Tetrahedron 67 (2011) 3374–3379

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of the new ring system pyrrolizino[2,3-*b*]indol-4(5*H*)-one

Patrizia Diana *, Antonina Stagno, Paola Barraja, Alessandra Montalbano, Anna Carbone, Barbara Parrino, Girolamo Cirrincione

Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari, Sezione Chimica Farmaceutica e Biologica, Università degli Studi di Palermo, Via Archirafi 32, 90123 Palermo, Italy

ARTICLE INFO

Article history:
Received 22 December 2010
Received in revised form 3 March 2011
Accepted 21 March 2011
Available online 26 March 2011

Keywords:
Pyrrolizino[2,3-*b*]indol-4(5*H*)-one
Tripentone
Antitumor activity
Antitubulin agents

ABSTRACT

Derivatives of the new ring system pyrrolizino[2,3-*b*]indol-4(5*H*)-one were prepared in four steps starting from substituted benzonitriles bearing a functionalized amino group in the adjacent position. The unsubstituted- and the dimethoxy-pyrrolizinoindolones **5a** and **5b** exhibited modest activity against the HL-60(TB) human leukemia cell line, whereas the *N*-methylated dimethoxy-pyrrolizinoindolone **6b** showed to be selective against MOLT-4 leukemia, A549/ATCC, HOP-92, and NCI-H460 non-small cell lung cancer, and CAKI-1 renal cancer cell lines.

1. Introduction

Cancer is a growing public problem estimated to have around seven million new incidences per year worldwide. Research toward the discovery of agents useful in cancer chemotherapy has identified tubulin as a possible molecular target. Molecules that interact with tubulin, the protein subunit of microtubules, cause mitotic arrest, interfering with the dynamic equilibrium of these organelles either by inhibiting tubulin polymerization or blocking microtubule disassembly. Many natural and synthetic substances are known to interfere with the dynamic assembly of tubulin and prevent the formation of microtubules, which are essential for cellular integrity and cell division. Microtubules are a well-validated target for anticancer therapy.

Currently, the most used among the antitubulin agents are natural products, such as paclitaxel,[1] vinca alkaloids,[2] colchicine,[3] and combretastatin A-4.[4]

A series of substituted heterocyclic ketones based on the 'tripentone' skeleton of thieno[2,3-*b*]pyrrolizin-8-ones of type 1 showed a remarkable cytostatic activity over all the tested lines with the highest effect against leukemia, central nervous system, ovarian, and breast cancers.[5]

In order to specify structural requirements, novel tripentone derivatives based on the bio-isosteric replacement of the sulfur atom were synthesized. In fact the thiophene moiety was replaced by a pyrrole (2), pyrazole (3), or furan (4) ring (Fig. 1). Most of these *new* derivatives exhibited interesting cytotoxic properties associated to an anti-tubulin effect and a cyclin-dependent kinase inhibition.[6]

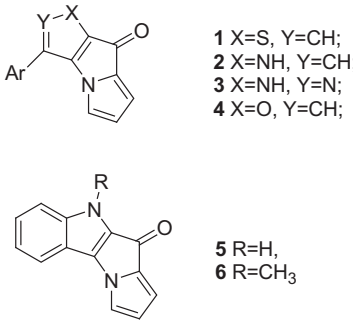


Fig. 1. 'Tripentone' structures.

Considering the interesting results of this class of compounds, and with the aim of searching for novel promising antimitotic agents, we focused our attention on the synthesis of new heteropyrrolizinone systems.

Herein we describe the synthesis of the new ring system pyrrolizino[2,3-*b*]indol-4(5*H*)-one 5, in which the indole nucleus replaces the thiophene ring, and the antiproliferative activity of the new derivatives was investigated.

2. Results and discussion

Pyrrolizino[2,3-*b*]indolones **5a**–**g** were prepared in four steps starting from 2-carbamoyl benzonitriles **7b**–**g** or carbonylmethylamino benzonitrile **7a**. Thus **7b**–**g**, prepared from substituted aminobenzonitriles in refluxing ethyl chloroformate,[7] were in turn

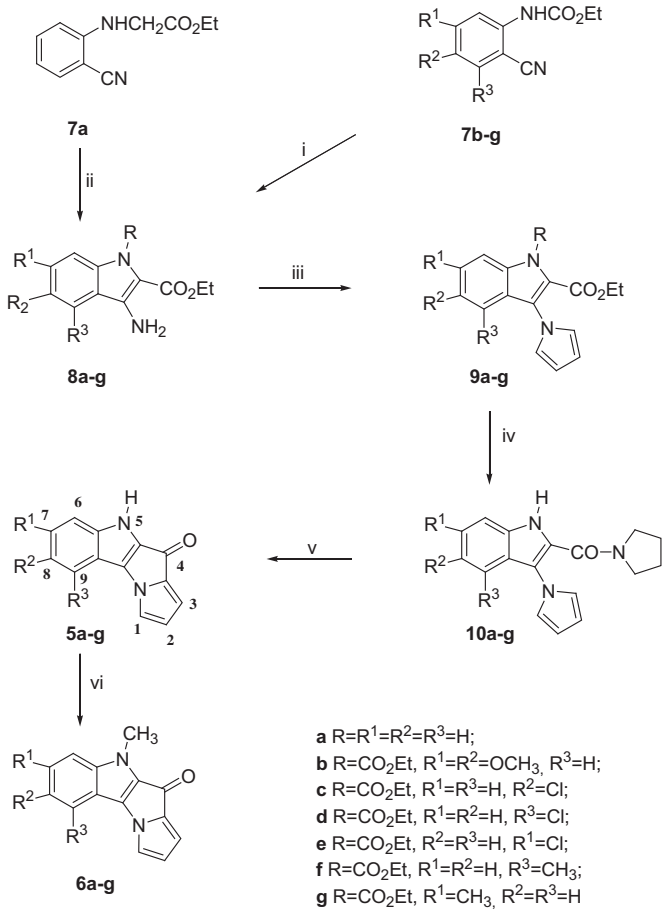
* Corresponding author. Tel.: +39 091 6161606; fax: +39 091 23860854; e-mail address: diana@unipa.it (P. Diana).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.060

converted into the 3-amino-substituted-1*H*-1,2-indole-dicarboxylates **8b**–**g**, in good to excellent yields (70–96%) by action of ethyl bromoacetate using NaH as base, in DMF, followed by intramolecular cyclization.

