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Research Article

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NOVEL SCHIFF AND MANNICH BASES OF ISATIN DERIVATIVES

Ramachandran S.*

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

*Corresponding Author: chandruchief@gmail.com

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 antibacterial and antifungal activities. Most of the compounds shown greater antibacterial and antifungal activities when compared with the standard drugs.

Keywords: Isatin, Schiff and Mannich bases, Antibacterial, Antifungal.

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

Antimicrobial Activity[8]

The antimicrobial activity of the synthesized compounds was determined by cup-plate method. The organisms selected for antibacterial activity were gram positive organisms like *Staphylococcus aureus, Streptococcus pyogenes,* gram negative organisms like *Escherichia coli, Klebsilla aerogenes.* Similarly the antifungal activity was carried out by using *Candida albicans.* The concentrations of sample compounds was 30 mcg/ml. Ciprofloxacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activity respectively. Control

test with solvents were performed for every assay but showed no inhibition of the microbial growth. The results are reported in Table-III and Chart-I to V.

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[9]

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.

Synthesis of Mannich bases[10]

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 antibacterial and antifungal activity by cup-plate method. All the compounds have shown significant antibacterial activity and moderate antifungal activity. With the suitable molecular modification of these compounds can prove as potent antimicrobial agents in future. Physical data of the synthesized compounds are listed in Table-I. The spectral data are mentioned in Table-II.

Chart I

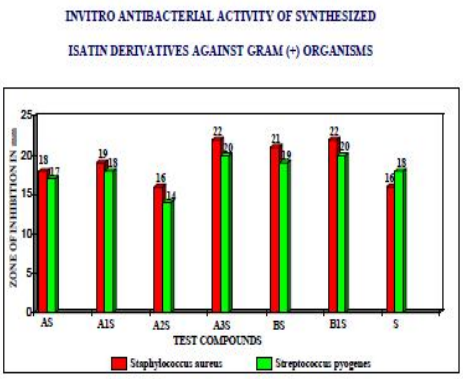


Chart II

INVITRO ANTIBACTERIAL ACTIVITY OF SYNTHESIZED

ISATIN DERIVATIVES AGAINST GRAM (+) ORGANISMS

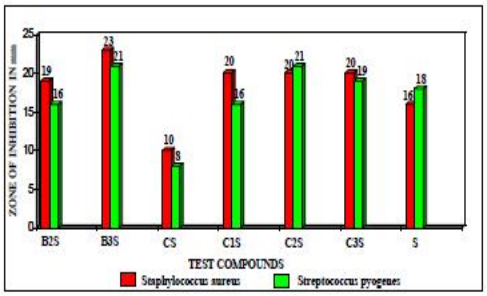


Chart IV

INVITRO ANTIBACTERIAL ACTIVITY OF SYNTHESIZED

ISATIN DERIVATIVES AGAINST GRAM (-) ORGANISMS

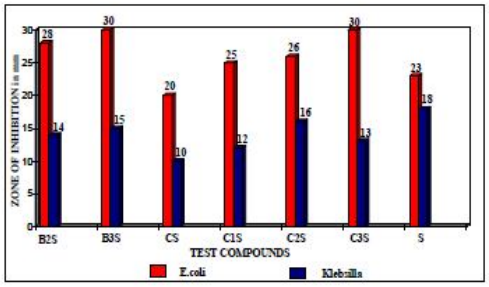


Chart III

INVITRO ANTIBACTERIAL ACTIVITY OF SYNTHESIZED

ISATIN DERIVATIVES AGAINST GRAM (-) ORGANISMS

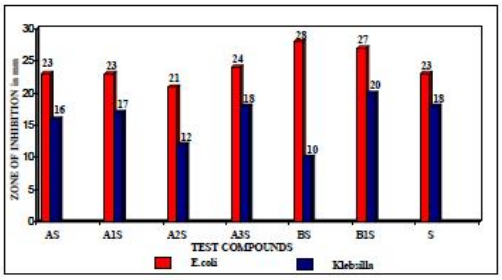
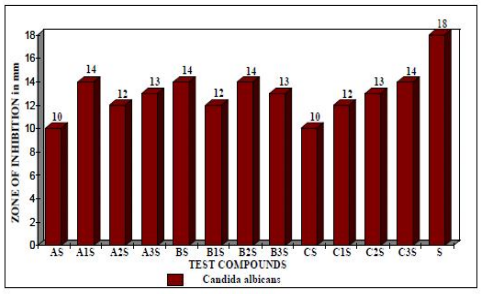


