. In contrast, heating the mixture of oxime ether **23** and sodium hydride in dioxan gave a complex product mixture. However, stirring compound **23** with sodium hydride in dioxan at room temperature for 24 h gave an orange solid, which was indicated to be the cyclic product **24**, on the basis of NMR spectra, although the compound could not be obtained fully pure.



20 **24** **25**

The indolobenzodiazepinedione **25** and related structures have been shown to behave as antibacterial agents against *Escherichia coli* and *Staphylococcus aureus*.[15] This information prompted an attempt to synthesise similar compounds by the oxime ether route. Thus, the 2-benzoyl indole **17** was benzoylated on nitrogen to give 1,2-dibenzoyl indole **26** in only a modest yield together with a range of minor products. All attempts to prepare the related oxime yielded only the 2-benzoyl oxime **18** as a result of hydrolysis of the *N*-benzoyl group. Alternative attempts to *N*-benzoylate the oxime ether **19** were unsuccessful, so the critical starting material for the potential cyclisation was unavailable.

3. Conclusion

The treatment of 2,4-dinitrophenyl ethers of a range of indole 7-ketoximes with base provides an effective method for the synthesis of the novel pyrazolo[4,5,1-*hi*]indoles. Further work aims to explore the scope and mechanism of the cyclisation reaction.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either Bruker FT-ICR MS (EI) or Micromass ZQ2000 (ESI) at UNSW, or Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 $60GF_{254}$.

4.1.1. Ethyl 2-[3-(4-chlorophenyl)-4,6-dimethoxyindol-2-yl]glyoxylate (3) and ethyl 2-[3-(4-chlorophenyl)-4,6-dimethoxyindol-7-yl]glyoxylate (5). This was prepared as described[2] for glyoxylamide **4** from indole **1** (1.00 g, 3.5 mmol) in anhydrous diethyl ether (30 mL) with oxalyl chloride (0.40 mL, 4.2 mmol) and the resulting red solid glyoxyloyl chloride was stirred at room temperature in absolute ethanol (15 mL) for 2 h. The precipitate was filtered off, washed until neutral and dried to give compound **3** (0.56 g, 42%) as an orange solid, mp 188 °C. Found: C, 61.9; H, 4.8; N, 3.7. $C_{20}H_{18}ClNO_5$ requires C, 61.9; H, 4.7; N, 3.6%. ν_{max}: 3323, 1741, 1600, 1571, 1236, 1206, 1132, 816 cm^{-1}. λ_{max}: 228 nm (ε 18,350 cm^{-1} M^{-1}), 264 (20,350), 334 (13,850). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 1.14 (3H, t, *J* 7.2 Hz, Me), 3.63, 3.86 (6H, 2s, OMe), 3.79 (2H, q, *J* 7.2 Hz, OCH_2), 6.11 (1H, d, *J* 1.9 Hz, H5), 6.41 (1H, d, *J* 1.9 Hz, H7), 7.34 (4H, m, ArH), 9.44 (1H, br s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 13.5 (CH_3), 55.1, 55.6 (OCH_3), 62.0 (OCH_2), 85.6 (C5), 93.8 (C7), 127.1, 132.2 (ArCH), 113.3, 127.1, 128.6, 131.9, 133.6, 139.8, 156.9, 162.4 (ArC), 163.9, 176.8 (C=O). Mass spectrum (EI): *m*/*z* 389 (M+2, ^{37}Cl, 20%), 387 (M, ^{35}Cl, 62), 316 (27), 314 (83), 279 (100), 264 (21).

Absolute ethanol (10 mL) was added to the filtrate and the mixture was refluxed for 2 h. Water was then added and

the mixture was extracted with dichloromethane. The organic layer was washed until neutral, dried and the solvent was removed under reduced pressure to give compound **5** (0.33 g, 24%) as a yellow solid, mp 188–189 °C. Found: C, 61.7; H, 4.5; N, 3.7. $C_{20}H_{18}ClNO_5$ requires C, 61.9; H, 4.7; N, 3.6%. ν_{max}: 3426, 1728, 1584, 1309, 1218, 1170, 1058 cm^{-1}. λ_{max}: 232 nm (ε 21,600 $cm^{-1}\,M^{-1}$), 256 (20,900), 336 (12,100). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.41 (3H, t, *J* 7.2 Hz, Me), 3.92, 3.94 (6H, 2s, OMe), 4.43 (2H, q, *J* 7.2 Hz, OCH_2), 6.18 (1H, s, H5), 7.09 (1H, d, *J* 2.2 Hz, H2), 7.31–7.48 (4H, m, ArH), 10.56 (1H, br s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.1 (Me), 55.4, 56.9 (OMe), 61.4 (OCH_2), 87.4 (C5), 121.9 (C7), 127.7, 130.6 (ArCH), 100.8, 110.7, 118.0, 131.9, 133.6, 138.4, 162.0, 162.1 (ArC), 165.9, 185.1 (C═O). Mass spectrum (EI): *m/z* 389 (M+2, ^{37}Cl, 16%), 387 (M, ^{35}Cl, 47), 316 (58), 314 (100).

