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Synthesis and evaluation of analgesic activity of novel series of Indole derivatives linked to isoxazole moiety

Dilli Varaprasad. E, Mastan. M*, Sobha Rani. T

Dravidian University, Kuppam-517425, Andhra Pradesh, India

ABSTRACT

A new series of 4-(3-(3-(4-substituted phenyl)-4, 5-dihydroisoxazol-5-yl)-1H-indol-2-yl) phenol (5a-5f) were synthesized for analgesic activity. Compounds 5b, 5c and 5d have significant analgesic activity of this series. All compounds were screened in vivo for their analgesic activity and acute toxicity studies. The structural assignment of these compounds has been made on the basis of elemental analysis, IR and ^{1}H-NMR, LCMS data.

Key words: Analgesic activity, Indole derivatives, Isoxazole.

INTRODUCTION

Indole alkaloids have been proved to be medicinally important natural compounds. Indole ring constitutes an important template for drug design such as the classical NSAIDs indomethacin and indoxole. Further Indole derivatives have been reported to possess promising biological activities including analgesic[1], antipyretic[2], antifungal[3], anti-inflammatory[4-6], anthelmintic[7], cardiovascular[8], anticonvulsant[9-10] ,antimicrobial[11-12] and selective COX-2 inhibitory activities[13-16] .Thus the efficient synthesis of novel substituted indole derivative compounds still represent highly pursued target. The substitution of heterocyclic moiety at the 3- position of Indole ring markedly influences the analgesic activity.

Considering the above observations and in connection to previous publications involving the synthesis of new biologically active heterocycles[17]. I hope to report here in the synthesis of new 3- substituted indoles incorporating an extra heterocyclic ring such as Isoxazole to screen in vivo for their analgesic activity and acute toxicity studies.

MATERIALS AND METHODS

2.1. Animals

The analgesic activity of newly synthesized compounds (5a-5f) was carried out on Male Swiss albino mice, body weight of 25-30 g. These animals were reared with robust health by providing standard pellet diet and water ad libitum in the animal house under standard environmental conditions of temperature, relative humidity, and 12 h dark/light cycle. After randomization into various groups and before initiation of experiment, animals were acclimatized for one week. The animal experiments were previously approved by Institutional Ethical Committee (IEC) and followed CPCSEA requirements[18].

2.2. Materials

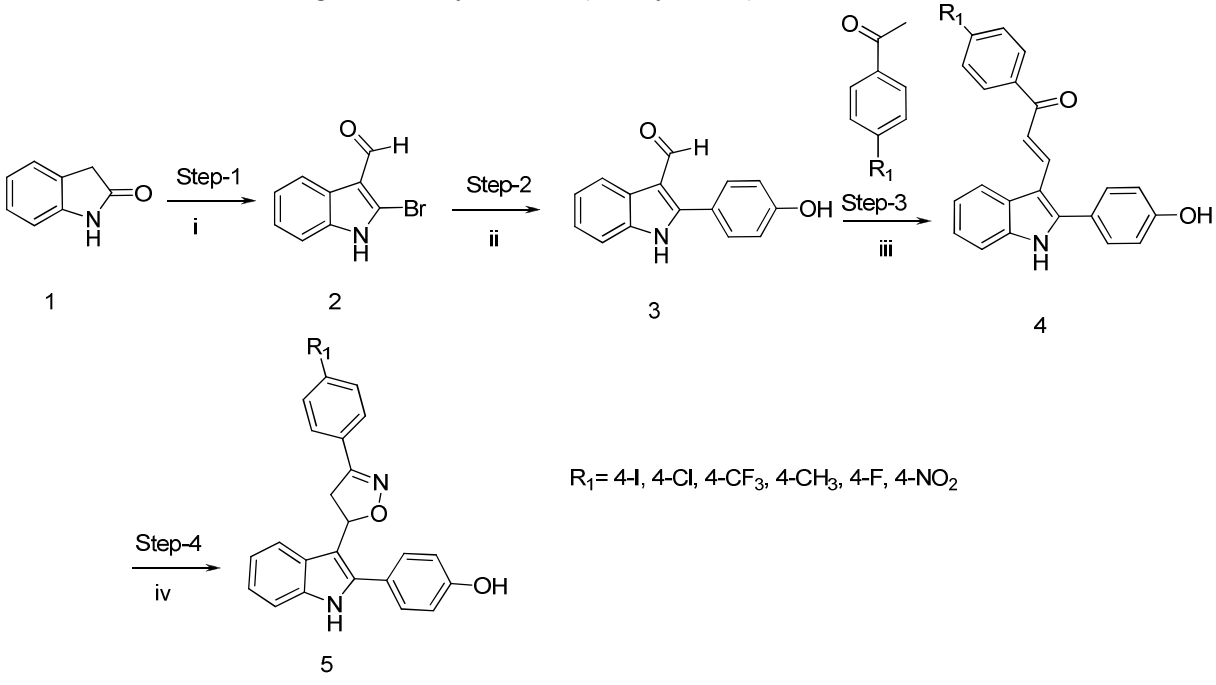
The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use. The melting points were determined in open capillary electronic apparatus. The IR spectra of synthesized compounds were recorded on IR Spectrophotometer using potassium bromide. The ^{1}H NMR were recorded in DMSO-d_6 using NMR Bruker 300 MHz spectrometer and chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard and analyzed by mass spectra using Agilent. To monitor the reactions and to establish the identity and purity of reactants and products, thin layer chromatography (TLC) was performed on pre-coated plastic sheets of silica gel using different solvent systems and the spots were visualized by exposure to iodine, $KmnO_4$ and UV chamber.