Chart V

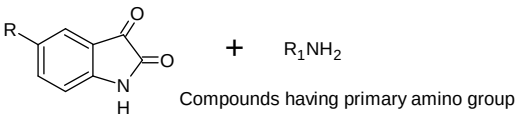
INVITRO ANTIFUNGAL ACTIVITY OF SYNTHESIZED

ISATIN DERIVATIVES AGAINST CANDIDA ALBICANS



GENERAL SCHEME OF REACTION
Synthesis of Schiff's bases of isatin

Step - I:

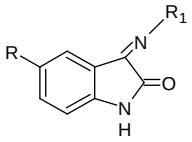


Compounds having primary amino group

Isatin

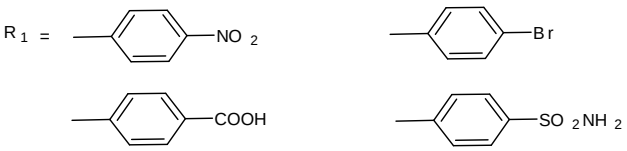
C_2H_5OH
CH_3COOH
(PH 4.5)

Reflux for 4 hours



Schiff's Base of Isatin

R = NO_2, Cl, H



Synthesis of Mannich Bases of Isatin

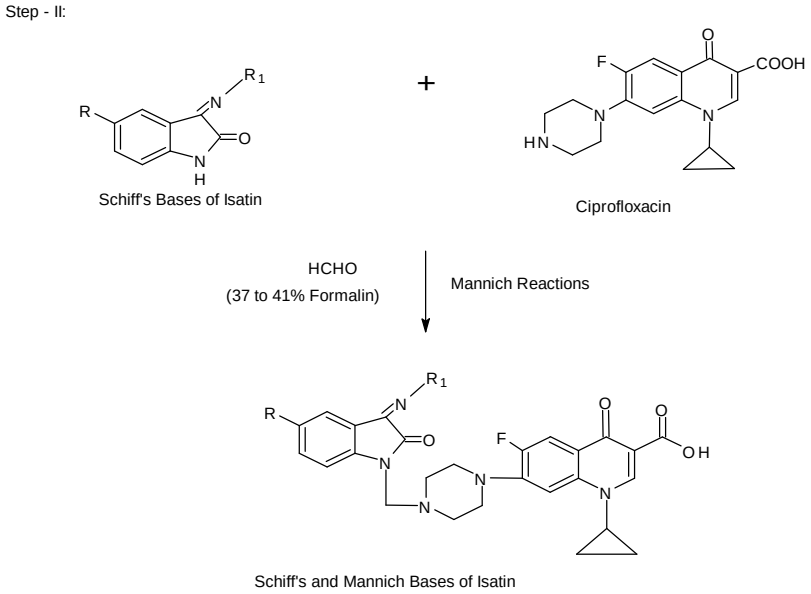


Table I: Physical data of the Synthesized Compounds

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).

Table III: Antibacterial and Antifungal Activity of Synthesized Compounds

S. No.	Compound Code	Zone of Inhibition (mm)				
		Staphylococci	*Streptococci*	*E.coli*	*Klebsilla*	*Candida albicans*
1	AS	18mm	17mm	23mm	16mm	10mm
2	A1S	19mm	18mm	23mm	17mm	14mm
3	A2S	16mm	14mm	21mm	12mm	12mm
4	A3S	22mm	20mm	24mm	18mm	13mm
5	BS	21mm	19mm	28mm	10mm	14mm
6	B1S	22mm	20mm	27mm	20mm	12mm
7	B2S	19mm	16mm	28mm	14mm	14mm
8	B3S	23mm	21mm	30mm	15mm	13mm
9	CS	10mm	8mm	20mm	10mm	10mm
10	C1S	20mm	16mm	25mm	12mm	12mm
11	C2S	20mm	21mm	26mm	16mm	13mm
12	C3S	20mm	19mm	30mm	13mm	14mm
13	Solvent Control	0mm	0mm	0mm	0mm	0mm
14	Standard	16mm	18mm	23mm	18mm	18mm

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