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SYNTHESIS, CHARACTERIZATION AND ANTIFUNGAL ACTIVITY OF SOME NEW SCHIFF BASE DERIVATIVES

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ABSTRACT

*A new series of Schiff base derivatives **(3a-0)** from Schiff base containing pyridine moiety are synthesized. The Schiff's bases on treatment with various aromatic aldehydes in ethanol in presence of a few drops of glacial acetic acid to afforded Schiff bases **(3a-o).** The structure of all synthesized compounds has been established on the basis of their spectral (IR, H^1&C^{13} NMR and Mass) and analytical data. The purity of the compounds was confirmed by TLC. All the synthesized compounds were evaluated for their antifungal activity against fungi. Some of the compounds exhibited moderate activity when compared with reference standard Miconazole.*

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INTRODUCTION

Schiff bases are usually formed by condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable[1-3] while those of aromatic aldehydes, having an effective conjugation system, are more stable[4-7].The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating. The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolysed back to their aldehydes or ketones and amines by aqueous acid or base. Schiff bases are appear to be important in a number of enzymatic reactions involving interaction of an enzyme[8] with an amino or a carbonyl group of the substrate. One of the most prevalent types of catalytic mechanisms in biochemical processes involves condensation of a primary amine in an enzyme, usually that of a lysine residue, with a carbonyl group of a substrate[9] to form an imine, or Schiff base. The rapid development of these ligands resulted in an enhanced research activity in the field of coordination chemistry leading to very interesting conclusions. Many biologically important Schiff bases have been reported in the literature possessing, antibacterial[10-14], antifungal[15-17], antioxidant[18], anticonvulsant[19], anti HIV[20], anti-inflammatory[21] and anti tumor[22-23] activity.

EXPERIMENTAL:

The melting points were determined by open capillaries on an electric melting point apparatus and are uncorrected. The purity of the compound was confirmed by TLC sing silica gel precoated

plates (0.25mm,60 F254,MERCK) using ethylacetate and ethanol (2:3). The IR Spectra were recorded on Perkin Elmer BXF1, FTIR Spectrophotometer using KBr disc method H^1 and C^{13} Spectra were recorded on Bruker AMX,400MHz and using TMS as an internal standard. Chemical shifts are described as singlet (s), doublet (d), broad and multiplet (m), FAB Mass spectra were recorded on angilent 1100 ESI-MASS (Turbospray) spectrometer. Elemental analysis was carried out using Carlo Erba 1108 Elemental Analyser.

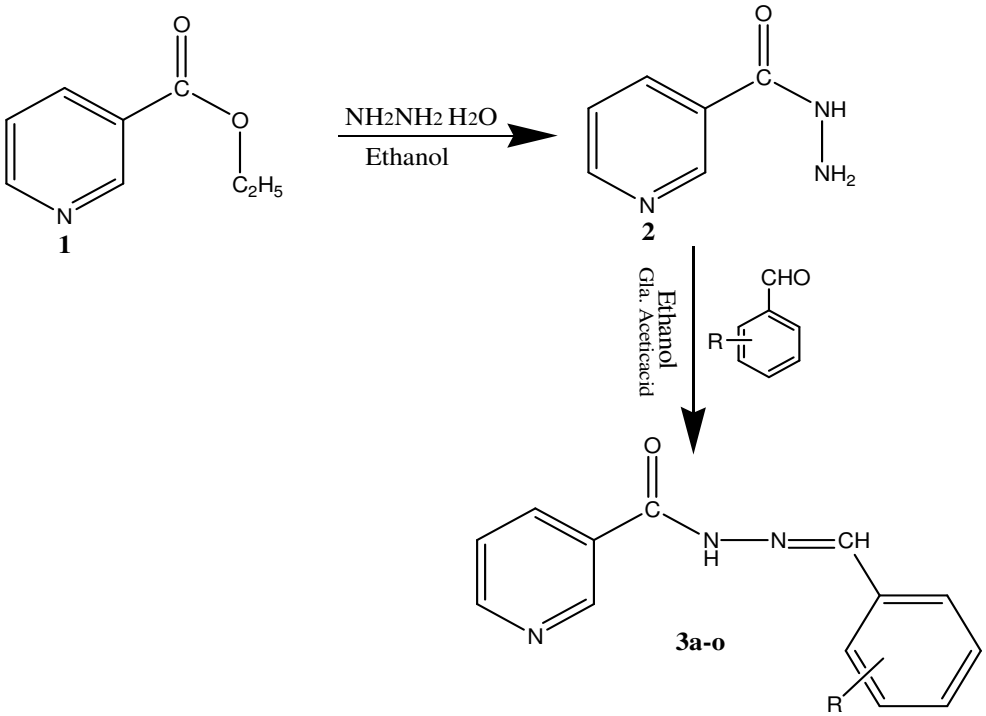
MATERIALS AND METHODS:

