ISSN 0975-6299 Vol 2/Issue 1/ Jan-Mar 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

MEDICINAL CHEMISTRY

SYNTHESIS, ANALGESIC AND ULCEROGENIC EVALUATION OF SOME NOVEL SCHIFF AND MANNICH BASES OF ISATIN DERIVATIVES

Corresponding Author

RAMACHANDRAN S

Department of Pharmaceutical Chemistry, S.B College of Pharmacy, Anaikuttam, Sivakasi, Tamilnadu, India

Co Authors

UMA MAHESWARI V

[2]Department of Pharmaceutical Chemistry, Padmavathi College of Pharmacy, Dharmapuri, Tamilnadu, India

ABSTRACT

Novel schiff and mannich bases of isatin derivatives were synthesized. The structures of these compounds were established by means of IR, ^{1}H-NMR analysis. All the compounds were evaluated for analgesic and ulcerogenic activities. Most of the compounds shown significant analgesic activity and lesser ulcerogenic property, when compared with the standard drugs.

KEYWORDS

Isatin, Schiff and Mannich bases, Analgesic, Ulcerogenic.

INTRODUCTION

Drug discovery has its beginning the root of mankind [1]. Medicinal chemistry is an interdisciplinary science that by its very nature encompasses the sciences of chemistry, biochemistry, physiology, pharmacology and molecular modeling. It has been stated that medicinal chemistry concern with the discovery, development, identification and interpretation of the mode of action of biologically active compounds at molecular level [2]. The synthetic compounds offered an opportunity to medicinal screening. The inventions of new lead molecules are used to design effective and safe drugs and also to reduce drug toxicities [3]

Isatin is a resourceful endogenous heterocyclic molecule identified in human being and rat tissues[4]. Isatin, chemically known as 1H-Indole-2, 3-dione, has become a popular topic due to its various uses. Isatin was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric acid and chromic acids. The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis[5].

The presence of several reaction centers in isatin and its derivatives makes it possible to bring these compounds into various types of reactions. Thus, keto group at position 2 and particularly, at position 3 can enter into addition at the c-o bond and into condensation with release of water. Through the NH group compounds of the isatin series are capable of entering into N-alkylation and N-acylation and into the Mannich and Michael reactions[6]. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives. Schiff and Mannich bases of isatin derivatives are reported to show variety of biological activities like antibacterial, antifungal, anticonvulsant, anti-HIV, anti-depressant and anti-inflammatory activities[7].

MATERIALS AND METHODS

Analgesic activity[8, 9, 10]:

The analgesic activities of various synthesized compounds were screened by using acetic acid induced writhing test in mice. Mice of either sex weighing between 20 –25 gm were taken in 14 groups of each 4 animals. Diclofenac sodium 10mg/kg was used as a standard drug for comparison of analgesic activity. Writhing was induced by administration 0.2ml of 1%v/v of aceticacid through intraperitoneally. Record the number of abdominal contractions, trunk twist response and extension of hind limbs as well as the number of animals showing such response during a period of 25 min.

Administer all synthesized compound through I.P. Half an hour later administer acetic acid solution at 1ml/100gm. Note and calculate onset and severity of writhing response. Note the inhibition of pain response by synthesized drugs. The results are reported in the table-III.

Table III
Effect of Analgesic Activities of Synthesized Compounds Against Acetic Acid Induced Writhing Tests in Mice.

Group	Compd	Dose	No fo writhes in 25min (mean±.sem)	%inhibition
G1(Normal control)	Normal saline	10 ml / kg	27.82±.0.42	-----
G2 (STD)	Diclofenac sodium	10 mg / kg	7.50±0.58.	73.04%
G3(Treatment control)	AS	5mg/ kg	8.60±0.43	69.08%*a
G4	A1S	5 mg/ kg	8.30±0.50	70.16%*a
G5	A2S	5 mg / kg	12.65±1.20	54.52%
G6	A3S	5 mg / kg	13.22±1.60	52.48%
G7	BS	5 mg / kg	8.90±0.71	68.00%*a
G8	B1S	5 mg / kg	13.05±1.12	53.09%
G9	B2S	5 mg / kg	8.58±0.70	69.15%*a
G10	B3S	5 mg / kg	12.60±1.20	54.70%
G11	CS	5 mg / kg	12.15±1.06	56.09%
G12	C1S	5 mg / kg	12.12±1.33	56.55%
G13	C2S	5 mg / kg	8.45±0.66	69.62%*a
G14	C3S	5 mg / kg	8.55±0.40	69.26%*a