4.1.2. Ethyl 2-[3-(4-chlorophenyl)-4,6-dimethoxyindol-2-yl]-2-(hydroxyimino)acetate (7). This was prepared from indole glyoxylic ester **5** (0.40 g, 1.0 mmol), hydroxylamine hydrochloride (0.36 g, 5.2 mmol) and sodium acetate (0.4 g, 2.9 mmol) in absolute ethanol (40 mL) under reflux for 7 h. After extraction and concentration the residue was chromatographed with dichloromethane/ethyl acetate (95:5) as an eluent to give the oxime **7** (0.34 g, 82%) as a light brown solid, mp 183–184 °C. Found: C, 59.6; H, 4.8; N, 7.0. $C_{20}H_{19}ClN_2O_5$ requires C, 59.6; H, 4.8; N, 6.9%. ν_{max}: 3373, 1719, 1624, 1584, 1212, 1151, 1131, 998, 818 cm^{-1}. λ_{max}: 228 nm (ε 23,750 $cm^{-1}\,M^{-1}$), 255 (19,850), 337 (7,200). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 0.97 (6H, m, *syn* and *anti* Me), 3.51–3.76 (16H, m, *syn* and *anti* OCH_2 and OMe), 6.09, 6.17 (2H, 2s, *syn* and *anti* H5), 6.52, 6.56 (2H, 2d, *J* 1.5 Hz, *syn* and *anti* H7), 7.19, 7.32 (8H, 2d, *J* 8.3 Hz, *syn* and *anti* ArH), 11.17, 11.28 (2H, 2s, *syn* and *anti* NH), 11.64, 12.60 (2H, 2s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 13.7, 13.9 (Me), 55.3, 55.4, 55.6, 55.6 (OMe), 61.1, 61.2 (OCH_2), 87.2, 87.3 (C5), 92.4 (C7), 126.9, 127.3, 132.2, 133.4 (ArCH), 110.2, 112.4, 117.3, 117.6, 121.7, 123.4, 131.1, 131.8, 134.5, 138.3, 138.4, 143.4, 144.7, 154.9, 155.0 (ArC), 158.2, 158.7 (C═N), 162.2, 163.2. (C═O). Mass spectrum (EI): *m/z* 404 (M+2, ^{37}Cl, 31%), 402 (M, ^{35}Cl, 100), 385 (35), 313 (34), 312 (81), 291 (61), 262 (46).

4.1.3. *N*,*N*-Dimethyl 2-[3-(4-bromophenyl)-4,6-dimethoxyindol-2-yl]-2-(hydroxyimino) acetamide (8). This was prepared from indole glyoxylamide **6** (0.15 g, 0.3 mmol), hydroxylamine hydrochloride (0.08 g, 5.2 mmol), and pyridine (2 mL) in absolute ethanol (2 mL) under reflux overnight. After extraction and concentration, the residue was chromatographed with dichloromethane/methanol (95:5) as an eluent to give the oxime **8** (0.14 g, 90%) as a light brown solid, mp 134 °C (dec). Found: C, 53.1; H, 4.6; N, 9.3. $C_{20}H_{20}BrN_3O_4\cdot 0.3H_2O$ requires C, 53.2; H, 4.6; N, 9.3%. ν_{max}: 3263, 1629, 1585, 1513, 1285, 1205, 1151, 1131, 1074, 996 cm^{-1}. λ_{max}: 229 nm (ε 25,000 $cm^{-1}\,M^{-1}$), 262 (20,400), 327 (18,100). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 2.06, 2.30, 2.62, 2.73 (6H, s, *syn* and *anti* Me), 3.49, 3.53, 3.74 (6H, 2s, *syn* and *anti* OMe), 6.07, 6.10 (1H, d, *J* 1.9 Hz, *syn* and *anti* H5), 6.54, 6.71 (1H, d, *J* 1.9 Hz, *syn* and *anti* H7), 7.10, 7.43 (4H, 2d, *J* 8.3 Hz, *syn* and *anti* ArH), 11.06, 11.30 (1H, br, *syn* and *anti* NH), 11.34, 11.99 (1H, s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 31.0, 32.8, 36.6, 38.3 (Me), 55.4, 55.6 (OMe), 87.2, 87.5 (C5), 92.3, 92.5 (C7), 129.4, 133.2, 133.4 (ArCH), 112.6, 117.1, 120.1, 122.1, 124.2, 134.1, 134.4, 138.3, 147.1, 154.9 (ArC), 158.5 (C═N), 162.8 (C═O). Mass spectrum (EI): *m/z* 448 (M+2, ^{81}Br, 22%), 447 (86), 446 (M, ^{79}Br, 19), 445 (93), 428 (24), 372 (23), 356 (39), 333 (57), 331 (59), 292 (33), 291 (100), 263 (33).

