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ORIGINAL ARTICLE

Synergistic effect of schiff base ligands and its antibacterial potential

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ABSTRACT
We have developed a Nickel (II) chelate complex with a tridentate ONN-Schiff base ligand and the anion of salicyladehyde, showing a potent antibacterial activity against a panel of human pathogens. In this experiment we have explored the combination effect between the schiff base ligands. Previous theoretical quantum-chemical studies of this complex and its adducts with biological molecules elucidated the underlying mechanism of action of this complex Ni(II) complex interacts synergistically with the ligands for most schedules of administration. These findings call for prompting to search for possible interaction of this complex with other cellular elements of fundamental importance.
Keywords: Synergistic effect, Nickel (II) chelate complex, ONN-Schiff base ligand

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INTRODUCTION

Metal complexes play an essential role in agriculture, pharmaceutical and industrial chemistry . Ligand, a metal surrounded by a cluster of ions or molecule, is used for preparation of complex compounds named as Schiff bases [1], which are condensation products of primary amines and aldehydes or ketones (RCH=NR ′, where R & R ′ represents alkyl and / or aryl substituent's).This paper reviews uses of Schiff bases and their metal complexes as catalysts, in various biological systems, polymers and dyes, besides some uses as antifertility and enzymatic agents.

In recent years, the coordination of Schiff bases to transition metal ions has been extensively studied in medicine and diagnostics [2]. The substituted heterocyclic moiety in combination with transition metal salts generate coordination compounds which possess enhanced physiochemical and pharmacological properties [3-6]. Given the high costs and toxicity of platinum-based drugs, researchers have paid more attention to transition metals, such as Ni. Nickel is recognized as an essential trace element because several hydrogenases and carbon monoxide dehydrogenases [7] contain nickel ions in the active site. More specifically, nickel complexes with varied biological activities have been reported in the literature, for instance, with antibacterial [8-10], antifungal [9] and antiproliferative/anticancer properties [10-13]. In this , three Schiff base ligands (H_1L^1,H_1L^2 & H_1L^3) have been prepared by condensation of Triethylenetetraamine, N,N'-Bis (3-aminopropyl) ethylenediamine and Diethylenetriamine with Salicylaldehyde , respectively. The Ni(II) complexes with the two ligands have been synthesized, and characterized

MATERIAL AND METHODS

Chemicals and Instruments Salicylaldehyde was prepared by following literature [5] method, N.N'-bis-(3-aminopropyl) ethylenediamine, salicylaldehyde, Triethylenetetraamine and Diethylenetriamine was purchased from Sigma Aldrich, Nickel metal was purchased from Alfa Aesar, ethanol and methanol were purchased from Qualigens, IR spectra were recorded on a PerkinElmer FT-IR 8300 series

spectrophotometer on KBr disks from 4000 to 400 cm-1, Electronic spectral studies were carried out on a PerkinElmer lambda 35 UV-visible spectrophotometer

H_1L^1

An absolute methanol solution of 1 mM [0.16 ml] of Triethylenetetraamine was added gradually to a 2 mM [0.2ml] methanolic solution of salicylaldehyde . This reaction mixture was stirred on magnetic stirrer for 3 hours at room temperature. A green colour precipitate was obtained, it was filtered and washed with cold ethanol and dried overnight in a desiccator. The Schiff bases were recrystallized using methanol.

H_1L^2

An absolute methanol solution of 1 mM [0.18 ml] of N,N'-Bis (3-aminopropyl) ethylenediamine was added gradually to a 2 mM [0.2ml] methanolic solution of salicylaldehyde . This reaction mixture was stirred on magnetic stirrer for 3 hours at room temperature. A green colour precipitate was obtained, it was filtered and washed with cold ethanol and dried overnight in a desiccator. The Schiff bases were recrystallized using methanol.

H_1L^3

An absolute methanol solution of 1 mM [0.1 ml] of Diethylenetriamine was added gradually to a 2 mM [0.2ml] methanolic solution of salicylaldehyde . This reaction mixture was stirred on magnetic stirrer for 3 hours at room temperature. A green colour precipitate was obtained, it was filtered and washed with cold ethanol and dried overnight in a desiccators. The Schiff bases were recrystallized using methanol.

