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Iodine-catalyzed conjugate addition of indoles onto en-1,4-dione: A novel synthesis of 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-ones as antibacterial and antifungal agents

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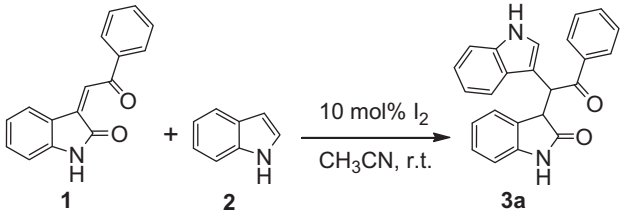
ABSTRACT

Indole and its derivatives undergo smooth conjugate addition onto en-1,4-dione derived from isatin and acetophenone, in the presence of a catalytic amount of molecular iodine in acetonitrile under mild conditions to afford a novel class of 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one derivatives in good yields with high degree of 1,4-selectivity. Some of these compounds are found to exhibit modest antibacterial and antifungal properties.

Indoles and its derivatives are found abundantly in nature and are known to exhibit potent physiological properties.[1] Therefore, the synthesis and reactions of indoles have attracted great prominence in organic synthesis.[2,3] Substituted Indoles are capable of binding to many receptors with high affinity. In particular, 3-substituted indoles are important building blocks for the synthesis of many biologically active natural products.[4] As a result, there is a growing interest in the development of improved methods for the synthesis of 3-substituted indoles.[5] Among various transformations, Lewis acid catalyzed C–C bond forming reactions are of great importance in Organic synthesis because of their high reactivity, selectivity, and mild reaction conditions.[6] Recently, molecular iodine has received considerable attention in organic synthesis because of its high tolerance to air and moisture, low-cost, nontoxic nature, and ready availability, affording the corresponding products in excellent yields. The mild Lewis acidity associated with iodine has led to its use in organic synthesis using catalytic to stoichiometric amounts.[7]

In continuation of our interest on the use of molecular iodine for various transformations,[8] we herein report for the first time, a direct and metal-free conjugate addition of indoles onto en-1,4-diketone derived from isatin and acetophenone using molecular iodine as a novel catalyst. As a preliminary experiment, en-1,4-dione (**1**) was treated with indole (**2**) in the presence of 10 mol % of molecular iodine. The reaction proceeded smoothly in acetonitrile at room temperature and the corresponding Michael adduct **3a** was obtained in 78% yield (Scheme 1).



Scheme 1. Preparation of 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one.

This result provided the incentive for further study of reactions with various indoles. Interestingly, substituted indoles such as 5-cyano-, 2-methyl-5-nitro-, 1-methyl-, 5-bromo-, 5-nitro-, methyl 5-carboxylate, 2-methyl-, 5-chloro-, and 2-phenyl derivatives reacted well with en-1,4-diketone to furnish the respective 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one deriva-

