A REVIEW ON PHARMACEUTICAL APPLICATIONS OF LANTHANIDE COMPLEXES WITH NICOTINOYL AND ISONICOTINOYL HYDRAZONES

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ABSTRACT
Lanthanide complexes are quiet divergent and possess interesting and promising medicinal properties. Isonicotinoyl hydrazones have been used in the treatment of diseases like tuberculosis, leprosy and mental disorders. Metal complexes of hydrazones have gained much attention because of their antifugial, antibacterial anticonvulsant, and analgesic, antiinflammatory, antimalarial, antimicrobial, antituberculosis, anticancer, and antiviral activities. The coordination chemistry of lanthanides, relevant to the biological, biochemical and medical aspects, makes a significant contribution to understanding the origin of application of lanthanides, particularly in biological and medical systems. The importance of the applications of lanthanides, as an excellent diagnostic and prognostic probe in clinical diagnostics, and an anticancer material, is remarkably increasing. Lanthanide complexes are very much used in X-ray contrast imaging and in magnetic resonance imaging (MRI). The images are used in radiological analysis of our body systems. In the light of the above, pharmaceutical applications of lanthanide complexes with nicotinoyl and isonicotinoyl hydrazones are discussed in this review article.

KEYWORDS: Pharmaceutical Applications, Lanthanide complexes, Nicotinoyl and Isonicotinoyl Hydrazones.

1.0 INTRODUCTION
Hydrazones are important class of peerless ligands in coordination chemistry. Interest in the study of hydrazones has been growing because of their antimicrobial, antituberculosis and antitumor activities. These observations have been guiding for the development of new hydrazones that possess varied biological activities.[1] Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. Isonicotinoylhdyrazones play an important role in medicinal chemistry. Many physiologically active hydrazones find application[2] in the treatment of diseases like tuberculosis, leprosy and mental disorders. Hydrazones also act as herbicides, insecticides, nematocides, rodenticides and plant growth regulators. Isonicotinimidic hydrazide (INH) is an important antitubercular agent and has potential sites for formation of complexes with metal ions. It is also observed, that isonicotinoyl hydrazones and their metal complexes possess higher activity and lower resistivity to tuberculosis bacteria.

Sah and Peoples[3] synthesized hydrazones by reacting isonicotinic acid hydrazide(INH) with various aldehydes and ketones. These compounds are reported to have inhibitory activity in mice infected by various strains of Mycobacterium tuberculosis. Metal complexes of hydrazones have gained much attention because of their antifungal, antibacterial anticonvulsant, and analgesic, antiinflammatory, antimalarial, antimicrobial, antituberculosis, anticancer, and antiviral activities. Additionally, some of the hydrazone complexes were used in treatment of iron overload diseases. However, studies on metal complexes of nicotinoyl and isonicotinoyl hydrazones are very limited.[4]

The coordination chemistry of hydrazones is an intensive area of study and numerous transition metal complexes of these hydrazones as ligands have been investigated in view of their application in various Fields.[5-7] Hydrazones are interesting ligands with multiple functional groups, which display variable coordination modes under different chemical environment.[8] The chemical properties of hydrazones have been widely investigated due to their chelating capability[9] pharmacological activity[10,11] and analytical applications.[12,13]

2.0 Coordination Chemistry of Lanthanides
Lanthanides generally form stable compounds in +3 oxidation state. The chemistry of lanthanide compounds is mainly determined by the ionic radii, which decrease from lanthanum to lutetium.[14, 15] Lanthanide(III) forms coordination complexes with a wide variety of ligands. Ln(III) ions are typically hard Lewis acids because of the
high charge density and they prefer to bind to hard base atoms, viz. oxygen. Since the 4f electrons are spatially buried, the mixing of ligand and metal orbitals becomes insignificant and bonding between the ligands and the Ln(III) ions is largely electrostatic in nature. Lanthanides generally form complexes with high coordination number (> 6). It is due to lack of any directional bonding character and large ionic size. Therefore, the coordination environment around the Ln(III) centre often cannot be regarded as an idealized coordination polyhedron.