4.1.4. Ethyl 2-[3-(4-chlorophenyl)-4,6-dimethoxyindol-2-yl]-2-(*O*-2,4-dinitrophenyloxyimino)acetate (9). This was prepared from indole oxime **7** (0.27 g, 0.66 mmol), absolute ethanol (25 mL), sodium (22 mg, 0.96 mmol) and fluoro-2,4-dinitrobenzene (0.12 mL, 0.66 mmol) in an ice bath. After filtration and washing, the product was dried to yield the oxime ether **9** (0.34 g, 89%) as an orange solid, mp 214–216 °C. Found: C, 54.3; H, 3.7; N, 9.5. $C_{26}H_{21}ClN_4O_9\cdot 0.3H_2O$ requires C, 54.4; H, 3.8; N, 9.8%. ν_{max}: 3383, 1736, 1605, 1565, 1536, 1340, 1251, 1137, 1089 cm^{-1}. λ_{max}: 231 nm (ε 34,950 $cm^{-1}\,M^{-1}$), 327 (17,150). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.12–1.18 (6H, m, *syn* and *anti* Me), 3.59–3.92 (16H, m, *syn* and *anti* OCH_2 and OMe), 6.14 (2H, s, *syn* and *anti* H5), 6.47, 6.61 (2H, 2d, *J* 1.5 Hz, *syn* and *anti* H7), 7.33 (8H, s, *syn* and *anti* ArH), 7.89 (1H, d, *J* 9.4 Hz, ArH), 8.23 (1H, d, *J* 9.4, ArH), 8.43–8.56 (2H, m, ArH), 8.88, 9.09 (2H, 2d, ArH), 8.68, 10.77 (2H, 2s, *syn* and *anti* NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 386 (23%), 384 (59), 314 (32), 312 (100), 295 (27), 269 (19).

4.1.5. *N*,*N*-Dimethyl 2-[3-(4-bromophenyl)-4,6-dimethoxyindol-2-yl]-2-(*O*-2,4-dinitrophenyloxyimino) acetamide (10). This was prepared from indole oxime **8** (0.15 g, 0.33 mmol), absolute ethanol (15 mL), sodium (20 mg, 0.87 mmol) and fluoro-2,4-dinitrobenzene (0.06 mL, 0.33 mmol) in an ice bath. After filtration and washing, the product was dried to yield the oxime ether **10** (0.20 g, 100%) as an orange solid, mp 182 °C. Found: C, 50.1; H, 3.5; N, 11.0. $C_{26}H_{22}BrN_5O_8\cdot 0.5\,H_2O$ requires C, 50.3; H, 3.7; N, 11.3%. ν_{max}: 3277, 1648, 1606, 1534, 1475, 1343, 1300, 1205, 1133, 1068, 928 cm^{-1}. λ_{max}: 229 nm (ε 26,900 $cm^{-1}\,M^{-1}$), 262 (19,800), 348 (15,100), 378 (15,350). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.40, 2.67, 2.74, 2.80 (6H, 4s, *syn* and *anti* Me), 3.50, 3.57, 3.83, 3.92 (6H, 4s, *syn* and *anti* OMe), 6.01, 6.11 (1H, d, *J* 1.9 Hz, *syn* and *anti* H5), 6.36, 6.61 (1H, d, *J* 1.9 Hz, *syn* and *anti* H7), 7.22, 7.50 (4H, d, *J* 8.3 Hz, *syn* and *anti* ArH), 7.83, 8.20 (1H, d, *J* 9.4 Hz, ArH), 8.32, 8.50 (1H, dd, *J* 9.4, 2.6 Hz, *syn* and *anti* ArH), 8.73, 9.10 (1H, d, *J* 2.6 Hz, *syn* and *anti* ArH), 9.43, 11.04 (2H, 2s, *syn* and *anti* NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 614 (M+2, 4%), 428 (27), 355 (100).