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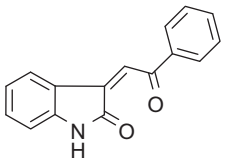
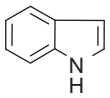
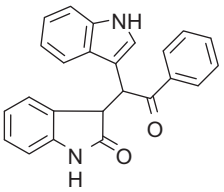
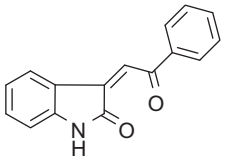
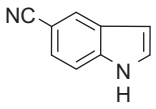
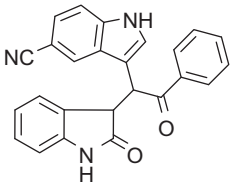
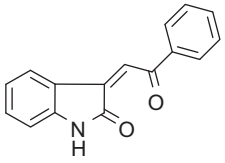
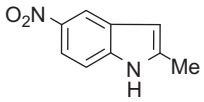
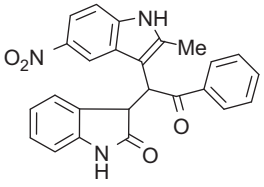
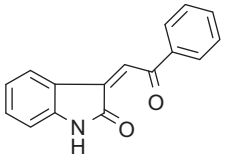
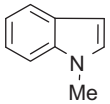
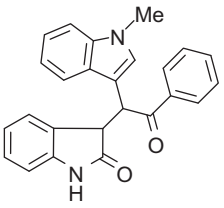
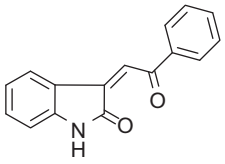
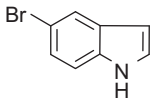
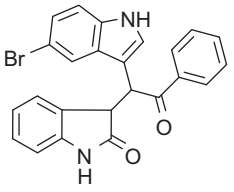
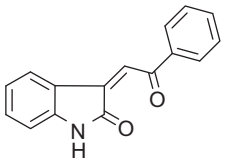
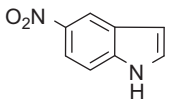
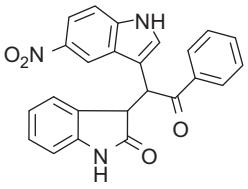
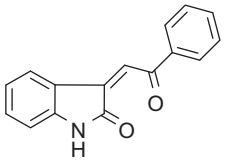
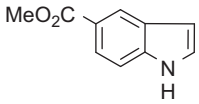
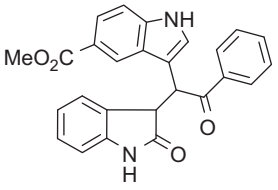
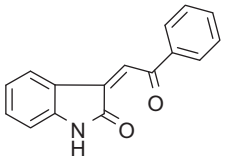
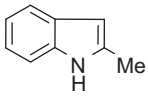
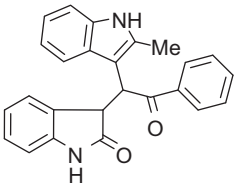
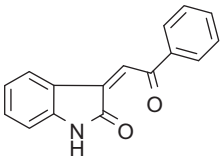
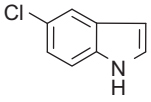
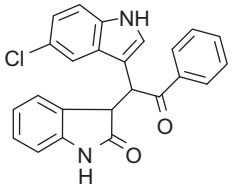
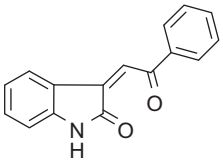
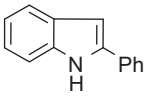
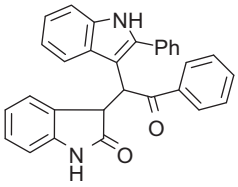
Table 1
Conjugate addition of indoles onto en-1,4-diketones

Entry	Isatin	Indole	Product[a]	Time (h)	Yield (%)[b]
a				12	78
b				15	85
c				22	84
d				18	85
e				18	90
f				20	75
g				14	82
h				18	90

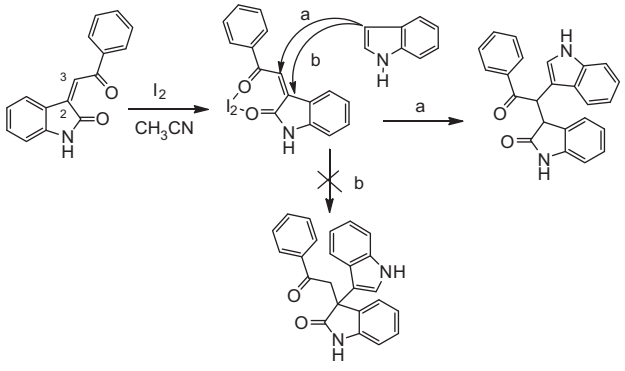
(*continued on next page*)

Table 1 (*continued*)

