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Synthesis, Characterization and *in vivo* Anti-Inflammatory Activity of Some Novel Schiff's Bases of Isatin Derivatives

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Abstract

In the present study, a series of novel Schiff bases of Isatin derivatives are incorporating different 5-sustituted N-benzyl Isatin derivatives with benzimmidazole derivatives (3a-3h) and with tryptamine (4a-ah) were synthesized and characterized by FTIR, ^{1}H-NMR, Mass spectroscopy. Further, the compounds were screened for *in vivo* anti-inflammatory activity by carrageenan induced paw edema method. The tested compounds have shown mild-to-moderate anti-inflammatory activity at dose of 10 and 20 mg/kg when compared to that of 10 and 20mg/kg dose slandered drug. the anti-inflammatory effect of compound 3e (55.9, 69.0), 3f (58.9, 77.4) and 4c (57.3, 73.2), 4e (51.3, 81.2) and 4g (50.5, 78.3) at 10 and 20mg/kg and Diclofenac sodium 63.5, 86.5 at 10 and 20mg/kg was found to be similar. The higher anti-inflammatory activity of compound 4j and 4n could be due to presence of higher hydrophobic planar substitutions.

Keywords
Substituted benzyl Chloride, Isatin, benzimmidazole, tryptamine, Anti-Inflammatory activity.

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INTRODUCTION:

Heterocyclic compounds containing a ring made up, in addition to carbon atoms, other elements (heteroatom's), most often nitrogen, oxygen, and sulfur, and less frequently phosphorus, boron, and silicon. Isatin (1H-indole-2, 3-Dione), an endogenous compound identified in many organisms, shows a wide range of biological activities [1]. The Isatin ring is a prominent structural motif found in several pharmaceutically active compounds. This is mainly due to the easy synthesis and the importance of pharmacological activity. Therefore, the synthesis and selective fictionalization of Isatin have been the focus of active research area over the years [2]. Isatin derivatives are reported to show antibacterial [3] and antifungal [4] activities. A number of Schiff bases derived from Isatin and its derivatives have been reported with various biological properties such as, antimicrobial [5], Central nervous system (CNS) depressant [6], anti-HIV [7], anti-inflammatory [8], analgesic [9] and as anticancer agents [10].

In the light of different applications of Schiff bases derived from Isatin, we hereby report the synthesis of new Schiff bases derived from Isatin, benzyl chloride, benzimmidazole and tryptamine derivatives, investigation of biological and catalytic

activities of these compounds is a subject of an ongoing research in our laboratory.

MATERIALS AND METHODS

The synthesized compounds were screened for anti-inflammatory activities. Fourier Transform IR spectrometer (model Shimadzu 8700) in the range of 400-4000 cm^{-1} Using KBr pellets and values are reported in cm^{-1} and the spectra were interpreted. ^{1}H-NMR spectra were recorded on DPX-200 MHz NMR spectrometer using DMSO-d_6 and chemical shifts (δ) are reported in parts per million down field from internal reference Tetramethylsilane (TMS) and the Spectra were interpreted. Mass spectra were recorded on Mass spectrophotometer (model Shimadzu) by LC- MS and the spectra were interpreted. Precoated Silica gel G plates were used to monitor the progress of reaction as well as to check the purity of the compounds: n-Hexane: Ethyl acetate (8:2).

General procedures

Synthesis of 2-(4-aminophenyl) benzimidazole (I): 2-(4-aminophenyl) benzimidazole was synthesized by the condensation of O-phenylenediamine and para amino benzoic acid in 4N hydrochloric acid (40 ml) and refluxed for 4 hrs, then cooled the reaction mixture at room temperature. The completion of this reaction was monitored by thin layer chromatography. The pH was adjusted to 7.2 using Sodium Hydroxide pellets. The resulting solid was filtered and washed with water, dried in vacuum and re-crystallized from methanol.

The yield of 2-(4-aminophenyl) benzimidazole was found to be 78.5% and the melting point is 168ºC - 170ºC. The completion of the reaction was monitored by thin layer chromatography using solvent system chloroform: methanol.

