

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL SCHIFF AND MANNICH BASES OF ISATIN

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ABSTRACT

Objective: Synthesis and antimicrobial evaluation of some novel Schiff and Mannich bases of Isatin.

Methods: A series of novel Schiff bases of Isatin (V) and (X) were synthesized by refluxing Isatin with p-amino ethyl benzoate (IV) and 4-(4'-amino phenyl)-6-substituted phenyl pyrimidine-2-thiol (IX). Mannich bases of ethyl-4-(2-oxindolin-3-ylidene amino) benzoate (VI) were synthesized by using various aromatic secondary amines. The chemical structures of synthesized compounds were confirmed by IR, ¹HNMR, Mass and elemental analysis. These compounds were also screened for their *in vitro* antibacterial and antifungal activities.

Results: The results of antibacterial and antifungal activities showed that some of the synthesized compounds were exhibited promising antimicrobial activities.

Conclusion: All the newly synthesized compounds were screened for antimicrobial activities by turbidity method using Ampicillin and Clotrimazole as standard against gram positive, gram negative bacteria and fungi.

Keywords: Schiff bases, Mannich Bases, Isatin, Antibacterial Activity, Antifungal Activity.

INTRODUCTION

The indole nucleus is found to be very active nucleus in pharmacy field, as several natural alkaloids having indole as their basic ring are found to be therapeutically active agents. Isatin (indole-2, 3-dione) is an indole derivative, an endogenous compound, widely distributed in mammalian tissues and body fluids [1]. Isatins are synthetically versatile substances that are employed for the synthesis of a very large variety of heterocyclic compounds and possess broad spectrum of biological activities like antibacterial [2], antiviral [2], antifungal [2], anti-inflammatory [3], analgesic [4], anti-tubercular [5], antidepressant [6]. In view of these facts, we contemplated to synthesize some new Schiff and Mannich bases of Isatin and planned to screen for their *in vitro* antibacterial and antifungal activities.

MATERIALS AND METHODS

All the chemicals used for this study were in analytical grade only. The melting points were determined by open capillary using Toshniwal melting point apparatus and are uncorrected. Purity of compounds was checked by TLC on Silica Gel precoated plates. IR spectra were recorded in KBr on FTIR Brucker spectrophotometer and frequencies are expressed in cm⁻¹. The ¹HNMR spectra were recorded on 400MHz Brucker DPX using CDCl₃ and DMSO as solvent. Chemical shift values are reported as values in ppm relative to TMS as internal standard. Mass spectra were recorded on VG AUTOSPEC using EI-MS mode. Elemental analysis was performed on Perkin-Elmer series-2400.

Isatin (III) and ethyl p-amino benzoate (IV) were synthesized by the methods available in the literature [6, 7]. The synthetic strategies adopted to obtain target compounds are depicted in Figure 1 and 2.

Synthesis of ethyl-4-(2-oxindolin-3-ylidene amino) benzoate (V)

An appropriate quantity of indole-2, 3-dione (III) (0.01mol) was dissolved in alcohol (20ml) and added ethyl p-amino benzoate (IV) (0.01mol) and few drops of glacial acetic acid. The reaction mixture was stirred well and refluxed for 3 hrs. The resultant yellow crystalline solid was filtered and washed repeatedly with small quantity of methanol. The product was dried and purified by recrystallization from chloroform. The yield was found to be 78%.

The melting point of the product was found to be 180-182°C, M.W:294.

Synthesis of 1-(substituted amino methyl)-4-ethyl-4-(2-oxindolin-3-ylideneamino) benzoate (VI)

Compound (V) ethyl-4-(2-oxindolin-3-ylidene amino) benzoate (0.001mol) suspended in minimum quantity of DMF. To that, formaldehyde (1ml, 37%) and various secondary amines (0.001mol) were added with vigorous stirring. Warm the solution on a water bath for 2min. and stirred for an hour. Then left at room temperature over night. By the addition of water, the compound was separated, filtered, washed thoroughly with water, dried and purified by recrystallization from ethanol. The yield was found to be 70%.

