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Original Article

Biological investigation of novel metal complexes of 2-amino-4-substituted phenylthiazole Schiff bases

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الملخص

أهداف البحث: المسئول عن تأخر الشفاء من الأمراض المعدية المختلفة هو الكائنات الحية الدقيقة الغازية والشوارد الحرة. هناك حاجة لجزيئات مهجنة جديدة تبقى فاعلة ضد الكائنات الحية الدقيقة الغازية ويمكن أن تمنع الشوارد الحرة. تم توليف سلسلة من ٢-أمينو-٤-فينيل ثيازول المستبدل والمعتمد على قاعدة "شيف" لتحمل المركبات المعدنية.

طرق البحث: تم تأكيد البنية الهيكلية للجزيئات المركبة بواسطة تحليل العناصر. كما تم التحقيق من النشاط المضاد للميكروبات لجميع الجزيئات المركبة بواسطة طريقة أجار للانتشار الجيد. وكذلك تم تحديد دراسة السمية الحادة للتوليفات والمركبات المجمعة بواسطة خط التوجيه. وتم التحقق من نشاط الكسح الجذري.

النتائج: وفقاً لنتائج دراسة السمية الحادة عن طريق الفم، فإن النظائر المؤلفة هي آمنة إلى جرعة تصل ٢٠٠٠ مجم/كجم من وزن الجسم. أظهرت المجمعات "٦أ" و "٦د" نشاطا مضادا للجراثيم كبيرا ضد سلالات من البكتيريا مقاومة للدواء فضلا عن خاصية الكسح الجذري المحتملة.

الاستنتاجات: تثبت هذه الدراسة أن خالبات المعادن مع روابط قاعدة "شيف هي المسئولة عن تعزيز النشاط البيولوجي ضد مقاومة السلالات الميكروبية.

الكلمات المفتاحية: مضادات الميكروبات؛ مضادات الأكسدة؛ القابلية المغناطيسية؛ قاعدة شيف؛ طيفي

Abstract

Objective: : Invasive microorganisms and free radicals are responsible for the delayed healing of various infections. It is necessary to discovery of novel molecules that are effective against invasive microorganisms and inhibit free radicals. Therefore, a series of metal complexes of 2-amino-4-substituted phenylthiazole Schiff bases were synthesized.

Methods: Structural characterization of the synthesized molecules was performed by elemental analysis, FT/IR, ^{1}H NMR, UV–Vis spectrophotometry, LC-MS, XRD, and SEM. The antimicrobial activities of all the synthesized molecules were investigated by an agar well diffusion method. An acute oral toxicity study of the synthesized ligands and their metal complexes was conducted according to OECD guidelines. The DPPH assay was used to evaluate the radical-scavenging activities of the compounds.

Results: Results of the oral acute toxicity study revealed that the synthesized analogues are safe up to a dose of 2000 mg/kg body weight. The complexes bis[{4-((4-bromo-3-methylphenyl)diazenyl)-2-((4-phenylthiazol-2-ylimino)methyl)phenoxy}]cobalt (**6a**) and bis[4-{(4-bromo-3-methylphenyl)diazenyl}-2-{(4-(4-chlorophenyl) thiazol-2-ylimino)methyl}phenoxy]cobalt (**6d**) exhibited significant antibacterial activities against drug-resistant bacterial strains as well as potent radical-scavenging properties.

Conclusion: The results justify that the chelation of metals with Schiff base ligands enhances their biological activities against drug-resistant microbial strains.

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Keywords: Antimicrobial; Antioxidant; Magnetic susceptibility; Schiff base; Spectroscopic

Introduction

Azo-linked Schiff bases exhibit diverse biological properties.[1] Compounds having an azomethine (−C═N−) functional group are known as Schiff bases; they function as organic synthons for the synthesis of new molecules. They exhibit anticancer,[2] anti-tubercular,[3] antiviral,[4] anticonvulsant,[5] and antimicrobial activities.[6] They are flexible and structurally similar to natural biological substances due to the presence of an imine (−N═CH−) group.[7]

