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REVIEW ARTICLE

METAL COMPLEXES OF PYRAZOLINES AND EFFECTS OF COMPLEXATION ON BIOLOGICAL ACTIVITY

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ABSTRACT

As evident from the literature, in recent years a significant portion of research work in heterocyclic chemistry has been devoted to pyrazolines containing different aryl groups as substituents. The coordination chemistry of pyrazoline derived ligands has received much attention, primarily due to their biological implications. Several studies have centered around synthesis and structural studies of metal complexes of pyrazolines containing bidentate ligands (S, N, O donors) due to the reported biological activities of these donor ligands and complexes obtained from them.

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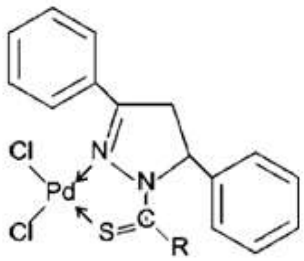
INTRODUCTION

Pyrazolines are weak bases and are good chelating agents due to the presence of donar nitrogen atom in the nucleus and this property has been utilized in the preparation of a large number of their coordination compounds with different metal ions. Metal complexes derived from pyrazolines have attracted considerable interest not only due to their extensive coordination chemistry but also to their catalytic and biological properties. The coordination bonds between transition metal ions and nitrogen containing heterocyclic ligands have proved to be useful for the construction of solid-state architectures and inorganic crystal engineering. Metal complexes of pyrazoline exihibit biological activities such as antimicrobial, antitubercular, anticonvulsant, antitumor, antivirus, antioxidant activity etc.

Effects of Complexation on Biological Activity

Anti-amoebic Activity

Budakoti *et al*. (2006) synthesized 1-N substituted thiocarbamoyl-3, 5-diphenyl-2-pyrazoline derivatives by a base-catalyzed Claisen-Schmidt condensation of benzaldehyde with acetophenone followed by cyclization with various N-4 substituted thiosemicarbazides. The palladium (II) complexes ($PdLCl_2$) [1] of these ligands were obtained by reacting them with $[Pd(DMSO)_2Cl_2]$. The in vitro antiamoebic activity was evaluated against the HM1: IMSS strain of Entamoeba histalytica and the results were compared with the standard drug, metronidazole. The preliminary test result showed that the complexes had better antiamoebic activity than their respective ligands. Moreover, the complexes showed better inhibition of the test organism.



[1]

Singh *et al*. (2013) synthesized copper complexes of 1-formyl-2-pyrazolines by the reaction of 1-formyl-2-pyrazolines with copper chloride and nitrate in methanol. The structure of copper complexes have been established by elemental analysis,

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FT-IR, UV and thermogravimetric analysis. These compounds were tested against HM1:IMSS strain of Entamoeba histolytica by micro dilution method. Husain *et al*. (2008) carried out cyclization of mannich base with N-substituted thiosemicarbazides by different aliphatic, aromatic and cyclic amines which afforded a series of new 1-N-substituted cyclised pyrazole analogues of thiosemicarbazones (PYZ-TSC). Reaction of $[Pd(DMSO)_2Cl_2]$ with pyrazoline derivatives led to new palladium (II) complexes $[Pd(PYZ\text{-}TSC)Cl_2]$. It was concluded that the pyrazoline thiosemicarbazone derivatives have two chelating arms one attached to the 2- position of the pyrazole ring (that is, N donor) and other (S donor) linked to the thiosemicarbazone branch. The determination of antiamoebic activity of all the compounds was done using HMI:IMSS strain of Entamoeba histolytica. All the complexes, showed the most promising activity $1C_{50}$ = 0.37 µM vs. IC_{50}= 1.81 µM of metronidazole.