Entry	Isatin	Indole	Product[a]	Time (h)	Yield (%)[b]
i				18	88
j				20	80

[a] The products were characterized by NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

tives in excellent yields (Table 1, entries b–j). Notably, electron-deficient indoles such as 5-cyano-, 2-methyl-5-nitro-, 5-nitro-, and 5-methoxycarbonyl derivatives participated efficiently in this reaction under similar conditions (Table 1, entries b, c, f, and g). Furthermore, *N*-methylindole also gave the desired product in 85% yield (Table 1, entry d). This method works well with both electron rich as well as electron deficient indoles. The products were characterized and confirmed by NMR, IR, and mass spectroscopy. In all the cases, the reactions proceeded well at room temperature affording the corresponding 1,4-adducts in excellent yields with high 1,4-selectivity (Table 1). However, in the absence of iodine, no reaction was observed even under reflux conditions. This clearly indicates that molecular iodine is essential to facilitate the reaction. The scope and generality of this process is illustrated with respect to various indoles and en-1,4-diketone and the results are presented in Table 1.[9] The salient features of this method are high 1,4-selectivity, excellent yields, mild reaction conditions and low cost of the catalyst.



Scheme 2. A plausible reaction mechanism.

Mechanistically, we assume that the reaction proceeds by the activation of en-1,4-dione by molecular iodine. Subsequent attack of indole on activated double bond would give the 1,4-addition product. Due to steric hindrance at C2 position of enone, indole selectively at C3 position of enone to give the desired product as depicted in Scheme 2.

Other alternative pathway is that HI being produced by interaction of iodine with NH could also catalyze the reaction. However, the reaction was not so effective when a solution of 10 mol % of HI was used as a catalyst. No electrophilic iodination was observed under the reaction conditions.[10] The reaction though proceeds with protic acids such as KSF clay, the desired products were obtained in low yields compared to molecular iodine. The efficacy of various Lewis acids such as $BiCl_3$, $ZrCl_4$ and $BF_3{\cdot}OEt_2$ was also tested for this conversion. However, the reactions are not clean and formed a mixture of products with other Lewis acids.

The minimum inhibitory concentrations (MIC) of various synthetic compounds were tested against three representative Gram-positive organisms viz. *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Staphylococcus epidermidis* and Gram-negative organisms viz. *Escherichia coli* (MTCC 443), *Pseudomonas*

Table 2
Antimicrobial activity of compounds

	MIC (μg/ml)					
Compd code	*B. subtilis*	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
3a	75	75	150	150	9.375	150
3b	150	150	150	150	150	150
3c	150	150	150	150	150	150
3d	150	150	150	150	18.75	150
3e	150	150	150	150	18.75	150
3f	75	150	150	150	9.375	150
3g	150	75	150	150	18.75	150
3h	150	37.5	150	150	18.75	150
3i	150	18.75	75	150	9.375	150
3j	150	75	75	150	9.375	150
Penicillin	1.562	1.562	3.125	12.5	12.5	6.25
Streptomycin	6.25	6.25	3.125	6.25	1.562	3.125

Table 3
Antifungal activity of compounds

Compd code	Zone of inhibition in MM							
	C. albicans		*C. rugosa*		*S. cerevisiae*		*A. flavus*	
	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg	100 μg	150 μg
3a	0	0	11	16	0	0	0	0
3b	0	0	8	11	0	0	0	0
3c	0	0	0	0	0	0	0	0
3d	0	0	10	16	0	0	0	0
3e	0	0	0	15	0	0	0	0
3f	0	0	0	0	0	0	0	0
3g	0	0	10	15	0	0	0	0
3h	0	0	9	13	0	0	0	0
3i	0	0	13	17	0	0	0	0
3j	0	0	12	17	0	0	0	0
Amphotericin-B (50)	23.5		21		22		25	

aeruginosa (MTCC 741), and *Klebsiella pneumoniae* (MTCC 618) by broth dilution method recommended by National Committee for Clinical Laboratory (NCCL) standards (1).[11] Standard antibacterial agents like Penicillin and Streptomycin were also screened under identical conditions for comparison. The minimum inhibitory concentration (MIC) values are presented in Table 2.

