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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 3-FORMYL INDOLE BASED SCHIFF BASES

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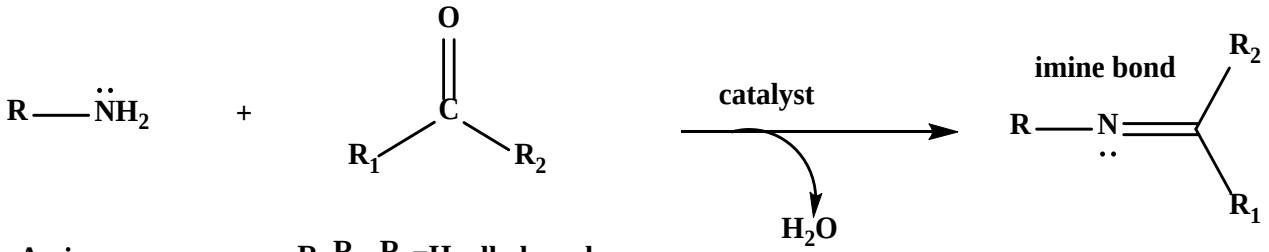
ABSTRACT:

In order to develop new antimicrobial agents, a series of 3-formyl indole based Schiff bases were synthesized by reacting 3-formyl indole(indole-3-carboxaldehyde) with substituted aniline taking ethanol as solvent. The reaction was carried in the presence of small amount of *p*-toluene sulphonic acid as catalyst.All the synthesized compounds were characterized by IR, ^{1}H-NMR spectral analysis. All the synthesized compounds were evaluated for antimicrobial activity against two gram positive bacterial strains (*B. subtilis*and *S. aureus*) and two gram negative bacterial strains (*P. aeruginosa*and *E. coli*) and one fungal strain (*C. albicans*). All the synthesized compounds were found to have moderate to good antimicrobial activity. The standard drug amoxicillin, fluconazole were used for antimicrobial activity. Among the synthesized compounds, the maximum antimicrobial activity was shown by compounds GS04, GS07, GS08 and GS10.

INTRODUCTION

Schiff base (also known as imine or azomethine) with an imine functional group, is produced by condensation of an aldehyde/ketone with a primary amine. **)**. It was discovered by a German chemist, Nobel Prize winner, Hugo Schiff about 150 years ago in 1864, and henceforth referred to his name Schiff. The general formula for Schiff base is RN = $CR_1R_2$where R, R_1, and R_2can be alkyl, aryl, heteroaryl, or cycloalkyl, etc.



Amine **R, R_1, R_2=H, alkyl, aryl, heteroaryl, or cycloalkyl** **Schiff base**

The -C = N- imine bond in Schiff bases is responsible for the broad-spectrum biological activities of these compounds. The imine bond in Schiff base i.e., -C = N- contains an electrophilic carbon and nucleophillic nitrogen which provides great binding possibilities with different nucleophiles and electrophiles, which in turn inhibits targeted diseases, enzymes, or DNA replication. Schiff bases additionally function versatile ligands for coordinating a range of metal ions in several coordination geometries and oxidation states. Schiff bases are well recognized to form metal complexes with all metals of d-block as well as with lanthanides [1]. Schiff bases are an important class of ligands; such ligands and their metal complexes have a variety of applications including biological, clinical, analytical and industrial, in addition to their important roles in catalysis and organic synthesis. Schiff bases and metal complexes have been playing an important role in the development of metal coordination chemistry due to their great versatility as chelating ligands displaying borderline characteristics between hard and soft Lewis bases [2,3]. Schiff base serve as a back bone for the synthesis of various heterocyclic compounds having a versatile use and a wide range of application such as antimicrobial [4-8], antiviral [9], anti-malarial [10], anticancer [11,14], anti-inflammatory [15], anti-amoebic activity[16]. In view of these above biological applications of Schiff bases, a simple and efficient synthesis was performed.

MATERIALS AND METHODS

Materials and solvents

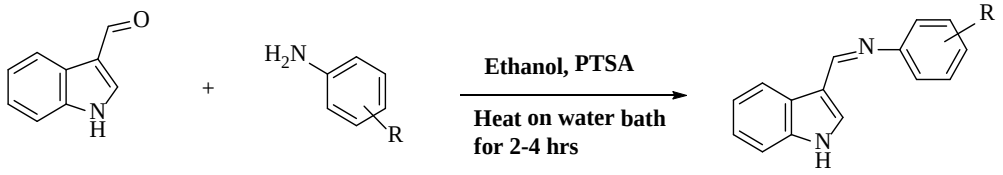
All chemical materials and solvents used in chemical synthesis of Schiff base were highest purity and used without further Purification, purchased from Spectrochem Pvt. Ltd., Mumbai, Central drug house (CDH) pvt. Ltd. Mumbai, Qualikems fine chem. Pvt. Ltd. Vadodara and Himedia laboratories pvt. Ltd. Mumbai, India.