Albino mice of either sex obtained from Central Animal Facility, Sree Siddaganga College of Pharmacy, Tumkur, were used for the study. The animals were acclimatized for a week and maintained under standard laboratory conditions, given free access to standard pelleted feed (M/s Pranava agro industries Sangli, Maharashtra and U.V. purified and filtered water, ad libitum. Tramadol (Trade name: Tramazac, Source: Zydus health care, B.N: ZHL 4312, Mfg date: Dec 2011, Exp. Date: May 2014), Acetic acid 3% v/v, Indomethacin (Source: Research Lab fine Chem Industries, B.N: 99550509, Mfg date: May 2009, Exp. Date: May 2014).

2.3. Scheme of synthesis

The synthesis of the title compounds (5a-5f) is outlined in Fig.1. The required intermediate-2 was prepared by following vilsmeier-haack conditions; intermediate-3 was prepared by following Suzuki conditions. The obtained aldehyde compound (intermediate-3) further treated with different *Para* substituted acetophenones to obtain chalcones (4a-4f) by following Clasein-Schimdt reaction. The treatment of chalcones with hydroxylamine hydrochloride in presence of base resulted in the cyclization of α, β-unsaturated ketone into the title compound (5a-5f) in 60-70% yield after column purification. The purity of the compounds was checked by TLC in ethylacetate:hexane (3:7). The structures of the all the compounds were established by ^{1}H - NMR, IR, LCMS and elemental analysis.

Fig.1. Scheme of synthesis for 3-(4, 5-dihydroisoxal)-Indole derivatives



i) DMF, $POBr_3$, DCM, 45^{O}C, 1h ii) $PdCl_2$ (dppf), Na_2CO_3, 1, 4-dioxane: H_2O (5:1), 95^{O}C, 5h iii) Piperidine, Ethylene glycol, 160^{O}C, 6h iv) $NH_2OH.HCl$, CH_3COONa, Ethanol, 80^{O}C, 12h

2.4. Synthesis of 2-Bromo-1H-indole-3-carbaldehyde (2)
To a solution of dimethylformamide (0.68 mmol) in dichloromethane (10 mL) was added drop wise a solution of phosphorus oxybromide (22.5 mmol) in dichloromethane (10 mL) at 0^oC. The white thick mixture was refluxed during 20 min, and then oxindole (7.5 mmol) was added portion wise. The mixture was stirred at reflux during 1h. Reaction was monitored by TLC. After completed the reaction, reaction mixture was quenched by addition of crushed ice to the media. The mixture was stirred for 30 min, and then layers were separated. The aqueous layer was neutralized with solid potassium carbonate. The pale yellow precipitate which appeared was washed with cold water, solid material taken in dichloromethane dried over Na_2SO_4 and concentrated completely. After concentration of solvent pale yellow solid (1.34 g, 80%) was obtained.