4.1.6. Ethyl 3-chloro-9,11-dimethoxyindolo[3,2-*c*]quinoline-6-carboxylate (11). This was prepared from indole oxime ether **9** (0.33 g, 0.59 mmol), and triethylamine (1 mL) in dry tetrahydrofuran (25 mL) under reflux overnight. After extraction and concentration, the residue was chromatographed with dichloromethane/methanol (95:5) as an eluent to give the product **11** (98 mg, 43%) as a pale yellow solid, mp 197–198 °C. Found: C, 55.4; H, 4.0; N,

6.1. $C_{20}H_{17}ClN_2O_4 \cdot 0.75CH_2Cl_2$ requires C, 55.6; H, 4.2; N, 6.2%. ν_{max}: 3431, 1702, 1621, 1345, 1247, 1190, 1152, 1101 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.58 (3H, t, *J* 7.1 Hz, Me), 3.95, 4.12 (6H, 2s, OMe), 4.66 (2H, q, *J* 7.1 Hz, OCH_2), 6.42 (1H, d, *J* 1.9 Hz, H5), 6.67 (1H, d, *J* 1.9 Hz, H7), 7.61 (1H, dd, *J* 7.2, 2.3 Hz, ArH), 8.36 (1H, d, *J* 2.3 Hz, ArH), 9.46 (1H, d, *J* 9.4 Hz, ArH), 10.36 (H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.3 (Me), 55.4, 55.6 (OMe), 62.4 (OCH_2), 86.9 (C5), 92.9 (C7), 128.1, 128.5, 129.7 (ArCH), 106.6, 123.7, 125.6, 129.7, 131.9, 132.6, 142.6, 143.2, 155.9, 162.1 (ArC), 166.7 (C═O).

4.1.7. *N,N*-Dimethyl 3-bromo-9,11-dimethoxy indolo[3,2-*c*]quinoline-6-carboxamide (12). This was prepared from indole oxime ether **10** (0.15 g, 0.24 mmol) and triethylamine (1 mL) in dry tetrahydrofuran (15 mL) under reflux overnight. After extraction and concentration, the residue was chromatographed with dichloromethane/methanol (95:5) as an eluent to give the product **12** (57 mg, 54%) as a yellow solid, mp 233–235 °C. Found: C, 56.1; H, 4.2; N, 9.8. $C_{20}H_{18}BrN_3O_3$ requires C, 56.1; H, 4.2; N, 9.8%. ν_{max}: 3423, 1610, 1491, 1347, 1329, 1148, 1115, 1077, 811 cm^{-1}. λ_{max}: 230 nm (ε 24,250 $cm^{-1}\,M^{-1}$), 281 (34,450), 386 (17,000). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.29, 3.50 (6H, 2s, Me), 3.82, 4.07 (6H, 2s, OMe), 6.31 (1H, s, H5), 6.49 (1H, s, H7), 7.69 (1H, dd, *J* 7.2, 1.9 Hz, ArH), 8.33 (1H, d, *J* 1.9 Hz, ArH), 9.33 (1H, d, *J* 9.0 Hz, ArH), 10.35 (H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 36.7, 39.7 (Me), 55.4, 55.5 (OMe), 86.9 (C5), 92.7 (C7), 128.8, 129.7, 132.0 (ArCH), 106.9, 119.2, 123.1, 124.7, 131.3, 138.4, 142.5, 142.6, 155.7, 161.6 (ArC), 167.6 (C═O). Mass spectrum (EI): *m/z* 430 (M+2, ^{81}Br, 4%), 429 (18), 428 (M, ^{79}Br, 4), 372 (25), 370 (28), 358 (94), 356 (100), 313 (21).

