SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND BIOLOGICAL STUDIES OF 2-[(2-HYDROXY-5-METHOXYPHENYL) METHYLIDENE] AMINO} NICOTINIC ACID AND ITS MANGANESE (II) COMPLEXES

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ABSTRACT
Manganese(II) complexes of 2-[(2-hydroxy-5-nitrophenyl) methylidene]amino} nicotinic acid derived from o-phenylenediamine and 5-nitrosalicaldehyde were synthesized and characterized by elemental analysis, using IR, ¹H NMR, ¹³C NMR, and GCMS. They were screened against known disease causative microbes to establish their potentials as antimicrobial agents compared with national standards drugs. Results showed that, a Schiff base exhibited antimicrobial action against all the bacteria and most of the fungi with exception of Candidas albicans isolate, which exhibited zero diameter zone of inhibition. It was also found that the synthesized Schiff base exhibited two digits purity range, implying that it was relatively stable. The metal complex was found to be more susceptible in overall biological activity due to the structural stability, showing their potency in pharmacognocy.

Keywords: Complexes of Manganese, Synthesis and characterization, antimicrobial agents.

INTRODUCTION
Several Schiff bases have been synthesized, characterized and most of them have been found to displayed strong antimicrobial activities. e.g 2-[(2-hydroxy-5-methoxyphenyl) methylidene] amino} nicotinic acid is a Schiff base and these bases are formed by the condensation of an aldehyde or ketone in which the C=O group is replaced by a C=N-R group, viz Scheme 1 [1].

Scheme 1:

where R may be an alkyl or an aryl group.

Those that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable [2], while those of aromatic aldehydes having effective conjugation are more stable [3]. According to [4], the formation of a Schiff base from an aldehydes or ketones is a reversible reaction and takes place under acid or base catalysis or upon heating as indicated in the scheme below:

Scheme 2:
The mechanism of Schiff base formation is another variation where the aldehyde / ketone gives an unstable carbinolamine, an alcohol, which loses water by acid or based catalysis as illustrated in scheme 3.

Scheme 3:  

\[
\text{Acid-Catalysed dehydration}
\]

Obviously, this takes place in a mildly acidic pH and proceeds in two steps through an anionic intermediate reaction, addition followed by elimination [5].

Metal-Schiff base complexes have been known since the mid nineteenth century [6], and even before the general preparation of Schiff baseligands themselves [7]. Metal–complexes of Schiff bases have occupied a central place in the development of coordination chemistry [8]. A typical illustration is seen in Schiff base complexes prepared metal salicyaldehyde with primary amines [9].

Subsequently, Schiff [10], prepared complexes from the condensates of urea and salicyaldehyde. Delepine [11], prepared complexes reacting metal acetates, salicyaldehyde and primary amine in alcohol demonstrated 2:1 stoichiometry. However, there has not been a comprehensive, systematic study on this structure, until the preparative work of Pfeiffer and associates [12]. Pfeiffer and his coworkers [13] reported a series of complexes derived from Schiff bases of salicyaldehyde and its substituent products [14]. According to [15], Schiff bases appear to be important intermediates in a number of enzymatic reactions involving interaction of the amino group of an enzyme, usually that of a lysine residue, with a carbonyl group of the substrate [16]. The study of the biological role of metal ions of V, Cr, Mn, Fe, Co, Ni, Cu, Zn, and Mo has a long history in chemistry, medicine, in pharmacology and in toxicology, but it is only recently that the extent and variety of metal ion involvement has been appreciated as a therapy or claimed to be of therapeutic value [8].

The behavior of metals in-vivo cannot be over emphasized, their chemistry is essentially that of the complexed ion, irrespective of whether more polar ions such as Na⁺ or K⁺ or more covalent species such as Au(III) or Pt(II) are being considered. Properties such as the effective size and solubility of a metal ion in-vivo are a function of ligand and solvent present as well as the metal ions themselves. Further, the correct metal ion balance in various in-vivo compartments is important for the functioning of specific metal containing sites in many enzymes and proteins.