Anti-microbial Activity

Chandra *et al*. (2009) prepared transition metal complexes of Co(II), Ni(II) and Cu(II) metal ions with general stoichiometry [M(L)X]X and $[M(L)SO_4]$, where M=Co(II), Ni(II) and Cu(II), L=3, 3'-thiodipropionic acid bis [4-amino-5-ethylimino-2, 3-dimethy-1-phenyl-3-pyrazoline) and X=NO_3^-, Cl^- and OAc. The nickel(II) complexes were found to have octahedral geometry, where as cobalt(II) and copper(II) complexes were of tetragonal geometry. The ligands and its complexes have been observated for their antifungal and antibacterial activity against three fungi, i.e. Alternaria brassicae, Fusarium oxysporum and Aspergillus niger and two bacteria, i.e. Pseudomonas aeruginosa and Xanthomonas compestris. Patel *et al*. (2011) synthesized complexes of 2-(8-quinolinol-5-yl)-amino methyl-3-(phenyl)-5-(4-chlorophenyl)/pyrazoline with Cu(II), Mn(II) and Co(II) metal ions and characterized using elemental analysis, IR, PMR, reflectance spectra, conductivity measurements and antimicrobial activity. These studies revealed that they are having octahedral geometry of the type $(ML_2(H_2O)_2]$. The compounds show net enhancement in activity on coordination with metals ions but moderate activity as compared to standard drugs. Tripathi *et al*. (2012) synthesized mixed ligand complexes of iron(III) with aspartic acid and 3-(2-hydroxyphenyl)-5-(4'-substitutedphenyl) pyrazolines and physico-chemically characterized by elemental analysis (C, H, N and Fe), magnetic moment data, thermogravimetric analysis, molar conductance, cyclic voltammetry, spectral analysis (UV-VIS, IR, FT-IR and Fast atom bombardment MS). Antibacterial and antifungal potential of pyrazoline and some iron (III) complexes have been evaluated.

Anti-cancer Activity

Abu-Surrah *et al*. (2010) carried out reaction of 5-hydrazino-1, 3- dimethyl-4-nitro-1H-pyrazole with substituted benzalde-hydes in methanol giving the new substituted schiff base ligands in moderate to excellent yields. Reactions of the pyrazole-based schiff bases with $(PdCl_2 (NCPh)_2]$ in acetone at room temperature gave the trans-palladium(II) complexes trans-$[PdCl_2(L)_2]$. The isolated compounds were characterized by their physical properties, elemental analysis, IR, MS (EI) and NMR spectroscopy. The cytotoxic effect of these complexes against the fast growing head and neck squamous carcinoma cells has been studied. The influence was dose dependent and varies by cell type. The complexes had higher clonogenic cytotoxic effect than cisplatin when tested on cell line. Rathinasamy *et al*. (2006) have synthesized and characterized bis (1,10-phenan thraline/2,2'-bipyridine) ruthenium (II) complexes containing TCP,TTZOPBI, and BTSC ligands (where, TCP= 1-thiocarbamoyl-3,5-diphenyl -2-pyrazoline, TTZ= 2-(3,5-diphenyl-4,5- dihydropyrazol-1-yl)-4-phenylthiazole, OPBI-2-hydroxyphenyl benzimidazole and BTSC=benzoin thiosemicarbazone).

The spectral data suggested that the ligands were coordinated with the metal through N, S and O atoms. The target complexes were tested in vivo for anticancer activity against transplantable murine tumor cell line, Enrlich Ascitic Carcinoma (EAC). All these complexes increased the life span of the EAC earing mice, decreased their tumor volume and viable ascitic cell count as well as improved Hb, RBC and WBC counts. These results suggest that the Ru(II) complexes exhibit significant antitumor activity in EAC-bearing mice. It was also obseved that the ruthenium complexes protected RBC from 2, 2-azobis(2-methylpropionamidine) dihydrochloride (AAPH)-induced hemolysis. The inhibitory effect was dose-dependent at a concentration of 20-120 µg/ml. Saleem *et al*. (2013) synthesized pyrazoline-based ligands; (5-(4-chlorophenyl)-3-(4-fluorophenyl)-4,5–dihydro-1H-pyrazole-1-carbothioamide) by Claisen-Schmidt condensation reaction. DNA binding and in silico studies indicated quite good binding with DNA; requirements for good anticancer drugs. DNA binding constants for ligand, copper, nickel and iron complexes were 1.42 x 10^4, 3.16 x 10^4, 5.82 x 10^5 and 6.72 x 10^5 M^{-1}, respectively, indicating strong binding with DNA. All the reported compounds were slightly hemolytic towards rabbit red blood corpuscles and exhibited moderate activities against MCF-7 cancer cell lines.

Anti-bacterial Activity

El-Wahab *et al*. (2005) prepared a new series of Co(II), Ce(III), and UO_2(VI) schiff base complexes. The reactions of the schiff base ligand 2,3- dimethyl-1-phenyl –4-salicylidene-3-pyrazolin-5-one (HL) with the above metals in the presence of LiOH as a deprotonating agent yielded different types of mononuclear complexes. All the binary and mixed ligand complexes of Co(II) and Ce(III) have octahedral configuration while the UO_2 (VI) complexes have distorted dodecahedral geometries. HL is coordinated to the central metal atom as monoanionic tridentate ONO and/or monoanionic tetradentate ONON ligand. Binuclear Ce(III) complex was prepared pyrolytically through the metal transformation of the mononuclear complex. HL and some of its metal complexes show higher antibacterial effects than those of some of the investigated antibiotics.

