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ANTIFUNGAL ACTIVITY OF SOME NEWLY SYNTHESIZED SCHIFF BASES

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ABSTRACT

A series of 4-{[(4-substitutedphenyl)imino]methyl}-2-methoxyphenyl acetate have been synthesized by the condensation of 4-formyl-2-methoxyphenylacetate with substituted amines in ethanol. The synthesized compounds were identified by spectral studies and screened for their antifungal activities.

KEYWORDS: Schiff base; aromatic aldehyde; antifungal activity.

INTRODUCTION

Schiff bases, named after Hugo Schiff[1], are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C═O) has been replaced by an imine or azomethine group.

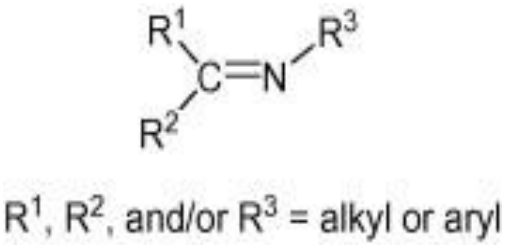


Fig.1 General structure of a Schiff base

Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis and as polymer stabilizers.[2] Schiff bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral and antipyretic properties.[2,3] Imine or azomethine groups are present in various natural, natural-derived and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities.[4-6]

The review of literature suggests that vanillin (4-hydroxy3-methoxybenzaldehyde) is very important flavoring materials worldwide. Synthetic vanillin is used in food and other applications, in fragrances and as a flavoring in pharmaceutical preparations. A new series of Schiff bases derived from 3-methoxy 4-hydroxy benzaldehyde and 4-formyl-2-methoxyphenylacetate were synthesized and screened for their fungicidal activity and it was found that the presence of methoxy and acetyloxy group in the compound enhances their fungicidal activity.[7] Schiff bases derived from various amine and carbonyl derivatives were reported to possess genotoxicity[8-9], antimicrobial[10] and antifungal activities.[11]

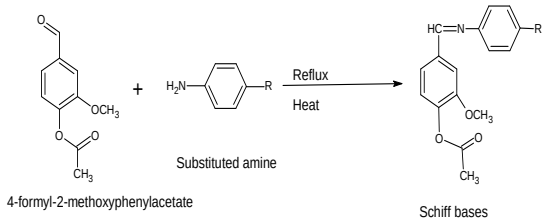
MATERIAL AND METHODS

2.1. Chemicals

All reagents and solvents were commercially available and used as supplied. All the chemicals used were of AR grade. The melting points of the compounds were determined in open capillaries on an electro thermal apparatus and are uncorrected. Analytical TLC was performed on silica gel plates; visualization was done by exposing to iodine vapor. Infrared spectra were measured using KBr pellets with Perkin Elmer BX series FT-IR spectrometer. ^{1}H-NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d^6as solvent and TMS as an internal standard (chemical shift in ppm). C, H, N, estimation was recorded on Carlo Erba 1108 (CHN) Elemental analyzer.

2.2. General procedure for the synthesis of Schiff bases (3a-f)

4-formyl-2-methoxyphenylacetate (0.005M) was dissolved in absolute ethanol and the contents were refluxed for 5 hrs. The reaction mixture was cooled in ice water and acidified with a drop of sulphuric acid. It was filtered under suction washed with ethanol and recrystallized from aqueous ethyl alcohol when yellow crystals of the Schiff bases was obtained.



R= Cl. CH_3, OCH_3, F, NO_2, H

Scheme-1: Syntheic scheme of newly synthesized Schiff bases

Table-1: Physical data of all the synthesized Schiff bases.

Sr.No.	Compounds	R	Molecular formula	Molecular weight	Melting point
1	3a	4Cl	$C_{16}H_{14}ClNO_3$	303	118
2	3b	$4CH_3$	$C_{17}H_{17}NO_3$	283	125
3	3c	$4OCH_3$	$C_{17}H_{17}NO_4$	299	128
4	3d	4F	$C_{16}H_{14}FNO_3$	287	111
5	3e	$4NO_2$	$C_{16}H_{14}N_2O5$	314	116
6	3f	H	$C_{16}H_{15}NO_3$	269	102

3. SPECTRAL ANALYSIS

4-{[(4-chlorophenyl)imino]methyl}-2-methoxyphenyl acetate (3a)

FT-IR (cm^{-1}): ν (O-H) 3000, ν (C-H aromatic) 3019, ν (C-H aliphatic) 2979, ν (C=N) 1623, ν (C=C phenyl) 1599, 1584, 1514, 1486 & 1463, ν (OCH3) 1434, ν (C-O) 1255, 1212 &1182 ν (C-Cl) 721. ^{1}H-NMR (DMSO): δ, ppm: 9.8 (s, 1H, -OH), 8.44 (s, 1H, -CH=N-), 7.33 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.13 (d, 1H, Ar-H), 6.91 (t, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 3.84 (s, 3H, -OCH3).

