



Research Article

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Design, synthesis and biological evaluation of N-phenyl substituted isatin derivatives

Yao Yang^{1,2,3}, Binbin Song^{1,2,3}, Kailin Han^{1,2,3}, Li Zhang^{1,2,3}, Dan Wu^{1,2,3}, Xin Qu^{1,2,3},
Huanhuan Li^{1,2,3}, Hua Sun^{1,2,3}, Yuou Teng^{1,2,3*} and Peng Yu^{1,2,3*}

¹Key Lab of Industrial Fermentation Microbiology, Tianjin University of Science and Technology, Ministry of Education, Tianjin, P. R. China

²Tianjin Key Lab of Industrial Microbiology, Tianjin University of Science and Technology, Tianjin, P. R. China

³Sino-French Joint Lab of Food Nutrition/Safety and Medicinal Chemistry, Tianjin University of Science and Technology, Tianjin, P. R. China

ABSTRACT

A series of N-phenyl substituted isatin derivatives were designed and synthesized about 40-80% overall yields. Three of the eleven newly synthesized compounds, compound **9**, **10** and **11**, have not been reported before. Their structures were characterized by ¹H and ¹³C NMR. All the newly synthesized derivatives were subjected to evaluate their cytotoxic properties against three human tumor cell lines, HepG2, HT-29 and K562. Results indicated that compounds **2**, **3**, **5**, **8**, **9** and **10** exhibited significant anti-tumor activities against liver cancer (HepG2), colon cancer (HT-29) and leukemia (K562) cell lines. Among, compound **9** with the IC₅₀ values of 24.09 μM, 20.27 μM, 6.10 μM against cancer cell lines HepG2, HT-29 and K562.

Keywords: isatin derivatives, anti-tumor activity, MTT

INTRODUCTION

Isatin is an endogenous a natural product which was identified in many organisms and possesses variety of biological activities [1-2]. It was reported that 1-, 3-, 4-, 5-, and 7-substituted isatin derivatives possess a wide range of pharmacological activities and biological activities, such as anticancer, antibacterial [3-4], et al. And the 4-substituted isatin derivatives exhibit a wide range of pharmacological and biological activities [5-6], such as anticancer [7], antibacterial [8-9], anti-inhibitor, anti-fungal [10-11] and sedative-hypnotic [12-14], et al [15-18]. N-naphthylmethyl isatin and N-phenethyl isatin derivatives can inhibit the growth of cancer cells. However, 3-(4-chlorobenzylidene)indolin-2-one and 3-(3,4-dichlorobenzylidene)indolin-2-one derivatives have not been reported yet.

Many researches have been focused on the synthesis and biological evaluation of the N-1, C-3 and C-5 position substituted isatin derivatives. In this paper, we would like to report the design, synthesis and biological evaluation of N-1 and C-3 substituted isatin derivatives. As part of our research program on the SAR study of isatin derivatives' anticancer property, herein we would like to report the synthesis and antitumor activity of a series of 1-substituted and 3-substituted isatin derivatives against three human cancer cell lines, including human leukemia K562, human liver cancer HepG2 and human colon cancer HT-29.

EXPERIMENTAL SECTION

2.1 Materials and measurements

Used in this article, all reagents and solvents were of analytical grade. The reaction temperature control uses the oil bath temperature modulator. Thin layer chromatography (TLC) with silica gel 60 GF₂₅₄ E.Merck precoated plates (0.25 mm) was visualized using UV. 0.1 for flash chromatography on silica gel (particle size 100-200 mesh). ¹H and ¹³C NMR spectra were recorded on Bruker AM-400 NMR spectrometers in deuterated chloroform and deuterated DMSO. The chemical shifts are reported in δ (ppm) relative to tetramethylsilane as internal standard.

