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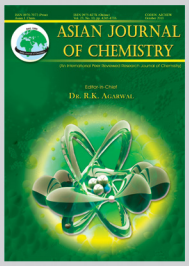

Synthesis and Biological Evaluation of Novel Indolyl Isoxazoline Derivatives as Analgesic and Antiinflammatory Agents

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A series of 3-(2-(4-substituted phenyl)-1*H*-indol-3-yl)-1-(4-substituted phenyl)prop-2-en-1-one **3(a-l)** were synthesized from substituted indole aldehydes. Using hydroxylamine hydrochloride the chalcones **3(a-l)** were cyclized to afford a novel series of 2-(4-substituted phenyl)-3-(3-(4-substituted phenyl)-4,5-dihydroisoxazol-5-yl)-1*H*-indole **4(a-l)**. The structure of all these compounds were established on the basis of spectral (IR, ^{1}H NMR) studies. The compounds **4(a-l)** were evaluated for the antiinflammatory and analgesic activity by using different pharmacological models. The most active compounds were subjected to acute ulcerogenesis activity and were found to be less ulcerogenic than the reference drug indomethacin.

Key Words: Indole, Isoxazoline, Antiinflammatory, Analgesic activity, Ulcerogenesis.

INTRODUCTION

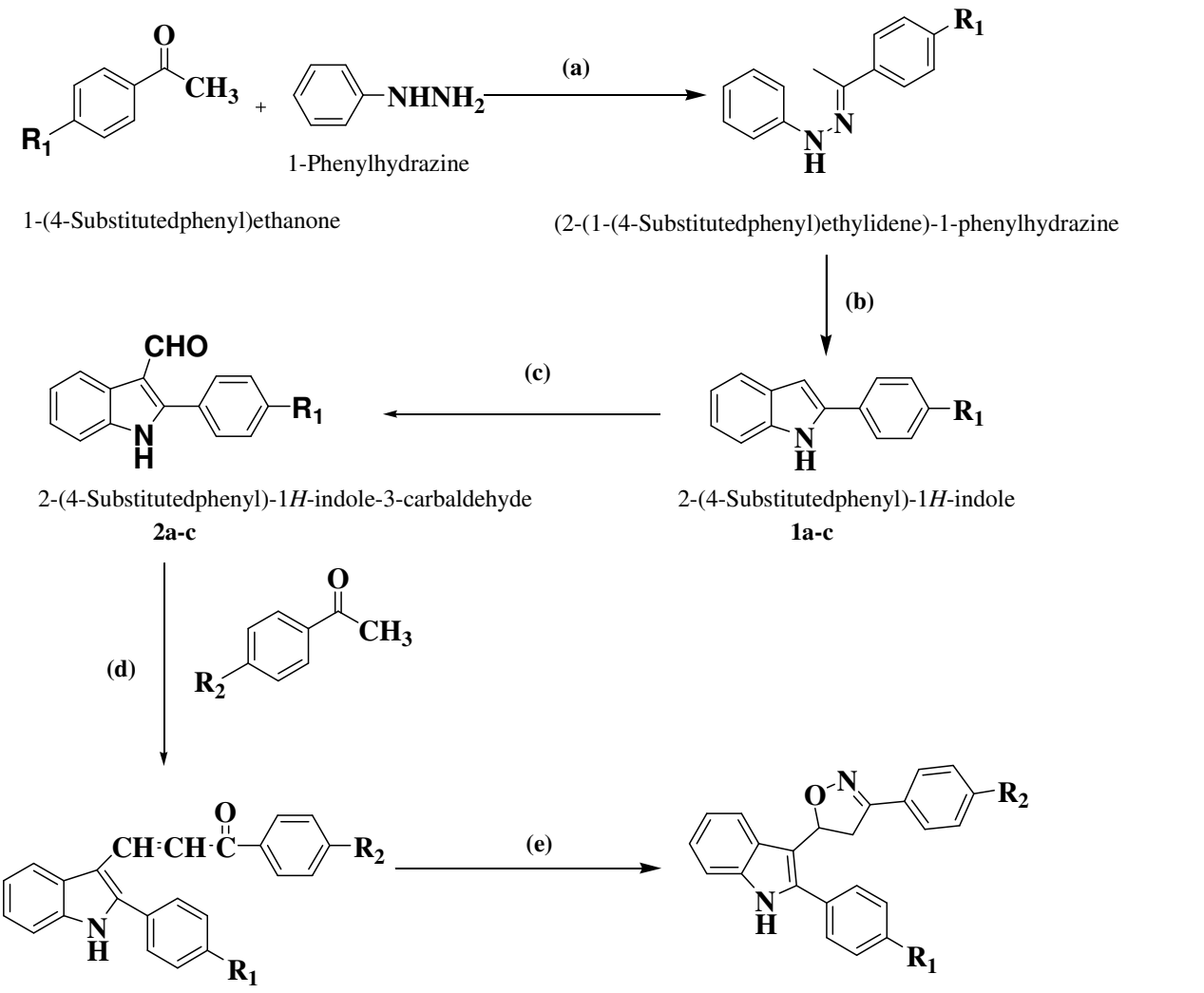
Inflammation is the result of concerted participation of a large number of vasoactive, chemotactic and proliferative factors at different stages of infections. The NSAIDs are popular in reducing the acute and chronic inflammation as they have no abuse liability[1,2]. Present NSAIDs have common side effects like gastric and peptic ulceration, acute renal failure, hypersensitivity reaction when administered in large dose or in long term therapy[3-6]. The search for newer non-steroidal antiinflammatory agents is the only way to fortify against these adverse effects. The discovery of indomethacin as a successful agent for clinical treatment of inflammatory disorders has led to the exploration of indole moiety to obtain better antiinflammatory agents[7-14]. In literature survey, we found that few isoxazoline derivatives possess good antiinflammatory and analgesic activity[15-19]. Valdecoxib is an isoxazoline derivative which is widely used in the market as antiinflammatory drug[20]. This prompted us to synthesize hybrid analogues of two pharmacophores *viz*., indole and isoxazoline in search to achieve safer and better NSAIDs having combined biological activities as antiinflammatory and analgesic activity with the lower incidences of gastrointenstine side effects.