Coordination chemistry of lanthanides has been regarded potential area for research. Besides the isolation of a large number of new complexes sometimes involving novel methods of synthesis, varied applications of these species have been recently suggested. The coordination chemistry of lanthanides, relevant to the biological, biochemical and medical aspects, makes a significant contribution to understanding the origin of application of lanthanides, particularly in biological and medical systems. The importance of the applications of lanthanides, as an excellent diagnostic and prognostic probe in clinical diagnostics, and an anticancer material, is remarkably increasing. As mentioned above, lanthanide complexes are very much used in X-ray contrast imaging and in magnetic resonance imaging (MRI). The images are used in radiological analysis of our body systems. The most important property of the chelating agents, in lanthanide chelate complex, is its ability to alter the behaviour of lanthanide ion with which it binds in biological systems, and the chelation markedly modifies the biodistribution and excretion profile of the lanthanide ions.

3.0 Analytical Applications

Isonicotinoylhydrazones are good analytical reagents due to their ability to form complexes and their ability to produce characteristic absorption spectra when with certain metal ions. Apart from those specified biological applications, these ligands are also potential analytical reagents for the determination of several metal ions by different physico-chemical techniques, of which the spectrophotometric determination occupies a special place. The analytical applications of hydrazones have reviewed by Singh[12] and Katyal.[13] Isonicotinoylhydrazones of carbonyl compounds act as good analytical reagents, but their metal complexes have not been fully exploited.

3.1 Therapeutic and Diagnostic Applications

Lanthanide complexes are of considerable interests for their therapeutic utility. Hence it provides strong impetus to explore their biological activities.[16-22] A brief account of the various therapeutic applications of lanthanides is presented below

1. High level of phosphate in the blood causes an electrolyte disturbance called hyperphosphatemia.[18, 21] The serum phosphate level in the end stage of renal disease (ESRD) patients is thus higher compared to the healthy persons. Lanthanum carbonate sold as Fosrenol™ is used in diet to prevent absorption of the dietary phosphate.

2. The most successful medicinal utility of lanthanides is the use of Gd(III) complexes as MRI contrast agents in clinical radiology.[21-27] Three dimensional (3D) images are significantly enhanced by the use of Gd(III) contrast agents that decrease the relaxation rate of protons of water coordinated to the paramagnetic metal centre. About 30-40% of the clinical MRI scans are performed using Gd(III) contrast agents. Paramagnetic Gd(III) ion with seven unpaired electrons and a symmetric ground state (\(S_{7/2}\)) has high magnetic moment with suitable electronic relaxation rate. An increase in the relaxation rate of water protons results significant enhancement of their signal intensity.

3. However, free Gd(III) at high concentration is toxic. Therefore, Gd(III) chelates are used that are thermodynamically highly stable and kinetically inert. Examples of MRI agents are Gd(DTPA)(H2O)\(_2\)\(^{2-}\) (known as Magnevist™) and [Gd(DOTA)(H2O)]\(^{3+}\) (known as Dotarem™), where DTPA is diethylenetriaminepentaacetic and DOTA is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (Figure 1).

[Figure 1: Structures of A) Magnevist and B) Dotarem.]
bioml]28,29] supramolecular luminescent sensors and self-assemblies30 contrast enhancing agents in radiopharmaceuticals as MRI agents31 and in medicine.32 DNA binding and cleavage properties of lanthanide complexes33,34 have attracted much attention and curiosity of bio-inorganic chemists. Gd(III) complexes of macrocyclic organic ligands ideally suitable as contrast enhancement agents in clinical magnetic resonance imaging (MRI).

Lanthanide(III) complexes of hydrazones, has become a field of great interest because of the realization that these metal complexes can be used as building blocks with controllable molecular architecture and tunable properties. It has been established that suitably substituted hydrazones are capable of coordinating metals to give multinuclear square grid complexes, whose optical, photophysical and magnetic properties can be modulated by degree of protonation of the ligands.