Step.2: Synthesis of N-Benzyl indole 2, 3- dione (N-Benzyl Isatin): In the round bottomed flask take indole-2,3-dione (Isatin) 0.8gm (3.37mM) and equimolar quantity of benzyl chloride i.e. 6.5ml (3.7mM), mix with 20ml of DMF and to this mixture add 2gm of K_2CO_3. After gentle mixing of this reaction mixture, reflux for 2 hr, cool and pour to 100 ml of ice-cold water. The resultant orange red ppt. collected wash with water and dried and recrystallized from acetonitrile m.p:134-136^{0}C (Lit m.p:133-134^{0}C).

Step: 3: 3-((4-(1H-benzo[d]imidazol-2-yl) phenyl) imino)-1- benzyl-indolin-2-one. N-Benzyl indole 2, 3-dione (N-Benzyl Isatin) derivatives (2a-2d, 0.01 mol) was taken in a mixture of 2-(4-aminophenyl) benzimidazole (0.01 mol) and glacial acetic acid (5 mL) and Ethanol 30ml, then the reaction mixture was refluxing for 2hrs. The progress of the reaction was monitored by TLC (Hexane: EtoAc 1:4). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off and washed with hexane and recrystallized from methanol to give crystalline solid.

Step: 4: 3-((2-(1H-indol-3-yl) ethyl)imino)-1-(benzyl)indolin-2-one: N-Benzyl indole 2, 3- dione (N-Benzyl Isatin) derivatives (2a-2d, 0.01 mol) was taken in a mixture of tryptamine (0.01 mol) and glacial acetic acid (5 mL) and Ethanol 30ml and then the reaction mixture was refluxing for 2hrs. The progress of the reaction was monitored by TLC (Hexane: EtoAc 1:4). The reaction mixture was cooled to room temperature. A solid was obtained, which was filtered off and washed with hexane and recrystallized from methanol to give crystalline solid.

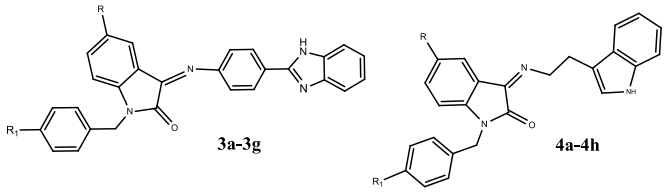


Table: 1. Physical data of novel Schiff's bases of Isatin (3a-3h, 4a-4h)

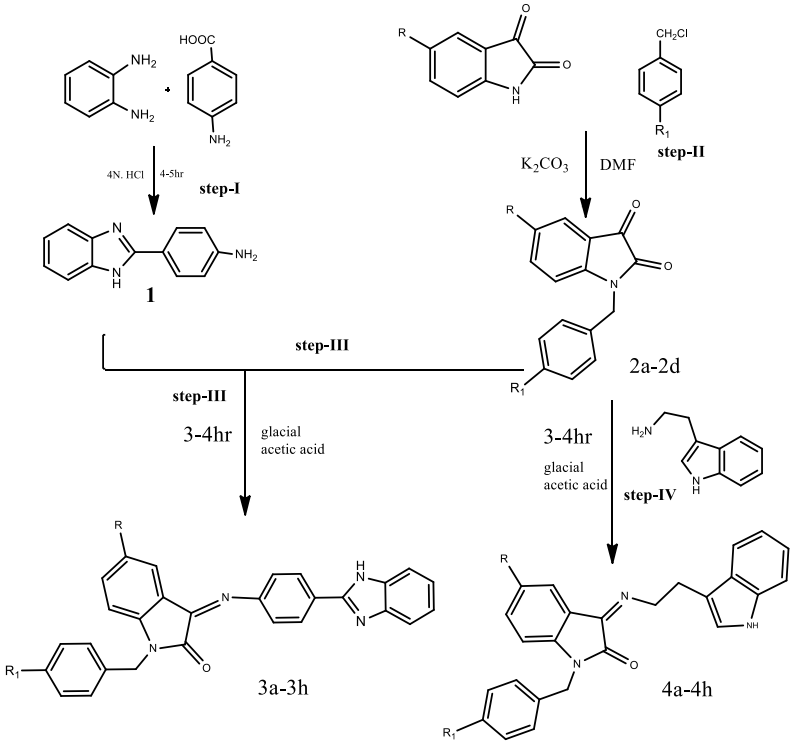
Compound	Molecular Formula	R	R_1	Molecular Weight (gms)	M.P (^{0}C)	%Yield	R_f value
3a	$C_{28}H_{20}N_4O$	H	H	428	223-225	82	0.81
3b	$C_{28}H_{19}N_4OCl$	Cl	H	462	233-235	71	0.75
3c	$C_{29}H_{22}N_4O$	CH_3	H	442	217-219	76	0.69
3d	$C_{28}H_{19}N_5O_3$	NO_2	H	473	209-211	69	0.67
3e	$C_{28}H_{18}N_5O_3Cl$	Cl	NO_2	507	261-263	67	0.72
3f	$C_{29}H_{21}N_5O_3$	CH_3	NO_2	487	257-259	73	0.80
3g	$C_{28}H_{19}N_5O_3$	NO_2	H	473	249-251	70	0.64
4a	$C_{25}H_{21}N_3Ol$	H	H	379	228-230	80	0.59
4b	$C_{25}H_{20}N_3OCl$	Cl	H	413	215-217	78	0.66
4c	$C_{26}H_{23}N_3O$	CH_3	H	393	207-209	74	0.79

