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Synthesis and Antimicrobial Activity of Schiff Bases Derived from 2-Formylphenoxy Acetic Acid

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A series of seven Schiff bases were synthesized by reacting 2-formylphenoxy acetic acid with aromatic amines. The chemical structures of these compounds were confirmed by means of IR and ^{1}H NMR. The compounds were assayed by the disc diffusion method for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Among the compounds tested, **V_1, V_3, V_4** and **V_6**, exhibited good antibacterial activity, almost equal to that of ampicillin used as standard drug.

Key Words: 2-Formylphenoxy acetic acid, Schiff base, Antibacterial activity.

INTRODUCTION

It is evident that in Schiff base, the C=N linkage is an essential structural requirement for biological activity. Numerous Schiff bases have been reported to possess remarkable antibacterial[1-5], antifungal[6-8], anticancer and diuretic activities. Phenoxy acetic acid is among the most vital moieties which are associated with potent fungicidal activities. Aryloxyacetic acid derivatives possess a wide array of diverse bioactivities including antimycobacterial, antiinflammatory, antioxidant, antibacterial, analgesic, antisickling, antilipaemic and antiplatelet, non-prostanoid prostacyclin (PGI_2) mimetics, gastrin/cholecystokinin (CCK)-B receptor antagonistic activity, diuretic and growth regulators. This study is aimed to explore the potential antibacterial activity resulting from the combination of pharmacophores in one structure. The results of this study may be useful to gain more insight into the antibacterial activity of Schiff bases[6-12].

EXPERIMENTAL

2-Formylphenoxy acetic acid was prepared by reaction of salicylaldehyde with monochloro acetic acid along with slow addition of NaOH solution followed by continuous stirring. The final compound 2-formylphenoxy acetic acid was obtained in excellent yield (82-83 %) as a white crystalline solid. Aniline, *p*-toluidine, *p*-anisidine, *p*-aminophenol, *p*-chloro aniline, *p*-amino benzoic acid, 2,3-dimethyl aniline were obtained from central drug house limited. Solvents used were of analytical grade. ^{1}H NMR spectra were recorded on a Bruker DPX-300 instrument at

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300 MHz using DMSO as solvent. Chemical shifts are reported in ppm reference to the residual solvent signal. Purity of all the compounds was checked by TLC on precoated silica gel G plates. IR spectra were recorded on Shimadzu 8700 fourier transform infrared spectrophotometer using a thin film supported on KBr pellets.

2-(Phenylimino methyl)phenoxy acetic acid (V_1): 2-Formylphenoxy acetic acid (0.01 mol) was added to aniline (0.01 mol) in methanol (dehydrated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_1}$ was found to be 76 %. m.p. 132-133 ºC, IR (KBr, ν_{max}, cm^{-1}): 3510 (OH stretching), 2924, 2363 (azomethine C-H stretching), 1698 (C=O stretching), 1595 (C=N stretching), 1448 (azomethine C-H bending), 1114, 1057 (C-O stretching). ^{1}H NMR (DMSO) δ 8.95 (1H, s, N=C-H), δ 6.69-8.22 (8H, m, aromatic C-H), δ 4.76 (2H, s, CH_2), δ 10.49 (1H, s, COOH).

2-(4-Methyl phenylimino methyl)phenoxy acetic acid (V_2): 2-Formylphenoxy acetic acid (0.01 mol) was added to *p*-toluidine (0.01 mol) in methanol (dehydrated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_2}$ was found to be 90 %. m.p. 216 ºC, IR (KBr, ν_{max}, cm^{-1}): 3500 (OH stretching), 2918, 2352 (azomethine C-H stretching), 1667 (C=O stretching), 1598 (C=N stretching), 1442 (azomethine C-H bending), 1120, 1058 (C-O stretching). ^{1}H NMR (DMSO) δ 8.78 (1H, s, N=C-H), δ 7.1-8.35 (8H, m, Aromatic C-H), δ 4.66 (2H, s, CH_2), δ 10.30 (1H, s, COOH), 2.62 (3H, s, CH_3).

