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Microwave Assisted Synthesis and Antimicrobial Evaluation of Schiff Bases of Indole-3-aldehyde

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Abstract: In order to develop new antimicrobial agents, a series of Schiff bases of indole-3-aldehyde were synthesized by microwave assisted synthesis by taking DMF as solvent and evaluated for their antimicrobial activity. All the synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral analysis. All compounds were tested against five gram positive and five gram negative bacterial strains and one fungal strain. All compounds exhibited better activity against gram positive strains than against gram negative strains and the compounds were found more active against *S.aureus* and *B.subtilis*.

Keywords: Antibacterial, Antifungal, Schiff base, Indole-3-aldehyde.

Introduction

A Schiff base (or azomethine) is a functional group that contains a carbon nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group but not hydrogen[1]. Schiff bases are usually synthesized from the condensation of primary amines and active carbonyl group[2]. Schiff bases have been reported to possess antimicrobial properties[3-7]. Schiff bases are characterized by the –N=CH– (imines) group which is important for elucidating the mechanism of transamination and racemisation reactions in biological systems and are also known to have biological activities such as antimicrobial[8] antifungal[9], antitumor[10] and herbicidal[11] activity. Indole derivatives found to possess antibacterial[12], anticonvulsant[13] and antihypertensive activity. These observations led to the conception that Schiff bases of indole-3-aldehyde would possess potential antimicrobial properties. Microwave assisted organic synthesis (MAOS) accelerate the course of many organic reactions, producing high yields and higher selectivity, lower quantities of side products and consequently, easier work-up and purification of the products[14]. In the present study a series of Schiff base of Indole-3-aldehyde were synthesized by use of conventional microwave and characterized by

IR,^{1}H NMR and mass spectroscopy. The compounds were screened for antibacterial and antifungal activities. The minimum inhibitory concentrations of the compounds were also determined by serial dilution method.

Indole-3-aldehyde on condensation with different aromatic or aliphatic amine in presence of DMF as solvent yields Schiff bases (Scheme 1).

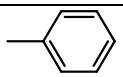
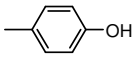
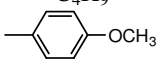
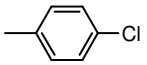
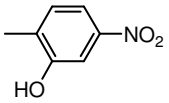
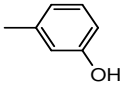
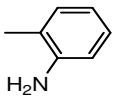
Indole-3-aldehyde Alkyl/aryl amine Schiff base of Indole-3-aldehyde

Figure 1. Scheme for the synthesis of Schiff bases

Experimental

A mixture of 2 mmole of indole-3-aldehyde and 2 mmole of different aryl or alkyl amines was taken and triturated in a mortar pestle. Then above mixture was transferred to a vessel which was then kept in microwave for synthesis. 4 to 5 mL of DMF was also added to mixture before putting it in microwave. Microwave was run at 400-480 W for different time for different reaction mixtures. Reaction completion was monitored continuously after each run by TLC. Then product was washed with ethanol, solvent was evaporated, dried and recrystalized with ethanol. Structures, time in microwave assisted synthesis and % yield are given in Table 1

Table1. Structures, time in microwave assisted synthesis and % yield of synthesized compounds.

Compound code	R	Time in microwave assisted synthesis, min.	% yield
PK1		4	71.52
PK2		6	64.2
PK3	C_4H_9	3	71.0
PK4		5	65.6
PK5		7	68.2
PK6		12	64.5
PK7		9	62.3
PK8		5	62.7

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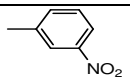
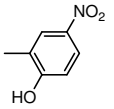
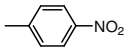
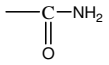
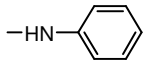
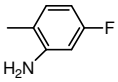
PK9		7	72.6
PK10		10	53.3
PK11		5	74.8
PK12		11	55.5
PK13		12	61.6
PK14		15	51.7

Physicochemical and spectroscopic determination of synthesized compounds

The melting points were taken in open capillary tube and were uncorrected. Reactions were monitored by thin layer chromatography using silica gel-GF_{254} as adsorbent on glass plate. The spots were applied on silica gel plate and the plate was run in (ethyl acetate: hexane (3:7)) in a closed chamber. The spots on the plate were detected in UV cabinet. The differences in R_f value between starting compound and product were indicative of the conversion of starting compound into the product.

IR spectra were recorded on FTIR-8400F model in KBr. NMR spectra were recorded on Broker A VANCE DPX 300 instrument using TMS as internal reference and chemical shift value are expressed in delta units. The mass spectra (ESI) were recorded on Waters @Micromass *Q*-Tof Micro. It showed fragmentation pattern as *m/z* values. All physical and spectral data are given in Table 2.

