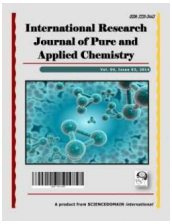

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Synthesis, Characterization and Antibacterial Studies of Some Isoniazid-derived Schiff Bases

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Authors' contributions

This work was carried out in collaboration between all authors. Author JNY designed the study, wrote the protocol and the first draft of the manuscript. Authors ENM and SJEN interpreted the spectral data and provided the literature review. Authors ENM and SJEN performed the experiments and participated in writing the first draft of the manuscript and author PTN followed part of the synthesis, antimicrobial studies and provided part of the literature for of the work. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To synthesize some isoniazid-derived imines by the condensation of isoniazid (INH) with some substituted benzaldehydes as well as pyridine carboxaldehydes and to determine their structures by spectroscopic methods.
Methodology: Isoniazid was mixed with equimolar amounts of some substituted benzaldehyes as well as pyridine carboxaldehydes and refluxed for 4-7 hours. The solid products were filtered by gravity and dried over anhydrous $CaCl_2$ in a desiccator. The ligands were screened for the biological activities against *Salmonella typhi, Staphylococcus aureus, Escherichia coli, Shiegella*

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flexneri, and *Salmonella enterica* by paper disc diffusion method.
Results: Nine Schiff bases were synthesized and characterized by elemental analyses, ^{1}H NMR, and^{13}C NMR. Their melting temperatures were determined and their purity ascertained by HPLC.
Conclusion: Nine isoniazid-derivedimines were synthesized and characterized. The antibacterial activities of some of the imines were comparable to the activity of isoniazid against *E. coli*, whereas the other Schiff bases were more active than isoniazid against the other tested pathogens. Compound **7** showed good antibacterial activity compared to isoniazid against all the tested pathogens and compound **4** was inactive against all pathogens.

Keywords: Isoniazid; hydrazones; schiff bases; antibacterial.

1. INTRODUCTION

Isoniazid is a pro-drug with established therapeutic applications and has been in clinical use for almost half a century as a front-line drug for prophylaxis and treatment of tuberculosis [1,2]. It is a nicotinamide analog made up of a pyridine ring and a hydrazide group [3]. The free $–NH_2$ group in the hydrazine moiety can be condensed with various carbonyl compounds (aldehydes and ketones) to form hydrazones (Schiff bases), containing the characteristic H-C=N-NH- group. The presence of a carbonyl group adjacent to the -NH- group in hydrazine provides a possibility of tautomerism in some cases [4]. It is well established that the presence of OH or NH groups in an appropriate position relative to the -C=N group provides greater chances for increased intramolecular as well as intermolecular interactions [5]. This implies that hydrazones derived from isoniazid may show greater biological activities due to improved interactions with the binding sites.

Hydrazones have been reported to possess antitumoral, antimicrobial, antitubercular, anticonvulsant, analgesic antifungal, antiviral and antibacterial activities [6]. Mainsah et al. [7] recently reported, for the first time, the anti-onchocercal activity of some isoniazid-derived Schiff bases and their copper(II) and zinc(II) complexes with the copper(II) complexes showing significant activity against both micro- and macrofilariae.

Antimycobacterial activities of Schiff bases derived from isoniazid or those that possess a pyridine moiety have also been reported [8,9]. Numerous studies have pointed out the importance of developing novel isoniazid hydrazones as promising anti-tubercular agents [10]. Chemical modification of the hydrazine portion of isoniazid with a functional group that blocks acetylation, while maintaining strong biological action has the potential to improve clinical outcomes and reduce the emergence of acquired isoniazid resistance in patients. Thus, hydrazones, which contain the –HN-N=CH- moiety from isoniazid [11], constitute an important class of compounds for drug development.

Schiff bases derived from isoniazid have been synthesized by classical methods in which the aldehydes and ketones are refluxed with isoniazid in organic solvents [12,13], in a catalytic amount of acetic acid. Other environmentally friendly and less costly synthetic methods have been attempted including green synthesis of hydrazones using natural fruit-derived organic acids as catalysts [14,15].

