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An Efficient, Eco-Friendly Synthesis of Pyran Annulated Indole Analogs under Conventional Heating and Microwave Irradiation, and Their Anticancer and Antioxidant Activity[1]

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Abstract—A rapid, facile, green, eco-friendly, cost effective, and efficient method for the synthesis of pyran annulated indole analogs via one-pot, three components reaction is developed. According to the developed method 2,5-disubstituted-1*H*-indol-3-carboxaldehyde, malononitrile and various phenols react under MW assisted solvent-free conditions. These compounds can be also prepared under a conventional method that is characterized by some disadvantages in comparison with the above approach. Structures of products are confirmed by FT-IR, ^{1}H and ^{13}C NMR, and mass spectral data. The in vitro antioxidant and cytotoxic activities of the products are evaluated against three tumor cell lines and discussed in terms of structure—activity analysis. Among the screened compounds **3d, 4a, 4b, 5a,** and **5b** exhibit excellent antioxidant activity. Compounds **4b, 5a,** and **5b** demonstrate strong cytotoxic activity.

Keywords: indole, phenols, pyran, MW-irradiation, green synthesis, catalyst, anticancer and antioxidant activities

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INTRODUCTION

Cancer and atherosclerosis are two major causes of death promoted by the salient "free radical" impact. Development of new drugs against cancer continues to be the main objective for fundamental research [1–3].

Probably, endogenous free radical reactions, like those initiated by ionizing radiation, can lead to tumors formation. One of correlations between reactive oxygen species (ROS) and cancer is the increased death rates from leukemia and malignant neoplasia of breast, ovaries and rectum induced by a greater impact of lipid peroxidation [1, 4, 5]. ROS may cause initiation of lipid peroxidation, direct inhibition of mitochondrial respiratory enzymes, deactivation of glyceraldehyde-3-phosphate dehydrogenase, inhibition of membrane sodium/potassium ATPase activity, deactivation of membrane sodium channel and other oxidative alteration of proteins. All these toxic effects are likely to play a crucial role in pathophysiology of shock, inflammation and ischemia-reperfusion injury [6–8].

Indole and its analogs comprise a significant class of therapeutic agents including anticancer [3, 5], antioxidant [9, 10], antirheumatoidal, and anti-HIV [11, 12]. Many indole analogs are considered to be potent scavengers of free radicals [3, 4, 9, 10].

MW-Assisted organic synthesis in many instances is an ecologically friendly solvent free and catalyst free method that can influence upon chemo-, regio-, and stereo-selectivity [8].