4.1.8. Ethyl 2-(4,6-dimethoxy-3-methylindol-2-yl)glyoxylate (14). This was prepared from 3-methyl-4,6-dimethoxyindole **13** (2.0 g, 10.5 mmol) in anhydrous diethyl ether (75 mL) with oxalyl chloride (1.15 mL, 11.5 mmol) and the resulting red solid was stirred at room temperature in absolute ethanol (50 mL) for 1 h. Water was then added and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried and concentrated. The residue was chromatographed with dichloromethane as an eluent to give the indole **14** (2.32 g, 69%) as an orange solid, mp 96–97 °C. Found: C, 62.1; H, 6.0; N, 4.9. $C_{15}H_{17}NO_5$ requires C, 61.9; H, 5.9; N, 4.8%. ν_{max}: 3384, 1736, 1712, 1627, 1597, 1508, 1448, 1299, 1209, 1155, 1075, 1019 cm^{-1}. λ_{max}: 227 nm (ε 10.000 $cm^{-1}\,M^{-1}$), 262 (13,100), 342 (12,550). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.43 (3H, t, *J* 7.2 Hz, OCH_2Me), 2.76 (3H, s, Me), 3.84, 3.88 (6H, 2s, OMe), 4.42 (2H, q, *J* 7.2 Hz, OCH_2), 6.07 (1H, d, *J* 1.9 Hz, H5), 6.30 (1H, d, *J* 1.9 Hz, H7), 9.68 (1H, br, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 12.6, 13.9 (Me), 55.2, 55.5 (OMe), 62.4 (OCH_2), 85.5 (C5), 92.9 (C7), 114.3, 127.5, 139.9 (ArC), 157.8, 162.2 (C═O). Mass spectrum (EI): *m/z* 291 (M, 26%), 218 (100), 145 (20).

4.1.9. Ethyl 2-(4,6-dimethoxy-3-methylindol-2-yl)-2-(hydroxyimino)acetate (15). This was prepared from indole glyoxylic ester **14** (0.60 g, 2.1 mmol), hydroxylamine hydrochloride (1.4 g, 20.6 mmol) and pyridine (6 mL) in absolute ethanol (6 mL) under reflux for 17 h. After extraction and concentration, the residue was chromatographed with dichloromethane/ethyl acetate (95:5) to give the oxime **15** (0.40 g, 63%) as a pale brown oil. Found: C, 57.8; H, 5.9; N, 9.0. $C_{15}H_{18}N_2O_5 \cdot 0.3H_2O$ requires C, 57.8; H, 6.0; N, 9.0%. ν_{max}: 3407, 1731, 1627, 1588, 1464, 1211, 1155, 1031, 807 cm^{-1}. λ_{max}: 229 nm (ε 18,850 $cm^{-1}\,M^{-1}$), 319 (7,900). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 1.25 (3H, m, *syn* and *anti* OCH_2Me), 2.18, 2.30 (3H, s, *syn* and *anti* Me), 3.72–3.78 (6H, m, *syn* and *anti* OMe), 4.20–3.32 (2H, m, *syn* and *anti* OCH_2), 6.07, 6.08 (1H, s, *syn* and *anti* H5), 6.42, 6.46 (1H, d, *J* 1.9, 1.9 Hz, *syn* and *anti* H7), 10.72, 10.75 (1H, s, *syn* and *anti* NH), 11.49, 12.46 (1H, s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 10.8, 12.3, 14.2, 14.4 (Me), 55.5 (OMe), 61.7, 61.8 (OCH_2), 87.0 (C5), 91.5, 91.8 (C7), 112.1, 113.0, 113.1, 120.7, 122.2, 138.3, 138.8, 143.1, 145.2, 155.7, 155.8, 158.0 (ArC), 158.5, 164.0 (C═N), 164.2, 170.7 (C═O). Mass spectrum (EI): *m/z* 306 (M, 100%), 289 (29), 243 (31), 230 (27), 217 (59), 215 (63), 200 (36), 173 (31), 158 (43).

4.1.10. Ethyl 2-(4,6-dimethoxy-3-methylindol-2-yl)-2-(*O*-2,4-dinitrophenyloxyimino)acetate (16). This was prepared from indole oxime **15** (0.17 g, 0.6 mmol), absolute ethanol (15 mL), sodium (24 mg, 1.0 mmol) and fluoro-2,4-dinitrobenzene (0.1 mL, 0.6 mmol) to yield the oxime ether **16** (0.25 g, 97%) as an orange solid, which could not be obtained analytically pure, mp 166–168 °C. ν_{max}: 3392, 1743, 1605, 1570, 1522, 1469, 1340, 1248, 1231, 1149, 906 cm^{-1}. λ_{max}: 228 nm (ε 23,050 $cm^{-1}\,M^{-1}$), 256 (22,350), 334 (18,100). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.45 (3H, t, *J* 7.1 Hz, OCH_2Me), 2.51 (3H, s, Me), 3.88, 3.89 (6H, 2s, OMe), 4.49 (2H, q, *J* 7.1 Hz, OCH_2), 6.11 (1H, d, *J* 1.5 Hz, H5), 6.50 (1H, d, *J* 1.9 Hz, H7), 8.22 (1H, d, *J* 9.4 Hz, ArH), 8.51 (1H, dd, *J* 9.4, 2.6 Hz, ArH), 9.06 (1H, d, *J* 2.6 Hz, ArH), 10.58 (1H, br, NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 472 (M, 14%), 290 (100), 217 (50).