Alternatively 3-amino-1*H*-indole-2-carboxylate **8a** was prepared, in high yield (90%), from 2-aminobenzonitrile **7a** and ethyl bromoacetate by reaction with *t*-BuOK.[8]

Reaction of 3-amino-substituted-indoles **8a**–**g** with 2,5-dimethoxytetrahydrofuran and 4-chloropyridine hydrochloride in dioxan, through a modified Clauson–Kaas reaction, gave 3-pyrrolyl-indolo-2-carboxylates **9a**–**g** (78–91% yields). These latter led, in refluxing pyrrolidine, to the corresponding indole-2-carboxamides **10a**–**g** (81–97% yields). In this step, the original reaction conditions (basic medium and temperature) favor hydrolysis of the ester moiety bound to the indole nitrogen to form the carbamic acid. The following decarboxylation gives the 1-unsubstituted indoles (Scheme 1).



Scheme 1. Reagents and conditions. (i) NaH/DMF rt, 1 h, then ethyl bromoacetate rt, 22 h, 70–96% yields; (ii) *t*-BuOK/THF, rt, 2 h, 90% yield; (iii) 2,5-dimethoxytetrahydrofuran/dioxan, 4-chloropyridine hydrochloride, rt, 15 min, then reflux 1–4 h, 78–91% yields; (iv) pyrrolidine, reflux 18 h, 81–97% yields; (v) $POCl_3$/DMF, 70 °C, 3–7 h, 88–98% yields; (vi) *t*-BuOK/toluene, TDA-1, rt, 5–6 h, then CH_3I, rt, 18 h, 72–84% yields.

Cyclization of indole-2-carboxamides **10a**–**g** was performed, in excellent yields, under Vielsmeier–Haack conditions by action of phosphorus oxychloride and dimethylformamide to give, via an intermediate iminium salt subsequently hydrolyzed in alkaline conditions, the new ring system pyrrolizinoindolones **5a**–**g** (88–98% yields). Treatment of the tetracyclic derivatives **5b**–**g** with *t*-BuOK as the base, tris(2-(2-methoxyethoxy)ethyl)amine (TDA-1) as catalyst and methyl iodide in toluene yielded the corresponding *N*-methyl-pyrrolizinoindolones **6b**–**g** in good yields (72–90%).

Biological screenings were performed, on nine pyrrolizinoindolones (**5a**, **5b**, **5c**, **5d**, **5e**, **6b**, **6c**, **6d**, **6e**), selected by the National Cancer Institute (Bethesda, MD), at one dose concentration (10^{-5} M), for the in vitro disease-oriented antitumor screenings against a panel of about 60 human tumor cell lines grouped in disease sub-panel including leukemia, non-small lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumors cell lines.[9] The results obtained take into consideration the growth inhibitory power (GI_{50}).

The unsubstituted- and the dimethoxy-pyrrolizinoindolones **5a** and **5b** exhibited modest activity against the HL-60(TB) of the leukemia sub-panel.

More interesting results were obtained from the dimethoxy-*N*-methyl-pyrrolizinoindolones **6b**, which showed to be selective against the MOLT-4 of leukemia sub-panel, the A549/ATCC, HOP-92, and NCI-H460 of non-small cell lung cancer sub-panel, and the CAKI-1 of renal cancer sub-panel cell lines.

3. Conclusions

In conclusion, we have reported a versatile method, which allows the synthesis of derivatives of the new ring system pyrrolizino [2,3-*b*]indol-4(5*H*)-one of type 5 and 6 in good overall yields (52–72%). Three derivatives of this series showed antitumor activity against some tumors cell lines at micromolar concentrations.

4. Experimental section

4.1. General

All melting points were taken on a Büchi–Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ^1H and ^{13}C NMR spectra were measured at 200 and 50.3 MHz, respectively, in DMSO-d_6 or $CDCl_3$ solution, using a Bruker Avance II series 200 MHz spectrometer (TMS as internal reference). Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with Büchi Sepacore chromatography module (prepacked cartridge system). Elemental analyses (C, H, N) were within ±0.4% of the theoretical values.

4.2. General method for the synthesis of diethyl 3-amino-1*H*-indole-1,2-dicarboxylates 8b–g

To a stirred solution of the appropriate *N*-ethoxycarbonylaniline **7b**–**g** (2 mmol) in DMF (5 mL), sodium hydride (192 mg, 60% dispersed in mineral oil, 4 mmol) was added. The mixture was stirred for 1 h, then ethyl bromoacetate (2 mmol, 0.22 mL) was added and the resulting mixture was stirred at room temperature for 22 h. The reaction mixture was poured into ice and washed with water, and the precipitate was filtered off, air dried, and purified by chromatography column using dichloromethane as eluant to afford 3-amino-1*H*-indole-1,2-dicarboxylates **8b**–**g**.

*4.2.1. Diethyl 3-amino-5,6-dimethoxy-1H-indole-1,2-dicarboxylate (**8b**).* Yellow oil, yield 96%. IR: 3465 and 3361 (NH_2), 1711 (CO), 1660 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (t, J=7.2 Hz, 3H, CH_3), 1.38 (t, J=7.2 Hz, 3H, CH_3), 3.92 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 4.34 (q, J=7.2 Hz, 2H, CH_2), 4.38 (q, J=7.2 Hz, 2H, CH_2), 5.16 (br s, 2H, NH_2), 6.88 (s, 1H, CH), 7.65 (s, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 14.3 (q), 14.6 (q), 56.2 (q), 56.3 (q), 60.1 (t), 63.1 (t), 98.6 (d), 99.9 (d), 104.4 (s), 114.0 (s), 134.0 (s), 142.3 (s), 146.6 (s), 151.7 (s), 152.5 (s), 162.8 (s). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99; N, 8.33. Found: C, 57.48; H, 6.13; N, 8.09.

*4.2.2. Diethyl 3-amino-5-chloro-1H-indole-1,2-dicarboxylate (**8c**).* Yellow solid from ethanol, mp 77–78 °C, yield 86%. IR: 3469 and 3363 (NH_2), 1730 (CO), 1659 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.37 (t, J=7.1 Hz,

3H, CH_3), 1.39 (t, J=7.1 Hz, 3H, CH_3), 4.36 (q, J=7.1 Hz, 2H, CH_2), 4.40 (q, J=7.1 Hz, 2H, CH_2), 5.11 (br s, 2H, NH_2), 7.40 (dd, J=8.9, 2.1 Hz, 1H, CH), 7.47 (d, J=2.1 Hz, 1H, CH), 7.98 (d, J=8.9 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 14.5 (q), 60.5 (t), 63.4 (t), 108.4 (s), 116.8 (d), 118.6 (d), 123.2 (s), 128.4 (s), 129.1 (d), 136.6 (s), 140.3 (s), 151.8 (s), 162.6 (s). Anal. Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.11; H, 4.87; N, 9.02. Found: C, 54.36; H, 4.62; N, 9.29.

