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SYNTHESIS, CHARACTERISATION AND ANTIBACTERIAL ACTIVITY OF BENZOHYDRAZONES DERIVED FROM 3-HYDROXY-5-HYDROXYMETHYL-2-METHYLPYRIDINE-4-CARBOXALDEHYDE

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ABSTRACT
New Schiff bases(**5a-j**) derived from 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde have been synthesized and characterized by various spectro-analytical techniques like IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy. The compounds were screened for their antibacterial activity against Gram negative bacteria (Escherichia coli and Pseudomonas aeruginosa and Gram positive bacteria (Staphylococcus aureus and Bacillus cereus). Compounds **5h** and **5j** showed excellent antibacterial activity while compounds **5c, 5e** and **5f** showed good activity. The remaining compounds (**5a,b,d,g,i**)exhibited moderate activity.

KEY WORDS: Pyridoxal, Hydrazones, Antibacterial activity, Synthesis**.**

INTRODUCTION
The studies on Schiff bases derived from 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde (pyridoxal) one of the forms of vitamin B6, has been the subject of great interest of many researchers [i, ii]. These compounds can serve as models for enzyme catalyzed reactions [i, iii]. In the presence of metal ions, free pyridoxal can catalyze a variety of metabolic reactions such as transmination, decarboxylation and racemization of amino acids, in which pyridoxal phosphate acts as a co-enzyme [i, iv]. The pharmacological studies [v] on Schiff bases of pyridoxal and aminoguanidine suggest that the Schiff base is more effective than aminoguanidine in treatment of diabetic complications.
Hydrazones are a class of organic compounds in the Schiff base family [vi]. The hydrazone Schiff bases of aroyl, acyl, and heteroaroyl compounds are known to have an additional donor site, C=O which make them more versatile and flexible [vii, viii]. The general method for the synthesis of the hydrazones is the reaction of hydrazine with carbonyl compounds such as aldehydes and ketones in alcoholic solvents [ix–xi]. Hydrazones are of wide interest due to their diverse biological activities such as antihelmentic, antiviral, analgesic, anticancer, antimalarial, antimicrobial, antidepressant and antidiabetic activities [xii - xx].

In view of the pharmacological importance of pyridoxal and hydrazone derivatives [xxi - xxvi] we report here in the synthesis, characterization and antibacterial activity of pyridoxal-benzohydrazone derivatives **5a-5j** prepared from 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde.

EXPERIMENTAL

Material and methods:

All the solvents and chemicals used were of Analytical reagent grade. TLC was run on silica gel GF-254 (Merck & Co) and visualisation was done using iodine vapour or UV lamp. Melting points were recorded on a Toshniwal hot stage apparatus in open capillary tubes. The IR spectra were recorded on Shimazdu Prestige-21 FT-IR spectrometer. The ^{1}H-NMR spectra was recorded on Varian MR 400 MHz spectrometer and ^{13}C-NMR spectra were recorded on Bruker WH-270 MHz spectrometer. The chemical shifts were reported in δ/ ppm relative to TMS. The mass spectra were recorded on Agilent Ion Trap mass spectrometer.

General Experimental procedure for synthesis of 2a-2j

To the stirred solution of benzoic acids **1a-1j** (6.42 mmol) in ethanol catalytic amount of Conc.H_2SO_4 was added and refluxed for 10 h. The reaction mixture was diluted with ethylacetate followed by water. The organic layer was washed with saturated $NaHCO_3$ followed by water and brine solution. The organic layer was dried over anhydrous Na_2SO_4. The organic solvent was distilled at 70° C under vaccum to obtain respective ethyl benzoates **2a-2j**.

To the stirred solution of ethyl benzoates **2a-2j** (3 mmol) in ethanol hydrazine-hydrate (5.44 mmol) was added and refluxed for 10 h. The reaction mixture was diluted with ethylacetate followed by water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was distilled at 70° C under vaccum to obtain respective benzohydrazides **3a-3j**. The yields of the products varied from 75 – 90%.