Synthesis of Nickel Schiff base complex [Ni(H_1L^2)(H_2O)]

An absolute methanol solution of 1 mM [0.18 ml] of N,N'-Bis (3-aminopropyl) ethylenediamine was added gradually to a 2 mM [0.2ml] methanolic solution of salicylaldehyde . This reaction mixture was stirred on magnetic stirrer for 3 hours at room temperature. A green colour precipitate was obtained, it was filtered and washed with cold ethanol and dried overnight in a desiccator. The Schiff bases were recrystallized using methanol. The Nickel (II) Schiff base complex was synthesized by the following procedure, 1:1 ratio of Schiff base ligand and Nickel (II) chloride [0.237g] was mixed under stirring condition and this mixture was stirred on magnetic stirrer for 2 hours, a brown colour solution was obtained and it was cooled to room temperature for 24 hours, brown colour solid was obtained. The crude product was recrystallized by methanol.

Median-effect analysis and Combination Index

The combined drug interaction was assessed with the median-effect analysis and the CI – isobologram method, using CalcuSyn computer software. The analysis compared the effects of drug combinations to the effects of individual drugs, indicating if the interaction is synergistic, additive or antagonistic. The general equation for dose-effect was proposed by Chou and Talalay [14] and it calculates the Dose and the Effect as follows: fa/fu = (D/Dm)m, where D represents the dose of the drug , Dm represents the median-effect dose, fa is the fraction affected by the dose, fu is the unaffected fraction (fu = 1 – fa) and m is an exponent signifying the sigmoidicity (shape) of the dose-effect curve. The CI value is derived from the following equation: CI = (D1/Dx1)+ (D2/Dx2) + a(D1*D2/x1*Dx2), where Dx1,Dx2 represent the doses of drugs (1 & 2 respectively) needed to obtain a certain effect when they are given alone (SF of x), D1,D2 the doses of the same drugs producing an equal effect when used in combination and finally, a = 1 formutually non-exclusive drugs (have totally independent modes of action) and a = 0 for mutually exclusive drugs (have the same or similar modes of action). Dx1 and Dx2can be determined by drawing a least square regression line on a computer graphic system. When CI <1, =1 or >1, synergism, additivity or antagonism is indicated respectively. The interaction of the agent was quantitated by the CI method across the entire dose-effect range. As a general rule in the current experiments, the interaction between Cu-Sal and the chemotherapeutic drugs was considered to be non-exclusive (a = 1), implying an independent or different mechanism of action between the combined agents

RESULTS AND DISCUSSION

Spectroscopic Characterization

In the IR spectra of the compounds, the bands at 2845–3105 cm^{-1} are assigned to C–H stretching absorptions. The IR spectra of the Schiff base ligands H_1L^1 (E)-1-((1-(2-hydroxyethyl)-1H-pyrazol-5-ylimino) methyl) -naphthalen-2-ol) and (E)-ethyl-5-((2-hydroxynaphthalen-1-yl) methyleneamino)-1-methyl-1H-pyrazole-4-carboxylate show sharp strong bands at around 1622 and 1624 cm^{-1}, respectively, which are characteristic of C=N bands. No significant change was found in this band position in complex **1**. As a result of coordination, the spectral band was shifted to lower frequency in **2**, indicating that the amido nitrogen atom takes part in the coordination with the nickel ion [15]. In addition, the hydroxyl groups (–OH) of the Schiff bases show the absorption bands in the region of 3203–3430 cm^{-1}. However,