Interaction of various metal ions with antibiotics may enhance or suppress their antimicrobial activity. The pharmacological activity of antibiotics, after complexation with metals, is enhanced as compared to that of the free ligands [17]. Many of the well-known antibiotics, penicillin, streptomycin, bacitracin and tetracycline are chelating agents and their action is improved by the presence of small amount of metal ions [18]. Antibiotics like Streptomycin, Cycloserine, Ampicillin, Isoniazid and others are also known to have chelating properties and some antibiotics are delicately balanced so as to be able to compete successfully with the metal binding agents of bacteria while not disturbing the metal processing by the host. The chelating properties of antibiotics may be used in metal transport across membrane or to attach the antibiotics to passive/specific site from which it can interfere with the growth of bacteria ([19]. Tetracycline forms are important group of antibiotics. Their activity appears to results from their ability to chelate metals. The extent for antibacterial
activity parallels the ability to chelate metals. The extent for antibacterial activity parallels the ability to form a stable chelate. It has been shown in a study that tetracycline and cycloserine bindings to metal ions suppress their antimicrobial activity because the associative pH changes alter the intra- and inter – molecular interactions. A similar correlation has been drawn between active tetracycline and the ability to form 2:1 complexes with Cu (II), Ni (II) and Zn (II) [5].

Qualitative and quantitative differences in biological activities have been observed among metal chelates, differing in the metal ion or in the ligand. Metal chelates during chemical synthesis can be varied in size, charge distribution, stereochemistry redox potentials and other physical properties [20].

It is worthwhile to synthesize some the Schiff bases and study their biological behavior via coordination to metal ions with the expectation that these studies may result in achieving new targets in synthesizing/ designing of metal-based compounds that could fight more aggressively against such bacterial/fungal strains, which becomes resistant to certain presently available and commonly used antimicrobial agents. Previously, the synthesis of some target Schiff bases and possibility of altering their biological activity via coordination to metal ions has been extensively studied [21]. This present work is an extension to such studies and deals with the synthesis and biological evaluation (antibacterial and antifungal activity) of Mn (II) complexes of the above Schiff base derived from aromatic/hetero-aromatic carboxyaldehyde and (un)-substituted hetero aromatic amines. A detailed literature survey revealed that the synthesis of the Schiff base reported in this thesis has not been carried out earlier by any other researcher. However, some references exist which report synthesis similar types of Schiff bases. This Schiff base, had not been investigated further, particularly in combination with the above choice metal.

**MATERIALS AND METHOD**

**Reagents:** 2-aminonicotinic acid (2-aminopyridine-3-carboxylic acid); Salicylaldehyde; 5-bromosalicylaldehyde (5-bromo-2-hydroxybenzaldehyde); 5-nitrosalicylaldehyde (2-hydroxy-5-nitrobenzaldehyde); 5-methoxysalicylaldehyde (2-hydroxy-5-methoxybenzaldehyde); 2-aminoo-1,3,4-thiodiazole; Furfuraldehyde; Thiophene-2-carboxaldehyde; Ethanol; Methanol; Nutrient agar.

All the reagents were of analytical grade obtained from Sigma-Aldrich, Merck, Germany and were used without further purification.

**Organisms**

**Bacteria:** *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Enterobacteria eruginosa*, and *Proteus mirabilis*.

**Fungi:** *Candida albicans*, *Penicillium notatum* and *Aspergillus niger*.

The microorganisms were obtained from the Department of Medical Microbiology, University of Benin Teaching Hospital (UBTH). All organisms were checked for purity at Pax Herbal Clinic and Research Laboratories, Ewu, Edo State and were maintained at 4°C in slants of Nutrient Agar and Sabour and Dextrose Agar (SDA) for bacteria and fungi respectively.

**Equipment/Apparatus**

Gas chromatography, Mass spectrometry (GCMS); Thermal Scientific DSQ II Focus Instrument model; Fourier Transform Nuclear Magnetic Resonance Spectrometer (FTNMR) – Bruker machine; Ultra-violet spectra were recorded on a Hitachi U-2000 double beam spectrophotometer; Infra-red spectra (KBr Discs) were recorded on a Hitachi Model 200-50 IR spectrophotometre.

Melting points were taken on a Gellenkamp apparatus and are uncorrected. All instrumental determinations were carried out in Durham University, Chemistry Department, United Kingdom.