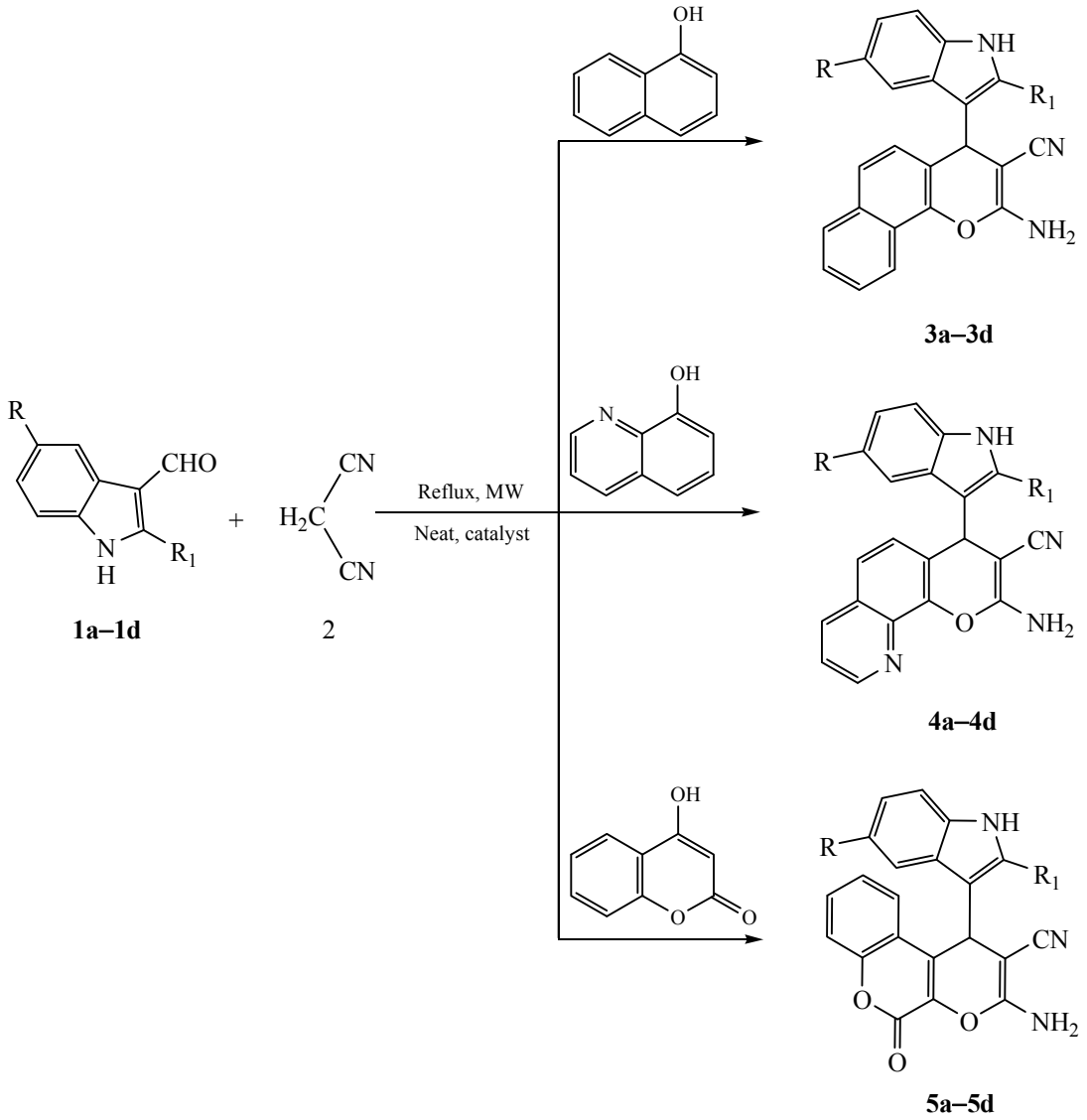
As an extension of our interest in green chemistry of bioactive indoles [1, 3, 4, 9–11], we present herein a rapid and ecofriendly synthesis of pyran annulated 2,5-disubstituted indole analogs by conventional method and MW irradiation (with and without a catalyst and neat) under solvent-free conditions (Scheme 1). The synthesized compounds were evaluated for cytotoxic and antioxidant activities.

RESULTS AND DISCUSSION

In the present study synthetic approach to indole analogs was carried out under two different reaction conditions, conventional method and solvent-free MW-

[1] The text was submitted by the authors in English.

Scheme 1. Synthetic approach to indole analogs.



R = Cl, R_1 = Ph (**a**), R = CH_3, R_1 = Ph (**b**), R = H, R_1 = Ph (**c**), R = R_1 = H (**d**).

irradiation (Scheme 1). According to the first approach heating of the mixture of equivalent amounts of 2,5-disubstituted-1*H*-indole-3-carboxaldehyde (**1a–1d**) with malononitrile (**2**) and α-naphthol, 8-hydroxyquinoline, and 4-hydroxycoumarin gave low yields (25–35%) of the products. Among other disadvantages of the method were use of a solvent and long reaction time.

Under solvent-free conditions and MW-irradiation the synthesis led to formation of the products with 80–94% yields (Table 1). In an attempt to improve the reaction yield the process was carried out under neat conditions (without a solvent or a catalyst). However, this approach suffered from very low yields and long reaction time, sometimes no reaction occurred. Catalysis by $KNaC_4H_4O_6 \cdot 4H_2O$ (10 mol %) under solvent-free conditions led to formation of the products **3a–3d**, **4a–4d**, **5a–5d** with high yields (80–94%). Structures of the synthesized compounds were elucidated from IR, ^1H and ^{13}C NMR, and mass spectra.