4.1.11. (4,6-Dimethoxyindol-2-yl)-phenylmethanone oxime (18). This was prepared from indole **17** (0.15 g, 0.4 mmol), hydroxylamine hydrochloride (0.30 g, 4.3 mmol) and pyridine (1.5 mL) in absolute ethanol (1.5 mL) under reflux for 2 h. After extraction and concentration, the residue was chromatographed with dichloromethane/ethyl acetate (95:5) to give the oxime **18** (0.11 g, 92%) as a brown solid, mp 90–92 °C. Found: C, 68.7; H, 5.7; N, 9.3. $C_{17}H_{16}N_2O_3$ requires C, 68.9; H, 5.4; N, 9.4%. ν_{max}: 3426, 3386, 1627, 1592, 1514, 1455, 1376, 1294, 1149 cm^{-1}. λ_{max}: 229 nm (ε 19,550 $cm^{-1}\,M^{-1}$), 251 (18,800), 317 (13,100). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 3.73–3.76 (6H, m, *syn* and *anti* OMe), 5.88, 6.13 (1H, d, *J* 1.9 Hz, *syn* and *anti* H5), 6.09, 6.27 (1H, d, *J* 1.9 Hz, *syn* and *anti* H7), 6.52, 6.69 (1H, s, *syn* and *anti* H3), 7.37–7.52 (5H, m, *syn* and *anti* ArH), 11.11, 11.30 (1H, s, *syn* and *anti* NH), 10.99, 11.85 (1H, s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 55.3, 55.3, 55.5 (Me), 87.4, 87.7 (C5), 91.6, 91.9 (C7), 102.7, 105.2 (C3), 128.2, 128.5, 128.8, 129.1, 129.2, 129.4 (ArCH), 112.1, 113.1, 127.7, 132.3, 133.2, 136.9, 138.6,

139.1, 148.6, 149.8, 153.5, 153.8 (ArC), 158.2, 158.5 (C=N). Mass spectrum (EI): *m/z* 296 (M, 92%), 278 (25), 263 (37), 235 (48), 220 (29), 201 (23), 149 (26), 77 (100).

4.1.12. (4,6-Dimethoxyindol-2-yl)-phenylmethanone *O*-2,4-dinitrophenyloxime (19). This was prepared from indole oxime **18** (0.20 g, 0.7 mmol), absolute ethanol (20 mL), sodium (30 mg, 1.3 mmol) and fluoro-2,4-dinitrobenzene (0.08 mL, 0.4 mmol) to yield the oxime ether **19** (0.28 g, 91%) as an orange solid, mp 198–200 °C. Found: C, 59.8; H, 3.7; N, 11.9. $C_{23}H_{18}N_4O_7$ requires C, 59.7; H, 3.9; N, 12.1%. ν_{max}: 3390, 1606, 1530, 1341, 1251, 1148 cm^{-1}. λ_{max}: 229 nm (ε 28,200 $cm^{-1}\,M^{-1}$), 255 (32,250), 325 (23,300). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.87, 3.92 (6H, 2s, OMe), 6.17 (1H, d, *J* 1.5 Hz, H5), 6.64 (1H, s, H3), 6.69 (1H, d, *J* 2.2 Hz, H7), 7.51–7.68 (5H, m, ArH), 8.30 (1H, d, *J* 9.4 Hz, ArH), 8.50 (1H, dd, *J* 9.4, 2.6 Hz, ArH), 9.11 (1H, d, *J* 2.6 Hz, ArH), 11.11 (1H, br, NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI): *m/z* 463 (M+1, 22%), 297 (80), 281 (100).