Spectral data of compound (V)

IR (KBr in cm⁻¹): 3187(NH stretch), 2984(CH aliphatic stretching), 1654 (C=N stretching), 1751 (C=O ester stretching), 1272 (C-O ester stretching). ¹H NMR (CDCl₃) (δppm): 1.4(t, 3H, CH₃), 4.4 (q, 2H, CH₂), 6.5-8.1 (m, H, Aromatic), 9.2 (s, 1H, NH). MS: (m/z) 294.2 (M⁺). Analysis (C₁₇H₁₄N₂O₃) Cal. (Found)%: C 69.38 (69.35), H 4.79 (4.22), N 9.52 (9.05), O 16.31 (16.28).

Spectral data of compound (VIa)

IR (KBr in cm⁻¹): 3356 (NH stretching), 2992 (aliphatic CH stretching), 1728 (C=O ester stretching), 1274 (C-O ester stretching), 1598 (C=N stretching), 1469 (C=C aromatic stretching). ¹HNMR (CDCl₃) (δppm): 1.4 (t, 3H, CH₃), 2 (s, 1H, NH- piperazino), 2.4 (t, 4H, CH₂ piperazino), 2.7 (t, 4H, CH₂ piperazino), 3.9 (s, 2H, -N-CH₂-N-), 4.4 (q, 2H, CH₂ of ester), 6.5-8.1 (m, 8H, Ar). MS: (m/z) 392 (M⁺). Analysis (C₂₂H₂₄N₄O₃) Cal. (Found)%: C 67.33 (68.05), H 6.16 (6.15), N 14.28 (13.05), O 12.23 (12.68).

Spectral data of compound (VI b)

IR (KBr in cm⁻¹): 2980(aliphatic CH stretching), 1729 (C=O ester stretching), 1296 (C-O ester stretching), 1608 (C=N stretching), 1470 (C=C aromatic stretching).

¹HNMR (CDCl₃) (δppm): 1.2 (t, 3H, CH₃), 1.4 (t, 6H, CH₃ of diethyl amino group), 3.5 (s, 2H, N-CH₂-N), 4.1 (q, 2H, CH₂ of ester), 4.3 (q, 4H, CH₂ of diethyl amino group), 6.5-7.4 (m, 8H, Ar). MS: (m/z) 379

(M⁺). Analysis (C₂₂H₂₅N₃O₃) Cal. (Found)%: C 69.64 (68.55), H 6.64 (6.22), N 11.07 (11.19), O 11.31 (11.88).

Spectral data of compound (VI c)

IR (KBr in cm⁻¹): 2936 (aliphatic CH stretching), 1733 (C=O ester stretching), 1271 (C-O ester stretching), 1605 (C=N stretching), 1469 (C=C aromatic stretching)

¹HNMR (CDCl₃) (δppm): 1.3 (t, 3H, CH₃), 2.6 (s, 6H, CH₃ of dimethyl amino group), 4.5 (s, 2H, N-CH₂-N), 4.3 (q, 2H, CH₂ of ester), 6.5-8 (m, 8H, Ar). MS: (m/z) 351 (M⁺). Analysis (C₂₀H₂₁N₃O₃) Cal. (Found)%: C 68.36 (68.25), H 6.02 (6.26), N 11.96 (12.07), O 13.66 (13.16).

