Tetrahedron 69 (2013) 2193–2198

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 5-(7′-indolyl)oxazoles and 2,5-di-(7′-indolyl)oxazoles

Hakan Kandemir, Kasey Wood, Naresh Kumar, David StC. Black *

School of Chemistry, The University of New South Wales, Sydney, NSW 2052, Australia

ARTICLE INFO

Article history:
Received 30 October 2012
Received in revised form 7 December 2012
Accepted 21 December 2012
Available online 11 January 2013

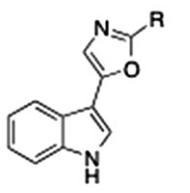
Keywords:
Bis-indoles
Oxazoles
7-Aminoacetylindoles
Indoles

ABSTRACT

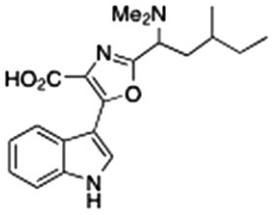
The synthesis of 7-aminoacetylindoles was achieved via the hydrogenation of 7-acylcyanides, which were produced through the oxidation of indole-7-cyanohydrin silylether intermediates. 7-Oxotryptamines were subsequently converted into 5-(7′-indolyl)oxazoles by reaction with acetic anhydride followed by phosphoryl chloride, and to 2,5-di-(7′-indolyl)oxazoles by reaction with 7-trichloroacetylindoles followed by phosphoryl chloride.

1. Introduction

Indole-related natural products bearing the oxazole moiety are an important class of heterocyclic scaffolds as they are naturally occurring and known to display diverse biological activity. To date, however, the structural variations offered in these systems are confined to those with 5,3′-linkages. For example, the naturally occurring 5-(3′-indolyl)oxazoles, such as the dipeptide derivative almazole C,[1] the extracellular alkaloid pimprinine **1**,[2,3] which possesses antiepileptic effects and its analogues WS-30581 A and B, which show inhibitory effects of platelet aggregation.[4] The labradorins, such as labradorin 1 **2** are other 2-substituted-5-(3′-indolyl) oxazoles, which display inhibitory activity against various human cancer cells,[5] while martefragin A **3** has been reported to be a strong inhibitor of lipid peroxidation.[6]



1 R = Me
2 R = CH_2CHMe_2



3

In view of the interesting biological activities exhibited by indole linked oxazoles, we were interested in the development of novel 5-(7′-indolyl)oxazoles and 2,5-di(7′-indolyl)oxazoles.

Many synthetic approaches have been reported for the synthesis of indole linked oxazoles. Some of these protocols involve rhodium catalysed reactions of diazoacetylindoles with nitriles,[7] aza-Wittig reactions of iminophosphoranes derived from 3-azidoacetyl-1-methylindole with isocyanates[8] and the conversion of 3-acetylindole into 5-(3′-indolyl)oxazoles using metal free [hydroxyl(2,4-dinitrobenzenesulfonyloxy)iodo]benzene.[9] Alternatively, the indole ring can be derived from a 5-acylmethylene-substituted-oxazole using the Fischer synthetic sequence.[10] Recently, the synthetic preparation of indolyloxazoles has been facilitated by the use of oxotryptamine via cyclodehydration of acylaminoketones.[5,6,11–13]

3-Aminoacetylindole is most typically synthesised from the corresponding 3-acylcyanide via hydrogenation using Pd/C in acetic acid. In turn, the substrate indolyl-3-carbonyl nitrile can be prepared via treatment of the readily available indole 3-acid chloride with copper (I) cyanide.[14] Another efficient synthesis of the acylcyanide can be achieved via the cyanohydrin silylether intermediate, which is prepared through the heating of indole-3-carbaldehyde with trimethylsilylcyanide (TMSCN) under reflux in acetonitrile. Oxidation of the silyl cyanohydrin intermediate with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane at room temperature then affords the corresponding indole carbonyl nitrile.[15] It has been previously reported that 4,6-dimethoxyindoles can react with oxalyl chloride to yield 7-glyoxyloyl chlorides and some derived acids, esters or amides in 20–74% yields.[16] In contrast, indole-7-carbaldehydes can be prepared in 70–100% yields via

* Corresponding author. Tel.: +61 2 9385 4657; fax: +61 2 9385 6141; e-mail address: d.black@unsw.edu.au (D.StC. Black).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.12.084

Vilsmeier formylation.[17] We therefore followed this latter approach for the synthesis of 7-aminoacetylindoles followed by their use as precursors for the preparation of 5-(7′-indolyl)oxazoles and 2,5-di(7′-indolyl)oxazoles.

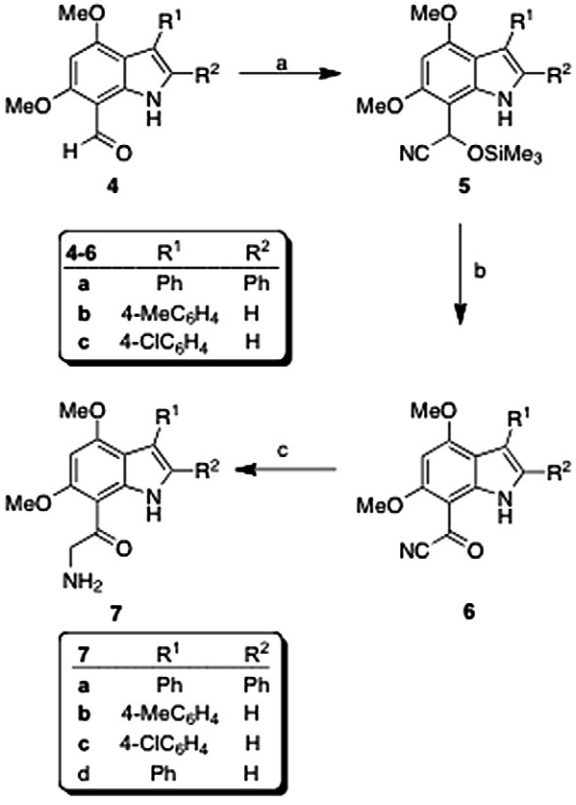
2. Results and discussion

2.1. Synthesis of 7-aminoacetylindoles

The synthesis of 7-acylcyanides **6a**–**c** was successfully accomplished over two consecutive steps as illustrated in Scheme 1. The first step involved the treatment of 7-formylindoles **4a**–**c** with TMSCN in acetonitrile at reflux to afford the 7-cyanohydrin silylether intermediates **5a**–**c** in good yields. The stability of these 7-indolyl silylethers at room temperature was found to be very high in comparison to the 3-indolyl silylethers.

