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Synthesis and pharmacological evaluation of novel bisindolylalkanes analogues

Ya-Li Song [a,b], Yun-Fang Dong [a,b], Tao Yang [a,b], Chao-Chao Zhang [a,b], Li-Min Su [a,b], Xin Huang [a,b], Dong-Nuan Zhang [c], Geng-Liang Yang [a,b,*], Yu-Xin Liu [a,b,*]

[a] Key Laboratory for Pharmaceutical Quality Control of Hebei Province, College of Pharmaceutical Sciences, Hebei University, Wusi East Road No. 180, Baoding, Hebei 071002, China
[b] Key Laboratory of Medical Chemistry and Molecular Diagnosis, Ministry of Education, Wusi East Road No. 180, Baoding, Hebei 071002, China
[c] College of Science, Agricultural University of Hebei, Baoding, Hebei 071001, China

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ABSTRACT

In an effort to develop potent anti-cancer chemopreventive agents that act on topoisomerase II, a novel series of bisindolylalkanes analogues such as 3,3′-(thiochroman-4,4-diyl)bis(1*H*-indole) are synthesized. Structures of all compounds are elucidated by ^{1}H NMR, ^{13}C NMR and HRMS. Anti-proliferative activities for all of these compounds are investigated by the method of MTT assay on 7 human cancer lines. Most of them showed antitumor activities in vitro, the half maximal inhibitory concentration (IC_{50}) value is 7.798 μg/mL of **3a** against MCF7. Compound **3a** showed comparable topoisomerase II inhibitory activity to etoposide (VP-16) at 100 μM concentration. The rest of the compounds also showed varying degree topoisomerase II inhibitory activity.

1. Introduction

Indoles are one of the most important nitrogen containing heterocyclic molecules, found extensively in biological system which play vital role in biochemical process.[1] Indole ring is found in many natural products, pharmaceuticals agents and polymer materials. The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives.[2,3]

Bisindolylalkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin. During the last few years a large number of natural products containing bisindolylmethanes and trisindolylethanes have been isolated from various terrestrial and marine natural sources.[4,5] These natural products have novel structures and exhibit a range of important biological activities cancer chemotherapy with bis(3-indolyl) methane was recently reviewed and numerous activities are reported.[6]

Gong[7] et al. reported that 3,3′-diindolylmethane is a novel topoisomerase IIα catalytic inhibitor that induces S-phase retardation and mitotic delay in Human Hepatoma HepG2 Cells. Diindolylmethane also use for the treatment of multiple cancers.[8] 3,3′-Diindolylmethane can also inhibit prostate cancer development in Transgenic Adenocarcinoma mouse prostate model.[9] Recent reports show that the highly absorbable microencapsulated formulation of 3,3′-diindolymethane is in I/III phases of clinical trials for treatment of cervical displasia and prostate cancer.[10] Chao et al. Speculated that the N–N′ distance might play an important role in their anticancer effects. Computational analysis of the low-energy of diindolymethane, using the SYBYL 7.0 software package, revealed that the N–N′ distance is 5.9 Å.[11] In our continued effort to develop anti-cancer drug candidates, we designed a series of new 3,3′-diindolylmethane analogues prossessing thiochroman. Here we report the synthesis of new diindolylmethane analogues and their pharmacological activities, including cytotoxicity and topoisomerase II inhibition. The N–N′ distance of these novel diindolylmethane is 5.9–6.0 Å.

2. Experimental

2.1. Materials and methods

Substituted benzenethiols (chemically pure) were from Shou & Fu Chemical Co., Ltd (Zhejiang, China), and the other reagents were obtained from Tianjin Kemiou Chemical Reagent Co., Ltd (Tianjin, China). ^{1}H NMR and ^{13}CNMR were measured on a Bruker AVANCE

* Corresponding authors. Tel.: +86 312 5071108; fax: +86 312 5071107 (G.-L.Y.); tel.: +86 312 5071108 (Y.-X.L.).
E-mail addresses: ygl@hbu.edu.cn (G.-L. Yang), yuxinliu@hbu.edu.cn (Y.-X. Liu).

