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Synthesis, structural investigations, and anti-cancer activity of new methyl indole-3-carboxylate derivatives

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HIGHLIGHTS

- Syntheses of two new bis-indoles were reported.
- Solid-state structures were solved by X-ray or ^{13}C CP/MAS NMR.
- DFT computations were used to propose stable conformation in solid-state.
- Both compounds inhibited human cancer cell lines.

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ABSTRACT

Two new methyl indole-3-carboxylate derivatives: methyl 1-(3′-indolylmethane)-indole-3-carboxylate (**1**), and methyl 1-(1′-benzenosulfonyl-3′-indolylmethane)-indole-3-carboxylate (**2**) were synthesized. They are interesting as the analogs of 3,3′-diindolylmethane, which is intensively tested as a potent anti-tumor agent. Their solid-state structure was characterized using ^{13}C CP/MAS NMR or X-ray diffraction measurements. Molecular modeling was used as a help in the structure elucidation. The solid-state NMR spectroscopy showed only one stable conformer of **1**, but the X-ray diffraction results indicate that compound **2** crystallizes in the triclinic space group $P\bar{1}$ with two molecules, **A** and **B**, in the asymmetric unit. Both compounds inhibited the growth of melanoma, renal and breast cancers cell lines.

1. Introduction

The dietary plants such as cabbage, broccoli, cauliflower and Brussels sprouts produce compounds that can be used as protective agents against tumorigenesis in a variety of human cancers, including breast cancer and prostate cancer [1–3]. Indole-3-carbinol and its acid condensation product 3,3′-diindolylmethane (DIM) are among such compounds. Both compounds are intensively tested in many bioassays [4–9] to elucidate their impact on signal transduction, which leads to cell cycle arrest, apoptosis, down regulation of cancer cell migration, modulation of expression of the CDK inhibitor, $p21^{Cip1/Waf1}$, and stimulation of mitochondrial reactive oxygen species production. Although their activity is well documented, several factors may limit their as chemotherapeutics (due to low bioavailability and promoting of some cancer cells proliferation) [10]. The substitution of indole nitrogen by alkoxy, benzyl and toluenesulfonyl groups enhanced the potency of anti-proliferative properties of indole-3-carbinol [11–13]. These observations suggest that synthetic analogs of DIM substituted at indole nitrogen could also be more potent than DIM which is a very promising compound and can be used as the lead compound to develop new chemotherapeutics with anti-cancer properties. All the facts considered, two new bis-indoles were synthesized which have a methylene linker between the N1 and C3′ atoms (Scheme 1). In this paper, as a part of systematic studies on the structural characterization of bis-indoles [14–16], the synthesis and the spectroscopic characterization of methyl 1-(3′-indolylmethane)-indole-3-carboxylate (**1**) and methyl 1-(1′-benzenosulfonyl-3′-indolylmethane)-indole-3-carboxylate (**2**) were reported. The crystal structure of **2**, and the solid-state analysis of a powder sample of **1** using the ^{13}C CP/MAS NMR method and molecular modeling was also shown.

2. Experimental

2.1. Chemistry

The transformation of methyl 3-indolecarboxylate to bis-indoles **1** and **2** was made using 3-hydroxymethylindole (for **1**) or