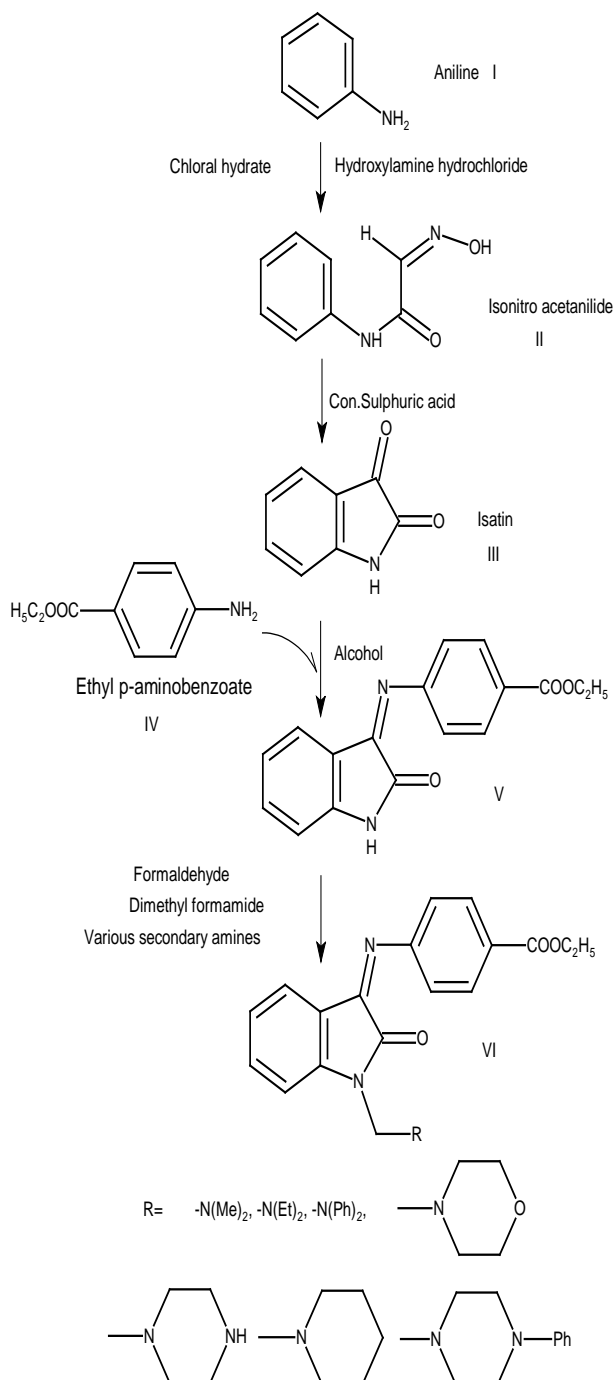


Fig. 1: Experimental scheme (I) for the synthesis of 1-(substituted amino methyl)-4-ethyl-4-(2-oxoindolin-3-ylidene amino) benzoate (VI a-g)

