

A REVIEW ON SYNTHESIS, LANTHANIDE COMPLEXES AND BIOLOGICAL ACTIVITIES OF HYDRAZONE DERIVATIVES OF HYDRAZINE CARBOTHIOAMIDES

ABSTRACT

Hydrazinecarbothioamides are important intermediates with biological activities in organic chemistry synthesis, especially in the synthesis of biologically active heterocyclic scaffolds and compounds. The uniqueness in of synthesis and a wide range of pharmaceutical, medicinal biological potentials and properties, their preferred application as building block and the synthesis of heterocyclic and other important organic compounds and nonlinear optical (NLO) materials have made them attractive derivatives of thiosemicarbazides in the recent years. In this review, a detailed account in terms of synthesis and applications of their hydrazone derivatives and their lanthanide complexes are presented. Further, the biological and analytical applications of newly reported ligands and their complexes are reported. The wide investigation of the lanthanide (III) coordination complexes with organic ligands are mainly due to their structures and strong potential biological and pharmacological properties of hydrazones as derivatives of hydrazinecarbothioamides possess sites that play important roles in the formation of heterocyclics and other biologically active scaffolds

Keywords: Analytical applications · Biological applications · hydrazinecarbothioamide · Lanthanide complexes · thiosemicarbazide.

INTRODUCTION

Organic compounds containing the CH=N, N=N, N-N and N-C-S moiety and their metal complexes have shown a wide range of biological properties. Intermediates such as hydrazinecarbothioamides containing -moiety and their lanthanide complexes have not been extensively studied. Hydrazinecarbothioamides are used in organic synthesis usually as building blocks with several N-deficient compounds for the synthesis of different heterocyclic compounds such as 1,3,4-thiadiazoles and d1,3,4-thiadiazepine [1]. Since the last decade, researchers have shown increased interest in the studies of diagnosis and treatment of cancer and other diseases. This has resulted in the development of theragnostic and improved MRI agents as well as other

advances in techniques and pharmaceuticals. Coordination compounds are at the center of these advances as new and more suitable ligands are desired for the development of antennas and chelates which will find applications in the development of metal-based drugs.

It has become a way of life that from the most sophisticated instruments in defense to the advanced equipment in medicine up to mobile phones, it will be impossible to uphold the current digital life without the lanthanide metals [2]. The coordination chemistry of lanthanides in the modern and Bio-technological applications are mainly due to their spectroscopic, magnetic, photophysical and biological properties. Lanthanide complexes and chelates of organic ligands find application in diagnosis and treatments of diseases as **theragnostic**, MRI imaging and fluorescence probes, defense equipment, mobile phones and in many digital instruments. The Lanthanide chelates find application in the development of metal-based drugs

Metals generally occupy an esteemed and precious place in medicine and medicinal chemistry [3]. In the last decade, lanthanide (III) coordination compounds have gained much attention due to their various uses and application in numerous fields such as fluorescent probes, sensors organic light emitting diodes, MRI agents, Laser materials, theragnostic molecular optoelectrical devices, biomarkers, therapeutic and therapy, antitumor and anti-HIV activities [4][5],[6],[7],[8]. Thiosemicarbazones and thiosemicarbazides, their derivatives and their metal complexes are emerging as anticancer chemotherapeutic agents, showing remarkable inhibitory activity against cancer cells [9],[10]. In this review, we have made attempts to provide update on the lanthanide complexes of hydrazones derivatives of hydrazinecarbothioamides. Arylhydrazone compounds have been reported to use in clinical applications due to their ability to scavenge ferric ion.

SYNTHESIS OF HYDRAZINECARBOTHIOAMIDES DERIVATIVES

Al-Amiry et al.,2012 reported the synthesis and characterization of 2-(2-1mino-1-methylimidaolide n-4-ylidene) hydrazinecarbothioamide from the reaction of creatine with thiosemicarbazide. The antioxidant, antibacterial and antifungal properties were investigated with the ligand. It was found to be a potential agent against the gram negative organisms. The ligand was characterized using spectroscopic and physical methods.[11].

