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Facile and One-Pot Access of 3,3-Bis(indol-3-yl)indolin-2-ones and 2,2-Bis(indol-3-yl)acenaphthylen-1(2*H*)-one Derivatives via an Eco-Friendly Pseudo-Multicomponent Reaction at Room Temperature Using Sulfamic Acid as an Organo-Catalyst

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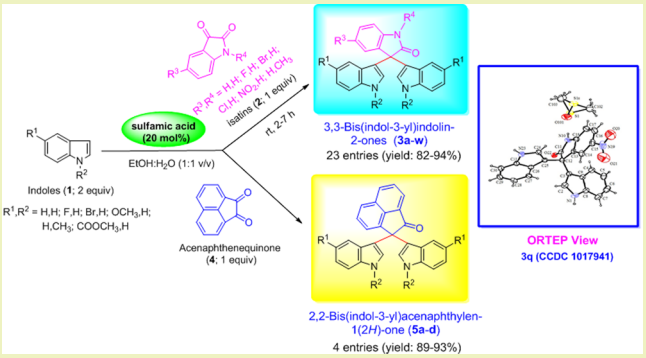
Supporting Information

ABSTRACT: A simple, straightforward, and highly efficient pseudo-three-component one-pot synthesis of a series of pharmaceutically interesting functionalized 3,3-bis(indol-3-yl)indolin-2-ones (**3a**−**3w**) and 2,2-bis(indol-3-yl)-acenaphthylen-1(2*H*)-one derivatives (**5a**−**5d**) has been developed based on a low-cost and environmentally benign commercially available sulfamic acid as an organo-catalyst in aqueous ethanol at room temperature. The salient features of the present protocol are mild reaction conditions, excellent yields, high atom-economy, eco-friendliness, easy isolation of products, no column chromatographic separation, and reusability of reaction media.



KEYWORDS: *Bis-indolyl derivatives, Medicinal chemistry, Multicomponent reactions, Sulfamic acid, Aqueous ethanol, Room temperature, Chemoselectivity, No column chromatography, Green and sustainable chemistry*

INTRODUCTION

Indoles and their derivatives are very common in bioactive natural products and are known to exhibit potent pharmacological properties.[1−3] Bis-indoles, in particular, are regarded as scaffolds of pharmaceutical promise due to their several biological efficacies including potent anticancer activity;[4−10] this framework is much pronounced in nature also. Figure 1 represents a glimpse of some of the naturally occurring bioactive bis-indoles.[11−14] In addition, the oxindole (indolin-2-one) framework is a privileged heterocyclic motif in numerous bioactive natural products such as arundaphine,[15] donaxaridine,[16] paratunamide,[17] maremycins,[18] and convolutamydine,[19] and also in a series of pharmaceutically active compounds.[20−24] 3,3-Diaryloxindole moiety is frequently found in clinical drugs and biologically active compounds and are known to possess antiproliferative,[25] antibacterial,[26] and eIF2.GTP.Met-tRNA$_i^{Met}$ ternary complex inhibitor[27] activities. Moreover, some oxindole-based lead molecules showed micromolar activity against lung cancer cells by partial depletion of intracellular Ca^{2+}, which inhibit translation initiation.[28]

Hence, it is very logical to conceive an idea in combining the structural characteristics of both these scaffolds to design molecules wherein the two indolyl moieties are linked to the same carbon atom of an indoline-2-one framework with enhanced biological efficacy. In addition, synthesis of such a framework involves the participation of isatin as synthon, which is a privileged lead molecule for designing potential bioactive agents, and its derivatives have been shown to possess a broad spectrum of bioactivity including antiplasmodial,[29] antiviral,[30] antibacterial[31] antitumor,[32,33]antifungal,[34,35] antiangiogenic,[36] anticonvulsants,[37] anti-Parkinson's disease therapeutic,[38] and effective SARS coronavirus 3CL protease inhibitor.[39] In compliance with this fact, bis(indolyl)indolin-2-ones are found to possess significant anti-inflammatory,[40] anti-HIV,[41] and antitumor[42] activities. Recently, a series of synthetic 3,3-bis(indol-3-yl)indolinones (Figure 2) have been evaluated to possess potent spermicidal potential,[43] anticancer,[44] and cytotoxic[45] properties. Interestingly, certain bis(indolyl)-indolin-2-one derivatives have been reported to exhibit strong cytotoxicity against a series of cancer cell lines but not against the normal cells.[45]

Such a handful of diverse applications of bis(indolyl)indolin-2-one scaffolds in medicinal chemistry have drawn considerable interest during the last several years among synthetic chemists to develop useful synthetic routes to these heterocycles of potential interest; as a result, a number of methods are already reported. Among the known procedures, the most straightforward method for the synthesis of this class of heterocycle

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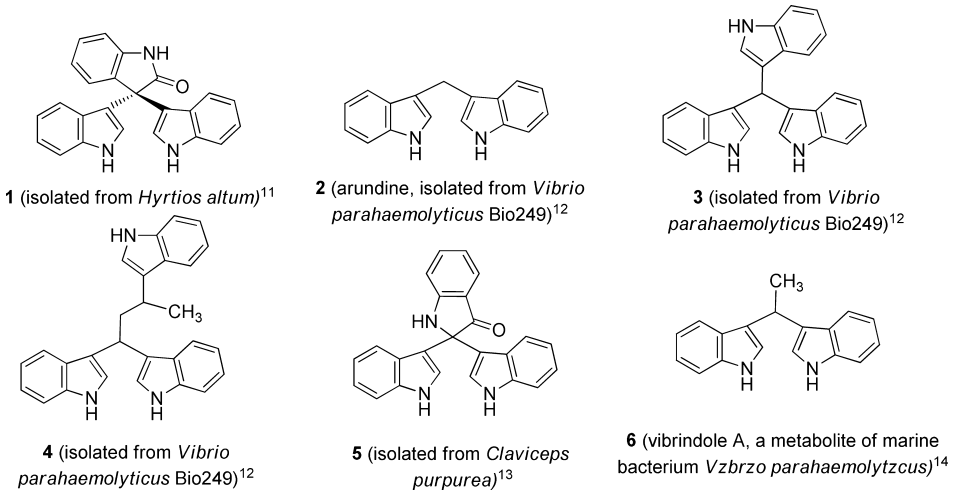


Figure 1. Some of the naturally occurring bioactive compounds bearing the bis-indole moiety.[11−14]