*4.2.3. Diethyl 3-amino-4-chloro-1H-indole-1,2-dicarboxylate (**8d**).* Yellow solid from ethanol, mp 81–82 °C, yield 75%. IR: 3500 and 3375 (NH_2), 1732 (CO), 1670 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J=7.2 Hz, 3H, CH_3), 1.38 (t, J=7.2 Hz, 3H, CH_3), 4.35 (q, J=7.2 Hz, 2H, CH_2), 4.39 (q, J=7.2 Hz, 2H, CH_2), 5.86 (br s, 2H, NH_2), 7.14 (dd, J=7.9, 0.8 Hz, 1H, CH), 7.33 (t, J=7.9 Hz, 1H, CH), 7.97 (dd, J=7.9, 0.8 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 14.5 (q), 60.3 (t), 63.5 (t), 106.8 (s), 114.0 (d), 118.6 (s), 123.6 (d), 127.42 (s), 129.2 (d), 139.8 (s), 141.7 (s), 151.9 (s), 162.8 (s). Anal. Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.11; H, 4.87; N, 9.02. Found: C, 54.40; H, 4.74; N, 8.75.

*4.2.4. Diethyl 3-amino-6-chloro-1H-indole-1,2-dicarboxylate (**8e**).* Yellow solid from ethanol, mp 72–73 °C, yield 70%. IR: 3479 and 3367 (NH_2), 1730 (CO), 1670 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.37 (t, J=7.1 Hz, 3H, CH_3), 1.40 (t, J=7.1 Hz, 3H, CH_3), 4.36 (q, J=7.1 Hz, 2H, CH_2), 4.41 (q, J=7.1 Hz, 2H, CH_2), 5.17 (br s, 2H, NH_2), 7.21 (dd, J=8.4, 1.8 Hz, 1H, CH), 7.42 (d, J=8.4 Hz, 1H, CH), 8.07 (d, J=1.8 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 14.2 (q), 14.5 (q), 60.4 (t), 63.5 (t), 107.7 (s), 115.8 (d), 119.8 (d), 120.6 (s), 123.4 (d), 135.1 (s), 138.7 (s), 140.9 (s), 151.8 (s), 162.6 (s). Anal. Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.11; H, 4.87; N, 9.02. Found: C, 53.89; H, 5.22; N, 9.33.

*4.2.5. Diethyl 3-amino-4-methyl-1H-indole-1,2-dicarboxylate (**8f**).* Yellow solid from ethanol, mp 75–76 °C, yield 80%. IR: 3504 and 3369 (NH_2), 1725 (CO), 1666 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, J=6.9 Hz, 3H, CH_3), 1.39 (t, J=6.9 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.34 (q, J=6.9 Hz, 2H, CH_2), 4.37 (q, J=6.9 Hz, 2H, CH_2), 5.43 (br s, 2H, NH_2), 6.93 (d, J=8.0 Hz, 1H, CH), 7.31 (t, J=8.0 Hz, 1H, CH), 7.90 (d, J=8.0 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 14.3 (q), 14.5 (q), 19.7 (q), 60.2 (t), 63.1 (t), 106.8 (s), 113.1 (d), 120.7 (s), 124.6 (d), 128.9 (d), 132.2 (s), 139.0 (s), 143.8 (s), 152.2 (s), 163.2 (s). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.34; H, 6.11; N, 9.87.

*4.2.6. Diethyl 3-amino-6-methyl-1H-indole-1,2-dicarboxylate (**8g**).* Yellow oil, yield 82%. IR: 3456 and 3369 (NH_2), 1726 (CO), 1676 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 1.43 (t, J=7.1 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.27 (q, J=7.1 Hz, 2H, CH_2), 4.40 (q, J=7.1 Hz, 2H, CH_2), 5.19 (br s, 2H, NH_2), 7.07 (dd, J=8.0, 0.6 Hz, 1H, CH), 7.38 (d, J=8.0 Hz, 1H, CH), 7.88 (d, J=0.6 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 14.3 (q), 14.5 (q), 22.3 (q), 60.2 (t), 63.1 (t), 106.7 (s), 115.6 (d), 118.5 (d), 119.8 (s), 124.2 (d), 136.9 (s), 139.9 (s), 141.9 (s), 152.4 (s), 163.0 (s). Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.95; H, 6.58; N, 9. 41.

4.3. General method for the synthesis of substituted ethyl 3-(1*H*-pyrrol-1-yl)-1*H*-indole-2-carboxylates (9a–g)

A solution of 2,5-dimethoxytetrahydrofuran (0.14 mL, 1.1 mmol) in dioxan (10 mL), was stirred for 15 min with 4-chloropyridine hydrochloride (165 mg, 1.1 mmol). The appropriate 3-aminoindole (**8a**–**g**) (1.1 mmol) was added and the reaction mixture was refluxed for 1–4 h and, then filtered through a small pad of Celite. The solvent was evaporated to give a brown residue that was dissolved in dichloromethane (100 mL). The solution was washed with a 1 M aqueous hydrochloric acid solution. The organic layer was dried (Na_2SO_4) and evaporated to give a crude solid, which was purified by chromatography column using dichloromethane as eluant, to give 3-(1*H*-pyrrol-1-yl)-indoles (**9a**–**g**).

*4.3.1. Ethyl 3-(1H-pyrrol-1-yl)-1H-indole-2-carboxylate (**9a**).* White solid from ethanol, mp 114–115 °C, yield 91%. IR: 3437 and 3325 (NH), 1682 (CO). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J=7.1 Hz, 3H, CH_3), 4.33 (q, J=7.1 Hz, 2H, CH_2), 6.35 (d, J=2.1 Hz, 2H, 2×CH), 6.98 (d, J=2.1 Hz, 2H, 2×CH), 7.12–7.67 (m, 4H, Ar), 9.12 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.1 (q), 61.3 (t), 108.6 (d×2), 112.0 (d), 119.4 (s), 120.4 (d), 121.4 (d), 123.3 (d×2), 123.7 (s), 124.4 (s), 126.4 (d), 134.3 (s), 161.0 (s). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02 Found: C, 70.64; H, 5.69; N, 11.29.

*4.3.2. Diethyl 5,6-dimethoxy-3-(1H-pyrrol-1-yl)-1H-indole-1,2-dicarboxylate (**9b**).* White solid from ethanol, mp 95–97 °C, yield 88%. IR: 1736 (CO), 1716 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J=7.1 Hz, 3H, CH_3), 1.44 (t, J=7.1 Hz, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 4.26 (q, J=7.1 Hz, 2H, CH_2), 4.47 (q, J=7.1 Hz, 2H, CH_2), 6.36 (t, J=1.9 Hz, 2H, 2×CH), 6.92 (s, 1H, CH), 7.03 (d, J=1.9 Hz, 2H, 2×CH), 7.74 (s, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 13.9 (q), 14.1 (q), 56.1 (q), 56.2 (q), 61.8 (t), 64.1 (t), 98.2 (d), 100.3 (d), 109.4 (d×2), 117.5 (s), 121.0 (s), 122.8 (d×2), 127.1 (s), 130.0 (s), 147.7 (s), 150.6 (s), 150.8 (s), 161.1 (s). Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.23; H, 5.88; N, 7.17.