2-Bromo-1H-indole-3-carbaldehyde (compound 2)
^{1}H NMR (DMSO-d_6): δ 7.2- 8.0 (m, 4 H, Ar), 9.88 (s, 1H, CHO), 12.48 (brs, 1H, NH) MS: [M+2] m/z 226

2.5. Synthesis 2-(4-Hydroxy-phenyl)-1H-indole-3-carbaldehyde (3)
The mixture of compound-2 (4.46 mmol), phenyl boronic acid(4.9 mmol), Pd(dppf)Cl_2(0.0002 mmol),Na_2CO_3 (8.9 mmol) in dioxane:H_2O(5:1) was heated to 90^oC under nitrogen atmosphere for 5h.Reaction was monitored by TLC. When reaction was completed the mixture was filtered through celite pad, washed with ethyl acetate, layers were separated. Organic layer was dried over Na_2SO_4, concentrated under reduced pressure. Crude compound was purified by column chromatography to obtained(0.74 g, 70%) as a brown color solid.

2-(4-Hydroxy-phenyl)-1H-indole-3-carbaldehyde (compound 3)
^{1}HNMR(DMSO-d_6):δ 6.99-8.10 (m, 8H, Ar),12.2 (brs, 1H, NH),10.04(s,1H,CHO),9.9(S,1H,OH) MS:[M+H] m/z 238

2.6. General procedyre for synthesis of (E)-3-(2-(4-substitutedphenyl)-1H-indol-3- yl)-1-(4-substituted phenyl) prop-2-en-1-one (4a-4f)
Indole-3-carbaldehyde (4.2 mmol), 4- substituted acetophenone (8.4 mmol) and piperidine (8.4 mmol) were mixed into 10 mL ethylene glycol. The solution was refluxed at 150-160^0C for 5-6 h. The solution was cooled; diluted with water and extracted with ethylacetate. Organic layer was dried over Na_2SO_4 and concentrated and crude was purified by column chromatography to obtained (1.33 g, 68%, compound 4a) as a solid.

The spectral analysis of the synthesized compounds is as follows:

(E)-3-[2-(4-Hydroxy-phenyl)-1H-indol-3-yl]-1-(4-iodo-phenyl)-prop-2-en-1-one (compound 4a)
^{1}H NMR (DMSO-d_6): δ 7.59-7.64 (d, *J*=15.6Hz, 1H, =CH-Ar), 6.99-8.1 (m, 12H, Ar), 8.06 (d, *J*=15.9 Hz, 1H-COCH=), 12.2 (brs, 1H, NH), 10.01(s, 1H, OH) MS: [M+H] m/z 466

(E)- 3-[2-(4-hydroxy-phenyl)-1H-indol-3-yl]-1-(4-Chloro-phenyl) - prop-2-en-1-one (compound 4b)
^{1}H NMR (DMSO-d_6): δ 7.46-7.48 (d, J=15Hz, 1H, =CH-Ar), 6.99-8.1 (m, 12H, Ar), 8.07 (d, *J*=15.6Hz, 1H-COCH=), 12.13 (brs, 1H, NH), 10.02(s, 1H, OH) MS: [M+H] m/z 374.6

(E)-3-[2-(4-Hydroxy-phenyl)-1H-indol-3-yl]-1-(4-trifluoromethyl-phenyl)-prop-2-en-1-one (compound 4c)
^{1}H NMR (DMSO-d_6): δ 7.63-7.68 (d, *J*=15 Hz, 1H, =CH-Ar), 6.99-8.1 (m, 12H, Ar), 8.09 (d, *J*=15.3 Hz, 1H-COCH=), 12.18 (brs, 1H, NH), 10.02(s, 1H, OH) MS: [M+H] m/z 408