Synthesis of Nicotino hydrazide (2):

A mixture of 0.1M (15.1gm) of ethyl nicotinate and 0.2M (10gm) of hydrazine hydrate with 50% ethanol taken in round bottomed flask and then refluxed for 16hrs.Then the reaction mixture concentrated to half volume and poured it into the crushed ice. The reaction was identified by TLC using silica gel (100-200 #, Merck) and ethyl acetate: ethanol (2:3) as mobile phase. The white precipitate was separated and recrystallised from ethanol. It was confirmed by spectral data; IR (Cm^{-1}); N-H, C=O and C=N observed at 3325, 1661 and 1587 respectively, H^1NMR (δ ppm); N-H singlet proton at 9.58, NH_2 singlet, two protons at 4.581and the pyridine hydrogens observed in between 7.42 – 8.98.

SYNTHESES OF COMPOUNDS (3a-o):

Synthesised compound 2 (1.47gm, 0.001M) and substituted benzaldehydes (0.001M) were dissolved in absolute ethanol (40ml) by the addition of a few drops of glacial acetic acid and refluxed for 6hrs. The reaction was identified by TLC using silica gel (100-200 #, Merck) and ethyl acetate: ethanol (2:3) as mobile phase. Then the reaction mixture poured into a ice cold water.



Scheme

3a: N^1- (4^1 - fluoro benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 180-182^{0}C; **yield (%):** 98.5; **Rf:** 0.71; **Molecular formula:** $C_{13}H_{10}N_3OF$; **Molecular weight:** 243; **IR (cm^{-1}):** 3462 (N-H, str.), 1566 (N-H;def), 1658 (C=O, str.), 1595 (C=N, str.),1413 (C-N, str.), 3180 (= C-H, str.), 1152 (C-F, str.); **H^1 NMR (δ ppm):** 12.04 (1H, s, N-H),9.09(1H,s,=C-H),7.2-8.96 (8H, m, aromatic protons); **C^{13}NMR(δppm)**:161.98 (C=O),Pyridine(152.22-C_2,130-C_3,137-C_4,149-

C_5)149(=C-H),Benzene(135,123,123,115,115 ,164); **Mass (m/z):** 242 (M-H); **Elemental analysis:** calcd.(found):**C:** 64.19(64.22) **H:** 4.11 (4.09) **N:** 17.28 (17.30).

3b: N^1- (4^1 - bromo benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 190-192^{0}C; **yield (%):** 98.2; **Rf**: 0.53; **Molecular formula:** $C_{13}H_{10}N_3OBr$; **Molecular weight:** 304; **IR (cm^{-1}):** 3378.92 (N-H, str.),1553(N-H;def),3175.44(=C-H, str.),1646.56 (C=O str.), 1589.35 (C=N, str.),667 (C-Br, str.); **H^1 NMR (δ ppm):** 12.08 (1H, s, N-H),9.07(1H,s,=C-H),7.5-8.7(8H,m ,aromatic protons); **Elemental analysis:** calcd.(found): **C:** 51.31(51.33) **H:** 3.28 (3.25) **N:**13.81 (13.83).

3c: N^1- (4^1 - methyl benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 90-92^{0}C; **yield (%):** 97.7 ; **Rf**: 0.65; **Molecular formula:** $C_{14}H_{13}N_3O$; **Molecular weight:**239; **IR (cm^{-1}):** 3377 (N-H, str.),1566 (N-H;def), 3184.5(=C-H, str.),1671 (C=O str.), 1566 (C=N, str.),3020 (C-H, str.); **H^1 NMR (δ ppm):** 11.95 (1H, s, N-H),9.08(1H,s,=C-H),7.23-8.77(8H,m ,aromatic protons),2.31-2.51(3H,s,-CH_3); **Elemental analysis:** calcd.(found): **C:** 70.29 (70.18) **H:** 5.44 (5.56) **N:** 17.57(17.68).