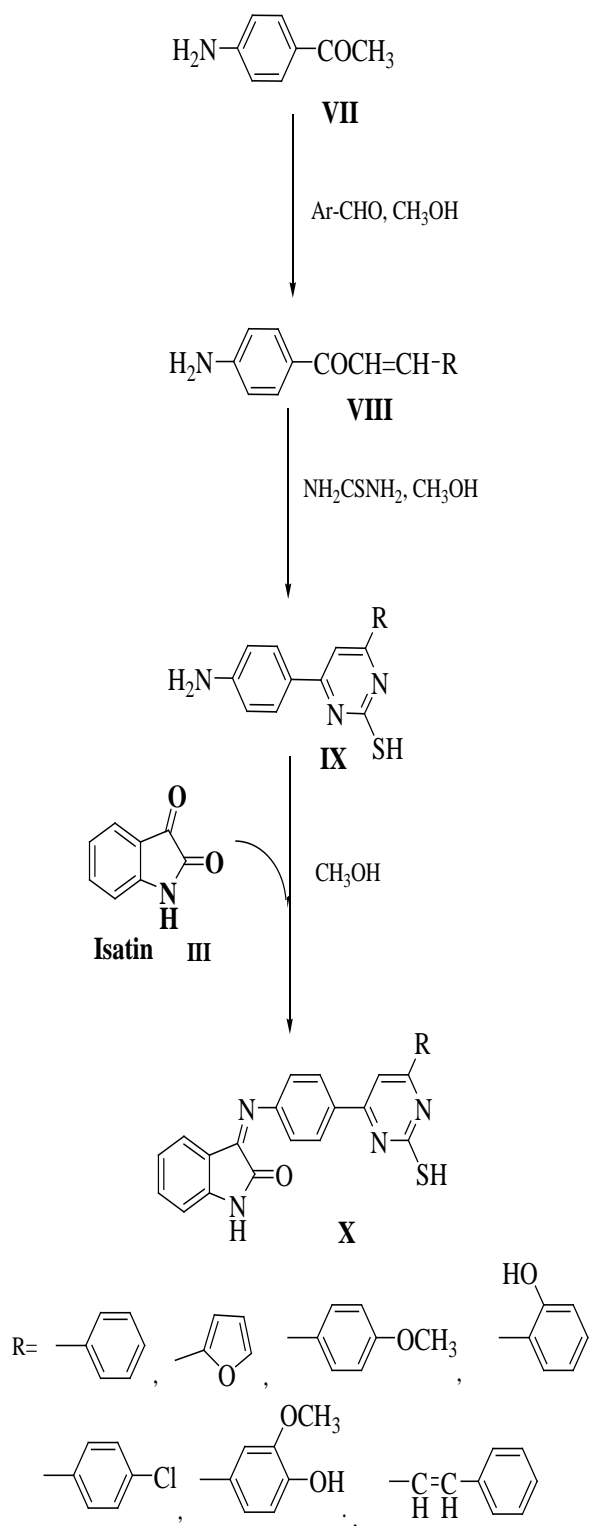


Fig. 2: Experimental scheme (II) for the synthesis of Isatin-3-(4'-(6''-substituted phenyl-2-thiopyrimidin-4-yl) phenyl) imine (Xa-g).

Spectral data of compound (VI e)

IR (KBr in cm⁻¹): 2906 (aliphatic CH stretching), 1728 (C=O ester stretching), 1274 (C-O ester stretching), 1598 (C=N stretching), 1469 (C=C aromatic stretching).

¹HNMR (CDCl₃) (δppm): 1.3 (t, 3H, CH₃), 2.1 (t, 4H, CH₂ of morpholino), 3.6 (t, 4H, CH₂ of morpholino), 4 (s, 2H, N-CH₂-N), 4.3

(q, 2H, CH₂ of ester), 6.5-8.1 (m, 8H, Ar). MS: (m/z) 393 (M⁺). Analysis (C₂₂H₂₃N₃O₄) Cal. (Found)%: C 67.16 (67.35), H 5.89 (5.18), N 10.68 (10.95), O 16.27 (16.88).

Synthesis of 1-(4-amino phenyl)-3- substituted phenyl prop-2-en-1-one (VIII)

An appropriate quantity (0.01 moles) of p-amino acetophenone (VII) was refluxed with equimolar quantity (0.01 moles) of aromatic substituted aldehydes in methanol for 24 hrs. The completion of the reaction was checked by TLC. The solvent has been evaporated; the product was washed with ice cold water, dried and purified by recrystallization from ethanol.

Synthesis of 4-(4'-amino phenyl)-6- substituted phenyl pyrimidin-2-thiol (IX)

Compound 1-(4-amino phenyl)-3- substituted phenyl prop-2-en-1-one (VIII) (0.01 mole) and thiourea (0.01 mole) were dissolved in methanol and few drops of conc. HCl was added. The mixture was refluxed for 5 hrs. The crystalline solid separated out on cooling, which was collected by filtration and washed with ice cold water, dried. The product was recrystallised from ethanol.