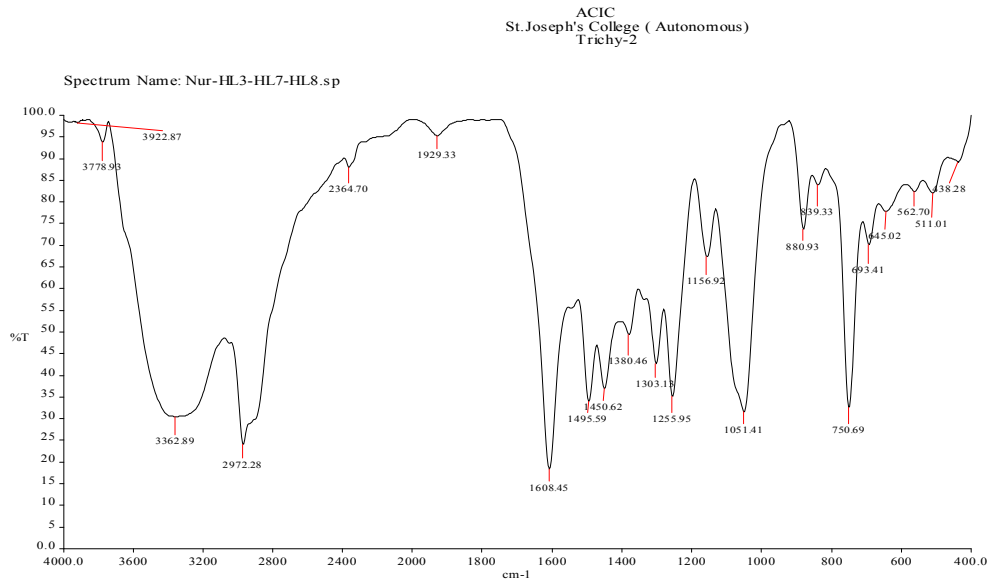
the corresponding strong absorption of *n*(OH) for **1** and **2** were exhibited at around 3420 cm^{-1}. The UV-Vis absorption spectra for both H_1L^1, H_1L^2, **1** and **2** were recorded in solid state and aqueous solution at room temperature. The spectra of H_1L^1 and H_1L^2 reveal significantly intense regions of absorbance at around 208 nm, which can be attributed to _ ! _* transitions of the ligands. Compared with their ligands, the visible spectrum of **1** and **2** show typical bands of octahedral and square Ni(II) at 600 and 650 nm, respectively. These bands are assigned to 3A2g ! 3T1g, and 1B1g ! 1A1g transitions, respectively. The stability of all complexes in DMSO and Tris-HCl buffer has been determined via UV-Vis (shown in Figure S1) spectroscopy. No distinct UV-Vis changes for any complexes in test were found for 48 h and just tiny changes in the absorptive intensities were observed, confirming the stability of all complexes at room temperature. Therefore, the solutions were allowed to employ further experiments.

The mass spectra of ligands H_1L^1 and H_1L^2 show similar fragmentation patterns and give molecular ion peaks [M]+ at m/z 280 and 322.9, respectively, corresponding to the exact mass of the organic motif. The positive mode ESI-MS of **1** and **2** revealed molecular ion peaks (m/z) at 417.06 and 494.15, respectively. $[Ni(H_1L^1)(H_2O)]+$, 417.06 (fit: 417.0), indicated one H_1L^1 ligand and the OAcℵmight be a discrete species obtained from the neutral molecule under electrospray ionization conditions. Meanwhile, $[Ni(H_1L^2)(H_2O)]+$, 494.9 (fit: 494.6), manifested that one L2□ anion was presumably ionized from the parent species under electrospray ionization conditions.