2-(4-Hydroxy phenylimino methyl)phenoxy acetic acid (V_3): 2-Formylphenoxy acetic acid (0.01 mol) was added to *p*-amino phenol (0.01 mol) in methanol (dehydrated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_3}$ was found to be 83 %. m.p. 236-237 ºC, IR (KBr, ν_{max}, cm^{-1}): 3500, 3399 (OH stretching), 2927, 2363 (azomethine C-H stretching), 1667 (C=O stretching), 1605 (C=N stretching), 1401 (azomethine C-H bending), 1168, 1038 (C-O stretching). ^{1}H NMR (DMSO) δ 8.91 (1H, s, N=C-H), δ 7.12-8.64 (8H, m, aromatic C-H), δ 4.83 (2H, s, CH_2), δ 10.45 (1H, s, COOH), 4.43 (1H, s, OH).

2-(4-Methoxy phenylimino methyl)phenoxy acetic acid (V_4): 2-Formylphenoxy acetic acid (0.01 mol) was added to *p*-anisidine (0.01 mol) in methanol (dehydrated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_4}$ was found to be 87 %. m.p. 135-136 ºC, IR (KBr, ν_{max}, cm^{-1}): 3498 (OH stretching), 2934, 2362 (azomethine C-H stretching), 2836 (CH_3 stretching), 1649 (C=O stretching), 1602 (C=N stretching), 1401 (azomethine C-H bending), 1185, 1033 (C-O stretching). ^{1}H NMR (DMSO) δ 8.95 (1H, s, N=C-H), δ 6.69-8.22 (8H, m, aromatic C-H), δ 4.76 (2H, s, CH_2), δ 10.93 (1H, s, COOH), δ 3.77 (3H, s, OCH_3).

2-(4-Chloro phenylimino methyl)phenoxy acetic acid (V_5): 2-Formylphenoxy acetic acid (0.01 mol) was added to *p*-chloro aniline (0.01 mol) in methanol (dehy-

drated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_5}$ was found to be 59 %. m.p. 86-87 ºC, IR (KBr, ν_{max}, cm^{-1}): 3515 (OH stretching), 2914, 2360 (azomethine C-H stretching), 1668 (C=O stretching), 1612 (C=N stretching), 1432 (azomethine C-H bending), 1107, 1075 (C-O stretching), 714, 678 (C-Cl stretching). ^{1}H NMR (DMSO) δ 8.86 (1H, s, N=C-H), δ 6.89-8.5 (8H, m, aromatic C-H), δ 4.63 (2H, s, CH_2), δ 10.11 (1H, s, COOH).

2-(4-Carboxy phenylimino methyl)phenoxy acetic acid ($\mathbf{V_6}$): 2-Formylphenoxy acetic acid (0.01 mol) was added to *p*-amino benzoic acid (0.01 mol) in methanol (dehydrated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_7}$ was found to be 83 %. m.p. 218-220 ºC, IR (KBr, ν_{max}, cm^{-1}): 3515, 3491 (OH stretching), 2923, 2363 (azomethine C-H stretching), 1695, 1693 (C=O stretching), 1599 (C=N stretching), 1381 (azomethine C-H bending), 1163, 1041 (C-O stretching). ^{1}H NMR (DMSO) δ 8.92 (1H, s, N=C-H), δ 7.1-8.68 (8H, m, aromatic C-H), δ 4.85 (2H, s, CH_2), δ 10.75 (1H, s, COOH).

2-(2,3-Dimethyl phenylimino methyl)phenoxy acetic acid ($\mathbf{V_7}$): 2-Formyl phenoxy acetic acid (0.01 mol) was added to 2,3-dimethyl aniline (0.01 mol) in methanol (dehydrated with molecular sieves) and stirred at room temperature with the help of magnetic stirrer. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_8}$ was found to be 53 %. m.p. 50-51 ºC, IR (KBr, ν_{max}, cm^{-1}): 3543 (OH stretching), 2960, 2362 (azomethine C-H stretching), 1658 (C=O stretching), 1608 (C=N stretching), 1498 (azomethine C-H bending), 1185, 1033 (C-O stretching). ^{1}H NMR (DMSO) δ 8.77 (1H, s, N=C-H), δ 7.03-8.45 (8H, m, aromatic C-H), δ 4.83 (2H, s, CH_2), δ 10.44 (1H, s, COOH), δ 2.25 (6H, s, CH_3).