**Syntheses of Schiff Base, 2-[[2-hydroxy-5-methoxyphenyl]methylidene]amino nicotinic acid**

Equimolar portion of 2-aminonicotinic acid (0.01mol) with 5-methoxysalicylaldehyde (0.01mol) were mixed in ethanol (30-40mL) containing five drops of conc. H2SO4 at a pH of 3.5 to 4.5. The resultant mixture was then heated under reflux for 2 hours and filtered hot by suction filtration. The product of reaction was allowed to crystallize from filtrate left at room temperature of 25°C over two days. The crystals
formed were re-crystallized hot in ethanol and dried in a desiccator over CaCl₂ vacuum and the yield was calculated using the equation below.

\[
\text{yield} = \frac{\text{mass of product}}{\text{mass of reactants}} \times 100\%
\]

Synthesis of Manganese Complex of 2-\{[(2-hydroxy-5-methoxyphenyl) methylidene]amino\} nicotinic acid

Metal complex of Manganese (II), was prepared by reaction of equimolar (0.01 mol) of each metal salt with a corresponding (0.01 mol) of the Schiff base ligand. The various 0.01 mol of the metal salts were each refluxed with 0.01 mol of the ligand in ethanol then filtered and washed with ethanol after which they were allowed to stand for 24 hrs. The resulting crystals were then dried in a desiccator and melting point determined. All synthesized complexes were coloured.

Antimicrobial Assay

The synthesized compounds were assayed for their antimicrobial activity using the disc diffusion technique by Kirby-Bauer [22]. Whatman filter paper (No.1) were cut into sizes of 6 mm diameter with office perforator and sterilized at 105°C for 1 hour. The sterile discs were impregnated with 20 μL of 100 mg/mL of the synthesized Schiff base or complex and dried in the oven at 60°C for about 15-30 min. The sterilized medium was poured into sterile petri-dishes and further allowed to cool and solidify at room temperature. The plates were labeled with the test microorganism (each plate with a test microbe). The microbes were spread evenly over the surface of the medium with the aid of a glass spreader. The plates were dried at 37°C for 30 min respectively.

Minimum Inhibitory Concentration – Broth Dilution Method

The minimum inhibitory concentration of the compound was carried out using Macro Broth Dilution Technique [24]. 9.0 mL of each broth was dispersed into separate test-tubes and was sterilized at 121°C for 15 min and then allowed to cool. Serial dilutions of the compounds were made from the stock concentration to obtain 0.6, 0.9, 1.2, 1.5, 1.8 and 2.1 mg/mL. The standardized inoculum (0.1 mL) of the microbes was inoculated into the different concentrations of the compound in the broth. For the bacteria, the test tubes of the broth were incubated at 37 °C for 24 hours and 30 °C for 1-7 days for the
fungi. They were all observed for turbidity and recorded as the MIC.

**Minimum Bactericidal/Fungicidal Concentration – Macro Broth Dilution Method**

Fresh Muller Hinton agar media were prepared, sterilized at 121°C for 15 min and was poured into sterile petri-dishes and left to cool and solidify. The contents of the MIC tubes (that is the tubes that showed no growth) were then sub-cultured onto the media and incubated at 37°C for 24 hours and 30°C for 1-3 days for bacteria and fungi respectively. It was then observed for colony growth. The MBC/MFC was the plate with the lowest concentration of extract and without colony growth.

**RESULTS AND DISCUSSION**

**Characterization**

*Chemistry of the Schiff Base 2-{{(2-hydroxy-5-methoxysalicylaldehyde) methyldene}amino nicotinic acid}_* - The yield was found to be 65% as yellow powder; m.p. 136-137°C; IR (KBr, cm\(^{-1}\)): 2876.92 (OH, Carboxylic acid), 3282.95 (OH, Phenol), 1382.01 (C=O, carboxylic acid), 1635.65 (HC=N). IR (KBr, cm\(^{-1}\)): 1581, 1531.53 (C=N, pyridine); the \(^1\)H NMR (DMSO-d$_6$, ppm): 3.79 (S,3H, OCH$_3$), 7.16 (d, IH, d=7.83, 2.53H, phenyl C$_6$-H), 7.21 (dd, IH, j =7.80, 5.21H, phenyl C$_4$-H), 7.38 (dd, IH, j = 7.80, 5.21H, pyridine C$_3$-H), 7.86 (dd, IH, j=2.52H, phenyl C$_6$-H), 8.31 (d, IH, d=7.80H, pyridine C$_3$-H), 8.72 (d, IH, j =5.21, phenyl C$_9$-H), 8.66 (S, IH, CH=H), 10.22 (S, IH, COOH), 530(M-N), 460 (M-O).