In continuation of our research on the isoniazid-derived hydrazones, the present study describes the synthesis, characterization of some imines and their antibacterial activity on selected pathogens.

2. EXPERIMENTAL

2.1 Materials

All chemicals used were analytical grade (Sigma-Aldrich), and used as purchased without further purification.

2.2 Physical Measurements

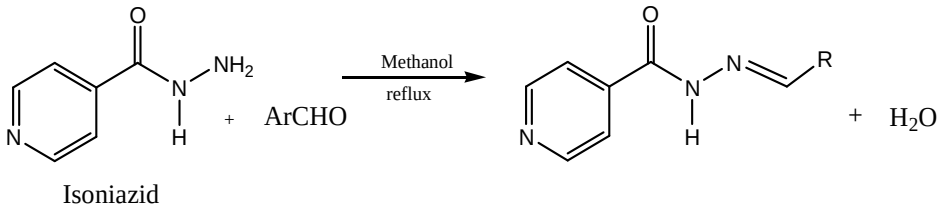
^{1}H-NMR and ^{13}C-NMR spectra were recorded with a 600 MHz Brucker Advanced II spectrophotometer in dimethylsulfoxide (DMSO-d_6) as solvent and were reported relative totetramethylsilane (TMS) as internal standard. CHN contents of the hydrazones were performed using the FLASH 2000 Organic Elemental Analyzer, CHNS-O analyzer (Thermo Scientific), melting temperatures were determined using a Mel-Temp II laboratory device, while infrared (IR) spectroscopy was performed on a Perkin-Elmer FT-IR 100 spectrometer. The spectra were

recorded from 4000 to 600 cm^{-1} in attenuated total reflectance (ATR) mode.HPLC chromatograms of the compounds were obtained on the HEWLETT PACKARD, Agilent 1100 series, using the OpenLAB ChemStation, 2010-2014 software, in acetonitrile/water (1:9) solvent.

2.3 Synthesis of the Schiff Bases

The Schiff bases were obtained by refluxing equimolar proportions of isoniazid and the various aldehydes in methanol as solvent at 70℃ with continuous stirring for 4-7 hours as shown in Scheme 1. For example, isoniazid (0.274 g, 2.0 mmol) was dissolved in 5.0 mL of warm methanol and to this solution was added to 0.258 g (2.0 mmol) of 4-(dimethylamino)benzaldehyde, dissolved in 5.0 mL of warm methanol, as well (Scheme 1). The mixture was refluxed at 70℃, with continuous stirring for 4 hours in a water bath, resulting in a yellow solution. The progress of the reaction was monitored by TLC using a 40% isopropyl alcohol/60% hexane solvent system. The solution was allowed to cool as the solvent evaporated and yellow crystals were obtained after two days [4,16-18]. The product was filtered, washed with cold methanol, and dried in a desiccator over anhydrous $CaCl_2$. The same compound was synthesized from the isonicotinic acid hydrazide salt in an ethanol/water solvent system and refluxed for 24 hours [16]. The purity of the compounds was ascertained by HPLC analysis and melting temperature determination (Table 2).

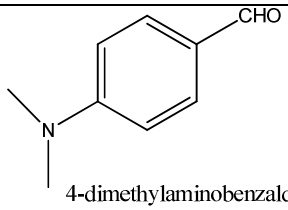
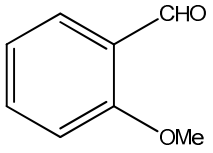
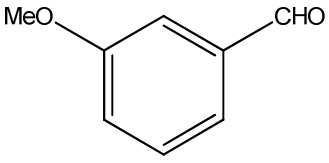
The aldehydes used for the synthesis of the Schiff bases are shown in Table 1.