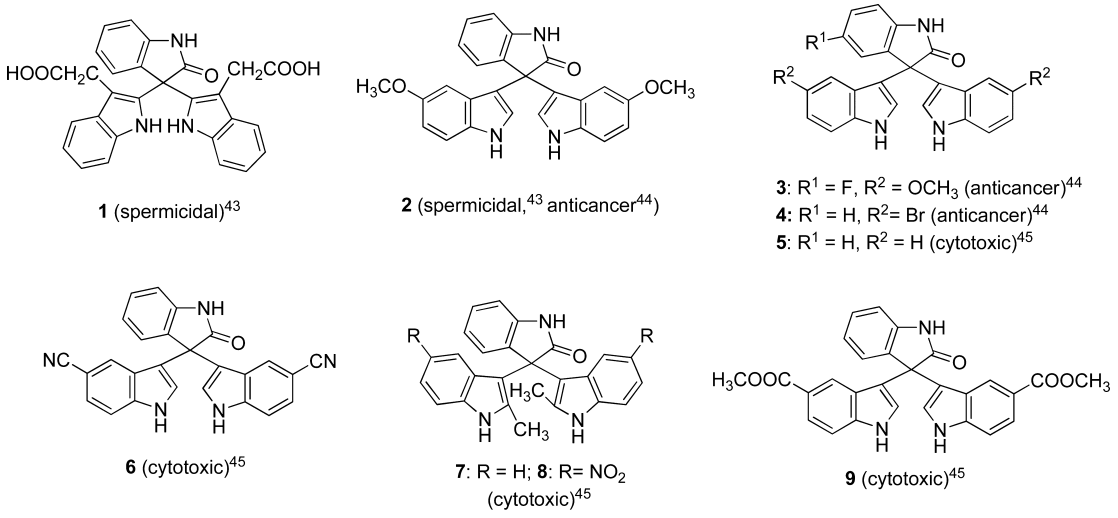


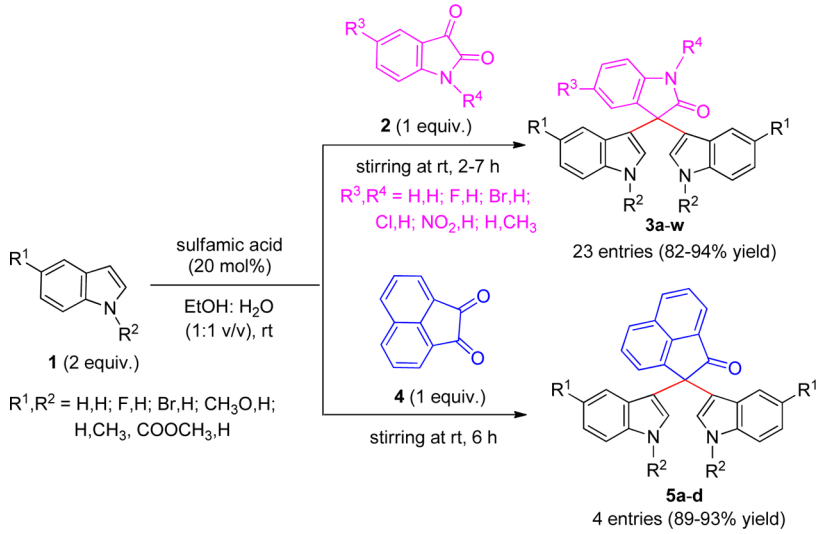
Figure 2. Representative examples of pharmacologically active synthetic 3,3-bis(indol-3-yl)indolinones.[43−45]

involves a pseudo-three-component tandem reaction of different indoles and isatin using a number of homo- and heterogeneous catalysts such as I_2,[43,45] $FeCl_3$,[44] amberlyst 15,[46] $H_6P_2W_{18}O_{62}$,[47] cellulose sulfuric acid,[48] tungstic acid,[49] KSF,[50] CAN,[51] montmorillonite K10 clay,[52] KAl$(SO_4)_2.12H_2O$,[53] β-cyclodextrin,[54] $ZrO_2/S_2O_8^{2-}$ solid superacid,[55] ionic liquids,[56,57] and silica-supported indium(III) acetylacetonate.[58] Although these protocols reported by others find certain merits of their own, still they suffer from a number of demerits such as long reaction time, harsh reaction conditions, heating, toxic organic solvents, and expensive catalyst/reagents. Besides, most of these reported methods involve the use of a limited number of isatin derivatives (mainly, isatin). Therefore, a search for a more general, clean, efficient, and eco-friendly high-yielding route to the synthesis of diverse 3,3-bis(indol-3-yl)indolin-2-one scaffolds remains a valid exercise.

Sulfamic acid (NH_2SO_3H) is a commercially available, inexpensive, and eco-friendly substance that has found considerable catalytic applications in organic transformations in recent time. It exists in the zwitterionic state rather than the aminosulfonic acid form as evidenced from X-ray and neutron diffraction experiments.[59] Sulfamic acid has been successfully used as an effective catalyst in carrying out certain useful organic reactions including Friedel−Crafts reaction,[60] Aldol condensation,[61] Michael addition,[62] Mannich-type reactions,[63−65] Strecker reaction,[66] Biginelli reaction,[67] one-pot synthesis of triazolo[5,1-*b*] quinazolines,[68] dihydropyridines,[69] 1,4-dihydropyrano[2,3-*c*]pyrazoles,[70] esterification reaction,[71] and many others.[72−78] This successful prehistory of sulfamic acid as a commercially available low-cost and environmentally benign ogano-catalyst with an intrinsic zwitterionic property encouraged us to investigate its further applications in some other carbon−carbon bond forming reactions. In this paper, we wish to extend the synthetic applicability of this unique catalyst in the one-pot synthesis of both the 3,3-bis(indol-3-yl)indolin-2-one (**3**) and 2,2-di(1*H*-indol-3-yl)acenaphthylen-1(2*H*)-one (**5**) scaffolds of pharmacological interest under the same optimized reaction conditions.

In recent times, multicomponent reactions (MCRs) have gained eminence as a synthetic tool for producing structurally complex molecular entities with attractive biological features through the formation and breakage of several carbon−carbon and carbon−heteroatom bonds in one pot.[79−92] It is becoming increasingly important both in academia and in industry to design less toxic and more environmentally friendly MCRs. In

Scheme 1. One-Pot Synthesis of Functionalized 3,3-Bis(indol-3-yl)indolin-2-ones (3a−3w) and 2,2-Bis(indol-3-yl)acenaphthylen-1(2*H*)-one derivatives (5a−5d)



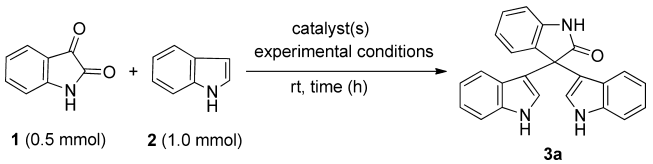
addition, implementation of several transformations in a single manipulation in the MCR strategy is highly compatible with the goals of sustainable and "*green*" chemistry.[93,94] As part of our continuing efforts to develop green synthetic methodologies for useful organic transformations,[95−109] herein, we wish to report a straightforward, efficient, clean, and high-yielding one-pot pseudo-multicomponent reaction protocol for synthesis of a series of functionalized 3,3-bis(indol-3-yl)indolin-2-ones (**3**) and 2,2-di(1*H*-indol-3-yl)acenaphthylen-1(2*H*)-ones (**5**) from the condensation reaction between different indoles and a variety of isatins/acenaphthaquinone in aqueous ethanol at room temperature using commercially available sulfamic acid as the inexpensive, reusable, and environmentally benign organo-catalyst. The results are summarized in Scheme 1 and Tables 1 and 2.

EXPERIMENTAL SECTION

General. Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using a KBr disc. ^{1}H and ^{13}C NMR spectra were obtained at 500 and 400 MHz and 125 and 100 MHz, respectively, using Bruker DRX- 500 and Bruker DRX- 400 spectrometers and DMSO-d_6 as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 microanalyzer instrument. Melting point was recorded on a Chemiline CL-726 melting point apparatus and is uncorrected. Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates.

