International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.5, No.3, pp 1404-1409, July-Sept 2013

Comparative Study And Synthesis Of Some 5-Fluoro Isatin Schiff Bases And Evaluation Of Their Pharmacological Actions

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Abstract: 5-Fluoro isatin Schiff base compounds were prepared by the condensation of 5-Fluoro isatin with different aromatic aldehydes in ethanol and reaction is carried out by H_2SO_4 or glacial acetic acid by conventional microwave method. The structures of the synthesized compound (A1-A5) were assigned for FT-IR, ^{1}HNMR spectroscopy and these compounds were screened out for antimicrobial and anti-inflammatory activity.
Key words: Schiff base, isatin, anti inflammatory and anti microbial activity.

Introduction:

Isatin is found in plants of Isatis tincotorra is a member of brassica family. Isatin is also known as Indole-2,3-dione with molecular formula $C_8H_5NO_2$ and molecular weight is 147.13.

Isatin and substituted compounds possess various biological activities such as analgesic, anti-inflammatory, anti-convulsant, antipyretic, anti-HIV, antimicrobial, antiviral, antimycobacterial, and anti cancer activity.

Microwave induced organic reaction enhancement chemistry is used for rapid organic synthesis. It maintains higher temperature conditions and it has rapidly rotating stirrer to complete the reaction in minimum time.

Experimental Work:

All the melting points were determined by a melting point apparatus and were uncaliberated. IR spectra were recorded on Bruker DPX 200 spectrophotometer and H^1 NMR spectra were recorded by Bruker AV 400 MHZ using TMS as an international standard.

Synthesis Of 5-Fluoro Isatin 3-Semicarbazid:

A mixture of 5-Fluroisatin (0.01M), 3-semicarbazide (0.01M) and glacial acetic acid(7-8drops) were taken and then 30ml of absolute alcohol was added and heated under reflux on water bath for 3hrs and checked for TLC, poured in ice cold water and then filtered through the Buchner funnel and dried.

Microwave:

A mixture of 5-Fluroisatin (0.01M), 3-semicarbazide (0.01M) and glacial acetic acid(7-8drops) were taken and then 30ml of absolute alcohol was added and reaction was irradiated for 15min at 420 watts and checked for TLC, poured in ice cold water and then filtered through the Buchner funnel and dried.