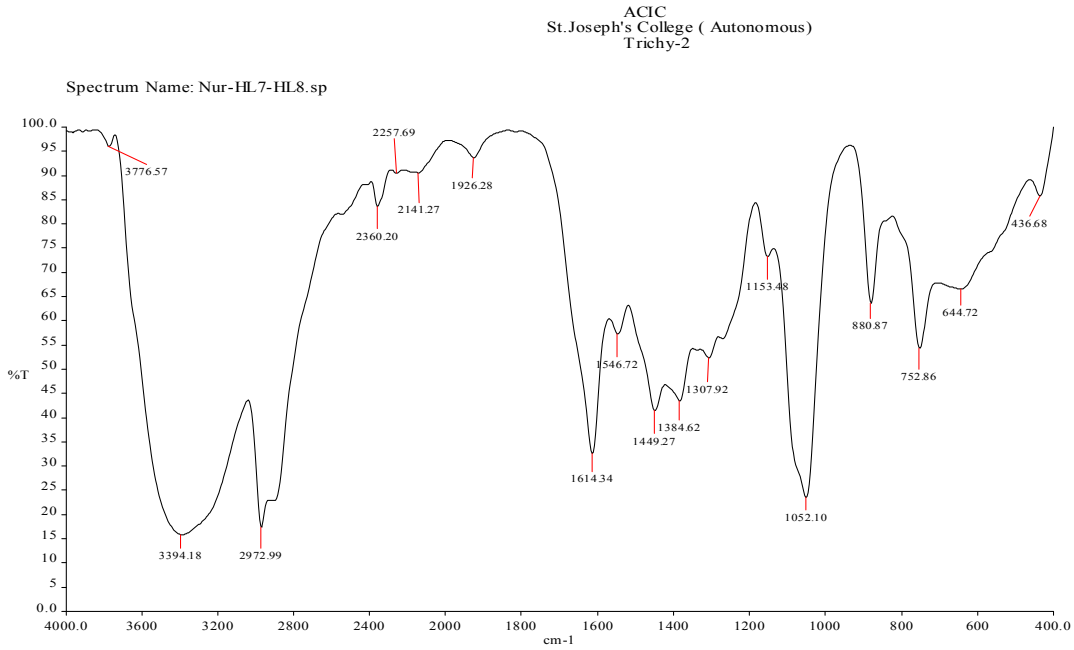
Biological Activity

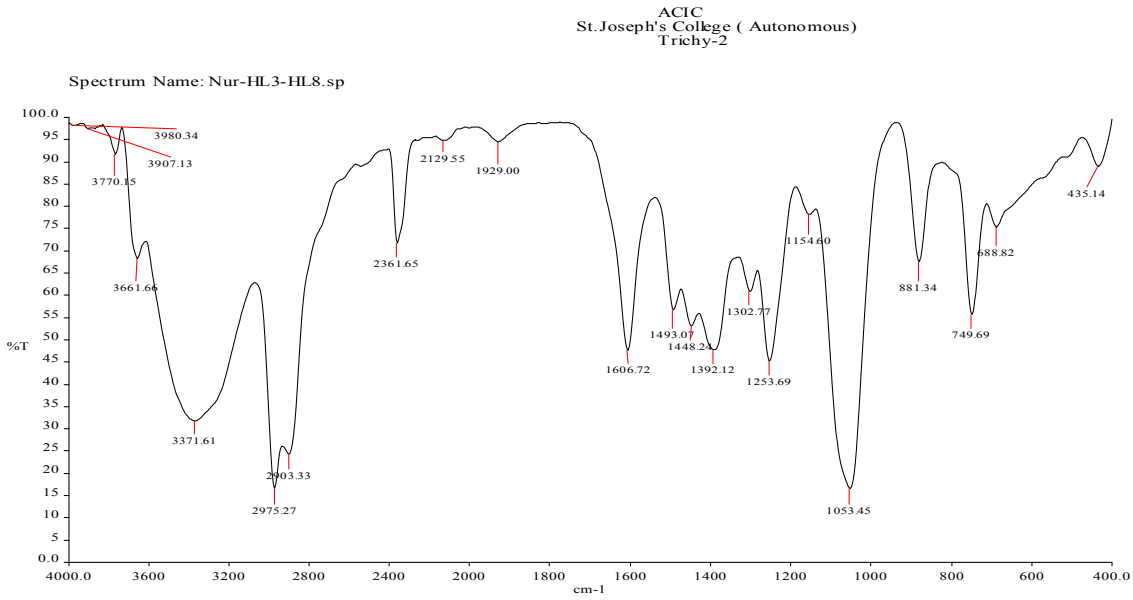
A 0.5 mL spore suspension (10 −6-10−7 spore/mL) of each of the investigated organisms was added to a sterile agar medium just before solidification, then poured into sterile petri dishes (9 cm in diameter) and left to solidify. Using a sterile cork borer (6 mm in diameter), 3 holes (wells) were made in each dish, and then 0.1 mL of the tested compounds, dissolved in DMF (100μg/mL), was poured into these holes. Finally, the dishes were incubated at 37°C for 48 hours. Then clear or inhibition zones were detected around each hole.DMF alone (0.1 mL) was used as a control under the same condition for each organism, and, by subtracting the diameter of inhibition zone resulting with DMF from that obtained in each case, both antibacterial activities were calculated as a mean of 3 replicates [16,17].