*4.3.3. Diethyl 5-chloro-3-(1H-pyrrol-1-yl)-1H-indole-1,2-dicarboxylate (**9c**).* White solid from ethanol, mp 114–115 °C, yield 78%. IR: 1740 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, J=7.1 Hz, 3H, CH_3), 1.45 (t, J=7.1 Hz, 3H, CH_3), 4.31 (q, J=7.1 Hz, 2H, CH_2), 4.50 (q, J=7.1 Hz, 2H, CH_2), 6.36 (d, J=2.1 Hz, 2H, 2×CH), 6.99 (d, J=2.1 Hz, 2H, 2×CH), 7.41 (dd, J=8.9, 2.1 Hz, 1H, CH), 7.56 (d, J=2.1 Hz, 1H, CH), 8.10 (d, J=8.9 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 13.9 (q), 14.1 (q), 62.3 (t), 64.5 (t), 109.9 (d×2), 116.7 (d), 119.3 (d), 122.6 (d×2), 124.0 (s), 124.9 (s), 126.2 (s), 127.8 (d), 130.0 (s), 132.9 (s), 150.2 (s), 161.0 (s). Anal. Calcd for $C_{18}H_{17}ClN_2O_4$: C, 59.62; H, 4.75; N, 7.76. Found: C, 59.28; H, 4.59; N, 7.82.

*4.3.4. Diethyl 4-chloro-3-(1H-pyrrol-1-yl)-1H-indole-1,2-dicarboxylate (**9d**).* White solid from ethanol, mp 100–101 °C, yield 89%. IR: 1737 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J=7.1 Hz, 3H, CH_3), 1.44 (t, J=7.1 Hz, 3H, CH_3), 4.22 (q, J=7.1 Hz, 2H, CH_2), 4.50 (q, J=7.1 Hz, 2H, CH_2), 6.29 (d, J=2.1 Hz, 2H, 2×CH), 6.80 (d, J=2.1 Hz, 2H, 2×CH), 7.26 (dd, J=7.9, 1.0 Hz, 1H, CH), 7.37 (t, J=7.9 Hz, 1H, CH), 8.13 (dd, J=7.9, 1.0 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 13.8 (q), 14.0 (q), 62.2 (t), 64.7 (t), 108.9 (d×2), 113.9 (d), 122.5 (s), 124.4 (d×2), 124.5 (s), 125.3 (d), 126.4 (s), 127.6 (d), 128.1 (s), 135.5 (s), 149.9 (s), 160.6 (s). Anal. Calcd for $C_{18}H_{17}ClN_2O_4$: C, 59.62; H, 4.75; N, 7.76. Found: C, 59.34; H, 4.96; N, 7.43.

*4.3.5. Diethyl 6-chloro-3-(1H-pyrrol-1-yl)-1H-indole-1,2-dicarboxylate (**9e**).* White solid from ethanol, mp 77–78 °C, yield 85%. IR: 1733 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J=7.1 Hz, 3H, CH_3), 1.46 (t, J=7.1 Hz, 3H, CH_3), 4.30 (q, J=7.1 Hz, 2H, CH_2), 4.51 (q, J=7.1 Hz, 2H, CH_2), 6.36 (d, J=2.2 Hz, 2H, 2×CH), 7.01 (d, J=2.2 Hz, 2H, 2×CH), 7.29 (dd, J=8.5, 1.8 Hz, 1H, CH), 7.52 (d, J=8.5 Hz, 1H, CH), 8.19 (d, J=1.8 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 13.9 (q), 14.1 (q), 62.3 (t), 64.6 (t), 109.8 (d×2), 115.7 (d), 120.7 (d), 122.6 (d×2), 123.1 (s), 123.5 (s), 124.8 (d), 125.7 (s), 133.6 (s), 134.9 (s), 150.2 (s), 161.0 (s). Anal. Calcd for $C_{18}H_{17}ClN_2O_4$: C, 59.62; H, 4.75; N, 7.76. Found: C, 59.88; H, 4.79; N, 8.03.

*4.3.6. Diethyl 4-methyl-3-(1H-pyrrol-1-yl)-1H-indole-1,2-dicarboxylate (**9f**).* White solid from ethanol, mp 62–63 °C, yield 87%. IR: 1737 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, J=7.1 Hz, 3H, CH_3), 1.44 (t, J=7.1 Hz, 3H, CH_3), 1.98 (s, 3H, CH_3), 4.20 (q, J=7.1 Hz, 2H, CH_2), 4.48 (q, J=7.1 Hz, 2H, CH_2), 6.30 (d, J=2.0 Hz, 2H, 2×CH), 6.78 (d, J=2.0 Hz, 2H, 2×CH), 7.03 (d, J=7.9 Hz, 1H, CH), 7.34 (t, J=7.9 Hz, 1H, CH), 8.03 (d, J=7.9 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 13.8 (q), 14.1 (q), 16.41 (q), 61.9 (t), 64.3 (t), 109.2 (d×2), 112.8 (d), 124.0 (d×2), 124.3 (s), 125.7 (d), 126.5 (s), 126.9 (s), 127.2 (d), 131.8 (s), 134.8 (s), 150.4 (s), 160.9 (s). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.85; H, 6.02; N, 8.12.

*4.3.7. Diethyl 6-methyl-3-(1H-pyrrol-1-yl)-1H-indole-1,2-dicarboxylate (**9g**).* White solid from ethanol, mp 72–73 °C, yield 88%. IR:

1731 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27 (t, J=7.1 Hz, 3H, CH_3), 1.45 (t, J=7.1 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.28 (q, J=7.1 Hz, 2H, CH_2), 4.48 (q, J=7.1 Hz, 2H, CH_2), 6.35 (d, J=2.1 Hz, 2H, 2×CH), 7.04 (d, J=2.1 Hz, 2H, 2×CH), 7.14 (dd, J=8.2, 0.8 Hz, 1H, CH), 7.47 (d, J=8.2 Hz, 1H, CH), 7.99 (d, J=0.8 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 13.9 (q), 14.1 (q), 22.2 (q), 62.0 (t), 64.1 (t), 109.4 (d×2), 115.4 (d), 119.5 (d), 121.8 (s), 122.6 (s), 122.7 (d×2), 125.6 (d), 126.5 (s), 135.3 (s), 138.2 (s), 150.7 (s), 161.4 (s). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.27; H, 5.71; N, 7.99.