4.0 Past reviews and scope of present review article

The coordination chemistry of transition and lanthanide complexes with acyl, aroyl, heteroaryl hydrazones including nicotinoyl and isonicotinoyl hydrazones are extensively reviewed by Dutta and Hossain35 in the year 1985. The related reviews on the applications of hydrazones and their complexes are well contributed by Rollas et al14 Bakuleva et al36 Shakdofa et al37 and Ivan et al.38

Hydrazones possessing an azomethine-NHN=CH- proton and nicotine/isonicotine groups constitute an important class of compounds for new drug development. Hence recent past work on lanthanide complexes of nicotinoyl and isonicotinoyl hydrazones are reviewed. Isonicotinoylhydrazones play an important role in medicinal chemistry. Pyridoxal Isonicotinoylhydrazone is useful in the treatment of lymphoma and bladder cancer. 3,5-dichloro salicylaldehyde isonicotinoylhydrazone an analogue of the antituberculosis drug isoniazid, could prevent isoniazid induced liver damage.

4.1 Lanthanide (III) Complexes of 2-thienyl-trifluoroacetone isonicotinoylhydrazone

A series of lanthanide(III) complexes of the compositions M(HL)3 (M = La, Pr, Nd, Sm, Dy and Y; H2L = 2- thienyltrifluoroacetone isonicotinoyl hydrazone) and M(HL) (M = Er and Yb) were synthesized and characterized38 based on elemental analyses, conductance measurements, IR, 1H NMR and electronic spectral data. The ligand can coordinate as mono- and di- anions. The complexes are also analyzed by thermal methods.

4.2 Complexes of 1’-Formyl [(2,2-diferrocenyl)propane]isonicotinoyl hydrazone

A new di-ferrocene Schiff base was prepared39 by condensing 1’-formyl[(2,2-diferrocenyl)propane] with isonicotinoyl hydrazone. The ligand, 1’-formyl[(2,2-differrocenyl) propane] isonicotinoyl hydrazone (HL) and its chelates with lanthanide ions, Ln(HL)2Cl2(H2O)n (Ln=La, Dy, Yb, Gd, Sm, Nd; n=1–5) were prepared, isolated and characterized by elemental analysis, IR and 1H NMR spectra. In these chelates the ligand coordinates to lanthanide ions in the keto form, and some chloride ions and water molecules participate in coordination to the metal ion. The redox properties of the ligand and its complexes were investigated using cyclic voltammetric method. Both the ligand and its lanthanide complexes exhibit two distinct pairs of redox peaks displaying electrochemical characteristics of multi-component system.

4.3 Homobinuclear Lanthanide(III) complexes with isonicotinoyl hydrazone

Homobinuclear lanthanide(III) complexes with isonicotinoyl hydrazone ligand [Ho2(L)3(H2O)](NO3)2·2OH ·3.5H2O (I) and [Lu2(L)3](OH)3 (II) (where HL= N,N’-disonicotinoyl-2-hydroxy-5-methylisophthalaldehyde dihydrazone) were synthesized and characterized40 by infrared spectra, elemental analyses, thermal analyses and UV–Vis techniques. The crystal structures of both complexes have been determined by X-ray diffraction analysis. In complex I, the two intramolecular holmium(III) centers have different coordination environments with nine and ten coordination numbers, respectively; however, in complex II, both lutetium(III) centers have the same structure with nine coordination number. In both complexes, the lanthanide(III) ions are intramolecularly bridged by three phenolic oxygen atoms forming a dimeric complex with Ho···Ho distance of 3.5398(7) Å and Lu···Lu distance of 3.3960(9) Å, respectively. L acts as a pentadentate ligand with keto-form coordination in both complexes as indicated by the results of crystal structures and infrared spectral analysis.