EXPERIMENTAL

All the chemicals used in the synthesis were of laboratory grade. To monitor the progress of reactions and to establish the identity and purity of reactants and products, thin layer chromatography was performed on aluminium slides coated with silica gel 60, using appropriate solvent systems and the spots were visualized under ultra-violet light or by exposure to iodine vapors. Melting points were determined in open capillary on Veego (model: VMP-D) electronic apparatus and are uncorrected. The IR spectra of the synthesized compounds were recorded on Shimadzu 8400-S FT-IR spectrophotometer using potassium bromide. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO using NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are given in units as parts per million, downfield from tetramethyl silane (TMS) as an internal standard.

The steps followed in synthesis are depicted in following **Scheme-I**.

Synthesis of substituted indole 1(a-c)[21]: Equimolar quantities of substituted acetophenone and phenylhydrazine were added to 60 mL of distilled ethanol in 200 mL beaker. The solution was warmed for 15 min and few drops of glacial acetic acid added, with continuous stirring and the solution was cooled to room temperature. The crude acetophenone phenylhydrazone separated from the solution. The reaction mixture was filtered and the solid was washed with dilute hydrochloric acid followed by *ca.* 12 mL cold ethanol. The crude product was recrystallized from ethanol. 10 g of acetophenone phenylhydrazone was placed in a 250 mL beaker containing 60 g of polyphosphoric acid. The mixture



Scheme -Reagents and conditions (a) C_2H_5OH, glacial acetic acid,40°C ; (b)polyphosphoric acid,120°C; (c) $POCl_3$, anhydrous DMF;(d) piperidine,ethylene glycol,180°C,4 h ;(e) $NH_2OH.HCl$, C_2H_5OH,NaOH

Scheme-I

was heated and maintained at 100-120 ºC for 15 min. The reaction mixture was cooled to room temperature with continuous stirring. 150 mL of cold water was added and stirred well to complete solution of the polyphosphoric acid. The solution was filtered at the pump and washed well with water. The crude product was recrystallized from ethanol with a little decolorizing charcoal.