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III 600 (600 MHz, Switzerland) spectrometer using TMS as the internal standard. High Resolution Mass spectral data were determined on a Bruker apex ultra 7.0 T Fourier transform mass spectrometer. Melting points were determined with a SGW X-4 microscopic melting point apparatus (Shanghai Precision & Scientific Instrument Co., Ltd, China) in open capillaries and were uncorrected. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates, visualizing with ultraviolet light. The reaction mixture was separated by column chromatography on silica gel (200–300 mesh) eluted with a mixture of petroleum ether and ethyl acetate.

2.2. General methods for the preparation of compounds thiochroman-4-ones (1a–1f)

1:1.2:2.4 molar mixture of substituted benzenethiols (50 mmol), 3-chloropropanoic acid (6.5 g, 60 mmol), and NaOH (4.8 g, 120 mmol) in 5 mL water was irradiated under microwave irradiation for 5–6 min, the reactant was cooled to ambient temperature and then HCl (1 mol/L) was added to adjust the pH of solution below 2. Maintaining the temperature at <20 °C, a lot of white precipitate was created. The precipitate was filtered and washed with water.[12] The dried white precipitate and a solution of concentrated sulfuric acid (40 mL, 98%) were stirred sufficiently and then the reaction solution was mixed with ice water (100 mL) after 12 h at room temperature, the solid product formed was collected, washed with water and recrystallized from ethanol water solution (ethanol/H_2O = 8:2) (see Scheme 1).[13,14]

2.3. General procedure for the preparation of compounds 3a–3h

Indole (**2**, 1.0 mmol), substituted thiochroman-4-ones (**1**, 0.5 mmol), anhydrous ethanol (5 mL) and silicotungstic acid (0.05 mmol) were mixed in a 100 mL round flask. The mixture was stirred in refluxing ethanol for an appropriate time. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with H_2O (5 mL) and extracted three times with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtrated under suction. And then the solvent from the extract was evaporated under reduced pressure to give the residue, which was purified by column chromatography on silica gel (200–300 mesh), eluted with petroleum ether or mixture of petroleum ether/ethyl acetate.

2.3.1. 3,3′-(8-Chlorothiochroman-4,4-diyl)bis(1*H*-indole)

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.93 (s, 2H, NH), 7.42 (d, J = 8.2 Hz, 2H), 7.29 (dd, J = 7.8, 1.0 Hz, 1H), 7.15 (s, 2H), 7.05 (t, J = 7.6 Hz, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.86–6.82 (m, 3H), 6.55 (s,2H), 3.11–2.95 (m, 2H, CH_2S), 2.78–2.65 (m, 2H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 142.58, 137.81, 132.65, 129.62, 129.55, 127.74, 126.03, 125.39, 124.08, 121.34, 121.11, 120.66, 118.88, 112.36, 43.88, 41.70, 33.04. Mp 270–272 °C, ESI-MS: 415.1032 $[M+H]^+$, yield 28.9%.

2.3.2. 3,3′-(6-Chlorothiochroman-4,4-diyl)bis(1*H*-indole)

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.96 (s, 2H, NH), 7.44 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 8.6, 2.1 Hz, 1H), 7.15 (d, J = 5.2 Hz, 2H), 7.09 (t, J = 7.5 Hz, 2H), 6.88 (t, J = 7.5 Hz, 3H), 6.59 (s, 2H), 3.09–2.95 (m, 2H, CH_2S), 2.76–2.68 (m, 2H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 142.19, 137.77, 132.34, 130.04, 128.10, 128.01, 127.06, 125.90, 125.42, 121.38, 120.96, 120.23, 118.92, 112.40, 43.55, 41.71, 33.25. Mp 258–259 °C, ESI-MS: 415.1030 $[M+H]^+$, yield 33.5%.

2.3.3. 3,3′-(8-Methylthiochroman-4,4-diyl)bis(1*H*-indole)

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.91 (s, 2H, NH), 7.40 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 6.4 Hz, 2H), 7.09 (d, J = 7.7 Hz, 1H), 7.04 (t, J = 7.6 Hz, 2H), 6.84 (t, J = 7.5 Hz, 2H), 6.56 (s, 2H), 6.52 (d, J = 11.6 Hz, 1H), 3.00–2.94 (m, 2H), 2.70–2.63 (m, 2H, CH_2S), 2.17 (s, 3H, CH_3). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.73, 160.12, 136.19, 136.14, 133.77, 133.76, 128.72, 128.67, 128.34, 128.31, 126.70, 123.60, 122.50, 121.21, 120.18, 120.13, 116.09, 115.06, 114.90, 114.58, 114.43, 111.32, 25.36. Mp 225–227 °C, ESI-MS: 395.1523 $[M+H]^+$, yield 22.8%.

