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RESEARCH ARTICLE

SYNTHESIS AND IR SPECTROSCOPIC CHARACTERIZATION OF SOME SYNTHESIZED CHALCONE LINKED ISATIN DERIVATIVES -BASED SCHIFF BASES

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ABSTRACT

A new efficient and environmental friendly procedure for the synthesis Chalcone linked Isatin derivatives -Based Schiff Bases under microwave irradiation method also. The method is compared with the conventional method also. A series of novel Chalcone linked isatin derivatives were investigated for anti-inflammatory related activities such as cyclooxygenase inhibition. The results also showed that the chalcone derivatives with isatin moiety seem to be significant for inhibition of enzymes. Molecular docking experiments were carried out to elucidate the molecular aspects of the observed inhibitory activities of the investigated compounds. Present study findings increase the possibility that these newly synthesized chalcone linked isatin derivatives might act as a useful starting material for the design and synthesis of improved anti-inflammatory agents and synthesized compounds were characterized by IR spectroscopy.

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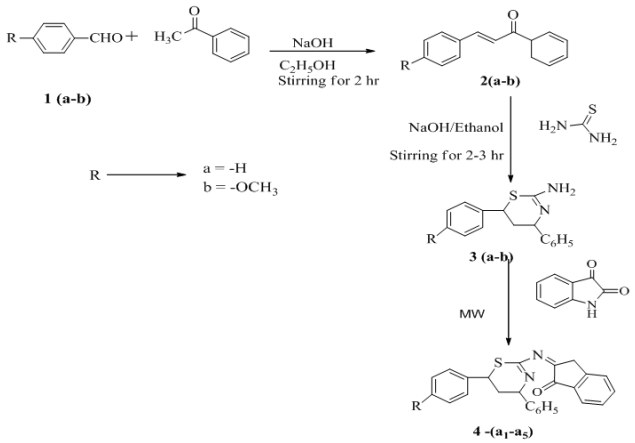
INTRODUCTION

Inflammation refers to your body's process of fighting against things that harm it, like infections, injuries, and toxins, in an effort to heal itself. It is body protection mechanism in order to remove or limit the widen of injurious agent as well to eliminate the necrosis cells[1]. Non-steroidalanti-inflammatory drug has been recognized as essential class of therapeutic agents for the healing of inflammation and pain. The pharmacological special effects of NSAIDs are due to inhibition of a membrane enzyme called cyclooxygenase (COX-1 and COX-2), which is involved in prostaglandin biosynthesis. COX-1 is predominantly expressed in most tissues, is responsible for the physiological production of prostaglandins, and COX-2, which is induced by mitogens, cytokines and endotoxins in inflammatory cells, is responsible for the elevated production of prostaglandins during inflammation process. For this reason, COX became an attractive target for the development of anti-inflammatory drugs. Long term use of NSAIDs has been accompanied with several side effects such as gastrointestinal mucosal damage, intolerance, bleeding, renal toxicity and hepatotoxicity.

Thus, the development of new anti- inflammatory agents with fewer side effects is a foremost challenge to medicinal chemists. Schiff bases, as the most widely used organic compounds, have been widely used in synthesis of intermediates (2), biological actions (3), polymers (4), and so forth and obtained a lot of progress. Schiff bases have been shown to exhibit a broad range of pharmacological activities.

Scheme



EXPERIMENTAL

Melting points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using chloroform: methanol, 7:3 solvent system and U.V lamp used as a visualizing agent. IR spectra were recorded using KBr pellets on a Thermo Nicolet Nexus 670 spectrophotometer.

METHODOLOGY

PREPARATION OF CHALCONES 2(a-b): Equimolar mixture of Benzaldehyde/Anisaldehyde (0.01 mol) and Acetophenone (0.01 mol) were dissolved in minimum amount of alcohol. Sodiumhydroxide (0.02 mol) was added slowly and the mixture stirred for 2 hr until mixture becomes very cloud. Then the mixture was poured slowly into 400 ml of water with constant stirring and kept in refrigerator for 24 hours. The precipitate obtained was filtered, washed and recrystalised from ethanol and the completion of the reaction was monitored by TLC[5].

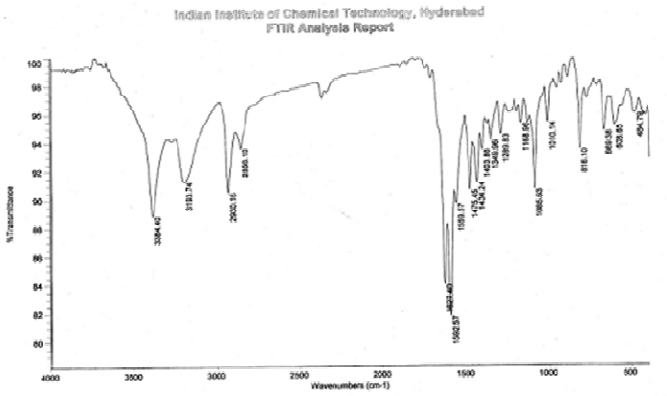
PREPARATION OF THIAZINE DERIVATIVES 3(a-b): A mixture of 2a/2b/2c (0.02 mol), thiourea (0.02 mol) were dissolved in ethanolic sodium hydroxide (10 ml) was stirred about 2-3 hours with a magnetic stirrer. This was then poured into 400 ml of cold water with continuous stirring for an hour and then kept in refrigerator for 42 hours. The precipitate obtained was filtered, washed and recrystalised and the completion of the reaction was monitored by TLC.