General Procedure for Synthesis of 3,3-Bis(indol-3-yl)-indolin-2-ones (3) and 2,2-Bis(indol-3-yl)acenaphthylen-1(2*H*)-ones (5). An oven-dried screw cap test tube was charged with a magnetic stir bar, indole (**1**, 1 mmol), isatin (**2**, 0.5 mmol)/acenaphthylene-1,2-dione (**4**, 0.5 mmol), sulfamic acid (20 mol % as organo-catalyst), and EtOH: H_2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for an appropriate range of time as indicated in Table 2. The progress of the reaction was monitored by TLC. On completion of the reaction, a solid mass precipitated out that was filtered followed by washing with aqueous ethanol to obtain crude product (**3**/**5**) purified just by recrystallization from ethanol without carrying out column chromatography. The filtrate containing residual solvent, catalyst, and substrates obtained upon filtration of the reaction mixture after completion of the reaction could be successfully reused for a particular entry up to three times without appreciable loss of catalytic activity. The structure of each of the purified products (**3**/**5**) was confirmed by analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR, and TOF-MS (Supporting Information).

Table 1. Optimization of Reaction Conditions in Synthesis of 3,3-Bis(indol-3-yl)indolin-2-ones

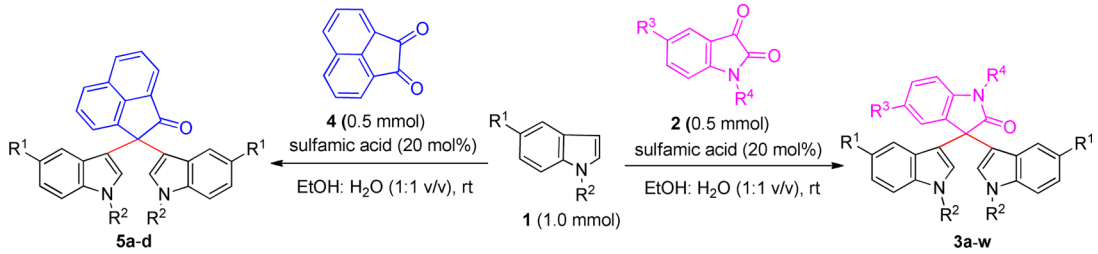


entry	catalyst	solvent	time (h)	yield (%)[a,b]
1	no catalyst	no solvent	10	0
2	sulfamic acid (20 mol %)	no solvent	10	46
3	sulfamic acid (20 mol %)	EtOH	6	72
4	sulfamic acid (20 mol %)	MeOH	6	79
5	sulfamic acid (20 mol %)	H_2O	10	66
6	**sulfamic acid (20 mol %)**	**EtOH:H_2O (1:1 v/v)**	**2**	**89**
7	no catalyst	EtOH:H_2O (1:1 v/v)	10	0
8	sulfamic acid (10 mol %)	EtOH:H_2O (1:1 v/v)	4.5	87
9	sulfamic acid (25 mol %)	EtOH:H_2O (1:1 v/v)	2	91
10	no catalyst	H_2O	10	0

[a]Reaction Conditions: Isatin (**1**, 0.5 mmol) and indole (**2**, 1 mmol) in the presence or absence of sulfamic acid in neat/4 mL of water/ethanol/methanol/ethanol−water at room temperature. [b]Isolated yields.

Characterization Data of New Entries. *5,5″-Difluoro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one (**3b**).* White solid. Yield 87%. Mp: 291−293 °C. IR (KBr) ν_{max}/cm^{-1}: 3424, 3384, 3316, 3122, 1683, 1624, 1581, 1484, 1471, 1454, 1389, 1344, 1295, 1240, 1215, 1187, 1163, 1122, 1105, 1071, 944, 916, 890, 806, 796, 749. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 11.11 (2H, s, -N*H*), 10.67 (s, 1H, -N*H*), 7.37 (2H, dd, J = 9.0, 5, and 4.5 Hz, aromatic H), 7.26−7.22 (2H, m, aromatic H), 7.01 (1H, d, J = 8.0 Hz, aromatic H), 6.98 (1H, d, J = 7.5

Table 2. One-Pot Synthesis of Functionalized 3,3-Bis(indol-3-yl)indolin-2-ones (3a−3w) and 2,2-Bis(indol-3-yl)acenaphthylen-1(2*H*)-one derivatives (5a−5d)



	indole (1)		isatin (2)						melting point (°C)	
entry	R^1	R^2	R^3	R^4	acenaphtha-quinone (4)	product (3/5)	Time (h)	yield (%)[a,b]	found	ref
1	H	H	H	H	–	**3a**	2	89	>300	311−313[46]
2	F	H	H	H	–	**3b**	3	87	291−293	–
3	CH_3O	H	H	H	–	**3c**	2	94	290−292	292−294[58]
4	Br	H	H	H	–	**3d**	4	92	>300	298−300[50]
5	H	CH_3	H	H	–	**3e**	3	88	>300	334−336[46]
6	H	H	F	H	–	**3f**	4	94	299−300	–
7	F	H	F	H	–	**3g**	3	92	>300	–
8	CH_3O	H	F	H	–	**3h**	2	91	270−272	–
9	H	CH_3	F	H	–	**3i**	3	82	>300	–
10	H	H	Cl	H	–	**3j**	3	86	294−296	295−297[50]
11	H	CH_3	Cl	H	–	**3k**	3	94	>300	–
12	F	H	Cl	H	–	**3l**	4	92	>300	–
13	H	H	Br	H	–	**3m**	7	88	>300	310−312[58]
14	CH_3O	H	Br	H	–	**3n**	2	91	283−285	–
15	H	CH_3	Br	H	–	**3o**	3	87	>300	325−326[46]
16	F	H	Br	H	–	**3p**	6	84	>300	–
17	H	H	NO_2	H	–	**3q**	6	90	298−299	296−298[58]
18	F	H	NO_2	H	–	**3r**	3	87	>300	–
19	CH_3O	H	NO_2	H	–	**3s**	2	92	286−288	–
20	H	H	H	CH_3	–	**3t**	2	91	290−291	291−292[46]
21	CH_3O	H	H	CH_3	–	**3u**	2	89	238−240	236−240[49]
22	F	H	H	CH_3	–	**3v**	2	94	>300	–
23	$COOCH_3$	H	H	H	–	**3w**	3	88	>300	–
24	CN	H	H	H	–	**3x**	12	0	–	–
25	H	H	–	–	**4**	**5a**	6	91	242−244	–
26	H	CH_3	–	–	**4**	**5b**	6	90	286−288	–
27	F	H	–	–	**4**	**5c**	6	93	268−270	–
28	OCH_3	H	–	–	**4**	**5d**	6	89	284−286	–
29	CN	H	–	–	**4**	**5e**	12	0	–	–
30	NO_2	H	–	–	**4**	**5f**	12	0	–	–

[a]Reaction conditions: Indoles (**1**, 1 mmol), isatins (**2**, 0.5 mmol)/acenaphthylene-1,2-dione (**4**, 0.5 mmol), and 20 mol % sulfamic acid as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

Hz, aromatic H), 6.96 (2H, br s, aromatic H), 6.90−6.85 (4H, m, aromatic H). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.58, 157.19, 155.35, 141.32, 133.93, 133.71 (2C), 128.19, 126.35 (2C), 125.88, 125.80, 124.97, 121.81, 114.28, 114.25, 112.80, 112.72, 109.84, 109.49, 109.28, 105.25, 105.06, 52.27. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{24}H_{15}F_2N_3ONa$ 422.1081. Found 422.1078. Elemental analysis: Calcd (%) for $C_{24}H_{15}F_2N_3O$: C, 72.17; H, 3.79; N, 10.52. Found: C, 72.15; H, 3.81; N, 10.50.