General experimental procedure for the preparation of novel Benzohydrazides derived from 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde 5(a-j):

To the stirred solution of pyridoxal HCl **4** (100 mg, 0.50 mmol) in ethanol was added triethylamine (0.50 mmol) followed by corresponding benzohydrazides (1.0 mmol) and refluxed for 5 h. The reaction was monitored by TLC. The reaction medium was poured into water and filtered to obtain the pure compounds. Yields of the products varied between 75 to 85%.

(E)-4-chloro-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide (5a):

Yellow solid; Yield: 75%; M. P: 150 ^{o}C; IR (KBr): υ_{max} 3418, 3151, 2838, 1641, 1599, 1562, 1494, 1445, 1401, 1278, 1157, 1096, 1045, 1016, 958, 918, 894, 855, 776, 752, 707, 654, 627 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.67 (s, 1H), 12.25 (s,1H), 8.96 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.96 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 5.42 (t, *J* = 5.2 Hz, 1H), 4.61 (d, *J* = 5.6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6- δ/ppm): δ 171, 161, 152, 145, 144, 143, 137, 130.8, 131.1, 129, 127, 116, 115, 57.8, 16.6. ESI-MS: m/z, 319.8 [M] $^{+}$.

(E)-4-bromo-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide (5b):

Yellow solid; Yield: 82%; M. P: 145 ^{o}C; IR (KBr): υ_{max} 3420, 3165, 2847, 1645, 1591, 1559, 1491, 1439, 1402, 1267, 1153, 1092, 1035, 1018, 951, 928, 892, 858, 769, 753, 708, 685, 656, 629 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.72 (s, 1H), 12.33 (s, 1H), 8.97 (s, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 6.4 Hz, 2H), 7.78 (d, *J* = 6.4 Hz, 2H), 5.44 (t, *J* = 5.2 Hz, 1H), 4.62 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 168, 163, 154.4, 145, 143.8, 142, 136, 130.5, 130, 129, 127, 115, 115, 57.8, 14.6. ESI-MS: m/z, 364.2 [M] $^{+}$.

(E)-4-hydroxy-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide (5c):

Yellow solid; Yield: 80%; M. P: 190 ^{o}C; IR (KBr): υ_{max}, 3336, 3055, 2910, 2808, 1662, 1602, 1577, 150, 1514, 1471, 1388, 1365, 1305, 1271, 1238, 1180, 1093, 1028, 981, 939, 893, 854, 758, 723, 623, 631 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.38 (s, 1H), 10.27 (s,1H), 8.92 (s, 1H), 7.95 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.40 (t, *J* = 5.6 Hz, 1H), 4.60 (d, *J* = 5.2 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 162, 161, 152, 144, 143, 143, 136, 130.8, 130.1, 129, 127, 115, 115, 57.8, 14.6. ESI-MS: m/z, 301.8 [M] $^{+}$.

(E)-4-methoxy-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide (5d):

Yellow solid; Yield: 85%; M. P: 155 ^{o} C; IR (KBr): υ_{max} 3291, 2840, 1665, 1605, 1557, 1510, 1403, 1365, 1315, 1252, 1180, 1117, 1068, 1026, 950, 895, 844, 787, 756, 673, 637, 615 cm^{-1}; ^{1}H-NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.58 (s, 1H), 12.48 (brs,1H), 8.97 (s, 1H), 8.00 (d, J = 6.4 Hz, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 5.46 (brs, 1H), 4.64 (s, 2H), 3.85 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 163, 161, 157, 144, 143, 143, 136, 130.5, 130.1, 129, 127, 116, 114, 58, 14. ESI-MS: m/z, 301.8 $(M+H)^{+}$.

ESI- MS: m/z, 315.8 [M] $^{+}$.

(E)-4-fluoro-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide (5e):

Yellow solid; Yield: 84%; M. P: 140 ^{o} C; IR (KBr): υ_{max} 3628, 3270, 2840, 1647, 1602, 1562, 1503, 1438, 1399, 1370, 1309, 1279, 1228, 1160, 1104, 1067, 1023, 984, 938, 894, 852, 818, 783, 752, 647, 613 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.64 (s, 1H), 12.28 (s,1H), 8.96 (s, 1H), 8.07 (t, *J* = 8.4 Hz, 2H), 7.96 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 5.43 (brs, 1H), 4.61 (d, *J* = 3.6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm) δ 163, 162, 155, 152, 143, 136, 130, 130, 129, 127, 126, 115, 115, 57.9, 14.7. ESI-MS: m/z, 303.8 [M] $^{+}$.