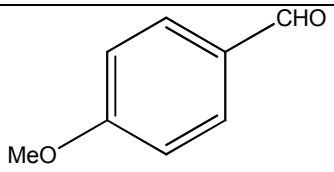
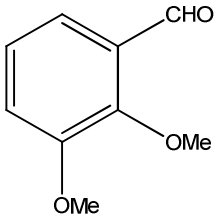
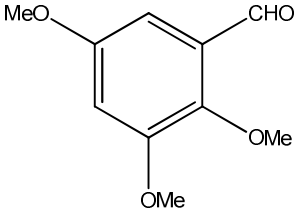
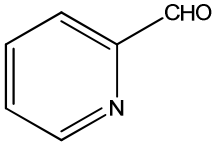
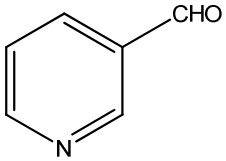
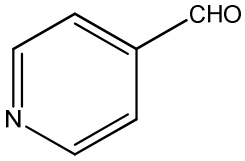


Isoniazid

Scheme 1. General method of synthesis of schiff bases

Table 1. Aromatic aldehydes used for synthesis of schiff bases

Compound	Structural formula and name of ArCHO
1	 4-dimethylaminobenzaldehyde
2	 2-methoxybenzaldehyde
3	 3-methoxybenzaldehyde

Compound	Structural formula and name of ArCHO
4	 4-methoxybenzaldehyde
5	 2,3-dimethoxybenzaldehyde
6	 2,3,5-trimethoxybenzaldehyde
7	 pyridine-2-carboxyldehyde
8	 pyridine-3-carboxyldehyde
9	 pyridine-4-carboxyldehyde

2.3.1 Characterization data of the schiff bases (See supplementary material)

N'-(4-(dimethylamino)benzylidene)isonicotinoylhydrazone monohydrate **(1):** ^{1}H NMR (δ ppm): 11.76 (s, 1H, NH); 8.76 (d, 2H, pyr); 8.32 (s, 1H, =C-H), 7.80 (d, 2H, pyr); 7.56 (d, 2H, benz); 6.74 (d, 2H, benz); 3.01 (s, 6H, $N(CH_3)_2$). ^{13}C NMR (δ ppm): 161.5 (C-7); 152.2 (C-14); 150.7 (C-2, C-6); 150.3 (C-10); 141.3 (C-4); 129.1 (C-12, C-16); 121.9 (C-3, C-5); 121.7 (C-11); 112.3 (C-13, C-15); 40.2 (C-18, C-19). IR (cm^{-1}): 3385 (O-H); 3190 (N-H, str); 2939 (=C-H, str); 1738 (s, amide II) 1662 (C=O); 1603 (-C=N); 1588(C=C).

Table 2. Physical properties of the schiff bases

Compound (molwt)	Color	mp (℃)	Yield (%)	Elemental analysis					
				Calculated			Experimental		
				%C	%H	%N	%C	%H	%N
1 (286.3)	yellow	205	72.99	62.94	5.59	19.58	63.54	5.56	19.92
2 (255.2)	colorless	190	83.35	65.62	5.13	16.46	65.87	5.04	16.45
3 (255.2)	colorless	195	78.47	65.87	5.13	16.46	65.91	4.98	16.50
4 (255.2)	colorless	160	82.00	61.54	5.49	15.38	62.99	4.18	15.92
5(285)	colorless	138	93.78	63.16	5.26	14.74	63.47	5.32	14.57
6(315)	yellow	193	99.28	60.95	5.40	13.33	60.91	5.42	13.28
7 (226.2)	white	175	66.86	63.71	4.46	24.77	63.46	4.31	24.80
8 (226.2)	white	238	79.09	63.71	4.46	24.77	63.77	4.27	24.80
9 (226.2)	white	235	88.27	63.71	4.46	24.77	62.55	4.37	24.68

***N'-(2-methoxybenzylidene)isonicotinoylhydrazone* (2):** ^{1}H NMR (δ ppm): 12.06 (s, 1H, NH); 8.84 (s, 1H, =C-H); 8.78 (d, 2H, pyr); 7.90 (d, 1H, benz), 7.85 (d, 2H, pyr); 7.43 (t, 1H, benz); 7.11 (d, 1H, benz) 7.04 (t, 1H, benz); 3.86 (s, 3H, OCH_3). ^{13}C NMR (δ ppm): 161.4 (C-7); 157.9 (C-16); 150.3 (C-2, C-6); 144.5 (C-10); 140.4 (C-4); 131.9 (C-14); 125.6 (C-12);122.0 (C-13); 121.5 (C-3, C-5); 120.8 (C-11); 111.9 (C-15); 55.7 (C-17). IR (cm^{-1}): 3195 (N-H, str); 1651 (C=O); 1598 (C=C); 1550 (C=N); 1252 (C-O-).