2-(Phenylamino methyl)phenoxy acetic acid ($\mathbf{V_{1R}}$): 2-(Phenylimino methyl) phenoxy acetic acid (V_1) was reduced with sodium borohydride ($NaBH_4$, 0.01 mol) added in small portions with stirring at 80-90 ºC. Methanol (dehydrated with molecular sieves) was used as a solvent. After addition of complete sodium borohydride, it was refluxed for 0.5 h. Then the reaction mixture was acidified to pH 6 with dilute HCl to precipitate the product. After filtration, evaporation and recrystallization from EtOH, the yield of $\mathbf{V_{1R}}$ was found to be 80 %. m.p. 201-202 ºC, IR (KBr, ν_{max}, cm^{-1}): 3519 (OH stretching), 3457 (N-H stretching), 2885 (CH stretching in CH_2), 1694 (C=O stretching), 1540 (N-H bending), 1104, 1057 (C-O stretching), 1062 (C-N stretching). ^{1}H NMR (DMSO) δ 6.97 (1H, s, $NHCH_2$), δ 7.18-8.2 (8H, m, aromatic C-H), δ 4.67 (2H, s, CH_2), δ 3.49 (2H, s, $NHCH_2$), δ 10.85 (1H, s, COOH).

2-(4-Methyl phenylamino methyl)phenoxy acetic acid ($\mathbf{V_{2R}}$): 2-(4-Methyl phenylimino methyl phenoxy) acetic acid (0.01 mol) ($\mathbf{V_2}$) was reduced with sodium borohydride ($NaBH_4$, 0.01 mol) added in small portions with stirring at 80-90 ºC. Methanol (dehydrated with molecular sieves) was used as a solvent. After addition of complete sodium borohydride, it was refluxed for 0.5 h. Then the reaction mixture was acidified to pH 6 with dilute HCl to precipitate the product. After filtration,

evaporation and recrystallization from EtOH, the yield of **V_{2R}** was found to be 52 %. m.p. 120-121 ºC, IR (KBr, ν_{max}, cm^{-1}): 3550 (OH stretching), 3443 (N-H stretching), 2889 (CH stretching in CH_2), 1657 (C=O stretching), 1530 (N-H bending), 1118, 1043 (C-O stretching), 1068 (C-N stretching). ^{1}H NMR (DMSO) δ 6.81 (1H, s, $NHCH_2$), δ 6.9-8.12 (8H, m, aromatic C-H), δ 4.56 (2H, s, CH_2) δ 3.37 (2H, s, $NHCH_2$), δ 11.01 (1H, s, COOH).

2-(4-Hydroxy phenylamino methyl)phenoxy acetic acid (V_{3R}): 2-(4-Hydroxy phenylimino methyl phenoxy)acetic acid (0.01 mol) (**V_3**) was reduced with sodium borohydride (0.01mol) added in small portions with stirring at 80-90 ºC. Methanol (dehydrated with molecular sieves) was used as a solvent. After addition of complete after addition of complete sodium borohydride, it was refluxed for 0.5 h. Then the reaction mixture was acidified to pH 6 with dilute HCl to precipitate the product. After filtration, evaporation and recrystallization from EtOH, the yield of **V_{3R}** was found to be 74 %. m.p. 170-171 ºC, IR (KBr, ν_{max}, cm^{-1}): 3534 (OH stretching), 3424 (N-H stretching), 2880 (CH stretching in CH_2), 1668 (C=O stretching), 1567 (N-H bending), 1103, 1055 (C-O stretching), 1038 (C-N stretching). ^{1}H NMR (DMSO) δ 6.91 (1H, s, $NHCH_2$), δ 7.08-7.89 (8H, m, aromatic C-H), δ 4.76 (2H, s, CH_2), δ 3.44 (2H, s, $NHCH_2$), δ 10.44 (1H, s, COOH), δ 4.35 (1H, s, OH).