All synthesized compounds were tested for in vitro antimicrobial activity. The MIC values of the compounds against pathogenic bacteria are presented in Table 2. The experimental results of antimicrobial activity indicated a variable degree of efficacy of the compounds against different strains of bacteria. Compounds **3a**, **3f**, **3i**, and **3j** showed very strong activity (9.375 μg/mL), whereas **3d**, **3e**, **3g**, **3h** showed significant activity against *P. aeruginosa* (18.75 μg/ml). However, the compounds are effective against *P. aeruginosa* only. They did not show any considerable effect on other strains (75–150 μg/ml) as indicated in Table 2. The substitution at 5th position on indole moiety with NO_2, and Cl and phenyl group at 2nd position and unsubstituted indole have shown more activity, when compared to methyl substitutions at 1st and 2nd positions.

In vitro antifungal activity of the newly synthesized compounds was studied against the fungal strains such as *Candida albicans* (MTCC 227), *Saccharomyces cerevisiae* (MTCC 36), *Rhizopus oryzae* (MTCC 262), *Aspergillus niger* (MTCC 282) by Agar Well Diffusion Method (2). Agar well bioassay was employed for testing antifungal activity.[12] The ready-made Potato Dextrose Agar (PDA) medium (Hi-media, 39 g) was suspended in distilled water (1000 mL) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at pressure of 15 lb/inc for 20 min. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber.

When the medium in the plates was solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO and different concentrations were made. After inoculation, the wells were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each well different concentrations of test solutions were added. Controls were maintained. The treated samples and the controls were kept at 27 °C for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter. Three to four replicates were maintained for each treatment.

The antifungal activity was started with pathogenic fungi and the results are given in Table 3. Amphotericin was used as a standard. The compounds showed significant artificial activity only against Candida rugosa at 100 μg and 150 μg concentrations.

In summary, we have developed a novel method for the synthesis of 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one derivatives by means of a conjugate addition of indoles onto en-1,4-dione using a catalytic amount of molecular iodine under mild conditions. This method is simple and convenient to prepare a wide range of indolinone derivatives which are found to possess interesting antibacterial properties.

Acknowledgments

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9. *General procedure*: To a stirred solution of en-1,4-diketone (1 mmol) in acetonitrile (4 mL) were added molecular iodine (25.3 mg, 10 mol %) followed by indole (1 mmol) at room temperature. The resulting mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was quenched by saturated sodium thiosulphate solution (4 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate/hexane, 3:7) to afford the pure 3-(1-(1*H*-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one. Spectral data for the selected products:
3-(1-(1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3a**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 4.10 (d, 1H, J = 3.5 Hz), 5.72 (d, 1H, J = 3.5 Hz), 6.30 (d, 1H, J = 7.7 Hz), 6.66–6.82 (m, 2H), 6.90–7.40 (m, 6H), 7.41–7.45 (m, 1H), 7.50 (s, 1H), 7.84 (d, 2H, J = 8.3 Hz), 8.04 (s, 1H), 10.12 (br s, 1H, NH), 10.80 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 193.2, 175.4, 140.1138.3, 132.7, 130.5, 125.1, 124.2, 122.7, 122.5, 122.2, 121.1, 120.9,

119.6, 119.0, 109.2, 107.3, 101.2, 46.6, 44.7, 39.5, 37.7, 36.8, 36.3; IR (KBr): ν 3229, 2211, 1700, 1453 cm^{-1}; ESI (MS): 367 (M+H).

3-(2-Oxo-1-(2-oxoindolin-3-yl)-2-phenylethyl)-1H-indole-5-carbonitrile (**3b**): White solid, mp 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 4.21 (d, 1H, J = 3.7 Hz), 5.66 (d, 1H, J = 3.7 Hz), 6.60 (d, 1H, J = 7.7 Hz), 6.75-6.85 (m, 2H), 6.99 (t, 1H, J = 7.1 Hz), 7.23–7.40 (m, 4H), 7.41–7.49 (m, 1H), 7.66 (s, 1H), 7.95 (d, 2H, J = 8.3 Hz), 8.17 (s, 1H), 10.12 (br s, 1H, NH), 11.0 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 197.12, 177.9, 142.3, 136.9, 134.9, 132.1, 127.8, 127.7, 126.9, 126.5, 125.6, 123.8, 123.4, 120.5, 120.1, 111.8, 108.5, 101.5, 47.4, 45.4, 39.4, 39.1, 38.8; IR (KBr): ν 3255, 2222, 1700, 1468 cm^{-1}; ESI (MS): 392 (M+H); 414 (M+Na); HRMS ESI(M+H): Calcd for $C_{25}H_{18}N_3O_2$ 392.1386. Found: 392.1399.

