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Research Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF (E)-3-(2-(4-SUBSTITUTEDPHENYL)-1H-INDOLE-3-YL)-(4-SUBSTITUTEDPHENYL) PROP-2-EN-1-ONE AS ANTI-INFLAMMATORY AGENTS

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ABSTRACT

The reaction of 2-aryl-1H-indole-3-carboxaldehydes with substituted acetophenones in ethylene glycol and piperidine as a base gives the (E)-3-(2-(4-substitutedphenyl)-1H-indol-3-yl)-(4-substitutedphenyl) prop-2-en-1-one [4a-4f] 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, LCMS analysis. The synthesized compounds (4a-4f) were evaluated for their anti-inflammatory activity.

Key words: Anti-inflammatory activity, Indole derivatives, chalcones.

INTRODUCTION

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial[1, 2, 3] anti-inflammatory[4], antimalarial[5,6], antileishmanial[7], antioxidant[8], antitubercular[9,10],The presence of a reactive α,β-unsaturated keto function in chalcones was found to be responsible for their anti-inflammatory activity. In the present work we report the reaction of various substituted acetophenone with different substituted aromatic aldehyde to form chalcones (4a-4f).

Chalcones are α,β-unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-. These are coloured compounds because of the Presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. Different methods are available for the preparation of chalcones.The most convenient method is the claisen-Schimdt condensation of equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic alkali.

Indoles are one of the most important nitrogen containing heterocyclic molecules, found extensively in biological system which play vital role in biochemical process. 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. The substitution of heterocyclic moiety at the 2- position of Indole ring markedly influences the anti-inflammatory activity. A literature survey reveals that very few references are available on the synthesis of chalcones associated with indole compounds.

Considering the above observations and in connection to previous publications involving the synthesis of new biologically active heterocycles. I hope to report here in the synthesis of new series of chalcones incorporating an extra heterocyclic ring such as indole to screen in vivo for their anti-inflammatory activity and acute toxicity studies.

MATERIALS AND METHODS

Animals

The anti-inflammatory activity of newly synthesized compounds [4a-4f] was carried out on Albino Wistar rats, Male (100-150 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, the rats were acclimatized for one week. The animal experiments were previously approved by Institutional Ethical Committee (IEC) and followed CPCSEA requirements.

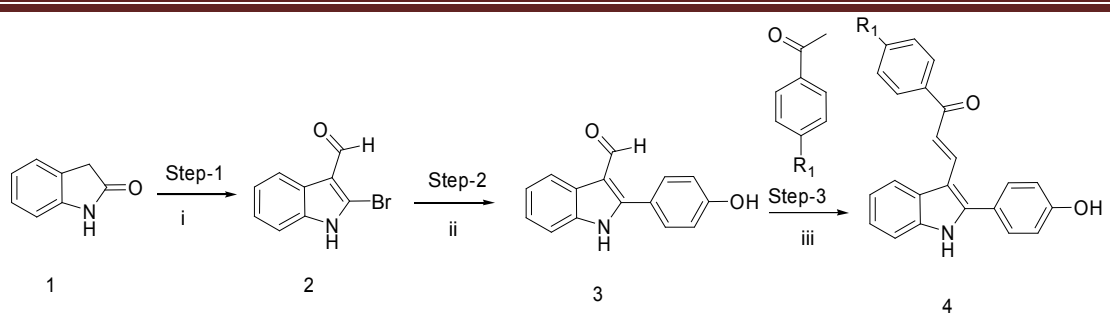
Materials

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 ^{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.

Carrageenan, Formaldehyde solution, Dimethylformamide, Tragacanth and all chemicals used in this study were laboratory grade. Indomethacin used as a standard drug purchased form Research Lab fine Chem Industries.

Scheme of Synthesis

The synthesis of the title compounds [4a-4f] is outlined in Figure 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 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, LCMS.