(E)-3-[2-(4-Hydroxy-phenyl)-1H-indol-3-yl]-1-p-tolyl- prop-2-en-1-one (compound 4d)
^{1}H NMR (DMSO-d_6): δ 7.64-7.69 (d, *J*=15 Hz, 1H, =CH-Ar), 6.99-8.1 (m, 12H, Ar), 8.09 (d, *J*=15.3 Hz, 1H-COCH=), 12.07 (brs, 1H, NH), 9.99(s, 1H, OH), 2.45 (S, CH_3) MS: [M+H] m/z 354

(E)- 3-[2-(4-hydroxy-phenyl)-1H-indol-3-yl]-1-(4-Fluoro phenyl) - prop-2-en-1-one (compound 4e)
^{1}H NMR (DMSO-d_6): δ 7.63-7.68 (d, *J*=15 Hz, 1H, =CH-Ar), 6.99-8.1 (m, 12H, Ar), 8.06 (d, *J*=15.3 Hz, 1H-COCH=), 12.11 (brs, 1H, NH), 10.02 (s, 1H, OH) MS: [M+H] m/z 358

(E)-3-[2-(4-Hydroxy-phenyl)-1H-indol-3-yl]-1-(4-nitro-phenyl) - prop-2-en-1-one (compound 4f)
^{1}H NMR (DMSO-d_6): δ 7.71-7.76 (d, *J*=15 Hz, 1H, =CH-Ar), 6.99-8.1 (m, 12H, Ar), 8.18 (d, *J*=15.3 Hz, 1H-COCH=), 12.3 (brs, 1H, NH), 10.1 (s, 1H, OH) MS: [M+H] m/z 385

2.7. General procedure for Synthesis of 4-{3-[3-(4-substituted phenyl)-4, 5-dihydro-isoxazol-5-yl]-1H-indol-2-yl}-phenol (compound 5a-5f)

Chalcones (2.149 mmol, compound 4a), hydroxylamine hydrochloride (4.298 mmol) and sodium acetate (4.298 mmol) were added in ethanol (10 mL) , the mixture was refluxed for 12 h. Reaction was monitored by TLC. The Mixture was concentrated by distilling out the solvent under reduced pressure. Crude was purified by column chromatography to obtained (0.67 g, 67%) as a solid. The spectral analysis of the synthesized compounds is as follows:

4-{3-[3-(4-Iodo-phenyl)-4, 5-dihydro-isoxazol-5-yl]-1H-indol-2-yl}-phenol (compound 5a)

IR (cm^{-1} , KBr): 3870, 3468, 3354, 1612, 1237, 1060, 591; ^{1}H NMR (DMSO-d_6): δ 3.64 (dd, *J*=10.2 Hz, 1H, CH_2 isoxazoline), 3.82 (dd, *J*=11.1 Hz, 1H, CH_2 isoxazoline), 5.96 (dd, *J*=10.8 Hz, 1H, CH isoxazoline), 6.91-7.88 (m, 12H, aromatic), 11.39 (brs, 1H, NH),9.77(s,1H,OH) ; Anal. Calcd for $C_{23}H_{17}IN_2O_2$ C, 57.52; H, 3.57; N, 5.83; O, 6.66 Found: C, 57.02; H, 3.65; N, 5.70; O, 6.20; MS: [M-H] m/z 479

4-{3-[3-(4-Chloro-phenyl)-4, 5-dihydro-isoxazol-5-yl]-1H-indol-2-yl}-phenol (compound 5b)

IR (cm^{-1} , KBr): 3359,3299, 1612, 1236, 1090, 739; ^{1}H NMR (DMSO-d_6): δ 3.83 (dd, *J*=12 Hz, 1H, CH_2 isoxazoline), 3.89 (dd, *J*=12.6 Hz, 1H, CH_2 isoxazoline), 5.96 (dd, *J*=10.8 Hz, 1H, CH isoxazoline), 6.92-7.8 (m, 12H, aromatic), 11.4 (brs, 1H, NH),9.78(s, 1H, OH) ; Anal. Calcd for $C_{23}H_{17}ClN_2O_2$ C, 71.04; H, 4.41; Cl, 9.12; N, 7.2; O, 8.23 Found: C, 70.80; H, 4.11; Cl, 9.22; N, 6.98; O, 8.11 MS: [M+H] m/z 389