4.4 La(III), Sm(III) & Eu(III) complexes of 2-Carboxybenzaldehyde isonicotinoylhydrazone La(III), Sm(III) and Eu(III) complexes of 2-Carboxybenzaldehyde isonicotinoylhydrazone (HL), and its three lanthanide complexes, LnL3(3-H2O) [Ln=La(I), Sm(2), Eu(3)], were synthesized and characterized41 on the basis of elemental analyses, molar conductivities, IR spectra and thermal analyses. In addition, the DNA-binding properties of the ligand and its complexes have been investigated by absorption, fluorescence and viscosity measurements. The experimental results indicated that the complexes (2) and (3) can bind to DNA, but the ligand and the complex (1) cannot; the binding affinity of the complex (3) is higher than that of the complex (2) and the intrinsic binding constant Ks of the complex (3) is 7.86x10^3 M⁻¹.

4.5 Ln(III) complexes with 7-methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone
The neutral mononuclear Ln(III) complexes (Ln = La, Sm) with 7-methoxychrom-one-3-carbaldehyde-isonicotinoyl hydrazone ligand (L) were synthesized, characterized, and investigated with calf-thymus DNA. The results show that the binding affinity of the La(III) complex is stronger than that of the Sm(III) complex and that of the ligand (L). Furthermore, the antioxidant activities of the ligand (L) and its Ln(III) complexes (Ln = La, Sm) were also studied.

4.6 Binuclear lanthanide(III) complexes of 8-hydroxyquinoline-7-carbaldehyde-isonicotinyl)hydrazone

Binuclear complexes [LnL(NO₃)(H₂O)₂]₂ were prepared from the Schiff base 8-hydroxyquinoline-7-carbaldehyde-isonicotinyl)hydrazone (H₂L) and equivalent molar amounts of Ln(NO₃)₃·6H₂O (Ln = La³⁺, Nd³⁺, Sm³⁺, Eu³⁺, Gd³⁺, Dy³⁺, Ho³⁺, Er³⁺, Yb³⁺), respectively. The ligand is dibasic tetradeinate and the dimerization occurs through the phenolato oxygen atoms leading to a central four-membered (LnO)₂-ring. The ligand and all the Ln(III) complexes can bind to calf thymus DNA through intercalation with binding constants of 10⁵–10⁶ (mol L⁻¹)⁻¹, and they show strong scavenging abilities on hydroxyl radicals and superoxide radicals. The values of SCSO of Ln(III) complexes for HO² and O²⁻ are 2.34±13.33 and 4.45±28.48 µmol L⁻¹, respectively. Ln(III) complexes present stronger binding abilities to DNA and stronger anti-oxidation properties than ligand. Complex containing hydroxyl unit shows stronger scavenging abilities on hydroxyl radical, while complex containing N-heteroaromatic substituent shows stronger scavenging abilities on superoxide radicals. Furthermore, earlier rare metal complexes show stronger scavenging abilities on hydroxyl radicals and superoxide radicals.

4.7 Lanthanide complex of 1-Phenyl-3-methyl-5-hydroxypyrazole-4-carbaldehyde-(isonicotinoyl) hydrazone

A Schiff-base ligand derived from 1-phenyl-3-methyl-4-formyl-2-pyrazolin-5-one (PMFP) andisoniazid was prepared and its La(III) complex was characterized by X-ray single crystal diffraction. The La(III) complex is nine-coordinate in a space group P2₁/n. DNA-binding was investigated by UV-Vis, fluorescence titration, ethidium bromide displacement experiments, and viscosity measurements, which indicated that the ligand and La(III) complex strongly binds to calf thymus DNA presumably via groove binding and intercalation. The intrinsic binding constants of the ligand and La(III) complex were 0.86×10⁵ and 2.4×10⁴ M⁻¹, respectively. Antioxidant data from hydroxyl radical scavenging experiments in vitro suggest that the La(III) complex possesses higher scavenging ratio than the free ligand, metallic salt, and some standard antioxidants like mannitol.

