

Brief Report

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Synthesis and biological evaluation of novel indoline-2,3-dione derivatives as antitumor agents

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Summary A new series of 1,5-disubstituted indolin-2,3-diones was synthesized and their inhibition of the growth of a human acute promyelocytic leukemia (HL-60) cell line was evaluated. These compounds had promising inhibition of HL-60 cell growth *in vitro*. Results indicated that compounds with a benzyl substituent at the N-1 position on the indolin-2,3-dione ring had more potent antiproliferative activity than those with a (4-fluorobenzyl) amino-2-oxoethyl substituent at the N-1 position. Among the compounds synthesized, compound 8l inhibited half of cell growth at a concentration of 0.07 μM and compound 8p did so at a concentration of 0.14 μM . These compounds may serve as lead compounds for further optimization in order to develop novel anticancer agents.

Keywords: Indoline-2,3-diones, anticancer agent, HL-60 human leukemia cells

1. Introduction

Indole derivatives have attracted considerable attention in medicinal chemistry because of their pharmacological activities (1,2). During drug design, substituted indoles are considered a "privileged scaffold" for numerous pharmacologically active lead compounds because of their substantial affinity for many receptors (3,4). Isatin (indoline-2, 3-dione, **1**, Figure 1), one of the simplest indole derivatives, has led to numerous analogues with a wide range of biological properties, including anti-cancer activity (5-9). Indirubin (**2**, Figure 1), the active ingredient in the traditional Chinese medicine preparation Danggui Longhui Wan used to treat myelocytic leukemia, is reported to have antiproliferative action against human cancer cells by inhibiting the genes or proteins that regulate cell cycle progression; indirubin arrests the G2/M phase, although its mechanism of action in cells is not fully understood (10). Inhibited growth induced by indirubin-3-oxime (**3**, Figure 1) is associated with induction of cyclin-

dependent kinase inhibitor p21, inhibition of cyclin D1, and activation of caspase-3 (11). Indirubin derivatives are reported to inhibit signal transducer and activator of transcription 3 (Stat3) signaling and induce apoptosis in human cancer cells (12). Indoline-2,3-dione might be used as a privileged scaffold to design a variety of therapeutic molecules, and many indoline-2,3-dione derivatives have been studied as antitumor agents (13-18). Among the reported indoline-2,3-dione derivatives, 5,7-dibromo-1-(naphthalen-1-yl methyl)indoline-2,3-dione (**4**, Figure 1) has potent anti-tumor properties with

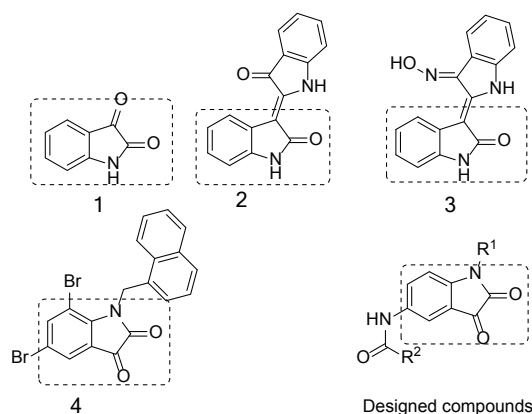


Figure 1. Structures of indoline-2,3-dione derivatives and designed compounds

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an IC_{50} value of 0.19 mM against human monocytic-like histiocytic lymphoma (U937) cells (19). Thus, the current study introduced different substituents at the N-1 and C-5 positions on the indoline-2,3-dione ring in order to synthesize a series of novel 1,5-disubstituted indoline-2,3-diones and evaluate their antiproliferative activity on HL-60 human leukemia cells.

2. Materials and Methods

2.1. Chemistry

The synthesis of target compounds is shown in Diagram 1. The starting material, indolin-2,3-dione (**1**) was purchased from Aladdin Industrial Corporation, Shanghai, China. Intermediate **5** was produced from compound **1** using fuming nitric acid as a nitrating agent and sulfuric acid as a solvent. Intermediate **6** was prepared by treating **5** with 2,2-dimethylpropane-1,3-diol with catalysis by *p*-toluenesulfonic acid. The key intermediate **7** was obtained from **6** that had reacted with 2-chloro-*N*-(4-fluorobenzyl) acetamide (or benzyl chloride) under alkaline conditions *via* electrophilic substitution. With Pd/C (10%, w/w) as the catalyst, the nitro group in intermediate **7** was converted to an amino group by hydrogenation. The resulting compound was allowed to react with acyl chloride in the presence of anhydrous potassium carbonate to yield acylated products, and then the acylated products were converted to target compound **8** by deprotection under acidic conditions.