5′-Fluoro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3f).*** White solid. Yield 94%. Mp: 299−300 °C. IR (KBr) ν_{max}/cm^{-1}: 3437, 3389, 3317, 3119, 3057, 1692, 1626, 1609, 1482, 1453, 1416, 1337, 1261, 1250, 1174, 1128, 1104, 1013, 976, 861, 817, 795, 750, 734. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 11.11 (2H, s, -N*H*), 10.76 (1H, s, -N*H*), 7.48 (2H, d, J = 8.5 Hz, aromatic H), 7.33 (2H, d, J = 8.0 Hz, aromatic H), 7.19 (2H, td, J = 9.0, 3.0, and 2.4 Hz, aromatic H), 7.14 (2H, t, J = 7.5 Hz, aromatic H), 7.11 (1H, t, J = 4.5 and 4.0 Hz, aromatic H), 7.01 (2H, d, J = 2.0 Hz, aromatic H), 6.93 (2H, t, J = 8.0 and 7.0 Hz, aromatic H). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.79, 158.87, 156.99, 136.98 (2C), 136.36, 125.58 (2C), 124.46 (2C), 121.16 (2C), 120.62 (2C), 118.48 (2C), 114.41, 114.22, 113.72 (2C), 112.53, 112.34, 111.78 (2C), 53.12. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{24}H_{16}FN_3ONa$ 404.1175. Found 404.1172. Elemental analysis: Calcd (%) for $C_{24}H_{16}FN_3O$: C, 75.58; H, 4.23; N, 11.02. Found: C, 75.54; H, 4.22; N, 11.07.

5,5′,5″-Trifluoro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3g).*** White solid. Yield 92%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3425, 3373, 3296, 3121, 1689, 1630, 1611, 1580, 1482, 1454, 1344, 1296, 1262, 1243, 1181, 1134, 1107, 1072, 944, 928, 867, 844, 806, 792, 747. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 11.27 (2H, s, -N*H*), 10.83 (s, 1H, -N*H*), 7.49 (2H, dd, J = 8.75, 5.0, and 4.5 Hz, aromatic H), 7.22 (1H, td, J = 9.5 and 2.0 Hz, aromatic H), 7.14 (2H, dd, J = 8.0 and 3.0 Hz, aromatic H), 7.10 (2H, d, J = 3.0 Hz, aromatic H), 7.01 (2H, td, J = 9.0, 2.5, and 2.0 Hz, aromatic H), 6.96 (2H, dd, J = 10.5 and 2.5 Hz, aromatic H). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.58, 158.99, 157.24, 157.10, 155.41, 137.43, 135.58, 135.52, 133.66, 126.44, 125.67, 125.59, 114.75, 114.57, 113.61, 113.58, 112.93, 112.86, 112.58,

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112.38, 110.81, 110.75, 109.66, 109.45, 105.07, 104.88, 52.27. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{14}F_3N_3ONa$ 440.0987. Found 440.0985. Elemental analysis: Calcd (%) for $C_{24}H_{14}F_3N_3O$: C, 69.06; H, 3.38; N, 10.07. Found: C, 69.03; H, 3.41; N, 10.03.

5′-Fluoro-5,5″-dimethoxy-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3h)***. White solid. Yield 91%. Mp: 270−272 °C. IR (KBr) ν_{max}/cm^{-1}: 3371, 3339, 3120, 2933, 2832, 1693, 1624, 1581, 1483, 1456, 1348, 1297, 1262, 1212, 1181, 1129, 1105, 1080, 1043, 1022, 977, 932, 873, 827, 810, 794, 749. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 10.96 (2H, s, -N*H*), 10.77 (1H, s, -N*H*), 7.39 (2H, d, J = 9.0 Hz, aromatic H), 7.21 (1H, td, J = 9.0, 2.5, and 2.0 Hz, aromatic H), 7.13 (1H, q, J = 4.5, and 4.0 Hz, aromatic H), 7.10 (1H, dd, J = 8.0 and 2.5 Hz, aromatic H), 7.00 (2H, d, J = 2.5 Hz, aromatic H), 6.83 (2H, dd, J = 8.5, 2.5, and 2.0 Hz, aromatic H), 6.78 (2H, d, J = 2.0 Hz, aromatic H), 3.64 (6H, s, 2 × -OC*H*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.86, 158.92, 157.03, 152.60 (2C), 137.64, 136.31, 136.25, 132.23 (2C), 125.99 (2C), 125.33 (2C), 114.44, 114.26, 113.01 (2C), 112.53, 112.31, 110.61 (2C), 103.20 (2C), 55.21 (2C), 53.12. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}FN_3O_3Na$ 464.1386. Found 464.1384. Elemental analysis: Calcd (%) for $C_{26}H_{20}FN_3O_3$: C, 70.74; H, 4.57; N, 9.52. Found: C, 70.71; H, 4.59; N, 9.49.

5′-Fluoro-1,1″-dimethyl-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3i)***. White solid. Yield 82%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3364, 3124, 3060, 2932, 1713, 1686, 1628, 1548, 1539, 1483, 1426, 1370, 1333, 1291, 1263, 1203, 1181, 1132, 1075, 1015, 975, 938, 887, 865, 830, 817, 795, 749. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 10.68 (1H, s, -N*H*), 7.39 (2H, d, J = 8.0 Hz, aromatic H), 7.26 (2H, d, J = 8.0 Hz, aromatic H), 7.10 (2H, t, J = 8.0 and 7.5 Hz, aromatic H), 7.06 (2H, dd, J = 5.5, 2.5, and 3.0 Hz, aromatic H), 6.99 (1H, dd, J = 8.5 and 4.5 Hz, aromatic H), 6.95 (2H, s, aromatic H), 6.87 (2H, t, J = 8.0 and 7.0 Hz, aromatic H), 3.71 (6H, s, 2 × −C*H*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.55, 158.90, 157.02, 137.58, 137.43 (2C), 136.30, 136.24, 128.68 (2C), 125.97 (2C), 121.26, 120.86, 118.64 (2C), 114.48, 114.29, 112.87 (2C), 112.62, 112.42, 110.53, 109.93 (2C), 53.01, 32.43 (2C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}FN_3ONa$ 432.1488. Found 432.1483. Elemental analysis: Calcd (%) for $C_{26}H_{20}FN_3O$: C, 76.27; H, 4.92; N, 10.26. Found: C, 76.24; H, 4.95; N, 10.27.

5′-Chloro-1,1″-dimethyl-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3k)***. White solid. Yield 94%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3246, 3055, 2930, 1717, 1612, 1535, 1475, 1246, 1194, 1177, 1068, 1016, 870, 816, 748. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 10.81 (1H, s, -N*H*), 7.39 (2H, d, J = 8.0 Hz, aromatic H), 7.30 (1H, dd, J = 8.4 and 2.0 Hz, aromatic H), 7.22−7.19 (3H, m, aromatic H), 7.10 (2H, t, J = 7.6 Hz, aromatic H), 7.03 (1H, d, J = 8.0 Hz, aromatic H), 6.93 (2H, br s, aromatic H), 6.86 (2H, t, J = 7.6 Hz, aromatic H), 3.68 (6H, s, 2 × −C*H*$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 178.68, 140.52, 137.72 (2C), 136.86, 128.91 (2C), 128.37, 126.19 (2C), 126.00, 125.04, 121.68 (2C), 121.04 (2C), 119.04 (2C), 112.97 (2C), 111.66, 110.35 (2C), 53.06, 32.77 (2C). HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}ClN_3ONa$ 448.1193. Found 448.1191. Elemental analysis: Calcd (%) for $C_{26}H_{20}ClN_3O$: C, 73.32; H, 4.73; N, 9.87. Found: C, 73.33; H, 4.71; N, 9.89.