The ^{1}H NMR spectrum of compound **5c**, for example, displayed the trimethylsilyl protons at δ 0.2, the CH proton at 6.19 and the H5 proton at 6.26. This assignment was confirmed by both HSQC and HSBC analysis. The ^{13}C NMR spectrum indicated the presence of the trimethylsilyl groups and the nitrile groups with carbon resonances at δ 0.58 and 119.2, respectively. Also, the nitrile absorption band was seen at 3428 cm^{-1} in the infrared spectrum.

The compounds **5a**–**c** were subsequently oxidised with DDQ in dioxane at room temperature to the corresponding 7-acylcyanides **6a**–**c**. Although a single product was isolated from the reaction mixture, the residue was subjected to column chromatography in order to eliminate baseline impurities. The orange products were obtained in 80–90% yields. The ensuing step was hydrogenation of the 7-acylcyanides to the 7-aminoacetylindoles as shown in Scheme 1. Accordingly, 7-acylcyanides **6a**–**c** were stirred under hydrogen in the presence of 10% Pd/C in a mixture of ethyl acetate and acetic acid (2:3) for 20 h to afford 7-aminoacetylindoles **7a**–**c** in 65–91% yields.



4-6	R^1	R^2
a	Ph	Ph
b	4-MeC$_6$H$_4$	H
c	4-ClC$_6$H$_4$	H

7	R^1	R^2
a	Ph	Ph
b	4-MeC$_6$H$_4$	H
c	4-ClC$_6$H$_4$	H
d	Ph	H

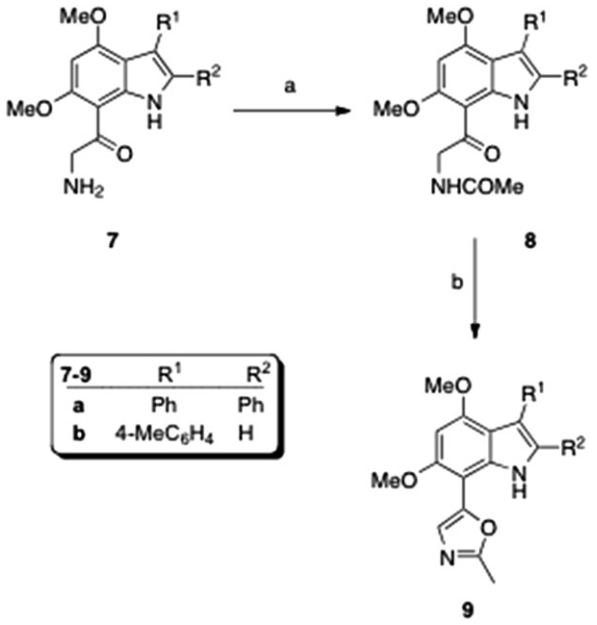
Scheme 1. Reagents and conditions: (a) TMSCN, CH_3CN, reflux, overnight (64–78%); (b) DDQ, dioxane, rt (80–90%); (c) H_2, 10% Pd/C, EtOAc/AcOH, rt (only **7a**,**b** 77–91% as HCl and HOAc salts, respectively).

Interestingly, the ^{1}H NMR spectrum of the anticipated compound **7c** demonstrated resonances for two H5 protons at δ 6.5 and two indole NHs at 11.58 and 11.63. Two carbonyl resonances at 190.0 and 190.1 were observed in the ^{13}C NMR spectrum, indicating a mixture of halogenated and dehalogenated 7-aminoacetylindoles **7c** and **d**, respectively. The formation of this mixture was further confirmed by a high-resolution mass spectrum, which showed two molecular ions at 345.0998 $(M+H)^+$ and 311.1389 $(M+H)^+$ corresponding to oxotryptamines **7c** and **d**, respectively. Attempts to separate the mixture failed because of the high polarity of the compounds, which remained on the baseline during attempted thin layer chromatography.

2.2. Synthesis of 5-(7′-indolyl)oxazoles

It was of interest to use a monomeric model for the preparation of 7-oxazole substituted indoles before extending the chemistry to bis-indole systems. Therefore, the synthetic study began with the acylation of readily available 7-oxotryptamines **7a**, **b** with acetic anhydride at 0–10 °C for 4 h to produce the corresponding ketoamides **8a**, **b** in 72% and 71% yield, respectively.

The next step involved the treatment of indoles **8a**, **b** with excess phosphoryl chloride at reflux in ethyl acetate for 2 h. This process afforded the 7-methyloxazoles **9a**, **b** in 79% and 51% yield, respectively (Scheme 2).