2.2. Cell line

Human acute promyelocytic leukemia (HL-60) cells (obtained from the American Type Culture Collection) were cultured in RPMI 1640 medium. The medium consisted of 10% heat-inactivated fetal bovine serum (FBS) (Gibco®, Invitrogen, Carlsbad, CA, USA), 100 IU/mL penicillin, 100 µg/mL streptomycin, and 1

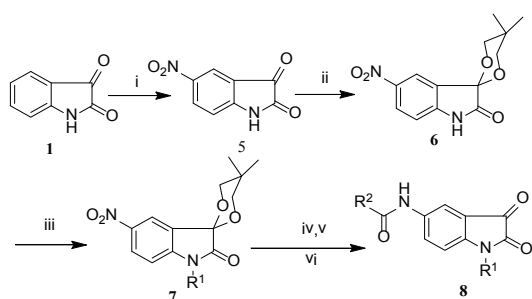


Diagram 1. Synthesis of target compounds. Reagents and conditions. (i) Fuming nitric acid and sulfuric acid; $-10-0^{\circ}\text{C}$, 1 h; (ii) 2,2-dimethylpropane-1,3-diol, *p*-toluenesulfonic acid, and cyclohexane; reflux, 14 h; (iii) 2-chloro-*N*-(4-fluorobenzyl)acetamide or benzyl chloride, dimethylformamide, and potassium carbonate; 85°C , 40 min; (iv) H_2 and 10% Pd/C; room temperature, 4 h; (v) Acyl chloride and potassium carbonate; 0°C - room temperature, 2 h; (vi) Hydrochloric acid and acetic acid; 30°C , 12 h.

mmol/L L-glutamine. Cells were incubated in a humid atmosphere of 5% CO_2 at 37°C .

2.3. Cell viability assay using the trypan blue exclusion method

Trypan blue was ground with a small amount of distilled water, diluted with double-distilled water to 4%, filtered, and then stored at 37°C . The stock solution was diluted to 0.4% with PBS when used. HL-60 cells ($1 \times 10^5/\text{mL}$) were seeded in 12-well plates with a volume of 2 mL in each well. A single cell suspension was prepared after incubation with different concentrations of target compounds. The single cell suspension (50 mL) and the trypan blue solution (0.4 %, 50 mL) were mixed well and observed for up to 3 min under a microscope. Dead cells stained blue while living cells did not. The numbers of dead cells and living cells were calculated with a hemocytometer and cell viability was expressed as the percentage of viable cells.

3. Results and Discussion

The extent to which compounds **8a-8p** inhibited HL-60 cell growth was measured and results are shown in Table 1. Results indicated that compounds with a benzyl substituent (R^1) at the N-1 position on the indolin-2,3-dione ring (**8k-8p**) had more potent antiproliferative activity against HL-60 cells than those with a (4-fluorobenzyl)amino-2-oxoethyl substituent at the N-1 position (**8a-8j**). The effect of the substituent (R^2) on inhibiting HL 60 cell growth depended on the substituent (R^1) at the N-1 position on the indolin-2,3-dione ring. When R^1 was a 4-fluorobenzylamino-2-oxoethyl group, compounds with an aryl group (R^2) (**8a-8g**) had greater inhibition than those with an aliphatic group (**8h** and **8i**). When R^1 was a benzyl group at the N-1 position, compounds with either an aryl group (**8k-8n**) or an aliphatic group (**8o-8p**) had antiproliferative activity with IC_{50} values of less than 1.1 µM. Among compounds **8k-8p** that have a benzyl group at the N-1 position on the indolin-2,3-dione ring, **8l** with a phenyl acetamide group at the C-5 position inhibited HL-60 cell growth the most with an IC_{50} value of 0.07 µM. The next most potent inhibitor of growth was **8p**, which had an IC_{50} value of 0.14 µM and a cyclopropane carboxamide group at the C-5 position.

In conclusion, sixteen 1,5-disubstituted indolin-2,3-diones were synthesized and their inhibition of HL-60 cell growth was evaluated. Findings indicated that compounds with a benzyl substituent at the N-1 position on the indolin-2,3-dione ring had more potent inhibition of HL-60 cell growth than those with a 4-fluorobenzylamino-2-oxoethyl substituent at the N-1 position. Among the compounds with a benzyl substituent group at the N-1 position, the most potent inhibitors of HL-60 cell growth were compound **8l**, which had a phenyl acetamide group at the C-5 position, and compound **8p**, which had a cyclopropane carboxamide group at the C-5 position. The mechanisms by which these compounds inhibited growth are being investigated.

Table 1. Inhibition of HL-60 cell growth by target compounds

Designation	R ¹	R ²	IC ₅₀ (μM) ^a
8a			4.8
8b			7.2
8c			7
8d			3.4
8e			8.8
8f			NT ^b
8g			9.2
8h			15.6
8i			15.4
8j			19.3
8k			0.98
8l			0.07
8m			0.63
8n			1.1
8o			0.7
8p			0.14

^a IC₅₀ indicates the concentration of each compound required for a 50% decrease in cell viability. ^b Not tested.

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Appendix

Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra and carbon nuclear magnetic resonance ($^{13}\text{C-NMR}$) spectra were determined with a Bruker Avance ATC600 instrument at 600 MHz with tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) were reported in parts per million (ppm) and were relative to the central peak of the solvent, which was DMSO- d_6 or CDCl_3 . Coupling constants (J) are given in Hz. Reported $^1\text{H-NMR}$ data are as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, or m = multiplet), coupling constants, and number of protons. Infrared (IR) spectra were measured with a Nicolet Nexus 470FT-IR spectrometer and are expressed in cm^{-1} . Mass spectra (MS) were measured with an API 4000, and high resolution mass (HRMS) spectra were recorded with an LTQ Orbitrap mass spectrometer. The melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification.

