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Synthesis of 3,3-di(1-(2-phenylbenzyl)indole-3-yl)-5-bromoindoline-2-one

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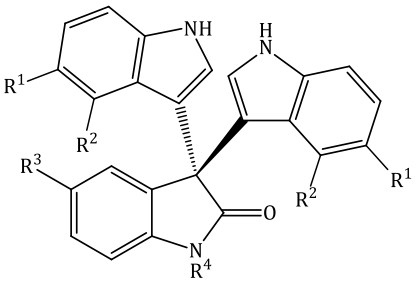
Abstract

3,3-Di(indol-3-yl)indoline-2-one **(1a)** was firstly isolated from the culture of a bacterium of *Vibrio* sp., which was separated from marine sponge *Hyrtios altum*. This natural microbial product exhibited various bioactivities for examples antimicrobial, antifungal, anticonvulsant, anticancer, antidiabetic. Herewith we report synthesis of 3,3-di(1-(2-phenylbenzyl)indol-3-yl)-5-bromoindoline-2-one **(3)** as a new analogue of 3,3-di(indol-3-yl)indoline-2-one **(1a)**. *N*-Alkylation of indole gave 1-(2-phenylbenzyl)indole **(4)**, which on treatment with 5-bromoisatin under acidic condition afforded 3,3'-di(1-(2-phenylbenzyl)indol-3-yl)-5-bromoindoline-2-one **(3)**. Structure of compound **(3)** was established by NMR and high-resolution mass spectroscopies.

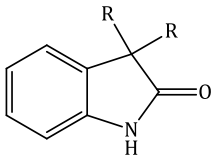
Keywords: *Synthesis, 3,3-di(indol-3-yl)indoline-2-one, analogue*

1. Introduction

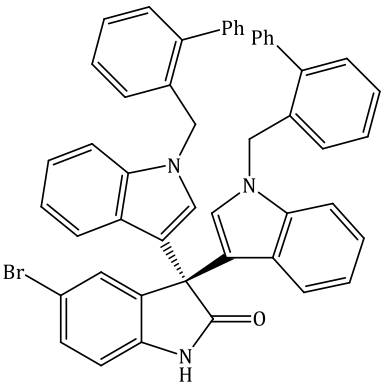
Isatin derivatives are heterocyclic compounds with various biological and pharmaceutical properties[1], [2]. 3,3-Di(indol-3-yl)indolin-2-one **(1a)** as an isatin derivative, was isolated from the culture of a bacterium of *Vibrio* sp. that was separated from the Okinawan marine sponge *Hyrtios altum*[3] and also isolated from a North Sea bacterium that was closely related to *Vibrio parahaemolyticus* Bio249[3], [4]. 3,3-Di(indol-3-yl)indolin-2-one **(1a)** was synthesized by refluxing indolin-2-one **(2a)** and copper(II) bromide in ethyl acetate for 3 h to afford 3,3-dibromoxindole **(2b)** in 72% yield, which on reaction with indole and silver carbonate at 25 °C for 1.5 h gave trisindoline **(1a)** in 65% yield. Following the same procedure, reaction of 3,3-dibromoxindole **(2b)** with other indoles gave the corresponding 3,3-di(indol-3-yl)indolin-2-one **(1b-d)**[3]. 3,3-Di(indol-3-yl)indolin-2-ones were most notable synthesized by reaction of indoles and isatins with various catalysts such as molecular iodine[5], [6], iron(III) chloride[7], Wells–Dawson heteropolyacid[8], amberlyst 15[9], sulfonic acid functionalized nanoporous SBA-Pr-SO_3H[10], magnetite sulfuric acid (Fe_3O_4-SO_3H) magnetic nanoparticles[11], *p*-toluenesulfonic acid[12]. 3,3-Di(indol-3-yl)indolin-2-ones showed various biological activities such as antimicrobial[3], [10], [11]·[13]–[15], antifungal[10], [11], [13], anticonvulsant[13], spermicidal[5], xanthine oxidase inhibition[16], tyrosinase inhibitor[17], anticancer[6], [7], [14], [15], [18], [19], antidiabetic[12]. Recently, we found that 3,3-di(indol-3-yl)indolin-2-ones **(1a, 1d, 1e)** exhibited promising activity against *Mycobacterium tuberculosis* H_{37}Rv[20]. This finding intrigued us to synthesis a series of new 3,3-di(indol-3-yl)indolin-2-ones and explore their bioactivities. We herein report synthesis of 3,3-di(1-(2-phenylbenzyl)indol-3-yl)-5-bromoindoline-2-one **(3)** as a new analogue of 3,3-di(indol-3-yl)indoline-2-one **(1a)** for further application.