4.8 Lanthanide (III) complexes with N-(furfuralidene)-N'-isonicotinoylhydrazine

A series of lanthanide nitrato complexes with N-(furfuralidene)-N'-isonicotinoylhydrazine (INH-FF) were synthesized and characterized by elemental analysis, conductance, magnetic moment measurements, IR, UV-visible, TGA-DTA and luminescence studies. In these complexes the hydrazone, N-(furfuralidene)-N'-isonicotinoylhydrazine behave as a neutral bidentate ligand with the carbonyl oxygen and azomethine nitrogen as two coordinating sites. All the three nitrate ions also coordinate unidentately with seven coordination for the lanthanide (III) ions with a tentative monocapped octahedral geometry for the complexes. All the complexes have a general formula, [LnL(NO₃)₃] where Ln= Pr(III), Nd(III), Sm(III), Gd(III) or Tb(III) and L= N-(furfuralidene)-N'-isonicotinoylhydrazine. Spectroscopic determination of nephelauxetic ratio(β), covalency factor(b₁/₂), Sinha parameter(δ%) and covalency angular overlap parameter (η) show a weak covalent bond formation between the metal ion and the ligand in the complexes.

4.9 2-acetylpyridine nicotinoyl and isonicotinoyl hydrazones

The details of other lanthanide complexes with 2-acetylpyridine isonicotinoyl hydrazine are summarized in Table 1.
Table 1: Summary of lanthanide complexes with 2-acetylpyridine isonicotinoyl hydrazine and 2-acetylpyridine nicotinoyl hydrazine.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Name of the compound</th>
<th>Structure of the ligand</th>
<th>Coordination Number and Geometry of the complex</th>
<th>General formula of the complex</th>
<th>Studies</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-acetylpyridine isonicotinoyl hydrazone</td>
<td><img src="image1.png" alt="Structure1" /></td>
<td>12 bicapped pentagonal-antiprism (X-ray)</td>
<td>[Ce(NO$<em>3$)$<em>3$(C$</em>{13}$H$</em>{12}$N$_4$O)$_2$]</td>
<td>…</td>
<td>[46]</td>
</tr>
<tr>
<td>2</td>
<td>2-acetylpyridine isonicotinoyl hydrazone</td>
<td><img src="image2.png" alt="Structure2" /></td>
<td>9</td>
<td>M(2-ApINH)$_2$Cl$_3$ (M= La, Ce, Pr, Nd, Sm, Eu)</td>
<td>…</td>
<td>[47]</td>
</tr>
<tr>
<td>3</td>
<td>2-acetylpyridine isonicotinoyl hydrazone</td>
<td><img src="image3.png" alt="Structure3" /></td>
<td>8</td>
<td>[M(2-ApINH)$_2$Cl]Cl (M = Y, Gd, Tb, Dy)</td>
<td>…</td>
<td>[48]</td>
</tr>
<tr>
<td>4</td>
<td>2-acetylpyridine isonicotinoyl hydrazone</td>
<td><img src="image4.png" alt="Structure4" /></td>
<td>Distorted bi capped square antiprism (X-ray)</td>
<td>[Ln(L$_2$(NO$_3$)$_3$)(CH$_3$OH)$_2$.CH$_3$OH] Ln = Pr, Nd</td>
<td>DNA binding &amp; Anti-oxidant Property</td>
<td>[49]</td>
</tr>
<tr>
<td>5</td>
<td>2-acetylpyridine nicotinoyl hydrazone</td>
<td><img src="image5.png" alt="Structure5" /></td>
<td>8</td>
<td>[Ln(Hapnh)Cl]Cl$_2$·nH$_2$O (Ln = Pr, Nd, Sm, Dy)</td>
<td>…</td>
<td>[50]</td>
</tr>
</tbody>
</table>
4.10 Complexes with nicotinic and isonicotinic acids
One dimensional coordination polymer [Nd$_6$(INA)$_6$(H$_2$O)$_6$]$_2$(I) and a dimeric complex with mononuclear asymmetric unit [Nd(NA)$_2$(H$_2$O)$_2$]$_2$(II) (HINA = isonicotinic acid and HNA = nicotinic acid) were synthesized.[51] The compounds were characterized by elemental analyses, infrared spectroscopy and single crystal X-ray diffraction studies. X-ray crystal structure analysis reveals that both compounds exhibit rich structural chemistry. Compounds I and II belong to the monoclinic system with space group P2$_1$/c. Thermogravimetric analysis has been performed to investigate their thermal stability. The coordination polymer I has meso-porous structure with average diameter of pores (~4 nm) and BET surface area 13.62 m$^2$/g.