Darell et al.,2018 reported the synthesis of series of substituted methylene hydrazinecarbothioamides derived from 2-oxoquinoline-3-carbaldehyde and were characterized with **FTIR and ¹H-NMR and ¹³C-NMR** spectroscopy. They investigated the anti-plasmodial and

antitrypanosomal properties of the ligands. Most of the compounds were found to exhibit poor antiplasmodial and antitrypanosomal properties. The compounds (E) - 2- ((7-chloroquinoline-4-yl) amino)propyl)-2-oxo-1,2-dihydroquinoline -3 -yl) methylene) hydrazinecarbothioamide and (E)-2-(- 1-(2-((7-chloroquinolin-4-yl) amino)ethyl)-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazinecarbothioamide showed promising potency against the organisms.[12]

Guzeldemira and his coworkers reported the synthesis of some novel hydrazine carbothioamide. They prepared 2-[(b-(4-bromophenyl) imidazol(2,1-]thiazol-1-3-yl)acetal)-N-cycloalkylhydrazinecarbothioamides from 2-(6-(4-bromophenyl) imidazol ((2,1-b)thiazole-3-yl] acetohydrazide. The compounds were characterized with FTIR and ¹H-NMR¹³C-NMR spectrophotometer. They also synthesized hydrazine carbothioamides derivatives bearing thiazolidines. The results showed the inhibiting activity of the hydrazine carbothioamides against Aldose Reductase.[13]

Fig.1- 2-(2-(1-amino-1-methylimidazole n-4-ylidene)

Goktas et al.,2014 reported a series of novel hydrazine carbothioamides. New 2-(imidazo(1,2-a)pyridine-2-yl carbonyl) substitutes hydrazine carbothioamides were prepared and characterized using FTIR and ¹H-NMR and ¹³C-NMR spectroscopic methods. The compounds were synthesized in good yields using ethanol as solvent. The antifungal properties of the hydrazine carbothioamides were investigated with *C. albicans* and *C. parapsilosis* for 48 hrs. the compounds showed activity against the organisms.[14]

Fig.2-Hydrazine carbothioamides [2-(imidazo(1,2-a)pyridine-2-yl carbonyl)]

El-Tabl et al.,2012 synthesized and characterized 2-(5-((2-chlorophenyl) Diaznyl)-2-hydroxybenzylidene) hydrazine carbothioamide using FTIR, UV – Visis, ¹H-NMR and thermal analysis. The ligand synthesized were confirmed by spectroscopic methods. The antibacterial and antifungal screening with the hydrazine carbothioamide were investigated. The found that the ligand was biologically inactive against gram positive bacterium (Bacillus subtilis and gram-negative bacterium (E. coli).[15]

Hassan et al.,2019 studied the synthesis and reactivity of N- substituted alkylidene hydrazine carbothioamide derived from hydrazine carbothioamide and aldehydes. The reaction of the ligands with tetracyanoethylene (TCNE) were investigated in anhydrous. THF at room temperature without the use of any catalyst. The compounds were characterized by FTIR, ¹H-NMR ¹³C-NMR and UV – Vis spectroscopic methods. The reaction of the N- Substituted hydrazine carbothioamide with TCNE yields (Z) – (4-amino-3-(Z) substituted amino) – 2-(substituted imino)-2,3- dihydrothiazole-5-carbonitriles and (Z)-(4-amino-5-cyano-thiazol-2-(3H)-ylidene) carbon – hydrazonoyldicyanides.[16]

Aly et al.,2018 prepared a series of N – substituted hydrazine carbothioamides. The compounds were characterized with IR, ¹H and ¹³C NMR. The rxns N-substituted hydrazine carbothioamide with ethyl-2-cyano-3, 3-bis(methylthio) acrylate and 2-(bis(methylthio) methylene) malononitrile were investigated. The reaction afforded various heterocyclic rings such as 5 – amino-4-cyano-3-(methylthio) N-phenyl-1H-Pyrazole-1-carbothioamide, 5-amino-3-(methylthio) -1H pyrazole-4-carbonitrile, 4-substituted-3-(substituted amino)-1H-1, 2,4triazole-5-(4H)-thione, ethyl 5-amino-3-(methylthio)-1-(substituted carbamothioyl)-1H-phrazole-4-carboxylate ad (z)-ethyl 2-cyano-2-(5-(substituted amino)-1,3,4-thiadiazol-2(3H)-ylidene acetate in good to excellent yield. the compounds were all characterized using spectral techniques including, FTIR, ¹H-NMR ¹³C-NMR, MS and elemental analysis single-crystal X-ray diffractions studies were carried on the compounds. [17]