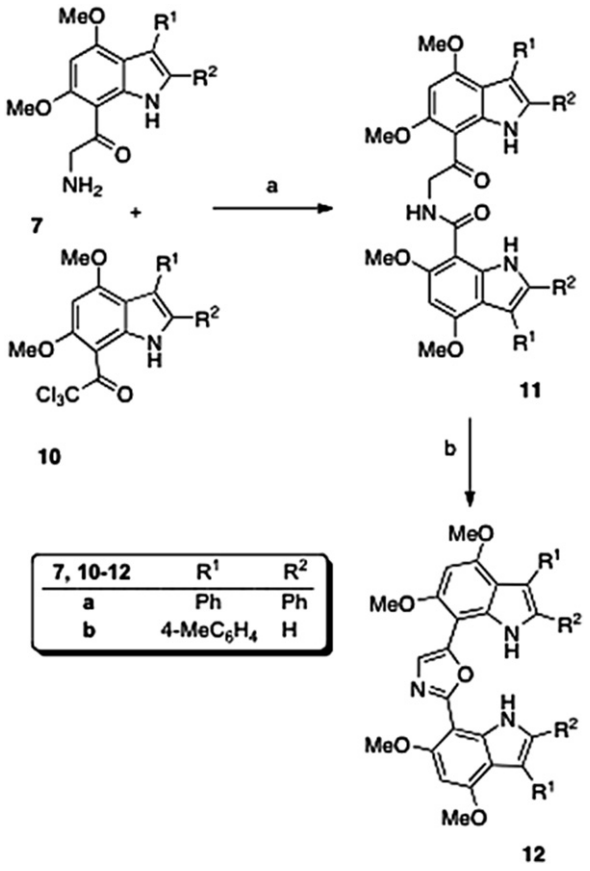
7-9	R^1	R^2
a	Ph	Ph
b	4-MeC$_6$H$_4$	H

Scheme 2. Reagents and conditions: (a) $(CH_3CO)_2$, 0–10 °C, 4 h (71–72%); (b) $POCl_3$, EtOAc, reflux, 2 h (51–79%).

2.3. Synthesis of 2,5-di(7-indolyl)oxazoles

With the successful execution of the monomeric model in hand, preparation of related bis-indole systems was examined. The successful preparation of 7,7′-bis-oxazoles **12a**, **b** was achieved with a convenient two-step process as shown in Scheme 3. The first step involved heating 7-aminoacetylindoles **7a**, **b** with 7-trichloroacetylindoles **10a**, **b** at reflux overnight in the presence of triethylamine in acetonitrile to afford the unsymmetrical 7,7′-amide linked bis-indoles **11a**, **b** in 61% and 55% yield, respectively.

The new amide functionality was clearly evident in the ^{1}H NMR and ^{13}C NMR spectra of compound **11a**, with the appearance of an amide NH proton as a triplet at δ 9.33 (J 8.5 Hz) and the carbonyl



Scheme 3. Reagents and conditions: (a) Et_3N, CH_3CN, reflux (55–61%); (b) $POCl_3$, ethyl acetate, reflux, 2 h (61–63%).

groups at 167.5 and 194.1. The ^1H NMR spectrum also showed the indole NH protons as downfield singlets at δ 11.10 and 11.29, indicating strong hydrogen bonding between the carbonyl groups and the indole NHs. The methylene protons appeared as a broad singlet at δ 4.93. In addition, the infrared spectrum also showed two carbonyl resonances at 1588 and 1615 cm^{-1}.

In the next step, cyclodehydration was carried out by the treatment of bis-indoles **11a**, **b** with excess phosphoryl chloride at reflux in ethyl acetate for 2 h. The process afforded the desired diindolyloxazoles **12a**, **b** in 63% and 61% yield, respectively (Scheme 3). Purification by column chromatography removed baseline impurities.

The high-resolution mass spectrometry of indole **12b** showed a molecular ion at 640.2414, which was consistent with the structure **12b** $(M+Na)^+$. The ^1H NMR spectrum of the compound **12b** indicated the disappearance of the amide nitrogen protons of the starting material **11b** at δ 9.37 and the appearance of a CH proton at 7.64. The indole nitrogens remained as downfield singlets at δ 10.56 and 11.31. The compound **12b** was not soluble enough to obtain a ^{13}C NMR spectrum.

3. Conclusions

In conclusion, the synthesis of 7-aminoacetylindoles was successfully achieved via hydrogenation of the corresponding indole-7-acylcyanides. Amide linked bis-indoles were obtained upon reaction of 7-aminoacetylindoles with indole-7-trichloroacetyl chlorides and underwent cyclisation with phosphoryl chloride to form oxazole linked bis-indoles. The preparation of monomeric 7-oxadiazoles from 7-ketoamides was also achieved in the same manner.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Genesis Series FTIR spectrophotometer as KBr disks. Ultraviolet spectra were measured using a Varian Cary 100 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker DPX 300. High-resolution mass spectrometry was performed by the Mass Spectrometry unit at the Bioanalytical Mass Spectrometry unit in the School of Chemistry, UNSW. Microanalysis was performed on a Carlo Erba Elemental Analyzer EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Anhydrous solvents were obtained using a PureSolv MD Solvent Purification System. Ajax Finechem Silica 200–325 mesh was used for column chromatography and Merck silica gel 60H was used for flash chromatography.

4.2. 2-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-2-(trimethylsilyloxy)acetonitrile (5a)

Indole-7-carbaldehyde **4a** (1.70 g, 4.76 mmol) was heated under reflux with TMSCN (3.00 mL, 22.5 mmol) in acetonitrile (30 mL) overnight. The solution was cooled and the solvent removed under reduced pressure. The residue was purified by flash chromatography using dichloromethane as eluent to afford the title compound **5a** (1.70 g, 78%) as a white solid, mp 171–173 °C; ν_{max} (KBr): 3474, 3054, 3003, 2957, 2842, 1599, 1518, 1448, 1354, 1254, 1076 cm^{-1}; λ_{max} (THF): 245 nm (ε 37,900 cm^{-1} M^{-1}), 324 (21,250); ^1H NMR (300 MHz, $CDCl_3$): δ 0.26 (9H, s, Me), 3.73 (3H, s, OMe), 3.95 (3H, s, OMe), 6.22 (1H, s, CH), 6.24 (1H, s, H5), 7.25–7.42 (10H, m, aryl H), 8.97 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.51 (Me), 55.3, 56.7 (OMe), 57.2 (CH), 88.0 (C5), 98.9 (C), 114.1 (C), 114.5 (C), 119.3 (CN), 126.0 (CH), 127.1 (CH), 127.3 (CH), 127.8 (CH), 128.5 (CH), 131.4 (CH), 132.6 (C), 132.9 (C), 135.4 (C), 135.6 (C), 152.7 (C), 156.1 (C); HRMS (ESI^+): $[M+H]^+$, found 457.1941. $C_{27}H_{29}N_2O_3Si$ requires 457.1947.