Al-Jibori *et al*. (2013) prepared the solid complexes of Cr(III), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) with 2-[5-(2-hydroxy phenyl)-1, 3, 4–oxadiazol-2yl]-5-methyl-2, 4-dihydro-3H-pyrazol-3-one]. The physicochemical data suggested the octahetral gemoetry for all complexes except for Ni(II) and

Zn(II) complexes which were square planaer and tetrahedral respectively. The ligand (L) and its metal complexes were screened for antibacterial activity against E. coli with respect to standard antibiotic drug tetracycline. Tripathi *et al*. (2009) have synthesized arsenic (III) tripyrazolinates and bismuth (III) tripyrazolinates of the type $M(C_{15}H_{12}N_2OX)_3$ [where $C_{15}H_{12}N_2OX$=3(2'-hydroxyphenyl)-5-(4-substitutted phenyl) pyrazoline] by the reaction of MCl_3 and sodium salt of pyrazolines in 1:3 molar ratio in anhydrous benzene at elevated temperatures. The antibacterial activity of the free ligand and their complexes was tested against the bacterial species Bacillus lichaniformis and Vibrio spp.

Anti-fungal Activity

Sangwan *et al*. (2000) carried out cyclization of 3-aryl-1-(2-hydroxyphenyl) prop-2-en-1-ones with hydrazine hydrate in formic acid which afforded ligands HL^1-HL^4 on reaction with the divalent metal ions, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} novel complexes of the type $[ML_2]$ (M=metal ion; L=deprotonated ligand) were formed which were characterized by elemental analysis, molecular weight determinations, molar conductances, magnetic moments and electronic and infrared spectral data. The ligands behaved as tridentate, coordinating through the phenolic oxygen after deprotonation, N-2 of the pyrazole ring and oxygen of the 1-formyl group. The ligands and their complexes were evaluated for growth-inhibiting activity against four phytopathogenic fungi. Macrophomina phaseoli was generally most sensitive followed by Alternaria alternata and Colletotrichum falcatum while Fusarium oxysporum was least sensitive to the tested compounds. The ligand HL^1 and its complexes showed the activity against the fungi tested.

Dhindsa *et al*. (1993) prepared metal complexes of 1-acetyl-5-aryl-3-l-(substituted thienyl)-2-pyrazolines with cobalt(II), nickel (II) and copper(II) and characterized by elemental analysis, molar conductance magnetic suspectibility and electronic and infrared spectral data. The ligands behaved as bidentate, coordinating through carbonyl oxygen and azomethine nitrogen. The ligands and their complexes have been evaluated for the antifungal activity against phytopathogenic fungi viz., Alternaria alternata, Collectorichum capsicum, Fusarium oxysporum and Rhizoctonia solani at 37ºC. The trend of growth inhibition in the complexes was found to be in the order Ni $\geq$ Cu > Co. Ali *et al*. (2012) developed a pyrazoline based ligand [5-(4-chlorophenyl)-3-phenyl-4, 5-dihydro-1H-pyrazole-1-carbothi-oamide] by Claisen-Schmidt condensation of acetophenone with p-chlorobenzadehyde, followed by sodium hydroxide assisted cyclization of the resulting chalcone with thiosemicarbazide. Metal ion complexes of the synthesized ligand were prepared with Cu(II) and Ni(II) metal ions.

The ligand and their metal complexes were characterized by elemental analysis, FT-IR, UV-Vis, ^{1}HNMR, ESI-MS and ^{13}CNMR spectroscopic techniques. Molar conductanace measurements in DMSO suggested non-electrolytic nature of the complexes. Tetragonally distorted octahedral geometry for copper and octahedral geometry for the nickel complexes was proposed on the basis of UV-Vis spectroscopic studies and magnetic moments measurements. The complexes were investigated for their ability to kill human fungal pathogen Candida by determining MIC_s (Minimum Inhibitory Concentrations), inhibition in solid media.

Conclusion

In addition to the effect of substitutional modifications, the activity of the ligands is often altered on coordination with the metal ions. Several investigations on metal drug interaction and microbiocidal ligands have been resulted in complexes with more effective and site specific action.

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