2.2 Synthesis route of isatin derivatives

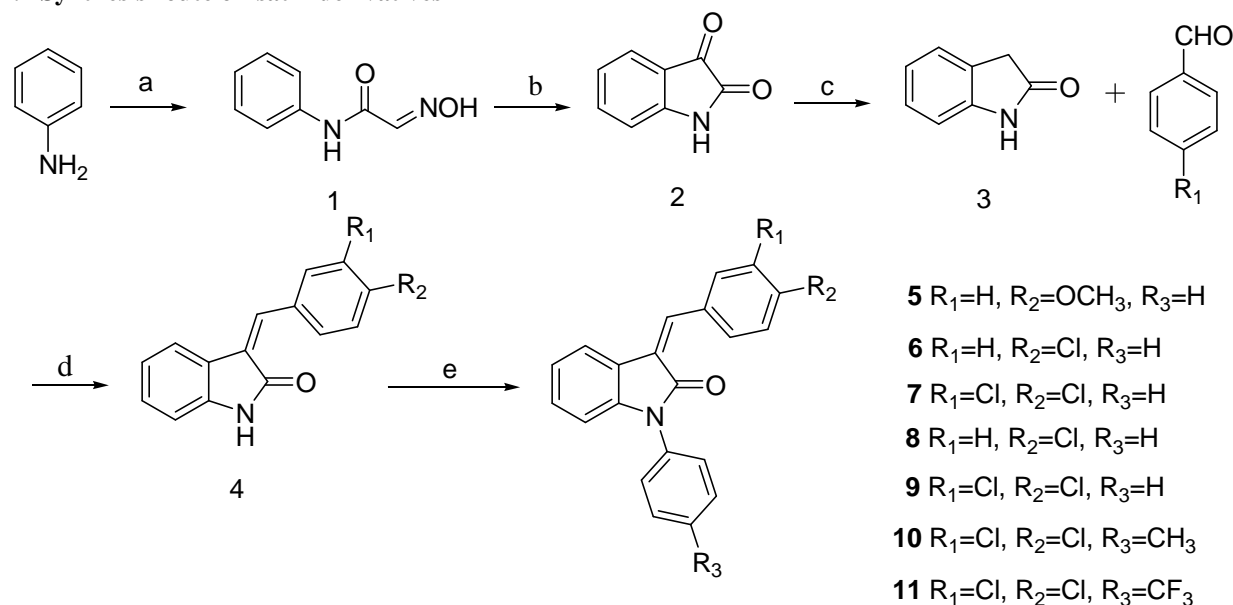


Fig 1: synthesis route of isatin derivatives

Reagents and conditions: (a) Na₂SO₄, NH₂OH·HCl, CCl₃CH(OH)₂, 2 mol·L⁻¹ HCl, H₂O, 90 °C; (b) conc. H₂SO₄, 65 °C; (c) Ethanol, NH₂NH₂·H₂O, NaOH, 65 °C, 82%; (d) Ethanol, Piperidine, 75 °C; (e) DCM, Cu(OAc)₂, CH₃COOK, rt, 36-43%.

2.2.1 Synthesis of indolin-2-one (compound 1)

Fetch isatin (5.00 g, 34.00 mmol) into 100 mL round bottom flask with 20 mL DMF, then add 85% hydrazine hydrate (2.40 g, 37.40 mmol), Sodium acetate (1.25 g, 15.23 mmol), stir at room temperature for 15 min, and then reacted at 90 °C for 9 h. The reaction was monitored by TLC to confirm whether the starting material was disappeared, put the reaction mixture into ice water mixture to give a yellow solid, then filtered, dried in vacuum to give a indolin-2-one (3.13 g, 82.00%).

2.2.2 Synthesis of 3-(4-methylbenzylidene)indolin-2-one (compound 2)

Fetch compound 3 (0.50 g, 3.70 mmol) into 50 mL round bottom flask with ethanol (5 mL), add p-tolualdehyde (0.54 g, 4.50 mmol), piperidine (0.15 mL), reflux for 3h. When the reaction completed, the reaction mixture collected by filtration, and wash it with ethanol, then dried in vacuum to given 3-(4-methylbenzylidene)indolin-2-one (0.60 g, 69.00%).

2.2.3 Synthesis of 3-benzylideneindolin-2-one (compound 3)

Fetch compound 1 (0.50 g, 3.70 mmol) into 25 mL round bottom flask with ethanol (5 mL), add benzaldehyde (0.43 g, 4.12 mmol), piperidine (0.15 mL), reflux for 3h. When the reaction completed, the reaction mixture collected by filtration, and wash it with ethanol, then dried in vacuum to given 3-benzylideneindolin-2-one (0.60 g, 73.00%).

2.2.4 Synthesis of 3-(4-(trifluoromethyl)benzylidene)indolin-2-one (compound 4)

Fetch compound 1 (0.50 g, 3.50 mmol) into 50 mL round bottom flask with ethanol (5 mL), add trifluoromethylbenzaldehyde (0.80 g, 4.50 mmol), piperidine (0.15 mL), reflux for 3h. When the reaction completed, the reaction mixture collected by filtration, and wash it with ethanol, then dried in vacuum to give 3-(4-(trifluoromethyl)benzylidene)indolin-2-one (0.63 g, 59.00%).