4.3. 2-(4,6-Dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-yl)-2-((trimethylsilyl)oxy)-acetonitrile (5b)

Indole-7-carbaldehyde **4b** (3.69 g, 12.5 mmol) was heated under reflux with TMSCN (7 mL, 52.5 mmol) in acetonitrile (60 mL) overnight. The solution was cooled and the solvent removed under reduced pressure. The residue was purified by flash chromatography using dichloromethane as eluent to afford the title compound **5b** (3.16 g, 64%) as a white solid, mp 119–121 °C; (found: C, 67.08; H, 6.92; N, 7.14; $C_{22}H_{26}N_2O_3Si$ requires C, 66.97; H, 6.64; N, 7.10%); ν_{max} (KBr): 3348, 1620, 1589, 1466, 1343, 1254, 1215, 1072, 849 cm^{-1}; λ_{max} (MeOH): 295 nm (ε 13,550 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 0.01 (9H, s, Me), 2.19 (3H, s, Me), 3.62 (3H, s, OMe), 3.72 (3H, s, OMe), 6.0 (1H, s, CH), 6.05 (1H, s, H5), 6.87 (1H, d, *J* 2.4 Hz, H2), 7.00, 7.29 (4H, 2d, *J* 8.3 Hz, aryl H), 8.68 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.47 (Me), 21.2 (Me), 55.3, 56.8 (OMe), 57.0 (CH), 87.9 (C5), 99.4 (C), 111.6 (C), 118.6 (C), 119.4 (CN), 121.5 (C2), 128.4 (CH), 129.5 (CH), 132.8 (C), 135.4 (C), 136.5 (C), 152.8 (C), 156.0 (C); HRMS (ESI^+): $[M+H]^+$, found 395.1785. $C_{22}H_{27}N_2O_3Si$ requires 395.1791.

4.4. 2-(3-(4-Chlorophenyl)-4,6-dimethoxy-1*H*-indol-7-yl)-2-(trimethylsilyloxy)acetonitrile (5c)

Indole-7-carbaldehyde **4c** (1.70 g, 5.39 mmol) was heated under reflux with TMSCN (3 mL, 22.5 mmol) in acetonitrile (40 mL) overnight. The solution was cooled and the solvent was removed under reduced pressure. The residue was purified by flash

chromatography using dichloromethane as eluent to afford the title compound **5c** (1.60 g, 71%) as a white solid, mp 155–157 °C; ν_{max} (KBr): 3428, 2962, 1594, 1518, 1462, 1343, 1255, 1212, 1052 cm^{-1}; λ_{max} (THF): 234 nm (ε 34,550 cm^{-1} M^{-1}), 285 (17,500); ^1H NMR (300 MHz, $CDCl_3$): δ 0.20 (9H, s, Me), 3.83 (3H, s, OMe), 3.93 (3H, s, OMe), 6.19 (1H, s, CH), 6.26 (1H, s, H5), 7.08 (1H, d, *J* 2.4 Hz, H2), 7.33, 7.51 (4H, 2d, *J* 8.6 Hz, aryl H), 8.93 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.58 (Me), 55.2, 56.7 (OMe), 56.9 (CH), 87.8 (C5), 99.3 (C), 111.2 (C), 117.4 (C), 119.2 (CN), 121.7 (C2), 127.6 (CH), 130.7 (CH), 131.6 (C), 134.2 (C), 136.4 (C), 152.8 (C), 155.7 (C); HRMS (ESI^+): $[M+H]^+$, found 415.1237. $C_{21}H_{24}ClN_2O_3Si$ requires 415.1245.

4.5. 4,6-Dimethoxy-2,3-diphenyl-1*H*-indole-7-carbonyl cyanide (6a)

A solution of DDQ (0.760 g, 3.35 mmol) in dioxane (15 mL) was added dropwise to the indole **5a** (1.02 g, 2.23 mmol) dissolved in dioxane (30 mL) at room temperature. The mixture was stirred for 3 h and the solid formed was thereafter filtered off. The filtrate was concentrated, the resulting residue was treated with water, the solid obtained was filtered and washed with water until a colourless filtrate was observed. The red solid was dissolved in dichloromethane and the solution passed through a plug of silica to yield the title compound **6a** (0.77 g, 90%) as an orange solid, mp 208–210 °C; ν_{max} (KBr): 3403, 1675, 1574, 1501, 1467, 1352, 987 cm^{-1}; λ_{max} (THF): 231 nm (ε 33,250 cm^{-1} M^{-1}), 293 (23,900), 363 (16,250); ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (3H, s, OMe), 4.09 (3H, s, OMe), 6.13 (1H, s, H5), 7.24–7.34 (10H, m, aryl H), 10.53 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 56.4 (OMe), 87.3 (C5), 103.3 (C), 113.0 (C), 115.4 (C), 115.6 (CN), 126.6 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.5 (CH), 131.1 (CH), 131.4 (C), 133.6 (C), 134.5 (C), 137.2 (C), 161.3 (C), 163.2 (C), 164.2 (C=O); HRMS (ESI^+): $[M]^+$, found 382.1306. $C_{24}H_{18}N_2O_3$ requires 382.1317.