	R^1	R^2	R^3	R^4
(1a)	H	H	H	H
(1b)	H	OH	H	H
(1c)	CO_2H	H	H	H
(1d)	H	H	Br	$CH_2C_6H_5$
(1e)	H	H	Br	$CH_2C_6H_4NO_2$



(2a) R = H
(2b) R = Br



(3)

2. Experimental

2.1. General

Infrared spectra were recorded in KBr disc using FTIR Shimadzu 8400S (Shimadzu Co., Kyoto, Japan). ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were taken on a JEOL ECS400 (JEOL Ltd., Tokyo, Japan using DMSO-d_6 (25°C) or $CDCl_3$ (20°C) as solvent. High resolution mass spectra were obtained on a Waters Q-TOF Xevo mass spectrometer (Waters, Milford, USA). Melting points were measured by Fischer John apparatus (Cole Parmer, Illionis, USA) and uncorrected. All materials and reagents were purchased from commercial suppliers and used as received. Gravity column chromatography was carried out on 70-230 mesh silica gel (Merck, Darmstadt, Germany). Thin layer

chromatography (TLC) was performed 0.20 mm silica gel 60 F254 (Merck, Darmstadt, Germany). Compounds were detected by ultraviolet light at 254 nm.

2.2. Synthesis of 1-(2-phenylbenzyl)indole (4)

To a solution of indole (0.20 g, 1.70 mmol) in anhydrous DMF (20 mL) was added sodium hydride (0.12 g, 5.10 mmol), the reaction mixture was then stirred at room temperature for 30 minutes. 2-Phenylbenzyl bromide (0.42 g, 1.70 mmol) was added to the solution, and the mixture was stirred for an additional 1 h. Cold water was added; the resulting precipitate was filtered off, washed with cold water, and dried to afford 1-(2-phenylbenzyl)indole **(4)** as a white solid (0.38 g, 80%), m.p. 137-138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, $Si(CH_3)_4$ = 0 ppm): δ = 7.67-7.65 (m, 1H), 7.45–7.33 (m, 7H), 7.26-7.23 (m, 1H), 7.17-7.09 (m, 3H), 6.99 (d, *J*=2.4 Hz, 1H), 6.90 (d, *J*=7.6 Hz, 1H), 6.53 (d, *J*=2.4 Hz, 1H), 5.27 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz, $Si(CH_3)_4$ = 0 ppm): δ = 141.3, 140.6, 136.3, 134.8, 130.3, 129.2, 128.7, 128.6, 128.3, 128.0, 127.6, 127.6, 127.4, 121.6, 121.0, 119.5, 109.8, 101.6, 48.1. HRESIMS m/z (pos): 284.1439 $C_{21}H_{18}N$ (calcd. 284.1439).