Biological evaluation. Melatonin and other indole analogs may reduce incidence and growth of tumors probably due to their antioxidant activity [12, 13]. In

Table 1. Synthesis of novel indole derivatives data

Comp. no	Conventional		MW-irradiation at 125–150°C						mp, °C
	reflux–EtOH		neat			neat + $KNaC_4H_4O_6 \cdot 4H_2O$			
	time, h	yield, %	time, min	power, W	yield, %	time, min	power, W	yield, %	
3a	12	35	10	450	50	5	350	94	248–249
3b	12	30	10	450	42	5	350	92	258–259
3c	10	25	8	450	50	6	350	90	249–250
3d	10	25	8	450	–[a]	6	350	90	209–210
4a	12	35	10	450	50	5	350	92	259–260
4b	12	32	10	450	45	5	350	90	250–251
4c	9	35	9	450	42	5	350	89	218–219
4d	9	30	9	450	–[a]	5	350	88	220–221
5a	12	35	10	450	40	6	350	94	225–226
5b	12	31	10	450	40	6	350	92	238–239
5c	9	25	9	450	–[a]	6	350	88	186–187
5d	9	25	8	450	–[a]	6	350	88	210–211

[a] (–) No reaction occurred.

the current study the antioxidant activity of 2,5-disubstituted indole analogs was evaluated.

Free radical scavenging activity (FRSA). Samples were prepared at concentrations of 25, 50, 75, and 100 μg/mL. Butylated hydroxyanisole (BHA) and ascorbic acid (AA) were used as standards. The presence of different substituents at the position C_5 of indole allowed to compare the influence of these upon scavenging activity. It is noteworthy that the unsubstituted in position C_5 compounds **3d, 4d** demonstrated the highest scavenging activity. Whereas compounds **5b–5d** were of moderate activity. The compounds scavenged the DPPH radical in a concentration dependent manner (Fig. 1).

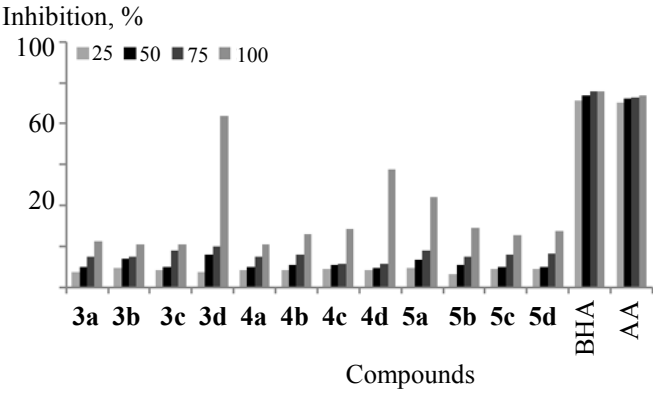


Fig 1. DPPH free radical scavenging activity; (BHA) butylated hydroxyanisole and (AA) ascorbic acid.

Total antioxidant capacity (TAC). Antioxidant capacity is expressed as equivalents of ascorbic acid. Some of the synthesized ring systems demonstrated positive tendency towards TAC. According to the earlier reports [4, 9, 10], indole derivatives exhibited moderate to low activity. It was also observed that chlorine and methyl group substituents at the position C_5 of the indole ring **4a, 4b, 5a,** and **5b** stimulated the antioxidant capacity. In contrast unsubstituted derivatives demonstrated lower activity (Fig. 2).

Ferric reducing antioxidant power activity (FRAPA). The synthesized compounds reduced Fe^{+3} cations in a concentration dependent manner. Butylated hydroxyanisole and ascorbic acid were used as standards. Screening results indicated that all newly synthesized indole analogs were active ferric reducing antioxidant agents, with varying degree of potency. Indol derivatives **4a, 4b** demonstrated excellent ferric reducing activity. The other analogues were of moderate to high activity. Substituents Cl and CH_3 at C_5 position of the indole ring supported high activity of the products (Fig. 3).