4-{3-[3-(4-Trifluoromethyl-phenyl)-4,5-dihydro-isoxazol-5-yl]-1H-indol-2-yl}-phenol (compound 5c)

IR (cm^{-1} , KBr): 3369, 2923, 1609, 1259, 1165, 1062, 1124; ^{1}H NMR (DMSO-d_6): δ 3.73 (dd, *J*=12 Hz, 1H, CH_2 isoxazoline), 3.88 (dd, J=12.6 Hz, 1H, CH_2 isoxazoline), 5.97 (dd, *J*=10.8 Hz, 1H, CH isoxazoline), 6.6-8.1 (m, 12H, aromatic), 11.56 (brs, 1H, NH),9.82(s,1H,OH) ; Anal. Calcd for $C_{24}H_{17}F_3N_2O_2$ C, 68.24; H, 4.06; N, 6.63; O, 7.58 Found: C, 68.11; H, 4.10; N,6.57; O,7.32 MS: [M+H] m/z 423

4-[3-(3-p-Tolyl-4, 5-dihydro-isoxazol-5-yl)-1H-indol-2-yl]-phenol (compound 5d)

IR (cm^{-1} , KBr): 3358, 3274, 2917, 1609, 1235, 1438, 1070; ^{1}H NMR (DMSO-d_6): δ 3.63 (dd, *J*=12 Hz, 1H, CH_2 isoxazoline), 3.82 (dd, *J*=12.6 Hz, 1H, CH_2 isoxazoline), 5.93 (dd, *J*=10.8 Hz, 1H,CHisoxazoline),6.91-7.67(m,12H,aromatic),11.37(brs,1H,NH),9.77 (s,1H,OH),2.37(s,3H,CH_3); Anal. Calcd for $C_{24}H_{20}N_2O_2$ C, 78.24; H, 5.47; N, 7.60; O, 8.68 Found: C, 78.31; H, 5.24; N, 7.57; O, 8.71 MS: [M+H] m/z 369

4-{3-[3-(4-Fluoro-phenyl)-4, 5-dihydro-isoxazol-5-yl]-1H-indol-2-yl}-phenol (compound 5e)

IR (cm^{-1} , KBr): 3094, 2930, 1602, 1237, 1017, 1099; ^{1}H NMR (DMSO-d_6): δ 3.8 (dd, *J*=12 Hz, 1H, CH_2 isoxazoline), 3.87 (dd, *J*=12.6 Hz, 1H, CH_2 isoxazoline), 5.9 (dd, *J*=10.8 Hz, 1H, CH isoxazoline), 6.9-7.9 (m, 12H, aromatic), 11.3 (brs, 1H, NH),9.79 (s,1H,OH) ; Anal. Calcd for $C_{23}H_{17}FN_2O_2$ C, 74.18; H, 4.6; N, 7.52; O, 8.59 Found: C, 74.22; H, 4.42; N,7.32; O,8.41 MS: [M-H] m/z 371

4-{3-[3-(4-Nitro-phenyl)-4, 5-dihydro-isoxazol-5-yl]-1H-indol-2-yl}-phenol (compound 5f)

IR (cm^{-1} , KBr): 3394, 3261, 1605, 1510, 1342, 1256, 1095; ^{1}H NMR (DMSO-d_6): δ 3.75 (dd, *J*=12 Hz, 1H, CH_2 isoxazoline), 3.89 (dd, *J*=12.6 Hz, 1H, CH_2 isoxazoline), 5.98 (dd, *J*=10.8 Hz, 1H, CH isoxazoline), 6.8-8.1 (m, 12H, aromatic), 11.5 (brs, 1H, NH),9.8(s,1H,OH) ; Anal. Calcd for $C_{23}H_{17}N_3O_4$ C, 69.17; H, 4.29; N, 10.52; O, 16.02% Found: C, 69.23; H, 4.15; N,10.39; O,15.89 MS: [M+H] m/z 398