Fig.3- N – substituted hydrazine carbothioamides

Hassan et al.,2013 prepared a series of 2-substituted hydrazine carbothioamides. The intermediates were cyclized to thiazolidine-4-ones by reactions with dimethyl acetylene dicarboxylates (DMAD) to give 4-oxo-Z-(thiazolidine-5-ylidene) acetate derivatives. The compounds were characterized with spectral techniques including FTIR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, UV-Vis and mass spectroscopic techniques. The reactions were carried out in microwave assisted environment.[18]

Hassan et al.,2016 reported the preparation and reaction of (1-Aryl-ethylidene) hydrazine carbothioamide derived from the rxns of hydrazine carbothioamides with tetracyanoethylene were investigated. The reactions yielded novel 1,3-thiazine and pyrimidinethione derivatives in good yield. The compounds were characterized by IR, ^1H and ^{13}C NMR spectroscopy.[19]

Al-Amiery, Kadhum, Mohamad and Junaedi (2013) reported the synthesis of novel 2-(1-methyl-4-(E)-(2-methylbenzylidene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)-hydrazine carbothioamide (HCB) from 4-aminoantipyrine with 2-methylbenzaldehyde and thiosemicarbazide. The compounds were investigated for corrosion inhibition potentials using potentiodynamic polarization (PDP) and electrochemical impedance spectroscopy (EIS).

They found that HCB inhibited the corrosion of mild steel in acid solution with increase in inhibition efficiency with increasing concentration of HCB ligand with efficiency of up to 96.5% at 5.0mm. the hydrazine carbothioamide was characterized with FTIR and $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy.[20]

Mehdi et al (2017) investigated the synthesis of novel 2-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl) hydrazine carbothioamide from thiosemicarbazide derivatives. The compound was investigated for its stability due to H-bonding and packed cells. The chemical and topological analysis were carried out using density functional group DFT. The interactions were studied using the Bader's Quantum theory of atoms in molecules (QTAIM) for characterization binding energy, chemical reactivity along with the molecular electrostatic potential and to total electron density were investigated.[21]

Bhat et al (2016) reported the synthesis of N-(4-chlorophenyl)-2-(pyridine-4-ylcarbonyl) hydrazine carbothioamide from pyridine-4-carbohydrazide and p-chlorophenylisothiocyanate. The compounds was characterized using FTIR and $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectroscopy. X-ray

crystallographic and antimicrobial analysis were carried out to investigate the structures and biological activities of the compound. The compound was found to be biologically active against gram positive bacillus subtilis ATCC 10400 and methicillin – resistant. Staphylococcus aureus strains Viz MRSA 85N, MRS 66N and MRSA 15G than the references drugs ampicillin and ceftriaxone.[22]

Qin et al ,(2014) reported the construction of two lanthanide complexes based on N-and O-donors. Their luminescence and biological activities were also reported. $\text{Ln}_2(4\text{-cpa})_6(\text{phen})_2$ (Ln = EU, Tb, 4-CPa = 4-chlorophenylacetate, phen = 1,10-phenanthroline) were hydrothermally synthesized.

The complexes were characterized by FTIR, elemental thermogravimetry, powder X-ray diffraction, and single crystal X-ray diffractions. The complexes were found to be distorted tricapped trigonal prismatic in geometry and exhibited antimicrobial activities against *Brassica napus* L and *Echinochloa crusgalli*. [23]

Barbuceanu et al (2014) reported the synthesis of a series of hydrazine carbothioamide from acid hydrazides and 2,4-difluorophenyl isothiocyanate.