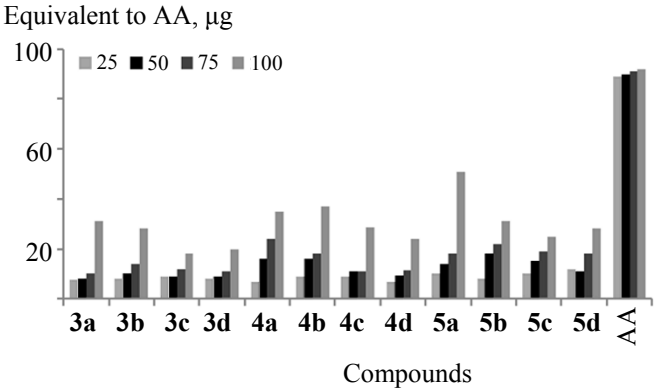


Fig. 2. Total antioxidant capacity; (AA) ascorbic acid.

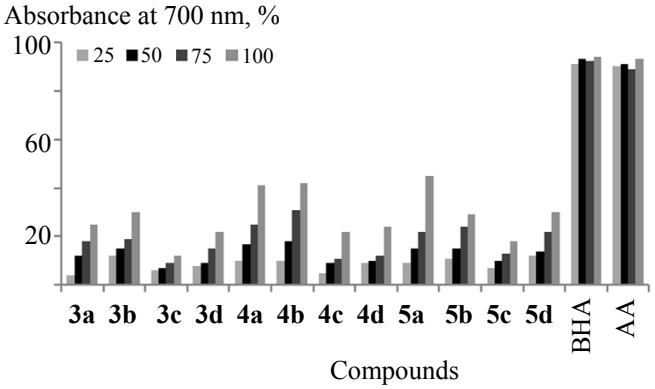


Fig. 3. Influence of the synthesized compounds upon FRPA; (BHA) butylated hydroxyanisole and (AA) ascorbic acid.

In vitro cytotoxic studies. Preliminary evaluation of antitumor cytotoxicity of the synthesized compounds was studied against three different tumor cell lines, A-549 (Lung carcinoma), HEp-2 (Laryngeal carcinoma) and HeLa (Cervical carcinoma) by the MTT assay with Doxorubicin as a positive reference [3, 4] (Table 2). The compounds **5b** demonstrated effective cytotoxicity against all three cell lines. Compound **4b** exhibited high cytotoxic activity against A-549 (IC_{50} 22.61 μM) and HeLa (IC_{50} 88.16 μM) but not against HEp-2. In contrast, compounds **3a, 3b** demonstrated the lowest activity against HeLa (IC_{50} 84.28, 83.04 μM), and compounds **3a, 3b,** and **4b** failed to show any activity against cell lines A-549 and HEp-2. The results clearly indicated indolyl–dihydropyrano–chromene **5a, 5b** as a system with potentially strong cytotoxicity against all three cell lines. Whereas, the compounds with Cl and CH_3

Table 2. *In vitro* cytotoxicity of indol analogues[a]

Comp. no.	IC_{50}, μM		
	A-549 (lung carcinoma)	HEp-2 (laryngeal carcinoma)	HeLa (cervical carcinoma)
3a	>100	>100	84.28
3b	71.02	>100	83.04
3c	>100	70.15	68.52
3d	85.46	46.92	54.21
4a	>100	>100	71.09
4b	22.61	>100	80.16
4c	51.29	35.55	49.52
4d	45.06	50.92	66.56
5a	>100	18.56	56.90
5b	24.30	50.53	59.77
5c	85.21	45.21	72.12
5d	56.54	63.32	32.12
Doxorubicin	0.70	8.70	0.71

[a] (>100) active but IC_{50} could not be calculated due to lesser % inhibition, (IC_{50}) the compound concentration for which the growth of treated cells from time "0" was only 50%.

substitution at C_5 position of indole had some tendency to initiate the activity.

EXPERIMENTAL

All chemicals used were purchased from Merck, Himedia and SD fine chemicals and used as such. Reaction progress was monitored by TLC (Merck Silica gel 60 F_{245} plates). The spots were visualized by UV light at 254 nm. Melting points were measured in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer for KBr discs. ^{1}H and ^{13}C NMR spectra were measured on a Bruker 400MHz, SAIF in DMSO-d_6 using TMS as an internal standard. LCMS spectra were measured on a SHIMADZU, LCMS 2O1OA, Mass spectrometer. MW-Irradiation reactions were carried out in a ONIDA 20STP21 800W multimode microwave oven.