4.6. 2-(4,6-Dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-carbonyl cyanide) (6b)

A solution of DDQ (2.40 g, 10.6 mmol) in dioxane (50 mL) was added dropwise to the indole **5b** (2.61 g, 6.62 mmol) dissolved in dioxane (30 mL) at room temperature. The mixture was stirred for 3 h and the solid formed was thereafter filtered off. The filtrate was concentrated, the resulting residue was treated with water, the solid obtained was filtered and washed with water until a colourless filtrate was observed. The red solid was dissolved in dichloromethane and the solution passed through a plug of silica to yield the title compound **6b** (1.69 g, 80%) as an orange solid, mp 220–222 °C; (found: C, 71.18; H, 4.99; N, 8.75; $C_{19}H_{16}N_2O_3$ requires C, 71.24; H, 5.03; N, 8.74%); ν_{max} (KBr): 3381, 1583, 1502, 1466, 1350, 1313, 1284, 1213, 1091, 976 cm^{-1}; λ_{max} (MeOH): 305 nm (ε 14,250 cm^{-1} M^{-1}), 364 (10,450); ^1H NMR (300 MHz, DMSO-d_6): δ 2.32 (3H, s, Me), 3.96 (3H, s, OMe), 4.06 (3H, s, OMe), 6.47 (1H, s, H5), 7.12 (1H, s, H2), 7.15, 7.37 (4H, 2d, *J* 8.1 Hz, aryl H), 11.57 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.2 (Me), 56.7, 57.4 (OMe), 88.9 (C5), 103.4 (C), 110.5 (C), 116.3 (C), 119.0 (CN), 123.8 (C2), 128.8 (CH), 129.5 (CH), 132.3 (C), 135.5 (C), 136.9 (C), 160.3 (C), 163.6 (C), 164.4 (C=O); HRMS (ESI^+): $[M+H]^+$, found 321.1239. $C_{19}H_{16}N_2O_3$ requires 321.1239.

4.7. 3-(4-Chlorophenyl)-4,6-dimethoxy-1*H*-indole-7-carbonyl cyanide (6c)

A solution of DDQ (1.64 g, 7.22 mmol) in dioxane (35 mL) was added dropwise to the indole **5c** (1.50 g, 3.62 mmol) dissolved in dioxane (30 mL) at room temperature. The mixture was stirred for 3 h and the solid formed was thereafter filtered off. The filtrate was concentrated, the resulting residue was treated with water, the solid obtained was filtered and washed with water until a colourless filtrate was observed. The red solid was dissolved in dichloromethane and the solution passed through a plug of silica to yield the title compound **6c** (1.05 g, 85%) as an orange solid, mp 230–232 °C; ν_{max} (KBr): 3411, 1590, 1471, 1352, 1248, 1219, 1094, 796 cm^{-1}; λ_{max} (THF): 218 nm (ε 27,700 cm^{-1} M^{-1}), 266 (21,850), 364 (12,100); ^1H NMR (300 MHz, DMSO-d_6): δ 3.96 (3H, s, OMe), 4.04 (3H, s, OMe), 6.46 (1H, s, H5), 7.18 (1H, d, *J* 2.4 Hz, H2), 7.36, 7.48 (4H, 2d, *J* 8.8 Hz, aryl H), 11.63 (1H, d, *J* 2.4 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.7, 57.4 (OMe), 88.9 (C5), 103.3 (C), 110.2 (C), 116.1 (C), 117.6 (CN), 124.3 (C2), 128.0 (CH), 131.1 (CH), 131.1, 134.0 (C), 136.8 (C), 160.3 (C), 163.5 (C), 164.1 (C=O); HRMS (ESI^+): $[M+Na]^+$, found 363.0502. $C_{18}H_{13}ClN_2NaO_3$ requires 363.0512.

4.8. 2-Amino-1-(4,6-dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-ethanone hydrochloride (7a)

A mixture of 7-carbonyl cyanide **6a** (1.08 g, 2.82 mmol) and 10% Pd/C (0.4 g) in a mixture of ethyl acetate/acetic acid solution (20:40, 60 mL) was stirred under a balloon of hydrogen gas. After 20 h, the reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in ethanol containing concentrated hydrochloric acid (5% by volume). Concentration under reduced pressure yielded the title compound **7a** (1.09 g, 91%) as a yellow solid, mp 262 °C (dec); ν_{max} (KBr): 3423, 2848, 2578, 1624, 1590, 1544, 1462, 1393, 1360, 1252, 1168, 1146, 989 cm^{-1}; λ_{max} (MeOH): 328 nm (ε 22,150 cm^{-1} M^{-1}); ^1H NMR (300 MHz, DMSO-d_6): δ 3.80 (3H, s, OMe), 4.06 (3H, s, OMe), 4.30 (2H, d, *J* 4.0 Hz, CH_2), 6.48 (1H, s, H5), 7.23–7.32 (10H, m, aryl H), 8.45 (3H, br s, NH_3), 11.08 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 48.6 (CH_2), 56.3, 57.4 (OMe), 89.0 (C5), 101.7 (C), 112.8 (C), 114.8 (C), 126.9 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 129.1 (CH), 131.5 (CH), 132.1 (C), 132.9 (C), 135.5 (C), 137.4 (C), 161.3 (C), 162.2 (C), 190.8 (C=O); HRMS (ESI^+): $[M+H]^+$, found 387.1702. $C_{24}H_{23}N_2O_3$ requires 387.1709.

4.9. 2-Amino-1-(4,6-dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-yl)-ethanone hydroacetate (7b)

A mixture of 7-carbonyl cyanide **6b** (1.00 g, 3.12 mmol) and 10% Pd/C (0.40 g) in a mixture of ethyl acetate/acetic acid (30:60, 90 mL) was stirred under a balloon of hydrogen. After 20 h, the reaction mixture was filtered over Celite and the filtrate concentrated under reduced pressure to yield the title compound **7b** (0.886 g, 77%) as a white solid, mp 181–183 °C; ν_{max} (KBr): 3289, 2941, 1563, 1465, 1397, 1344, 1248, 1217, 1184, 1104, 791 cm^{-1}; λ_{max} (MeOH): 330 nm (ε 28,050 cm^{-1} M^{-1}); ^1H NMR (300 MHz, DMSO-d_6): δ 1.84 (3H, s, Me), 2.32 (3H, s, Me), 3.90 (3H, s, OMe), 4.02 (3H, s, OMe), 4.93 (2H, br s, CH_2), 6.48 (1H, s, H5), 7.23–7.32 (5H, m, aryl H+H2), 8.45 (3H, br s, NH_3), 11.08 (1H, br s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.2, 22.5 (Me), 52.2 (CH_2), 56.0, 57.1 (OMe), 88.5 (C5), 102.9 (C), 110.5 (C), 117.5 (C), 123.3 (C2), 128.7 (CH), 129.4 (CH), 133.1 (C), 134.9 (C), 137.9 (C), 159.9 (C), 161.2 (C), 173.1 (C=O), 197.2 (C=O); HRMS (ESI^+): $[M+H]^+$, found 325.1546. $C_{19}H_{21}N_2O_3$ requires 325.1552.