Synthesis of indole aldehyde 2(a-c)[22]: 25 mL of dry dimethylformamide was stirred at 0 ºC for 15 min. Phosphoryl chloride (2 mol) was added drop wise using dropping funnel for 0.5 h. Substituted indole (1 mol) was dissolved in 50 mL dry DMF and added drop wise into the formylated solution below 10 ºC over the period of 2 h. After the completion of addition the reaction mixture was stirred for another 0.5 h. The temperature was brought to 35-40 ºC and maintained for 2 h. Then 100 g of crushed ice added slowly. Sodium hydroxide solution (10 mol) was added drop wise. The suspension was heated to boiling to remove diethylamine. The suspension was cooled to room temperature and kept overnight. The reaction mixture was diluted with water and filtered. The crude product obtained was washed with water to remove inorganic material. The crude aldehyde was recrystallized from ethanol.

Synthesis of 3-[2-(4-substituted phenyl)-1*H*-indol-3-yl]-1-(4-substituted phenyl)prop-2-en-1-one 3(a-l): Equimolar quantity of indole-3-aldehyde and substituted acetophenone was dissolved in 50 mL ethylene glycol. Equimolar quantity of piperidine was added and refluxed for 4 h. The reaction mixture was cooled to room temperature. The crude chalcone was filtered and washed with cold ethanol and water. The chalcone was recrystallized from ethanol.

Synthesis of 2-(4-substituted phenyl)-3-[3-(4-substituted phenyl)-4,5-dihydroisoxazol-5-yl]-1*H*-indole 4(a-l)[23]: The target compound was synthesized by reacting the corresponding chalcone (0.01 mol) with hydroxylamine hydrochloride (0.02 mol) in presence of NaOH (0.01 mol) using distilled ethanol as solvent. The reaction mixture was refluxed for 14-16 h. The progress of reaction was monitored with TLC. After completion of the reaction, an excess of the solvent was removed by distillation and the resultant mass was poured into ice water with vigorous stirring. The solution was acidified with dilute HCl. It was kept in cool overnight. The crude solid obtained was filtered, washed with sufficient cold water, dried and purified by recrystalization from ethanol. The physical data of target compounds are given in Table-1.

Antiinflammatory activity: Antiinflammatory activity was evaluated by carrageenin induced rat paw edema method developed by Winter *et al.*[24]. The suspensions of test compounds were prepared in sterile 0.9 % NaCl solution. In all cases control received the same quantity of sterile 0.9 % NaCl solution as vehicle. Sprague Dawley rats of either sex weighing between 150-250 g were randomly distributed in control and experimental group of six animals each. At 0 h the target compounds **4(a-l)** (40 mg/kg) and standard (20 mg/kg) doses were administered orally. After 1 h compounds and standard were administered orally; 0.1 mL of 1 % (w/v) suspension of carrageenin in distilled water was injected into the planter tissue of right paw of rat by using 27 gauge needles. The paw was marked with ink at the level of the tibia-tarsal junction and the initial volume of paw was measured by plathysmometer within 30 s of injection. The relative increase in paw volume was found by remeasuring the paw volume after 3 h of carrageenin injection.

The percentage inhibition of edema was calculated by following formula and the results are shown in Table-2.

$$\text{Inhibiton of edema (3 h)} = \left(1 - \frac{V_t}{V_c}\right) \times 100$$

where, V_t = mean relative change in paw volume in test group. V_c = mean relative change in paw volume in control group.

Analgesic activity: The target compounds **4(a-l)** were screened for their analgesic activity by the following two methods.

Acetic acid induced writhing in mice: Analgesic activity was determined *in vivo* by calculating total number of writhings, following intraperitonial (IP) administration of 0.6 % (0.1 mL/10 g) acetic acid in mice[25,26]. Albino mice of either sex (25-30 g) were used. Target compounds **4(a-l)** were administered orally (40 mg/kg) as a suspension in sterile 0.9 % NaCl solution as vehicle.

