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Pharmacological Activities of Some 5-Substituted-3-phenyl-Nβ-(substituted-2-oxo-2H-pyrano [2, 3-b] quinoline-3-carbonyl)-1H-indole-2-carboxyhydrazides

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Abstract

Indoles are amongst the most important class of heteroaromatics in organic chemistry, being generally found in biologically active natural products. Indole motifs have become noteworthy compounds because of their ample assortment of applications in medicine, synthetic chemistry, coordination chemistry, as well as in the field of industrial chemistry. Ethyl-3-oxo-3-{2-[(5-substituted-3-phenyl-1H-indol-2-yl) carbonyl] hydrazinyl} propanoates 5a-b were synthesized according to the literature method. These on further reaction with substituted-2-hydroxy-3-formylquinolines 3a-e yielded 5-substituted-Nβ-(2-oxo-2H-pyrano [2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole- 2- carbohydrazide 6a-j. Spectral techniques were used to confirm the structures of the all synthesized compounds. All these compounds have been screened for their pharmacological activities such as anti-inflammatory and analgesic activities.

Keywords: Heterocyclic compounds; Indole; Pharmacological activities; Pyrano-quinoline-2-one; Quinoline

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Introduction

Heterocyclic moieties endow with as model scaffold on which pharmacophore can be efficiently attached to create novel drugs. Indoles are amongst the most imperative class of heteroaromatics in medicinal chemistry, which are ever-present in natural artefacts. The foresaid analogues have become noteworthy compounds because of their wide variety of applications in drug design and development. Numerous indole derivatives accounted in the literature are identified to acquire diverged biological potentials viz., antimalarial activity [1], anti-TB evaluation [2] and anti-inflammatory [3]. Quinolines analogues have been engrossed the interest of the many chemists because of their existence in various natural products exhibiting considerable biological activities [4-8]. Many indolo[2, 3-c] isoquinolines investigated from our laboratory have been found to possess bactericidal and fungicidal activities[9-11]. Earlier we have disclosed the synthesis of 3, 5-disubstituted-N_{β}-(2-oxobenzopyran-3-carbonyl)- 1H-indole-2-carbohydrazide [12] by making use of ethyl 3-oxo-3-{2-[(5-substituted-3-phenyl-1H-indol-2-yl)carbonyl] hydrazinyl}propanoates [13] 5a, b, which in turn were prepared by the reaction of 5-substituted-3-phenyl-1H-indole-2-carbohydrazides 4a, b and diethylmalonate. In vision of these findings and in persistence of our research work on heterocyclic compounds, [14-23] we hereby account the pharmacological activities of some 5-substituted-N_{β}-(2-oxo-2H-pyrano[2, 3- b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazides 6a-j by ethyl 3-oxo-3-{2-[(5-substituted-3-phenyl-1H-indol-2-yl) carbonyl] hydrazinyl} propanoates 5a, b and substituted- 2-hydroxy-3-formylquinolines 3a-e as starting materials wherein substituted-2H-pyrano[2, 3-b]quinoline moiety attached to β-nitrogen of 5-substituted-3-phenyl-1H-indole-2-carbohydrazide at its 3-positon via carbonyl group **(Figure 1).**

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr discs (ν_{max} in cm-1) on Perkin- Elmer FT-IR (Spectrum ONE) spectrophotometer, 1H NMR spectra on a Bruker AMX (400 MHz) spectrophotometer using DMSO-d_6 as solvent using TMS as an internal standard (chemical shifts in d) and mass spectra on a mass spectrometer JEOL sx-102 (FAB) instrument (m/z in %). Compounds were checked for their purity by TLC on silica gel 60G F254 plates and iodine vapors were used as visualizing agent. Elemental analysis