(E)-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)3-nitro benzohydrazide (5f):

Yellow solid; Yield: 70%; M. P: 210 ^{o} C; IR (KBr): υ_{max} 3425, 3276, 3067, 1689, 1669, 1619, 1559, 1531, 1439, 1399, 1374, 1348, 1326, 1274, 1217, 1167, 1116, 1068, 1017, 978, 952, 927, 905, 858, 856, 824, 759, 714, 672 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.88 (s, 1H), 12.20 (s,1H), 8.99 (s, 1H), 8.83 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 7.96 (s,1H), 7.88 (t, *J* = 8.0 Hz, 1H), 5.45 (t, *J* = 5.2 Hz, 1H), 4.62 (d, *J* = 5.6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR(270 MHz, DMSO-d_6 - δ/ppm): δ 161, 152, 147, 144, 143, 141, 136, 134, 132, 130, 130, 127, 126, 58.0, 15.0. ESI-MS: m/z, 330.8 [M] $^{+}$.

(E)-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)2-iodo-benzohydrazide (5g):

Yellow solid; Yield: 85%; M. P: 160 ^{o} C; IR (KBr): υ_{max} 3523, 3174, 3031, 1652, 1600, 1558, 1396, 1380, 1291, 1267, 1218, 1163, 1128, 1102, 1020, 996, 949, 894, 831, 785, 753, 700, 665 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.58 (* 12.41, s, 1H), 12.12 (* 9.89, s, 1H), 8.81 (*8.61, s, 1H), 7.96 (* 7.91, s, 1H), 7.54 (brs, 2H), 7.38 (*7.28, d, *J* = 8.0 Hz, 1H), 5.38 (* 5.30, s, 1H), 4.58 (* 4.51, brs, 2H), 2.43 (* 2.22, brs, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 164, 161, 152, 144, 143, 142, 136, 131, 130, 129, 127, 116, 115, 57.8, 14.6. ESI-MS: m/z, 301.8 $(M+H)^{+}$ .ESI- MS: m/z, 411.8 [M] $^{+}$.

(E)-2,4-dichloro-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl) methylene)benzohydrazide (5h):

Yellow solid; Yield: 78%; M. P: 220^{o} C; IR (KBr): υ_{max} 3225, 3085, 2832, 2706, 1698, 1661, 1588, 1554, 1465, 1384, 1361, 1273, 1217, 1166, 1096, 1048, 957, 899, 867, 828, 797, 754,

673, 648 cm^{-1} ; ^{1}H NMR(400 MHz, DMSO-d_6- δ/ppm): δ 12.68 (s, 1H), 12.02 (* 9.92, s, 1H), 8.80 (*8.61, s, 1H), 7.96 (* 7.93, s, 1H), 7.82 (d, *J* = 10.8 Hz, 1H), 7.70 (d, *J* = 10.8 Hz, 1H), 7.60 (d, *J* = 6.4 Hz, 1H), 5.93 (* 5.29, brs, 1H), 4.58 (* 4.50, brs, 2H), 2.42 (* 2.25, s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 162, 144, 151, 152, 136, 127, 143, 130, 133, 129, 140, 126, 129, 58.2, 14.8. ESI- MS: m/z, 353.8 $[M]^+$.

(E)-2,5-difluoro-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide (5i):

Yellow solid; Yield: 80%; M. P: 225 ^{o}C; IR (KBr): υ_{max} 3418, 3304, 3024, 2899, 1654, 1588, 1530, 1485, 1421, 1400, 1373, 1346, 1267, 1225, 1178, 1141, 1086, 1021, 993, 894, 835, 757, 716, 690, 646 cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6- δ/ppm): δ 12.64 (s, 1H), 12.04 (s,1H), 8.88 (s, 1H), 7.98 (s, 1H), 7.65-7.61 (m, 1H0, 7.55-7.45 (m, 2H),5.40 (t, *J* = 7.0 Hz, 1H), 4.60 (t, *J* = 5.6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 165, 162, 153, 146, 144, 143, 136, 132, 131, 129, 127, 117, 115, 57.8, 14.6. ESI-MS: m/z, 321.8 $[M]^+$.