Values are expressed as Mean ± SEM
Values are finding out by using one way ANOVA followed by Newman-Keuls multiple range tests.
**a Values are significantly different from normal control at P<0.01.*

Ulcerogenic property [9, 10, 11]***:***
Acute Ulcerogenic test was carried out according to the Method of Cioli et al. Wistar rats were divided into 14 Groups consisting of Six animals in each group. Group I Served as Normal Control (Received 0.5 ml of DMSO as Vehicle). Group II Served as Ulcer Control (Received Diclofenac Sodium 30mg/Kg). Groups III to XIV Served as Treatment Control (Received Synthetic Compounds at 5 mg/Kg respectively through I.P). All animals were tested 24 h before administration of the test compounds. After the drug treatment, the rats were fed normal diet for 17 h then they were sacrificed. The stomach was removed and opened along the Greater Curvature, washed with distilled water

and cleaned gently by dipping in saline. The mucosal damage examined by means of a Magnifying lens (10X).

For each stomach the mucosal damage was assessed according to the following scoring system.

Score	Description
0.0	Normal (no injury, bleeding and latent injury)
0.5	Latent injury (or) Widespread bleeding (>2 mm)
1.0	Slight injury (2-3 dotted lines)
2.0	Severe injury (Continuous lined injury (or) 5-6 dotted injuries)
3.0	Very severe injury (Several Continuous lined injuries)

The Mean Score of each treated group minus Mean Score of control group was regarded as the Severity Index of Gastric Mucosal damage. The results are reported in the table-IV.

EXPERIMENTAL

Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on PERKIN-ELMER FT-IR spectrophotometry using potassium bromide disc method. ^{1}H-NMR spectra were recorded on sophisticated BRUCKER 300 MHz FT- NMR using TMS (Tetramethyl Silane) as internal standard.

Synthesis of Schiff bases[12]:

Synthesis of Schiff base using p-nitro aniline

Equimolar quantities of isatin derivatives (0.01 mol) and p-nitro aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Synthesis of Schiff base using PABA

Equimolar quantities of isatin derivatives (0.01 mol) and PABA (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Synthesis of Schiff base using p-bromo aniline

Equimolar quantities of isatin derivatives (0.01 mol) and p- bromo aniline (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Synthesis of Schiff base using Sulphanilamide

Equimolar quantities of isatin derivatives (0.01 mol) and sulphanilamide (0.01 mol) were added into 20 ml of absolute ethanol containing a few drops of glacial acetic acid in a 250-ml round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Table IV
Ulcerogenic Effects of Synthesized Compounds in Comparison with Diclofenac Sodium.

Group	Dose (mg/Kg)	Ratio of ulcerated animals	Ulcer Index (Mean ± SEM)
G1	0.5 ml DMSO	0/6	0.0 ± 0.0
G2	30mg/Kg Diclofenac sodium	6/6	2.1 ± 0.2
G3	5 mg/Kg AS	5/6	1.8 ± 0.3
G4	5 mg/Kg A1S	3/6	0.6 ± 0.1*a
G5	5 mg/Kg A2S	2/6	0.5 ± 0.1*a
G6	5 mg/Kg A3S	4/6	1.9 ± 0.4
G7	5 mg/Kg BS	1/6	0.5 ±0.2 *a
G8	5 mg/Kg B1S	5/6	2.0 ± 0.3
G9	5 mg/Kg B2S	1/6	0.8 ± 0.2*a
G10	5 mg/Kg B3S	1/6	0.8 ± 0.2*a
G11	5 mg/Kg CS	5/6	1.5 ±0.5
G12	5 mg/Kg C1S	5/6	1.6 ± 0.3
G13	5 mg/Kg C2S	2/6	0.6 ± 0.1*a
G14	5 mg/Kg C3S	2/6	0.6 ± 0.1*a

Values are expressed as Mean ± SEM.
Data analyzed by one way ANOVA followed by Newman-Keuls multiple range tests.
a – Values were significantly different from control at p < 0.01.

Synthesis of Mannich bases[13]

To a solution of 1-cyclo propyl-6-fluoro-1, 4-dihydro-7-piperazin-1-yl-4-oxo quinoline-3-carboxylic acid (Ciprofloxacin 0.0025 mol) in glacial acetic acid (20 ml), was added Schiff bases of isatin derivatives (0.0025 mol) and 37% formalin (1 ml). The reaction mixture was refluxed over a water bath for 1–3 h. The reaction mixture was concentrated to approximately half of the initial volume, and the resulting precipitate was recrystallized from a mixture of DMF and water.