The IR Spectra of Schiff base due to 2-aminonicotinic acid and the Salicylaldehyde

The IR spectra of the Schiff base showed bands at 3282-3286 cm\(^{-1}\) resulting from the OH stretching of the phenol and carboxyl groups at 1735-1741 cm\(^{-1}\) regions respectively, the carboxyl (C=O) stretching 1382-1383 cm\(^{-1}\) were observed in the regions, indicating that there is a change in the structure of the Shift base. The azomethine (HC=N) stretching were observed in the 1630-1635 cm\(^{-1}\) region, and the pyridine (C=N) stretching at 1610 cm\(^{-1}\) in all the structures synthesized showing that there is a combination of amines and aldehydes in the structure.

**The \(^1\)H-NMR spectra**

For Schiff bases of 5-bromo, 5-nitro and 5-methoxysalicylaldehyde, the \(^1\)H-NMR spectra exhibited the OH protons of the phenol at \(\delta\) 10.21 – 10.45 and the carboxyl OH protons at \(\delta\) 11.31 – 11.42 as three separate singlets. The azomethine (HC=N) protons of all the Schiff bases appeared as singlets at \(\delta\) 8.66 – 8.93. The \(^1\)H-NMR spectrum of 5-bromo, 5-nitro, and 5-methoxysalicylaldehyde displayed phenyl C$_6$-H as a doublet at \(\delta\) 7.15 and \(\delta\) 7.16, respectively. The phenyl C$_6$-H, experiencing a de-shielding effect due to the inductive effect of HC=N function, resonated as a doublet at \(\delta\) 7.15 and \(\delta\) 7.16, respectively.

**The \(^13\)C-NMR**

The \(^13\)C-NMR spectra of 5-bromo-, 5-nitro- and 5-methoxy displayed peaks at \(\delta\) 165, \(\delta\) 158, \(\delta\) 147, \(\delta\) 143, \(\delta\) 110, and \(\delta\) 108. The carbonyl in carboxylic group experiencing a de-shielding effect occurs at the downfield of \(\delta\) 165. The imine group was found at \(\delta\) 158 while the benzene carbon occurred at \(\delta\) 108 - \(\delta\) 143.
The GC-MS fragmentation of 2-\{[(2-hydroxy-5-methoxyphenyl) methylidene]amino\} nicotinic acid

Figure 4: The GC-MS fragmentation of 2-\{[(2-hydroxy-5-methoxyphenyl) methylidene]amino\} nicotinic acid

The GC-MS showed the mass ion at 272.3 and major fragment at 200, 152, 151, 123, 119, 120, 57, 45(base peaks) 43 and 43.

Biological Activities of Ligands and Its Metal Complexes
Preliminary Screening

Table 1: Result of \textit{in vitro} antibacteria activities of the Schiff base

| Compounds | \textit{B. subtilis} | \textit{E. coli} | \textit{E. aerogenes} | \textit{K. pneumonia} | \textit{P. Aeruginosa} | \textit{S. aureus} | \textit{P. mirabilis} |
|-----------|----------------------|-----------------|----------------------|-----------------------|-----------------------|------------------|---------------------|
| 2-\{[(2-hydroxy-5-methoxyphenyl) methylidene]amino\} nicotinic acid | 15 | 20 | 13 | 10 | 9 | 15 | 0 |
| Ampiclox | 19 | 0 | 0 | 0 | 0 | 17 | 19 | 0 |
| DMSO | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 2: Result of \textit{in vitro} antifungi activities of Schiff base

| Compounds | \textit{Aspergillus niger} | \textit{Candida albicans} | \textit{Penicillium notatum} |
|-----------|----------------------------|---------------------------|-----------------------------|
| 2-\{[(2-hydroxy-5-methoxyphenyl) methylidene]amino\} nicotinic acid | 0 | 0 | 0 |
| Ampiclox | 0 | 0 | 0 |
| Ketoconazole | 0 | 0 | 9 |
| DMSO | 0 | 0 | 0 |
Table 3: Results of Min. Inhibitory Conc. (MIC) and Min. Bactericidal Conc. (MBC) (mg/ml) of Schiffs bases

| Compounds                                                                 | Min. Inhibitory concentration (MIC) and Min. Bactericidal (MBC mg/ml) |
|---------------------------------------------------------------------------|------------------------------------------------------------------------|
|                                                                           | B. subtilis | E. coli | E. aerogenes | K. pneumonia | P. aeruginosa | S. aureus | P. mirabilis |
|                                                                           | MIC        | MBC     | MIC        | MBC         | MIC         | MBC       | MIC        | MBC       |
| 2-[(2-hydroxy-5-methoxyphenyl)methylidene]amino] nicotinic acid           | 1.2        | 1.5     | 0.9        | 1.2         | 1.5         | 1.5       | 1.5        | 1.2       |