Table 2. Physical and spectroscopic data of synthesized compounds

Compd code	Physical and spectral data
PK1	Yield:72.6%; R_f: 0.63{ethyl acetate: hexane (3:7)}; M.P:120-125 °C; IR(KBr cm^{-1}) :1570(C=C),1682.11(C=N),3042.32(C-H),1244.86(C-N),2852.41(N=CH); NMR:^{1}H NMR (400MHz,$CDCl_3$) δ(ppm): 6.87-7.22(m,10H,ArH), 8.51 (s,1H; N=CH), 7.60 (s,1H,CH); (m+1)221.1
PK2	Yield:64.2%;R_f:0.82{ethyl acetate: hexane(3:7)}; M.P:160-165 °C;IR(KBr cm^{-1}) 1502.71(C=C), 1646.39(C=N), 3090.32(C-H), 1177.41(C-N), 2856.32 (N=CH), 3310.52(OH); NMR: ^{1}H NMR (400MHz,$CDCl_3$) δ(ppm):6.73-7.45(m,9H,ArH), 8.63(s,1H;N=CH), 7.84(s,1H,CH), 5.30(t,1H,ArOH);(m+1) 237.1
PK3	Yield:71.0%;R_f:0.73{ethyl acetate: hexane (3:7)};M.P: 170-175 °C; IR (KBr cm^{-1}) 1520.34(C=C),1676.34(C=N),3108.19(C-H),1243.06(C-N),2859.34(N=CH),1444.33 (CH_3)bend; NMR:^{1}H NMR(400MHz,$CDCl_3$) δ(ppm):7.28-7.41 (m,5H,ArH), 8.61 (s,1H;N=CH),7.68(s,1H,CH),2.4(s,2H,CH_2),1.7(m,5H,CH_2),1.4(m,6H,CH_2);(m+1)201.2
PK4	Yield:65..6%; R_f: 0.72 {ethyl acetate: hexane (3:7)}; M.P:115-120 °C; IR (KBr cm^{-1}) 1618.17(C=C), 1682.41(C=N), 2943.37, 2903(C-H), 1244.92(C-N), 2854.56(N=CH), 1072.34(C-O); NMR: ^{1}H NMR (400MHz, $CDCl_3$) δ: 6.81-7.29 (m,9H,ArH), 8.53 (s,1H;N=CH),7.71(s,1H,CH),3.61(s,3H,CH_3) ;(m+1) 251.1