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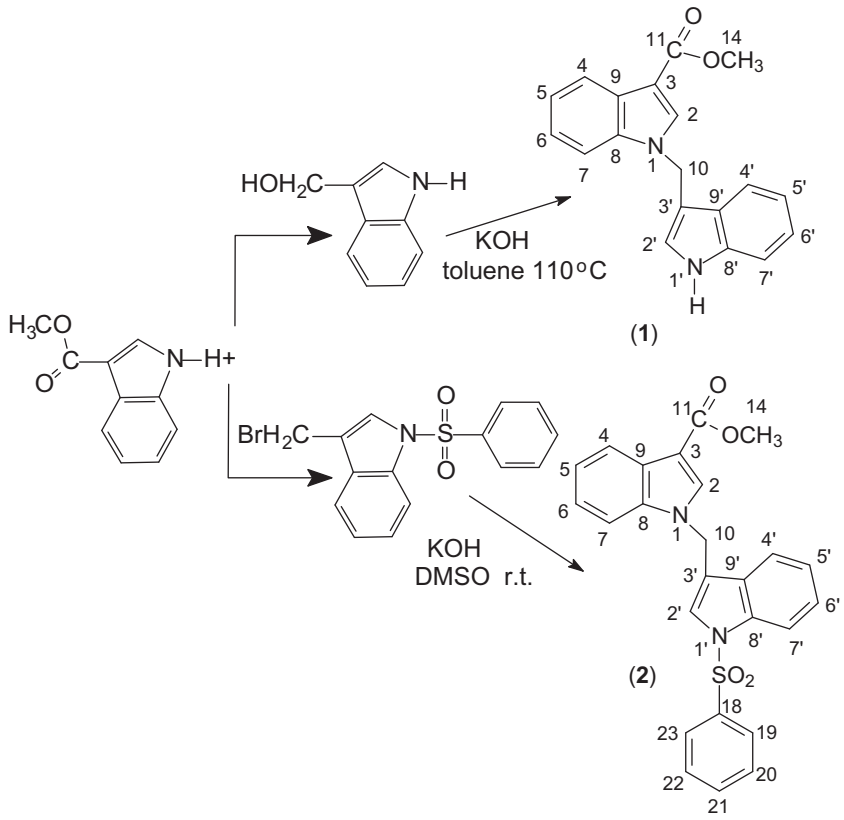

Scheme 1. Syntheses of methyl indole-3-carboxylate derivatives **1** and **2**, their chemical formulas together with the atoms numbering.

1-benzenesulfonyl-3-bromomethylindole (for **2**) as the substrates. 1-Benzenesulfonyl-3-bromomethylindole was synthesized from 1-benzenesulfonyl-3-methylindole as was described earlier [17]. Alkylation of the indole ring at the N atom was reported with reagents such as alcohols in the Pd/Fe_2O_3 catalyzed system [18] or with aldehydes in a benzoic acid catalyzed redox isomerization [19]. The formation of *N*-alkylindoles was also shown for simple alkylhalides [20]. *N*-alkylation of the indole moiety in our experiments was performed by treating equimolar amounts of reagents with sodium in toluene (for **1**) or with potassium hydroxide in dimethylsulfoxide (for **2**) leading to the desired products with good yields. To the best of our knowledge, this is the first report on the 1-(3′-indolylmethane)-indoles. Indispensable chemicals were obtained from major chemicals suppliers as high or highest purity and were used without further purification. Melting points were determined with an Electrothermal 9001 Digital Melting Point Apparatus and are uncorrected. Elemental analyses were performed on a C, H, N, S Elementar GmbH Vario EL III analyzer. IR spectra were recorded on Schimazu FTIR-8300 in KBr tablets.