3-(1-(2-methyl-5-nitro-1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3c**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 2.45 (s, 3H), 4.23 (d, 1H, J = 3.5 Hz), 5.67 (d, 1H, J = 3.5 Hz), 6.73–7.51 (m, 9H), 7.86 (d, 2H, J = 8.3 Hz), 8.21 (s, 1H), 10.14 (br s, 1H, NH), 11.08 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 201.2, 178.7, 142.7, 137.3, 135.2, 132.5, 128.4, 128.1, 127.7, 126.9, 126.5, 124.7, 124.1, 121.5, 121.0, 112.5, 109.3, 102.7, 51.2, 49.7, 47.9, 45.8, 40.4, 39.1, 38.8; IR (KBr): ν 3610, 2230, 1689, 1472 cm^{-1}; ESI (MS): 426 (M+H).

3-(1-(1-Methyl-1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3d**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 3.92 (s, 3H), 4.16 (d, 1H, J = 3.6 Hz), 5.59 (d, 1H, J = 3.6 Hz), 6.52 (d, 1H, J = 7.4 Hz), 6.68–6.79 (m, 2H), 6.93 (t, 1H, J = 7.0 Hz), 7.16–7.34 (m, 5H), 7.38–7.45 (m, 1H), 7.60 (s, 1H), 7.84 (d, 2H, J = 8.3 Hz), 8.17 (s, 1H), 10.04 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 192.4, 175.1, 139.6, 138.0, 132.5, 130.1, 125.0, 123.7, 123.2, 122.0, 121.7, 121.3, 119.9, 118.7, 118.6, 109.0, 106.6, 101.4, 50.7, 46.2, 43.9, 38.9, 37.4, 36.3, 36.0; IR (KBr): ν 3310, 1690, 1468 cm^{-1}; ESI (MS): 381 (M+H).

3-(1-(5-Bromo-1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3e**): Orange color solid, mp 190–192 °C, ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 4.22 (d, 1H, J = 4.1 Hz), 5.56 (d, 1H, J = 4.1 Hz), 6.57–6.66 (m, 2H), 6.76–7.53 (m, 9H), 7.88–8.05 (m, 2H), 10.0–10.07 (br s, 1H, NH), 10.45–10.53 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 197.4, 177.9, 143.0, 135.9, 134.6, 132.9, 128.6, 128.5, 128.0, 127.8, 127.6, 127.0, 125.4, 123.8, 121.3, 120.8, 113.6, 111.8, 109.0, 108.2, 47.0, 45.2; IR (KBr): ν 3296, 1687, 1465, 1332, 749 cm^{-1}; ESI (MS): 445 (M+H); 467 (M+Na); HRMS (ESI) m/z: Calcd for $C_{24}H_{17}N_2O_2NaBr$, 467.0359 (M+Na). Found: 467.0371.

3-(1-(5-Nitro-1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3f**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 4.28 (d, 1H, J = 3.9 Hz), 5.73 (d, 1H, J = 3.9 Hz), 6.78-7.63 (m, 9H), 7.66 (s, 1H), 7.89 (d, 2H, J = 8.6 Hz), 8.21 (s, 1H), 10.14 (br s, 1H, NH), 11.08 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 201.3, 178.1, 142.4, 136.9, 135.0, 132.7, 128.2, 127.9, 127.2, 126.2, 126.0, 123.9, 123.4, 121.0, 120.6, 112.1, 108.7, 101.8, 49.5, 47.3, 44.9, 40.0, 38.7, 37.9; IR (KBr): ν 3450, 1710, 1435 cm^{-1}; ESI (MS): 412 (M+H).