Contd…

PK5	Yield:68.2%;R_f:0.62 {ethyl acetate: hexane(3:7)};M.P:140-145 °C; IR (KBr cm^{-1}) 1568.59(C=C), 1656.32(C=N), 3112.12(C-H), 1242.88(C-N),2857.55 (N=CH), 755.30(C-Cl); NMR:^{1}H NMR (400MHz, $CDCl_3$) δ:7.19-7.34(m,9H,ArH), 8.52 (s,1H;N=CH),7.60(s,1H,CH); (m+1) 255.1
PK6	Yield:64.5%;R_f: 0.79{ethyl acetate: hexane(3:7)};M.P:205-210 °C; IR (KBr cm^{-1}) 1575.20(C=C), 1665.67(C=N), 3077.79(C-H), 1329.45(C-N), 2856.61(N=CH), 3322.97(-OH)H bonded,1498.71(R-NO_2);NMR:^{1}H NMR(400MHz,$CDCl_3$)δ:7.71-8.13(m,9H,ArH, 8.49(s,1H;N=CH),7.32(s,1H,CH),6.23(d,1H;ArOH); (m+1) 282.3
PK7	Yield:62.3%;R_f:0.72{ethyl acetate:hexane(3:7)};M.P:180-185 °C; IR(KBr cm^{-1}) 1490.75(C=C), 1675.45(C=N), 3092.12(C-H), 1110.32(C-N), 2846.72(N=CH) 3220.67(-OH) H bonded; NMR:^{1}H NMR(400MHz,$CDCl_3$)δ:6.75-7.1(m,8H,ArH), 8.60(s,1H;N=CH),7.4(s,1H,CH),5.5(t,1H,ArOH); (m+1) 237.1
PK8	Yield:62.7%; R_f:0.80 {ethyl acetate:hexane (3:7)};M.P:155-160 °C; IR(KBr cm^{-1}) 1530.34(C=C),1647.31(C=N),3087.42(C-H) ,1010.11(C-N),2840.42 (N=CH); NMR: ^{1}H NMR(400MHz,$CDCl_3$) δ:6.52-7.01(m,9H,ArH), 8.55 (s,1H;N=CH), 7.12(s,1H,CH),4.41(s,1H,CH); (m+1) 236.3
PK9	Yield:72.6%;R_f:0.77{ethyl acetate:hexane (3:7)};M.P:145-150 °C; IR (KBr cm^{-1}) 1545.32(C=C), 1652.32(C=N), 3085.51(C-H), 1090.17(C-N), 2842.91(N=CH), 1552.31(R-NO_2); NMR:^{1}H NMR(400MHz,$CDCl_3$)δ:7.52-7.88(m,9H,ArH), 8.52 (s,1H;N=CH),7.41(s,1H,CH); (m+1) 266.2
PK10	Yield:53.3%; R^f: 0.65 {ethyl acetate: hexane (3:7)}; M.P:200-205 °C; IR (KBr cm^{-1}) 1551.43(C=C), 1672.13(C=N), 3073.62(C-H), 1213.12(C-N), 2850.11 (N=CH) 3321. 51(-OH) H bonded, 1473.91(R-NO_2); NMR :^{1}H NMR (400MHz,$CDCl_3$) δ:7.83-8.13 (m,8H,ArH), 8.51(s,1H;N=CH) ,7.32(s,1H,CH), 6.74(d,1H,ArOH) ; (m+1) 282.1
PK11	Yield:74.8%; R_f:0.70 {ethyl acetate: hexane(3:7)};M.P:130-135 °C; IR (KBr cm^{-1}) 1530.42(C=C), 1654.56(C=N), 3092.34(C-H), 1203.56(C-N), 2848.43(N=CH), 1555.10(R-NO_2); NMR:^{1}H NMR(400MHz,$CDCl_3$) δ:7.85-8.3(m,9H,ArH), 8.53 (s,1H;N=CH),7.6(s,1H,CH); (m+1) 266.1
PK12	Yield:55.5%;R_f:0.66 {ethyl acetate: hexane (3:7)};M.P:150-155 °C; IR (KBr cm^{-1}) 1562.16(C=C), 1664.31(C=N), 3175.34(C-H), 1092.42(C-N), 2845.31(N=CH) 1642.51(C=O); NMR:^{1}H NMR(400MHz,$CDCl_3$) δ:7.25-7.50(m,5H,ArH),8.50 (s,1H;N=CH),7.71(s,1H,CH),5.71,6.12(s,2H,NH_2); (m+1) 188.0
PK13	Yield:61.6 %;R_f:0.57 {ethyl acetate:hexane (3:7)};M.P:140-145 °C; IR(KBr cm^{-1}) 1547.23(C=C), 1649.13(C=N), 3082.43(C-H), 1101.38(C-N), 2852.44(N=CH) 3392.12(R_2-NH); NMR:^{1}H NMR(400MHz,$CDCl_3$) δ:6.70-7.17(m,8H,ArH), 8.69 (s,1H;N=CH),7.71(s,1H,CH),4.65(s,1H,ArNH); (m+1) 236.0
PK14	Yield:51.7%;R_f:0.74 {ethyl acetate: hexane(3:7)};M.P:210-215 °C; IR(KBr cm^{-1}) 1490.34(C=C), 1674.36(C=N), 3095.65(C-H), 1215.38(C-N), 2857.13(N=CH), 1321.42(C-F); NMR:^{1}H NMR(400MHz,CDCl3) δ:7.52-7.78(m,9H,ArH), 8.57 (s,1H; N=CH),7.21(s,1H,CH), 3.54(s,1H,ArNH); (m+1) 254.1

Antimicrobial activity

The antimicrobial activities of synthesized Schiff bases were evaluated against eleven different strains of microorganism (Five gram positive, Five gram negative bacteria and one fungus) using nutrient agar medium (Hi-Media Laboratories, India) and sabouraud dextrose agar medium (Hi-Media Laboratories, India) respectively. Zone of inhibition of compounds were determined by Cup plate method and minimum inhibitory concentration of the test compounds were determined by two fold serial dilution technique. Dimethyl sulfoxide (DMSO) was used as solvent for both techniques. Paper disc diffusion method for zone of

inhibition & minimum inhibitory concentrations of the synthesized compounds were determined by serial dilution method. Ciprofloxacin, ampicilin and fluconazole were used as reference standards for antibacterial and antifungal activity respectively.

The lowest concentration of the test compounds showing no visible microbial growth were considered as minimum inhibitory concentration. The observed zone of inhibition and MIC values for bacterial and fungal strains are given in Table 3 and 4 respectively.