Synthesis of 2,5-disubstituted indole-3-carboxaldehydes (1a–1d). The precursors 2,5-disubstituted indole-3-carboxaldehydes **1a–1d** were synthesized by the Vilsmeier–Haack formylation reaction of 2,5-disubstituted indoles [1].

Synthesis of 3a–3d, 4a–4d, and 5a–5d. *A. Conventional method.* A mixture of 2,5-disubstituted indole-3-carboxaldehyde (0.01 mmol) with malononitrile (0.01 mmol) and α-naphthol, 8-hydroxyquinoline, 4-hydroxycoumerin (0.01 mmol) in ethanol (15 mL) was heated for certain time intervals (Table 1).

B. MW-assisted synthesis. (1). Neat reaction. A mixture of 2,5-disubstituted indole-3-carboxaldehyde (0.01 mmol) with malononitrile(0.01mmol) and α-naphthol, 8-hydroxyquinoline, 4-hydroxycoumerin (0.01 mmol) was mixed with finely powdered 5 Å molecular sieves (0.5–1.0 g). The mixture was subjected to MW irradiation at moderate power (350–450 W) for 8–10 min and loaded into an open borosil glass vessel (to decrease internal pressure). This was subjected to MW irradiation for 10 min at 125–150°C followed by the corresponding manipulations as reported [4].

(2) Neat with $KNaC_4H_4O_6{\cdot}4H_2O$. A mixture of 2,5-disubstituted indole-3-carboxaldehyde (0.01 mmol) with malononitrile (0.01 mmol) and α-naphthol, 8-hydroxyquinoline, 4-hydroxycoumerin (0.01 mmol) was combined with powdered $KNaC_4H_4O_6{\cdot}4H_2O$ (10 mol %), and mixed with finely powdered 5 Å molecular sieves (0.5–1.0 g). The mixture was subjected to MW irradiation at moderate power (350–450 W) for 5–6 min and introduced in an open borosil glass vessel (to decrease internal pressure). This was subjected to MW irradiation for 10 min at 125–150°C followed by the corresponding manipulations developed earlier [4].

After completion of the process (TLC), the reaction mixture was poured into crushed ice. The crude product was filtered off on a Buchner funnel and purified by crystallization from hot ethanol.

2-Amino-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile (3a). Light yellow crystals, yield 96%, mp 248–249°C. IR spectrum, ν, cm^{-1}: 3450(NH), 3353(NH_2), 3001(Ar-H), 2920 (CH), 2143 (CN), 1298(O), 710 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 4.45 s (1H, CH), 7.29–7.82 m (14H, Ar-H), 9.98 s (2H, NH_2), 12.60 s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 112, 113, 120,123, 126, 129, 130, 134 (Ar-C), 150 (C–NH_2). MS: *m/z* 447 $[M]^+$ (27%), 449 $[M + 2]^+$ (9%).

2-Amino-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile (3b). Yellowish-green powder, yield 98%, mp 258–259°C. IR spectrum, ν, cm^{-1}: 3584 (NH), 3231 (NH_2), 2941 (CH_3), 2147 (CN), 1320 (O). ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 4.35 s (1H, CH), 7.10–8.04 m (14H, Ar-H), 9.95 s (2H, NH_2), 12.30 s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 21.54 (CH_3), 71 (C–CN), 108, 112, 115, 116, 122, 124, 125, 129, 130, 131, 135, 149 (Ar-C), 154 (C–NH_2). MS: *m/z* 427 $[M]^+$ (13%).

2-Amino-4-(2-phenyl-1*H*-indol-3-yl)-4*H*-benzo-[*h*]chromene-3-carbonitrile (3c). Light brownish powder, yield 90%, mp 249–250°C. IR spectrum, ν, cm^{-1}: 3351 (NH), 3323 (NH_2), 2900 (CH), 2183 (CN), 1208 (O). ^{1}H NMR spectrum, δ, ppm: 4.01 s (1H, CH), 6.29–7.10 m (15H, Ar-H), 9.80 s (2H, NH_2), 12.20 s (1H, NH indole). MS: *m/z* 413 $[M]^+$.