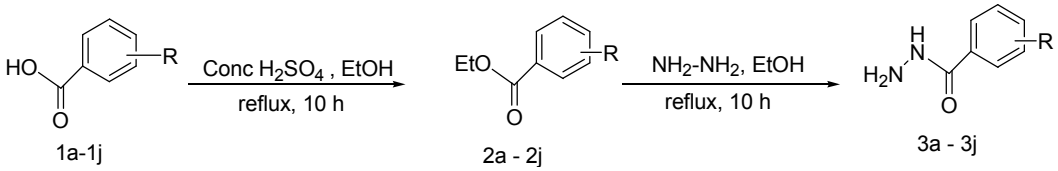
(E)-N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)-3,4,5-trimethoxybenzohydrazide (5j):

Yellow solid; Yield: 82%; M. P: 205 ^{o}C; IR (KBr): υ_{max} 3486, 3186, 2942, 2840, 1650, 1586, 1556, 1502, 1462, 1416, 1394, 1329, 1265, 1225, 1182, 1127, 1067, 1028, 1003, 962, 867, 817, 766, 728, 696, 667 cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6- δ/ppm): δ 12.45 (s, 1H), 12.30 (s, 1H), 8.94 (s, 1H), 7.96 (s, 1H), 7.32 (s, 2H), 5.42 (t, *J* = 3.6 Hz, 1H), 4.62 (d, *J* = 4.4 Hz, 2H), 3.88 (s, 6H), 3.75 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (270 MHz, DMSO-d_6 - δ/ppm): δ 162, 143.2, 143.6, 152, 136, 126, 141, 129, 105, 152, 137, 152, 105, 60, 57, 56, 48.4, 14.8. ESI-MS: m/z, 374.0 $[M-1]^+$.

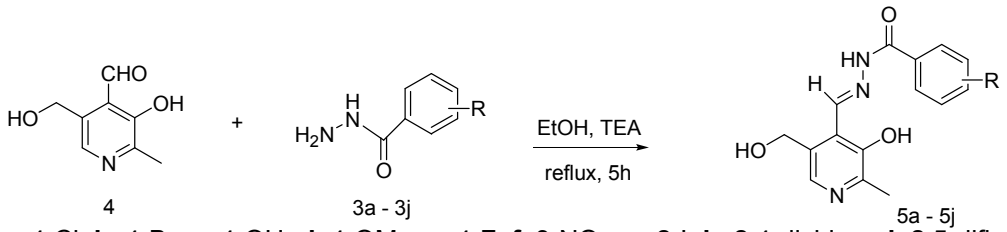
Antibacterial Bioassay

The antimicrobial assay was performed by agar well diffusion method. The compounds were evaluated for antibacterial activity against *Escherichia coli* (MTCC 1687), *Pseudomonas aeruginosa* (MTCC 424), *Staphylococcus aureus* (MTCC 96) and *Bacillus cereus* (MTCC 442). An antibiotic, Ampicillin (500 µg/mL) was used as reference for antibacterial activity. Dimethyl sulphoxide (1%, DMSO) was used as control. The molten Mueller Hinton Agar was inoculated with the 100 µL of the inoculum and poured into the Petri plate. A well was prepared in the plates with the help of a cork-borer (0.85cm). 100 µL of the test compound was introduced into the well. The plates were incubated overnight at 37 °C. Microbial growth was determined by measuring the diameter of zone of inhibition. For each bacterial strain, controls were maintained where pure solvents were used. The result was obtained by measuring the zone diameter (**Table-1**). The results of the antibacterial bioassay of compounds **5a to 5j** (Concentration used 500 µg/ mL of DMSO) was obtained by measuring the zone of diameter.

RESULTS AND DISCUSSION



1a-1j 2a - 2j 3a - 3j



4 3a - 3j 5a - 5j

R = **a**: 4-Cl, **b**: 4-Br, **c**: 4-OH, **d**: 4-OMe, **e**: 4-F, **f**: 3-NO_3, **g**: 2-I, **h**: 2,4-dichloro, **i**: 2,5-difluoro, **j**: 3,4,5- trimethoxy.