5′-Chloro-5,5″-difluoro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3l)***. White solid. Yield 93%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3414, 3350, 3119, 1699, 1624, 1578, 1533, 1474, 1296, 1236, 1177, 1113, 1068, 937, 806, 752. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 11.20 (2H, s, -N*H*), 10.86 (s, 1H, -N*H*), 7.40 (2H, dd, J = 8.8 and 3.0 Hz, aromatic H), 7.33 (1H, dd, J = 8.0 and 2.0 Hz, aromatic H), 7.20 (1H, d, J = 2.0 Hz, aromatic H), 7.05 (1H, d, J = 8.4 Hz, aromatic H), 7.01 (2H, d, J = 2.4 Hz, aromatic H), 6.91 (2H, td, J = 8.8, 2.8, and 2.4 Hz, aromatic H), 6.86 (2H, dd, J = 10.4, 2.8, and 2.4 Hz, aromatic H). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 178.59, 157.83, 155.53, 140.61, 136.22, 134.06 (2C), 128.58, 126.86 (2C), 126.13, 126.01, 125.91, 125.12, 113.82, 113.78, 113.32, 113.22, 111.77, 110.02, 109.76, 105.42, 105.19, 52.87. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{14}ClF_2N_3ONa$ 456.0691. Found 456.0689. Elemental analysis: Calcd (%) for $C_{24}H_{14}ClF_2N_3O$: C, 66.44; H, 3.25; N, 9.69. Found: C, 66.41; H, 3.26; N, 9.71.

5′-Bromo-5,5″-dimethoxy-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3n)***. White solid. Yield 91%. Mp: 283−285 °C. IR (KBr) ν_{max}/cm^{-1}: 3368, 2936, 2854, 1693, 1619, 1580, 1506, 1479, 1454, 1439, 1344, 1294, 1247, 1210, 1176, 1104, 1080, 1046, 1023, 929, 874, 805, 750. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 10.98 (2H, s, -N*H*), 10.91 (1H, s, -N*H*), 7.55 (1H, d, J = 7.5 Hz, aromatic H), 7.41−7.38 (3H, m, aromatic H), 7.12 (1H, d, J = 8.0 Hz, aromatic H), 7.00 (2H, br s, aromatic H), 6.84 (2H, d, J = 8.5 Hz, aromatic H), 6.74 (2H, br s, aromatic H), 3.64 (6H, s, 2 × -OC*H*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.48, 152.62, 140.72, 136.91, 132.21 (2C), 130.81, 127.43, 125.91 (2C), 125.33, 125.20, 113.31, 112.83 (2C), 112.41 (2C), 112.19, 111.78, 110.65, 110.50, 103.38, 103.06, 55.22 (2C), 52.81. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}BrN_3O_3Na$ 524.0586. Found 524.0588. Elemental analysis: Calcd (%) for $C_{26}H_{20}BrN_3O_3$: C, 62.16; H, 4.01; N, 8.36. Found: C, 62.18; H, 4.03; N, 8.34.

5′-Bromo-5,5″-difluoro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3p)***. White solid. Yield 84%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3416, 3346, 3118, 1698, 1618, 1580, 1484, 1472, 1456, 1429, 1343, 1295, 1243, 1225, 1179, 1122, 1105, 1072, 943, 921, 865, 840, 820, 806, 795, 749. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 11.30 (2H, s, -N*H*), 10.96 (1H, s, -N*H*), 7.57 (1H, dd, J = 8.0 and 2.0 Hz, aromatic H), 7.51 (2H, dd, J = 9.0 and 5.0 Hz, aromatic H), 7.42 (1H, d, J = 1.5 Hz, aromatic H), 7.12−7.08 (3H, m, aromatic H), 7.02 (2H, td, J = 9.5, 2.5, and 2.0 Hz, aromatic H), 6.98 (2H, dd, J = 8.0, 3.0, and 2.5 Hz, aromatic H). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.12, 157.27, 155.44, 140.69, 136.27, 133.73 (2C), 131.08, 127.47, 126.53 (2C), 125.67, 125.59, 113.51, 113.48 (2C), 112.98, 112.90, 111.97, 109.66, 109.45, 105.06, 104.87, 52.50. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{14}BrF_2N_3ONa$ 500.0186. Found 500.0183. Elemental analysis: Calcd (%) for $C_{24}H_{14}BrF_2N_3O$: C, 60.27; H, 2.95; N, 8.79. Found: C, 60.25; H, 2.98; N, 8.75.

5,5″-Difluoro-5′-nitro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3r)***. White solid. Yield 87%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3370, 3117, 1703, 1625, 1607, 1581, 1529, 1485, 1454, 1423, 1343, 1296, 1244, 1217, 1181, 1123, 1106, 1083, 944, 926, 880, 842, 806, 748. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 11.51 (1H, s, -N*H*), 11.36 (2H, s, -N*H*), 8.37 (1H, dd, J = 8.5 and 2.0 Hz, aromatic H), 8.08 (1H, d, J = 2.5 Hz, aromatic H), 7.51 (2H, dd, J = 9.0 and 4.5 Hz, aromatic H), 7.34 (1H, d, J = 8.5 Hz, aromatic H), 7.18 (2H, d, J = 2.5 Hz, aromatic H), 7.03 (2H, td, J = 9.0, 2.5, and 2.0 Hz, aromatic H), 6.96 (2H, dd, J = 10.5 and 2.0 Hz, aromatic H). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.76, 157.32, 155.49, 147.68, 142.49, 134.58, 133.79 (2C), 126.66 (2C), 125.73, 125.57, 125.49, 120.18, 113.12, 113.04, 112.80, 112.77, 110.22, 109.82, 109.61, 104.86, 104.67, 52.48. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{14}F_2N_4O_3Na$ 467.0932. Found 467.0930. Elemental analysis: Calcd (%) for $C_{24}H_{14}F_2N_4O_3$: C, 64.87; H, 3.18; N, 12.61. Found: C, 64.88; H, 3.15; N, 12.63.

5,5″-Dimethoxy-5′-nitro-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3s)***. White solid. Yield 92%. Mp: 286−288 °C. IR (KBr) ν_{max}/cm^{-1}: 3389, 3121, 2933, 2830, 1712, 1624, 1603, 1581, 1520, 1481, 1454, 1332, 1293, 1248, 1211, 1177, 1127, 1106, 1079, 1042, 1023, 950, 931, 918, 879, 843, 804, 748. ^{1}H NMR (500 MHz, DMSO-d_6) δ/ppm: 11.36 (1H, s, -N*H*), 10.95 (2H, s, -N*H*), 8.25 (1H, dd, J = 9.0, 2.5, and 2.0 Hz, aromatic H), 8.02 (1H, d, J = 2.0 Hz, aromatic H), 7.30 (2H, d, J = 8.5 Hz, aromatic H), 7.22 (1H, d, J = 9.0 Hz, aromatic H), 6.97 (2H, d, J = 2.5 Hz, aromatic H), 6.74 (2H, dd, J = 9.0, 2.5, and 2.0 Hz, aromatic H), 6.69 (2H, d, J = 2.5 Hz, aromatic H), 3.55 (6H, s, 2 × -OC*H*$_3$). ^{13}C NMR (125 MHz, DMSO-d_6) δ/ppm: 178.99, 152.75 (2C), 147.93, 142.30, 135.27, 132.36 (2C), 125.89 (2C), 125.52 (2C), 125.49, 120.18, 112.48 (2C), 112.19 (2C), 110.81 (2C), 109.88, 102.91 (2C), 55.23 (2C), 52.55. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{20}N_4O_5Na$ 491.1331. Found 491.1329. Elemental analysis: Calcd (%) for $C_{26}H_{20}N_4O_5$: C, 66.66; H, 4.30; N, 11.96. Found: C, 66.63; H, 4.32; N, 11.95.