***N'-(3-methoxybenzylidene)isonicotinoylhydrazone* (3):** ^{1}H NMR (δ ppm): 12.09 (s, 1H, N-H); 8.78 (d, 2H, pyr); 8.45 (s, 1H, N=C-H); 7.83 (d, 2H, pyr); 7.38 (t, 1H, benz); 7.31 (d, 2H, benz); 7.02 (dd, 1H, benz); 3.80 (s, 3H, OCH_3). ^{13}C NMR (δ ppm): 162.2 (C-7); 160.0 (C-13); 150.8 (C-2, C-6); 149.5 (C-10); 140.9 (C-4); 135.9 (C-11); 130.5 (C-15); 122.0 (C-3, C-5); 120.7 (C-16). 117.0 (C-14); 111.9 (C-12); 55.6 (C-17). IR (cm^{-1}): 3188 (N-H, str); 3011 (=C-H, str); 1677 (C=O); 1582 (C=N); 1276 (C-O-).

***N'-(4-methoxybenzylidene)isonicotinoylhydrazone* (4):** ^{1}H NMR (δ ppm): 11.95 (s, 1H, N-H); 8.78 (dd, 2H, pyr); 8.41 (s, 1H, N=C-H); 7.82 (dd, 2H, pyr); 7.70 (dd, 2H, benz); 7.02 (dd, 2H, benz); 3.80 (s, 3H, OCH_3). ^{13}C NMR (δ ppm): 161.5 (C-7); 161.1 (C-14); 150.3 (C-2, C-6); 149.0 (C-10); 140.6 (C-4); 129.0 (C-12, C-16); 126.6 (C-11); 121.5 (C-3, C-5); 114.4 (C-13, C-15); 55.3 (C-17). IR (cm^{-1}): 3435 (O-H,str); 3139 (=C-H, str); 1653 (C=O); 1597 (C=N); 1253 (C-O-).

***N'-(2,3-dimethoxybenzylidene)isonicotinoylhydrazone* (5)**: ^{1}H NMR (δ ppm): 12.12 (s, 1H, NH); 8.79 (d, 2H, pyr); 8.78 (s, 1H, =C-H); 7.86 (d, 2H, pyr); 7.51 (dd, 1H, benz); 7.13 (m, 2H, benz); 3.83 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3). ^{13}C-NMR (δ ppm): 162.0 (C-7); 153.1 (C-16); 150.8 (C-2, C-6); 148.7 (C-15); 145.2 (C-10); 140.8 (C-4); 127.9 (C-13); 122.0 (C-3, C-5); 117.6 (C-11); 115.0 (C-14); 61.7 (C-17); 56.2 (C-18). IR (cm^{-1}): 3455(N-H, str); 3147 (=C-H, str); 1659 (C=O); 1557 (C=N); 1262 (C-O-).

***N'-(2,3,5-trimethoxybenzylidene)isonicotinoylhydrazone* (6):** ^{1}H NMR (δ ppm): 11.96 (s, 1H, NH); 8.77 (m, 2H, pyr); 8.76 (s, 1H, =C-H); 7.84 (d, 2H, pyr); 7.40 (s, 1H, benz); 6.74 (s, 1H, benz); 3.86 (d, 6H, OCH_3); 3.76 (s, 3H, OCH_3). ^{13}C-NMR (δ ppm): 161.7 (C-7); 154.1 (C-13); 152.8 (C-15); 150.7 (C-2, C-6); 145.2 (C-16); 143.7 (C-10); 141.0 (C-4);121.9 (C-3, C-5); 113.7 (C-11); 108.2 (C-12); 98.2 (C-14); 56.9 (C-19); 56.3 (C-17); 56.2 (C-18). IR (cm^{-1}): 3568 (O-H, str); 3197 (=C-H); 1663 (C=O); 1595 (C=C); 1554 (C=N); 1276, 1222, 1206 (3C-O-).