3d: N^1- (4^1 - hydroxy benzilidine) - pyridin-3-yl – carbohydrazide

m.p:230-232 ^{0}C; **yield (%):** 92.5; **Rf**: 0.81; **Molecular formula:** $C_{13}H_{11}N_3O_2$; **Molecular weight:**241; **IR (cm^{-1}):** 3389 (N-H, str.), 1512 (N-H;def), 3073 (=C-H, str.),1657 (C=O str.), 1601(C=N, str.), 1288 (C-O, str.),3073(Ar-OH,str.); **H^1 NMR (δ ppm):** 11.81 (1H, s, N-H), 9.06 (1H,s,= C-H),9.95(1H,s,Ar-OH),6.79-8.76(8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:** 64.73(64.75) **H:**4.56(4.60) **N:** 17.43(17.25).

3e: N^1- (2^1 - hydroxy benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 172-174^{0}C; **yield (%):**87.9 ; **Rf**: 0.45; **Molecular formula:** $C_{13}H_{11}N_3O_2$; **Molecular weight:**241; **IR (cm^{-1}):** 3485(N-H, str.), 1483 (N-H;def), 3056 (=C-H, str.),1644 (C=O str.), 1565(C=N, str.), 1298 (C-O, str.); **H^1 NMR (δ ppm):** 12.24 (1H, s, N-H), 9.10 (1H,s,= C-H),11.15 (1H,s,Ar-OH),6.92-8.79 (8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:**64.73 (64.80) **H:**4.56(4.58) **N:** 17.43(17.26).

3f: N^1- (4^1 - nitro benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 250-252^{0}C; **yield (%):**68.0 ; **Rf**: 0.78; **Molecular formula:** $C_{13}H_{10}N_4O_3$; **Molecular weight:**270; **IR (cm^{-1}):** 3413(N-H, str.), 1513 (N-H;def), 3184 (=C-H, str.),1661(C=O str.), 1572(C=N, str.),1418(Anti N=O),1340(Syn N=O) ;**H^1 NMR (δ ppm):** 12.31 (1H, s, N-H), 9.10 (1H,s,= C-H),7.58-8.79(8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:**57.78 (58.12) **H:**3.70(3.86) **N:** 20.74(21.20).

3g: N^1- (5^1 - nitro - 2^1- hydroxy benzilidine) pyridin-3-yl – carbohydrazide

m.p: 260-262^{0}C; **yield (%):** 98.5 ; **Rf**: 0.55; **Molecular formula:** $C_{13}H_{10}N_4O_4$; **Molecular weight:**286; **IR (cm^{-1}):** 3303(N-H, str.), 1482 (N-H;def), 3075 (=C-H, str.),1602 (C=O str.), 1552 (C=N, str.), 1482(Anti N=O),1336(Syn N=O) ; **H^1 NMR (δ ppm):** 12.40 (1H, s, N-H), 9.12 (1H,s,OH),7.13-8.76 (7H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:** 54.54 (54.56) **H:** 3.50(3.55) **N:** 19.58(19.68).

3h: N^1- (4^1 - N,N- dimethyl amino benzilidine) - pyridin-3-yl – carbohydrazide

m.p:140-144 ^{0}C; **yield (%):**94.0 ; **Rf**: 0.67; **Molecular formula:** $C_{15}H_{16}N_4O$; **Molecular weight:**268; **IR (cm^{-1}):** 3439(N-H, str.),3188 (=C-H, str.),1601 (C=O str.),1523 (C=N, str.), 1365(C-N str.) ; **H^1 NMR (δ ppm):** 11.72 (1H, s, N-H), 9.06 (1H,s,= C-H),2.51-3.35 (6H,s, (-CH_3)$_2$),6.75-8.75 (8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:**67.16(67.19) **H:** 5.97(5.99) **N:**20.89(20.93).