2.2.5 Synthesis of 3-(4-methoxybenzylidene)indolin-2-one (compound 5)

Fetch compound 1 (0.50 g, 3.70 mmol) into 50 mL round bottom flask with ethanol (5 mL), add

methoxybenzaldehyde (0.60 g, 4.50 mmol), piperidine (0.15 mL), reflux for 3h. When the reaction completed, the reaction mixture collected by filtration, and wash it with ethanol, then dried in vacuum to give 3-(4-methoxybenzylidene)indolin-2-one (0.73 g, 68.00%).

2.2.6 Synthesis of 3-(4-chlorobenzylidene)indolin-2-one (compound 6)

Fetch compound 1 (0.50 g, 3.70 mmol) into 50 mL round bottom flask with ethanol (5 mL), add chlorobenzaldehyde (0.60 g, 4.50 mmol), piperidine (0.15 mL), reflux for 3h. When the reaction completed, the reaction mixture collected by filtration, and wash it with ethanol, then dried in vacuum to give 3-(4-chlorobenzylidene)indolin-2-one (0.65 g, 68.00%).

2.2.7 Synthesis of 3-(3,4-dichlorobenzylidene)indolin-2-one (compound 7)

Fetch compound 1 (0.50 g, 3.70 mmol) into 50 mL round bottom flask with ethanol (5 mL), add 3,4-dichlorobenzaldehyde (0.42 g, 4.10 mmol), piperidine (0.15 mL), reflux for 3h. When the reaction completed, the reaction mixture collected by filtration, and wash it with ethanol, then dried in vacuum to give 3-(3,4-dichlorobenzylidene)indolin-2-one (0.73 g, 68.00%).

2.2.8 Synthesis of 3-(4-chlorobenzylidene)-1-phenylindolin-2-one (compound 8)

Fetch compound 6 (0.40 g, 1.70 mmol) into 100 mL round bottom flask, add CH₂Cl₂ (12 mL), copper acetate (0.30 g, 1.70 mmol), phenylboronic acid (0.40 g, 3.50 mmol), triethylamine (0.40 mL, 3.50 mmol), reflux at 30 °C for 1-2 days. The reaction was monitored by TLC to confirm whether the starting material was disappeared, put water 15 mL into the reaction mixture, extract the mixture with dichloromethane three times and combine the organic phase. Wash the organic phase with saturated salt water and dry it with anhydrous sodium sulfate. Finally chromatography by using 200 mesh silica gel column with petroleum ether and ethyl acetate to give 3-(4-chlorobenzylidene)-1-phenylindolin-2-one (0.25 g, 43.00%).

2.2.9 Synthesis of 3-(3,4-dichlorobenzylidene)-1-phenylindolin-2-one (compound 9)

Fetch compound 7 (0.70 g, 2.40 mmol) into 100 mL round bottom flask, add CH₂Cl₂ (15 mL), copper acetate (0.50 g, 2.40 mmol), phenylboronic acid (0.60 g, 4.80 mmol), triethylamine (0.70 mL, 4.80 mmol), reflux at 30 °C for 1-2 days. The reaction was monitored by TLC to confirm whether the starting material was disappeared, put water 15 mL into the reaction mixture, extract the mixture with dichloromethane three times and combine the organic phase. Wash the organic phase with saturated salt water and dry it with anhydrous sodium sulfate. Finally chromatography by using 200 mesh silica gel column with petroleum ether and ethyl acetate to give 3-(3,4-dichlorobenzylidene)-1-phenylindolin-2-one (0.36 g, 41.00%).

2.2.10 Synthesis of (Z)-3-(3,4-dichlorobenzylidene)-1-(p-tolyl)indolin-2-one (compound 10)

Fetch compound 7 (0.10 g, 0.30 mmol) into 50 mL round bottom flask, add CH₂Cl₂ (5 mL), copper acetate (0.10 g, 0.30 mmol), methylbenzeneboronic acid (0.05 g, 0.60 mmol), triethylamine (0.10 mL, 0.60 mmol), reflux at 30 °C for 1-2 days. The reaction was monitored by TLC to confirm whether the starting material was disappeared, put water 10 mL into the reaction mixture, extract the mixture with dichloromethane three times and combine the organic phase. Wash the organic phase with saturated salt water and dry it with anhydrous sodium sulfate. Finally chromatography by using 200 mesh silica gel column with petroleum ether and ethyl acetate to give 3-(3,4-dichlorobenzylidene)-1-(4-methylphenyl)indolin-2-one (0.04 g, 36.00%).