***N'-(pyridine-2-carboxaldehyde)isonicotinoylhydrazone* (7):** ^{1}H NMR (δ ppm): 12.24 (s, 1H, -NH); 8.80 (d, 2H, INH); 8.63 (d, 1H, pyr); 8.48 (s, 1H, -N=C-H); 7.99 (d, 1H, pyr); 7.90 (td, 1H, pyr); 7.83(d, 2H, INH); 7.44 (ddd, 1H, pyr). ^{13}C-NMR (δ ppm): 161.9 (C-7); 152.9 (C-12); 150.4 (C-2, C-6); 149.6 (C-14); 149.2 (C-11); 140.2 (C-4); 137.0(C-15); 124.7 (C-16); 121.5 (C-3, C-5); 120.1 (C-17). IR (cm^{-1}): 3296 (N-H, str); 1672 (C=O); 1584 (C=N); 1546 (C=C).

***N'-(pyridine-3-carboxaldehyde)isonicotinoylhydrazone* (8):** ^{1}H NMR (δ ppm): 12.20 (s, 1H, -NH); 8.88 (s, 1H, pyr); 8.78 (d, 2H, INH); 8.63 (dd, 1H, pyr); 8.51 (s, 1H, -N=C-H); 8.17 (d, 1H, pyr); 7.83 (d, 2H, INH); 7.51 (dd, 1H, pyr). ^{13}C-NMR (δ ppm): 161.9 (C-7); 151.0 (C-15); 150.3 (C-2, C-6); 148.9 (C-

13); 146.3 (C-11); 140.3 (C-4); 133.6 (C-17); 129.9 (C-12); 124.0 (C-16); 121.5 (C-3, C-5). IR (cm^{-1}) :3180 (N-H, str); 1673 (C=O); 1590 (C=N); 1547 (C=C).

N'-(pyridine-4-carboxaldehyde)isonicotinoylhydrazone **(9)**: ^{1}H NMR (δ ppm): 12.32 (s, 1H, -NH); 8.80 (d, 2H, INH); 8.67 (d, 2H, pyr); 8.46 (s, 1H, -N=C-H); 7.84 (d, 1H, INH); 7.68 (d, 2H, pyr); ^{13}C-NMR(δ ppm): 162.0 (C-7); 150.4 (C-2,C-6); 150.3 (C-14,C-16); 146.7 (C-11); 140.2 (C-12); 121.6 (C-3,C-5); 120.8 (C-13, C-17). IR (cm^{-1}): 3181 (N-H, str); 1690 (C=O); 1572 (C=N); 1546 (C=C).

2.4 Biological Activity

In vitro antibacterial activities of the ligands were evaluated by the disc–diffusion method. Mueller – Hinton agar was employed as microbial growth medium. The antibacterial diffusion tests were carried out as described by Berghe and Vlientink [19] using a cell suspension of about 1.5 x 10^{6} CFU/mL obtained from the McFarland Turbidity Standard N^{o} 0.5. Antibacterial activity was evaluated by measuring the diameter of the inhibition zone (IZ) around the discs. Three replicates were made for each sample and mean values of the growth inhibition zone were measured. Compounds were considered active only when inhibition zone was greater than 6 mm as indicated in Table 3.

3. RESULTS AND DISCUSSION

3.1 Elemental Analysis

The physical properties of the isoniazid-derived Schiff bases including molecular weight, color, melting point and elemental analysis are tabulated in Table 2. The experimental and theoretical values of elemental analysis agree very closely. The compounds had sharp melting points which differ from those of the starting materials confirming that new compounds were formed. These high melting temperatures indicate that the molecules are held together in a lattice by strong intermolecular hydrogen bonds.