4.10. *N*-(2-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-2-oxoethyl)-acetamide (8a)

7-Aminoacetylindole **7a** (0.340 g, 0.880 mmol) was dissolved in acetic anhydride (15 mL) and the mixture was stirred for 4 h in an ice-water bath. Ice-water was added and the resulting solid was filtered, washed with water and dried. The crude product was recrystallised from dichloromethane/*n*-hexane to give the title compound **8a** (0.25 g, 72%) as a yellow solid, mp 220–222 °C; (found: C, 72.76; H, 5.60; N, 6.56; $C_{26}H_{24}N_2O_4$ requires C, 72.88; H, 5.65; N, 6.54%); ν_{max} (KBr): 3405, 1614, 1587, 1390, 1223, 1165,

990 cm^{-1}; λ_{max} (THF): 324 nm (ε 33,750 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.13 (3H, s, Me), 3.80 (3H, s, OMe), 4.04 (3H, s, OMe), 4.74 (2H, d, *J* 4.2 Hz, CH_2), 6.16 (1H, s, H5), 6.89 (1H, br s, NH), 7.23–7.40 (10H, m, aryl H), 11.06 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3 (Me), 50.9 (CH_2), 55.4, 56.2 (OMe), 87.0 (C5), 102.2 (C), 113.1 (C), 114.5 (C), 126.3 (CH), 127.3 (CH), 127.5 (CH), 127.8 (CH), 128.5 (CH), 131.4 (CH), 132.3 (C), 132.9 (C), 135.5 (C), 138.1 (C), 160.8 (C), 161.6 (C), 170.1 (C=O), 193.5 (C=O); HRMS (ESI^+): $[M+Na]^+$, found 451.1623. $C_{26}H_{24}N_2NaO_4$ requires 451.1634.

4.11. *N*-(2-(4,6-Dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-yl)-2-oxoethyl)-acetamide (8b)

7-Aminoacetylindole **7b** (0.330 g, 1.02 mmol) was dissolved in acetic anhydride (15 mL) and the mixture was stirred for 4 h in an ice-water bath. Ice-water was added and the resulting solid was filtered, washed with water and dried. The crude product was recrystallised from dichloromethane/*n*-hexane to give the title compound **8b** (0.23 g, 71%) as a yellow solid, mp 208–210 °C; (found: C, 68.78; H, 6.27; N, 7.53; $C_{21}H_{22}N_2O_4$ requires C, 68.84; H, 6.05; N, 7.65%); (ν_{max} KBr): 3408, 1615, 1583, 1345, 1222, 1085 cm^{-1}; λ_{max} (THF): 328 nm (ε 13,300 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.13 (3H, s, Me), 2.41 (3H, s, Me), 3.93 (3H, s, OMe), 4.06 (3H, s, OMe), 4.72 (2H, d, *J* 3.7 Hz, CH_2), 6.22 (1H, s, H5), 6.88 (1H, br s, NH), 7.10 (1H, d, *J* 2.4 Hz, H2), 7.21, 7.48 (4H, 2d, *J* 8.1, aryl H), 10.93 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 23.3 (Me), 50.9 (CH_2), 55.4, 56.2 (OMe), 86.8 (C5), 102.4 (C), 110.5 (C), 118.7 (C), 121.4 (C2), 128.5 (CH), 129.4 (CH), 132.5 (C), 135.6 (C), 139.0 (C), 160.7 (C), 161.7 (C), 170.1 (C=O), 193.4 (C=O); HRMS (ESI^+): $[M+H]^+$, found 367.1653. $C_{21}H_{23}N_2O_4$ requires 367.1658.

4.12. 5-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-2-methyloxazole (9a)

To a solution of the indole **8a** (0.120 g, 0.280 mmol) in ethyl acetate (20 mL), phosphoryl chloride (5 mL) was added and the solution was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water (20 mL) and made strongly alkaline by the addition of 5 N NaOH (20 mL). The resulting precipitate was collected by filtration, washed with water, dried and purified by flash chromatography using dichloromethane as eluent to afford the title compound **9a** (0.092 g, 79%) as a brown solid, mp 229–231 °C; (found: C, 74.75; H, 5.31; N, 6.61; $C_{26}H_{22}N_2O_3$ 0.1 CH_2Cl_2 requires C, 74.82; H, 5.34; N, 6.69%); ν_{max} (KBr): 3364, 2931, 2838, 1603, 1451, 1433, 1347, 1298, 1266, 1209, 1071, 990, 699 cm^{-1}; λ_{max} (THF): 334 nm (ε 32,050 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (3H, s, Me), 3.77 (3H, s, OMe), 4.03 (3H, s, OMe), 6.37 (1H, s, H5), 7.28–7.45 (11H, m, CH, aryl H), 9.33 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (Me), 55.4, 56.5 (OMe), 88.9 (C5), 94.3 (C), 113.7 (C), 114.7 (C), 124.0 (CH), 126.1 (CH), 127.2 (CH), 127.4 (CH), 127.9 (CH), 128.6 (CH), 131.5 (CH), 132.6 (C), 132.9 (C), 133.6 (C), 135.7 (C), 148.0 (C), 153.7 (C), 155.0 (C), 158.0 (C); HRMS (ESI^+): $[M+H]^+$, found 411.1706. $C_{26}H_{23}N_2O_3$ requires 411.1709.