Diclofenac sodium (20 mg/kg) was used as the standard drug under same conditions. Acetic acid solution was administered intraperitonialy 0.5 h after the administration of the compounds. After 10 min, intraperitonial injection of the acetic acid solution, the number of writhings per animal were recorded for 20 min. Control animals received an equal volume of vehicle. Analgesic activity was expressed as percentage of inhibition of number of writhings, when compared with the vehicle control group. Results of percentage analgesic activity of compounds were calculated using following formula and shown in Table-3.

TABLE-1
PHYSICAL DATA OF THE TARGET COMPOUNDS **4(a-l)**

Code	R_1	R_2	m.f.	m.w.	m.p. (ºC)	R_f	Yield (%)
4a	-H	H	$C_{23}H_{18}N_2O$	338	195-197	0.60	90
4b	-H	-Cl	$C_{23}H_{17}N_2OCl$	372.5	199-201	0.65	94
4c	-H	-Br	$C_{23}H_{17}N_2OBr$	417	200-202	0.62	93
4d	-H	$-CH_3$	$C_{24}H_{20}N_2O$	352	212-214	0.61	90
4e	-H	$-OCH_3$	$C_{24}H_{20}N_2O_2$	368	194-196	0.63	87
4f	-Cl	H	$C_{23}H_{17}N_2OCl$	372.5	215-217	0.56	93
4g	-Cl	-Cl	$C_{23}H_{16}N_2OCl_2$	407	191-193	0.76	89
4h	-Cl	-Br	$C_{23}H_{16}N_2OBrCl$	451.5	193-195	0.55	88
4i	-Cl	$-CH_3$	$C_{24}H_{19}N_2OCl$	386.5	198-200	0.56	85
4j	-Cl	$-OCH_3$	$C_{24}H_{19}N_2O_2Cl$	402.5	202-204	0.67	78
4k	$-CH_3$	$-CH_3$	$C_{25}H_{21}N_2O$	366	189-191	0.76	89
4l	$-CH_3$	$-OCH_3$	$C_{25}H_{21}N_2O_2$	382	199-201	0.71	76

TABLE-2
ANTIINFLAMMATORY AND ULCEROGENIC ACTIVITIES OF TARGET COMPOUNDS **4(a-l)**

Groups (n = 6)	180 min (mean vol ± SEM)	Inhibition (%) (180 min)	Ulcerogenic index	Groups (n = 6)	180 min (mean vol ± SEM)	Inhibition (%) (180 min)	Ulcerogenic index
Control (saline)	1.39 ± 0.0081	00 [a,****]	–	**4f**	1.21 ± 0.0025	40.48 [a,****]	2.0
Indomethacin	1.07 ± 0.0036	73.8[a]	3.0	**4g**	1.21 ± 0.0036	38.09 [a,****]	3.0
4a	1.19 ± 0.0077	50 [a,****]	–	**4h**	1.20 ± 0.0073	42.86 [a,****]	–
4b	1.18 ± 0.0109	50 [a,****]	–	**4i**	1.19 ± 0.0073	45.24 [a,****]	–
4c	1.14 ± 0.0146	57.14 [a, ns]	–	**4j**	1.19 ± 0.0073	47.62 [a,****]	–
4d	1.17 ± 0.0219	54.76 [a,***]	–	**4k**	1.13 ± 0.0109	64.29 [a, ns]	2.0
4e	1.10 ± 0.0365	64.29 [a, ns]	–	**4l**	1.09 ± 0.0292	69.05 [a, ns]	2.0

Data were analyzed by one-way ANOVA followed by Bonferroni's multiple comparison test. Values were expressed as mean ± SEM**** $p <$ 0.0001***, $p < 0.001$, **$p < 0.01$, *$p < 0.05$, [ns]: Non significant as compared with standard group. [a]Statistically significant from the control at $p <$ 0.05.