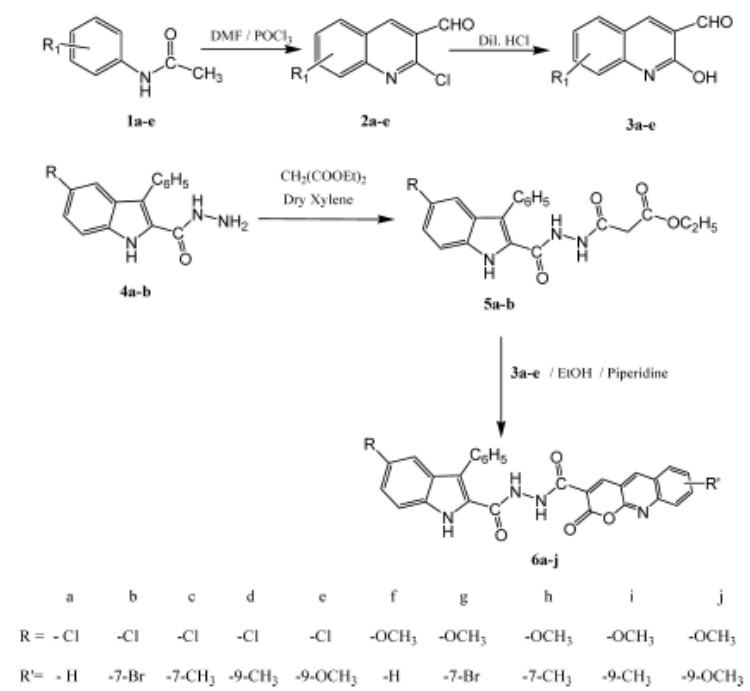

Figure 1 Pharmacological activity of drugs.

carried out using Flash EA1112 series elemental Analyser.

General methods

The starting materials ethyl 3-oxo-3-{2-[(5-substituted-3-phenyl-1H-indol-2-yl) carbonyl] hydrazinyl} propanoates [13] 5a, b and substituted-2-hydroxy- 3-formyl quinolines [8, 9] 3a-e were papered according to reported methods. Synthesis and antimicrobial activities of all the 5-Substituted-N_β-(2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazides 6a-j were already reported by us [15].

Synthesis of Substituted-2-chloro-3-formyl quinolines 2a-e: Dimethyl formamide (0.006 mol) was cooled to 0°C in a flask equipped with a drying tube and phosphorous oxychloride (0.006 mol) was added dropwise with stirring. To this solution acetanilide (1a-e) (0.001 mol) was added in small portions and after 5 min the reaction mixture was heated for 16 h on boiling water bath. The reaction mixture was poured into ice water and stirred for 30 min. The solid separated was filtered, dried and recrystallized from ethyl acetate to get substituted-2-chloro-3-formyl quinolines 2a-e in good yield.

Synthesis of Substituted-2-hydroxy-3-formyl quinolines 3a-e: A mixture of 2-chloro-3-formylquinolines 2a-e (0.001 mol) and aqueous hydrochloric acid 3.5 mL (4 N) was heated under reflux conditions for 1 h and then allowed to cool to room temperature. The reaction mixture was poured on to crushed ice and the solid separated filtered, washed with water, dried and recrystallized from aqueous acetic acid to get substituted-2-hydroxy-3-formyl quinolines 3a-e in good yield.

Synthesis of 5-Substituted-N_β-(2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazides 6a-j: A mixture of compounds ethyl 3-oxo-3-{2-[(5-substituted-3-phenyl-1H-indol-2-yl)carbonyl] hydrazinyl}propanoates 5a, b (0.001 mol) and various substituted-2-hydroxy-3-formylquinolines 3a-e (0.001 mol) in ethanol (10 mL) was refluxed for 5 h in the presence of catalytic amount of piperdine. Excess of ethanol was removed by distillation. Crystalline residue obtained was filtered, washed with little amount of ethanol, dried and crystallized from suitable solvent to afford 5-substituted-N_β-(2-oxo-2H-pyrano[2,3-b] quinoline-3-carbonyl)-3-phenyl-1*H*-indole-2-carbohydrazides 6a-j in good yield. The compounds 6a, 6b, 6c, 6d, 6e and 6g were recrystallized from ethanol and the compounds 6f, 6h, 6i and 6j were recrystallized from isopropyl alcohol.