The synthesized compounds were characterized using $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, FTIR, Mass spectral and elemental analysis. The hydrazine carbothioamide were investigated for their biological activities. The hydrazine carbothioamides studied were found to show excellent antioxidant activities. They concluded that the compounds from hydrazine carbothioamide might be useful compounds for the development of new antioxidant agents.[24]

Guzeldemirci et al. (2013) studied the synthesis of some new hydrazine carbothioamide, 1,2,4-triazolo and characterized the compound using spectroscopic methods with FTIR, $^1\text{H NMR}$, $^{13}\text{C NMR}$ & EIMS. They study the antimicrobial activities of the compound using *C. albicans*, *C. parasitosis*, *C. kersey*, *T. mentagrophytes*, and *microsporum*. The compound was found to possess antimicrobial activities against the organism. The authors recommended the compound as a potential antimicrobial agent.[25]

lanthanide complexes of hydrazones their biological activities

Sankheet al (2021) reported the preparation and characterization of Biacetalmonoximehydrozonicsalicylidno complex of lanthanoid (III) ions. The complexes were of the general formula $(\text{LnCDMHSA})_3\text{NO}_3$ where Ln represents the lanthanoid metal (fig1). Nd(III), Tb(III), La(III) and Sm(III) ions were complex with the BiacetalmonoximeHydrazonesalicylidene Ligand. The spectral, electronic and magnetic properties of the ligands and the metal complexes were studied using UV-visible, FTIR and elemental analysis. The physical analysis shows that the ligand HDMHSA is a yellow crystalline substance. The ligand was found to act as a bidentate ligand coordinating through the azomethine nitrogen and deprotonated oximino proton. The results obtained from this work agree with literature as compounds containing azomethine group are known to show biological activity.[26]

Fig.4- structure of metal complexes of HDMHSA

Babu et al (2017) reported the preparation of Lanthanodde complexes of Schiff base ligands (N,N-bis (2-hydrxy-1-naphthylidene) acetylhydrazone (Hl). The complexes are of the general formula $(LnCHL)_2(NO)_2NO_3$. The compound were evaluated using Spectroscopic, electronic and thermal studies, using UV, FTIR, ¹H-NMR mass spec and element analysis. La (III), Pr (III), Nd(III), Sm (III) ndEu (III) metal ions were complexes with the ling, HL. X-ray diffraction studies reveal that the neodymium complex has an orthorhombic system with different unit cell parameters. E(III), SmVNd and Pr complexes exhibited Fluorescence properties. The ligand was found to act as a bidentate ligand. Antimicrobial evaluation of the ligand and its metal complexes in bacteria revealed that the lanthanide complexes possess improved or better antimicrobial activity compared to the ligand.[27]

A series of Dinuclear lanthanide (III) complexes with Schiff base were prepared by Tamboura et al (2019). The compounds were characterized using elemental, spectroscopy and physical analysis. The ligand N¹-(2-hydroxy-3-methoxybenzylidene) nicotinohydrazide (h₂L) was prepared from nicotinohydrazide. The complexes are of the general formula (Ln(HL)(+₂O)₂(NO₃)₂(NO₃)₂(H₂O)₂). The Ln [Gd(III), Tb(III), Eu(II)] were found to be nine coordinates in the complexes. The ligand H₂L was found to act as a tetradentate ligand. In all the complexes, the ligand acts as a bridge in tetradentate fashion. The complexes are found to be monomeric capped square antiprism in geometry. Lanthanides are known to form higher coordination numbers above six coordinates.[28]

Raja et al (2016) reported the synthesis of series of lanthanide (III) complexes of 2-benzoylpyridine benzhydrazone. The compounds were characterized using physical and spectroscopic methods. UV and FTIR spectroscopic method were used. Elemental, molar conductance, electrochemical and single crystal X-ray diffraction studies were carried out on the compounds. DNA binding studies were performed on the complexes of La(III), Ce(III) and Nd(III) ions. The complexes are of the general formula (Ln(BPBH)₂(NO₃)₂). The structures of the complexes were determined using single X-ray diffraction studies. The binding studies on DNA suggest groove binding of the complexes with DNA.[29]

Hegazy et al (2011) reported the synthesis of Sc (III), Y(III), Ce(III) and L(III) complexes with a series of B-diketone derivative by condensation with aromatic aldehydes followed by reaction with phenylhydrazine. The complexes and the ligands were characterized using spectroscopic and thermal studies, UV, FTIR, elemental X-ray and fluorescence studies. Ligands were further characterized using ¹H-NMR. The compounds (fig 2) were evaluated for their antibacterial and antifungal properties. The lanthanide (III) complexes were found to possess greater potential antimicrobial activities against B. subtilis, S. aureus, E. coli, S. typhi and A. niger compared to the ligand. They found that in some cases like against B. subtilis, the lanthanide (III) complexes with Sc showed almost same effect as the standard, tetracycline.[30]