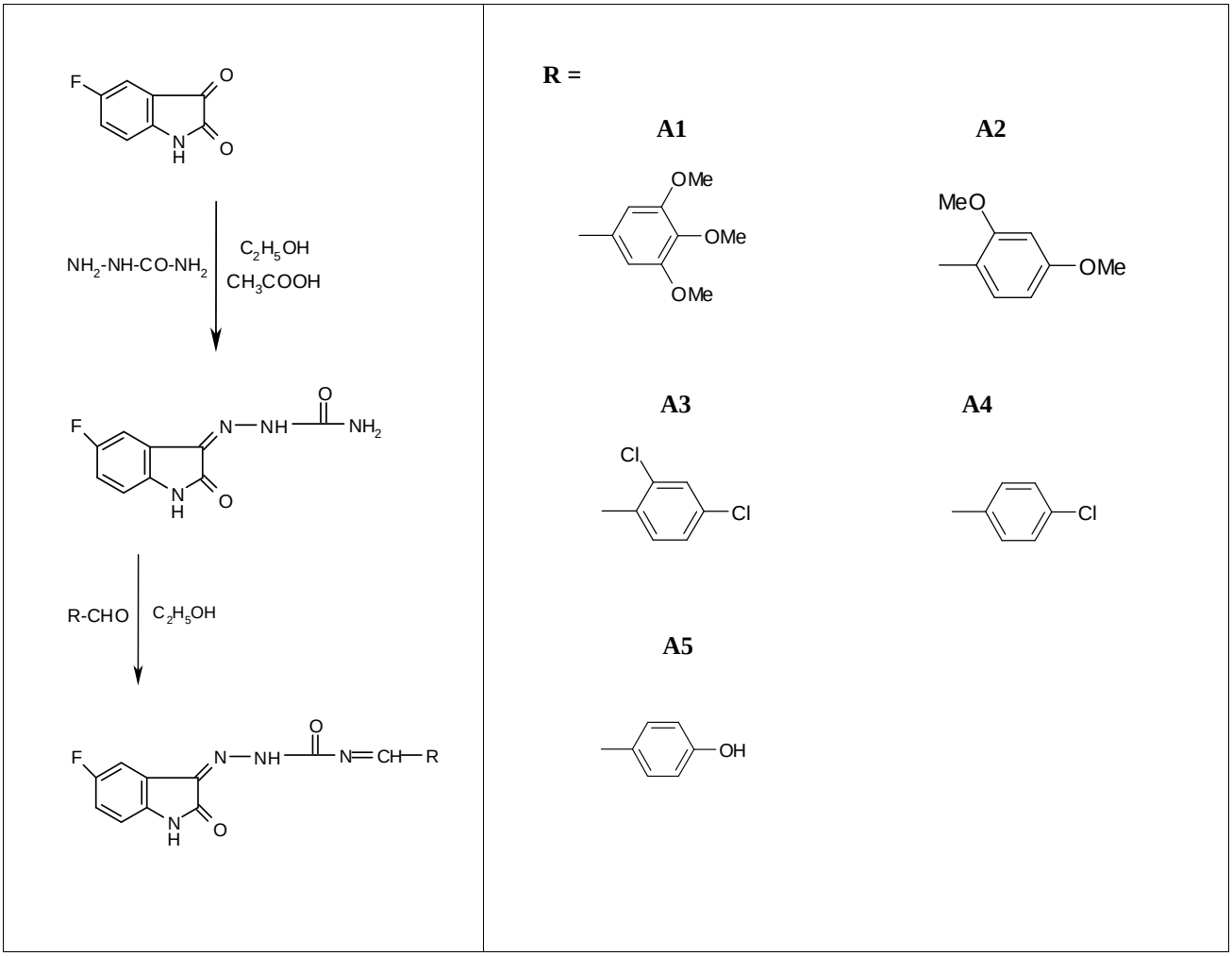
Synthesis Of Title Compounds:

A mixture of 5-Fluroisatin, 3-semicarbazide (0.01M) and various aromatic aldehydes (0.01M) were dissolved in 30ml absolute alcohol and H_2SO_4 or glacial acetic acid were added by drop by drop with stirring and then refluxed for 22-24hrs and checked for TLC, poured in ice cold water and then filtered through the Buchner funnel, dried and recrystallised from ethanol. Some of compounds were purified on silicagel G column using hexane and ethyl acetate mixture (95:5) solvent system.

Microwave:

A mixture of 5-Fluroisatin, 3-semicarbazide (0.01M) and various aromatic aldehydes (0.01M) were dissolved in 30ml absolute alcohol and H_2SO_4 or glacial acetic acid were added by drop by drop with stirring and reaction was irradiated for 90 min.420watts and checked for TLC, poured in ice cold water and then filtered through the Buchner funnel, dried and recrystallised from ethanol. Some of compounds were purified on silicagel G column using hexane and ethyl acetate mixture (95:5) solvent system.

Synthetic Scheme



Biological Screening:

The synthesized compounds were evaluated for anti inflammatory and anti microbial activity.

Anti Inflammatory Activity:

The anti inflammatory activity was determined by carrageenan induced paw oedema method in wistar albino rats by using Zetlins apparatus. Indomethacin (100mg/kg) was taken as standard drug. The test compounds were administered orally at 100mg dose level intraperitoneally 30 min prior to administration of carrageenan (0.1 ml of 1% w/v) in the plantar region of the paw. The paw volumes were measured at 30, 1, 2, 3, 4 and 6 hr after carrageenan administration. The results are presented in table.