4.13. 5-(4,6-Dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-yl)-2-methyloxazole (9b)

To a solution of the indole **8b** (0.105 g, 0.287 mmol) in ethyl acetate (30 mL), phosphoryl chloride (5 mL) was added and the solution was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water (20 mL) and made strongly alkaline by the addition of 5 N NaOH (20 mL). The resulting precipitate was collected by filtration, washed with water, dried and purified by flash chromatography using dichloromethane as eluent to afford the title compound **9b** (0.051 g, 51%) as a white solid, mp 202–204 °C; ν_{max} (KBr): 3253, 2956, 2923, 1596, 1541, 1459, 1339, 1299, 1208, 1121, 1098, 814 cm^{-1}; λ_{max} (THF): 322 nm (ε 24,000 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.31 (3H, s, Me), 2.51 (3H, s, Me), 3.76 (3H, s, OMe), 3.91 (3H, s, OMe), 6.28 (1H, s, H5), 7.01 (1H, d, *J* 2.4 Hz, H2), 7.10–7.42 (4H, 2d, *J* 8.1 Hz, aryl H), 7.33 (1H, s, CH), 9.23 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.2 (Me), 55.3, 56.5 (OMe), 88.6 (C5), 94.6 (C), 111.2 (C), 118.6 (C), 121.1 (CH), 124.0 (C2), 128.4 (CH), 129.5 (CH), 132.9 (C), 134.5 (C), 135.4 (C), 148.0 (C), 153.6 (C), 154.8 (C), 158.0 (C); HRMS (ESI^+): $[M]^+$, found 348.1472. $C_{21}H_{20}N_2O_3$ requires 348.1474.

4.14. (*N*-(2-(4,6-Dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-2-oxoethyl)-4,6-dimethoxy-2,3-diphenyl-1*H*-indole-7-carboxamide) (11a)

To a suspension of 7-aminoacetylindole **7a** (0.215 g, 0.557 mmol) and 7-trichloroacetylindole **10a** (0.240 g, 0.510 mmol) in acetonitrile (40 mL), triethylamine (10 drops, ~0.5 mL) was added and the mixture was heated under reflux overnight. The solvent was removed under reduced pressure and the resulting solid was treated with water, filtered, dried and washed with methanol to give the title compound **11a** (0.23 g, 61%) as a white solid, mp 291–293 °C; ν_{max} (KBr): 1615, 1588, 1493, 1461, 1388, 1340, 1221, 1165, 994, 697 cm^{-1}; λ_{max} (THF): 325 nm (ε 52,800 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (3H, s, OMe), 3.71 (3H, s, OMe), 3.98 (3H, s, OMe), 4.09 (3H, s, OMe), 4.93 (2H, d, *J* 4.4 Hz, CH_2), 6.09 (1H, s, H5), 6.16 (1H, s, H5), 7.09–7.35 (20H, m, aryl H), 9.33 (1H, t, *J* 8.5 Hz, NH), 11.10 (1H, br s, NH), 11.29 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.4 (CH_2), 55.3, 55.3, 56.3, 57.2 (OMe), 87.0 (C5), 87.8 (C5), 97.7 (C), 102.5 (C), 113.0 (C), 113.6 (C), 113.7 (C), 114.4 (C), 125.9 (CH), 126.2 (CH), 126.9 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 131.4 (CH), 131.6 (CH), 132.6 (C), 132.7 (C), 133.0 (C), 133.1 (C), 135.6 (C), 136.1 (C), 138.2 (C), 138.7 (C), 157.1 (C), 157.5 (C), 160.5 (C), 161.4 (C), 167.5 (C=O), 194.1 (C=O); HRMS (ESI^+): $[M+H]^+$, found 742.2916. $C_{47}H_{40}N_3O_6$ requires 742.2917.

4.15. *N*-(2-(4,6-Dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-yl)-2-oxoethyl)-4,6-dimethoxy-3-(*p*-tolyl)-1*H*-indole-7-carboxamide (11b)

To a suspension of 7-aminoacetylindole **7b** (0.241 g, 0.744 mmol) and 7-trichloroacetylindole **10b** (0.270 g, 0.650 mmol) in acetonitrile (40 mL), triethylamine (10 drops, ~0.5 mL) was added and the mixture was heated under reflux overnight. The solvent was removed under reduced pressure and the resulting solid was treated with water, filtered, dried and washed with methanol to give the title compound **11b** (0.22 g, 55%) as a brown solid, mp 284–286 °C; ν_{max} (KBr): 1618, 1585, 1492, 1462, 1332, 1212, 1150, 1105, 794 cm^{-1}; λ_{max} (THF): 323 nm (ε 45,950 cm^{-1} M^{-1}); ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (3H, s, Me), 2.33 (3H, s, Me), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 4.05 (3H, s, OMe), 4.13 (3H, s, OMe), 4.92 (2H, d, *J* 4.3 Hz, CH_2), 6.19, 6.26 (2H, 2s, H5), 7.04, 7.05 (2H, 2d, *J* 2.5 Hz, H2), 7.10, 7.13 (4H, 2d, *J* 7.8 Hz, aryl H), 7.41, 7.43 (4H, 2d, *J* 8.0 Hz, aryl H), 9.37 (1H, t, *J* 4.3 Hz, NH), 11.0 (1H, br s, NH), 11.12 (1H, br s, NH); HRMS (ESI^+): $[M+Na]^+$, found 640.2414. $C_{37}H_{35}N_3NaO_6$ requires 640.2424. The sample was not soluble enough for ^{13}C NMR measurement.