4.4. General method for the synthesis of pyrrolidin-1-yl[3-(1*H*-pyrrol-1-yl)-1*H*-indol-2-yl]methanones (10a–g)

A solution of the appropriate ethyl 3-(1*H*-pyrrol-1-yl)-1*H*-indole-2-carboxylate **9a–g** (1 mmol) in pyrrolidine (4 mL) was refluxed for 18 h. The resulting mixture was cooled and evaporated under reduced pressure, the yellow oil was crystallized by washing with diethyl ether and the residue was filtered and purified by chromatography column using dichloromethane/ethyl acetate (9:1) as eluant to afford indole-2-carboxamides **10a–g**.

*4.4.1. Pyrrolidin-1-yl[3-(1H-pyrrol-1-yl)-1H-indol-2-yl] methanone (**10a**).* White solid from ethanol, mp 178–180 °C with dec, yield 87%. IR: 3230 (NH), 1597 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.63 (t, J=6.8 Hz, 2H, CH_2), 1.82 (q, J=6.8 Hz, 2H, CH_2), 2.60 (q, J=6.8 Hz, 2H, CH_2), 3.66 (t, J=6.8 Hz, 2H, CH_2), 6.34 (d, J=2.0 Hz, 2H, 2×CH), 6.95 (d, J=2.0 Hz, 2H, 2×CH), 7.14 (t, J=7.9 Hz, 1H, CH), 7.27 (t, J=7.9 Hz, 1H, CH), 7.51 (d, J=7.9 Hz, 1H, CH), 7.66 (d, J=7.9 Hz, 1H, CH), 10.33 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 24.0 (t), 25.9 (t), 46.5 (t), 46.7 (t), 109.8 (d×2), 112.3 (d), 118.7 (s), 119.0 (d), 120.7 (d), 121.8 (d×2), 122.9 (s), 123.4 (s), 124.7 (d), 134.6 (s), 162.1 (s). Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 72.78; H, 6.22; N, 15.35.

*4.4.2. [5,6-Dimethoxy-3-(1H-pyrrol-1-yl)-1H-indol-2-yl]-(pyrrolidin-1-yl)methanone (**10b**).* White solid from ethanol, mp 219–220 °C, yield 96%. IR: 3227 (NH), 1596 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.26 (q, J=6.8 Hz, 2H, CH_2), 1.67 (q, J=6.8 Hz, 2H, CH_2), 2.58 (t, J=6.8 Hz, 2H, CH_2), 3.67 (t, J=6.8 Hz, 2H, CH_2), 3.88 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 6.35 (d, J=2.1 Hz, 2H, 2×CH), 6.94 (d, J=2.1 Hz, 2H, 2×CH), 6.97 (s, 1H, CH), 6.97 (s, 1H, CH), 10.10 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 24.0 (t), 26.0 (t), 46.5 (t), 46.6 (t), 56.1 (q), 56.2 (q), 94.4 (d), 99.3 (d), 109.8 (d×2), 116.0 (s), 118.9 (s), 121.8 (d×2), 122.0 (s), 129.4 (s), 146.3 (s), 149.5 (s), 162.1 (s). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.96; H, 6.17; N, 12.55.

*4.4.3. [5-Chloro-3-(1H-pyrrol-1-yl)-1H-indol-2-yl]-(pyrrolidin-1-yl) methanone (**10c**).* White solid from ethanol, mp 252–253 °C, yield 91%. IR: 3221 (NH), 1596 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.65 (q, J=6.6 Hz, 2H, CH_2), 1.82 (q, J=6.6 Hz, 2H, CH_2), 2.58 (t, J=6.6 Hz, 2H, CH_2), 3.65 (t, J=6.6 Hz 2H, CH_2), 6.35 (d, J=1.6 Hz, 2H, 2×CH), 6.91 (d, J=1.6 Hz, 2H, 2×CH), 7.22 (d, J=8.7 Hz, 1H, CH), 7.43 (d, J=8.7 Hz, 1H, CH), 7.62 (s, 1H, CH), 10.67 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 24.0 (t), 25.9 (t), 46.6 (t), 46.7 (t), 110.2 (d×2), 113.5 (d), 118.2 (s), 118.4 (d), 121.7 (d×2), 123.9 (s), 124.7 (s), 125.3 (d), 126.5 (s), 132.9 (s), 161.7 (s). Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 64.79; H, 5.01; N, 13.58.

*4.4.4. [4-Chloro-3-(1H-pyrrol-1-yl)-1H-indol-2-yl]-(pyrrolidin-1-yl) methanone (**10d**).* White solid from ethanol, mp 191–192 °C, yield 95%. IR: 3251 (NH), 1589 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.66 (q, J=6.9 Hz, 2H, CH_2), 1.84 (q, J=6.9 Hz, 2H, CH_2), 2.62 (t, J=6.9 Hz, 2H, CH_2), 3.65 (t, J=6.9 Hz, 2H, CH_2), 6.28 (t, J=2.1 Hz, 2H, 2×CH), 6.88 (t, J=2.1 Hz, 2H, 2×CH), 7.10 (dd, J=7.7, 1.3 Hz, 1H, CH), 7.18 (t, J=7.7 Hz, 1H, CH), 7.42 (dd, J=7.7, 1.3 Hz, 1H, CH), 11.07 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 23.9 (t), 26.0 (t), 46.8 (t), 47.0 (t), 108.9 (d×2), 117.6 (s), 120.3 (s), 111.1 (d), 121.9 (d), 124.5 (d×2), 124.7 (d), 125.7 (s), 126.9 (s), 135.8 (s), 161.5 (s). Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.41; H, 5.28; N, 13.30.

*4.4.5. [6-Chloro-3-(1H-pyrrol-1-yl)-1H-indol-2-yl]-(pyrrolidin-1-yl) methanone (**10e**).* White solid from ethanol, mp 198–199 °C, yield 97%. IR: 3222 (NH), 1594 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.65 (q, J=6.6 Hz, 2H, CH_2), 1.85 (q, J=6.6 Hz, 2H, CH_2), 2.59 (t, J=6.6 Hz, 2H, CH_2), 3.68 (t, J=6.6 Hz, 2H, CH_2), 6.36 (t, J=2.1 Hz, 2H, 2×CH), 6.93 (t, J=2.1 Hz, 2H, 2×CH), 7.11 (dd, J=8.6, 1.8 Hz, 1H, CH), 7.50 (d, J=1.8 Hz, 1H, CH), 7.57 (d, J=8.6 Hz, 1H, CH), 10.55 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 24.0 (t), 26.0 (t), 46.5 (t), 46.6 (t), 110.1 (d×2), 112.1 (d), 118.8 (s), 120.1 (d), 121.6 (s), 121.7 (d×2), 121.8 (d), 124.0 (s), 130.7 (s), 134.8 (s), 161.8 (s). Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.34; H, 4.87; N, 12.91.