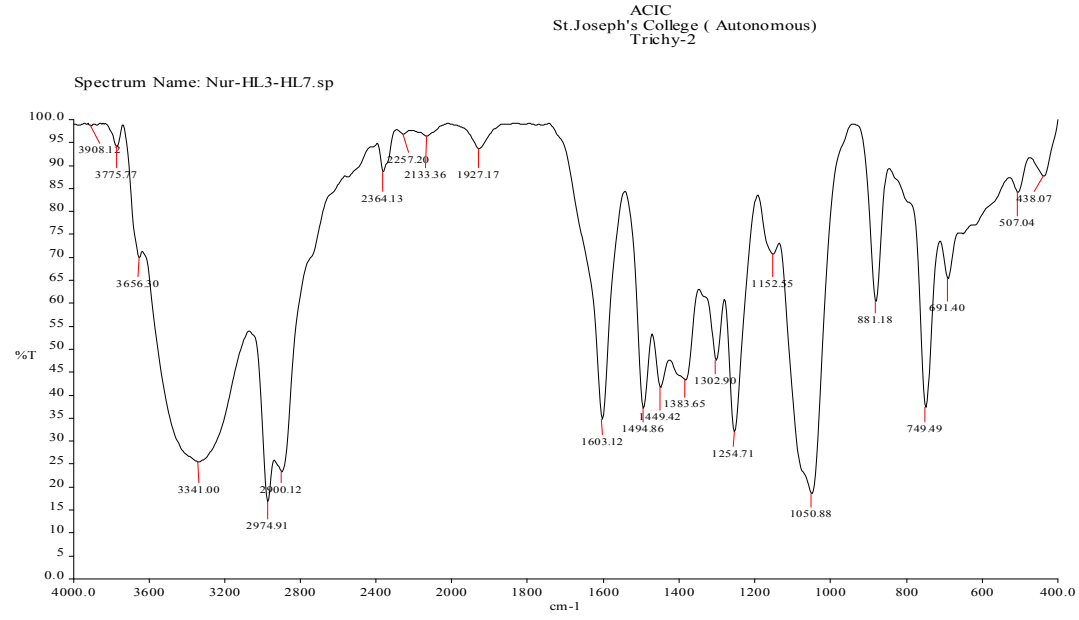
In testing the antibacterial activity of these compounds we used more than one test organism to increase the chance of detecting the antibiotic potential of the tested materials. The sensitivity of a microorganism to antibiotics and other antimicrobial agents was determined by the assay plates, which were incubated at 28°C for 2 days (for yeasts) and at 37°C for 1 day (for bacteria). All of the tested compounds showed a remarkable biological activity against different types of Gram-positive and Gram-negative bacteria. The data are listed in Tables 11 and 12. Upon comparison of the biological activity of the Schiff bases and their metal complexes with the standard (Traivid and Tavinic), it is seen that the biological activity of the Schiff bases increases in the order H_1L^2 >L1. The biological activity of L1 and H_1L^2 are less than that of Tavinic, but higher than that of Traivid. For Schiff base (L^1) complexes, the biological activity of Fe(III),Co(II), Cu(II), and UO_2 (II) complexes is higher than that of the ligand and Traivid, while their activity is comparable with that of standard Tavinic. For Ni(II) complexes, their biological activity is nearly the same as that of L^1. The importance of this lies in the fact that these complexes could reasonably be used for the treatment of some common diseases caused by E. coli , e.g., septicemia, gastroenteritis, urinary tract infections, and hospital-acquired infections.



However, Ni(II), complexes of L^1 and H_1L^1 ligands, respectively, were specialized in inhibiting Gram-positive bacterial strains (*Staphylococcus pyogenes* and *Pseudomonas aeruginosa*). The importance of this unique property of the investigated Schiff base complexes is that they could be administered safely for the treatment of infections caused by any of these particular strains. In addition, metal complexes of L^1 and complexes of H_1L^2 inhibit fungi at high concentration (5 mg/L), more so than the parent ligands and standards. Therefore, it is claimed here that such compounds might have a possible antitumor effect since Gram-negative bacteriaare considered a quantitative microbiological method for testing beneficial and important drugs, in both clinical and experimental tumor chemotherapy .







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