2-methoxy-4-{[(4-methylphenyl)imino]methyl}phenyl acetate (3b)

FT-IR (cm^{-1}): ν (O-H) 3261, ν (C-H aromatic) 3029, ν (C-H aliphatic) 2920, ν (C=N) 1616, ν (OCH3) 1456, ν (C=C phenyl) 1595, 1575, 1509, ν (C-O) 1255. ^{1}H-NMR (DMSO): δ, ppm: 13.35 (s, 1H, -OH), 8.93 (s, 1H, -CH=N-), 7.33 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.13 (d, 1H, Ar-H), 6.91 (t, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 3.84 (s, 3H, -OCH3), 2.35 (s, 3H, -CH3).

2-methoxy-4-{[(4-methoxyphenyl)imino]methyl}phenyl acetate (3d)

FT-IR (cm^{-1}): ν (O-H) 3261, ν (C-H aromatic) 3029, ν (C-H aliphatic) 2920, ν (C=N) 1616, ν (OCH3) 1456, ν (C=C phenyl) 1595, 1575, 1509, ν (C-O) 1255. ^{1}H-NMR (DMSO): δ, ppm: 13.35 (s, 1H, -OH), 8.93 (s, 1H, -CH=N-), 7.33 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.13 (d, 1H, Ar-H), 6.91 (t, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 3.84 (s, 3H, -OCH3), 2.35 (s, 3H, -CH3).

4-{[(4-fluorophenyl)imino]methyl}-2-methoxyphenyl acetate (3f)

FT-IR (cm^{-1}); ν (C=N) 1588, ν (C=C) 1514, ν (C–H) 2964-2941, ν (C–O) 1283-1160. ^{1}H-NMR (DMSO, δ ppm): 3.85 (3H, s, OCH_3), 6.93 (1H, d, Ar-H); 7.28–7.18 (4H, m, Ar-H), 7.37 (1H, dd, Ar-H), 7.55 (H9, s, 1H, s, Ar-H), 8.46 (1H, s, HC=N), 9.86 (1H, s, OH).

2-methoxy-4-{[(4-nitrophenyl)imino]methyl}phenyl acetate (3h)

FT-IR (cm^{-1}): ν (O-H) 3323, ν (C-H aromatic) 3219, ν (C-H aliphatic) 1550, ν (C=N) 1628, ν (OCH3) 1456, ν (C=C phenyl) 1589, ν (C-O) 1367, ν (N=O) 1504. ^{1}H-NMR (DMSO): δ, ppm: 13.65 (s, 1H, -OH), 8.68 (s, 1H, -CH=N-), 7.52 (d, 2H, Ar-H), 7.36 (d, 2H, Ar-H), 7.06 (d, 1H, Ar-H), 6.93 (t, 1H, Ar-H), 3.98 (s, 3H, -OCH3).

2-methoxy-4-[(phenylimino)methyl]phenyl acetate (3j)

FT-IR (cm^{-1}): ν (O-H) 3212, ν (C-H aromatic) 3206, ν (C-H aliphatic) 3116, ν (C=N) 1614, ν (OCH3) 1456, ν (C=C phenyl) 1632, 1616, 1493, ν (C-O) 1249. ^{1}H-NMR (DMSO): δ, ppm: 13.35 (s, 1H, -OH), 8.93 (s, 1H, -CH=N-), 7.33 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.13 (d, 1H, Ar-H), 6.91 (t, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 3.84 (s, 3H, -OCH3), 2.35 (s, 3H, -CH3).

4. ANTIFUNGAL ACTIVITY

The present study comprised of screening the newly synthesized Schiff bases against fungal pathogens namely *C. albicans, C. tropicalis, A. flavus and A. niger*, in order to explore their antifungal efficacy. The antifungal sensitivity test has been assessed by using disc diffusion technique.[12] Clotrimazole was used as the standard drug.