Instruments

Synthesis of compounds was performed on waterbath from Perfit India. Thin layer chromatographic (TLC) analyses were performed on pre-coated silica plates ($60F_{254}$, Merck Specialities). TLC spots were visualized in UV cabinet, International Scientific Corporation.Co. Melting points were measured in open capillary tubes on melting point apparatus, Perfit India. The IR spectra of samples were recorded in region 4000-400cm-1 byNICOLET iS5 (THERMO FISHER SCIENTIFIC) FT-IR spectrophotometer. 1H,13C-NMR spectra (300MHz) recorded in d_6-DMSO by employing TMS as an internal standard on JEOL 300MHz NMR spectrophotometer. Mass spectral analysis was performed on Bruker HRMS.

General procedure for Synthesis of 3-formyl indole based Schiff bases

The Schiff base was prepared by mixing an ethanolic solution (25 ml) of 3-formylindole (0.01 mol) with substituted aniline (0.01 mol) in the same volume of ethanol in the presence of *p*-toulene sulphonic acid as catalyst. The mixture was then heat on water bath with continuous stirring for 2-4 h. Then, solution was poured on ice cold water. The precipitate was collected by filtration through Buchner funnel, recrystallized from ethanol, and dried at room temperature.



1*H*-indole-3-carbaldehyde **Substituted Aniline** **GS01-GS11**

Scheme 1

Compound	R
GS01	4-F
GS02	4-Cl
GS03	4-Br
GS04	4-NO_2
GS05	4-COOH
GS06	4-OCH_3
GS07	4-CN
GS08	4-SO_2NH_2
GS09	3-COOH
GS10	3-CF_3
GS11	2-Cl-4-F

Antimicrobial activity

The synthesized compounds (GS01-GS11) were screened for in-vitro antibacterial activity against gram positive species *Bacillus subtilis*(MTCC 1133)*, Staphylococcus aureus*(MTCC 121) and gram negative species *Pseudomonas aeruginosa* (MTCC 1688)*, Escherichia coli* (MTCC 1575)and for antifungal *Candida albicans* (MTCC 4748)species by Agar diffusion technique. Amoxicillin and Fluconazole were used as reference compounds for antibacterial and antifungal activities respectively.

Result and discussion

The Schiff's bases **GS01-GS11** was prepared by react 3-formylindole with substituted aniline at ratio (1:1). The purity of the synthesized compounds was controlled by using TLC. Physical properties of synthesize compounds **GS01-GS11** were presented in table 1.

Table 1: Physicochemical characterization of novel synthesized compounds

Compounds	M.F	Mol. Wt (g/mol)	M. P. (ºC)	R_f	% Yield (%)
GS01	$C_{15}H_{11}FN_2$	238.27	216-218	0.58	51
GS02	$C_{15}H_{11}ClN_2$	254.72	218-221	0.76	54
GS03	$C_{15}H_{11}BrN_2$	299.17	215-216	0.68	42
GS04	$C_{15}H_{11}N_3O_2$	265.27	211-214	0.86	61
GS05	$C_{16}H_{12}N_2O_2$	264.28	216-220	0.65	46
GS06	$C_{16}H_{14}N_2O$	250.30	216-219	0.51	82
GS07	$C_{16}H_{11}N_3$	245.29	220-222	0.74	75
GS08	$C_{15}H_{13}N_3O_2S$	299.35	219-220	0.42	35
GS09	$C_{16}H_{12}N_2O_2$	264.28	216-218	0.82	76
GS10	$C_{16}H_{11}F_3N_2$	288.27	216-220	0.73	86
GS11	$C_{15}H_{10}ClFN_2$	272.71	217-218	0.71	65
TLC mobile phase – Hexane : Ethyl acetate (6:4)					

The structures of the synthesized compounds were determined on the basis of their FT-IR, 1H-NMRdata were as a following:

***(E)-N-((1H-indol-3-yl)methylene)-4-fluoroaniline* (GS01)**

FT-IR (cm^{-1}): 1645.30(HC=N), 3210(N-H), 1048.45(C-F), 3110(C-H). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.24-7.29(m, 4H, Ar-H), 7.52-7.55(d, 2H, Ar-H), 7.89- 7.91(d, 2H, Ar-H), 9.24 (s, 1H, CH=N), 11.29 (s, 1H, NH).