*4.4.6. [4-Methyl-3-(1H-pyrrol-1-yl)-1H-indol-2-yl]-(pyrrolidin-1-yl) methanone (**10f**).* White solid from ethanol, mp 174–175 °C, yield 81%. IR: 3241 (NH), 1594 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.66–1.84 (m, 4H, 2×CH_2), 2.15 (s, 3H, CH_3), 2.67 (t, J=6.8 Hz, 2H, CH_2), 3.63 (t, J=6.8 Hz, 2H, CH_2), 6.27 (t, J=2.1 Hz, 2H, 2×CH), 6.82 (t, J=2.1 Hz, 2H, 2×CH), 6.87 (d, J=8.2 Hz 1H, CH), 7.20 (d, J=8.2 Hz, 1H, CH), 7.30 (t, J=8.2 Hz 1H, CH), 10.10 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 18.2 (q), 23.8 (t), 26.1 (t), 46.7 (t), 47.0 (t), 109.0 (d×2), 109.8 (d), 118.6 (s), 122.3 (d), 123.0 (s), 124.4 (d×2), 124.5 (d), 126.0 (s), 131.1 (s), 134.5 (s), 161.6 (s). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.89; H, 6.41; N, 14.25.

*4.4.7. [6-Methyl-3-(1H-pyrrol-1-yl)-1H-indol-2-yl]-(pyrrolidin-1-yl) methanone (**10g**).* White solid from ethanol, mp 164–165 °C, yield 88%. IR: 3436 (NH), 1596 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.59–1.88 (m, 4H, 2×CH_2), 2.46 (s, 3H, CH_3), 2.58 (t, J=6.8 Hz, 2H, CH_2), 3.67 (t, J=6.8 Hz, 2H, CH_2), 6.33 (d, J=1.6 Hz, 2H, 2×CH), 6.95 (d, J=1.6 Hz, 2H, 2×CH), 6.98 (d, J=8.2 Hz, 1H, CH), 7.25 (s, 1H, CH), 7.53 (d, J=8.2 Hz, 1H, CH), 10.19 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 21.9 (q), 24.0 (t), 25.9 (t), 46.5 (t), 46.6 (t), 109.7 (d×2), 111.9 (d), 118.7 (d), 118.8 (s), 120.9 (s), 121.8 (d×2), 121.7 (d), 121.8 (s), 134.9 (s), 135.0 (s), 162.2 (s). Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.57; H, 6.48; N, 13.93.

4.5. General method for the synthesis of pyrrolizino[2,3-*b*]indol-4(5*H*)-one (5a–g)

A solution of the appropriate pyrrolidin-1-yl[3-(1*H*-pyrrol-1-yl)-1*H*-indol-2-yl]methanone **10a–g** (1 mmol), in phosphorus oxychloride (2.5 mL), was stirred at 70 °C for 3–7 h. After cooling, the reaction mixture was concentrated to give the iminium salt as black solid. This was shaken with diethyl ether and filtered. The dark residue was slowly added to a 10% aqueous sodium hydroxide solution (10 mL) and heated to reflux for 2–6 h. After cooling, the resulting suspension was extracted with ethyl acetate and the combined organic layers were washed with water and brine, dried, and evaporated to give a dark red solid. This residue was purified by silica gel chromatography, eluting by dichloromethane/ethyl acetate (95:5), to afford pyrrolizinoindolones **5a–g**.

*4.5.1. Pyrrolizino[2,3-b]indol-4(5H)-one (**5a**).* Red solid from ethanol, mp 250–251 °C, yield 92%. IR: 3180 (NH), 1655 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.05 (dd, J=3.7, 2.6 Hz, 1H, CH), 6.58 (d, J=3.7 Hz, 1H, CH), 7.12 (t, J=8.0 Hz, 1H, CH), 7.25 (t, J=8.0 Hz, 1H, CH), 7.36 (d, J=8.0 Hz, 1H, CH), 7.50 (d, J=2.6 Hz, 1H, CH), 7.84 (d, J=8.0 Hz, 1H, CH), 11.82 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 112.3 (d), 112.9 (s), 114.1 (d), 114.6 (d), 119.1 (d), 121.2 (d), 123.2 (d), 125.8 (d), 128.6 (s), 133.6 (s), 134.2 (s), 140.6 (s), 172.0 (s). Anal. Calcd for $C_{13}H_8N_2O$: C, 74.99; H, 3.87; N, 13.45; Found: C, 75.08; H, 4.11; N, 13.26.

*4.5.2. 7,8-Dimethoxypyrrolizino[2,3-b]indol-4(5H)-one (**5b**).* Red solid from ethanol, mp 277–278 °C, yield 98%. IR: 3195 (NH), 1658

(CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.82 (s, 6H, 2×CH_3), 6.01 (t, J=3.4, 2.8 Hz, 1H, CH), 6.48 (d, J=3.4 Hz, 1H, CH), 6.74 (s, 1H, CH), 7.30 (s, 1H, CH), 7.50 (d, J=2.8 Hz, 1H, CH), 11.49 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 55.5 (q), 55.8 (q), 95.3 (d), 99.4 (d), 105.9 (s), 111.8 (d), 113.5 (d), 122.6 (d), 126.5 (s), 134.2 (s), 135.0 (s), 136.7 (s), 146.6 (s), 150.4 (s), 170.9 (s). Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.38; H, 4.17; N, 10.31.

*4.5.3. 8-Chloropyrrolizino[2,3-b]indol-4(5H)-one (**5c**).* Red solid from ethanol, mp 294–295 °C, yield 96%. IR: 3170 (NH), 1685 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.06 (dd, J=3.7, 2.6 Hz, 1H, CH), 6.61 (d, J=3.7 Hz, 1H, CH), 7.22 (dd, J=9.0, 1.7 Hz, 1H, CH), 7.37 (d, J=9.0 Hz, 1H, CH), 7.60 (d, J=2.6 Hz, 1H, CH), 8.05 (d, J=1.7 Hz, 1H, CH), 12.08 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 112.5 (d), 113.4 (s), 115.0 (d), 115.8 (d), 118.3 (d), 123.7 (d), 125.6 (d), 125.8 (s), 130.2 (s), 133.0 (s), 133.4 (s), 138.8 (s), 171.8 (s). Anal. Calcd for $C_{13}H_7ClN_2O$: C, 64.34; H, 2.91; N, 11.54. Found: C, 64.65; H, 3.03; N, 11.85.