1. Procedure for preparation of intermediate 5

Fuming nitric acid (3.0 mL, 0.065 mol) was added dropwise to a solution of indoline-2,3-dione (7.35g, 0.05 mol) in sulfuric acid (50 mL) under 0°C . The mixture was stirred for 1 h at 0°C and then slowly poured into 500 mL of crushed ice. The precipitate was filtered, washed three times with water, and then dried to yield intermediate 5.

5-nitroindoline-2,3-dione (5). Yield: 78%; light yellow powder; mp: 257.8-258.5 $^\circ\text{C}$. $^1\text{H-NMR}$ (DMSO- d_6) δ : 11.67 (s, 1H, NH), 8.44 (m, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 7.09 (d, $J = 8.4$ Hz, 1H, Ar-H).

2. Procedure for preparation of intermediate 6

5-nitroindoline-2,3-dione (3.5 g, 0.018 mol),

p-toluenesulfonic acid (0.4 g), and neopentyl glycol (3.8 g, 0.018 mol) were successively added and dissolved in cyclohexane (80 mL). The mixture was heated to 80°C for 14 h. The reaction mixture was cooled to room temperature and then filtered. The precipitate was sequentially washed with saturated sodium carbonate solution and water and then further purified by column chromatography with petroleum ether/ethyl acetate (6:1 to 3:1) to yield intermediate 6.

5,5-Dimethyl-5'-nitrospiro[[1,3]dioxane-2,3'-indolin]-2'-one (6). Yield: 88%; white solid; mp: 212.3-214.1 $^\circ\text{C}$. $^1\text{H-NMR}$ (DMSO- d_6) δ : 11.21 (s, 1H, NH), 8.28 (dd, $J_1 = 9.0$ Hz, $J_2 = 1.8$ Hz, 1H, Ar-H), 8.08 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.04 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.49 (d, $J = 9.6$ Hz, 2H, CH_2), 3.55 (d, $J = 10.8$ Hz, 2H, CH_2), 1.35 (s, 3H, CH_3), 0.90 (s, 3H, CH_3).

3. General procedure for preparation of intermediate 7

2-Chloro-*N*-(4-fluorobenzyl) acetamide or benzyl chloride (4.3 mmol) was added to a solution of intermediate 6 (1.0 g, 3.6 mmol) and anhydrous potassium carbonate (1 g, 7.2 mmol) in dried dimethylformamide (10 mL). The mixture was heated to 85°C for 40 min and then cooled to room temperature. The reaction mixture was poured into ice water (100 mL) and a precipitate was produced. The precipitate was then filtered, washed with water, and further purified by column chromatography with petroleum ether/ethyl acetate (6:1 to 1:1) to yield 7.

2-(5,5-Dimethyl-5'-nitro-2'-oxospiro[[1,3]dioxane-2,3'-indolin]-1'-yl)-N-(4-fluorobenzyl)acetamide (7a). Yield: 75%; white solid; mp: 231.9-232.1 $^\circ\text{C}$. $^1\text{H-NMR}$ (CDCl_3) δ : 8.33 (d, $J = 1.8$ Hz, 1H, Ar-H), 8.31 (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H, Ar-H), 7.19 (dd, $J_1 = 12$ Hz, $J_2 = 8.4$ Hz, 2H, Ar-H), 7.00 (t, $J = 8.4$ Hz, 2H, Ar-H), 6.96 (d, $J = 8.4$ Hz, 1H, Ar-H), 6.10 (s, 1H, N-H), 4.59 (d, $J = 11.4$ Hz, 2H, CH_2), 4.41 (d, $J = 5.4$ Hz, 2H, CH_2), 4.35 (s, 2H, CH_2), 3.55 (d, $J = 10.8$ Hz, 2H, CH_2), 1.56 (s, 3H, CH_3), 0.90 (s, 3H, CH_3). MS (ESI) m/z : 444.5 $[\text{M}+\text{H}]^+$.

1'-benzyl-5,5-dimethyl-5'-nitrospiro[[1,3]dioxane-2,3'-indolin]-2'-one (7b). Yield: 63%; Pale yellow solid; mp: 154.4-155.4 $^\circ\text{C}$. $^1\text{H-NMR}$ (CDCl_3) δ : 8.31 (d, $J = 2.4$ Hz, 1H, Ar-H), 8.18 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.35 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.30 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.26 (t, $J = 3.0$ Hz, 2H, Ar-H), 6.71 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.88 (s, 2H, CH_2), 4.73 (d, $J = 11.4$ Hz, 2H, CH_2), 3.57 (d, $J = 11.4$ Hz, 2H, CH_2), 1.45 (s, 3H, CH_3), 0.92 (s, 3H, CH_3). MS (ESI) m/z : 369.2 $[\text{M}+\text{H}]^+$.