4d	$C_{25}H_{20}N_4O_3$	H	NO_2	424	253-255	78	0.72
4e	$C_{26}H_{22}N_4O_3$	NO_2	CH_3	438	237-239	81	0.88
4f	$C_{25}H_{19}N_4ClO_3$	NO_2	Cl	458	213-215	74	0.69
4g	$C_{25}H_{19}N_5O_5$	NO_2	NO_2	469	191-193	77	0.73
4h	$C_{25}H_{20}N_4O_3$	NO_2	H	424	221-223	73	0.68

RESULTS AND DISCUSSION:

Chemistry: In this study, we synthesized a series of novel Schiff bases of Isatin derivatives are prepared by the reaction between different 5-sustituted N-benzyl Isatin derivatives with benzimmidazole to give a 3-((4-(1H-benzo[d]imidazol-2-yl) phenyl) imino)-1-benzyl-indolin-2-one derivatives (3a-3h) and with tryptamine to give a 3-((2-(1H-indol-3-yl) ethyl)imino)-1-(benzyl)indolin-2-one (4a-ah). The synthesized compounds were screened for Anti-inflammatory activity.

Spectral data:



R= H, CH_3, NO_2,Cl

R_1 = H, NO_2

SCHEME

Compound(3a):3-((4-(1H-benzo[d]imidazol-2-yl)phenyl)imino)-1-(benzyl)indolin-2-one: Mol. formula: $C_{28}H_{20}N_4O$, Conventional yield 82%, IR (ν cm−1): 3379 (N-H Str, benzimmidazole), 3021(A-H Str), 2950, 2964(C–H Str, Aliphatic), 1712 (-CO Str), 1554(C=N Str), 1287(C-N Str). ^{1}H-1H-NMR (DMSO) $\delta\delta$ ppm: 12.01(s, 1H, -NH in benzimidazole), 8.49-8.37(d, 2H, Ar-H), 7.97-7.89 (d, 2H, Ar-H), 7.87-7.84 (d, 2H, Ar-H), 7.79-7.78(d, 2H, Ar-H), 7.69-7.68(d, 2H, Ar-H), 7.60-7.59(t, 2H, Ar-H), 7.58-6.51 (t, 2H, Ar-H), 7.49-7.14(t, 3H, Ar-H), 5.209-5.243(s, 2H, Ar-CH_2-). Mass (ESI-MS): m/z 428(M), 429(M + 1, 100%).

Compound(3b):3-((4-(1H-benzo[d]imidazol-2-yl)phenyl)imino)-5-chloro-1-(benzyl) indolin-2-one: Mol. formula: $C_{28}H_{19}N_4OCl$, Conventional yield 71%, IR (ν cm−1): 3414 (N-H Str, benzimmidazole), 3076(A-H Str), 2961, 2890 (C–H Str, Aliphatic), 1717 (-CO Str), 1576(C=N Str), 1227(C-N Str), 793(Cl Str, Ar-Cl). ^{1}H-1H-NMR (DMSO) $\delta\delta$ ppm: 10.98 (s, 1H, -NH in benzimidazole), 7.97(s, 1H, Ar-H), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.53 (d, 2H, Ar-H), 7.52-7.48(d, 2H, Ar-H), 7.437-7.432 (d, 2H, Ar-H), 7.39-7.38(d, 2H, Ar-H), 6.76-6.58 (t, 2H, Ar-H), 6.20-6.10 (t, 3H, Ar-H), 5.48-5.43(s, 2H, Ar-CH_2-), 2.106-2.103(s, 3H, -$(CH_3)_2$. Mass (ESI-MS): m/z 462(M), 463(M + 1, 100%).