4.16. 2,5-Bis-(4,6-dimethoxy-2,3-diphenyl-1*H*-indol-7-yl)-oxazole (12a)

To a solution of the bis-indole **11a** (0.130 g, 0.175 mmol) in ethyl acetate (30 mL), phosphoryl chloride (10 mL) was added and the solution was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water (30 mL) and made strongly alkaline by the addition of 5 N

NaOH (30 mL). The resulting precipitate was collected by filtration, washed with water, dried and recrystallised from methanol to afford the title compound **12a** (0.081 g, 63%) as a yellow solid, mp 278–280 °C; ν_{max} (KBr): 3384, 1599, 1449, 1427, 1299, 1165, 1143, 991, 697 cm^{-1}; λ_{max} (THF): 326 nm (ε 39,300 cm^{-1} M^{-1}), 358 (38,600), 377 (48,450), 398 (38,650); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44 (3H, s, OMe), 3.77 (3H, s, OMe), 3.78 (3H, s, OMe), 4.08 (3H, s, OMe), 6.28 (1H, s, H5), 6.41 (1H, s, H5), 7.27–7.45 (20H, m, aryl H), 7.74 (1H, s, CH), 10.35 (1H, br s, NH), 11.32 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.5, 56.6, 57.8 (OMe), 88.9 (C5), 89.3 (C5), 93.3 (C), 95.0 (C), 113.4 (C), 113.7 (C), 114.5 (C), 114.6 (C), 123.5 (CH), 125.8 (CH), 126.0 (CH), 127.1 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.0 (CH), 131.5 (CH), 131.6 (CH), 132.9 (C), 133.2 (C), 133.5 (C), 133.8 (C), 135.6 (C), 135.8 (C), 135.9 (C), 136.0 (C), 146.0 (C), 153.5 (C), 155.0 (C), 155.8 (C), 156.7 (C), 157.0 (C); HRMS (ESI$^+$): $[M+H]^+$, found 724.2811. $C_{47}H_{38}N_3O_5$ requires 724.2804.

4.17. 2,5-Bis-(4,6-dimethoxy-3-(*p*-tolyl)-1*H*-indol-7-yl)-oxazole (12b)

To a solution of the bis-indole **11b** (0.112 g, 0.182 mmol) in ethyl acetate (25 mL), phosphoryl chloride (10 mL) was added and the solution was heated under reflux for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water (30 mL) and made strongly alkaline by the addition of 5 N NaOH (30 mL). The resulting precipitate was collected by filtration, washed with water, dried and recrystallised from methanol to afford the title compound **12b** (0.067 g, 61%) as a white solid; mp 294 °C (dec); ν_{max} (KBr): 3406, 3377, 2934, 2838, 1596, 1463, 1340, 1305, 1208, 1153, 791 cm^{-1}; λ_{max} (THF): 375 nm (ε 49,050 cm^{-1} M^{-1}), 396 (39,900); ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.35 (3H, s, Me), 2.36 (3H, s, Me), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 4.09 (3H, s, OMe), 4.25 (3H, s, OMe), 6.63 (1H, s, H5), 6.69 (1H, s, H5), 7.18, 7.20 (4H, 2d, *J* 7.1 Hz, aryl H), 7.31 (1H, br s, H2), 7.46, 7.50 (4H, 2d, *J* 7.8 Hz, aryl H), 7.57 (1H, br s, H2), 7.64 (1H, s, CH), 10.56 (1H, br s, NH), 11.31 (1H, br s, NH). HRMS (ESI$^+$): $[M+H]^+$, found 600.2490. $C_{37}H_{34}N_3O_5$ requires 600.2498. The sample was not soluble enough for ^{13}C NMR measurement.

Acknowledgements

We thank the University of New South Wales and the Turkish Government for their financial support.

References and notes

1. Guella, G.; Mancini, I.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1999–2006.
2. Naik, S. R.; Harindran, J.; Varde, A. B. *J. Biotechnol.* **2001**, *88*, 1–10.
3. Koyama, Y.; Yokose, K.; Dolby, L. J. *Agric. Biol. Chem.* **1981**, *45*, 1285–1287.
4. Kelly, T. R.; Fu, Y.; Xie, R. L. *Tetrahedron Lett.* **1999**, *40*, 1857–1860.
5. Pettit, G. R.; Knight, J. C.; Delbert, L.; Davenport, R.; Pettit, R. K.; Tucker, B. E.; Schmidt, J. M. *J. Nat. Prod.* **2002**, *65*, 1793–1797.
6. Nishida, A.; Fuwa, M.; Fujikawa, Y.; Nakahata, E.; Furuno, A.; Nakagawa, M. *Tetrahedron Lett.* **1998**, *39*, 5983–5986.
7. Doyle, K. J.; Moody, C. J. *Synthesis* **1994**, *1994*, 1021–1022.
8. Molina, P.; Fresneda, P. M.; Almendros, P. *Synthesis* **1993**, *1993*, 54–56.
9. Kumar, D.; Sundaree, S.; Patel, G.; Kumar, A. *J. Heterocycl. Chem.* **2010**, *47*, 1425–1428.
10. Grotkopp, O.; Ahmad, A.; Frank, W.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 8130–8140.
11. Johns, B. A. PCT Int Appl. WO 101512, 2004.
12. Kumar, D.; Sundaree, S.; Patel, G.; Rao, V. S. *Tetrahedron Lett.* **2008**, *49*, 867–869.
13. Miyake, F.; Hashimoto, M.; Tonsiengsom, S.; Yakushijin, K.; Horne, D. A. *Tetrahedron* **2010**, *66*, 4888–4893.
14. Hogan, I. T.; Sainsbury, M. *Tetrahedron* **1984**, *40*, 681–682.
15. Janosik, T.; Johnson, A. L.; Bergman, J. *Tetrahedron* **2002**, *58*, 2813–2819.
16. Black, D. StC.; Kumar, N.; McConnell, D. B. *Tetrahedron* **1996**, *52*, 8925–8936.
17. Black, D. StC.; Bowyer, M. C.; Kumar, N.; Mitchell, P. S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 819–821.