RESULTS AND DISCUSSION

Schiff and Mannich bases of isatin derivatives were synthesized and the structures of the compounds were established by means of IR

and ^{1}H NMR analysis. All the compounds were evaluated for analgesic activity and ulcerogenic property. Compounds such as AS, A1S, BS, B2S, C2S, and C3S posses significant Analgesic activity and the maximum reduction in Ulcerogenic property (Mean Severity Index ± SEM, n=6) was 0.5 ± 0.1 to 0.8 ± 0.2, found in compounds A1S, A2S, BS, B2S, B3S, C2S, C3S. With the suitable molecular modification of these compounds can prove as potent analgesic agents with low ulcerogenic property in future. Physical data of the synthesized compounds are listed in Table-I. The spectral data are mentioned in Table-II.

Table-I
Physical data of the Synthesized Compounds

Compound Code	Molecular Formula	Molecular Weight (grams)	Melting point (°C)	Percentage Yield
AS	$C_{32}H_{26}FN_7O_8$	655.589	126-129	94.05%
A1S	$C_{33}H_{27}FN_6O_8$	654.601	124-128	92.86%
A2S	$C_{32}H_{26}BrFN_6O_6$	689.488	142-145	92.08%
A3S	$C_{32}H_{28}FN_7O_8S$	689.670	134-138	94.87%
BS	$C_{32}H_{26}ClFN_6O_6$	645.037	115-118	94.14%
B1S	$C_{33}H_{27}ClFN_5O_6$	644.049	136-138	95.27%
B2S	$C_{32}H_{26}BrClFN_5O_4$	678.935	151-155	92.99%
B3S	$C_{32}H_{28}ClFN_6O_6S$	679.118	141-143	95.88%
CS	$C_{32}H_{27}FN_6O_6$	610.592	124-126	98.36%
C1S	$C_{33}H_{28}FN_5O_6$	609.604	131-134	97.83%
C2S	$C_{32}H_{27}BrFN_5O_4$	644.490	147-151	94.38%
C3S	$C_{32}H_{29}FN_6O_6S$	644.673	159-162	95.09%

Table II

Infra Red /^{1}H NMR spectral study of the synthesized compounds

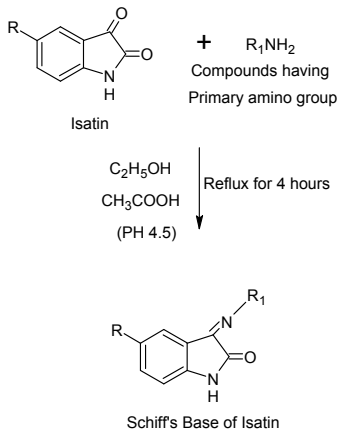
Compound	IR (cm^{-1})	^{1}H NMR (δ, ppm)
AS	3320.85 (=NH imino str.), 3050.30 (cyclo propane str.), 2934.33(CH_2 str.), 2596.59(COOH str.), 1695.65(C=O str.), 1635.10(C=N str.), 1590.26 (C=C Aryl str.), 1550.26 & 1350.73 (Aromatic NO_2 str.), 1030.07(C-F str.), 945.03 (OH bend for COOH), 832.39 (p-sub).	1.3(t, 2H, cyclopropane), 1.6(s, 2H, CH_2.), 3.123 (m, 8H, piperazine), 7.218-7.645(m, 6H, Aromatic protons.) 7.972(m, 4H, indole), 11.4(s, H, COOH).
A1S	3352.86 (=NH imino str.), 3082.33 (cyclo propane str.), 2925.47(CH_2 str.), 2856.66(COOH str.), 1677.51(C=O str.), 1595.69(C=N str.), 1330.57 (Aromatic NO_2 str.), 1048.12(C-F str.), 964.50 (OH bend for COOH), 832.24 (p-sub).	1.4(t, 2H, cyclopropane), 1.6(s, 2H, CH_2.), 3.011-3.148 (m, 8H, piperazine), 7.282-7.735(m, 6H, Aromatic protons.) 8.178(m, 4H, indole), 11.5(s, H, COOH).
A2S	3412.25 (=NH imino str.), 3053.98 (cyclo propane str.), 2924.54(CH_2 str.), 2501.53(COOH str.), 1745.26(C=O str.), 1641.22(C=N str.), 1615.05 (C=C Aryl str.),1350.56 (Aromatic NO_2 str.), 1035.96(C-F str.), 954.87 (OH bend for COOH), 835.26 (p-sub), 592.45 (C-Br str.).	
A3S	3356.89 (=NH imino str.), 3053.98 (cyclo propane str.), 2930.33(CH_2 str.), 2515.87(COOH str.), 1721.16(C=O str.), 1638.77(C=N str.), 1603.55 (C=C Aryl str.), 1540.15(aromatic NO_2 str.), 1332.66(SO_2 asymmetric str.), 1155.23(SO_2 sym str.), 1096.18(C-F str.), 901.33 (S-N str.), 858.43 (p-sub).	
BS	3364.94 (=NH imino str.), 3062.09 (cyclo propane str.), 2924.73(CH_2 str.), 2839.89(COOH str.), 1724.37(C=O str.), 1678.84(C=N str.), 1597.22 (C=C Aryl str.), 1354.26(Aromatic NO_2 str.), 1111.98(C-F str.), 963.11(OH bend for COOH), 830.65(p-sub), 751.73(C-Cl str.).	1.3(t, 2H, cyclopropane), 1.6(s, 2H, CH_2.), 3.035-3.171 (m, 8H, piperazine), 7.047-7.784(m, 6H, Aromatic protons.) 8.001(m, 4H, indole), 11.4(s, H, COOH).
B1S	3399.98 (=NH imino str.), 3064.91 (cyclo propane str.), 2922.45(CH_2 str.), 2516.98(COOH str.), 1760.11(C=O str.),	