5-Chloro-N_β-(2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazide (6a): Colourless crystals in 71% yield, mp 212°C: IR (KBr) in cm-1: 1149 (COC), 1597 (CN), 1668, 1695, 1733 (CO/CO/CO), 3065, 3201, 3386 (NH/NH/NH). 1H NMR in d: 7.14-7.92 (m, 14H, ArH), 9.42 (s, 1H, indole NH), 9.71 (s, 1H, CONH), 10.20 (s, 1H, CONH). FAB-MS m/z (in %): 508, 510 (33%, 12%), 311, 313 (48%, 19%), 255, 257 (100%, 31%), 225, 227 (24%, 9%), 190 (36%). Anal. Calcd for C28H17N4O4Cl: C, 66.08; H, 3.34; N, 11.01; Found: C, 65.91; H, 3.42; N, 10.89.

5-Chloro-N_β-(7-bromo-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3- phenyl-1H-indole-2- carbo hydrazide (6b): Pale yellow crystals in 69% yield, mp185°C: IR (KBr) cm-1: 1158 (COC), 1593 (CN), 1663, 1701, 1731 (CO/CO/CO), 3050, 3211, 3305 (NH/NH/NH). 1H NMR in δ : 6.80-7.84 (m, 13H, ArH), 9.58 (s, 1H, indole NH), 9.95 (s, 1H, CONH), 10.19 (s, 1H, CONH). Anal. Calcd for C28H16N4O4ClBr: C, 57.19; H, 2.72; N, 9.53; Found: C, 56.98; H, 2.58; N, 9.34.

5-Chloro-N_β-(7-methyl-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazide (6c): Colourless

crystals in 75% yield, mp 145°C: IR (KBr) cm-1: 1154 (C–O–C), 1564 (CN), 1667, 1689, 1713 (CO/CO/CO), 3060, 3195, 3281 (NH/NH/NH). 1H-NMR in δ: 1.74 (s, 3H, CH3), 7.12-7.80 (m, 13H, ArH), 9.48 (s, 1H, indole NH), 9.84 (s, 1H, CONH), 10.28 (s, 1H, CONH). Anal. Calcd for C29H19N4O4Cl: C, 66.60; H, 3.64; N, 10.71; Found: C, 66.48; H, 3.52; N, 10.55.

5-Chloro-N_{β}-(9-methyl-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazide (6d): Colourless crystals in 64% yield, mp 191°C: IR (KBr) cm-1: 1162 (C–O–C), 1579 (CN), 1668, 1695, 1723 (CO/CO/CO), 3061, 3187, 3258 (NH/NH/NH). ^{1}H NMR in δ: 1.98 (s, 3H, CH3), 7.21-7.91 (m, 13H, ArH), 9.18 (s, 1H, indole NH), 9.70 (s, 1H, CONH), 10.18 (s, 1H, CONH). Anal. Calcd for C29H19N4O4Cl: C, 66.60; H, 3.64; N, 10.71; Found: C, 66.41; H, 3.48; N, 10.61.

5-Chloro-N_{β}-(9-methoxy-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazide (6e): Brown crystals in 71% yield, mp 231°C: IR (KBr) cm-1: 1162 (COC), 1578 (CN), 1671, 1692, 1719 (CO/CO/CO), 3081, 3188, 3280 (NH/NH/NH). 1H NMR in δ: 2.28 (s, 3H, –OCH3), 7.32—7.98 (m, 13H, ArH), 9.61 (s, 1H, indole NH), 10.0 (s, 1H, CONH), 10.36 (s, 1H, CONH). Anal. Calcd for C29H19N4O5Cl: C, 64.62; H, 3.53; N, 10.40; Found: C, 64.40; H, 3.35; N, 10.25.

5-Methoxy-N_{β} -(2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl- 1H-indole-2-carbohydrazide (6f): Pale yellow crystals in 69% yield, mp 189°C: IR (KBr) cm-1: 1166 (COC), 1578 (CN), 1681, 1698, 1719 (CO/CO/CO), 3083, 3105, 3187 (NH/NH/NH). 1H NMR in δ: 2.15 (s, 3H, –OCH3), 7.01-7.78 (m, 14H, ArH), 9.65 (s, 1H, indole NH), 9.91 (s, 1H, CONH), 10.28 (s, 1H, CONH). FAB-MS m/z (in %): 504 (42%), 307 (21%), 251 (100%), 221(15%), 190 (41%). Anal. Calcd for C29H20N4O5: C, 69.05; H, 3.97; N, 11.11; Found: C, 68.80; H, 3.75; N, 11.05.