Fig.5- The lanthanide (III) complexes

Babu et al (2018) reported the synthesis of Ln(III), Sm(III), Eu(III), Tb(III), Dy(III) and Yb(III) complexes of N,N-bis(2-hydroxy-1-naphthylidene) isonicotinythrazone (fig3). The metal complexes were characterized by elemental, molar conductance, UV-visible, FTIR, mass spectroscopy, ¹HNMR, thermogravimetric analysis, powder X-ray diffraction and fluorescence studies. The molar conductance data showed that the synthesized lanthanide (III) complexes were non electrolytes. They screened for their antimicrobial activities. The complexes show significant antimicrobial activities against E. coli, klebsiella, staphylococcus aureus, B. subtilis compares with the free ligand. The metal complexes are potential antimicrobial agents.[31]

Fig.6-N,N-bis(2-hydroxy-1-naphthylidene) isonicotinythrazone

Haba et al (2006) reported the preparation of Y(III), Lu(III), Ce(III), Pr(III), Nd(III), Sm(III), Gd(III), Dy(III), Er(III) and Yb(III) complexes with 2,6-diformyl-4-chlorophenol-bis-(2¹-hydroxybenzoylthrazone). The compounds were characterized by molar conductance, magnetic moments, infrared spectral and X-ray diffraction. The analytical data obtained showed the metal-

ligand ratio of 1:3 stoichiometry. The complexes were non-electrolyte. The complexes were found to be tricappedtrigonal prism with coordination number of 9 in all the complexes 9(fig4). The coordination number of 9 is characteristics of lanthanides.[32]

Fig.7- 2,6-diformyl-4-chlorophenol-bis-(2¹-hydroxybenzoylhydrazone)

Pospieszna-Markiewicz and his co-workers reported the synthesis and Characterization of Lanthanide Metal Ion Complexes of New PolydentateHydrazone Schiff Base Ligand. The homodinuclear complexes are of the general formular $[Ln_2L_3(NO_3)_3]$ with a newly synthesized

ligand 2-(2-benzoxazol-2-yl)-2-methyl phenol and Ln^{3+} (Sm^{3+} , Eu^{3+} , Tb^{3+} , Dy^{3+} , Ho^{3+} , Er^{3+} , Tm^{3+} , and Yb^{3+}). They found the complexes to be in 2:3 metal ligand ratio. This was further confirmed by structural data. They suggested a nine coordinated metal ion center for the complexes. The complexes were characterized using spectroscopic methods of ESI-MS, FTIR, UV/Vis, luminescence and XRD. The result obtained assigning nine coordination to the metal ions agree with the literature for lanthanide metals. The authors did not evaluate the biological activities of the ligands and their metal complexes.[33]

CONCLUSION

Hydrazone based hydrazinecarbothioamidethiosemicarbazide derivatives and their lanthanide complexes, have been reported in this review for their synthesis, structural characterization and biological activities. In the recent times, a number of reviews have been reported on the metal complexes including a series of novel compounds of thiosemicarbazide. The derivatives of thiosemicarbazide have several potential, antimicrobial, antifungal anti-cancer and other industrial applications including anti corrosion effects. These have made them target molecules for medical, industrial and pharmaceutical researchers. The coordination chemistry of lanthanides with organic ligands is one of the most interesting fields of research in inorganic chemistry due to its growing and astonishing potentials and applications. This is widening the rapidly developing, research field of pharmaceutical inorganic chemistry as a result of their broad range of biological, diagnostic and therapeutic potentials.

Abbreviations

SOCl_2 Thionyl chloride

PCl_5 Phosphorus pentachloride

CH_3COCl Acetyl chloride

LiOH Lithium hydroxide

NaBH_4 Sodium borohydride

H_2O_2 Hydrogen peroxide

Fig Figure

UV–Vis Ultraviolet–visible

IR Infrared

FTIR Fourier transform infrared

NMR Nuclear magnetic resonance

XRD X-ray diffraction

DNA Deoxyribose nucleic acid

CT-DNA Calf thymus deoxyribose nucleic acid

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