	1738.62(C=N str.), 1605.79 (C-Cl aryl str.), 1001.11(C-F str.), 955.43(OH bend for COOH), 832.79 (p-sub).	
B2S	3398.76 (=NH imino str.), 3127.49 (cyclo propane str.), 2927.19(CH_2 str.), 2837.99(COOH str.), 1720.64(C=O str.), 1621.09(C=N str.), 1580.80 (C=C Aryl str.), 1084.86(C-F str.), 951.31 (OH bend for COOH), 823.46 (p-sub), 746.18(C-Cl str.), 549.62(C-Br str.).	1.3(t, 2H, cyclopropane), 1.6(s, 2H, CH_2.), 3.009-3.101 (m, 8H, piperazine), 7.028-7.761(m, 6H, Aromatic protons.) 7.964(m, 4H, indole), 11.5(s, H, COOH).
B3S	3387.45 (=NH imino str.), 3039.71 (cyclo propane str.), 2924.31(CH_2 str.), 2749.12(COOH str.), 1748.23(C=O str.), 1680.34(C=N str.), 1615.09 (C=C Aryl str.), 1330.45(SO_2 asymmetric str.), 1151.29(SO_2 symmetric str.), 1091.96(C-F str.), 900.11(S-N str.), 835.26 (p-sub), 736.45 (C-Cl str.).	
CS	3370.28 (=NH imino str.), 3103.80(cyclo propane str.), 2925.61(CH_2 str.), 2855.52(COOH str.), 1737.25(C=O str.), 1678.98(C=N str.), 1596.90 (C=C Aryl str.), 1351.35(Aromatic NO_2 str.), 1110.28(C-F str.), 945.39(OH bend for COOH), 831.70(p-sub).	
C1S	3423.89 (=NH imino str.), 3090.86(cyclo propane str.), 2927.71(CH_2 str.), 2843.56(COOH str.), 1736.64(C=O str.), 1678.82(C=N str.), 1607.98 (C-Cl aryl str.), 1065.20(C-F str.), 966.32(OH bend for COOH), 833.94(p-sub).	
C2S	3385.92(=NH imino str.), 3052.91(cyclo propane str.), 2924.23(CH_2 str.), 2698.74(COOH str.), 1711.48(C=O str.), 1690.12(C=N str.), 1614.65 (C=C Aryl str.), 1108.34(C-F str.), 955.31 (OH bend for COOH), 847.21 (p-sub).	1.3(t, 2H, cyclopropane), 1.6(s, 2H, CH_2.), 3.010-3.102 (m, 8H, piperazine), 7.037-7.646(m, 6H, Aromatic protons.) 7.857(m, 4H, indole), 11.4(s, H, COOH).
C3S	3383.34 (=NH imino str.), 3100.31 (cyclo propane str.), 2925.80(CH_2 str.), 2831.12(COOH str.), 1739.04(C=O str.), 1666.74(C=N str.), 1611.46 (C=C Aryl str.), 1334.25(SO_2 asymmetric str.), 1153.37(SO_2 symmetric str.), 1095.05(C-F str.), 900.97(S-N str.), 830.83(p-sub).	1.3(t, 2H, cyclopropane), 1.6(s, 2H, CH_2.), 7.037-7.646(m, 6H, Aromatic protons.) 7.857(m, 4H, indole), 9.8(s, 2H, SO_2NH_2), 10.9(s, H, COOH).