4. General procedure for preparation of compound 8

Intermediate 7 (2.26 mmol) and 10% Pd/C (0.4g, 10%) were added to 50 mL of distilled ethyl acetate. The mixture reacted with hydrogen for 4 h at room

temperature and then the reaction mixture was filtered. Anhydrous potassium carbonate (0.34 g, 2.5 mmol) was added to the filtrate, and then acyl chloride (2.5 mmol) was added dropwise at 0°C. After the resulting solution was stirred for 2 h at room temperature, the mixture was filtered. The organic phase was washed successively with 5% sodium hydroxide (3 × 15 mL), 3% hydrochloric acid (3 × 15 mL), and saturated brine (3 × 15 mL) and then evaporated in a vacuum to yield a white solid., Glacial acetic acid (63 mL) and hydrochloric acid (7 mL) were added to the solid. The mixture was stirred overnight at 30°C and then poured into distilled water (50 mL), and a precipitate was produced. The precipitate was filtered and purified by recrystallization in 95% ethanol to yield compound **8**.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)benzamide (**8a**). Yield: 89%; purple solid; mp: 305.3-306.5°C. ¹H-NMR (DMSO-*d*₆) δ: 10.39 (s, 1H, NH), 8.77 (t, *J* = 6.0 Hz, 1H, NH), 8.05 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.97 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.94 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.4 Hz, 1H, Ar-H), 7.61 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.55 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.26 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.14 (t, *J* = 9.0 Hz, 2H, Ar-H), 7.09 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.40 (s, 2H, CH₂), 4.29 (d, *J* = 6.0 Hz, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ: 183.43, 166.59, 165.60, 162.43, 160.82, 159.07, 146.60, 135.52, 134.88, 132.21, 130.02, 129.54, 129.48, 128.90, 128.90, 128.07, 128.07, 118.10, 116.89, 115.51, 115.36, 111.27, 43.13, 41.81. IR (KBr, cm⁻¹): *v*_{NH}: 3,409.78, 3,282.05; *v*_{CH}: 3,066.89; *v*_{CH₂}: 2,929.70; *v*_{C=O}: 1,740.92, 1,659.42; *v*_{C=C}: 1,625.12, 1,606.10, 1,547.80, 1,510.18, 1,495.13, 1,454.36; *δ*_{CH}: 1,361.73, 1,310.36; *γ*_{CH}: 823.81, 708.86. HRMS (ESI) *m/z* calculated for C₂₄H₁₉F₁N₃O₄ [M+H]⁺: 432.1354, found 432.1347.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl) furan-2- carboxamide (**8b**). Yield: 41%; Purple solid; mp: 309.5-312.2°C. ¹H-NMR (DMSO-*d*₆) δ: 10.37 (s, 1H, NH), 8.76 (t, *J* = 5.4 Hz, 1H, NH), 7.99 (s, 1H, FU-H), 7.97 (s, 1H, Ar-H), 7.91 (d, *J* = 6.6 Hz, 1H, Ar-H), 7.33 (d, *J* = 3.0 Hz, 1H, FU-H), 7.25 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.13 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.08 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.72 (s, 1H, FU-H), 4.38 (s, 2H, CH₂), 4.28 (d, *J* = 6.0 Hz, 2H, CH₂). IR (KBr, cm⁻¹): *v*_{NH}: 3,366.07, 3,283.56; *v*_{CH}: 3,116.07; *v*_{CH₂}: 2,929.99; *v*_{C=O}: 1,742.21, 1,671.43, 1,651.30; *v*_{C=C}: 1,626.82, 1,607.51, 1,584.76, 1,553.03, 1,510.75, 1,494.39; *δ*_{CH}: 1,426.20, 1,362.83, 1,341.25, 1,316.50; *v*_{C-O}: 1,225.46; *γ*_{CH}: 1,009.95, 829.14, 760.00. HRMS (ESI) *m/z* calculated for C₂₂H₁₇F₁N₃O₅ [M+H]⁺: 422.1147, found 422.1141.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl) phenylacetamide (**8c**). Yield: 92%; orange-red solid; mp: 263.7-265.3°C. ¹H-NMR (DMSO-*d*₆) δ: 10.32 (s, 1H, NH), 8.74 (t, *J* = 6.0 Hz, 1H, NH), 7.89 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.70 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.8 Hz, 1H, Ar-H), 7.33 (d, *J* = 4.2 Hz,