*4.5.4. 9-Chloropyrrolizino[2,3-b]indol-4(5H)-one (**5d**).* Red solid from ethanol, mp 290–291 °C, yield 88%. IR: 3174 (NH), 1673 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.10 (t, J=3.1 Hz, 1H, CH), 6.67 (d, J=3.1 Hz, 1H, CH), 7.20–7.39 (m, 4H, 4×CH), 12.32 (br s, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 112.6 (s), 112.8 (d), 113.3 (d), 115.4 (d), 121.0 (d), 122.9 (s), 124.4 (d), 126.2 (d), 129.8 (s), 132.4 (s), 133.8 (s), 141.1 (s), 171.5 (s). Anal. Calcd for $C_{13}H_7ClN_2O$: C, 64.34; H, 2.91; N, 11.54. Found: C, 64.10; H, 2.76; N, 11.74.

*4.5.5. 7-Chloropyrrolizino[2,3-b]indol-4(5H)-one (**5e**).* Red solid from ethanol, mp 283–284 °C, yield 94%. IR: 3163 (NH), 1670 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 6.07 (dd, J=3.4, 2.6 Hz, 1H, CH), 6.60 (d, J=3.4 Hz, 1H, CH), 7.15 (dd, J=8.7, 1.8 Hz, 1H, CH), 7.38 (d, J=1.8 Hz, 1H, CH), 7.54 (d, J=2.6 Hz, 1H, CH), 7.90 (d, J=8.7 Hz, 1H, CH), 12.00 (br s, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 111.6 (s), 112.5 (d), 113.5 (d), 115.0 (d), 120.7 (d), 121.8 (d), 123.4 (d), 129.5 (s), 130.1 (s), 133.5 (s), 133.9 (s), 140.6 (s), 171.7 (s). Anal. Calcd for $C_{13}H_7ClN_2O$: C, 64.34; H, 2.91; N, 11.54. Found: C, 64.40; H, 3.14; N, 11.19.

*4.5.6. 9-Methylpyrrolizino[2,3-b]indol-4(5H)-one (**5f**).* Red solid from ethanol, mp 281–282 °C, yield 92%. IR: 3210 (NH), 1656 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 6.07 (dd, J=3.7, 2.6 Hz, 1H, CH), 6.62 (d, J=3.7 Hz, 1H, CH), 6.87–6.91 (m, 1H, CH), 7.12–7.19 (m, 3H, 3×CH), 11.89 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 21.1 (q), 111.6 (d), 112.4 (d), 114.0 (s), 114.7 (d), 121.6 (d), 123.8 (d), 126.0 (d), 128.3 (s), 128.9 (s), 134.2 (s), 134.6 (s), 140.7 (s), 171.8 (s). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.84; H, 4.41; N, 12.76.

*4.5.7. 3-Methylpyrrolizino[2,3-b]indol-4(5H)-one (**5g**).* Red solid from ethanol, mp 248–249 °C, yield 90%. IR: 3176 (NH), 1662 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 6.03 (t, J=3.4, 2.7 Hz, 1H, CH), 6.55 (d, J=3.4 Hz, 1H, CH), 6.96 (d, J=8.3 Hz, 1H, CH), 7.12 (s, 1H, CH), 7.47 (d, J=2.7 Hz, 1H, CH), 7.72 (d, J=8.3 Hz, 1H, CH), 11.67 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 21.5 (q), 110.9 (s), 112.2 (d), 113.4 (d), 114.3 (d), 118.9 (d), 123.0 (d), 123.4 (d), 127.9 (s), 133.7 (s), 134.5 (s), 135.8 (s), 141.2 (s), 171.9 (s). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.38; H, 4.67; N, 12.43.

4.6. General method for the synthesis of 5-methylpyrrolizino [2,3-*b*]indol-4(5*H*)-ones (6b–g)

To a stirred solution of the appropriate indole-pyrrolizinone **5b–g** (1 mmol) in anhydrous toluene (10 mL), *t*-BuOK (1.36 mmol, 153 mg) and 1–2 drops of TDA-1 were added at 0 °C. The reaction mixture was kept at room temperature for 5–6 h, then iodomethane (1 mmol, 0.06 mL) was added dropwise and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was debated into water, filtered off, air dried, and recrystallized from diethyl ether to afford *N*-methyl-pyrrolizinoindolones **6a–g**.

*4.6.1. 5-Methylpyrrolizino[2,3-b]indol-4(5H)-one (**6a**).* Red solid from ethanol, mp 182–183 °C, yield 75%. IR: 1668 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.79 (s, 3H, CH_3), 6.00 (dd, J=3.6, 2.6 Hz, 1H, CH), 6.55 (d, J=3.6 Hz, 1H, CH), 6.85 (d, J=2.6 Hz, 1H, CH), 7.11 (t, J=8.1 Hz, 1H, CH), 7.22 (t, J=8.1 Hz, 1H, CH), 7.28 (d, J=8.1 Hz, 1H, CH), 7.47 (d, J=8.1 Hz, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 30.5 (q), 111.4 (d), 112.4 (d), 113.3 (s), 114.7 (d), 119.0 (d), 121.4 (d), 121.5 (d), 125.6 (d), 129.5 (s), 133.6 (s), 134.7 (s), 141.4 (s), 173.2 (s). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60; Found: C, 75.38; H, 4.67; N, 12.74.

*4.6.2. 7,8-Dimethoxy-5-methylpyrrolizino[2,3-b]indol-4(5H)-one (**6b**).* Red solid from ethanol, mp 228–229 °C, yield 84%. IR: 1658 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.70 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 5.96 (t, J=3.5, 2.3 Hz, 1H, CH), 6.48 (d, J=3.5 Hz, 1H, CH), 6.51 (s, 1H, CH), 6.68 (s, 1H, CH), 6.76 (d, J=2.3 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 30.6 (q), 56.1 (q), 56.2 (q), 92.8 (d), 98.7 (d), 106.2 (s), 112.0 (d), 113.7 (d), 120.7 (d), 127.8 (s), 134.0 (s), 135.3 (s), 137.4 (s), 146.8 (s), 150.4 (s), 172.1 (s). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.87; H, 5.32; N, 10.02.

*4.6.3. 8-Chloro-5-methylpyrrolizino[2,3-b]indol-4(5H)-one (**6c**).* Red solid from ethanol, mp 237–238 °C, yield 83%. IR: 1671 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.78 (s, 3H, CH_3), 6.06 (dd, J=3.7, 2.5 Hz, 1H, CH), 6.63 (d, J=3.7 Hz, 1H, CH), 7.27 (dd, J=9.1, 2.1 Hz, 1H, CH), 7.54 (d, J=9.1 Hz, 1H, CH), 7.59 (d, J=2.5 Hz, 1H, CH), 8.03 (d, J=2.1 Hz, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 30.6 (q), 112.6 (d), 113.0 (s), 114.0 (d), 115.2 (d), 118.4 (d), 123.7 (d), 125.5 (d), 126.1 (s), 130.1 (s), 131.6 (s), 133.4 (s), 139.3 (s), 171.8 (s). Anal. Calcd for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.36; H, 3.86; N, 11.03.