3.2 Infrared

The average stretching frequency of N-H band of the compounds ranges from 3139 to 3296 cm^{-1} and the characteristic υC=N (imine) peak varies between 1603 and 1550 cm^{-1}. The band due to NH-stretching in **6** occurs at 3197 $cm^{-}1$ which is lower than that of its isomer, N'-(3,4,5-trimethoxybenzylidene) isonicotinoyl hydrazone whose NH stretching frequency falls in the 3350 to 3230 cm^{-1} region [20]. The NH band of mono-substituted methoxy-aldehydes shows a slight increase due to resonance effects with the *p*-substituted Schiff base having the highest frequency and the *m*-substituted isomer the lowest. Some strong bands are clustered around the 1500 cm^{-1} range in all the compounds and this can be assigned to the C=N and C=C bonds of the pyridine/aromatic rings. The υO-H bands which appear in compounds **1**, **4**, **5** and **6** can be attributed to water molecules trapped in the crystal. It has been reported that compound **5** traps chloroform when it is slowly crystallized in this solvent as indicated by X-ray diffraction analysis [21].

3.3 ^{1}H and ^{13}C NMR

A sharp singlet centered on 3.80 ppm in Schiff bases formed from methoxy-substituted aldehydes is assigned to methyl protons. The dimethylaminobenzaldehyde Schiff base also gives a singlet at δ 3.01 attributed to methyl protons. The aromatic protons for both the pyridine and phenyl ring range from 6.74 to 8.88 ppm in the hydrazones. The azomethine proton, which confirms the formation of the product, appears as a sharp singlet in the range 8.32 – 8.78 ppm [20,22] while the N-H proton can be assigned to the signals which appear at 11.76 to 12.32 ppm range. The ^{13}C NMR confirms the formation of the hydrazones with the azomethine carbon at δ 143.7-150.3. The chemical shift of the carbonyl carbon varies very little from 160.0 – 162.0 ppm in the Schiff bases. The presence of the O-H protons in compounds **1**, **4**, **5** and **6** is confirmed by the chemical shifts in the 3.38 – 3.49 ppm range contrary to similar compounds [20].

3.4 Antibacterial Activity

From the data, the zones of inhibition for the Schiff bases are relatively low (7-11 mm) when compared to those of the standard antibiotics, gentamicin and chloramphenicol. This suggests weak antibacterial activity. However, the activities of these Schiff bases are comparable to those of the parent compound, isoniazid, which in itself is an antibiotic of proven therapeutic applications. *E. coli* and *S. typhi* were the most susceptible to the synthesized ligands. Compound **7** was the most active and showed activity against all the bacterial strains used and compound **4** was inactive against all strains.

Table 3. Antibacterial screening of isoniazid derivatives by disc diffusion method

Compound	*E. coli BL-21*	*S. enterica NR-4311*	*Salmonella typhi*	*S. flexneri*	*S. aureus NR-46003*
1	10	-	-	-	-
2	10	-	10	-	-
3	9	-	9	-	
4	-	-	-	-	-
5	10	-	-	-	9
6	-	-	-	-	-
7	11	10	11	7	10
8		-	10	-	-
9	11	-	10	-	-
INH	10	**-**	**-**	**-**	**-**
DMSO	**-**	**-**	**-**	**-**	**-**
gentamicin	24	*		*	*
chloramphenicol	*	25	*	*	*

**Positive control not tested*

Compound **7** proved to be better than the parent isoniazid against all the bacterial strains. The Minimum Inhibitory Concentration (MIC) results for these compounds that were active against at least two bacterial strains were very high, that is 1000 µg/mL. The MIC of INH was greater than 1000 µg/mL, implying that the synthesized compounds had better antibacterial properties than the parent compound although the bacterial species tested are not the primary target of INH.

4. CONCLUSION

Nine Schiff bases derived from isoniazid were synthesized in good yield and analytical purity. They were characterized by elemental analyses, ^{1}H and ^{13}C NMR spectroscopy. Compound **7** was the most biologically active and showed activity against all the bacterial strains used and compound **4** was inactive against all strains. Compound **7** proved to a better antibacterial than the parent compound, isoniazid against all the bacterial strains. The biological activities of the Schiff bases showed that some of the compounds synthesized have the potential for the development of good therapeutic agents against a few selected bacterial strains.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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