The azomethine group is a good electron donor, and forms stable complexes with transition metal ions.[8] Both azo and azomethine groups in azo-linked Schiff bases are capable of forming coordination bonds with metal ions; however, metal ions interact preferentially with the azomethine group, leaving the azo group free.[8] Coordination of an organic compound with a metal drastically changes its biological properties.[9] Metal complexes of Schiff bases exhibit anticancer,[10] antimicrobial,[9,10,1] and antioxidant activities[11] as well as decreased cytotoxicities compared to individual metal ions and Schiff bases.[11] The treatment of infections is challenged by multidrug resistance in pathogenic organisms and oxidative stress. Hence, the development of newer molecules for the management of infections and oxidative stress is warranted.[12,13] Metal complexation alters the therapeutic efficiency of azo-linked ligands.[14] Azo-linked Schiff bases contain both azomethine and azo groups. Coordination of metals to such groups is responsible for their versatile biological properties.[8] Schiff bases derived from salicylaldehyde are known as polydentate ligands; they can coordinate with metals in both their deprotonated and neutral forms.[15] Salicylaldehyde-bearing molecules exhibit antineoplastic, antimicrobial,[15] antiviral,[16] cytotoxic,[17] DNA-binding,[18] and antioxidant[19] activities.

The objective of the study was to synthesize a series of metal complexes retaining both azo and azomethine groups and identify molecules that are effective against drug-resistant microbial strains and possess significant antioxidant properties, thereby acting as efficient anti-infective agents. Antimicrobial activities were evaluated using drug-resistant bacterial strains. This study is a continuation of our earlier reported study.[6] In this study, different transitional metals were conjugated with Schiff base intermediates of 5-[(4-bromo-3-methylphenyl)diazenyl]-2-hydroxybenzaldehyde, (**4e**),[6] and their biological properties were evaluated.

Materials and Methods

All the chemicals (Merck) used were of synthesis grade. Melting points were determined by the open capillary method (Elico), and were uncorrected. The IR spectra of the synthesized molecules were recorded by a JASCO FT/IR 4100 Spectrophotometer using KBr pellets. A mass spectrophotometer with a C_6 column (150 mm × 4.6 mm, 5 μm) was used to determine the molecular mass (Shimadzu). ^{1}H NMR spectra were recorded using tetramethylsilane as an internal standard (Bruker ^{1}H NMR, 400 MHz), and chemical shifts (δ) were reported in ppm. UV and elemental analyses were performed using a JASCO V-630 spectrophotometer and a Perkin Elmer 2400 CHNS/O analyser, respectively. XRD analysis was performed using a Cu Kα X-ray source; step = 0.02(2θ), run 2θ = 2−80°, scanning speed = 2°/min (Shimadzu XRD 7000). Structure elucidation was performed using the Origin data analysis software. A scanning electron microscope (EGOMA 15 ZEISS) was used to study the structural environment. Magnetic susceptibility was analysed by a Faraday balance.

The synthesis of 5-[(4-bromo-3-methylphenyl)diazenyl]-2-hydroxybenzaldehyde (**4e**) was carried out as previously reported.[6]

*Synthesis of Schiff base ligands **5** (**a**−**b**) **Lig***

An ethanolic solution (50 mL) of 2-amino-4-substituted phenylthiazole **4** (**a**−**b**) was mixed with an aqueous solution (100 mL) of **4e** in equimolar concentrations, and the mixture was refluxed in the presence of glacial acetic acid for 2 h at 70 °C to obtain Schiff base ligands **5** (**a**−**b**).[20] The precipitates obtained were repeatedly washed with a mixture of ethanol and diethyl ether.

*Synthesis of complexes **6** (**a**−**f**)*[6]

Each Schiff base ligand (2 mmol) was mixed with an equal proportion of respective metal chlorides (Co^{2+}, Cu^{2+}, and Ni^{2+}; 1 mmol) and refluxed with ethanol for 2 h at 70 °C, followed by recrystallization in ethanol. The progression of the reaction was monitored by TLC with a solvent system containing ethyl acetate and cyclohexane (1:3).

Antimicrobial activity

Antimicrobial activities of the synthesized molecules were studied by an agar well diffusion method using nutrient agar and Sabouraud dextrose agar media for bacterial and fungal pathogens, respectively.[21] Freshly subcultured microbial strains of *Klebsiella pneumoniae* (MTCC 109) and *Candida albicans* (MTCC 3017) were procured from the Institute of Microbial Technology and Gene bank (IMTECH), Chandigarh, India. *Escherichia coli (res)* (resistant to norfloxacin, ofloxacin, ampicillin, cefixime, and nitrofurantoin) and *Staphylococcus aureus (res)* (resistant to norfloxacin, ofloxacin, ampicillin, and cefotaxime) were isolated at the Pharmaceutical Biotechnology Division of the

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