Table 1 Physical data of the newly synthesized 3-(4, 5-dihydro isoxazole)-indole derivatives (5a-5f)

Compound	R_1	Molecular Weight	MP (^{0}C)	Yield (%)	Rf values
5a	I	480.31	228-230	65	0.50
5b	Cl	388.86	236-238	68	0.56
5c	CF_3	422.41	211-213	70	0.45
5d	CH_3	368.44	199-202	65	0.50
5e	F	372.4	110-113	60	0.53
5f	NO_2	399.41	225-227	62	0.58

3. Biological screening for synthesized compounds (5a-5f)
Animal experimentation:
Test substance:
The test compounds titled as 5a, 5b, 5c, 5d, 5e and 5f were screened for the analgesic activity in mice at the dose of 10 mg/kg. All the standard drug and test compounds were dissolved in 0.1% DMF and further made it into suspension by using 1% Tragacanth in water.

Tail immersion method[18]: Swiss Albino mice were fasted for 12 hours and randomly allocated to eight groups of 5 mice. Each mouse tail was dipped at a depth of 3 cm from the tip into a thermo regulated water bath containing warm water maintained at the temperature of 56 ± 2°C and the time taken for a mouse to withdraw the tail known as the pain reaction time (PRT) was recorded for all the mice, in 0.01 s units using a stopwatch. The cut off time was 10 s. Group I served as control and received vehicle only (10 ml/kg b.w), Group II to VII administered with the test substances 5a, 5b, 5c, 5d, 5e and 5f respectively (10 mg/kg b.w.) and Group VIII received tramadol (50 mg/kg b.w.) *p.o.*. PRT was recorded for all the mice at 0.5, 1, 2 and 3h post treatment. The withdrawal time of untreated animals is between 1 and 5.5 s. the increase in mean reaction withdrawal time and percentage of protection was calculated.

Abdominal writhing test using acetic acid in mice[19]: Mice were fasted for 12 hours and randomly divided to eight groups and n=5. Group I served as control and received vehicle alone (10 ml/kg b.w), Group II to VII treated with the test substances 5a, 5b, 5c, 5d, 5e and 5f respectively (10 mg/kg b.w.) and Group VIII received indomethacin (10 mg/kg b.w.) via oral route. Writhings were induced i.p. administration of 3% v/v acetic acid at a dose of 1 ml/100 g b.w., 30 min post treatment. The number of writhes was counted from 0 to 30 min after acetic acid injection. Percentage protection was calculated for all the groups by applying the formula: (Writhings in control - Writhings in test)/Writhings in control X 100.