Table 3. Antibacterial activity of the synthesized compounds

Compd. code	*In vitro* activity-zone of inhibition in mm, (MIC in µg/mL) for gram positive strains				
	S. aureus	*B. subtilis*	*B. cereus*	*P. fluorescence*	*S. epidermidis*
PK1	14(50)	19(25)	18(50)	16(25)	15(50)
PK2	15(50)	19(25)	14(100)	13(50)	12(100)
PK3	17(25)	14(50)	21(25)	14(50)	13(100)
PK4	18(25)	17(25)	17(50)	13(50)	16(25)
PK5	13(50)	24(6.25)	18(50)	12(50)	18(12.5)
PK6	12(50)	22(12.5)	15(100)	15(25)	16(25)
PK7	22(6.25)	23(6.25)	20(25)	14(50)	14(50)
PK8	12(50)	18(25)	13(100)	11(100)	14(50)
PK9	15(50)	14(50)	19(50)	14(50)	17(25)
PK10	20(12.5)	20(12.5)	20(25)	16(25)	10(>100)
PK11	15(25)	16(25)	18(50)	18(12.5)	12(100)
PK12	13(50)	13(50)	16(100)	12(50)	12(100)
PK13	19(12.5)	22(12.5)	15(100)	14(50)	16(25)
PK14	21(6.25)	18(25)	12(>100)	13(50)	15(50)
Ciprofl-oxacin	25(3.12)	26(3.12)	23(6.25)	21(6.25)	19(12.5)
Amoxi-cillin	33(3.12)	34(3.12)	25(6.25)	22(6.25)	20(12.5)
	In vitro activity-zone of inhibition in mm (MIC in µg/mL) For gram negative strains				
	E. coli	*P. aeruginosa*	*K. pneumonae*	*P. vulgaris*	*S. Typhimurium*
PK1	18(25)	19(25)	13(100)	14(100)	14(100)
PK2	16(50)	16(50)	21(25)	16(50)	18(50)
PK3	15(50)	21(25)	13(100)	11(>100)	10(>100)
PK4	18(25)	20(25)	19(50)	9(>100)	9(>100)
PK5	22(12.5)	17(50)	17(50)	12(100)	17(50)
PK6	19(25)	16(50)	12(100)	13(100)	11(>100)
PK7	21(12.5)	20(25)	17(50)	13(100)	14(100)
PK8	16(50)	13(100)	16(50)	16(50)	15(100)
PK9	15(50)	15(50)	10(>100)	17(50)	17(50)
PK10	16(50)	17(50)	9(>100)	15(50)	13(100)
PK11	12(100)	22(25)	15(50)	10(>100)	16(50)
PK12	14(50)	12(100)	20(25)	15(50)	18(50)
PK13	15(50)	15(50)	18(50)	13(100)	15(100)
PK14	15(100)	14(50)	14(100)	11(>100)	12(>100)
Ciprofl-oxacin	28(3.12)	32(3.12)	24(6.25)	20(12.5)	21(12.5)
Amoxi-cillin	3(3.12)	24(3.12)	25(6.25)	23(12.5)	20(12.5)

Table 4. Antifungal activity of the synthesized compounds

Comp. Code	Zone of inhibition in mm, (MIC in µg/mL) *C. albicans*
PK1	15(50)
PK2	18(25)
PK3	19(25)
PK4	16(50)
PK5	20(12.5)
PK6	13(100)
PK7	18(25)
PK8	17(25)
PK9	17(25)
PK10	15(50)
PK11	12(>100)
PK12	16(50)
PK13	13(100)
PK14	11(>100)
Fluconazole	21(12.5)

Results and Discussion

We have synthesized a series of Schiff bases of indole-3-aldehyde by microwave assisted synthesis. This protocol presented many advantages, such as good to excellent yields, much shorter reaction time (3-15 min) and simple purification procedure. The bioassay results revealed that most of the synthesized compounds exhibited good antimicrobial activity. Compound (*Z*)-3-((1*H*-indol-3-yl) methyleneamino)phenol and (*E*)-*N*1-((1*H*-indol-3-yl)methylene)-4-fluorobenzene-1,2-diamine showed highest antibacterial activity with MIC of 6.25 µg/mL against *S. aureus* and compound (*E*)-*N*-((1*H*-indol-3-yl)methylene)-4-chlorobenzenamine and (*Z*)-3-((1*H*-indol-3-yl)methyleneamino) phenol showed highest antibacterial activity with MIC of 6.25 µg/mL against *B. subtilis.* Compound (*E*)-*N*-((1*H*-indol-3-yl)methylene)-4-chlorobenzenamine was found to have highest antifungal activity with MIC of 12.5 µg/mL against *C. albicans.*

Conclusion

The structures of synthesized compounds were confirmed by IR and NMR spectroscopy. All compounds exhibited significant antibacterial activity but they showed moderate antifungal activity. Further bioassay, optimization and structure-activity relationship of the title compounds are underway.

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