Antimicrobial Activity:

Evaluation of antibacterial activity was carried out by cup plate method. The microorganisms used were procured from dept. of biotechnology, Andhra University. All the bacteria were grown on Agar Hi-Media plated (37^0C, 24h) and fungi were grown on potato dextrose agar (Hi-media) plates (26^0C, 48-72h), the minimum inhibitory concentration (MIC) was considered to the lowest concentration that completely inhibited the growth on agar plates, disregarding a single colony or faint haze caused by the inoculum.

Results:

Compound name with code (A_1): 2Z-2-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)-N-(3,4,5-trimethoxy benzylidine) hydrazine carbixamide

Molecular formula: $C_{18}H_{17}N_4f$
Molecular weight : 388
Melting point : 228-232˚C
Solubility : freely soluble in MeOH, $CHCl_3$, DMSO & DMF
TLC R_f value : 0.65 (Ethylacetate:n-hexane, 40%).
Yield : 55% (Conventional)
65% (Microwave oven)
IR (KBr cm^{-1}) **:**3069.56(C-H Ar), 1751.75(C=O), 1623.34 (C=N), 1241.98(C-N), 1360.12 (C-F), 1278.59(C-OCH_3).
^{1}H NMR (DMSO-d_6, ppm) :7.0-7.67 (m 6 Ar-**H**), 8.39 (s, 1H,-N=C**H**-), 3.7(s,9**H**,O**CH**$_3$)

Compound name with code (A_2): (2Z)-N-(2,4-dimethoxy benzylidene)-2-(5-fluoro-2-oxo-1,2-dihydro-3H-indol—3-ylide3ne) hydrazine carboxamide

Molecular formula: $C_{15}H_{14}0_4N_4F$
Molecular weight : 333
Melting point : 239-243˚C
Solubility : freely soluble in MeOH, $CHCl_3$, DMSO & DMF
TLC R_f value : 0.65 (Ethylacetate:n-hexane, 40%)
Yield :48% (Conventional)
53% (Microwave oven)
IR (KBr cm^{-1}) : 3068.45(C-H Ar), 1361.57(C-F), 1751.08(C=O), 1622.14(C=N), 1241.98(C-N), 1278.59(C-OCH_3)
^{1}H NMR (DMSO-d_6, ppm):7.0-7.67 M (6^1 Ar-H), 8.39 (s,1H,-N=C**H**-), 3.7[s,6H,-oCH_3]

Compound name with code (A_3) (2 Z)-N-(2,4-dichlorobenzylidene)-2-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazine carboxamide.

Molecular formula : $C_{15}H8N_4O_2Cl_2F$
Molecular weight : 366
Melting point : 241-244˚C
Solubility : freely soluble in MeOH, $CHCl_3$, and DMSO & DMF
TLC R_f value : 0.55(Ethylacetate:n-hexane, 40%)
Yield : 40% (Conventional)
55% (Microwave oven)
IR (KBr cm^{-1}) :3066.45(C-H Ar), 1360.12(C-F), 1751.75 (C=O), 1623.34(C=N), 1242.77(C-N), 1278.59(C-OCH_3)
^{1}H NMR (DMSO-d_6, ppm):7.067 -7M (6^1 Ar-H), 8.39 (s,1H,-N=C**H**-), 5.0 (1H-O**H**).

Compound name with code (A_4): 2(Z)-N- (4-chlorobenzylidene)-2-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazine carboxamide

Molecular formula: $C_{15}H_9N_4O_2FCl$
Molecular weight : 331.5
Melting point : 245-249˚C
Solubility : freely soluble in MeOH, $CHCl_3$, and DMSO & DMF
TLC R_f value : 0.55 (Ethylacetate:n-hexane, 40%)
Yield : 53% (Conventional)
64% (Micro wave oven)
IR (KBr cm^{-1}) : 3070.12(C-H Ar), 1382.22(C-F), 1748.98(C=O), 1619.45(C=N), 1242.12(C-N), 754.48(C-Cl)
^{1}H NMR (DMSO-d_6, ppm):7.0-7.67 M (7^1 Ar-H), 8.39 (s,1H,-N=C**H**-), 8.39(s,1H,-N=C**H**-), 3.7(3-H).