5,5″-Difluoro-1′-methyl-1H,1″H-[3,3′:3′,3″-terindol]-2′(1′H)-one ***(3v)***. White solid. Yield 94%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3346, 3115, 2931, 1664, 1629, 1611, 1581, 1539, 1486, 1471, 1455, 1419, 1373, 1353, 1298, 1243, 1223, 1181, 1169, 1121, 1103, 1088, 1069, 1021, 947, 913, 837, 795, 747. ^{1}H NMR (400 MHz, DMSO-d_6) δ/

ppm: 11.15 (2H, s, -NH-), 7.39−7.35 (3H, m, aromatic H), 7.29 (1H, d, J = 7.2 Hz, aromatic H), 7.19 (1H, d, J = 8.0 Hz, aromatic H), 7.06 (1H, t, J = 7.6 and 7.2 Hz, aromatic H), 6.95 (2H, d, J = 2.4 Hz, aromatic H), 6.88 (2H, td, J = 8.8, 2.4, and 2.0 Hz, aromatic H), 6.79 (2H, dd, J = 10.4 and 2.0 Hz, aromatic H), 3.27 (3H, s, -NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 177.02, 157.75, 155.46, 143.05, 134.03 (2C), 133.37, 128.66, 126.71 (2C), 126.14, 126.04, 124.95, 122.85, 114.30 (2C), 113.19, 113.09, 109.91, 109.65, 109.31, 105.52, 105.29, 52.17, 26.69. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{17}F_2N_3ONa$ 436.1237. Found 436.1235. Elemental analysis: Calcd (%) for $C_{25}H_{17}F_2N_3O$: C, 72.63; H, 4.14; N, 10.16. Found: C, 72.61; H, 4.11; N, 10.18.

Dimethyl 2′-oxo-1′,2′-dihydro-1H,1″H-[3,3′:3′,3″-terindole]-5,5″-dicarboxylate ***(3w)***. White solid. Yield 88%. Mp: >300 °C. IR (KBr) ν_{max}/cm^{-1}: 3340, 3236, 3025, 2949, 2865, 1697, 1610, 1447, 1358, 1273, 1119, 978, 914, 822, 758. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 11.42 (2H, s, 2 × -NH), 10.82 (1H, s, -NH), 8.06 (2H, s, aromatic H), 7.69 (2H, dd, J = 8.8, 1.6, and 1.2 Hz, aromatic H), 7.47 (2H, d, J = 8.8 Hz, aromatic H), 7.28 (1H, td, J = 7.6 and 0.8 Hz, aromatic H), 7.17 (1H, d, J = 7.2 Hz, aromatic H), 7.05 (1H, d, J = 8.0 Hz, aromatic H), 6.98 (2H, d, J = 2.4 Hz, aromatic H), 6.97 (1H, d, J = 8.0 Hz, aromatic H), 3.75 (6H, s, 2 × −$COOCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 178.78, 167.58 (2C), 141.72, 140.07 (2C), 134.18, 128.71, 126.68 (2C), 125.53 (2C), 125.24, 123.94 (2C), 122.54 (2C), 122.19, 120.39 (2C), 116.15 (2C), 112.17 (2C), 110.28, 52.78, 52.05 (2C). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{28}H_{21}N_3O_5Na$ 502.1379. Found 502.1376. Elemental analysis: Calcd (%) for $C_{28}H_{21}N_3O_5$: C, 70.14; H, 4.41; N, 8.76. Found: C, 70.11; H, 4.43; N, 8.74.

2,2-Di(1H-indol-3-yl)acenaphthylen-1(2H)-one ***(5a)***. Yellow solid. Yield 91%. Mp: 242−244 °C. IR (KBr) ν_{max}/cm^{-1}: 3416, 3358, 3121, 3053, 1728, 1684, 1603, 1593, 1421, 1340, 1244, 1095, 1007, 834, 788, 744.^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 11.00 (2H, s, -NH), 8.36 (1H, d, J = 8.4 Hz, aromatic H), 8.01 (2H, d, J = 7.6 Hz, aromatic H), 7.90 (2H, q, J = 8.4 and 7.6 Hz, aromatic H), 7.69 (1H, t, J = 7.6 Hz, aromatic H), 7.56 (1H, d, J = 6.8 Hz, aromatic H), 7.36 (2H, d, J = 8.0 Hz, aromatic H), 7.03−6.99 (3H, m, aromatic H), 6.85 (1H, d, J = 2.4 Hz, aromatic H), 6.75 (2H, t, J = 7.6 Hz, aromatic H). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 203.07, 144.28, 140.01, 137.38 (2C), 132.69, 132.46, 131.93, 130.94, 130.88, 129.41, 129.32, 129.26, 128.89, 126.18, 125.08, 124.50, 122.64, 122.12, 121.68, 121.42, 121.01, 118.79, 115.25, 112.10 (2C), 58.09. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{28}H_{18}N_2ONa$ 421.1317. Found 421.1314. Elemental analysis: Calcd (%) for $C_{28}H_{18}N_2O$: C, 84.40; H, 4.55; N, 7.03. Found: C, 84.38; H, 4.53; N, 7.08.

2,2-Bis(1-methyl-1H-indol-3-yl)acenaphthylen-1(2H)-one ***(5b)***. Yellow solid. Yield 90%. Mp: 286−288 °C. IR (KBr) ν_{max}/cm^{-1}: 3053, 2934, 1718, 1609, 1539, 1475, 1421, 1367, 1329, 1250, 1207, 1159, 1128, 1067, 1013, 793, 743. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.36 (1H, d, J = 7.6 Hz, aromatic H), 8.01 (2H, d, J = 6.4 Hz, aromatic H), 7.89 (1H, t, J = 6.8 Hz, aromatic H), 7.69 (1H, t, J = 8.0 and 7.2 Hz, aromatic H), 7.56 (1H, d, J = 6.0 Hz, aromatic H), 7.37 (2H, d, J = 7.6 Hz, aromatic H), 7.05 (4H, t, J = 8.4 Hz, aromatic H), 6.88 (2H, br s), 6.79 (2H, t, J = 7.2 and 6.0 Hz, aromatic H), 3.67 (6H, s, 2 × -NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 202.87, 144.09, 139.93, 137.77 (2C), 132.55, 130.91, 129.50, 129.30, 129.22 (2C), 126.51 (2C), 124.58 (2C), 122.77, 122.13, 121.57 (2C), 121.17 (2C), 118.98 (2C), 114.34 (2C), 110.27 (2C), 57.86, 32.74 (2C). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{30}H_{22}N_2ONa$ 449.1630. Found: 449.1628. Elemental analysis: Calcd (%) for $C_{30}H_{22}N_2O$: C, 84.48; H, 5.20; N, 6.57. Found: C, 84.46; H, 5.17; N, 6.59.