2.2.11 Synthesis of (Z)-3-(3,4-dichlorobenzylidene)-1-(4-(trifluoromethyl)phenyl)indolin-2-one (compound 11)

Fetch compound 6 (0.10 g, 0.30 mmol) into 50 mL round bottom flask, add CH₂Cl₂ (5 mL), copper acetate (0.10 g, 0.30 mmol), chlorophenylboronic acid (0.10 g, 0.60 mmol), triethylamine (0.10 mL, 0.60 mmol), reflux at 30 °C for 1-2 days. The reaction was monitored by TLC to confirm whether the starting material was disappeared, put water 10 mL into the reaction mixture, extract the mixture with dichloromethane three times and combine the organic phase. Wash the organic phase with saturated salt water and dry it with anhydrous sodium sulfate. Finally chromatography by using 200 mesh silica gel column with petroleum ether and ethyl acetate to give 3-(3,4-dichlorobenzylidene)-1-(4-chlorophenyl)indolin-2-one (0.05 g, 43.00%).

2.3 Biological assay.

The cell lines HepG2, HT-29 and K562 were plated in 96-well plates at a density of 5×10^3 cells per well and cultured at 37°C in 5% CO₂ for 2 h (suspension cells) or 24 h (attached cell). Cells were treated with different concentrations of compounds and incubated at 37 °C for an additional 48 h. MTT assay was performed using Thermo microplate reader. The DMSO-treated controls were calculated as a cell viability value of 100%. The IC₅₀ values were obtained by nonlinear regression using GraphPad Prism 4.0. IC₅₀ measurements for each compound were done three times.

RESULTS AND DISCUSSION

3.1 Characterize isatin derivatives by ^1H and ^{13}C NMR.**3.1.1 3-(4-methylbenzylidene)indolin-2-one (compound 2) by ^1H and ^{13}C NMR.**

^1H NMR (400 MHz, DMSO): 2.41 (s, 3H), 6.90-6.92 (d, $J=8.0\text{Hz}$, 1H), 7.03-7.07 (t, $J=16.0\text{Hz}$, 1H), 7.38-7.42 (m, 3H), 7.87-7.89 (d, $J=8.0\text{Hz}$, 2H), 7.95-7.97 (d, $J=8.0\text{Hz}$, 1H), 7.87-7.89 (d, $J=8.0\text{Hz}$, 2H), 8.60 (s, 1H), 10.87 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 21.74, 111.29, 116.96, 122.81, 129.27, 129.39, 129.39, 130.30, 130.30, 131.27, 134.09, 142.93, 145.44, 150.92, 161.25, 165.04.

3.1.2 3-benzylideneindolin-2-one (compound 3) by ^1H and ^{13}C NMR.

^1H NMR (400 MHz, DMSO): 6.91-6.93 (d, $J=8.0\text{Hz}$, 1H), 7.03-7.07 (t, $J=16.0\text{Hz}$, 1H), 7.40-7.44 (t, $J=16.0\text{Hz}$, 1H), 7.59-7.60 (m, 3H), 7.92-7.94 (d, $J=8.0\text{Hz}$, 1H), 7.99-8.01 (d, $J=8.0\text{Hz}$, 2H), 8.63 (s, 1H), 10.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 114.34, 116.88, 122.84, 129.26, 129.30, 129.30, 129.68, 129.68, 132.55, 133.90, 134.20, 145.52, 150.81, 160.58, 164.95.

3.1.3 3-(4-(trifluoromethyl)benzylidene)indolin-2-one (compound 4) by ^1H and ^{13}C NMR.

^1H NMR (400 MHz, DMSO): 6.93-6.95 (d, $J=8.0\text{Hz}$, 1H), 7.02-7.05 (t, $J=15.2\text{Hz}$, 1H), 7.41-7.45 (t, $J=15.2\text{Hz}$, 1H), 7.78-7.81 (d, $J=8.0\text{Hz}$, 1H), 7.93-7.95 (d, $J=8.0\text{Hz}$, 2H), 8.18-8.10 (d, $J=8.0\text{Hz}$, 2H), 8.67 (s, 1H), 10.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 111.41, 116.63, 122.83, 126.44, 126.48, 129.17, 129.17, 129.71, 129.71, 131.91, 134.41, 137.57, 145.70, 150.35, 157.59, 164.71.