4H, Ar-H), 7.25 (m, 3H, Ar-H), 7.12 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.02 (d, *J* = 7.8 Hz, 1H, Ar-H), 4.36 (s, 2H, CH₂), 4.26 (d, *J* = 6.0 Hz, 2H, CH₂), 3.64 (s, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ: 183.44, 169.70, 166.58, 162.43, 160.82, 159.00, 146.28, 136.17, 135.59, 129.55, 129.55, 129.53, 129.48, 128.77, 128.77, 128.74, 127.04, 118.12, 115.60, 115.49, 115.35, 111.40, 43.61, 43.19, 41.80. IR (KBr, cm⁻¹): *v*_{NH}: 3,295.80; *v*_{CH}: 3,064.79; *v*_{CH₂}: 2,935.13; *v*_{C=O}: 1,740.64, 1,659.85; *v*_{C=C}: 1,623.61, 1,606.65, 1,552.75, 1,510.47, 1,493.13, 1,453.99; *δ*_{CH}: 1,359.98; *γ*_{CH}: 825.00, 728.32, 695.99. HRMS (ESI) *m/z* calculated for C₂₅H₂₁F₁N₃O₄ [M+H]⁺: 446.1511, found 446.1504.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)-3-chloro- benzamide (**8d**). Yield: 81%; pink solid; mp: 310.3-311.2°C. ¹H-NMR (DMSO-*d*₆) δ: 10.48 (s, 1H, NH), 8.77 (t, *J* = 6.6 Hz, 1H, NH), 8.02 (s, 2H, Ar-H), 7.92 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.69 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.59 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.25 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.14 (t, *J* = 9.0 Hz, 2H, Ar-H), 7.10 (d, *J* = 8.4 Hz, 1H, Ar-H), 4.40 (s, 2H, CH₂), 4.28 (d, *J* = 6.0 Hz, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ: 183.38, 166.57, 164.43, 162.43, 160.82, 159.04, 146.76, 136.82, 135.20, 133.72, 132.00, 130.88, 130.08, 129.53, 129.48, 127.81, 126.90, 118.10, 116.95, 115.50, 115.36, 111.30, 43.21, 41.81. IR (KBr, cm⁻¹): *v*_{NH}: 3,386.50, 3,291.67; *v*_{CH}: 3,067.66; *v*_{CH₂}: 2,931.61; *v*_{C=O}: 1,740.97, 1,653.98; *v*_{C=C}: 1,622.64, 1,607.07, 1,547.56, 1,510.85, 1,493.14, 1,453.60; *δ*_{CH}: 1,360.11, 1,314.51; *γ*_{CH}: 819.38, 738.47. HRMS (ESI) *m/z* calculated for C₂₄H₁₈Cl₁F₁N₃O₄ [M+H]⁺: 466.0964, found 466.0959.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)-3- phenylpropanamide (**8e**). Yield: 78%; Orange-red solid; mp: 264.1-265.8°C. ¹H-NMR (DMSO-*d*₆) δ: 10.06 (s, 1H, NH), 8.74 (t, *J* = 6.0 Hz, 1H, NH), 7.88 (s, 1H, Ar-H), 7.65 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.28 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.25 (m, 4H, Ar-H), 7.18 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.12 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.01 (d, *J* = 9.0 Hz, 1H, Ar-H), 4.35 (s, 2H, CH₂), 4.27 (d, *J* = 5.4 Hz, 2H, CH₂), 2.91 (t, *J* = 7.8 Hz, 2H, CH₂), 2.62 (t, *J* = 7.8 Hz, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ: 183.48, 170.95, 166.58, 162.42, 160.82, 158.99, 146.14, 141.48, 135.60, 129.53, 129.48, 128.77, 128.77, 128.68, 128.68, 128.59, 126.42, 118.10, 115.53, 115.48, 115.35, 111.37, 43.17, 41.79, 38.32, 31.21. IR (KBr, cm⁻¹): *v*_{NH}: 3,336.21, 3,297.32; *v*_{CH}: 3,063.99; *v*_{CH₂}: 2,928.64; *v*_{C=O}: 1,741.08, 1,655.82; *v*_{C=C}: 1,623.72, 1,606.97, 1,551.06, 1,510.67, 1,493.11, 1,454.12; *δ*_{CH}: 1,357.92, 1,302.92; *γ*_{CH}: 824.89, 752.43, 699.35. HRMS (ESI) *m/z* calculated for C₂₆H₂₃F₁N₃O₄ [M+H]⁺: 460.1667, found 460.1659.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)-4- methylbenzamide (**8f**). Yield: 75%; purple solid; mp: 299.2-300.6°C. ¹H-NMR (DMSO-*d*₆) δ: 10.30 (s, 1H, NH), 8.77 (t, *J* = 5.4 Hz, 1H, NH), 8.04 (s, 1H, Ar-H), 7.94 (d, *J* = 8.4 Hz, 1H,