Analgesic activity (%) = (No. of writhings for control – No. of writhings for test compound/No. of writings for control) × 100

Formalin induced licking and biting in mice[27]: The analgesic activity was determined by calculating total number of licking and biting in mice, following administration of 0.1 % (0.1 mL/10 g) formalin into the sub planter area of right hind paw of mice. Albino mice of either sex (25-30 g) were used. Target compounds **4(a-l)** were administered intraperitonialy (40 mg/kg) as a suspension in sterile 0.9 % NaCl solution as vehicle. Diclofenac sodium (20 mg/kg) was used as the standard drug under same conditions. 0.5 h after the administration of the compounds, number of paw licking, an index of noniception, was measured at 0-5 min (first phase, which indicates central analgesic activity) and 15-30 min (second phase, which indicates peripheral analgesic activity) after formalin administration. Control animals received an equal volume of vehicle. Analgesic activity was expressed as percent inhibition of paw licking, when compared with the vehicle control group and the results are shown in Table-3.

Analgesic activity (%) = (No. of paw licking for control – No. of paw licking test compound/No. of paw licking for control) × 100

Acute ulcerogenesis: Acute ulcerogenesis test was performed as reported by Cioli *et al*.[28]. The studies were carried out on healthy rats (150-200 g) at a dose three times the antiinflammatory dose. The animals were divided into three groups of six animals each, group I served as control and received vehicle only and group II received pure indomethacin (60 mg/kg). Group III was administered test compounds in dose of 120 mg/kg. The animals were fasted 8 h prior to a single dose of each of the vehicle, standard and test compounds, respectively and sacrificed 17 h later during which period food and water were available. The gastric mucosa of the rats was examined by means of a 4X binocular magnifier. For each stomach the severity of mucosal damage was assessed according to the following scoring system: 0- no lesions of up to five punctiform lesions; 1- more than five punctiform lesions; 2- one to five small ulcers; 3- more than five small ulcers of one large ulcer; 4 - more than one large ulcer. The mean score of each treated group minus the mean score of the control group was considered as the 'severity index' of gastric damage (Table-2).

Spectral data of target compounds 4(a-l)

3-(4,5-Dihydro-3-phenylisoxazol-5-yl)-2-phenyl-1*H*-indole 4(a): IR (KBr, ν_{max}, cm^{-1}): 3535 (N-H), 3061 (Ar-C-H), 1605 (Ar-C=C), 1562 (C=N), 1306 (C-O-N). ^{1}H NMR ($CDCl_3$, δ ppm): 3.539-3.632 (dd,1H, -CH_2), 3.698-3.786 (dd,1H, -CH_2), 5.995-6.064 (t, 1H, -CH), 7.105-7.129 (d, 4H,Ar-H), 7.263 (d, 3H, Ar-H),7.410-7.436 (d, 3H, Ar-H), 7.483-7.504 (d, 2H, Ar-H), 7.674-7.700 (d, 2H, Ar-H), 8.218 (s, 1H, NH).

3-[3-(4-Chlorophenyl)-4,5-dihydroisoxazol-5-yl]-2-phenyl-1*H*-indole 4(b): IR (KBr, ν_{max}, cm^{-1}): 3264 (N-H), 3017 (Ar-C-H), 1616 (Ar- C=C), 1562 (C=N), 1306 (C-O-N), 817 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 3.525-3.619 (dd, 1H, -CH_2), 3.690-3.780 (dd, 1H, -CH_2), 6.026-6.054 (t, 1H, -CH), 7.068-7.142 (m, 1H, -Ar-H), 7.166-7.256 (m, 2H, Ar-H), 7.396-7.423 (m, 4H, Ar-H), 7.468-7.532 (m, 2H, Ar-H), 7.561-7.585 (d, 2H, Ar-H), 7.666-7.695 (m, 2H, Ar-H), 8.428 (s, 1H, NH).

3-[3-(4-Bromophenyl)-4,5-dihydroisoxazol-5-yl]-2-phenyl-1*H*-indole 4(c): IR (KBr, ν_{max}, cm^{-1}): 3290 (N-H), 3054 (Ar-C-H), 1619 (Ar-C=C), 1562 (C=N), 1312 (C-O-N), 742 (C-Br). ^{1}H NMR ($CDCl_3$, δ ppm): 3.516-3.611 (dd, 1H, -CH_2), 3.682-3.772 (dd, 1H, -CH_2), 6.045-6.117 (t, 1H, -CH), 7.061-7.159 (m, 5H, Ar-H), 7.192-7.341 (m, 2H, Ar-H), 7.389-7.459 (m, 2H, Ar-H), 7.486-7.672 (m, 4H, Ar-H), 8.408 (s, 1H, NH).