3.1.4 3-(4-methoxybenzylidene)indolin-2-one (compound 5) by ^1H and ^{13}C NMR.

^1H NMR (400 MHz, DMSO): 3.87 (s, 3H), 6.91-6.93 (d, $J=8.0\text{Hz}$, 1H), 7.04-7.08 (t, $J=16.0\text{Hz}$, 1H), 7.13-7.15 (d, $J=8.0\text{Hz}$, 2H), 7.39-7.43 (t, $J=16.0\text{Hz}$, 1H), 7.96-7.98 (d, $J=8.0\text{Hz}$, 2H), 8.06-8.08 (d, $J=8.0\text{Hz}$, 1H), 8.65 (s, 1H), 10.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 55.99, 111.21, 115.23, 115.23, 117.13, 122.75, 126.55, 129.35, 131.49, 131.49, 133.91, 145.32, 151.21, 162.42, 163.09, 165.24.

3.1.5 3-(4-chlorobenzylidene)indolin-2-one (compound 6) by ^1H and ^{13}C NMR.

^1H NMR (400 MHz, DMSO): 6.91-6.93 (d, $J=8.0\text{Hz}$, 1H), 7.02-7.05 (t, $J=15.2\text{Hz}$, 1H), 7.40-7.43 (t, $J=15.2\text{Hz}$, 1H), 7.64-7.66 (d, $J=8.0\text{Hz}$, 2H), 7.87-7.89 (d, $J=8.0\text{Hz}$, 1H), 7.99-8.01 (d, $J=8.0\text{Hz}$, 2H), 8.63 (s, 1H), 10.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 111.37, 116.79, 122.86, 129.27, 129.83, 129.83, 130.91, 130.91, 132.75, 134.32, 137.17, 145.59, 150.83, 159.36, 164.89.

3.1.6 3-(3,4-dichlorobenzylidene)indolin-2-one (compound 7) by ^1H and ^{13}C NMR.

^1H NMR (400 MHz, DMSO): 6.85-6.87 (d, $J=8.0\text{Hz}$, 1H), 6.93 (t, $J=10.4\text{ Hz}$, 1H), 7.21-7.27 (t, $J=10.2\text{Hz}$, 1H), 7.32 (s, 1H), 7.43-7.45 (d, $J=8.0\text{Hz}$, 1H), 7.65-7.67 (d, $J=8.0\text{Hz}$, 2H), 8.47 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 111.23, 116.20, 122.11, 128.97, 129.42, 129.42, 130.05, 130.05, 131.43, 132.98, 136.17, 143.78, 150.49, 159.12, 165.03.

3.1.7 3-(4-chlorobenzylidene)-1-phenylindolin-2-one (compound 8) by ^1H and ^{13}C NMR.

^1H NMR (d_6 -DMSO, 400 MHz): δ /ppm 6.80(d, $J=8\text{Hz}$, 1H), 7.17(t, $J=7.6\text{Hz}$, 1H), 7.45 (t, $J=8\text{Hz}$, 1H), 7.51(t, $J=8.8\text{Hz}$, 3H), 7.61(t, $J=7.6\text{Hz}$, 2H), 7.68(d, $J=8\text{Hz}$, 2H), 8.05 (d, $J=8\text{Hz}$, 3H), 8.71(s, 1H); ^{13}C NMR (d_6 -DMSO, 100 MHz): δ /ppm 110.36, 116.41, 123.95, 127.38, 128.90, 129.42, 129.90, 130.17, 131.09, 132.70, 134.06, 134.24, 137.38, 146.48, 150.03, 160.10, 162.95.

3.1.8 3-(3,4-dichlorobenzylidene)-1-phenylindolin-2-one (compound 9) by ^1H and ^{13}C NMR.