Synthesis of Isatin-3-(4'-(6''-substituted phenyl)-2-thiopyrimidin-4-yl) phenyl imine (X)

Compound 4-(4'-amino phenyl)-6- substituted phenyl pyrimidin-2-thiol (IX) and Isatin (III) were dissolved in methanol in equimolar quantities and refluxed for 5 hrs. The crystalline solid separated out on cooling was collected by filtration and purified by recrystallization from ethanol.

Spectral data of compound (IX)

IR (KBr in cm⁻¹): 3442 (NH stretching), 2916 (aliphatic CH stretching), 2548 (SH stretching), 1460 (C=C aromatic stretching) ¹HNMR (CDCl₃) (δppm): 3 (s, 1H, SH), 3.7 (s, 3H, OCH₃), 4.0 (s, 2H,

NH₂), 6-8 (m, 9H, Ar). MS: (m/z) 309 (M⁺). Analysis (C₁₇H₁₅N₃O₅) Cal. (Found)%: C 66.16 (66.55), H 4.89 (4.43), N 13.58 (13.62), O 5.17. (5.18), S 10.36 (10.66).

Spectral data of compound (Xa)

IR (KBr in cm⁻¹): 3442 (NH stretching), 3010 (CH aromatic stretching), 2542 (SH stretching), 1730 (C=O stretching), 1617 (C=C aromatic stretching), 1331 (C-N stretching)

¹HNMR (CDCl₃) (δppm): 3.9 (s, 1H, SH), 6-9 (m, 14H, Ar), 11 (s, 1H, NH). MS: (m/z) 408 (M⁺). Analysis (C₂₄H₁₆N₄O₅) Cal. (Found) %: C 70.57 (70.52), H 3.95 (4.02), N 13.72 (13.97), O 3.92. (3.85), S 7.85(7.77)

Spectral data of compound (Xc)

IR (KBr in cm⁻¹): 3450 (NH stretching), 2929 (CH aliphatic stretching), 2540 (SH stretching), 1725 (C=O stretching), 1591 (C=C aromatic stretching), 1353 (C-N stretching), 1097 (C-O stretching).

¹HNMR (CDCl₃) (δppm): 3.1 (s, 1H, SH), 3.7 (s, 3H, OCH₃), 6-9 (m, 13H, Ar), 11 (s, 1H, NH). MS: (m/z) 438 (M⁺). Analysis (C₂₅H₁₈N₄O₂S) Cal. (Found)%: C 68.48 (68.52), H 4.14 (4.23), N 12.78 (12.92), O 7.30. (7.08), S 7.31(7.44).

In Vitro Antimicrobial Activity

The newly synthesised compounds ethyl-4-(2-oxoindolin-3-ylideneamino) benzoate (V), 1-(substituted amino methyl)-4-ethyl-4-(2-oxoindolin-3-ylideneamino) benzoate (VI), Isatin-3-(4'-(6''-substituted phenyl)-2-thio pyrimidin-4-yl) phenyl imine (X) were screened for antimicrobial activity studies[8-15] as primary screening in six sets at different concentrations against gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and gram negative (*Escherichia coli* and *Proteus vulgaris*) bacteria and fungi (*Candida albicans* and *Aspergillus niger*) by turbidity method in Muller Hinton broth medium and compared with that of standard drugs Ampicillin and Clotrimazole respectively.

Table : Physical properties of 1-(substituted amino methyl)-4-ethyl-4-(2-oxoindolin-3-ylideneamino) benzoate (V&VIa-g))