2-Amino-4-(1*H*-indol-3-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile (3d). Dark yellow powder, yield 95%, mp 209–210°C. IR spectrum, ν, cm^{-1}: 3411(NH), 3393 (NH_2), 2890 (CH), 2133 (CN), 1308 (O). ^{1}H NMR spectrum, δ, ppm: 4.82 s (1H, CH), 7.29–8.10 m (15H, Ar-H), 9.70 s (2H, NH_2), 11.80 s (1H, NH indole). MS: *m/z* 337 $[M]^+$.

2-Amino-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (4a). Gray powder, yield 97%, mp 259–260°C. IR spectrum, ν,

cm^{-1}: 3431 (NH), 3367 (NH_2), 2880 (CH), 2142 (CN), 1437 (C=N), 1318 (O), 711 (C–Cl). ^1H NMR spectrum, δ, ppm: 4.71 s (1H, CH), 7.30–8.20 m (13H, Ar-H), 9.96 s (2H, NH_2), 12.60 s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 112, 113, 120,123, 126, 129, 130, 134 (Ar-C), 150 (C–NH_2). MS: *m/z* 448 $[M]^+$ (20%), 450$[M + 2]^+$ (7%).

2-Amino-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (4b). Light greenish powder, yield 95%, mp 250–251°C. IR spectrum, ν, cm^{-1}: 3450 (NH), 3332 (NH_2), 2878–2961 (CH_3), 2143 (CN), 1437 (C=N), 1318 (O). ^1H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 4.42 s (1H, CH), 7.11–8.04 m (13H, Ar-H), 9.95 s (2H, NH_2), 12.36 s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 21.30 (CH_3), 111, 113, 120, 125, 126, 128,129, 131, 134 (Ar-C), 149 (C–NH_2). MS: *m/z* 428 $[M]^+$ (10%).

2-Amino-4-(2-phenyl-1*H*-indol-3-yl)-4*H*-pyrano-[3,2-*h*]quinoline-3-carbonitrile (4c). Greenish powder, yield 89%, mp 218–219°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 3337 (NH_2), 2980 (CH), 2170 (CN), 1450 (C=N), 1300 (O). ^1H NMR spectrum, δ ppm: 4.12 s (1H, CH), 7.50–8.10 m (14H, Ar-H), 9.86 s (2H, NH_2), 11.90 s (1H, NH indole). MS: *m/z* 414 $[M]^+$.

2-Amino-4-(1*H*-indol-3-yl)-4*H*-pyrano[3,2-*h*]-quinoline-3-carbonitrile (4d). Light greenish powder, yield 88%, mp 220–221°C. IR spectrum, ν, cm^{-1}: 3350 (NH), 3302 (NH_2), 2908 (CH), 2163 (CN), 1400 (C=N), 1320 (O). ^1H NMR spectrum, δ, ppm: 4.32 s (1H, CH), 7.01–8.00 m (10H, Ar-H), 9.05 s (2H, NH_2), 11.36 s (1H, NH indole). MS: *m/z* 338 $[M]^+$.

3-Amino-1-(5-chloro-2-phenyl-1*H*-indol-3-yl)-5-oxo-1,5-dihydropyrano[2,3-*c*]chromene-2-carbonitrile (5a). Light yellow powder, yield 94%, mp 225–226°C. IR spectrum, ν, cm^{-1}: 3435 (NH), 3410 (NH_2), 2996 (Ar-H), 2913 (C-H), 2173 (CN), 1656 (C=O), 1312 (O), 702 (C–Cl). ^1H NMR spectrum, δ, ppm: 3.62 s (1H, CH), 7.30–8.19 m (12H, Ar-H), 9.95 s (2H, NH_2), 12.63 s (1H, NH indole). ^{13}C NMR, spectrum, δ ppm: 74 (C–CN), 107, 112, 113, 114, 115, 116, 120, 123, 121, 126, 129, 130, 134, 135, 149, 150 (Ar-C), 154 (C–NH_2), 185.52 (C=O). MS: *m/z* 465 $[M]^+$ (10%), 467 $[M + 2]^+$ (3%).