3i: N^1- (4^1 - chloro benzilidine) - pyridin- 3-yl - carbohydrazide

m.p: 230-232^{0}C; **yield (%):**89.5 ; **Rf**: 0.38; **Molecular formula:** $C_{13}H_{10}N_3OCl$; **Molecular weight:**259; **IR (cm^{-1}):** 3431(N-H, str.), 1547 (N-H;def), 3256 (=C-H, str.),1660 (C=O str.), 1592 (C=N, str.),821 (C-Cl, str.) ; **H^1 NMR (δ ppm):** 12.08 (1H, s, N-H),9.08 (1H,s,= C-H),7.53-8.78 (8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:** 60.23 (60.26) **H:** 3.86(3.96) **N:** 16.21(16.29).

3j: N^1- (3^1 - bromo benzilidine) – pyridin-3-yl – carbohydrazide

m.p:100-102 ^{0}C; **yield (%):**88 ; **Rf**: 0.53; **Molecular formula:** $C_{13}H_{10}N_3OBr$; **Molecular weight:**304; **IR (cm^{-1}):** 3493(N-H, str.),1566(N-H; def),3152 (=C-H, str.),1668 (C=O str.), 1599 (C=N, str.),683(C-Br) ; **H^1 NMR (δ ppm):** 12.15 (1H, s, N-H), 9.08 (1H,s,= C-H), 7.42-8.77 (8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:** 51.31(51.42) **H:** 3.28(3.32) **N:**13.81(13.78).

3k: N^1- (2^1 - chloro benzilidine) - pyridin-3-yl – carbohydrazide

m.p:150-152 ^{0}C; **yield (%):** 99.3 ; **Rf**: 0.48; **Molecular formula:** $C_{13}H_{10}N_3OCl$; **Molecular weight:**259; **IR (cm^{-1}):** 3568(N-H, str.), 1555 (N-H; def),3178 (=C-H, str.),1674 (C=O str.), 1595 (C=N, str.), 763(C-Cl str.) ; **H^1 NMR (δ ppm):** 11.72 (1H, s, N-H), 9.06 (1H,s,= C-H),2.51-3.35 (6H,s, $(-CH_3)_2$),6.75-8.75 (8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:**60.23(60.34) **H:** 3.86(3.90) **N:**16.21(16.14).

3l: N^1- (2^1 - methoxy benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 130-132^{0}C; **yield (%):** 64 ; **Rf**: 0.28; **Molecular formula:** $C_{14}H_{13}N_3O_2$; **Molecular weight:**255; **IR (cm^{-1}):** 3386(N-H, str.), 1472(N-H; def),2940 (=C-H, str.),1653 (C=O str.), 1540 (C=N, str.), 1199(C-O-C str.) ; **H^1 NMR (δ ppm):** 12.23 (1H, s, N-H), 9.10 (1H,s,= C-H),7.42-8.78 (8H,m,aromatic protons),3.32(3H,s,O-CH_3); **Elemental analysis:** calcd.(found): **C:** 55.87(55.81) **H:** 5.09(5.07) **N:**16.7(16.4).

3m: N^1- (2^1 - 2^1,4^1 - dimethoxy benzilidine) - pyridin-3-yl - carbohydrazide

m.p: 152-154^{0}C; **yield (%):**78 ; **Rf**: 0.67; **Molecular formula:** $C_{15}H_{15}N_3O_3$; **Molecular weight:**285; **IR (cm^{-1}):** 3336(N-H, str.),3052 (=C-H, str.),1682 (C=O str.),1568 (C=N, str.), 1223(C-O-C, str.) ; **H^1 NMR (δ ppm):** 12.04 (1H, s, N-H), 9.10 (1H,s,= C-H),7.27-8.96 (7H,m,aromatic protons),3.4(3H,s,o-OCH_3),2.51(3H,s,p-CH_3); **Elemental analysis:** calcd.(found): **C:** 63.01 (63.04) **H:**5.21 (5.28) **N:** 14.7(14.1).