R_1= 4-I, 4-Cl, 4-CF_3, 4-CH_3, 4-F, 4-NO_2

Figure 1: Scheme of synthesis for (E)-3-(2-(4-substitutedphenyl)-1H-indol-3-yl)-(4-substitutedphenyl) prop-2-en-1-one (4a-4f)

i) DMF, $POBr_3$, DCM, 45^{O}C, 1h ii) PdCl2 (dppf), Na_2CO_3, 1, 4-dioxane: H_2O (5:1), 95^{O}C, 5h iii) Piperidine, Ethylene glycol, 160^{O}C, 6h

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^{o}C. 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

Synthesis of 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) Cl2 (0.0002 mmol), Na2CO3 (8.9 mmol) in dioxane: H2O (5:1) was heated to 90^{o}C 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

General procedure for synthesis of (e)-3-(2-(4-substituted phenyl)-1h-indole-3-yl)-(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^{0}C 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

Table 1: Physical data of the newly synthesized (E)-3-(2-(4-substitutedphenyl)-1H-indol-3-yl)-(4-substitutedphenyl) prop-2-en-1-one (4a-4f)

Compound	R_1	Molecular Weight	MP (^{0}C)	Yield (%)	Rf values
4a	I	465.29	135-137	68	0.60
4b	Cl	373.84	140-142	67	0.56
4c	CF_3	407.40	120-122	68	0.45
4d	CH_3	353.42	130-132	65	0.50
4e	F	357.4	118-120	60	0.45
4f	NO_2	384.4	125-127	62	0.58

Biological screening for synthesized compounds (4a-4f)

Animal experimentation

Test substance:

The test compounds titled as 4a, 4b, 4c, 4d, 4e and 4f were screened for the anti-inflammatory activity in rats 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.

Carrageenan induced paw edema model in rats[11]:

Wistar rats were fasted over night and randomly allotted to nine groups where n=5. Group I and II served as normal and disease control which receives vehicle alone. Group III to VIII administered with the test substances 4a, 4b, 4c, 4d, 4e and 4f respectively (10 mg/kg b.w.) and Group IX treated with indomethacin (10 mg/kg b.w.) *p.o.*. 0.1 ml of 1% w/v suspension of carrageenan was injected into the sub-plantar region of the right hind paw of each rat 30 mins post treatment with drug. The paw volume (in mL) was measured by using a digital plethysmometer, at different time intervals viz. 0, 30, 60,120, 180 and 240 min.

Formalin induced paw edema model in rats[12]:

Overnight fasted Wistar rats were randomly divided into nine groups of five animals each. Group I served as normal and Group II disease control and received vehicle, Group III to VIII received the test substances 4a, 4b, 4c, 4d, 4e and 4f respectively (10 mg/kg b.w.) and Group IX received Indomethacin (10 mg/kg b.w.) via oral route. 30 mins Post treatment of drugs, 0.1 ml of 10% v/v solution of formalin was injected into the sub-plantar region of the right hind paw of each rat. The paw volume was measured plethysmographically using a digital plethysmometer at several time points as fallows 0, 30, 60, 120, 180 and 240 min.

Statistical analysis of the data was performed using One way ANOVA followed by Tukeys's multiple comparison tests.

Table 2: **Effect of Test compounds 4a, 4b, 4c, 4d, 4e, and 4f on Carrageenan induced paw edema**