4.1.13. 2-Benzoyl-1-benzyl-4,6-dimethoxyindole (21). The mixture of 2-benzoyl-4,6-dimethoxyindole **17** (0.40 g, 1.4 mmol) and potassium hydroxide (0.32 g, 5.7 mmol) in dry dimethyl sulfoxide (8 mL) was stirred at room temperature for 1 h. Benzyl bromide (0.4 mL, 3.4 mmol) was added dropwise and the mixture was stirred for another 2 h. Water was added and the reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried and concentrated. The residue was chromatographed with dichloromethane/light petroleum (7:3) to give the indole **21** (0.40 g, 76%) as a yellow solid, mp 128–130 °C. Found: C, 77.8; H, 5.8; N, 3.7. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%. ν_{max}: 1613, 1586, 1484, 1268, 1250, 1203, 1156, 1096, 1044 cm^{-1}. λ_{max}: 228 nm (ε 22,650 $cm^{-1}\,M^{-1}$), 263 (22,400), 324 (14,200), 364 (11,100). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.80, 3.89 (6H, 2s, OMe), 5.84 (2H, s, CH_2), 6.19 (1H, s, H5), 6.35 (1H, s, H7), 7.12–7.86 (11H, m, H3 and ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 48.3 (CH_2), 55.3, 55.5 (OMe), 85.0, (C5), 92.8 (C7), 114.6 (C3), 126.4, 127.0, 127.9, 128.5, 129.4, 131.5 (ArCH), 112.5, 132.7, 138.3, 139.7, 142.3, 155.4, 161.1 (ArC), 187.4 (C=O). Mass spectrum (EI): *m/z* 371 (M, 19%), 105 (22), 91 (100).

4.1.14. (1-Benzyl-4,6-dimethoxyindol-2-yl)-phenylmethanone oxime (22). This was prepared from indole **21** (0.23 g, 0.6 mmol), hydroxylamine hydrochloride (0.44 g, 6.4 mmol) and pyridine (2 mL) in absolute ethanol (3 mL) under reflux for 19 h. After extraction and concentration, the residue was chromatographed with dichloromethane/ethyl acetate (95:5) to give the oxime **22** (0.20 g, 81%) as a pale yellow solid, mp 180–182 °C. Found: C, 74.8; H, 5.9; N, 7.4. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.7; N, 7.3%. ν_{max}: 3243, 1627, 1580, 1503, 1455, 1361, 1249, 1203, 1155, 1094 cm^{-1}. λ_{max}: 231 nm (ε 34,800 $cm^{-1}\,M^{-1}$). ^1H NMR spectrum (300 MHz, d_6-DMSO): δ 3.69–3.82 (6H, m, *syn* and *anti* OMe), 5.17, 5.79 (2H, s, *syn* and *anti* CH_2), 6.18, 6.23 (1H, d, *J* 1.9 and 1.9 Hz, *syn* and *anti* H5), 5.98, 6.33 (1H, s, syn and anti H7), 6.53, 6.60 (1H, s, H3), 6.93–7.42 (10H, m, *syn* and *anti* ArH), 11.15, 11.84 (1H, s, *syn* and *anti* OH). ^{13}C NMR spectrum (75 MHz, d_6-DMSO): δ 48.3 (CH_2), 55.4, 55.5, 55.8 (OMe), 86.8, 87.1, (C5), 92.0, 92.1 (C7), 101.4, 105.7 (C3), 126.8, 127.1, 127.2, 127.2, 127.4, 128.2, 128.6, 128.5, 128.8, 129.2, 129.4 (ArCH), 112.3, 112.8, 129.2, 133.2, 134.4, 136.5, 138.4, 138.7, 139.2, 140.7, 149.2, 151.0, 153.6, 153.7 (ArC), 157.9, 158.7 (C=N). Mass spectrum (EI): *m/z* 386 (M, 38), 369 (44), 266 (40), 91 (100).