PREPARATION OF SCHIFF'S BASE DERIVATIVES 4(a_1-a_5) by

Conventional method: Equimolar quantities (0.01mol) of Isatin and the corresponding amino compound were dissolved in warm ethanol (50 ml) containing glacial acetic acid (0.5 ml). The reaction mixture was refluxed for 4 hrs and then kept at room temperature overnight. The resultant solid was washed with dilute ethanol, dried and recrystallized from ethanol-water (1:2) mixture to afford compounds.

PREPARATION OF SCHIFFS BASE DERIVATIVES 4(a_1-a_5) by Microwave method: Equimolar quantities (0.01mol) of Isatin and the corresponding amino compound were dissolved in warm ethanol (50 ml) containing glacial acetic acid (0.5 ml) added in microwave tube.

The reaction content were subjected to microwave irradiation at 200 W for about25sec - 25 min. Progress of the reaction was monitored by TLC.After completion reaction, solid product was obtained in reaction mixture which was filtered and recrystalised with ethanol to afford compounds[6].



IR spectra:4a1

IR Spectra: In the IR spectra of the Schiff base shows band at 1627 cm-1 assigned to the azomethine group (HC=N), this confirms the condensation between the amino group of 2-amino thiazine and the aldehyde group of benzaldehyde in formation of Schiff base. The intensity peak of absorption in the Schiff base around 1627cm-1 due carbonyl group of ketones and CH-stretching observed at 2930 cm-1.

RESULTS AND DISCUSSION

All the synthesized Fen Isatin derivatives ($4a_1$, $4a_2$, $4a_3$, $4a_4$, $4a_5$) were tested for anti inflammatory activity at the dose of 100 mg \ kg in acute inflammatory models in rats. The compounds under the study exhibited moderate to good anti-inflammatory activity and the results are tabulated in the table. Compound $4a_1$ and $4a_2$ shown maximum inhibition of 70.44%;74.01% respectively and, where as the rest of the compounds tested exhibited a minimum inhibition compared to the standard Diclofenac sodium which shown a reduction in Oedema volume by 93.76% in carrageen induced rat hind paw Oedema model. From anti-inflammatory evaluations data it is clear that some of the substituted Isatin derivatives posses' significant anti-inflammatory activity and some of them posses moderate anti-inflammatory activity.

Table 1. Comparison of microwave and Conventional method

Microwave Method					Conventional Method		
Compounds	Power	Temperature	Time(Sec)	Yield %	Temperature	Time(hrs)	Yield %
$4a_1$	200 w	70 -75 ^{0}C	50	90	Ambient	1	65
$4a_2$	200 w	70 -75 ^{0}C	60	85	Ambient	2	70
$4a_3$	200 w	70 -75 ^{0}C	55	93	Ambient	1.5	66
$4a_4$	200 w	70 -75 ^{0}C	45	88	Ambient	2	64
$4a_5$	200 w	70 -75 ^{0}C	40	86	Ambient	1.5	72

Table 2. I R Spectral Data

Types of vibration	Group frequency in Wave number (cm^{-1})
3384	NH
2930	CH Stretching
1640	NH
1627	C=N
1475, 1559,1592	Aromatic ring stretching
840	1,4-distretching Benzene
669	C-S

Table 3. Data showing anti-inflammatory activity of chalcone linked isatin derivatives in carrageenan induced acute rat paw oedema model[7-10]

Group	Treatment	Dose Mg/kg	Paw edema volume							
			After 1/2 hr		After 1 sthr		After 2nd hr		After 4th hr	
			Mean	% ROV	Mean	% ROV	Mean	% ROV	Mean	% ROV
1	Control	0.5ml	0.19	-	0.52	-	0.59	-	0.56	-
2	Standard	20	0.100	43.36	0.16	66.55	0.107	70.02	0.013	93.76
3	$4a_1$	100	0.14	22.20	0.39	37.33	0.47	71.68	0.49	70.44
4	$4a_2$	100	0.080	72.00	0.14	79.99	0.19	81.50	0.19	74.01
5	$4a_3$	100	0.17	41.00	0.22	54.33	0.23	55.71	0.21	64.53
6	$4a_4$	100	0.12	21.35	0.31	32.87	0.41	49.02	0.30	55.96
7	$4a_5$	100	0.17	42.00	0.17	55.00	0.31	56.14	0.33	53.00

ROV- Reduction in paw oedema volume.

The significant anti-inflammatory property of compounds 4a1and 4a2 may be due to the substituted on chalcone nucleus which is attached to the third position of the Indole ring system.

CONCLUSION

Synthesis of Chalcone linked Isatin derivatives -Based Schiff Bases derived from Acetophenone were synthesized and characterized by IR spectroscopy. In the synthesis at first step new HC=CH bond formed between acetyl group of Acetophenone and aldehyde group of benzaldehyde which confirmed chalcone formation. In second step new HC=NH bond formed between amine group of thiazines of Schiff base and aldehyde group of which confirmed Schiff base formation and showing significant anti-inflammatory activity.

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