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Synthesis, Characterization and Pharmacological Evaluation of Some Novel 2-Indole Derivatives with Their Cyclooxygenase-2 Inhibitory As an Anti-Inflammatory Activity

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Keywords: 2-anilineindole, FTIR, 1H NMR, anti-inflammatory activity.

ABSTRACT

Various derivatives of Indole were synthesized using 2-anilineindole as a precursor. The structures of synthesized compounds were confirmed by the use of their spectral data FTIR, 1H NMR, and elemental analysis. The IR spectra of newly synthesized compounds showed the presence of characteristic absorption bands in the region 3100-3400, 3000-3100,1750-1800,1680-1700 and1100-1240 cm^{-1} which can be N-H stretching, Ar-H stretching, C=O stretching, C=N stretching and C-N stretching respectively. The anti-inflammatory activity of the synthesized Indole derivatives was determined in vivo using Plethysmometer, method. The zone of inhibition was measured and compared with standard drugs ibuprofen at 50 mg/kg concentration resp. Anti-inflammatory activity was carried out using the carrageenan-induced rat paw edema method by Winter et al. The results revealed that a newly synthesized compound was found to the most potent Anti-inflammatory compounds.

INTRODUCTION

Indole containing the pyrrole ring with benzene ring fused to α, β-position, such bicyclic heterocyclic. Indole has a benzene ring and pyrrole ring sharing one double bond. It is an important heterocyclic system with 10 electrons from four double bonds and the lone pair from the nitrogen atom. Chemical degradation of the dye gave rise to oxygenated indoles which were named indoxyl and oxoindole. Indole occurs in coal tar and in the oils of jasmine and orange blossoms. Indole is an important heterocyclic system because it is built into proteins in the form of amino acid tryptophan, because it is the basis of drugs like indomethacin and because it provides the skeleton of indole alkaloids- biologically active compounds from plants including strychnine and LSD. Most indoles are quite stable in air, with the exception of those which carry a simple alkyl group at C-2: 2-methylindole auto oxidized easily even in a dark brown bottle. Indole may also be known as 2, 3-benzopyrrole Indole is an important heterocyclic system because it is built into proteins in the form of amino acid tryptophan, because it is the basis of drugs like indomethacin and because it provides the skeleton of Indole alkaloids- biologically active compounds from plants including strychnine and LSD. [1-7].

MATERIALS AND METHODS

Reagents and solvents

The chemicals used for the experimental work were commercially procured from various chemical units from the Sigma Aldrich, HiMedia, Lobachem India Ltd. and CDH. These compounds were purified and dried before their use.

Instrument and Equipment

Melting point- Melting points of the synthesized compounds were determined by the open capillary method.

Solubility- The solubility of the compounds was checked in various solvents at room temperature.

^{1}H NMR –The proton magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker 300 MHz instrument in DMSO/$CDCl_3$using tetramethylsilane as internal standard. The ^{1}H NMR spectroscopy was done at CDRI, Lucknow.

IR - The infrared spectra of the compounds were recorded in KBr on PERKIN ELMER FTIR spectrometer. The FTIR spectroscopy was performed at CDRI, Lucknow.

TLC - Iodine chamber and U.V lamp were used for visualization of TLC spots.

Synthesis of 2-(2-chlorophenyl)-3-[4-(1*H*-indol-2-yl)phenyl]-1,3-thiazolidin-4-one.(1)

A solution of 2.0 gm (0.01mol) of 4-(1H-indol-2-yl) aniline dissolved in 30 mL DMF containing few drops of glacial acetic acid (GAA), 1-cholorobenzaldehyde (0.01mol) was added in a round bottom flask and the mixture was reflux for 3 hrs. It was cooled at room temperature, poured into cold water, Solid product was filtered, dried and then recrystallized from ethanol. Then added thioglycolic acid (0.04mol) dissolve in 1, 4, dioxane (20mL), (0.5g) anhydrous zinc chloride were added and reflux for 8hrs. The solvent was distilled off and the crude product was poured into ice cold water. The compound obtained was washed with a sodium bicarbonate solution and recrystallized from ethanol to give compound 1 (1.20g, 60. %).