3-(4,5-Dihydro-3-*p*-tolylisoxazol-5-yl)-2-phenyl-1*H*-indole 4(d): IR (KBr, ν_{max}, cm^{-1}): 3442 (N-H), 3051 (Ar-C-H), 2925 (aliphatic C-H),1602 (Ar- C=C), 1557 (C=N), 1305 (C-O-N). ^{1}H NMR ($CDCl_3$, δ ppm): 2.396 (s, 3H, -CH_3), 3.533-3.628 (dd, 1H, -CH_2), 3.708-3.798 (dd, 1H, -CH_2), 6.015-6.088 (t, 1H, -CH), 7.070-7.187 (m, 2H, Ar-H), 7.206-7.243 (m, 4H, Ar-H), 7.310-7.334 (m, 1H, Ar-H), 7.376-7.474 (m, 2H, Ar-H), 7.545-7.571 (m, 2H, Ar-H), 7.612-7.634 (m, 2H, Ar-H), 8.435 (s, 1H, NH).

3-[4,5-Dihydro-3-(4-methoxyphenyl)isoxazol-5-yl]-2-phenyl-1*H*-indole 4(e): IR (KBr, ν_{max}, cm^{-1}): 3290 (N-H), 3027 (Ar-C-H), 2878 (-OCH_3) 1628 (Ar-C=C), 1567 (C=N), 1361 (C-O-N). ^{1}H NMR ($CDCl_3$, δ ppm): 3.519-3.612 (dd, 1H, -CH_2), 3.691-3.780 (dd, 1H, -CH_2), 3.84 (s, 3H, -OCH_3), 5.978-6.050 (t, 1H, -CH), 7.064-7.113 (m, 2H, Ar-H), 7.195-7.259 (m, 4H, Ar-H), 7.395-7.448 (m, 2H, Ar-H), 7.474-7.520 (m, 2H, Ar-H), 7.550-7.606 (m, 2H, Ar-H), 8.441 (s, 1H, NH).

TABLE-3
ANALGESIC ACTIVITY OF TARGET COMPOUNDS **4(a-x)**

Group (n = 6)	Analgesic activity (%)			Group (n = 6)	Analgesic activity (%)		
	Acetic acid induced writhing method	Formalin induced licking and biting method			Acetic acid induced writhing method	Formalin induced licking and biting method	
		Phase1	Phase 2			Phase1	Phase 2
Control	0	0	0	**4f**	29.96 [a,****]	10.49[ns]	36.42***
Diclofenac	73.25 [a]	65.19***	85.18***	**4g**	35.69 [a,****]	23.47***	40.19***
4a	54.55 [a, ns]	43.10***	59.79***	**4h**	43.33 [a, **]	10.49[ns]	59.55***
4b	50.32 [a, ns]	25.69***	53.26***	**4i**	59.23 [a, ns]	9.95[ns]	51.50***
4c	35.04 [a,****]	10.78[ns]	40.95***	**4j**	50.97 [a, ns]	16.29**	41.20***
4d	47.15 [a,*]	25.69***	39.95***	**4k**	65.61 [a, ns]	30.38***	64.31***
4e	63.05 [c, ns]	24.02***	55.78***	**4l**	61.79 [a, ns]	30.66***	61.81***

Dose- control = 0.1 mL/kg reference = 20 mg/kg derivatives = 40 mg/kg. Data were analyzed by one-way ANOVA followed by Bonferroni's multiple comparison test. Values were expressed as mean ± SEM **** $p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, [ns]: Non significant as compared with control (saline) group and standard drug induced group. From control group: **** = a *** = b ** = c * = d [ns] = non significant. From standard group: **** $p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, [ns]: Non significant.