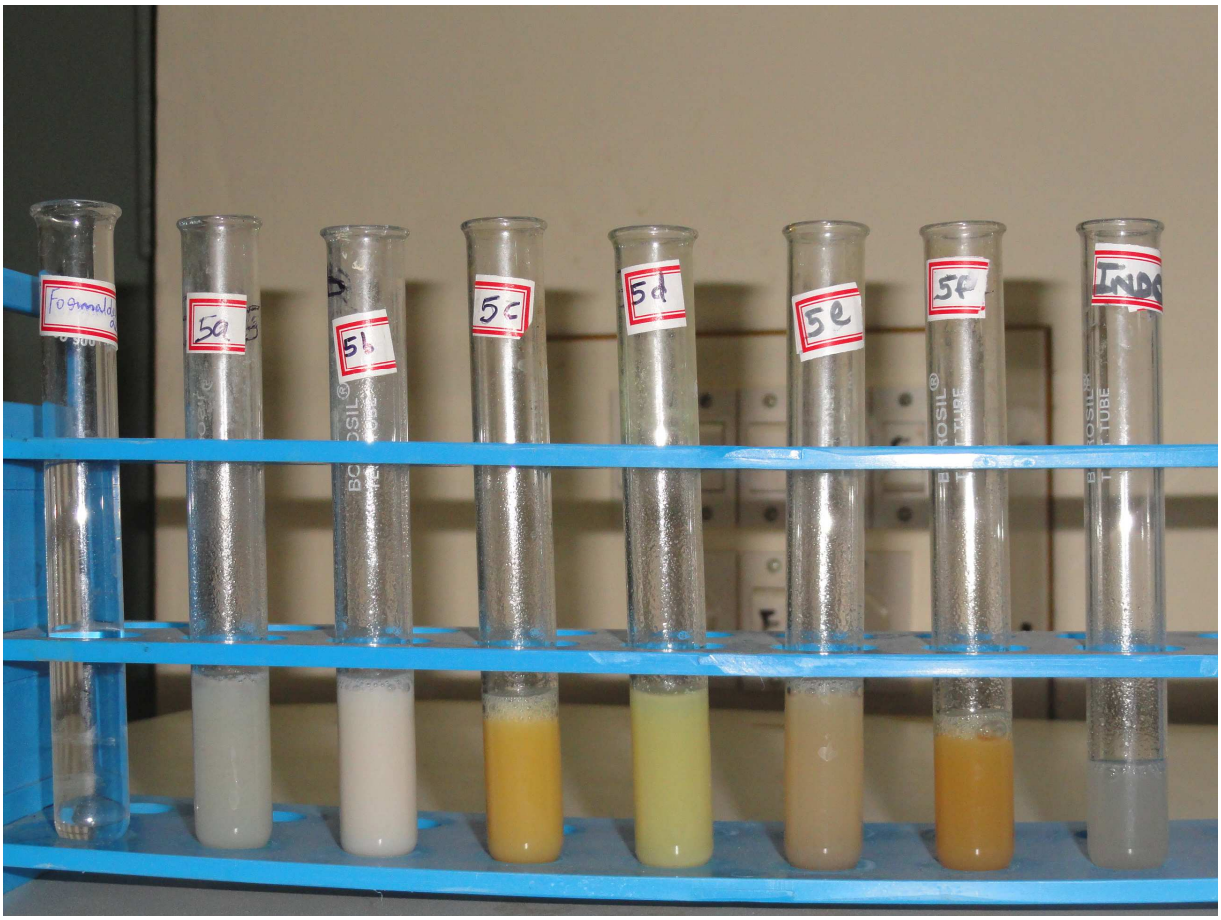


Table-1 Analgesic index (values in parenthesis) of compounds 5a, 5b, 5c, 5d,5e, and 5f evaluated by tail immersion method

Treatment (Dose mg/kg. p.o.)	Reaction time in seconds				
	0 min	30 min	60 min	120 min	180 min
Positive control (saline treated)	3.24 ± 0.61	4.41 ± 1.11	1.48 ± 0.42	1.11 ± 0.14	2.35 ± 1.07
%change		(26.58)	(-118.91)	(-190.58)	(-37.69)
5a (10 mg/Kg)	4.6 ± 0.73	2.15 ± 0.37	1.74 ± 0.58	4.61 ± 1.45	3.47 ± 2.17
%change		(-114.02)	(-164.06)	(0.15)	(-32.68)
5b (10 mg/Kg)	4.26 ± 0.42	4.79 ± 1.80[a]	6.12 ± 2.23[c]	6.98 ± 1.91[c]	5.36 ± 1.67
%change		(11.04)	(30.31)	(38.88)	(20.49)[b]
5c (10 mg/Kg)	4.37 ± 0.69	6.24 ± 1.28	5.46 ± 2.19[b]	5.22 ± 1.94[a]	4.44 ± 1.98
%change		(29.97)[c]	(19.94)	(16.18)	(1.57)
5d (10 mg/Kg)	4.13 ± 0.83	4.20 ± 0.80	4.29 ± 1.93	7.81 ± 2.16[c]	5.28 ± 1.65
%change		(1.47)	(3.72)	(47.01)	(21.70)
5e (10 mg/Kg)	2.40 ± 0.26	2.96 ± 0.85	1.04 ± 0.16	1.62 ± 0.52	1.43 ± 0.16
%change		(18.78)	(-131.53)	(-47.91)	(-67.45)
5f (10 mg/Kg)	1.81 ± 0.30	3.14 ± 0.89	0.78 ± 0.04	1.22 ± 0.27	4.61 ± 1.80
%change		(42.35)	(-132.05)	(-47.75)	(60.73)
Tramadol (50 mg/kg)	2.91 ± 0.32	4.29 ± 1.90[c]	9.60 ± 0.31[c]	6.38 ± 2.09[c]	3.88 ± 2.04[b]
%change		(32.02)	(69.61)	(54.26)	(24.85)