	Paw Volume(mL) after different time interval (Time in minutes)					
Groups	**0**	**30**	**60**	**120**	**180**	**240**
Normal	0.91 ± 0.04	1.03 ± 0.05^{b}	0.98 ± 0.03^{c}	1.01 ± 0.06^{c}	1.03 ± 0.05^{c}	1.02 ± 0.06^{c}
Carrageenan (1%, 0.1 ml)	1.02 ± 0.01	1.33 ± 0.01	1.46 ± 0.03	1.64 ± 0.06	1.76 ± 0.10	1.97 ± 0.15
4a (10 mg/Kg)	0.92 ± 0.03	1.15 ± 0.06	1.23 ± 0.07^{a}	1.34 ± 0.06^{a}	1.43 ± 0.08^{a}	1.53 ± 0.08^{b}
4b (10 mg/Kg)	0.93 ± 0.03	1.03 ± 0.02^{b}	1.17 ± 0.03^{c}	1.35 ± 0.07^{a}	1.44 ± 0.03^{b}	1.44 ± 0.05^{b}
4c (10 mg/Kg)	0.95 ± 0.04	1.26 ± 0.07	1.23 ± 0.02^{a}	1.35 ± 0.02^{a}	1.55 ± 0.02	1.60 ± 0.08
4d (10 mg/Kg)	0.92 ± 0.04	1.24 ± 0.04	1.27 ± 0.02^{a}	1.45 ± 0.01	1.43 ± 0.01^{a}	1.41 ± 0.01^{c}
4e (10 mg/Kg)	0.94 ± 0.06	1.30 ± 0.03	1.36 ± 0.02	1.32 ± 0.33^{a}	1.56 ± 0.06^{b}	1.49 ± 0.06^{b}
4f (10 mg/Kg)	1.05 ± 0.03	1.23 ± 0.06	1.38 ± 0.03	1.42 ± 0.05	1.48 ± 0.05^{a}	1.50 ± 0.07^{a}
Indomethacin (10 mg/Kg)	0.96 ± 0.03	1.21 ± 0.06	1.34 ± 0.06	1.27 ± 0.06^{b}	1.27 ± 0.06^{c}	1.32 ± 0.06^{c}

Values are expressed in MEAN±SEM. n=5. ANOVA followed by Tukeys multiple comparison tests. Values are stastically $^{a}p<0.05$, $^{b}p<0.01$, and $^{c}p<0.001$ when compared with carrageenan control.

Table 3: **Effect of compounds 4a, 4b, 4c, 4d, 4e, and 4f on formalin induced paw edema**

Treatment (Dose mg/kg. p.o.)	**Paw Volume, ml after different time interval (Time in minutes)**					
	0	**30**	**60**	**120**	**180**	**240**
Normal	1.02 ± 0.01	1.05 ± 0.02^{c}	1.07 ± 0.02^{c}	1.13 ± 0.01^{c}	1.08 ± 0.02^{c}	1.07 ± 0.01^{c}
Formalin (10%, 0.1 ml)	1.03 ± 0.01	1.42 ± 0.03	1.66 ± 0.03	1.77 ± 0.02	2.13 ± 0.18	1.97 ± 0.03
4a (10 mg/Kg)	1.05 ± 0.02	1.24 ± 0.02	1.63 ± 0.08	1.69 ± 0.07	1.70 ± 0.08^{a}	1.77 ± 0.06^{a}
4b (10 mg/Kg)	1.07 ± 0.07	1.34 ± 0.02	1.46 ± 0.04	1.45 ± 0.02	1.60 ± 0.03^{b}	1.64 ± 0.02^{c}
4c (10 mg/Kg)	0.95 ± 0.04	1.45 ± 0.01	1.52 ± 0.03	1.64 ± 0.04^{b}	1.69 ± 0.03^{a}	1.66 ± 0.01^{c}
4d (10 mg/Kg)	1.05 ± 0.01	1.36 ± 0.01	1.45 ± 0.01	1.50 ± 0.02^{b}	1.68 ± 0.03^{b}	1.60 ± 0.03^{c}
4e (10 mg/Kg)	1.04 ± 0.06	1.33 ± 0.11	1.48 ± 0.07	1.64 ± 0.08	1.66 ± 0.06^{b}	1.73 ± 0.06^{b}
4f (10 mg/Kg)	1.15 ± 0.06	1.50 ± 0.03	1.54 ± 0.02	1.63 ± 0.03	1.67 ± 0.01^{b}	1.70 ± 0.02^{c}
Indomethacin (10 mg/Kg)	0.95 ± 0.03	1.34 ± 0.06	1.38 ± 0.04^{b}	1.44 ± 0.03^{c}	1.47 ± 0.02^{c}	1.46 ± 0.01^{c}

Values are expressed in MEAN±SEM. n=5. $^{a}p<0.05$, $^{b}p<0.01$, and $^{c}p<0.001$ when compared with Formalin Control.