2.3. Synthesis of 3,3-di(1-(2-phenylbenzyl)indol-3-yl)-5-bromoindoline-2-one (3)

To a solution of 1-(2-phenylbenzyl)indole (0.12 g, 0.53 mmol) **(4)** and 5-bromoisatin (**5**) (0.30 g, 1.06 mmol) in THF (15 mL) was added a catalytic amount of sulfuric acid, and stirred at room temperature for 8 h. Cold water was added; the resulting precipitate was filtered off, washed with cold water, dried, and purified by gravity column chromatography with dichloromethane eluant (Rf 0.47) to furnish 3,3-di(1-(2-phenylbenzyl)indole-3-yl)-5-bromoindoline-2-one (**3**) as a white solid (0.11 g, 27 %), m.p. 154-155°C. ^{1}H-NMR (DMSO-d_6, 400 MHz, $Si(CH_3)_4$ = 0 ppm): δ = 10.71 (s, 1H), 7.41-7.22 (m, 16H), 7.20-7.14 (m, 4H), 7.05 (d, *J*=8.2 Hz, 2H), 6.95-6.91 (m, 3H), 6.83 (d, *J*=7.2 Hz, 2H), 6.78 (t, *J*=7.4 Hz, 2H), 6.62 (s, 2H), 5.29 (s, 4H). ^{13}C-NMR (DMSO-d_6, 100 MHz, $Si(CH_3)_4$ = 0 ppm): δ = 178.3, 141.3, 141.1, 140.6, 137.2, 136.8, 135.4, 131.4, 130.6, 129.4, 128.9, 128.5, 128.2, 128.1, 127.9, 126.5, 121.9, 121.5, 119.3, 113.8, 112.3, 110.7, 52.9, 47.9. HRESIMS m/z (pos): 796.1937 $C_{50}H_{36}{}^{79}BrN_3NaO$ (calcd. 796.1939), 798.1942 $C_{50}H_{36}{}^{81}BrN_3NaO$ (calcd. 798.1919).

3. Results and discussion

3.1. Synthesis of 1-(2-phenylbenzyl)indole (4)

1-(2-Phenylbenzyl)indole **(4)** was synthesized by alkylation of indole, adapting previous procedure[21]. The alkylation involved reaction of indole with sodium hydride as a base in anhydrous DMF to yield indolyl anion and hydrogen gas as by-product. Reaction of this anion as nucleophile with 2-phenylbenzyl bromide as electrophile resulted 1-(2-phenylbenzyl)indole **(4)** in 80% yield, following S_N2 mechanism of nucleophilic substitution[22]. ^{1}H NMR spectrum of 1-(2-phenylbenzyl)indole **(4)** (in deuterochloroform) showed a singlet signal at 5.27 ppm for the methylene group protons which confirm that the alkylation reaction was successful, and aromatic protons provided multiplet signals in the region 7.41-6.62 ppm. Furthermore the ^{13}C NMR spectrum of 1-(2-phenylbenzyl)indole **(4)** (in deuterochloroform) gave a signal at 48.1 ppm for methylene group carbon, and aromatic carbons exhibited signals in the region 141.3-101.6 ppm.

3.2. Synthesis of 3,3-di(1-(2-phenylbenzyl)indol-3-yl)-5-bromoindoline-2-one (3)

Synthesis of 3,3-di(1-(2-phenylbenzyl)indole-3-yl)-5-bromoindoline-2-one **(3)** was carried out by adapting the previous procedure[20], which involved reaction of 1-(2-phenylbenzyl)indole **(4)** with 5-bromoisatin **(5)** in the presence of sulfuric acid as catalyst. Purification of trisindoline **(3)** was carried out by column chromatography. ^{13}C

NMR spectrum of trisindoline **(3)** showed characteristic signals at 178.3 and 52.9 ppm for the carbonyl group carbon and quaternary carbon respectively. The methylene carbon of trisindoline **(3)** gave signal at 47.9 ppm, whilst aromatic carbons gave signals in the region 141.3-110.7 ppm. ^{1}H NMR spectrum of trisindoline **(3)** presented prominent signals at 10.71 and 5.28 ppm for NH proton and methylene group protons respectively, whilst aromatic protons gave multiplet signals at 7.41-6.62 ppm. Comparison of the NMR spectral data of 1-(2-phenylbenzyl)indole **(4)** and trisindoline **(3)** is presented in Table 1 and 2. The plausible mechanism for the formation of 3,3-di(1-(2-phenylbenzyl)indole-3-yl)-5-bromoindoline-2-one **(3)** can be seen in Figure 1. Activation of the C-3 carbonyl of 5-bromoisatin **(5)** under acidic condition generates intermediate **(6)** which undergoes nucleophilic attack by 1-(2-phenylbenzyl)indole **(4)** to yield intermediate **(7)**. Deprotonation of the alcohol **(7)** to intermediate **(8)** is followed by protonation to form intermediate **(9)**. Dehydration of **(9)** generates iminium ion **(10)** which on reaction with the second molecule of 1-(2-phenylbenzyl)indole **(4)** and rearromatization **(11)** furnishing trisindoline **(3)**.