5-Methoxy-N_{β} -(7-bromo-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)- 3-phenyl-1H-indole-2-carbohydrazide (6g): Brown crystals in 72% yield, mp 225 °C: IR (KBr) cm-1: 1154 (C–O–C), 1599 (CN), 1678, 1698, 1728 (CO/CO/CO), 3058, 3108, 3281 (NH/NH/NH). 1H NMR in δ: 2.18 (s, 3H, –OCH3), 6.91-7.68 (m, 13H, ArH), 9.80 (s, 1H, indole NH), 10.28 (s, 1H, CONH), 10.57 (s, 1H, CONH). Anal. Calcd for C29H19N4O5Br: C, 59.69; H, 3.26; N, 9.60; Found: C, 59.48; H, 3.14; N, 9.39.

5-Methoxy-N_{β} -(7-methyl-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)- 3-phenyl-1H-indole-2-carbo hydrazide (6h): Colourless crystals in 64% yield, mp 251 °C: IR (KBr) cm-1: 1162 (C–O–C), 1580 (CN), 1661, 1680, 1723 (CO/CO/CO), 3061, 3188, 3251 (NH/NH/NH). 1H NMR in δ: 1.71 (s, 3H, CH3), 2.20 (s, 3H, –OCH3), 7.14-7.78 (m, 13H, ArH), 9.76 (s, 1H, indole NH), 10.19 (s, 1H, CONH), 10.56 (s, 1H, CONH). Anal. Calcd for C30H22N4O5: C, 69.50; H, 4.25; N, 10.81; Found: C, 69.36; H, 4.15; N, 10.60.

5-Methoxy-N_{β}-(9-methyl-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)- 3-phenyl-1H-indole-2-carbohydrazide (6i): Colourless crystals in 71% yield, mp 165 °C: IR (KBr) cm-1: 1166 (C–O–C), 1578 (CN), 1668, 1685, 1719 (CO/CO/CO), 3083, 3187, 3248 (NH/NH/NH).1H NMR in δ: 1.74 (s, 3H, CH3), 2.18 (s, 3H, –OCH3), 7.10-7.79 (m, 13H, ArH), 9.36 (s, 1H, indole NH), 9.78 (s, 1H, CONH), 10.08 (s, 1H, CONH). Anal. Calcd for C30H22N4O5: C, 69.50; H, 4.25; N, 10.81; Found: C, 69.70; H, 4.05; N, 10.58.

5-Methoxy-N_{β} -(9-methoxy-2-oxo-2H-pyrano[2, 3-b] quinoline-3-carbonyl)-3-phenyl-1H-indole-2-carbohydrazide (6j): Colourless crystals in 69% yield, mp 158 °C: IR (KBr) cm-1: 1162 (C–O–C), 1578 (C_N), 1661, 1678, 1723 (CO/CO/CO), 3057, 3186, 3281 (NH/NH/NH).1H NMR in δ: 2.19 (s, 3H, –OCH3), 2.41 (s, 3H, –OCH3), 7.21-7.79 (m, 13H, ArH), 10.00 (s, 1H, indole NH), 10.25 (s, 1H, CONH), 10.58 (s, 1H, CONH). Anal. Calcd for C30H22N4O6: C, 67.42; H, 4.12; N, 10.49; Found: C, 67.31; H, 4.19; N, 10.68.