2-(4-Methoxy phenylamino methyl)phenoxy acetic acid (V_{4R}): 2-(4-Methoxy phenylimino methyl phenoxy)acetic acid (0.01 mol) (**V_4**) was reduced with sodium borohydride (0.01 mol) added in small portions with stirring at 80-90 ºC. Methanol (dehydrated with molecular sieves) was used as a solvent. After addition of complete after addition of complete sodium borohydride, it was refluxed for 0.5 h. Then the reaction mixture was acidified to pH 6 with dilute HCl to precipitate the product. After filtration, evaporation and recrystallization from EtOH, the yield of **V_{4R}** was found to be 86 %. m.p. 110-111 ºC, IR (KBr, ν_{max}, cm^{-1}): 3497 (OH stretching), 3407 (N-H stretching), 2890 (CH stretching in CH_2), 2844 (CH stretching in CH_3), 1697 (C=O stretching), 1560 (N-H bending), 1115, 1051 (C-O stretching), 1057 (C-N stretching). ^{1}H NMR (DMSO) δ 7.08 (1H, s, $NHCH_2$), δ 6.89-8.95 (8H, m, aromatic C-H), δ 4.76 (2H, s, CH_2), δ 3.61 (2H, s, $NHCH_2$), δ 10.44 (1H, s, COOH), δ 4.24 (1H, s, OCH_3).

2-(4-Chloro phenylamino methyl)phenoxy acetic acid (V_{5R}): 2-(4-Chloro phenylimino methyl phenoxy)acetic acid (0.01 mol) (**V_5**) was reduced with sodium borohydride (0.01 mol) added in small portions with stirring at 80-90 ºC. Methanol (dehydrated with molecular sieves) was used as a solvent. After addition of complete after addition of complete sodium borohydride, it was refluxed for 0.5 h. Then the reaction mixture was acidified to pH 6 with dilute HCl to precipitate the product. After filtration, evaporation and recrystallization from EtOH, the yield of **V_{5R}** was found to be 86 %. m.p. 110-111 ºC, IR (KBr, ν_{max}, cm^{-1}): 3505 (OH stretching), 3438 (N-H stretching), 2885 (CH stretching in CH_2), 1680 (C=O stretching), 1578 (N-H bending), 1118, 1049 (C-O stretching), 1061 (C-N stretching). ^{1}H NMR (DMSO) δ 7.21 (1H, s, $NHCH_2$), δ 6.95-8.32 (8H, m, aromatic C-H), δ 4.63 (2H, s, CH_2). δ 3.79 (2H, s, $NHCH_2$), δ 10.86 (1H, s, COOH).

Antibacterial activity: The newly synthesized compounds were screened for their antibacterial activity against locally isolated *Escherichia coli* (AMJ-2006) and *Staphylococcus aureus* (AMJ-2005) bacterial strains by the disc diffusion method. Overnight incubated cultures of these bacteria were introduced onto the surface of sterile agar plates. The discs measuring 6.25 mm in diameter were prepared from Whatman No. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a 100 µg/mL of the test compound dissolved in DMSO were placed on the inoculated nutrient agar medium. After incubation the plates were inoculated at 37 ºC for 48 h. Ampicillin was used as standard drug. Zone of inhibition were measured and compared with control. The zone of inhibition values are summarized in Table-1. Minimum inhibitory concentrations (MIC) were determined by the broth dilution technique The Nutrient Broth, which contained logarithmic serially two fold, diluted amount of test compound and controls, were inoculated with bacterial strains. The cultures were incubated for 24 h at 37 °C and the growth was monitored visually and spectrophotometrically.