2-(4-Chlorophenyl)-3-(4,5-dihydro-3-phenylisoxazol-5-yl)-1*H*-indole 4(f): IR (KBr, ν_{max}, cm^{-1}): 3213 (N-H), 3056 (Ar-C-H), 1597 (Ar-C=C), 1544 (C=N), 1321 (C-O-N), 841 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 3.567-3.661 (dd, 1H, CH_2), 3.732-3.823 (dd, 1H, CH_2), 5.979-6.051 (t, 1H, -CH), 7.066-7.115 (m, 4H, Ar-H), 7.201-7.260 (m, 3H, Ar-H), 7.393-7.446 (m, 2H, Ar-H), 7.535-7.609 (m, 2H, Ar-H), 7.749-7.761 (m, 2H, Ar-H), 8.308 (s, 1H, -NH).

2-(4-Chlorophenyl)-3-(3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)-1*H*-indole 4(g): (KBr, ν_{max}, cm^{-1}): 3264 (N-H), 3017 (Ar-C-H), 1616 (Ar-C=C), 1562 (C=N), 1306 (C-O-N), 817 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 3.539, 3.593 (dd, 1H, a-CH_2), 3.632, 3.698 (dd, 1H, b-CH_2), 5.995-6.064 (t, 1H, c-CH), 7.105, 7.129 (d, 1H, d-Ar-H), 7.263 (s, 1H, e-Ar-H), 7.410, 7.436 (d, 1H, f- Ar-H), 7.483, 7.504 (d, 1H, g-Ar-H), 7.674, 7.70 (d, 1H, h-Ar-H), 8.218 (s, 1H, i-NH).

3-[3-(4-Bromophenyl)-4,5-dihydroisoxazol-5-yl]-2-(4-chlorophenyl)-1*H*-indole 4(h): (KBr, ν_{max}, cm^{-1}): 3436 (N-H), 3060 (Ar-C-H), 1596 (Ar-C=C), 1560 (C=N), 1306 (C-O-N), 823 (C-Cl), 753 (C-Br). ^{1}H NMR ($CDCl_3$, δ ppm): 3.529-3.625 (dd, 1H, -CH_2), 3.687-3.776 (dd, 1H, -CH_2), 5.988-6.061 (t, 1H, -CH), 7.076-7.152 (m, 4H, Ar-H), 7.232-7.263 (m, 2H, Ar-H), 7.388-7.456 (m, 2H, Ar-H), 7.527-7.556 (m, 2H, Ar-H), 7.614-7.689 (m, 2H, Ar-H), 8.314 (s, 1H, NH).

2-(4-Chlorophenyl)-3-(4,5-dihydro-3-*p*-tolylisoxazol-5-yl)-1*H*-indole 4(i): IR (KBr, ν_{max}, cm^{-1}): 3411 (N-H), 3056 (Ar-C-H), 1614 (Ar-C=C), 1555 (C=N), 1312 (C-O-N), 834 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 2.404 (s, 3H, -CH_3), 3.543-3.637 (dd, 1H, -CH_2), 3.706-3.796 (dd, 1H, -CH_2), 5.954-6.024 (t, 1H, -CH), 7.032-7.145 (m, 2H, Ar-H), 7.169-7.311 (m, 4H, Ar-H), 7.348-7.504 (m, 2H, Ar-H), 7.529-7.591 (m, 2H, Ar-H), 7.609-7.650 (m, 2H, Ar-H), 8.432 (s, 1H, NH).

2-(4-Chlorophenyl)-3-(4,5-dihydro-3-(4-methoxyphenyl)isoxazol-5-yl)-1*H*-indole 4(j): IR (KBr, ν_{max}, cm^{-1}): 3425 (N-H), 3052 (Ar-C-H), 1639 (Ar- C=C), 1548 (C=N), 1305 (C-O-N), 847 (C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 3.45-3.60 (dd, 1H, -CH_2), 3.65-3.80 (dd, 1H, -CH_2), 3.85 (s, 3H, -OCH_3), 5.90-6.10 (t, 1H, -CH), 6.942-6.971 (d, 2H, Ar-H), 7.200-7.321 (m, 4H, Ar-H), 7.388-7.418 (d, 2H, Ar-H), 7.486-7.510 (d, 2H, Ar-H), 7.672-7.702 (d, 2H, Ar-H), 8.380 (s, 1H, NH).