2.3.4. 3,3′-(6-Methylthiochroman-4,4-diyl)bis(1*H*-indole)

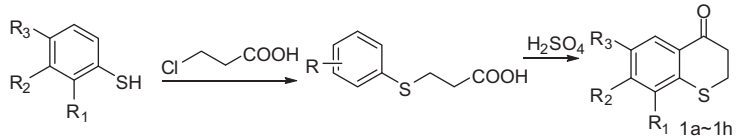
^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 2H, NH), 7.39 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.06–7.01 (m, 3H), 6.91 (dd, J = 8.1, 1.1 Hz, 1H), 6.82 (t, J = 7.5 Hz, 2H), 6.74 (s, 1H), 6.52 (s, 2H), 3.05–2.94 (m, 2H, CH_2S), 2.71–2.59 (m, 2H, CH_2), 1.94 (s, 3H, CH_3). ^{13}C NMR (151 MHz, DMSO-d_6) δ 137.74, 132.30, 131.29, 129.31, 127.90, 126.25, 125.96, 125.62, 121.24, 121.19, 121.06, 118.70, 112.28, 43.35, 33.99, 23.24, 21.18. Mp 296–298 °C, ESI-MS: 395.1525 $[M+H]^+$, yield 70.9%.

2.3.5. 3,3′-(6-Methoxythiochroman-4,4-diyl)bis(1*H*-indole)

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 2H, NH), 7.39 (d, J = 8.1 Hz, 2H), 7.12(s, 1H), 7.10 (d, J = 8.6 Hz, 2H), 7.03 (t, J = 7.5 Hz, 2H), 6.82 (t, J = 7.5 Hz, 2H), 6.78 (dd, J_1 = 8.7 Hz, J_2 = 2.8 Hz, 1H), 6.57 (s, 2H), 6.49 (d, J = 2.8 Hz, 1H), 3.36 (s, 3H, OCH_3), 3.00–2.98 (m, 2H, CH_2S), 2.67–2.65 (m, 2H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.09, 141.46, 137.68, 127.05, 125.77, 123.61, 121.19, 121.12, 120.86, 118.73, 117.61, 112.48, 112.26, 55.18, 43.57, 33.83, 23.11. Mp 248–250 °C, ESI-MS: 411.1531 $[M+H]^+$, yield 40.5%.

2.3.6. 3,3′-(7-Fluoro-6-methylthiochroman-4,4-diyl)bis(1*H*-indole)

^{1}H NMR (600 MHz, DMSO-d_6) δ 11.91 (s, 2H, NH), 7.40 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 6.2 Hz, 2H), 7.08 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.5 Hz, 2H), 6.84 (t, J = 7.5 Hz, 2H), 6.57–6.53 (m, 3H), 2.99–2.97 (m, 2H, CH_2S), 2.68–2.66 (m, 2H, CH_2), 2.16 (s, 3H, CH_3). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.82, 157.24, 139.64, 137.78, 128.66, 127.85, 125.86, 125.49, 123.52, 123.40, 121.29, 121.05, 120.58, 118.84, 116.81, 116.65, 112.33, 43.35, 33.42, 23.19, 14.11. Mp 262–264 °C, ESI-MS: 413.1431 $[M+H]^+$, yield 10.5%.



1a: R_1=Cl, 1b: R_3=Cl, 1c: R_1=CH_3, 1d: R_3=CH_3, 1e: R_3=OCH_3, 1f: R_2=F, R_3=CH_3, 1g: R_1=F, 1h: R_3=F.

Scheme 1. Synthesis of compounds **1a**–**1h**. Reagents and conditions: **1a**: R_1 = Cl, 1b: R_3 = Cl, 1c: R_1 = CH_3, 1d: R_3 = CH_3, 1e: R_3 = OCH_3, 1f: R_2 = F, R_3 = CH_3, 1g: R_1 = F, 1h: R_3 = F.