TABLE-1
ANTIMICROBIAL ACTIVATES OF COMPOUNDS $\mathbf{V_1}$-$\mathbf{V_7}$

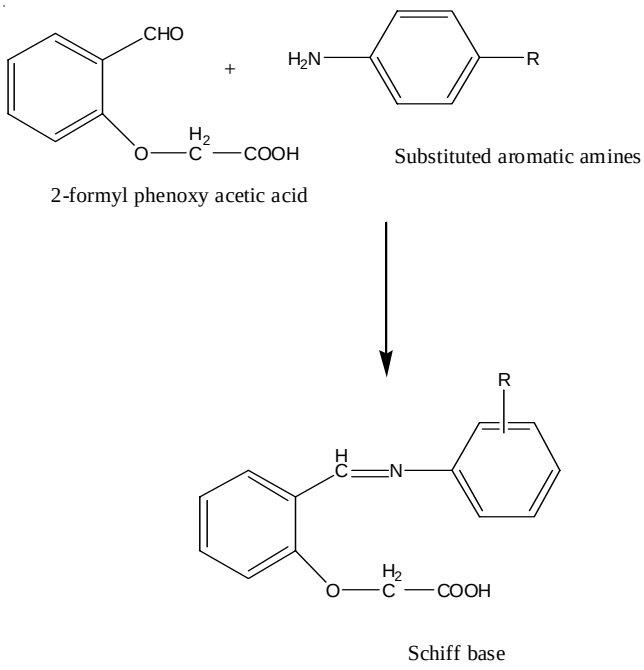
Compd.	Zone of inhibition (mm)			
	S. aureus (AMJ-2005)		*E. coli* (AMJ-2006)	
	50 µg	100 µg	50 µg	100 µg
$\mathbf{V_1}$	16	23	17	21
$\mathbf{V_2}$	13	16	12	17
$\mathbf{V_3}$	17	20	20	22
$\mathbf{V_4}$	19	20	21	22
$\mathbf{V_5}$	18	19	17	2
$\mathbf{V_6}$	12	22	14	16
$\mathbf{V_7}$	18	20	17	20
Ampicillin	23	25	22	25

RESULTS AND DISCUSSION

The Schiff bases were synthesized by reacting substituted aromatic amines with 2-formyl phenoxy acetic acid in methanol (used as a solvent) with addition of molecular sieves (as a dehydrating agent). Most of the compounds were synthesized by stirring at room temperature for *ca.* 3-5 h in order to maximum conversion of reactant into product. The progress of reaction was ascertained by TLC.

The structures of the title compounds were determined by IR, ^{1}H NMR and analytical data were in accord with the proposed structures. **Scheme-I** compounds $\mathbf{V_1}$-$\mathbf{V_7}$ showed, in the IR spectra an absorption band at 1620-1595 cm^{-1}, typical of the stretching vibrations of the C=N double bond, two more absorption bands in the 3580-3399 and 1710-1695 cm^{-1} range were also observed, due to -OH and C=O groups of the carboxylic acid substituent in each compound, respectively. ^{1}H NMR

spectra of $\mathbf{V_1}$-$\mathbf{V_7}$ contained multiplet signals due to aromatic protons in the δ 6.69-8.64 ppm regions and singlets at δ 8.77-8.95 ppm from the C-H protons of the CH=N groups.



Scheme-I: Synthesis of Schiff bases

REFERENCES

1. S.V. More, D.V. Dongarkhadekar, R.N. Chavan, W.N. Jadhav, S.R. Bhusare and R.P. Pawar, *J. Indian Chem. Soc.*, **79**, 768 (2002).
2. A.K. Bhendkar, K. Vijay and A.W. Raut, *Acta Cien. Indica*, **30C**, 29 (2004).
3. Y.K. Vaghasiya, R.S. Nair, M. Baluja and S.S. Chanda, *J. Serb. Chem. Soc.*, **69**, 991 (2004).
4. K. Vashi and H.B. Naik, *Eur. J. Chem.*, **1**, 272 (2004).
5. J. Rhodes, H. Chen, S.R. Hall, J.E. Beesley, D.C. Jenkins, P. Collins and B. Zheng, *Nature*, **377**, 71 (1995).
6. H.M. Safwat, F.A. Ragab, N.M. Eid and G.M. Abdel, *Egypt. J. Pharm. Sci.*, **29**, 99 (1988).
7. R. Mtrei, M. Yadawe and S. Patil, *Orient. J. Chem.*, **12**, 101 (1996).
8. M.E. Hossain, M.N. Allam, J. Begum, M.A. Akbar, M.N. Uddin, F.E. Smith and R.C. Hynes, *Inorg. Chim. Acta*, **249**, 207 (1996).
9. K.P. Sharma, V.S. Jolly and P. Pathak, *Ultra Scient Phys. Sci.*, **10**, 263 (1998).
10. V.E. Kuzmin, A.G. Artemenko, R.N. Lozytska, A.S. Fedtchouk, V.P. Lozitsky, E.N. Muratov, A.K. Mescheriakov, *QSAR Environ. Res.*, **16**, 219 (2005).
11. M.S. Shingare and D.B. Ingle, *J. Indian Chem. Soc.*, **53**, 1036 (1976).
12. D.R. Shkawat, S.S. Sabnis and C.V. Deliwala, *Bull. Haffkine Inst.*, **1**, 35 (1973).

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