2,2-Bis(5-fluoro-1H-indol-3-yl)acenaphthylen-1(2H)-one ***(5c)***. Yellow solid. Yield 93%. Mp: 268−270 °C. IR (KBr) ν_{max}/cm^{-1}: 3410, 3348, 3119, 3053, 2946, 1726, 1676, 1587, 1477, 1348, 1238, 1177, 1084, 1001, 935, 789.^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 11.18 (1H, s, -NH), 11.17 (1H, s, -NH), 8.38 (1H, d, J = 8.0 Hz, aromatic H), 8.04 (2H, dd, J = 7.6 and 1.2 Hz, aromatic H), 7.91 (1H, t, J = 7.6 Hz, aromatic H), 7.72 (1H, t, J = 8.0 and 7.2 Hz, aromatic H), 7.58 (1H, d, J = 6.8 Hz, aromatic H), 7.37 (2H, dd, J = 8.8 and 4.8 Hz, aromatic H), 6.97 (2H, d, J = 2.4 Hz, aromatic H), 6.88 (2H, td, J = 9.2, 2.8, and 2.4 Hz, aromatic H), 6.66 (2H, dd, J = 10.4 and 2.4 Hz, aromatic H). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 202.94, 157.79, 155.49, 143.50, 139.98, 134.08 (2C), 132.74, 132.69, 131.57, 130.89, 129.55, 129.40, 128.88, 127.01 (2C), 126.21, 124.76, 122.93, 122.17, 121.68, 115.09, 115.05, 113.29, 113.19, 109.94, 109.68, 105.41, 105.17, 57.65. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{28}H_{16}F_2N_2ONa$ 457.1128. Found: 457.1125. Elemental analysis: Calcd (%) for $C_{28}H_{16}F_2N_2O$: C, 77.41; H, 3.71; N, 6.45. Found: C, 77.38; H, 3.69; N, 6.48.

2,2-Bis(5-methoxy-1H-indol-3-yl)acenaphthylen-1(2H)-one ***(5d)***. Yellow solid. Yield 89%. Mp: 284−286 °C. IR (KBr) ν_{max}/cm^{-1}: 3389, 3130, 3055, 2932, 2826, 1707, 1614, 1585, 1481, 1447, 1350, 1215, 1169, 1030, 928, 812, 789. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 10.84 (2H, s, -NH), 8.37 (1H, d, J = 8.0 Hz, aromatic H), 8.01 (2H, d, J = 7.6, aromatic H), 7.91 (1H, q, J = 7.6 and 7.2 Hz, aromatic H), 7.71 (1H, t, J = 8.4 and 6.8 Hz, aromatic H), 7.54 (1H, d, J = 6.8 Hz, aromatic H), 7.26 (2H, d, J = 8.8 Hz, aromatic H), 6.86 (2H, d, J = 2.0 Hz, aromatic H), 6.68 (2H, dd, J = 8.8, 2.0, and 1.6 Hz, aromatic H), 6.42 (2H, d, J = 1.2 Hz), 3.40 (6H, s, 2 × -NCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 203.28, 152.86 (2C), 144.16, 140.09, 132.73, 132.60 (2C), 132.47, 132.07, 130.83, 129.48, 129.26, 128.91, 126.56, 125.85 (2C), 124.48, 122.51, 122.16, 121.71, 114.58 (2C), 112.61, 110.84, 103.53 (2C), 58.00, 55.34 (2C). HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{30}H_{22}N_2O_3Na$ 481.1528. Found: 481.1531. Elemental analysis: Calcd (%) for $C_{30}H_{22}N_2O_3$: C, 78.59; H, 4.84; N, 6.11. Found: C, 78.62; H, 4.81; N, 6.13.

RESULTS AND DISCUSSION

Herein, we report a facile access of a series of functionalized 3,3-bis(indol-3-yl)indolin-2-one scaffolds (**3a**−**3w**) and 2,2-bis(indol-3-yl)acenaphthylen-1(2*H*)-one derivatives (**5a**−**5d**) via pseudo-multicomponent one-pot synthesis from the reaction of indole (**1**, 1 mmol), respectively, with isatin (**2**, 0.5 mmol) or acenaphthaquinone (**4**, 0.5 mmol) in aqueous ethanol at room temperature using commercially available sulfamic acid as the inexpensive and environmentally benign organo-catalyst (Scheme 1).

To optimize the reaction conditions, we first conducted a series of trial reactions with indole (**1**, 1 mmol) and isatin (**2**, 0.5 mmol) in the absence or presence of sulfamic acid using water, ethanol, methanol, and/or ethanol−water (1:1 v/v) as solvent at room temperature (Table 1). From these preliminary experiments, 20 mol % of sulfamic acid in aqueous ethanol (1:1 v/v) at room temperature were determined as the optimized conditions for the reaction in terms of yield and time (Table 1, entry 6) for the desired product, 3,3-bis(indol-3-yl)indolin-2-one (**3a**), which was characterized by its physical and spectral properties.[46]

Under the optimized conditions, the reaction of 5-fluoroindole with isatin was then carried out, and it furnished the product 3,3-bis(5-fluoroindol-3-yl)indolin-2-one (**3b**) in 87% yield within 3 h (Table 2, entry 2). To check the generality as well as the scope of our newly developed method, a range of indoles (substituted at both its 1 and 5-positions) having substituents such as methyl, methoxy, carbomethoxy, and halogens were reacted with a variety of isatin derivatives under identical reaction conditions; all of them underwent the reaction smoothly furnishing the desired products of 3,3-bis(indol-3-yl)indolin-2-ones (**3c**−**3w**) (Table 2, entries 3−23) in excellent yields (82−94%) at room temperature within 2−7 h. However, 5-cyanoindole was observed not to undergo the reaction with isatin under these conditions, and no desired product was isolated even after continuing the process up to 12 h. This is possibly due to the strong electron-withdrawing effect

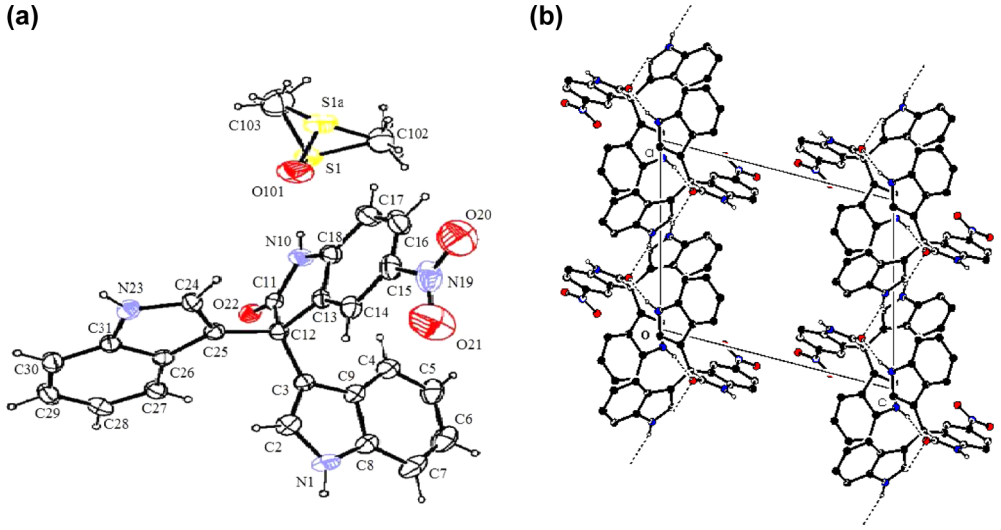
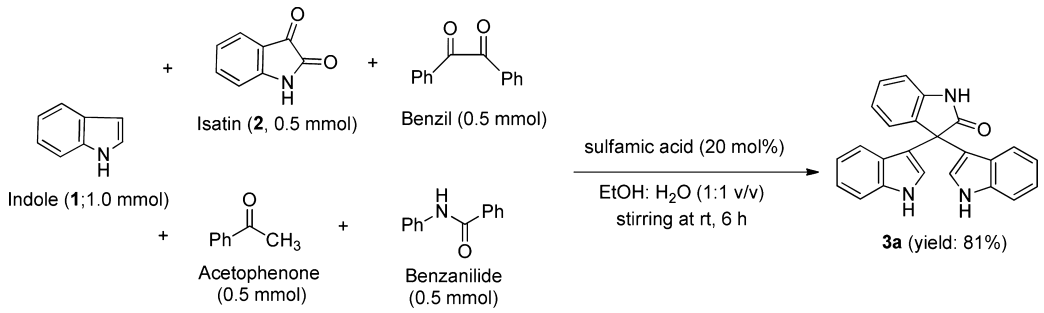