Pharmacological Activities

Ant-inflammatory activity by paw-edema method

In vivo anti-inflammatory activity was assessed by carrageen an induced rat hind paw oedema method. Albino rats of either sex weighing between 150-200 g were divided into groups of six animals each. The first group served as the control and received vehicle only (Tween-80, 1%), second group of animals were administered with standard drug Indomethacin 25 mg/kg body weight, orally. The animals of the other groups were treated with synthesized compounds at a dose of 25 mg/kg body weight, orally. A mark was made on both the hind paws just below the tibio-tarsal junction so that every time the paw could be dipped in the mercury column of plethysmo graph upto the mark to ensure constant paw volume. The normal paw volume was measured for both the legs, after 30 min. of above treatment an inflammation was induced in the left hind paw by injecting 0.1 ml of carrageen an (1%, w/v) in the planter tissue of the paw of all animals. The right paw served as a reference to non-inflammed paw for comparison. The initial paw volume was measured plethysmo graphically within 30 sec. of the injection. The relative increase in the paw served as a reference to non-inflammed paw for comparison. The relative increase in the paw volume was measured in control, standard and treated group, for 4 hr after carrageen an injection. The percent increase in paw volume over the initial reading was also calculated. This increase in paw volume in animals treated with standard drug and the synthesized indole and thiazole derivatives were compared with the increase in paw volume of control animals. Thus, percent inhibition of paw volume was calculated using the formula

% inhibition = (1-Vt / Vc) x 100.

Where, V_t and V_c are mean relative changes in the paw volume of the test and control respectively.

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control. The results of anti-inflammatory testing of all the tested compounds are summarized in the following **Table 1**.

Analgesic activity by tail flick method

Tail flick method was pursued for the testing of analgesic activity using the analgesiometer. Albino mice of either sex weighing between 25-30 g were randomly distributed into groups consisting of six animals in each group. The first group served as a control group and animals were administered with vehicle (Tween-80, 1%) orally. The second group was administered

Table 1. Anti-inflammatory activity of indole compounds.

Group (Compound)	Dose mg/kg b.w	Mean values (± SE) of oedema Volume at different intervals				% inhibition at 2hr
1 (Control)	1 ml	0.305 (± 0.014)	0.295 (± 0.024)	0.285 (± 0.022)	0.275 (± 0.019	-
2 (Indomethacin)	25	0.195** (± 0.010)	0.145 (± 0.012)	0.081*** (± 0.009)	0.091 (± 0.011)	72.47
6a	25	0.308 (± 0.008)	0.209** (± 0.016)	0.224 (± 0.016)	0.128* (± 0.016)	36.8
6b	25	0.188** (± 0.015)	0.119 (± 0.019)	0.088*** (± 0.021)	0.108 (± 0.015)	65.27
6c	25	0.218** (± 0.016)	0.125 (± 0.016)	0.118 (± 0.021)	0.104 (± 0.019)	60.51
6d	25	0.241** (± 0.011)	0.199 (± 0.021)	0.192 (± 0.018)	0.217 (± 0.012)	32.63
6e	25	0.213 (± 0.011)	0.154 (± 0.013)	0.104*** (± 0.009)	0.112 (± 0.011)	63.35
6f	25	0.287 (± 0.020)	0.264 (± 0.021)	0.255 (± 0.021)	0.231 (± .014)	10.52
6g	25	0.247** (± 0.021)	0.231 (± 0.012)	0.118** (± 0.021)	0.108 (± 0.017)	61.88
6h	25	0.288 (± 0.008)	0.241** (± 0.016)	0.238 (± 0.016)	0.224* (± 0.016)	12.8
6i	25	0.281 (± 0.008)	0.261** (± 0.016)	0.241 (± 0.016)	0.220* (± 0.016)	18. 10
6j	25	0.26 (± 0.018)	0.247 (± 0.016)	0.238 (± 0.021)	0.221 (± 0.019)	32.77

No. of animals for each group=6, Control= 1% Tween-80
Significance levels *P< 0.05, **P<0.01, ***P<0.001 compared with respective control (**ANOVA followed by Dunnet's test**). Each value represents ±SE (n=6).

with standard drug analgin at a dose of 25 mg/kg body weight, orally. The animals of the other groups were treated with indole derivatives at a dose of 25 mg/kg body weight, orally. The reaction time was noted at 0, 30, 60 and 90 min. of time intervals after the drug administration. Percent protection against tail flicking was calculated using the formula:

$$\% \text{ Protection} = (1-W_c/W_t) \times 100$$

Where W_c and W_t are the mean time for the tail flicking in the test and control groups, respectively.