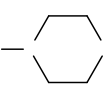



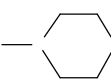
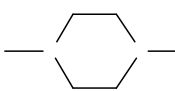
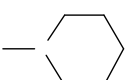
Compound No	R Group	Molecular Formula	Molecular Weight	Percentage % Yield	Melting Point °C	R _f Value
V	—	C ₁₇ H ₁₄ N ₂ O ₃	294	80%	180-182°C	0.56
VI a		C ₂₂ H ₂₄ N ₄ O ₃	392	70%	300-301°C	0.62
VI b		C ₂₂ H ₂₅ N ₃ O ₃	379	68%	240-242°C	0.61
VI c		C ₂₀ H ₂₁ N ₃ O ₃	351	60%	295-296°C	0.51
VI d		C ₃₀ H ₂₅ N ₃ O ₃	475	65%	160-161°C	0.51
VI e		C ₂₂ H ₂₃ N ₃ O ₄	393	72%	220-222°C	0.58
VI f		C ₂₈ H ₂₈ N ₄ O ₃	468	70%	145-146°C	0.70
VI g		C ₂₃ H ₂₅ N ₃ O ₃	391	67%	98-100 °C	0.80

Table 2: Physical properties of Isatin-3-(4'-(6''-substituted phenyl-2-thiopyrimidin-4-yl) phenyl) imine (Xa-g)


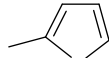
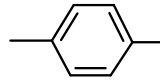
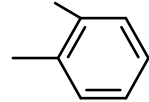
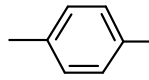
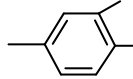
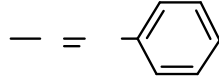
Compound No	R Group	Molecular Formula	Molecular Weight	Percentage Yield	Melting Point °C	R _f Value
Xa		C ₂₄ H ₁₆ N ₄ OS	408	70%	200-201°C	0.56
Xb		C ₂₂ H ₁₄ N ₄ O ₂ S	398	65%	215-217°C	0.68
Xc		C ₂₅ H ₁₈ N ₄ O ₂ S	438	65%	210-212°C	0.69
Xd		C ₂₄ H ₁₆ N ₄ O ₂ S	424	69%	222°C	0.44
Xe		C ₂₄ H ₁₆ N ₄ O ₂ OSCl	442	71%	198-200°C	0.73
Xf		C ₂₅ H ₁₈ N ₄ O ₃ S	458	68%	218-220°C	0.72
Xg		C ₂₆ H ₁₈ N ₄ OS	434	70%	215-216°C	0.68

Table 3: Antimicrobial activity of 1-(substituted amino methyl)-4-ethyl-4-(2-oxoindolin-3-ylideneamino) benzoate (V & VIa-g) by turbidity method

COMPOUNDS	ANTIBACTERIAL ACTIVITY (Minimum Inhibitory Concentration) (µg/ml)				ANTIFUNGAL ACTIVITY (Minimum Inhibitory Concentration) (µg/ml)	
	<i>B.subtilis</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>P.vulgaris</i>	<i>C.albicans</i>	<i>A.niger</i>
	V	25±1.45**	12.5±2.12***	12.5±1.11***	25±2.28**	25±1.15**
VI-a	12.5±2.60***	12.5±2.21***	12.5±1.80***	25±3.12**	25±1.18**	25±2.65**
VI-b	12.5±1.10***	50±1.28*	25±3.12**	100±2.12*	12.5±1.54***	25±1.95**
VI-c	25±1.25**	25±1.68**	12.5±1.96***	100±1.35*	12.5±1.76***	25±2.24**
VI-d	12.5±1.92***	12.5±1.36***	12.5±2.66***	100±1.45*	25±1.86**	12.5±1.89***
VI-e	12.5±2.12***	12.5±1.44***	12.5±1.28***	50±2.63*	12.5±2.21***	50±2.22*
VI-f	12.5±2.29***	50±2.56*	25±1.94**	50±1.95*	12.5±2.28***	12.5±3.14***
VI-g	50±1.96*	12.5±1.96**	25±2.02**	12.5±1.28***	12.5±3.12***	25±1.88**
AMPICILLIN	12.5±2.53***	12.5±2.22***	12.5±1.70***	12.5±2.94***	-	-
CLOTTRIMAZOLE	-	-	-	-	12.5±1.78***	12.5±1.64***

Values are expressed as Mean ± SD (n=6). ***P < 0.001, **P < 0.01, *P < 0.05. All significant differences are considered from control value 0.00