*2.1.1. Methyl 1-(3′-indolylmethane)-indole-3-carboxylate (**1**)*

Methyl indole-3-carboxylate (1.75 g, 0.01 mol) was dissolved in anhydrous toluene (80 ml) and 3-indolylmethanol (1.77 g, 0.12 mol) in 30 ml anhydrous toluene was added. Before addition of (0.1 g, 0.0043 mol) sodium, 10 ml of the toluene/water azeotrope was removed by distillation. The mixture was stirred at the solvent's boiling temperature for 10 h. To the obtained mixture 3 ml of methanol was added, then 50 ml of water. The organic phase was separated, washed in water and dried with $MgSO_4$. The toluene was evaporated in vacuo. The oily residue of the crude product crystallized after several hours at 4 °C (1.58 g, 51.97%). The crude precipitate was crystallized from ethanol/water (2:1); 0.52 g (17.10%) yield. M.p. 154.5–154.8 °C.-IR (KBr): ν = 3450–3150 (N—H associated), 3120–3000, 3000–2800, 1662 (C=O), 1610, 1535, 1482, 1461, 1446, 1338 (C—N) cm^{-1}. ^1H NMR (299.87 MHz, DMSO) δ = 3.772 (s, 3H, 10-H), 5.607 (s, 2H, 8-H), 6.988 (td, J = 0.9 Hz, 1H, 5′-H), 7.073 (td, J = 1.2 Hz, 1H, 6′-H), 7.190 (td, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H, 5-H), 7.241 (td, J_1 = 7.0 Hz, J_2 = 2.0 Hz, 1H, 6-H), 7.367 (bd, J = 8.0 Hz, 1H, 7′-H), 7.516 (bd, J = 8.0 Hz, 1H, 4′-H), 7.594 (d, J = 2.4 Hz, 1H, 2′-H), 7.796 (d, J = 2.0 Hz, 1H, 7-H), 7.969 (d, J = 8.1 Hz, 1H, 4-H), 8.203 (s, 1H, 2-H). ^{13}C NMR (75.41 MHz, DMSO): δ = 41.78 (10-C), 50.62 (14-C), 105.17 (3-C), 109.51 (3′-C), 111.39 (7-C), 111.71 (7′-C), 118.27 (4′-C), 119.03 (5′-C), 120.63 (4-C), 121.42 (6′-C), 121.51 (5-C), 122.30 (6-C), 125.56 (2′-C), 126.19 (9′-C), 126.30 (9-C), 134.93 (2-C), 136.25 (8-C), 136.31 (8′-C), 164.43 (11-C) ppm. $C_{19}H_{16}N_2O_2$ (304.33): calcd. C 74.98, H 5.30, N 9.21; found C 74.98, H 5.38, N 9.21.

*2.1.2. Methyl 1-(1′-benzenosulfonyl-3′-indolylmethane)-indole-3-carboxylate (**2**)*

Methyl indole-3-carboxylate (0.50 g, 0.009 mol) was added to a suspension of potassium hydroxide (0.50 g, 0.009 mol) in 15 ml DMSO. The mixture was stirred at room temperature for 45 min and then 1-benzenesulfonyl-3-bromomethylindole (1.05 g, 0.009 mol) dissolved in 8 ml DMSO was added dropwise. The stirring was continued for 2 h. Then 100 ml of water was added. The obtained beige solid was separated (0.96 g, 72.18%) and crystallized from methanol; 0.58 g bright yellow product (43.61%) yield. M.p. 175.7–176.2 °C. IR (KBr): ν = 3150–3000, 3000–2800, 1692 (C=O), 1533, 1490, 1465, 1446, 1362 (C—N) 1245, 1117 C—O—C, 1218, 1184 (SO_2) cm^{-1}. ^1H NMR (299.87 MHz, DMSO) δ = 3.791 (s, 3H,14-H), 5.638 (s, 2H, 10-H), 7.163–7.259 (m, 3H, 5-H, 5′-H, 6-H), 7.308 (t, J = 8.0 Hz, 1H,6′-H), 7.471 (d, J = 8.0 Hz, 1H, 4′-H), 7.539 (t, J = 7.6 Hz, 2H, 20-H, 22-H), 7.660 (t, J = 7.6 Hz, 1H, 21-H), 7.715 (d, J = 8.0 Hz, 1H, 7-H), 7.907 (d, J = 8.0 Hz, 1H, 7′-H), 7.933 (d, J = 7.6 Hz, 2H, 19-H, 23-H), 7.967 (d, J = 8.0 Hz, 1H, 4-H), 8.133 (s, 1H, 2-H), 8.356 (s, 1H, 2-H). ^{13}C NMR (75.40 MHz, DMSO): δ = 41.31 (10-C), 50.73 (14-C), 105.76 (3-C), 111.37 (7-C), 113.39