All the newly synthesized indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control. The results of analgesic testing of all the tested compounds are summarized in the following **Table 2**.

Results and Discussions

Pharmacological activities

Ant-inflammatory activity: All the indole derivatives were screened for their in vivo anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control [24].

From Table 1 of the results of anti-inflammatory evaluation of indole derivatives, it is clearly indicates that the compounds 6b, 6c, 6e and 6g have displayed excellent anti-inflammatory activity as compared with that of standard drug indomethacin. The compounds 6a, 6d and 6j showed moderate anti-inflammatory activity as compared with that of standard drug indomethacin. The remaining compounds 6f, 6h and 6i were less active when compared with that of standard drug indomethacin. Under these conditions, the standard drug indomethacin used exhibited 73.02% anti-inflammatory activity and control 1% Tween-80 used as a control did not show any anti-inflammatory activity.

Analgesic activity: All the indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control [25].

From the Table 2, it is clearly indicates that the compounds 6b, 6c, 6e and 6g revealed good analgesic potential as evaluated with that of standard drug analgin. The compounds 6a, 6d and 6j showed sensible analgesic activity as compared with that of standard drug analgin. The rest of the compounds 6f, 6h and 6i were less active when compared with that of standard drug. Under these conditions the standard drug analgin used exhibited 63.18% analgesia, after 60 min drug administration and 1% Tween-80 used as a control did not show any analgesic activity.

Conclusion

All the indole derivatives were evaluated for their in vivo pharmacological activities as compared with standard drug indomethacin and analgin respectively with 1% Tween-80 as a control. The results of anti-inflammatory and analgesic activities

Table 2: Analgesic activity of indole compounds.

Group (Compound)	Dose mg/kg b.w	Average (± SE) reaction time (sec.) Time after drug treatment (min.)				% Analgesia at 60 min
		0	30	60	90	
1 (Control)	1 ml	3.245 (± 0.219)	3.26 (± 0.223)	3.271 (± 0.230)	3.257 (± 0.212)	-
2 (Analgin)	25	3.895** (± 0.219)	5.278** (± 0.223)	8.884** (± 0.208)	9.057 (± 0.218)	63.18
6a	25	3.385 ** (± 0.219)	5.212 (± 0.223)	5.200* (± 0.2108)	5.12 (± 0.2108)	37.09
6b	25	3.715 ** (± 0.145)	5.001 (± 0.223)	7.982** (± 0.281)	8.015 (± 0.108)	59.02
6c	25	3. 724** (± 0.219)	4.648 (± 0.223)	6. 227* (± 0.210)	6. 725** (± 0.208)	47.47
6d	25	3.254 (± 0.219)	4. 628** (± 0.223)	5.228 (± 0.2108)	5.275 (± 0.2108)	37.43
6e	25	3.754 ** (± 0.070)	5.218 (± 0.223)	7.041** (± 0.218)	6.188 (± 0.208)	53.58
6f	25	3. 445* (± 0.219)	3. 828 (± 0.293)	3.791 (± 0.2108)	3. 788 (± 0.2108)	13.78
6g	25	3.919** (± 0.104)	4.068 (± 0.211)	5.557* (± 0.108)	4.725 (± 0.201)	41.11
6h	25	3.281 (± 0.219)	3.289 (± 0.223)	4.117 (± 0.2108)	3. 725 (± 0.2108)	21.65
6i	25	3.318 (± 0.019)	3.541 (± 0.224)	3.451 (± 0.219)	3.657 (± 0.2108)	5.22
6j	25	3.215 (± 0.104)	3.954 (± 0.423)	5.951* (± 0.108)	6.117 (± 0.109)	35.3

No. of animals for each group=6, Control= 1% Tween-80
Significance levels *P< 0.05, **P<0.01, ***P<0.001 compared with respective control (**ANOVA followed by Dunnet's test**). Each value represents ±SE (n=6).

of indole derivatives, it is clear that the compounds 6b, 6c, 6e and 6g have exhibited good pharmacological activities as compared with that of standard drugs.

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