Ar-H), 7.89 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.35 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.25 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.14 (t, $J = 8.4$ Hz, 2H, Ar-H), 7.08 (d, 1H, $J = 8.4$ Hz, Ar-H), 4.39 (s, 2H, CH₂), 4.28 (d, $J = 5.4$ Hz, 2H, CH₂), 2.39 (s, 3H, Ar-CH₃). ¹³C-NMR (DMSO-*d*₆) δ : 183.16, 166.58, 165.75, 162.42, 160.82, 159.06, 146.53, 142.26, 135.58, 131.97, 130.00, 129.53, 129.48, 129.41, 129.41, 128.10, 128.10, 118.09, 116.87, 115.50, 115.36, 111.24, 43.20, 41.78, 21.46. IR (KBr, cm⁻¹): ν_{NH} : 3,411.85, 3,288.56; ν_{CH} : 3,066.50; ν_{CH_2} : 2,924.11; $\nu_{\text{C=O}}$: 1,740.74, 1,657.81; $\nu_{\text{C=C}}$: 1,625.25, 1,608.70, 1,551.81, 1,509.61, 1,498.29, 1,452.81; δ_{CH} : 1,362.94, 1,324.94, 1,308.45; γ_{CH} : 842.44, 745.99. HRMS (ESI) m/z calculated for C₂₅H₂₁F₁N₃O₄ [M+H]⁺: 446.1511, found 446.1505.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)-2,4-dichloro-benzamide (**8g**). Yield: 84%; orange-red solid; mp: 304.7-305.3°C. ¹H-NMR (DMSO-*d*₆) δ : 10.69 (s, 1H, NH), 8.75 (t, $J = 6.0$ Hz, 1H, NH), 7.97 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.81 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H, Ar-H), 7.80 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.67 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.58 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, 1H, Ar-H), 7.25 (dd, $J_1 = 8.4$ Hz, $J_2 = 5.4$ Hz, 2H, Ar-H), 7.13 (t, $J = 9.6$ Hz, 2H, Ar-H), 7.08 (d, $J = 9.0$ Hz, 1H, Ar-H), 4.39 (s, 2H, CH₂), 4.28 (d, $J = 6.0$ Hz, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.33, 166.53, 164.50, 162.42, 160.82, 159.04, 146.82, 135.75, 135.53, 135.02, 131.73, 130.83, 129.74, 129.54, 129.48, 129.20, 127.97, 118.22, 116.02, 115.50, 115.36, 111.52, 43.21, 41.79. IR (KBr, cm⁻¹): ν_{NH} : 3,241.44; ν_{CH} : 3,055.05; ν_{CH_2} : 2,973.71; $\nu_{\text{C=O}}$: 1,729.76, 1,657.14; $\nu_{\text{C=C}}$: 1,622.08, 1,603.25, 1,583.27, 1,556.63, 1,537.15, 1,509.54, 1,496.91, 1,456.35; δ_{CH} : 1,363.94, 1,337.78, 1,320.71; γ_{CH} : 836.38, 818.75, 780.98, 682.46. HRMS (ESI) m/z calculated for C₂₄H₁₇Cl₂F₁N₃O₄ [M+H]⁺: 500.0575, found 500.0563.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)cyclopropane carboxamide (**8h**). Yield: 71%; pink solid; mp: 285.3-286.4°C. ¹H-NMR (DMSO-*d*₆) δ : 10.34 (s, 1H, NH), 8.75 (t, $J = 6.0$ Hz, 1H, NH), 7.89 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.69 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.24 (t, $J = 6.6$ Hz, 2H, Ar-H), 7.13 (t, $J = 8.4$ Hz, 2H, Ar-H), 7.02 (d, $J = 7.8$ Hz, 1H, Ar-H), 4.36 (s, 2H, CH₂), 4.27 (d, $J = 6.6$ Hz, 2H, CH₂), 1.73 (t, $J = 6.6$ Hz, 1H, CH), 0.81 (d, $J = 7.2$ Hz, 4H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.50, 172.17, 166.59, 162.42, 160.81, 158.99, 146.04, 135.78, 129.52, 129.47, 128.46, 118.10, 115.45, 115.46, 115.35, 111.36, 43.16, 41.78, 14.98, 7.74, 7.74. IR (KBr, cm⁻¹): ν_{NH} : 3,345.65, 3,261.80; ν_{CH} : 3,052.49; ν_{CH_2} : 2,942.81; $\nu_{\text{C=O}}$: 1,735.03, 1,655.16; $\nu_{\text{C=C}}$: 1,623.94, 1,604.93, 1,542.29, 1,511.22, 1,494.16, 1,459.03; δ_{CH} : 1,359.77, 1,342.21; γ_{CH} : 839.71, 822.92, 748.66, 714.68. HRMS (ESI) m/z calculated for C₂₁H₁₉F₁N₃O₄ [M+H]⁺: 396.1354, found 396.1348.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)pivalamide (**8i**). Yield: 63%; orange-

red solid; mp: 260.4-261.9°C. ¹H-NMR (DMSO-*d*₆) δ : 9.34 (s, 1H, NH), 8.75 (t, $J = 6.0$ Hz, 1H, NH), 7.91 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H, Ar-H), 7.88 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.24 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.14 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.13 (t, $J = 9.6$ Hz, 2H, Ar-H), 4.36 (s, 2H, CH₂), 4.27 (d, $J = 6.0$ Hz, 1H, CH₂), 1.23 (s, 9H, CH₃). ¹³C-NMR (DMSO-*d*₆) δ : 183.50, 177.01, 166.58, 162.42, 160.82, 159.01, 146.26, 135.72, 130.02, 129.51, 129.46, 117.94, 116.94, 115.48, 115.35, 110.03, 43.17, 41.79, 39.50, 27.58, 27.58, 27.58. IR (KBr, cm⁻¹): ν_{NH} : 3,265.79; ν_{CH} : 3,074.19; ν_{CH_3} : 2,968.59, 2,872.71; $\nu_{\text{C=O}}$: 1,746.57, 1,671.78, 1,652.98; $\nu_{\text{C=C}}$: 1,624.86, 1,605.91, 1,534.80, 1,509.89, 1,493.55, 1,452.28; δ_{CH} : 1,367.79, 1,335.79, 1,307.98; γ_{CH} : 901.66, 810.87, 712.86, 660.87. HRMS (ESI) m/z calculated for C₂₂H₂₃F₁N₃O₄ [M+H]⁺: 412.1667, found 412.1663.