Values are expressed in MEAN±S.E.M. n=5. (Parenthes is value indicates % protection) ANOVA followed by Tukeys multiple comparison test. Values are statically [a]p<0.05, [b]p<0.01, and [c]p<0.001 when compared with 0 min interval.

Table-2 Effect of compounds 5a, 5b, 5c, 5d,5e, and 5f on acetic acid induced writhing in mice.

Treatment (Dose mg/kg. p.o.)	Number of Writhings	% Protection
Acetic acid 3% v/v 1mL/100gm	27.8 ± 2.95	---
5a (10 mg/Kg)	10.0 ± 1.41[c]	64.02
5b (10 mg/Kg)	13.8 ± 3.48[c]	50.35
5c (10 mg/Kg)	8.20 ± 2.03	70.5
5d (10 mg/Kg)	19.2 ± 1.82[b]	30.93
5e (10 mg/Kg)	9.20 ± 2.72[c]	66.9
5f (10 mg/Kg)	6.80 ± 1.85[c]	75.53
Indomethacin (10 mg/kg)	6.60 ± 2.42[c]	76.25

Values are expressed in MEAN±SEM. n=5. ANOVA followed by Tukeys multiple comparison test. Values are stastically, [b]p<0.01, and [c]p<0.001 when compared with acetic acid control (saline treated).

RESULTS AND DISCUSSION

Oral administration of 5b, 5c and 5d in the dose of 10 mg/kg significantly ([a]p<0.005[b]p<0.001[c]p<0.001) increased the mean reaction time at 30, 60, 120, and 180 min interval as compared to initial value. Whereas in treatment with 5a, 5e and 5f failed increase the mean reaction time. Treatment with standard drug tramadol significantly increased the mean reaction time at 30, 60 120, and 180min interval Table-1.

Intraperitoneal administration of acetic acid (3% v/v, 1 ml for 100gm body weight) significantly ([c]p<0.001) increased the writhing effect in mice. Oral administration of 5a, 5b,5c,5d,5e and 5f in the dose of 10 mg/kg significantly ([b]p<0.001[c]p<0.001) inhibited the acetic acid induced writhing in mice as compared to acetic acid control. Whereas in treatment with standard drug indomethacin significantly also ([c]p<0.001) inhibited the acetic acid induced writhing in mice Table-2.

The purpose of the present study was to examine whether molecular modification of Indole and Isoxazole would result in molecules with good analgesic actions. A series of compounds was synthesized and evaluated for biological activities. In this study, synthesis and pharmacological screening of various derivatives of 4-{3-[3-(4-substituted-phenyl)-isoxazol-5-yl]-2-phenyl-1H-indoles. These compounds to be testing in vivo for their analgesic activities. The results showed that the incorporation of appropriately substituted Isoxazole ring in Indole nucleus can afford good analgesic. Isoxazoline having substituted phenyl ring at 3rd position were in general more active than unsubstituted ones, indicating that the presence of functional group may be helpful in orienting the molecule in active site. The compounds with 4-chloro phenyl, 4-trifluoromethyl phenyl and 4-methyl phenyl rings at 3rd position of the Isoxazoline ring showed good analgesic activity than other substitutions.

CONCLUSION

Various derivatives of 4-(3-(3-(4-substituted phenyl)-4,5-dihydroisoxazol-5-yl)-1H-indol-2-yl)phenol (5a-5f) were successfully synthesized and screened for their analgesic activity. The tested compounds 5b, 5c and 5d have significant analgesic activity. In acetic acid induced writhing test oral administration of 5a, 5b, 5c, 5d, 5e, and 5f significantly inhibited number of writhings as compared to acetic acid alone, indicates all the tested compound have analgesic activity.

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