Synthesis of 2-(4-hydroxyphenyl)-3-[4-(1H-indol-2-yl) phenyl]-1, 3-thiazolidin-4-one (2)

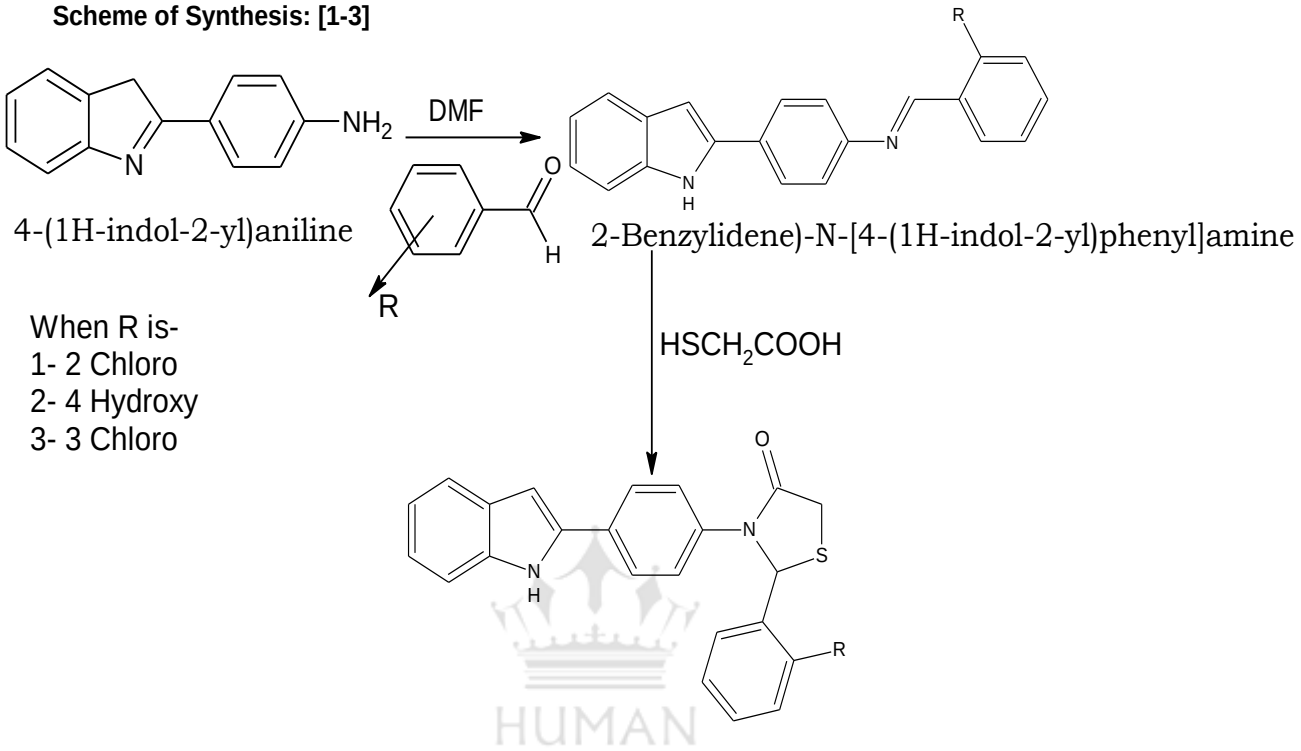
A solution of 2.0 gm (0.01mol) of 4-(1H-indol-2-yl) aniline dissolved in 30 ml DMF, containing, 1.40 gm (0.01mol) of 4- hydroxyl benzaldehyde was dissolved in the presence of glacial acetic acid (5ml). The reaction mixture was reflux on a water bath for 3 hrs. It was cooled at room temperature, poured into cold water, Solid product was filtered, dried and then recrystallized from ethanol.Then added thioglycolic acid (0.04mol) dissolve in 1,4, dioxane(20mL),(0.5g) anhydrous zinc chloride was added and reflux for 10hrs. . The solvent was distilled off and the crude product was poured into ice cold water. The compound obtained was washed with a sodium bicarbonate solution and recrystallized from ethanol to give compound 2 (1.40g, 70 %).