The MIC/MBC values were determined as mg/ml of active compound in medium.

Table 4: Results of Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC) of Schiff bases

| Compounds                                                                 | Dimeter zone of inhibition (mm) |
|---------------------------------------------------------------------------|---------------------------------|
|                                                                           | A. niger | C. albicans | P. notatum |
|                                                                           | MIC | MBC | MIC | MBC | MIC | MBC |
| 2-[(2-hydroxy-5-methoxyphenyl)methylidene]amino] nicotinic acid           | 0   | 0    | 0   | 0   | 0   | 0    |

The MIC/MBC values were determined as mg/ml of active compound in medium.

Biological Activity of Schiff Bases

From the presented in Tables 1-4, diameters of zones of inhibition were observed 24h after incubation at a constant temperature of 37°C for bacteria and 30°C for 2-5 days for fungi. The results indicated that, most of the Schiff bases were active against the bacteria and fungi isolates even better, when compared with standard drugs (Ampiclox for bacteria and ketoconazole for fungi).

According to the results of the antimicrobial screening, the Schiff base 2-[(2-hydroxy-5-methoxyphenyl)methylidene]amino] nicotinic acid was active, against most of the test bacteria isolates better than the standard drugs, showing the potential of the synthesized Schiff base as a pharmaceutical precursor in our pharmacies.

Biological Activity of Metal Complexes

In this work, antimicrobial activities of the metal complexes were also compared with those of the standard drugs Ampicillin-Cloxacillin(Ampiclox) and Ketoconazole. The overall results of diameter zone of inhibition obtained indicated that most of metal complexes were active against the bacteria and fungi isolates comparably, more active than the standard drugs used.

This result corresponds with the findings of [25] that reported antibacterial activity of some transition metal complexes of Schiff base derived from o-phenylenediamine and 5-nitrosalicaldehyde. In their work the Schiff bases were more active than the metal complexes against all bacteria. The activity of the complexes obtained appears to be dependent on the geometry of the metal complex. The variation in the activity of different metal complexes against different microorganisms depends on the impermeability of the microbe cell or differences in the ribosomes in the microbial cells [26].

MIC and MBC/MFC of Schiff bases

The MIC of the Schiff base,(table 3) exhibited high and good MIC and MBC results, but no MIC/MFC results on the fungi. The antimicrobial properties of the Schiff bases were further investigated by macro-dilution to determine their minimum inhibitory concentration (MIC) and Minimum Bactericidal Concentration for Bacterial isolates and Minimum Fungicidal Concentration (MFC) applicable to fungi isolates; Tables 3 and 4 showed that there was good MIC and MBC activity with the maximum being 2.5 and a
minimum of 0.9. This was used to show the bacteriostatic and the bactericidal activity of the Shift base.

**Conclusion**

The high affinity of the Schiff bases for chelation towards transition metals has been taken advantage of in synthesizing the complex earlier mentioned. Based on the IR, $^1$HNMR, $^{13}$CNMR and GCMS data of the Schiff bases and complex, a structure has been proposed. From the results of zones of inhibition it was established that the Schiff bases had better activity than Ampicloxfor bacteria and ketoconazole for fungi.

**Escherichia coli, Bacillus subtilis, Enterobacter aerogenes and P. aeruginosa** were most susceptible at minimum concentration of 0.9mg/ml, 1.2mg/ml, 1.2mg/ml and 1.5mg/ml respectively.

**RECOMMENDATION**

Based on the above results it was recommended that the Schiff base be tested on different disease causative microbes and that they could be integrated to the pharmaceutical industries for proper use after clinical studies have been done to attest to their toxicology. When properly harnessed, can enhance the pharmaceutical industry.

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