RESULTS AND DISCUSSION

Significant induction of paw inflammation observed in carrageenan control (1%, 0.1 ml and $^{b}p<0.01$ $^{c}p<0.001$) with increased paw volume in the all the time interval as compared to normal control. Treatment 4b at the dose of 10 mg/kg significantly ($^{a}p<0.005$$^{b}p<0.001$$^{c}p<0.001$) inhibited the carrageenan induced paw edema at 30, 60, 120, 180 and 240 min interval as compared to carrageenan control. Administration of 4a and 4c significantly reduced paw edema at 60, 120 and 240 min interval as compared to carrageenan control. Where as in 4d 4e, 4f treatment, the inhibition of carrageenan induced paw edema was found to significant at 120, 180 and 240 min interval. Treatment with standard drug indomethacin significantly inhibited the carrageenan induced paw edema at 120, 180 and 240 min intervals Table 2.

Administration of formalin (10%, 0.1 ml) significantly ($^{c}p<0.001$) increased the paw volume in the all the time interval as compared to normal control. Oral administration of 4a,4b,4c,4d,4e and 4f in the dose of 10 mg/kg significantly ($^{b}p<0.001$$^{c}p<0.001$ inhibited the formalin induced paw edema at 180 and 240 min interval as compared to formalin control. Whereas in treatment with standard drug indomethacin significantly ($^{b}p<0.001$$^{c}p<0.001$) inhibited the formalin induced paw edema at 60, 120, 180 and 240 min interval Table 3.

The purpose of the present study was to examine whether molecular modification of Indole and Isoxazole would result in molecules with good anti-inflammation actions. A series of compounds was synthesized and evaluated for biological activities. In this study, synthesis and pharmacological screening of various derivatives of (E)-3-(2-(4-substitutedphenyl)-1H-indol-3-yl)-(4-substitutedphenyl) prop-2-en-1-one. These compounds to be testing in vivo for their anti-inflammatory activities. The results showed that the incorporation of appropriately substituted phenyl ring in Indole nucleus can afford good anti-inflammation actions. α,β-unsaturated carbonyl group having substituted phenyl ring 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, 4-trifluoromethyl and 4-iodo

functional groups at 4th position of the phenyl ring showed good activity than other substitutions.

CONCLUSION

A new series of (E)-3-(2-(4-substitutedphenyl)-1H-indol-3-yl)-(4-substitutedphenyl) prop-2-en-1-one [4a-4f] were synthesized for anti-inflammatory activity. The test compounds 4b and 4e have significant anti-inflammatory activity against carrageenan induced paw edema. Chalcone derivatives contain α,β-unsaturated carbonyl moiety which is responsible for anti-inflammatory activity. Synthesized chalcone derivatives were subjected to anti-inflammatory screening using the carrageenan-induced rat hind paw edema model. Chalcone derivatives at dose 10 mg/kg by oral route inhibited significantly the formation of edema. The *P* value was found to be <0.05 showing significant anti-inflammatory activity. The compound '4-fluoro/4-chloro chalcone' showed more activity comparable to standard drug indomethacin due to -F/-Cl groups present in the compound. Hence, the anti-inflammatory activity of chalcone derivatives was increased when electron withdrawing groups (EWG) were present on the chalcone moiety.

The results indicated that these compounds have potential effect against acute as well as chronic inflammatory conditions. The compound 4c has acute anti inflammatory activity, whereas 4a, 4d, and 4f have also shown anti-inflammatory activity, indicates these compounds are active against chronic inflammatory conditions.

Further the detailed structural activity relationship studies are required along with the molecular manipulation i.e. molecular modeling may give better drugs. Molecules prepared for the biological testing do not always turn out as potential new drugs.

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