Synthesis of2-(4-chlorophenyl)-3-[4-(1H-indol-2-yl)phenyl]-1,3-thiazolidin-4-one(3)

A solution of 2.0 gm (0.01mol) of 4-(1H-indol-2-yl) aniline dissolved in 30 ml DMF, containing, 1.40 gm (0.01mol) of 4- chlorobenzelaldehyde was dissolved in the presence of glacial acetic acid (5ml). The reaction mixture was reflux on the water bath for 3 hrs.It was cooled at room temperature, poured into cold water, Solid product was filtered, dried and then recrystallized from ethanol.Then added thioglycolic acid (0.04mol) dissolve in 1,4,

dioxane(20mL),(0.5g) anhydrous zinc chloride was added and reflux for 10hrs. . The solvent was distilled off and the crude product was poured into ice cold water. The compound obtained was washed with a sodium bicarbonate solution and recrystallized from ethanol to give compound 2 (1.10g, 55%).

SYNTHETIC PROCEDURES
Scheme of Synthesis: [1-3]



2-(phenyl)-3-[4-(1H-indol-2-yl)phenyl]-1,3-thiazolidin-4-one [1-3]

Characteristic data of synthesized compounds

2-(2-chlorophenyl)-3-[4-(1*H*-indol-2-yl)phenyl]-1,3-thiazolidin-4-one

TLC (Ethyl Acetate: Chloroform 9:1, v/v): Rf:0.64, IR (KBr) υ: 3361.7(N-H stretching), 3017.3 (aromatic C-H stretching), 1729.7(C=O stretching), 1640.1(CH=CH- stretching), 1615.3(-C=C- of aromatic ring), 1236.8(C-N stretching) 1097.8(C-Cl stretching),629.9(C-S stretching)

1H NMR (DMSO): δ 7.26-8.0(m, 5H, Ar-H), 9.2(s, 1H, N-H), 3.4(s, 2H, CH2), 5.92(s,1H, C-H)

Calculated for $C_{23}H_{17}ClN_2OS$: C(68.22%); H(4.23%); Cl(8.76%); N(6.92%), O(3.95%); S(7.92%).

2-(4-hydroxyphenyl)-3-[4-(1H-indol-2-yl) phenyl]-1, 3-thiazolidin-4-one (2)

TLC (benzene: acetone 9:1, v/v): Rf: 0.75, IR (KBr) υ: 3487.7 (O-H stretching) 3335(N-H stretching),3083.8(Aromatic C-H stretching), 1753.1(C=O Stretching), 1531.7(-C=C- of aromatic ring), 1240.4 (C-O stretching), 1234.7(C-N Stretching)

1H NMR (DMSO): δ 7.26-8.0(m, 5H, Ar-H), 10 (s, 1H, N-H), 3.6(s, 2H, CH2), 5.92(s, 1H, C-H), 5.0 (s, 1H, -OH). Calculated for $C_{23}H_{18}N_2O_2S$: C(71.48%); H(4.69%); N(7.25%), O(8.28%); S(8.30%).

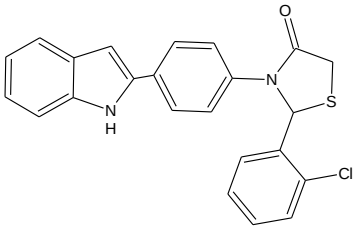
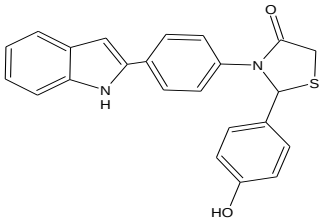
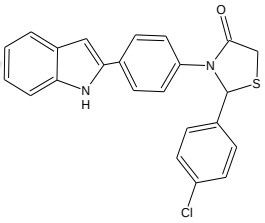
2-(4-chlorophenyl)-3-[4-(1H-indol-2-yl)phenyl]-1,3-thiazolidin-4-one(3)