***(E)-N-((1H-indol-3-yl)methylene)-4-chloroaniline* (GS02)**

FT-IR (cm-1): 1653.15(HC=N), 3140(N-H), 710.45(C-Cl), 3063(C-H). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.39-7.44(m, 4H, Ar-H), 7.51-7.53(d, 2H, Ar-H), 8.08- 8.11(d, 2H, Ar-H), 9.44 (s, 1H, CH=N), 11.04 (s, 1H, NH).

***(E)-N-((1H-indol-3-yl)methylene)-4-bromoaniline* (GS03)**

FT-IR (cm-1): 1654.3(HC=N), 3130(N-H), 583(C-Br), 3070(C-H). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.37-7.41(m, 4H, Ar-H), 7.61-7.63(d, 2H, Ar-H), 7.99- 8.01(d, 2H, Ar-H), 9.84 (s, 1H, CH=N), 12.04 (s, 1H, NH).

***(E)-N-((1H-indol-3-yl)methylene)-4-nitroaniline* (GS04)**

FT-IR (cm-1): 1632.53(HC=N), 3362.10(N-H), 1452.75(C=C), 3145.25(C-H), 1520.26(Ar-NO_2). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.38-7.46(m, 4H, Ar-H), 8.00-8.02(d, 2H, Ar-H), 8.19- 8.21(d, 2H, Ar-H), 12.04 (s, 1H, CH=N), 9.85 (s, 1H, NH).

***(E)-4-(((1H-indol-3-yl)methylene)amino)benzoic acid* (GS05)**

FT-IR (cm-1): 1653(HC=N), 2878.72(N-H), 1687.71(C=O), 1583.86(C=C sym), 2671.41(O-H), 3095.75(C-H). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.46-7.53(m, 4H, Ar-H), 7.68-7.71(d, 2H, Ar-H), 8.06- 8.10(d, 2H, Ar-H), 8.44 (s, 1H, CH=N), 9.52 (s, 1H, NH), 12.14(s, 1H, OH).

***(E)-N-((1H-indol-3-yl)methylene)-4-methoxyaniline* (GS06)**

FT-IR (cm-1): 1653.35(HC=N), 3193.53(N-H), 3118.25(C-H), 1480.35(C=C). 1H-NMR (400MHz, DMSO-d6): δ [ppm] 7.55-7.59(m, 4H, Ar-H), 7.65-7.69(d, 2H, Ar-H), 8.42- 8.44(d, 2H, Ar-H), 10.26(s, 1H, CH=N), 11.75(s, 1H, NH).

***(E)-4-(((1H-indol-3-yl)methylene)amino)benzonitrile* (GS07)**

FT-IR (cm-1): 1652(HC=N), 3143.52(N-H), 3095.86(C-H), 1505.35(C=C), 2225.46(Ar-CN). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.45-7.51(m, 4H, Ar-H), 7.35-7.37(d, 2H, Ar-H), 8.26- 8.28(d, 2H, Ar-H), 9.93(s, 1H, CH=N), 12.09(s, 1H, NH).

***(E)-4-(((1H-indol-3-yl)methylene)amino)benzenesulfonamide* (GS08)**

FT-IR (cm-1): 1653.07(HC=N), 3168.22(N-H,Str), 1615.45(N-H,bend), 3115.17(C-H), 1576.87(C=C). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.18-7.25(m, 4H, Ar-H), 7.46-7.49(d, 2H, Ar-H), 8.05- 8.07(d, 2H, Ar-H), 8.24- 8.26(d, 2H, Ar-H), 12.09(s, 1H, CH=N), 9.90(s, 1H, NH).

***(E)-3-(((1H-indol-3-yl)methylene)amino)benzoic acid* (GS09)**

FT-IR (cm-1): 1648.26(HC=N), 3178.22(N-H), 3105.45(C-H), 1580.36(C=C), 1690.54(C=O), 2685.21(C-OH) 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.52-7.57(m, 4H, Ar-H), 7.78-7.82(d, 2H, Ar-H), 8.16-8.20(d, 2H, Ar-H), 9.34(s, 1H, CH=N), 10.22(s, 1H, NH), 12.26(s, 1H, OH).