4.11 2-Benzoylpyridine nicotinoyl hydrazone
The synthesis, spectral characterization and crystal structure of 2-benzoylpyridine nicotinoyl hydrazone (HL) is reported.[52] Spectral techniques employed include $^1$H-NMR, COSY homonuclear, HSQC heteronuclear correlation techniques, electronic and IR. The infrared spectrum suggests the existence of the compound in keto form in solid state, which is further established by the single crystal X-ray analysis. The compound crystallizes into a triclinic lattice with P-1 symmetry with two molecules per unit cell.

4.12 Complexes of Salicylaldehyde nicotinoyl hydrazone
Complexes of salicylaldehyde nicotinoyl hydrazone with transition metals, Fe(II) and Cu(II) were synthesized in ethanol medium.[53] Formations of complexes are endothermic processes. The ligand was characterized by melting point, elemental analysis, absorption spectra, $^1$H-NMR prediction and antimicrobial activity while the complexes were characterized by melting point, absorption spectra. A simple & sensitive spectrophotometric method was developed for transition metal complexes of SANH. The optimum condition for complete colour development have been established. The stability constant, dissociation constant & change in free energy of Fe (II) & Cu (II) complexes with SANH are determined. Composition of the metal & ligand has been determined by Job’s variation & mole ratio method indicate that the M:L is 2:1. Tolerance limit of diverse ions in the determination of Fe (II) & Cu (II) with Salicylaldehyde nicotinoyl hydrazone are investigated.

4.13 p-Dimethylaminobenzaldehyde isonicotinoylhydrazide and 3-methoxy-4-hydroxy benzaldehyde isonicotinoylhydrazide
Complexes of La, Pr, Nd, Sm, Gd, Tb and Dy with p-dimethylaminobenzaldehyde isonicotinoylhydrazide and 3-methoxy-4-hydroxy benzaldehyde isonicotinoylhydrazide were synthesized and characterized[54] by analytical, magnetochemical, IR and UV-vis spectral methods. The thermal stabilities of these compounds were also investigated.

4.14 Lanthanide Complexes of Nicotinic Acid Hydrazide
Trivalent lanthanide complexes of nicotinic acid hydrazide (NicHz) of the type Ln(NicHz)$_2$Cl$_2$.n EtOH [Ln = La, Pr, Nd, Sm for n = 2; Ln = Eu, Gd, Tb, Dy and Y for n = 1] were synthesized. The hypersensitive band profile of the electronic spectrum indicates an eight-coordination around neodymium and the molar absorptivity has been found to increase with increasing pH and to decrease with increasing temperature (30–80°C). FT-far IR spectra indicate a trans configuration of the two chloro groups within the coordination sphere. A square antiprismatic structure has been proposed for the complexes.

5.0 Lacuna in the Literature
Investigation of metal-DNA interactions is the focus of current research. However, there have been only few reports[55] on the interactions of lanthanide complexes of with DNA.

6.0 CONCLUSIONS
The metal-based anticancer complexes have attracted many bioinorganic chemists’ interest since the success of platinum complexes as anticancer agents. Among various metal complexes, Ln(III) complexes have been intensively investigated due to their more physiological activities and lower toxicities after coordination with ligand. People have paid great interest to synthesis, DNA interaction, and anticancer activity of Ln(III) complexes in recent year in order to develop novel metal-based anticancer drugs. Because of special photophysical and biological properties, lanthanide complexes can be used as biological probes in the areas of clinical chemistry and molecular biology. Due to their special electronic configuration, lanthanide complexes have inspired many efforts on the design and synthesis as potential anticancer and antibacterial agents.

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