GENERAL SCHEME OF REACTION

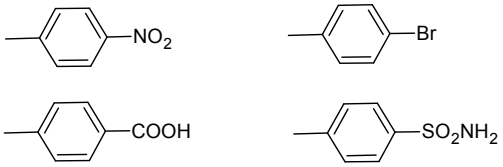
Synthesis of Schiff's Bases of Isatin

Step - I:



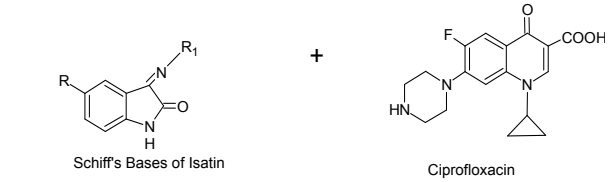
R = NO_2, Cl, H

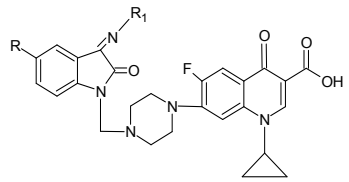
R_1 =



Synthesis of Mannich Bases of Isatin

Step - II:





6. REFERENCES

1. Alfred Burger, Medicinal Chemistry, Part I. 5th Edition, Wiley Inter Science ltd, New York: pp.1&3, (1970).
2. Medicinal Chemistry, Graham Patrick, Viva Books Pvt. ltd, pp.1.
3. Wilson and Gisvold's Text book of Organic Medicinal and Pharmaceutical Chemistry, 9th edition, Jaime.A.Delgade, William .A.Remers, J.B Lippincott, pp.1.
4. Prince P Sharma, S N Pandeya, Synthesis and Anticonvulsant activity of some Novel Isatin Schiff's bases, International Journal of ChemTech Research, 1 (3): 758-763, (2009).
5. Joaquim F. M. da Silva, Simon J. Garden, The Chemistry of Isatins: a Review from 1975 to 1999, J. Braz. Chem. Soc, 12 (3): 273-324, (2001).
6. M.-G. A. Shvekhgeimer, Synthesis Of Heterocyclic Compounds By The Cyclization of Isatin and Its Derivatives (Review), Chemistry of Heterocyclic Compounds, 32 (3): 249, (1996).
7. Olcay Bekircan and Hakan Bektas, Synthesis of Schiff and Mannich Bases of Isatin Derivatives with 4-Amino-4, 5-dihydro-1H-1,2,4-Triazole-5-Ones, Molecules, 13: 2126-2135, (2008).
8. K.D. Tripathi, Essentials of Medical Pharmacology, 6th Edition, Jaypee Brothers Medical Publishers, pp. 167-178 & 646-650.
9. V.Cioli, S.Putzolu, V.Rossi, P. Sorza Barcellona and C.Corradino, The Role of direct contact in the production of gastro intestinal ulcers by anti-inflammatory drugs in rats, Toxicol. Appl, Pharmacol, 50: 283-289, (1979).
10. Shastrikant, V.Bhandari, Kailash G. Bothara, Mayuresh k. Raut, Ajit A. Patil, Aniket P. sarkate, Vinod J. Mokale, Design, Synthesis and evaluation of Anti-inflammatory, Analgesic and Ulcerogenicity studies of Novel 5-substituted phenacyl-1,3,4-Oxadiazole-2-thiol and Schiff bases of Diclofenac acid as non Ulcerogenic derivatives, Bioorganic & Medicinal Chemistry, 16: 1822-1831, (2008).
11. Indian Pharmacopoeia, 1996, Volume II, Appendix 9.1-9.4, pp. A-100.
12. Manjusha Verma, Surendra Nath Pandeya, Krishna Nand Singh et.al, Anticonvulsant activity of Schiff bases of isatin derivatives, Acta Pharm, 54: 49–56, (2004).
13. Surendra N. Pandeya, Dhamrajan Sriram, Gopal Nath et.al, Synthesis, antibacterial, antifungal and anti-HIV activities of norfloxacin Mannich bases, Eur. J. Med. Chem, 35: 249−255, (2000).