In disc-diffusion assay, few colonies of organisms were inoculated in 2–5 mL Sabourauds broth and allow to grown for 2.5 h. The agar plates were dried and inoculated by spreading the fungal suspension evenly over it. The sterile paper discs (6 mm) impregnated with fixed dose viz., 800 µg/mL of compound were placed on the pre-inoculated surface. The disc-bearing plates were incubated at 37°C and examined at 72 h for zone of inhibition around the disc.

TABLE-2: *In-vitro* antifungal sensitivity of compounds (3a-f)

	FUNGAL PATHOGENS				
Sr. No.	**Compound no.**	***C.albicans***	***C.tropicalis***	***A.flavus***	***A.niger***
1	3a	22	18	16	14
2	3b	18	16	16	18
3	3c	20	18	16	14
4	3d	16	14	14	12
5	3e	18	14	16	14
6	3f	14	12	00	00
7	Clotrimazole	24	22	20	18

*Control DMF- No activity.

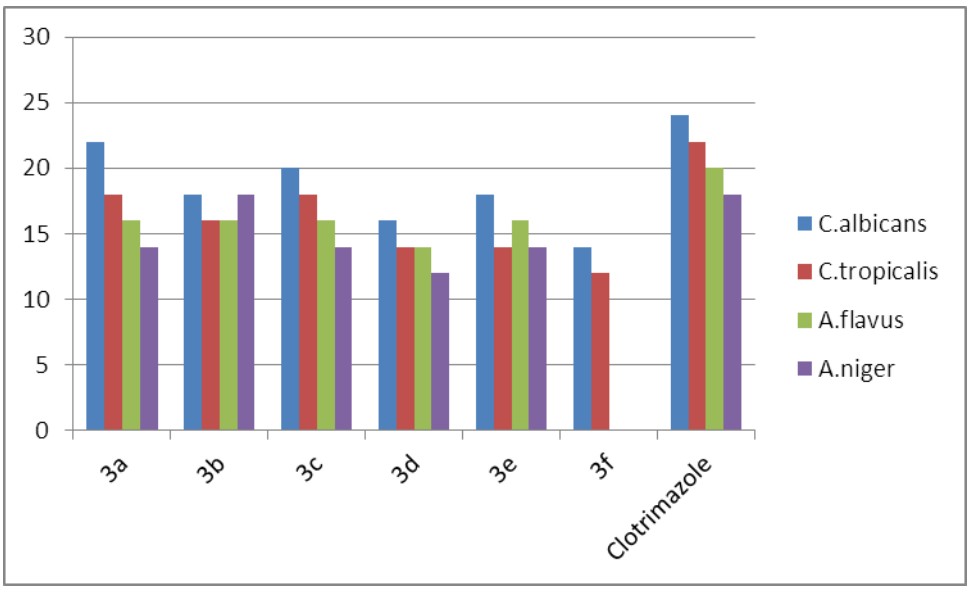


CHART-1 Activity profile of Schiff bases against 4 fungal pathogens @ 800µg/ml

5. RESULT AND DISCUSSION

4-formyl-2-methoxyphenylacetate was condensed with substituted anilines to yield new Schiff bases. The Schiff bases obtained were colored, soluble in dimethylformamide and they have been recrystallized by using ethanol; water (1:1) ratio mixture. The purity of azomethines was ascertained by thin layer & column chromatography using acetone; n-hexane (1:3) solvent mixture.

The synthesized compounds were screened for their *in vitro* antifungal activity by disc diffusion method *C. albicans, C. tropicalis, A. flavus and A. niger* fungal pathogens by preparing 800 µg/ml of test solution of each compound taking Clotrimazole as a standard drug. Zone of inhibitions in mm were noted. The zone of inhibition for Schiff bases varied from 0 to 20 mm. The results have been shown in Table-2, the activity of control (dimethylformamide) was also checked for its toxicity.

All the tested compounds exhibited promising antifungal activity comparable with standard drugs. The inhibition depends on the type of fungal strain, a solvent used as well as the structure of the compound. All the Schiff base compounds contain the same central moiety (-CH=N) with different side chains. So in a particular solvent, for a particular effect side chains play important role in inhibition.

6. CONCLUSION

All the compounds have shown mild to moderate antifungal activities. Among these Schiff bases having chloro and methoxy moieties have shown good activity in all the species. Two compounds (3a, 3c) were slightly more potent. It is observed that *C. albicans* show good to maximum inhibition nearly in all compounds while *C. tropicalis* show moderate inhibition antifungal activity. *A. flavus* and *A. niger* show less to good inhibition activity. All compounds show better activity in comparison to the reference drug.

7. ACKNOWLEDGEMENT

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