^1H NMR (d_6 -DMSO, 400 MHz): δ /ppm 6.80 (d, $J=8.0\text{ Hz}$, 1H), 7.15 (t, $J=6.8\text{ Hz}$, 1H), 7.43-7.59 (m, 4H), 7.6 (d, $J=7.2\text{ Hz}$, 2H), 7.71(d, $J=8.8\text{ Hz}$, 1H), 7.80 (d, $J= 8.4\text{ Hz}$, 1H), 7.92 (d, $J=7.6\text{ Hz}$, 1H), 8.05(s, 1H), 8.22(s, 1H); ^{13}C NMR (d_6 -DMSO, 100 MHz) : δ /ppm 110.39, 116.26, 124.00, 127.36, 128.59, 128.91, 129.40, 129.40, 130.17, 131.29, 131.29, 132.04, 132.58, 134.01, 134.38, 134.42, 135.06, 146.56, 149.80, 158.14, 162.82.

3.1.9 (Z)-3-(3,4-dichlorobenzylidene)-1-(p-tolyl)indolin-2-one (compound 10) by ^1H and ^{13}C NMR.

^1H NMR (d_6 -DMSO, 400 MHz) : δ /ppm 8.65 (s, 1H), 8.22 (s, 1H), 8.04 (d, $J = 8.4\text{ Hz}$, 1H), 7.94 (t, $J = 12.8\text{ Hz}$, 1H), 7.88 (d, $J = 8.3\text{ Hz}$, 1H), 7.54-7.26 (m, 4H), 7.16 (t, $J = 7.5\text{ Hz}$, 1H), 6.77 (d, $J = 7.9\text{ Hz}$, 1H), 2.41 (s, 3H); ^{13}C NMR (d_6 -DMSO, 100 MHz): δ /ppm 21.28, 110.39, 116.22, 123.92, 127.19, 128.58, 128.58, 129.36, 130.64, 130.64, 131.29, 131.38, 132.05, 132.58, 134.38, 134.43, 135.04, 138.48, 146.76, 149.82, 158.06, 162.88.

3.1.10 (Z)-3-(3,4-dichlorobenzylidene)-1-(4-(trifluoromethyl)phenyl)indolin-2-one (compound 11) by ¹H and ¹³C NMR.

¹H NMR (CDCl₃, 400 MHz): δ/ppm 8.56 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.87-7.75 (m, 3H), 7.63 (d, *J* = 8.2, 6.0 Hz, 3H), 7.41 (d, *J* = 7.9, 1.2 Hz, 1H), 7.21-7.15 (m, 1H), 6.93 (d, *J* = 7.8, 3.5 Hz, 1H);
¹³C NMR (CDCl₃, 100 MHz): δ/ppm 110.21, 115.69, 122.90, 124.55, 126.89, 127.98, 129.02, 129.02, 130.33, 130.99, 131.30, 131.30, 131.95, 132.24, 133.88, 134.03, 134.74, 137.56, 145.88, 150.12, 158.34, 161.93.

3.2 Anticancer activity assay.

All the above compounds were tested for their anticancer activity against HepG2, HT-29 and K562 by MTT based assay. The results were presented in Table 1. Results suggest that groups at the 1-position and 3-position could influence the antitumor potency.

As shown in the Table 1, placement of benzylidene at C-3 position on isatin in analogues 2, 3, 5, 6 and 7 resulted in increase in activity compared with the mother structure analogue 1. Among, compound 6 exhibited better anticancer activity, with the IC₅₀ values of 23.41 μM and 22.37 μM against cancer cell lines HepG2 and HT-29. This finding has prompted us to further investigate anticancer activity of N-1 derivatives. The introduction of Phenyl at N-1 position (8-11) showed stronger activity than compounds 6 and 7 against K562 cell lines.

Table 1 Inhibition Activity of isatin derivatives

Tested cells	Compounds (IC ₅₀ , μM)										
	1	2	3	4	5	6	7	8	9	10	11
HepG2	>100	34.47	35.36	>100	41.69	23.41	>100	5.54	24.09	60.24	>100
HT-29	>100	29.37	29.88	>100	26.75	22.37	>100	82.8	20.27	14.69	>100
K562	>100	25.22	26.27	>100	31.68	>100	40.35	36.35	6.10	4.40	23.84

CONCLUSION

A series of N-1 and C-3 substituted isatin derivatives were synthesized and tested for their in vitro antitumor activity against three strains of cancer cell lines HepG2, HT-29 and K562. The SAR study of these compounds led to the identification of a new isatin analogues 9, as higher potent anticancer compounds with the IC₅₀ values of 24.09 μM, 20.27 μM, 6.10 μM against cancer cell lines HepG2, HT-29 and K562. Further chemo-biological study of 9 with regards to their antitumor pathway and in vivo investigation are ongoing in this laboratory.

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