Figure 3. (a) ORTEP diagram of compound **3q** (in DMSO) (CCDC 1017941). (b) Packing arrangement of molecules viewed down the *b*-axis.

Scheme 2. Effect of Catalyst on Substrate Selectivity[a,b]



[a]Reaction Conditions: Indole (**1**, 1 mmol), isatin (**2**, 0.5 mmol), acetophenone (0.5 mmol), benzil (0.5 mmol), benzanilide (0.5 mmol), and 20 mol % sulfamic acid as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature; [b]Isolated yield.

of the 5-cyano group that eventually diminishes the nucleophilicity of indole nucleus.

To our delight, the optimized reaction conditions worked satisfactorily also in affording 2,2-bis(indol-3-yl)acenaphthylen-1(2*H*)-ones (**5a**−**5d**) in one-pot when the reaction was carried out in the presence of acenaphthylene-1,2-dione (**4**) instead of isatin (**2**). The desired products were isolated with excellent yield of 90−93% within 6 h. On studying the effect of strong electron-withdrawing substituents in the indole nucleus, we obtained the expected results in compliance with the aforementioned observation. Herein also, 5-cyanao- and 5-nitro-indoles did not take part in the reaction with acenaphthaquinone, and no desired product was isolated even after 12 h of reaction.

All products (**3** and **5**) were isolated pure just by washing with aqueous ethanol followed by recrystallization from ethanol; no tedious chromatographic purification was needed. The isolated products were fully characterized on the basis of analytical data and detailed spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR, and TOF-MS. All known compounds had physical and spectroscopic data identical to the literature values.[46,49,50,58] We have been successful in developing unit crystals for 5′-nitro-1*H*,1″*H*-[3,3′:3′,3″-terindol]-2′(1′*H*)-one (**3q**) (Table 2, entry 17), and single crystal X-ray analysis for the compound was documented in this paper (Figure 3).[110]

To study the substrate selectivity of this method, we carried out a competitive reaction of indole (**1**, 1 mmol) with the mixture of a number of carbonyl compounds (0.5 mmol each) such as isatin (**2**), benzil, acetophenone, and benzanilide, using 20 mol % of sulfamic acid as the catalyst in aqueous ethanol (1:1) at room temperature. Interestingly, only the desired product 3,3-bis(indol-3-yl)indolin-2-one (**3a**) was isolated as a sole product with 81% yield at 6 h, and the other starting carbonyl compounds were recovered intact (Scheme 2). Hence, the catalyst seems to have a preferential substrate-selective property.

We herein propose a mechanism for the formation of the 3,3-bis(indol-3-yl)indolin-2-one entity; sulfamic acid in its zwitterionic form activates isatin molecule (**2**), thereby facilitating a nucleophilic attack by the indole (**1**) through its C-3 carbon to the electron deficient carbonyl center of **2** to generate species **6**, followed by its dehydration to **9**. The nucleophilic addition of the second molecule of indole (**1**) to **9** eventually afforded the desired product **3** (Scheme 3).

It is worth noting that we successfully reused the reaction media containing residual solvent, catalyst, and substrates obtained upon filtration of the reaction mixture after completion of the reaction up to the third run in the case of both isatin and acenaphthaquinone derivatives (Table 3). The respective products, **3a** and **3j**, from the isatin series and **5a** from the acenaphthaquinone series were obtained in comparative yields in their first and second runs but in slightly reduced efficiency in the third run. This is also to be mentioned

Scheme 3. Proposed Mechanism for the Synthesis of 3,3-Bis(indol-3-yl)indolin-2-ones (3)

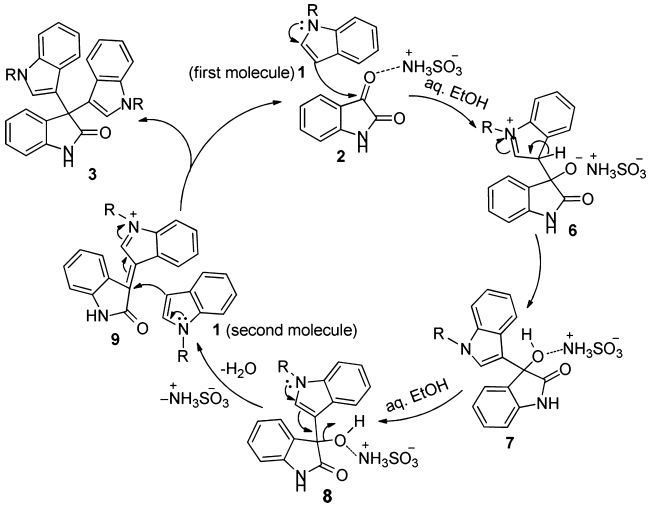


Table 3. Reuse of Reaction Media Containing Residual Solvent, Catalyst, and Substrates

	product **3a**		product **3j**		product **5a**	
no. of cycle	time (h)	yield (%)[a]	time (h)	yield (%)[a]	time (h)	yield (%)[a]
1st run	2	89	3	86	6	91
2nd run	2	82	3	79	6	84
3rd run[b]	3	79	4	71	8	66

[a]Isolated yield. [b]3rd run requires addition of 1 mL of aqueous ethanol (1:1 v/v) to compensate the solvent-loss occurred during filtrations in the earlier runs.

that each filtrate can only be used for the particular entry due to residual starting materials.

CONCLUSION

In conclusion, we have developed a very simple, facile, energy-efficient, and conveniently practical method for easy access of 3,3-bis(indol-3-yl)indolin-2-ones and 2,2-di(1*H*-indol-3-yl)-acenaphthylen-1(2*H*)-ones in the presence of sulfamic acid as a reusable organo-catalyst via a one-pot pseudo-multicomponent reaction in aqueous ethanol at room temperature. Mild reaction conditions, excellent yields, operational simplicity, absence of tedious separation procedures, clean reaction profiles, energy efficiency, and high atom-economy as well as the use of an inexpensive and environmentally benign catalyst are the key advantages of the present method. Moreover, reusability of the reaction media is an added advantage to this protocol. Keeping in mind that the synthetic importance of such biologically relevant bis-indolyl scaffolds directly relate to medicinal chemistry, the present methodology with mild reaction conditions and operational simplicity offers the possibility of its use with cost-effective and environmentally friendlier ways for large-scale industrial syntheses as well.

ASSOCIATED CONTENT

Supporting Information

Materials and apparatus, general experimental procedure, crystallographic data, spectral data, and respective scanned spectra (^{1}H- and ^{13}C NMR) of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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