3-Amino-1-(5-methyl-2-phenyl-1*H*-indol-3-yl)-5-oxo-1,5-dihydropyrano[2,3-*c*]chromene-2-carbonitrile (5b). Dark brown powder, yield 92%, mp 238–239°C. IR spectrum, ν, cm^{-1}: 3434 (NH), 3402 (NH_2), 2998 (Ar-H), 2913 (CH), 2144 (CN), 1658 (C=O), 1318 (O). ^1H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 4.54 s (1H, CH), 7.18–7.95 m (12H, Ar-H), 8.22 s (2H, NH_2), 11.71 s (1H, NH indole). ^{13}C NMR spectrum, δ, ppm: 21.29 (CH_3), 111, 113, 120, 125, 126, 128, 129, 131, 134 (Ar-C), 148 (C–NH_2), 185.39 (C=O). MS: *m/z* 445 $[M]^+$ (29%).

3-Amino-5-oxo-1-(2-phenyl-1*H*-indol-3-yl)-1,5-dihydropyrano[2,3-*c*]chromene-2-carbonitrile (5c). Yellow brown powder, yield 88%, mp 186–187°C. IR spectrum, ν, cm^{-1}: 3422 (NH), 3352 (NH_2), 2900 (CH), 2150 (CN), 1650 (C=O), 1350 (O). ^1H NMR spectrum, δ, ppm: 4.81 s (1H, CH), 7.01–8.20 m (13H, Ar-H), 9.06 s (2H, NH_2), 11.00 s (1H, NH indole). MS: *m/z* 431 $[M]^+$.

3-Amino-1-(1*H*-indol-3-yl)-5-oxo-1,5-dihydro-pyrano[2,3-*c*]chromene-2-carbonitrile (5d). Dark brown powder, yield 88%, mp 210–211°C. IR spectrum, ν, cm^{-1}: 3322 (NH), 3252 (NH_2), 2982 (CH), 2180 (CN), 1680 (C=O), 1310 (O). ^1H NMR spectrum, δ, ppm: 4.01 s (1H, CH), 7.20–8.00 m (9H, Ar-H), 9.01 s (2H, NH_2), 11.10 s (1H, NH indole). MS: *m/z* 355 $[M]^+$.

Biological activities. *Free radical DPPH scavenging activity.* The synthesized compounds were screened for *in-vitro* DPPH free radical scavenging activity according to the developed earlier method [4, 9, 10].

Total antioxidant capacity. The total antioxidant capacity of the synthesized compounds was evaluated by the phosphomolybdenum method as described [4, 9, 10].

Ferric reducing antioxidant power activity. The total reducing power of the synthesized compounds was determined according to the earlier developed method [4, 9, 10].

In vitro cytotoxic studies. A-549 (Lung carcinoma), HEp-2 (Laryngeal carcinoma) and HeLa (Cervical carcinoma) cell lines were procured from ATCC, stock cells were cultured in DMEM supplemented with 10% inactivated Fetal Bovine Serum (FBS), penicillin (100 IU/mL), streptomycin (100 μg/mL) in a humidified atmosphere of 5% CO_2 at 37°C until confluent. The cells were dissociated in TPVG solution (0.2% trypsin, 0.02% EDTA, 0.05% glucose in PBS), their viability was checked, and then those were centrifuged. 50,000 Cells/well of Jurkat was seeded in a 96 well plate and incubated for 24 h at 37°C, and incubated (5%CO_2) as reported [3, 4].

CONCLUSIONS

We have used efficient and ecologically safe methods for the synthesis of pyran annulated indole derivatives using two different reaction conditions. The MW-irradiation method has some advantages such as operational simplicity, neutral and clean reaction conditions, high yields, easy work-up. The synthesized compounds demonstrated moderate to good *in vitro* cytotoxic activity against A-549 (Lung carcinoma), HEp-2 (Laryngeal carcinoma) and HeLa (Cervical carcinoma). Compounds **4b** and **5b** exhibited potent growth inhibitory activity. Compounds **3d, 4a, 4b, 5a, 5b** exhibit excellent antioxidant activity.

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CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

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