N-(1-(2-(4-Fluorobenzylamino)-2-oxoethyl)-2,3-dioxindolin-5-yl)-2-hydroxybenzamide (**8j**). Yield: 78%; orange-red solid; mp: 308.7-309.4°C. ¹H-NMR (DMSO-*d*₆) δ : 11.73 (s, 1H, Ar-OH), 10.45 (s, 1H, NH), 8.76 (t, $J = 5.4$ Hz, 1H, NH), 7.99 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.94 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.87 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.45 (t, $J = 10.2$ Hz, 1H, Ar-H), 7.25 (m, 2H, Ar-H), 7.14 (t, $J = 6.0$ Hz, 2H, Ar-H), 7.10 (d, $J = 8.4$ Hz, 1H, Ar-H), 6.98 (m, 2H, Ar-H), 4.40 (s, 2H, CH₂), 4.29 (d, $J = 6.0$ Hz, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.33, 167.52, 166.58, 162.425, 160.82, 159.05, 159.02, 147.00, 134.41, 134.26, 130.75, 129.52, 129.47, 129.34, 119.48, 118.17, 117.70, 117.62, 117.60, 115.51, 115.37, 111.34, 43.22, 41.791. IR (KBr, cm⁻¹): ν_{OH} : 3,311.80; ν_{CH} : 3,082.92; $\nu_{\text{C=O}}$: 1,739.57, 1,666.67, 1,644.81; $\nu_{\text{C=C}}$: 1,627.13, 1,606.39, 1,558.03, 1,509.98, 1,496.31, 1,444.51; δ_{CH} : 1,329.79, 1,313.73; γ_{CH} : 831.30, 757.81. HRMS (ESI) m/z calculated for C₂₄H₁₉F₁N₃O₅ [M+H]⁺: 446.1511, found 446.1504.

N-(1-Benzyl-2,3-dioxindolin-5-yl)benzamide (**8k**). Yield: 77%; vermilion solid; mp: 197.2-198.1°C. ¹H-NMR (DMSO-*d*₆) δ : 10.30 (s, 1H, NH), 7.89 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.63 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.41 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.33 (m, 4H, Ar-H), 7.28 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.25 (m, 2H, Ar-H), 6.93 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.88 (s, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.64, 165.94, 158.93, 146.51, 135.97, 135.50, 134.90, 132.17, 129.85, 129.10, 129.10, 128.87, 128.87, 128.06, 128.06, 127.98, 127.81, 127.81, 118.03, 117.00, 111.62, 43.40. IR (KBr, cm⁻¹): ν_{NH} : 3,345.43; ν_{CH} : 3,061.69, 3,031.09; $\nu_{\text{C=O}}$: 1,738.95, 1,680.98; $\nu_{\text{C=C}}$: 1,624.14, 1,605.06, 1,548.19, 1,491.44, 1,453.53; δ_{CH} : 1,346.93; γ_{CH} : 827.86, 767.62, 719.86, 697.76. HRMS (ESI) m/z calculated for C₂₂H₁₇N₂O₃ [M+H]⁺: 357.1234, found 357.1247.

N-(1-Benzyl-2,3-dioxindolin-5-yl)-2-phenylacetamide (**8l**). Yield: 63%; vermilion solid; mp: 237.5-238.1°C. ¹H-NMR (DMSO-*d*₆) δ : 10.30 (s, 1H, NH), 7.88 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.63 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.42 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.32 (m, 4H, Ar-H), 7.28 (t, $J = 7.2$ Hz, 2H, Ar-H),

7.24 (m, 2H, Ar-H), 6.93 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.88 (s, 2H, CH₂), 3.62 (s, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.62, 169.64, 158.86, 146.21, 136.17, 135.96, 135.51, 129.51, 129.51, 129.08, 129.08, 128.77, 128.77, 128.56, 127.97, 127.77, 127.77, 127.03, 118.09, 115.71, 111.76, 43.58, 43.35. IR (KBr, cm⁻¹): ν_{NH} : 3,411.39; ν_{CH} : 3,062.87; $\nu_{\text{C=O}}$: 1,738.62, 1,652.37; $\nu_{\text{C=C}}$: 1,623.88, 1,605.09, 1,579.75, 1,543.55, 1,493.95, 1,454.39; δ_{CH} : 1,332.28, 1,308.90; γ_{CH} : 834.59, 796.04, 700.39. HRMS (ESI) m/z calculated for C₂₃H₁₉N₂O₃ [M+H]⁺: 371.1390, found 371.1408.

N-(1-Benzyl-2,3-dioxindolin-5-yl)-3-phenylpropanamide (**8m**). Yield: 68%; purple solid; mp: 224.2-225.1°C. ¹H-NMR (DMSO-*d*₆) δ : 10.03 (s, 1H, NH), 7.88 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.58 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.42 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.34 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.28 (m, 3H, Ar-H), 7.23 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.17 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.92 (d, $J = 7.8$ Hz, 1H, Ar-H), 4.88 (s, 2H, CH₂), 2.90 (t, $J = 7.8$ Hz, 2H, CH₂), 2.60 (t, $J = 8.4$ Hz, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.68, 170.02, 158.85, 146.08, 141.47, 135.95, 135.57, 129.08, 129.08, 128.75, 128.75, 128.66, 128.66, 128.47, 127.97, 127.78, 127.78, 126.39, 118.03, 115.68, 111.71, 43.36, 38.28, 31.20. IR (KBr, cm⁻¹): ν_{NH} : 3,360.01; ν_{CH} : 3,062.68, 3,027.27; ν_{CH_2} : 2,966.01, 2,929.00, 2,863.15; $\nu_{\text{C=O}}$: 1,735.82, 1,679.20; $\nu_{\text{C=C}}$: 1,626.21, 1,605.59, 1,558.72, 1,491.25, 1,454.00; δ_{CH} : 1,354.90, 1,330.60; γ_{CH} : 828.33, 751.50, 717.10, 696.51. HRMS (ESI) m/z calculated for C₂₄H₂₁N₂O₃ [M+H]⁺: 385.1547, found 385.1563.