4.1.15. (1-Benzyl-4,6-dimethoxyindol-2-yl)-phenylmethanone *O*-2,4-dinitrophenyloxime (23). This was prepared from indole oxime **22** (0.50 g, 1.3 mmol), absolute ethanol (50 mL), sodium (40 mg, 1.7 mmol) and fluoro-2,4-dinitrobenzene (0.23 mL, 1.3 mmol) to yield the oxime ether **23** (0.65 g, 91%) as a yellow solid, mp 115 °C. Found: C, 65.3; H, 4.6; N, 9.7. $C_{30}H_{24}N_4O_7$ requires C, 65.2; H, 4.4; N, 10.1%. ν_{max}: 1604, 1535, 1510, 1470, 1337, 1287, 1248, 1204 cm^{-1}. λ_{max}: 231 nm (ε 36,200 $cm^{-1}\,M^{-1}$). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.79, 3.81, 3.87, 3.92 (6H, s, *syn* and *anti* OMe), 5.15, 5.81 (2H, s, *syn* and *anti* CH_2), 6.22, 6.26 (1H, d, *J* 1.9 Hz, *syn* and *anti* H5), 6.31, 6.42 (1H, d, *J* 1.1 Hz, *syn* and *anti* H7), 6.63, 6.84 (1H, d, *J* 0.75 Hz, *syn* and *anti* H3), 6.86–6.93, 7.08–7.14, 7.33–7.40, 7.46–7.55 (10H, m, *syn* and *anti* ArH), 7.98, 8.42 (1H, dd, *J* 9.4, 2.6 Hz, *syn* and *anti* ArH), 8.01 (1H, d, *J* 9.4 Hz, *syn* and *anti* ArH), 8.70, 8.84 (1H, d, *J* 2.6 Hz, *syn* and *anti* ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 48.9, 49.6 (OCH_2), 55.3, 55.5, 55.6 (OMe), 85.0, 85.9 (C5), 92.5, 92.6 (C7), 106.5 (C3), 112.1, 116.8, 117.6, 121.6, 121.9, 125.6, 126.4, 127.2, 127.3, 127.9, 128.4, 128.5, 128.8, 128.9, 128.9, 129.1, 129.9, 131.4 (ArCH), 113.0, 113.1, 126.5, 129.7, 131.7, 133.8, 136.2, 137.3, 138.2, 140.2, 140.9, 142.4, 154.4, 154.5, 156.9, 157.2, 158.2, 158.9, 159.2, 160.5, 172.3 (ArC). Mass spectrum (EI): *m/z* 553 (M+1, 7%), 369 (100).

4.1.16. 7,9-Dimethoxy-12-phenylindolo[2,1-*c*][1,4]benzodiazepine (24). This was prepared from indole oxime ether **23** (0.42 g, 0.76 mmol) and sodium hydride (0.11 g, 80% dispersion in oil, 3.80 mmol) in dioxane at room temperature for 24 h. After extraction and concentration, the residue was chromatographed with dichloromethane as an eluent to yield the product **24** (91 mg, 32%) as a yellow solid, but which could not be obtained analytically pure. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.76, 3.84 (6H, 2s, OMe), 5.75 (2H, s, CH_2), 6.17 (1H, d, *J* 1.9 Hz, H5), 6.31 (1H, d, *J* 1.9 Hz, H7), 6.33 (1H, s, H3), 7.0–7.5 (9H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 49.0 (CH_2), 55.2, 55.5 (OMe), 85.8 (C5), 91.9 (C7), 107.4 (C3), 126.2, 126.7, 126.8, 127.9 (ArCH) (ArC). Mass spectrum (EI): *m/z* 369 (M+1, 100%), 282 (91).

4.1.17. 1,2-Dibenzoyl-4,6-dimethoxyindole (26). A mixture of 2-benzoyl-4,6-dimethoxyindole **17** (0.38 g, 1.3 mmol), sodium hydroxide (0.20 g, 5.0 mmol) and tetrabutyl ammonium hydrogen sulfate (30 mg) in dichloromethane (50 mL) was stirred at room temperature for 15 min. Benzoyl chloride (0.16 mL, 1.3 mmol) was added dropwise and the mixture was stirred for another 30 min. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed with dichloromethane as an eluent to give the indole **26** (0.21 g, 41%) as a pale yellow solid, mp 174–176 °C. Found: C, 74.5; H, 4.9; N, 3.5. $C_{24}H_{19}NO_4$ requires C, 74.8; H, 5.0; N, 3.6%.

ν_{max}: 1687, 1640, 1615, 1597, 1496, 1290, 1214, 1151 cm^{-1}. λ_{max}: 229 nm (ε 23,850 $cm^{-1}\,M^{-1}$), 251 (29,400), 348 (17,850), 361 (19,450). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.84, 3.91 (6H, 2s, OMe), 6.34 (1H, d, J 1.9 Hz, H5), 7.02 (1H, d, J 1.9 Hz, H7), 7.22 (1H, s, H3), 7.33–7.82 (10H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.5, 55.7 (OMe), 88.7, (C5), 95.2 (C7), 116.9 (C3), 128.3, 128.5, 128.8, 129.1, 132.4, 132.8 (ArCH), 112.8, 135.8, 137.4, 141.7, 155.0, 162.3 (ArC), 169.9, 184.8 (C═O). Mass spectrum (EI): m/z 385 (M, 18%), 105 (100), 77 (55).

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