3-(4,5-Dihydro-3-*p*-tolylisoxazol-5-yl)-2-*p*-tolyl-1*H*-indole 4(k): IR (KBr, ν_{max}, cm^{-1}): 3266 (N-H), 3029 (Ar-C-H), 2925 (aliphatic C-H), 1614 (Ar-C=C), 1555 (C=N), 1300 (C-O-N). ^{1}H NMR ($CDCl_3$, δ: 2.403-2.415 (s, 6H, -CH_3), 3.528-3.622 (dd, 1H, -CH_2), 3.709-3.799 (dd, 1H, -CH_2), 6.015-6.088 (t, 1H, -CH), 7.168-7.325 (m, 2H, Ar-H), 7.353-7.397 (m, 2H, Ar-H), 7.434-7.478 (m, 4H, Ar-H), 7.533-7.571 (m, 2H, Ar-H), 7.630-7.658 (m, 2H, Ar-H), 8.228 (s, 1H, -NH).

3-[4,5-Dihydro-3-(4-methoxyphenyl)isoxazol-5-yl]-2-*p*-tolyl-1*H*-indole 4(l): IR (KBr, ν_{max}, cm^{-1}): 3244 (N-H), 3056 (Ar-C-H), 2963 (alkyl-C-H),2840 (-OCH_3), 1606 (Ar-C=C), 1551 (C=N), 1257.63 (C-O-N). ^{1}H NMR ($CDCl_3$, δ ppm): 2.421 (s, 3H, -CH_3), 3.526-3.620 (dd, 1H, -CH_2), 3.707-3.796 (dd, 1H, -CH_2), 3.860 (s, 3H, -OCH_3), 6.006-6.077 (t, 1H, -CH), 6.942-6.971 (d, 2H, Ar-H), 7.178-7.229 (m, 2H, Ar-H), 7.382-7.409 (d, 4H, Ar-H), 7.463-7.490 (m, 2H, Ar-H), 7.544-7.571 (d, 2H, Ar-H), 8.190 (s,1H, -NH).

RESULTS AND DISCUSSION

Antiinflammatory activity was tested by carrageenin induced hind-paw edema in rats. All compounds **4(a-l)** showed a significant decrease in inflammation when compared with control. Among the 12 synthesized derivatives, compound **4(e)**, **4(k)**, **4(l)** exhibited promising activity as compared to indomethacin. Compound **4(l)** was found to be the most potent among the series while compound **4(g)** was found to be the least active.

The analgesic activity of compounds **4(a-l)** was evaluated by acetic acid induced writhing in mice and formalin induced licking and biting in mice. Among the 12 synthesized derivatives, compound **4(e)**, **4(k)**, **4(l)** exhibited promising analgesic activity as compared to diclofenac sodium in acetic acid induced model. In formalin induced licking and biting model, the most of compounds exhibited less or insignificant activity in first phase while these compounds exhibited significant activity in second phase. These observations depict that the compounds were peripherally active as analgesic agent. In this model **4(k)**, **4(l)** exhibited promising analgesic activity as compared to diclofenac sodium. The most active and the least active compounds were screened for gastric ulceration study and were found to be showing less gastric mucosal irritation than the standard drug indomethacin. The arrangement of benzene, indole and isoxazoline ring present in the series is favorable for analgesic and antiinflammatory activity. The deactivating electron withdrawing groups like -Cl, -Br showed significant decrease in antiinflammatory activity as compared to electron donating groups like -CH_3, -OCH_3, -H. Substitution with electron withdrawing at both R_1 and R_2 exhibited significant decrease in analgesic activity as well as antiinflammatory activity. Substitution with activating electron donating group -CH_3, -OCH_3 increases analgesic as well as antiinflammatory activity.

Conclusion

This paper described the process for the synthesis of novel indolyl isoxazolines. Most of the synthesized compounds exhibited analgesic and antiinflammatory activity with less gastrolesivity compared with standards. Thus, the synthesized indolyl isoxazoline derivatives with less bulky and less electronegative substituents at *para* position of phenyl rings hold potential for development as safer and better novel antiinflammatory agents.

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