TLC (Ethyl Acetate: Chloroform 9:1, v/v): Rf:0.64, IR (KBr) υ: 3262.7(N-H stretching), 3017.3 (aromatic C-H stretching), 1720.7(C=O stretching), 1605.1(CH=CH- stretching), 1615.3(-C=C- of aromatic ring), 1236.8(C-N stretching) 1097.8(C-Cl stretching),629.9(C-S stretching)

1H NMR (DMSO): δ 7.26-8.0(m, 5H, Ar-H), 9.2(s, 1H, N-H), 3.4(s, 2H, CH2), 5.92(s,1H, C-H)

Calculated for $C_{23}H_{17}ClN_2OS$: C (68.22%); H(4.23%); Cl(8.76%); N(6.92%), O(3.95%); S(7.92%).

Table 1: IUPAC name and structure of synthesized compounds

S. No		Structure	M.P. (°C)
1	2-(2-chlorophenyl)-3-[4-(1H-indol-2-yl)phenyl]-1,3-thiazolidin-4-one		230-232
2	2-(4-hydroxyphenyl)-3-[4-(1H-indol-2-yl) phenyl]-1, 3-thiazolidin-4-one (2)		315-317
3	2-(4-chlorophenyl)-3-[4-(1H-indol-2-yl)phenyl]-1,3-thiazolidin-4-one(3)		300-302

ANTI-INFLAMMATORY ACTIVITY

EXPERIMENTAL

MATERIAL AND METHOD

Animal Selection

Male albino Wister rats, weighing about 120-200g were used for the anti-inflammatory activity studies. Rats were procured from JNCHRC Bhopal (M.P.)

Rats were divided into 3 groups in a clean poly acrylic cage. The cages were changed every day using rice husk. The animals were maintained 12 hrs light and dark cycle. The animal was acclimatized for one week to the laboratory condition before starting the experiment. The animals were fed with standard pellet diet and water ad libitum.

All the animal studies were carried out as per CPCSEA (Committee for the purpose of control and supervision of experiment on the animal) norms after obtaining approval from the institutional animal ethical committee.

Principle- The inflammatory reaction is rapidly produced in rats in the form of paw edema with the help of irritant or inflamed. Carrageenan-induced paw edema is the most commonly used method in experimental pharmacology. Carrageenan is sulfated polysaccharide obtained from seaweeds (Rhodophyceae) causing the release of histamine, 5HT, Bradykinin, and PG. It produces inflammation and edema.

Requirement

A- Animal- Albino rats weighing 120-200g

B-Carragennan- 1%W/v solution injected (0.1mL) under planter region to introduces edema.

C- Contol group- (2ml/kg) saline solution

D- Drug- (Ibuprofen) 50mg/Kg prepared in 1% carboxymethyl cellulose solution administered orally according to the body weight of the animal.

E- Sample- Compound 1, 2, 3, were administered similarly to the standard drug.

F- Instrument- Plethysmometer, It is a glass tube of 20 mm internal diameter and one end fabricated to a glass tube with 0.5 mm bore. This tube is fused to a flexible tube and a pump (glass-syringe) and fixed to the other end of the tube. This pump is used to adjust the level of mercury in both the flexible tube and graduated glass tube up to zero levels.

Working procedure

1. 15 Albino rats of either sex weighing between 120-200 g were divided into 5 groups, of 3 animals each, they were numbered individually.

2. The animals have fasted for 24 hrs with water.

3. The animals were marked on their hind paws (left) just beyond tibiotarsal junction to ensure constant dipping in the mercury column up to the fixed mark.

4. Group, I administered with the only suspension, which served as control.

5. Group II administered with 50mg/kg body wt. of Ibuprofen, which served as a standard.

6. Group III-VI received the compounds1-3, respectively the dose being 50 Mg/kg body weight selected on the basis of the standard drug used.

7. After 30 minutes 0.1 ml of 1% w/v carrageenan solution was injected into the plantar region of the left paw to the control, standard and group III-VI animals.

8. The paw volume of both legs of control, standard, and group III-VI was measured with the help of plethysmometer at the end of 3 hrs after carrageenan administration.