Methyl 3-(2-oxo-1-(2-oxoindolin-3-yl)-2-phenylethyl)-1H-indole-5-carboxylate (**3g**): White solid, mp 231–233 °C; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO, 1:4): δ 3.92 (s, 3H), 4.29 (d, 1H, J = 4.1 Hz), 5.61 (d, 1H, J = 4.1 Hz), 6.62 (d, 1H, J = 7.3 Hz), 6.73–6.79 (m, 1H), 6.94–7.04 (m, 2H), 7.12–7.16 (m, 1H), 7.25–7.47 (m, 4H), 7.68–7.76 (m, 1H), 7.95 (d, 2H, J = 8.3 Hz), 8.50 (s, 1H), 10.0–10.06 (br s, 1H; NH), 10.81–10.85 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 197.4, 177.7, 167.2, 143.1, 138.5, 135.9, 132.9, 128.6, 128.4, 127.6, 127.5, 125.8, 125.4, 122.3, 121.9, 120.8, 120.6, 109.9, 109, 59.7, 47.1, 45.4; IR (KBr): ν 3628, 1694, 1249, 1108 cm^{-1}; ESI (MS): 425 (M+H); HRMS (M+H): m/z: Calcd for $C_{26}H_{20}N_2O_4$: 425.1495. Found: 425.1498.

3-(1-(2-Methyl-1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3h**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 2.35 (s, 3H), 4.45 (d, 1H, J = 3.5 Hz), 5.27 (d, 1H, J = 3.5 Hz), 6.63 (d, 1H, J = 7.2 Hz), 6.72–7.53 (m, 6H), 7.62–7.73 (m, 2H), 7.78 (s, 1H), 7.84 (d, 2H, J = 8.1 Hz), 8.07 (s, 1H), 10.07 (br s, 1H, NH), 10.19 (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, 1:4): δ 192.1, 174.8, 139.3, 137.8, 132.1, 129.7, 124.9, 123.2, 123.0, 121.9, 121.3, 120.9, 119.7, 118.4, 118.0, 108.7, 106.1, 100.9, 50.3, 46.0, 43.3, 38.7, 37.2, 36.0, 35.8; IR (KBr): ν 3290, 1693, 1472 cm^{-1}; ESI (MS): 381 (M+H).

3-(1-(5-Chloro-1H-indol-3-yl)-2-oxo-2-phenylethyl)indolin-2-one (**3i**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 4.16 (d, 1H, J = 4.1 Hz), 5.50 (d, 1H, J = 4.1 Hz), 6.49–6.54 (m, 2H), 6.69–7.46 (m, 9H), 7.82–7.90 (m, 2H), 9.90–10.04 (br s, 1H, NH), 10.20–10.26 (br s, 1H, NH); ^{13}C NMR (75 MHz,$CDCl_3$ + DMSO, 1:4): δ 196.7, 177.3, 142.7, 135.2, 134.0, 132.2, 128.1, 128.0, 127.8, 127.3, 127.0, 126.8, 124.6, 123.2, 121.0, 120.3, 113.2, 111.4, 108.7, 107.8, 46.9, 44.7; IR (KBr): ν 3496, 1687, 1459, 731 cm^{-1}; ESI (MS): 401 (M+H).

3-(2-Oxo-2-phenyl-1-(2-phenyl-1H-indol-3-yl)ethyl)indolin-2-one (**3j**): ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO, 1:4): δ 4.43 (d, 1H, J = 4.3 Hz) 5.87 (d, 1H, J = 4.3 Hz), 6.82–7.93 (m, 17H), 8.0 (s, 1H), 10.16–10.22 (br s, 1H, NH), 10.93–11.04 (br s, 1H, NH); IR (KBr): ν 3625, 1690, 1457, 735 cm^{-1}; ESI (MS): 443 (M+H).

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