Compound name with code (A_5): (2Z)-2-(5-fluoro-2-oxo-1,2-dihydro – 3H-indol-3-ylidene)-N-(4-hydroxybenxylidene) hydrazine carboxamide.

Molecular formula: $C_{15}H_{10}N_4O_3F$
Molecular weight : 313
Melting point : 208-210˚C
Solubility : freely soluble in MeOH, $CHCL_3$, and DMSO & DMF
TLC R_f value : 0.65 (Ethylacetate:n-hexane, 40-45%).
Yield : 49% (Conventional method)
56% (Microwave oven method)
IR (KBr cm^{-1}) **:** 3068.12(C-H Ar), 1361.57(C-F), 1742.18(C=O), 1616.45(C=N), 1240.88(C-N), 3620.22(C-OH).
^{1}H NMR (DMSO-d_6, ppm):7.0-7.67 M (7^1 Ar-H), 8.39 (s,1H,-N=C**H**-).

Compound	Conventional method			Microwave Irradiation		
	^{0}C	Time (Hrs)	% Yield	Watts(MHz)	Time	% Yield
A	100	3	65	420	15 min	75
A1	100	22	55	420	1.15 hr	65
A2	100	22	48	420	1.20 hr	53
A3	100	22	40	420	1.30 hr	55
A4	100	22	53	420	1.25 hr	63
A5	100	22	49	420	1.20 hr	56

Compound code	Zone of inhibition (in mm)							
	B.subtilis		S.aureus		E.coli		P.vulgaris	
	50 µl	100 µl	50 µl	100 µl	50 µl	100 µl	50 µl	100 µl
Benzyl pencillin	25	31	30	34	24	27	29	32
A_1	14	17	18	22	11	19	14	20
A_2	11	15	16	20	10	15	12	15
A_3	11	17	14	19	12	17	13	18
A_4	13	15	10	14	13	16	10	14
A_5	12	19	14	17	15	19	15	18

code	% inhibition in paw thickness at various time intervals					
	0.5hr	1hr	2hr	3hr	4hr	6hr
Std	20.26±0.64	23.95±0.85	58.02±1.54	67.93±1.65	97.09±1.95	98.98±1.96
1	24.20±2.43	39..03±3.57	69.65±2.05	86.27±2.84	93.65±2.84***	78.39±2.85
2	22.44±2.24	58.86±4.32	63.23±4.32	80.07±2.75	87.32±2.85	74.45±1.87
3	42.49±2.84	49.49±1.34	64.45±1.73	86.43±4.45**	88.43±2.60	69.36±1.72
4	40.12±1.45	31.62±2.45*	55.05±2.48	70.42±3.75	83.57±1.82	67.48±2.56
5	20.05±1.53	25.72±1.65	50.01±1.54	64.42±2.73	78.52±1.89	63.57±2.23

Results And Discussion:

- This study shows that isatin, a molecule with a broad range of applications in synthetic, biological and clinical activity undergoes structural modifications at various reactive sites. The fluoro groups can also be easily hydrolysed to give a free N-H containing compound necessary for hydrogen bonding which may be responsible for bioactivity,
- In the present study novel Schiff bases of isatin were synthesized and characterized by IR and ^{1}H-NMR spectral data.
- All the synthesized compounds were screened for anti-inflammatory and anti-microbial activity using Indomethacin (20 mg/kg b.w i.p), Indomethacin,Benzyl pencillin, Fluconazole as standard drugs respectively.
- Evaluation of anti-inflammatory activity was carried out by carrageenan induced rat paw oedema method. Compounds A_1, A_2, A_3, A_4, A_5 exhibited significant anti-inflammatory activity.
- Compounds were screened for anti-microbial activity (50,100µg/ml^{-} by cup plate method.
- Anti-bacterial activities of the synthesized compounds were tested against *S.aureus, B.subtilis, E.coli and P.vulgaris*. Anti-fungal activity of the compounds were tested against *A.niger* and *P.crysogenium* .
- Compounds A_1, A_2, A_3, A_4, A_5 were found to be exhibit good anti-microbial.

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