Compound (3c): Z)-3-((4-(1H-benzo[d]imidazol-2-yl)phenyl)imino)-5-methyl-1-(4-nitrobenzyl)indolin-2-one: Mol. formula: $C_{29}H_{22}N_4O$, Conventional yield 76%, IR (ν cm−1): 33 (63 N-H Str, benzimmidazole), 3060(A-H Str), 2927, 2878 (C–H Str, Aliphatic), 1729 (-CO Str), 1584(C=N Str), 1251(C-N Str). ^{1}H-1H-NMR (DMSO) $\delta\delta$ ppm: 10.98 (s, 1H, -NH

in benzimidazole), 7.97(s, 1H, Ar-H), 7.80-7.68 (d, 2H, Ar-H), 7.63-7.53 (d, 2H, Ar-H), 7.52-7.48(d, 2H, Ar-H), 7.437-7.432 (d, 2H, Ar-H), 7.39-7.38(d, 2H, Ar-H), 6.76-6.58 (t, 2H, Ar-H), 6.20-6.10 (t, 3H, Ar-H), 5.48-5.43(s, 2H, Ar-CH_2-), 2.106-2.103(s, 3H, -$(CH_3)_2$. Mass (ESI-MS): m/z 442(M), 443(M + 1, 100%).

Compound(4a):-3-((2-(1H-indol-3-yl)ethyl)imino)-1-(benzyl)indolin-2-one: Mol. formula: $C_{25}H_{21}N_3O$, Conventional yield 69%, IR (ν cm−1): 3447 (N-H Str, Indole), 3063(A-H Str), 2931, 2896 (C–H Str, Aliphatic), 1687 (-CO Str), 11509(C=N Str), 1227(C-N Str). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 11.95(s, 1H, -NH in Indole), 8.36(s, 1H, Ar-H), 8.29-8.11(d, 2H, Ar-H), 7.88-7.84 (d, 2H, Ar-H), 7.79-7.69 (d, 2H, Ar-H), 7.69-7.67(t, 2H), 7.55-7.45(t, 2H, Ar-H), 7.41-7.10(t, 3H, Ar-H), 5.34-5.30(s, 2H, Ar-CH_2-), 2.84(d, 2H, N=CH_2), 2.30(s, 2H, -CH_2-). Mass (ESI-MS): m/z 379(M), 380(M + 1, 100%).

Compound(4b):-3-((2-(1H-indol-3-yl)ethyl)imino)-5-chloro-1-(benzyl) indolin-2-one: Mol. formula: $C_{25}H_{21}N_3O$, Conventional yield 69%, IR (ν cm−1): 3401 (N-H Str, Indole), 3051(A-H Str), 2923, 2876 (C–H Str, Aliphatic), 1706(-CO Str), 1509(C=N Str), 1237(C-N Str), 770(Ar-Cl Str). ^{1}H-NMR (DMSO) $\delta\delta$ ppm: 12.04(s, 1H, -NH in Indole), 8.38(s, 1H, Ar-H), 7.97(s, 1H, Ar-H), 7.87-7.84 (d, 2H, Ar-H), 7.79-7.78 (d, 2H, Ar-H), 7.69-7.68(d, 2H), 7.60-7.59(t, 3H, Ar-H), 7.58-7.48(t, 2H, Ar-H), 5.38-5.34(s, 2H, Ar-CH_2-), 2.34(d, 2H, N=CH_2), 2.12(s, 2H, -CH_2-). Mass (ESI-MS): m/z 413(M), 414(M + 1, 100%).