3n: (3^1 ,4^1 ,5^1 - trimethoxy benzilidine) - pyridin-3-yl – carbohydrazide

m.p:150-152 ^{0}C; **yield (%):** 62 ; **Rf**: 0.68; **Molecular formula:** $C_{16}H_{17}N_3O_4$; **Molecular weight:** 315; **IR (cm^{-1}):** 3342(N-H, str.),3116 (=C-H, str.),1642 (C=O str.),1463 (C=N, str.), 1292(C-O-C, str.) ; **H^1 NMR (δ ppm):** 8.80 (1H, s, N-H), 8.10 (1H,s,= C-H),7.27-8.96 (6H,m,aromatic protons),3.2-4.8(9H,s,-OCH_3); **Elemental analysis:** calcd.(found):**C:** 60.09 (60.04) **H:** 5.39 (5.28) **N:** 13.31(13.28).

3o: N^1- (2^1 - nitro benzilidine) - pyridin-3-yl – carbohydrazide

m.p: 150-160^{0}C; **yield (%):**78 ; **Rf**: 0.64; **Molecular formula:** $C_{13}H_{10}N_4O_3$; **Molecular weight:**270; **IR (cm^{-1}):** 3386(N-H, str.),1540(N-H; def),3209 (=C-H, str.),1653 (C=O str.),1596 (C=N, str.),1470(Anti,N=O),1304(Syn N=O); **H^1 NMR (δ ppm):** 12.40 (1H, s, N-H), 9.12(1H,s,= C-H),7.13-8.76 (8H,m,aromatic protons); **Elemental analysis:** calcd.(found): **C:** 57.77(57.64) **H:**3.70(3.82) **N:** 20.74(20.68).

Antifungal activity:

All those compounds screened for their antifungal activity. The fungi employed for screening are Aspergillus niger and Candida albicans. Miconazole was employed as standard to compare the results. The test organisms were sub-cultured using potato-dextrose-agar (PDA) medium. The tubes containing sterilized medium were inoculated with test fungi and kept at room temperature for obtaining growth. After that they were stored at 4^0c in refrigerator.Each test compound (5mg) was dissolved in dimethyl sulfoxide (5 mL,AR grade) at a concentration of 1000 µg/ml. Miconazole solution was also prepared at a concentration of 1000 µg/ml in sterilized distilled water. The pH of all the test solutions and control was maintained at 2 to 3 by using conc.Hcl, All the compounds were tested at a concentration of 0.05 mL (50µg) and 0.1 mL (100µg/ml) level and DMSO used as a control.The solutions of each test compound, control and reference standards (0.05 and 0.1mL) were added separately in the cups and the plates were kept undisturbed for at least 2 hours in refrigerator to allow diffusion of the solution properly into potato dextrose agar medium. Petri dishes were subsequently kept at room temperature for 48 hrs.

After that, the diameter of zone of inhibition in mm surrounding each of the cups was measured with the help of an antibiotic zone reader. All the experiments were carried out in triplicate. The results are presented in **Table.**

RESULTS AND DISCUSSION:

The cup plate method employed for antifungal activity of schif bases against A. Niger, C. Albicans and Miconazole employed as a reference standard to compare the results. The results of antifungal activity were presented in **Table.**From the obtained results. it was found that all the fifteen schiff base derivatives **(3a-o)** showed significant activity, when compared with standard drug.Chloro and nitro Schiff base derivatives showed significant acitivity compared with other derivatives. Hydroxy and dimethoxy derivatives showed moderate activity where as nitro and bromo derivatives have no significant activity.

Table: Antifungal activity of 3a-o derivatives

S.NO	Compound code	Aspergillus Niger		Candida Albicans	
		50 µg/ml	100 µg/ml	50 µg/ml	100µg/ml
1.	3a	10	18	12	19
2.	3b	09	12	08	10
3.	3c	12	18	12	14
4.	3d	10	12	11	15
5.	3e	06	08	07	09
6.	3f	08	11	06	09
7.	3g	14	19	12	16
8.	3h	04	07	08	10
9.	3i	11	15	10	14
10.	3j	09	11	11	14
11.	3k	16	19	15	20
12.	3l	04	06	10	12
13.	3m	10	14	11	15
14.	3n	08	11	09	11
15.	3o	06	08	08	11
Standard	Miconazole	30	-	27	-
Control	DMSO	-	-	-	-

CONCLUSION:

The synthesized new compounds are characterized by spectral data and screened for antifungal activity.Among the synthesized compounds 3k, 3g, 3i, 3j which are having electron donating group on aryl ring exhibiting significant activity with cup plate method.the series of derivatives have given a key to do more modifications in pharmacophore replacements.

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