*4.6.4. 9-Chloro-5-methylpyrrolizino[2,3-b]indol-4(5H)-one (**6d**).* Red solid from ethanol, mp 239–240 °C, yield 72%. IR: 1659 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H, CH_3), 6.02 (d, J=3.4 Hz, 1H, CH), 6.62 (d, J=3.4 Hz, 1H, CH), 7.13–7.26 (m, 4H, 4×CH). ^{13}C NMR ($CDCl_3$): δ 30.8 (q), 109.9 (d), 112.4 (d), 113.4 (s), 115.7 (d), 121.3 (d), 124.5 (d), 124.7 (s), 125.7 (d), 130.3 (s), 132.3 (s), 134.5 (s), 141.8 (s), 172.7 (s). Anal. Calcd for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.75; H, 3.19; N, 10.82.

*4.6.5. 7-Chloro-5-methylpyrrolizino[2,3-b]indol-4(5H)-one (**6e**).* Red solid from ethanol, mp 174–175 °C, yield 75%. IR: 1673 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.78 (s, 3H, CH_3), 6.02 (dd, J=3.4, 2.0 Hz, 1H, CH), 6.57 (d, J=3.4 Hz, 1H, CH), 6.83 (d, J=2.0 Hz, 1H, CH), 7.08 (dd, J=8.7, 1.6 Hz, 1H, CH), 7.23 (d, J=1.6 Hz, 1H, CH), 7.40 (d, J=8.7 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 30.7 (q), 111.4 (d), 111.8 (s), 112.7 (d), 115.0 (d), 119.8 (d), 121.4 (d), 122.5 (d), 130.1 (s), 131.6 (s), 133.4 (s), 134.6 (s), 141.4 (s), 172.7 (s). Anal. Calcd for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91. Found: C, 65.66; H, 3.20; N, 11.11.

*4.6.6. 5,9-Dimethylpyrrolizino[2,3-b]indol-4(5H)-one (**6f**).* Red solid from ethanol, mp 132–133 °C, yield 80%. IR: 1671 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 5.99 (dd, J=3.4, 2.0 Hz, 1H, CH), 6.53 (d, J=3.4 Hz, 1H, CH), 6.83 (d, J=2.0 Hz, 1H, CH), 6.94 (d, J=8.4 Hz, 1H, CH), 7.00 (s, 1H, CH), 7.36 (d, J=8.4 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 22.2 (q), 30.5 (q), 111.0 (d), 111.3 (s), 112.2 (d), 114.4 (d), 118.6 (d), 121.2 (d), 123.6 (d), 128.9 (s), 133.9 (s), 134.8 (s), 136.2 (s), 142.0 (s), 173.1 (s). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.38; H, 4.97; N, 12.14.

*4.6.7. 5,7-Dimethylpyrrolizino[2,3-b]indol-4(5H)-one (**6g**).* Red solid from ethanol, mp 173–174 °C, yield 90%. IR: 1669 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.57 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.00 (dd, J=3.5, 2.6 Hz, 1H, CH), 6.57 (d, J=3.5 Hz, 1H, CH), 6.84 (d, J=2.6 Hz, 1H, CH), 6.87 (d, J=8.4 Hz, 1H, CH), 7.01 (d, J=8.4 Hz, 1H, CH), 7.17 (t, J=8.4 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$): δ 21.4 (q), 30.5 (q), 108.8 (d), 111.5 (s), 112.2 (d), 114.4 (s), 114.8 (d), 121.8 (d), 122.6 (d), 125.9 (d), 129.4 (s), 134.1 (s),

135.2 (s), 141.5 (s), 173.1 (s). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.09; H, 5.23; N, 12.01.

Acknowledgements

This work was financially supported by Ministero dell'Istruzione dell'Università e della Ricerca. We thank the National Cancer Institute (Bethesda, MD) for the antitumor tests.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.060. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. (a) Shahabi, S.; Yang, C. H.; Goldberg, G. L.; Horwitz, S. B. *Gynecol. Oncol.* **2010**, *119*, 345–350; (b) Kutuk, O.; Letai, A. *Cell Death Differ.* **2010**, *17*, 1624–1635.
2. (a) Kamath, K.; Oroudjev, E.; Jordan, M. A. *Methods Cell Biol.* **2010**, *97*, 1–14; (b) Smith, J. A.; Jordan, M. A. *Methods Cell Biol.* **2010**, *95*, 289–299.
3. (a) Kim, N. D.; Park, E. S.; Kim, Y. H.; Moon, S. K.; Lee, S. S.; Ahn, S. K.; Yu, D. Y.; No, K. T.; Kim, K. H. *Bioorg. Med. Chem.* **2010**, *18*, 7092–7100; (b) Chatterji, B. P.; Banerjee, M.; Singh, P.; Panda, D. *Biochem. Pharmacol.* **2010**, *80*, 50–61.
4. (a) Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1991**, *34*, 2579–2588; (b) Hofner, A. F.; Peifer, C. *Pharm. Ztg.* **2004**, *149*, 14–18.
5. (a) Lisowski, V.; Enguehard, C.; Lancelot, J.-C.; Caignard, D.-H.; Lambel, S.; Leonce, S.; Pierre, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2205–2208; (b) Lisowski, V.; Leonce, S.; Kraus-Berthier, L.; Sopkova-de Oliveira, S. J.; Pierre, A.; Atassi, G.; Caignard, D.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448–1464.
6. (a) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Tetrahedron Lett.* **2004**, *45*, 6353–6355; (b) Rochais, C.; Sopkova-de Oliveira, S. J.; Dallemagne, P.; Rault, S. *Heterocycles* **2006**, *68*, 2063–2077; (c) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Bioorg. Med. Chem.* **2006**, *14*, 8162–8175; (d) Rochais, C.; Duc, N. V.; Lescot, E.; Sopkova-de Oliveira, S. J.; Bureau, R.; Meijer, L.; Dallemagne, P.; Rault, S. *Eur. J. Med. Chem.* **2009**, *44*, 708–716.
7. Romagnoli, R.; Baraldi, P. G.; Sarkar, T.; Carrion, M. D.; Lopez, C. C.; Cruz-Lopez, O.; Preti, D.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Di Cristina, A.; Zonta, N.; Balzarini, J.; Brancale, A.; Hsich, H.; Hamel, E. *J. Med. Chem.* **2008**, *5*, 1464–1468.
8. Diana, P.; Barraja, P.; Lauria, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. *Tetrahedron* **2000**, *56*, 5177–5183.
9. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langely, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.