Scheme 1

The reaction sequence for the synthesis of novel hydrazone derivatives **5a-5j** is depicted in scheme **1.** Pyridoxal, 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carboxaldehyde **4** was reacted with corresponding benzohydrazides **3a-j** in ethanol in presence of triethylamine to afford N'-((3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)methylene)benzohydrazide **5a-j** in 75 -85% yield. The structures of the synthesized compounds were confirmed by spectroanalytical techniques *viz.,* ^{1}H NMR, ^{13}C NMR, IR and MS spectral data. The IR spectral bands of compound **5c** represents the following functional groups, the stretching bands at 3336 cm^{-1} (-OH, aromatic), 3055 cm^{-1}(=C-H, aromatic), 2808 (-C-H, aliphatic), 1662 cm^{-1}(-CO-NH-), 1602 cm^{-1}(-C=N), 1365 cm^{-1}(-C-N), 1238 cm^{-1}(Ar-C-O-) and 981 cm^{-1} (N-N) respectively. As a representative case, the ^{1}H NMR spectra of the compound **5j** can be characterized as follows, the signals in the aromatic region at δ 12.45, ppm (1H, phenolic OH); 12.30,s (1H, NH); 8.94 (1H, azomethine), 7.96,s (Pyridine ring proton) and 7.32,s (3,4,5-trimethoxy phenyl ring) as singlets confirms the basic skeleton of the scaffold. The methoxylated and the methyl protons appear as singlets at 3.88 ppm, 3.75 ppm and 2.50 ppm respectively. The triplet and doublet signals (with one proton and two proton integration) resonating at 5.42 and 4.62 ppm represents the presence of $–CH_2OH$ group.

The ^{1}H NMR data of the remaining hydrazone derivatives in the series are in agreement with the assigned structures. The mass spectra of compounds showed $[M]^{+}$ peaks, in agreement with their molecular formula. Compounds such as **5g** (2-I), **5h** (2,4-dichloro) were found to exist as a mixture of two rotameric forms in solution [xxvii] e.g. antiperiplanar (*ap*) and synperiplanar (*sp*) as indicated by their ^{1}H NMR spectra. Two sets of signals were observed for all groups in the ^{1}H NMR spectra of each compound indicating the possibility of equilibrium and interconversion between rotamers (and/or configurational isomers) in solution [xxvii].

Evaluation of antibacterial activity

It is observed from table-1 that most of the pyridoxal hydrazone derivatives **5a-5j** showed significant antibacterial activity. The compounds **5h** and **5j** showed excellent antibacterial activity while compounds **5c, 5e** and **5f** showed good activity and remaining compounds in the series exhibited moderate activity against *E.coli*, *P.aeruginosa* and *S. aureus*. It is observed in case of *Bacillus cereus* that except **5b** and **5g** all the compounds showed excellent activity.

Table I- Antibacterial Activity of pyridoxal-hydrazone derivatives **(5a-5j)**

Compound No	Conc (µg/mL) in DMSO	Gram negative bacteria		Gram positive bacteria	
		E.coli MTCC 1687	*P.aeruginosa MTCC 424*	*S.aureus MTCC 96*	*B.cereus MTCC 430*
		Zone of inhibition in mm [a]			
5a	500	16	19	15	16
5b	500	15	17	14	15

5c	500	24	25	18	20
5d	500	18	20	15	18
5e	500	22	23	20	22
5f	500	18	21	19	23
5g	500	12	16	15	17
5h	500	30	32	23	22
5i	500	16	19	14	16
5j	500	25	28	20	19
Ampicillin	500	36	39	34	32

CONCLUSION

The Schiff bases of 3-hydroxy-5-(hydroxymethyl)-2-methylpyridine-4-carboxaldehyde and benzohydrazides were synthesised and characterised. The compounds were screened for their antibacterial activity against Gram negative bacteria (Escherichia coli and Pseudomonas aeruginosa and Gram positive bacteria (Staphylococcus aureus and Bacillus cereus). The compounds showed moderate to excellent activity.

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