***(E)-N-((1H-indol-3-yl)methylene)-3-(trifluoromethyl)aniline* (GS10)**

FT-IR (cm-1): 1645.25(HC=N), 3145.23(N-H), 3125.48(C-H), 1075.29(C-F). 1H-NMR (400MHz, DMSO-d6): δ [ppm] 7.28-7.37(m, 4H, Ar-H), 7.59-7.62(d, 2H, Ar-H), 8.47- 8.49(d, 2H, Ar-H), 12.53(s, 1H, CH=N), 10.93(s, 1H, NH).

(E)-N-((1H-indol-3-yl)methylene)-2-chloro-4-fluoroaniline **(GS11)**

FT-IR (cm-1): 1654.92(HC=N), 3183.53(N-H), 3111.18(C-H), 783.89(C-Cl), 1083.99(C-F). 1H-NMR (300MHz, DMSO-d6): δ [ppm] 7.18-7.27(m, 4H, Ar-H), 7.49-7.52(d, 2H, Ar-H), 8.27- 8.28(d, 2H, Ar-H), 12.13(s, 1H, CH=N), 9.93(s, 1H, NH).

The synthesized 3-formylindole Schiff bases were tested for in-vitro antibacterial activity against gram positive bacteria[*Bacillus subtilis*(MTCC 1133)*, Staphylococcus aureus*(MTCC 121)], gram negative bacteria[*Pseudomonas aeruginosa*(MTCC 1688)*, Escherichia coli*(MTCC 1575)]and for antifungal activity against *Candida albicans*(MTCC 4748)species. The synthesized compounds **GS04**, **GS07**, **GS08** and **GS10** shows maximum antimicrobial activity. The zone of inhibition(mm) data of synthesized compounds was given in table 2.

Table 2: In vitro antimicrobial activity of synthesized derivatives against bacterial and fungal strains

Comp.	**Conc. (µg/ml)**	**Zone of inhibition (mm)**				
		Gram positive			**Gram negative**	**Fungal strain**
		B. subtilis (MTCC 1133)	*S. aureus* (MTCC 121)	*P.aeruginosa* (MTCC 1688)	*E.coli* (MTCC 1575)	*C.albicans* (MTCC 4748)
GS01	100	20.7±0.46	21.6±0.76	18.5±0.61	20.5±0.65	23.5±0.53
GS02	100	17.1±0.57	16.7±0.56	17.9±0.66	17.7±0.52	18.1±0.55
GS03	100	19.9±0.52	20.9±0.42	21.9±0.70	20.3±0.66	19.7±0.71
GS04	100	23.8±0.30	24.1±0.74	24.4±0.56	23.9±0.95	21.1±0.56
GS05	100	15.03±0.71	13.1±0.30	14.5±0.50	13.7±0.47	10.7±0.40
GS06	100	15.7±0.36	11.8±0.65	13.2±0.65	14.6±0.52	15±0.66
GS07	100	26.5±0.53	28.5±1.10	25.4±0.50	24.8±0.35	23.2±0.35
GS08	100	25.6±0.50	24.7±0.56	25.5±0.45	23.9±0.21	24.2±0.61
GS09	100	14.3±0.43	15.2±0.89	13.4±0.46	12.4±0.50	8.9±0.60
GS10	100	27.2±0.30	27.3±0.48	27.6±0.80	26.8±0.75	25.7±0.34
GS11	100	19.9±0.50	20.7±0.72	18.7±0.64	18.9±0.55	19.2±0.53
Amoxicillin	100	30.7±0.78	31.5±0.35	32.8±0.35	31.2±0.15	
fluconazole	100					30.5±0.35

Values are presented as mean ±SEM

Conclusion

Easy and quick single step synthesis for the preparation of Schiff base derivatives encouraged to prepare novel derivatives of 3-formylindole based Schiff base derivatives. A number of compounds with different substituents were synthesized. The reaction progress was monitored with the help of TLC

and the completion of reaction was confirmed by melting point determination. The synthesized compounds were finally analyzed by FTIR and ^{1}H-NMR spectroscopic analysis.

The synthesized compounds were also evaluated antimicrobial activity by agar diffusion method against two Gram positive [*B. subtilis* (MTCC 1133) and *S. aureus* (MTCC 121)], Gram negative [*P.aeruginosa*(MTCC 1688) and *E.coli*(MTCC 1575)] bacterial and one fungal strain [*C.albicans*(MTCC 4748)]. All the synthesized compounds were found to have moderate to good antimicrobial activity compared to standard drug amoxicillin and fluconazole.

Among the synthesized compounds, three compounds (GS05. GS06 and GS09) shows least activity and compounds (GS01, GS02, GS03 and GS11) showed moderate antimicrobial activity. The maximum activity was shown by compounds GS04, GS07, GS08 and GS10.

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