Pharmacological Evaluation:

Anti-Inflammatory: [12-13] Anti-inflammatory activity of the newly synthesized compounds was determined by carrageenan induced paw edema assay in rats. Two dose levels (10 mg/kg and 20 mg/kg) of synthesized compounds and Diclofenac sodium (10mg/kg and 20mg/kg) as standard were administered. The change in the paw volumes were measured before and 1h after carrageenan injection, using the mercury displacement technique with the help of plethysmograph. The percent inhibition of paw edema was calculated from percent inhibition formula.

% inhibition (I) = 100[1 - (a - x)/ (b - y)]

Where,

x=mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group)

a = mean paw volume of rats after the administration of carrageenan in the test group (drug treated)

b = is the mean paw volume of rats after the administration of carrageenan in the control group

y = mean paw volume of rats before the administration of carrageenan in the control group.

Anti-inflammatory activity of newly synthesized novel Schiff bases of Isatin derivatives Containing benzimidazol and tryptamine Moieties was evaluated by carrageenan induced paw edema bioassay in rats with Diclofenac sodium (10 and 20 mg/kg) as reference standard. Percentage inhibitions of the molecules are tabulated in Table 2 and Figure 2. The results indicated that all the compounds reported significantly higher anti-inflammatory activity at dose of 10 and 20mg/kg when compared to that of slandered drug doses. However, the anti-inflammatory effect of compound 3e (55.9, 69.0), 3f (58.9, 77.4) and 4c (57.3, 73.2), 4e (51.3, 81.2) and 4g (50.5, 78.3) at 10 and 20mg/kg and Diclofenac sodium 63.5, 86.5 at 10 and 20mg/kg was found to be similar. The higher anti-inflammatory activity of compound 4e and 3f could be due to presence of higher hydrophobic planar substitutions.

Table.2: Anti-Inflammatory activity of novel Schiff bases of Isatin derivatives (% inhibition of paw edema)

% Inhibition of Paw edema	Compounds															
	Diclofenac sodium	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
10mg/kg	**63.5± 0.015****	29.6	30.0	39.0	33.8	**55.9**	**58.9**	35.0	36.4	38.9	**57.0**	37.1	**51.3**	36.7	**50.5**	40.1
20mg/kg	**86.5± 0.005****	42.8	43.1	48.1	46.2	**69.0**	**77.4**	54.2	45.2	62.4	**73.2**	49.1	**81.2**	56.9	**78.3**	54.3

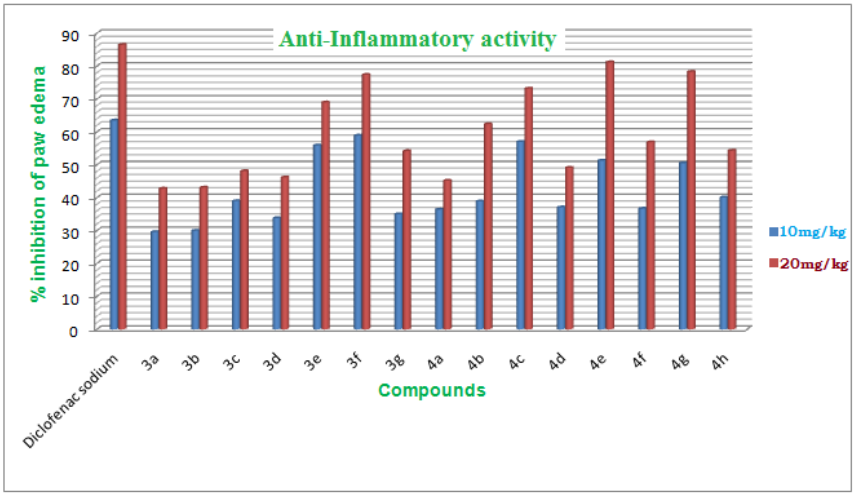


Figure.1: Comparison of Anti-Inflammatory activity of novel Schiff bases of Isatin derivatives (% inhibition of paw edema)

CONCLUSION:

The objective of the present work was to synthesize, purify, characterize and evaluate the biological activity of newly synthesized structural analogs of novel Schiff bases of Isatin derivatives containing benzimidazol and trypatamine moieties. The yield of the synthesized compounds was found to be in the range from 65-84 %. In conclusion, the present study highlights the importance of Schiff bases of Isatin derivatives having various heterocyclic moiety features responsible for the anti-inflammatory activities and may serve as a lead molecule for further modification to obtain clinically useful novel entities.

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