N-(1-Benzyl-2,3-dioxindolin-5-yl)-2,4-dichlorobenzamide (**8n**). Yield: 68%; pink solid; mp: 268.3-269.7°C. ¹H-NMR (DMSO-*d*₆) δ : 10.67 (s, 1H, NH), 7.97 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.78 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.74 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H, Ar-H), 7.64 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.57 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.8$ Hz, 1H, Ar-H), 7.43 (d, $J = 7.8$ Hz, 2H, Ar-H), 7.35 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.29 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.98 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.91 (s, 2H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.52, 164.46, 158.90, 146.74, 135.88, 135.75, 135.50, 134.99, 131.73, 130.80, 129.70, 129.08, 129.08, 129.03, 127.98, 127.94, 127.78,

127.78, 118.17, 116.15, 111.85, 43.40. IR (KBr, cm⁻¹): ν_{NH} : 3,274.61; ν_{CH} : 3,087.49, 3,062.10; $\nu_{\text{C=O}}$: 1,740.80, 1,721.83, 1,655.88; $\nu_{\text{C=C}}$: 1,624.58, 1,601.71, 1,583.30, 1,555.92, 1,533.52, 1,490.68, 1,452.88; δ_{CH} : 1,349.20, 1,330.00, 1,308.67; γ_{CH} : 836.63, 779.15, 720.75, 700.82. HRMS (ESI) m/z calculated for C₂₂H₁₅Cl₂N₂O₃ [M+H]⁺: 425.0454, found 425.0472.

N-(1-Benzyl-2,3-dioxindolin-5-yl) pivalamide (**8o**). Yield: 60%; purple solid; mp: 233.4-234.6°C. ¹H-NMR (DMSO-*d*₆) δ : 9.31 (s, 1H, NH), 7.88 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.73 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.42 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.34 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.28 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.92 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.88 (s, 2H, CH₂), 1.19 (s, 9H, CH₃). ¹³C-NMR (DMSO-*d*₆) δ : 183.69, 177.03, 158.92, 146.18, 135.99, 135.66, 129.80, 129.06, 129.06, 127.94, 127.73, 127.73, 117.93, 117.03, 111.43, 43.32, 39.50, 27.56, 27.56, 27.56. IR (KBr, cm⁻¹): ν_{NH} : 3,413.43; ν_{CH} : 3,060.11; ν_{CH_3} : 2,967.60, 2,869.76; $\nu_{\text{C=O}}$: 1,728.23, 1,677.41; $\nu_{\text{C=C}}$: 1,619.06, 1,604.10, 1,538.36, 1,491.97, 1,453.15; δ_{CH} : 1,398.83, 1,335.23, 1,314.85; γ_{CH} : 831.45, 788.33, 749.15, 717.95, 697.87. HRMS (ESI) m/z calculated for C₂₀H₂₁N₂O₃ [M+H]⁺: 337.1547, found 337.1572.

N-(1-Benzyl-2,3-dioxindolin-5-yl)cyclopropanecarboxamide (**8p**). Yield: 79%; pink solid; mp: 249.5-250.2°C. ¹H-NMR (DMSO-*d*₆) δ : 10.30 (s, 1H, NH), 7.88 (d, $J = 2.4$ Hz, 1H, Ar-H), 7.62 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H, Ar-H), 7.42 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.34 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.28 (t, $J = 7.8$ Hz, 1H, Ar-H), 6.92 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.88 (s, 2H, CH₂), 1.71 (m, 1H, CH), 0.79 (d, $J = 6.0$ Hz, 4H, CH₂). ¹³C-NMR (DMSO-*d*₆) δ : 183.69, 172.14, 158.85, 145.96, 135.98, 135.74, 129.07, 129.07, 128.32, 127.96, 127.78, 127.78, 118.05, 115.62, 111.71, 43.36, 14.95, 7.72, 7.72. IR (KBr, cm⁻¹): ν_{NH} : 3,340.81; ν_{CH} : 3,059.31; ν_{CH_2} : 2,925.08; $\nu_{\text{C=O}}$: 1,739.43, 1,714.20, 1,680.28; $\nu_{\text{C=C}}$: 1,621.56, 1,606.07, 1,553.06, 1,491.32, 1,454.23; δ_{CH} : 1,397.01, 1,351.43, 1,336.26, 1,301.19; γ_{CH} : 841.29, 822.95, 790.28, 718.39, 698.72. HRMS (ESI) m/z calculated for C₁₉H₁₇N₂O₃ [M+H]⁺: 321.1234, found 321.1213.