9. The percentage inhibition of the inflammation in the drug-treated animals were recorded and calculated using the formula

$$\% \text{ Inhibition} = 100\ (1\text{-}Vt/Vc)$$

Where t and care mean volumes of edema of drug-treated and control respectively.

RESULTS AND DISCUSSION

The results and statistical analysis of the anti-inflammatory activity of Ibuprofen and the compounds tested are shown in table 2 and Fig.1

Table 2 Effect of drug treatment on carrageenan-induced rat paw edema.

Group	Dose (mg/kg Body wt)	1 hr Mean ± SE	2 hr Mean ± SE	3 hr Mean ± SE
Control	50mg/kg	0.42± 0.012	0.70± 0.005	1.0± 0.057
Standard (IBUPROFEN)	50mg/kg	0.20± 0.005	0.22± 0.011	0.24± 0.014
1st drug	50mg/kg	0.30± 0.011	0.40± 0.014	0.45± 0.005
2nd drug	50mg/kg	0.28± 0.008	0.38± 0.008	0.30± 0.005
3rd drug	50mg/kg	0.27± 0.011	0.35± 0.005	0.43± 0.005

Table 3 Percentage inhibition of carrageenan-induced rat paw edema.

Treatment	Dose	% Inhibition		
		1hr	2hr	3hr
Standard	50mg/kg	52.30	68.57	76
1st drug	50mg/kg	28.57	42	55
2nd drug	50mg/kg	33.33	45	66
3rd drug	50mg/kg	35.71	50	57

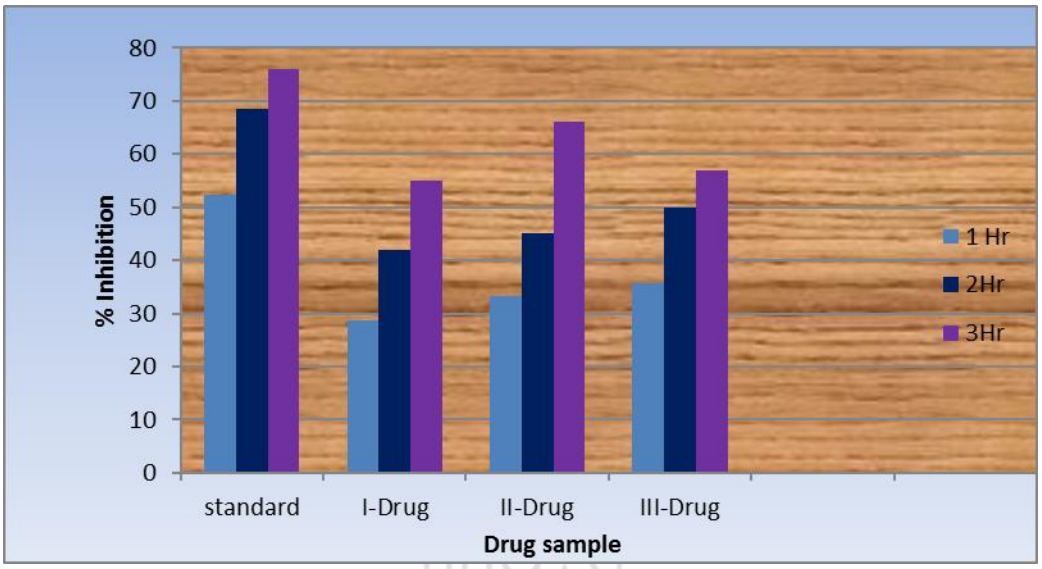


Fig 1 Graph showing Percentage inhibition on Carrageenan-induced Rat Paw edema with various treatments

CONCLUSION

The drugs at the oral dose of 50 mg/kg showed good results and caused a significant inhibition in the carrageen induced rat paw edema.

Among the synthesized compounds, compound 2nd was found to be most active and its inhibition in edema volume was noted to be (66%) near to the standard drug ibuprofen, which caused maximum inhibition of 76%.

The 3rd drug showed a little lesser inhibition of 57 % as compared to the standard drug and the 1st synthesized drug was found to be least active among the three.

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