Table 4: Antimicrobial activity of Isatin-3-(4'-(6''-substituted phenyl-2-thiopyrimidin-4-yl) phenyl) imine (X a-g) by turbidity method

COMPOUNDS	ANTIBACTERIAL ACTIVITY (Minimum Inhibitory Concentration) (µg/ml)				ANTIFUNGAL ACTIVITY (Minimum Inhibitory Concentration) (µg/ml)	
	<i>B.subtilis</i>	<i>S.aureus</i>	<i>E.coli</i>	<i>P.vulgaris</i>	<i>C.albicans</i>	<i>A.niger</i>
	X-a	50 ± 1.02*	50±2.02*	50±0.88*	100±1.12*	50±2.12*
X-b	12.5 ± 0.98***	12.5±1.98***	12.5±1.96***	100±0.89*	50±0.91*	25±1.22**
X-c	12.5 ± 0.45***	25±1.13**	25±0.75**	25±0.458**	12.5±0.8***	25±1.33**
X-d	50 ± 1.24*	50±1.96*	50±1.58*	100±0.58*	50±1.66*	50±1.62*
X-e	12.5 ± 0.96***	12.5±1.46***	12.5±1.40***	50±0.88*	12.5±1.46***	12.5±2.09***
X-f	50 ± 0.88*	50±1.45*	50±2.02*	100±1.11*	50±1.22*	50±2.12*
X-g	25 ± 1.34**	25±2.24**	50±2.12*	50±1.37*	25±0.98**	25±1.67**
AMPICILLIN	12.5 ± 1.88***	12.5±2.12***	12.5±1.34***	12.5±1.87***	-	-
CLOTTRIMAZOLE	-	-	-	-	12.5±1.99***	12.5±1.41***

Values are expressed as Mean ± SD (n=6). ***P < 0.001, **P < 0.01, *P < 0.05. All significant differences are considered from control value 0.00

Two fold serial dilutions of the test compounds and reference drugs were prepared in broth. Test compounds and standard drugs Ampicillin and Clotrimazole (10 mg) were dissolved in dimethyl formamide (10ml). Further progressive dilutions with Muller Hinton broth were performed to obtain the required concentrations of 200,100,50,25 and 12.5 µg/ml. The test tubes were inoculated with bacteria and fungi and incubated at 37°C for 24 h. The minimum inhibitory concentration (MIC) was the lowest concentration of the tested compound that yields no visible growth in the tube. To ensure that the solvent had no effect on the bacterial growth, a control was performed.

Statistical Analysis

Values are expressed as mean ± standard deviation and statistical analysis was carried out by one way ANOVA. P < 0.05 is considered as significant.

RESULTS AND DISCUSSION

A novel series of VIa-g and Xa-g derivatives have been synthesized and screened for their *in vitro* antibacterial and antifungal activities. The results of the physical data of the final synthesized compounds are presented in table 1 and 2.

The antibacterial activity results revealed that all compounds showed significant activity against *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli*. Compounds VIa, VIe, VIg, Xb, Xc showed excellent activity against all gram positive organisms and gram negative organism *E.coli*. In the antifungal activity, compounds VIg and Xe showed highly significant activity which was comparable with the standard drug clotrimazole. The results are presented in table 3 and 4.

The structures of the newly synthesized compounds were established on the basis of spectral data and elemental analysis. The compounds were purified by recrystallization from appropriate solvents. The completion of the reactions were monitored by TLC. The antibacterial activity of the compounds showed excellent activity against gram positive organisms and *E.coli*. The compounds also displayed significant activity against fungal organisms.

CONCLUSION

From the above results it can be concluded that the Mannich bases of isatin with heterocyclic secondary amines (VIa, VIe, VIg) exhibited more activity. In the Schiff bases of isatin, furfuryl derivative (Xb) and Chlorophenyl derivative (Xe) showed more antimicrobial activity.

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