Research Article

Synthesis, Characterization and Antibacterial Activity of Some New Schiff Base Derivatives from Nicotino Hydrazide

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ABSTRACT

A new series of Schiff base derivatives (3a-0) from Nicotino hydrazide containing pyridine moiety are synthesized. Nicotino structure hydrazide on treatment with various aromatic aldehydes in ethanol and in presence of a few drops of glacial acetic acid to afford Schiff base derivatives(3a-o).The 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 antibacterial activity exhibited moderate activity when compared with reference standard Ciprofloxacin.

Keywords: Nicotino hydrazide, Pyridine, Aldehyde, Schiff base, Antibacterial activity.

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 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 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(b) 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.

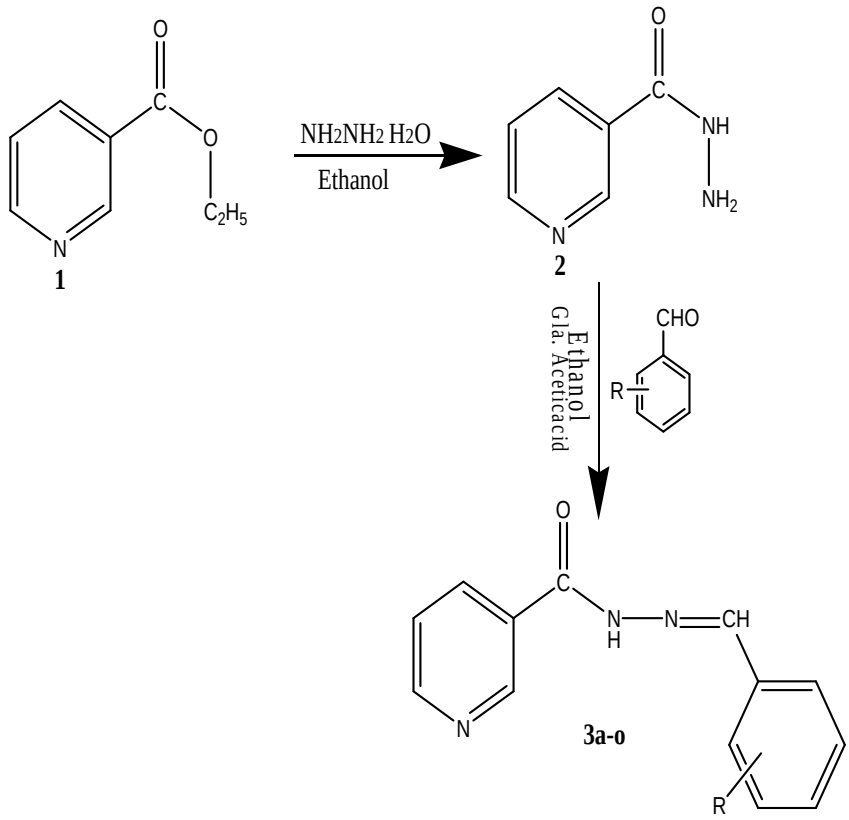
MATERIALS AND METHODS

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 recrystallized 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

Where **R=p- F (3a), R=p-Br(3b) , R=p-CH_3(3c), R= p-OH (3d), R= o-OH (3e), R= p-NO_2 (3f), R=o-OH & m-NO_2(3g), R=p-$N(CH_3)_2$ (3h), R=p-Cl(3i), R=m-Br(3j), R=o-Cl(3k) R=o-CH_3(3l) R=o,p-di OCH_3(3m) R= m,m,p-tri OCH_3(3n) R=o-NO_2 (3o)**

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- (2^1,4^1 - 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).

ANTIBACTERIAL ACTIVITY

The antibacterial activity of synthesized Schiff bases was conducted against two gram positive bacteria viz., Bacillus subtilis, Bacillus pumilis and two gram negative bacteria viz., Escherichia coli, Psuedomonas vulgaris by using cup plate method[24-26]. Ciprofloxacin was employed as reference standard to compare the results. Each test compound (5mg) was dissolved in dimethyl sulfoxide (5mL,AR) at a concentration of 1000µg/mL. Ciprofloxacin solutions were also prepared at a concentration of 1000µg/mL in sterilized distilled water. The pH of all the test solutions and control was maintained at 2 to 3 by using conc.HCl, because the compounds were not diffused through agar medium at pH below 2.All the compounds were tested at a pH concentration of 0.05 mL (50 µg) and 0.1 mL (100µg) level and DMSO used as a control. The solutions of each test compound, control and reference standards (0.05 and 0.1 mL) 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 nutrient agar medium. Petri dishes were subsequently incubated at 37^{0}C ± 1^{0}C for 24 hrs. After incubation, the diameter of zone of inhibition 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 were shown in Table 5.2.

Table 5.2: Antibacterial activity for Schiff base derivatives (3a-o)

S.NO	Compound Code	Gram +ve				Gram -ve			
		B. Subtilis		B. Pumilis		P. Vulgaris		E.Coli	
		50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
1.	3a	11	17	10	14	12	18	09	15
2.	3b	08	12	08	10	10	12	09	11
3.	3c	11	18	13	19	17	20	11	15
4.	3d	10	14	09	10	11	16	10	13
4.	3e	08	10	08	10	10	12	09	12
6.	3f	09	12	10	15	06	09	07	11
7.	3g	16	20	18	22	16	20	12	16
8.	3h	10	14	09	14	08	11	07	10
9.	3i	12	18	10	15	14	17	09	12
10.	3j	12	18	16	21	15	20	10	14
11.	3k	18	22	17	23	16	20	13	18
12.	3l	09	11	09	13	08	14	06	08
13.	3m	10	14	09	12	09	11	05	07
14.	3n	08	10	08	10	06	07	08	10
15.	3o	07	10	06	08	08	10	07	11
Std	Ciprofloxacin	28	-	32	-	30	-	24	-
Ctrl	DMSO	-	-	-	-	-	-	-	-

RESULTS AND DISCUSSION

All the **(3a-0)** derivatives have been evaluated for their antibacterial activity against B.Subtilis, B.Pimilis (gram^{+ve}) and P.Vulgaris, E.Coli (gram^{-ve}), using agar Cup plate method. The results were compared with Ciprofloxacin as standard. Compounds (3a-o) showed moderate to considerable activity, when compared with standard. Compounds 3k, 3i and 3j showed moderate activity on all bacterial strains which may be due to the presence of hydroxy, bromo and chloro groups at ortho and para positions of the aromatic ring. Whereas other derivatives showed considerable activity when compared with standard.

CONCLUSION

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

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