Table 1: Comparison of ^{1}H NMR data of 1-(2-phenylbenzyl)indole **(4)** and trisindoline **(3)**

Protons	1-(2-Phenylbenzyl)indole **(4)**	Trisindoline **(3)**
CH_2	5.27 (s, 2H)	5.29 (s, 4H)
ArH	6.53 (d, *J*=2.4 Hz, 1H)	6.62 (s, 2H)
	6.90 (d, *J*=7.6 Hz, 1H)	6.78 (t, *J*=7.4 Hz, 2H),
	6.99 (d, *J*=2.4 Hz, 1H)	6.83 (d, *J*=7.2 Hz, 2H)
	7.17-7.09 (m, 3H)	6.95-6.91 (m, 3H)
	7.26-7.23 (m, 1H)	7.05 (d, *J*=8.2 Hz, 2H)
	7.45–7.33 (m, 7H)	7.20-7.14 (m, 4H)
	7.67-7.65 (m, 1H)	7.41-7.22 (m, 16H)
NH		10.71 (s, 1H)

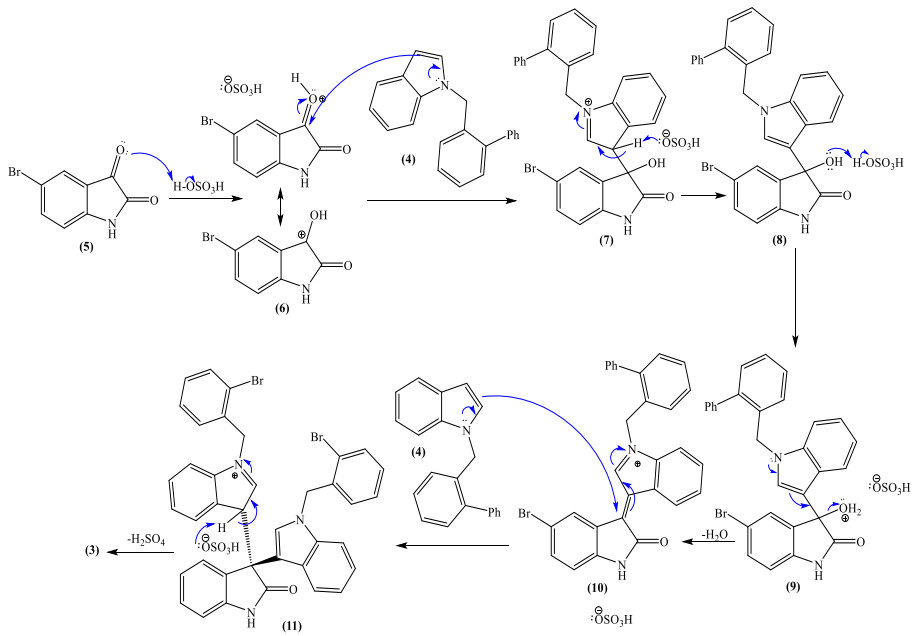


Figure 1: Proposed mechanism of acid-catalyzed formation of trisindoline **(3)**

Table 2: Comparison of ^{13}C NMR data of 1-(2-phenylbenzyl)indole **(4)** and trisindoline **(3)**

Carbons	1-(2-Phenylbenzyl)indole **(4)**	Trisindoline **(3)**
CH_2	48.1	47.9
>C<		52.9
ArCH, ArC	101.6	110.7
	109.8	112.3
	119.5	113.8
	121.0	119.3
	121.6	121.5
	127.4	121.9
	127.6	126.5
	128.0	127.9
	128.3	128.1
	128.6	128.2
	128.7	128.5
	129.2	128.9
	130.3	129.4
	134.8	130.6
	136.3	131.4
	140.6	135.4
	141.3	136.8
		137.2
		140.6
		141.1
		141.3
>C=O		178.3

4. Conclusion

N-Alkylation of indole provided 1-(2-phenylbenzyl)indole **(4)** in 80% yield. Electrophilic aromatic substitution of 1-(2-phenylbenzyl)indole **(4)** with 5-bromoisatin as electrophile under acidic condition afforded 3,3'-di(1-(2-phenylbenzyl)indol-3-yl)-5-bromoindoline-2-one **(3)** in 27% yield. The new compound **(3)** will be evaluated its bioactivities.

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