Synthesis of Hydrazones derivatives and their evaluation of Anticonvulsant and Anti-Inflammatory Activity

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Abstract: The synthesis of some oxovanadium (IV) complexes with bidentate ligands (new synthesized biologically active hydrazones) derived from 2-methyl-4-(N-cyanoethyl)-N-benzenesulphonyl-benzylidene-3-oxo-[N-(substituted-1-phenyl) propanamido] hydrazone were analyzed. The complexes prepared were of the type $[VO.L_2]$ (where L= different new synthesized hydrazones).The characterization of these newly synthesized hydrazones and their metal complexes were done by IR, ^{1}H-NMR spectral studies and elemental analysis. The infrared data of these complexes revealed the bidentate nature of the ligands and coordination to imino nitrogen of the amido group and azomethinic-nitrogen atoms. The new products were synthesized and evaluated for Anticonvulsant and Anti-Inflammatory Activity. The biological screening data indicates that the metal chelates are more potent than the parent ligands.

I. INTRODUCTION

Hydrazone compounds obtained by the reaction of aromatic and heterocyclic hydrazides with mono- and di-aldehydes or ketones have revealed very versatile behavior in metal coordination[1]. Many researchers have synthesized a number of new hydrazones because of their ease of synthesis[2].

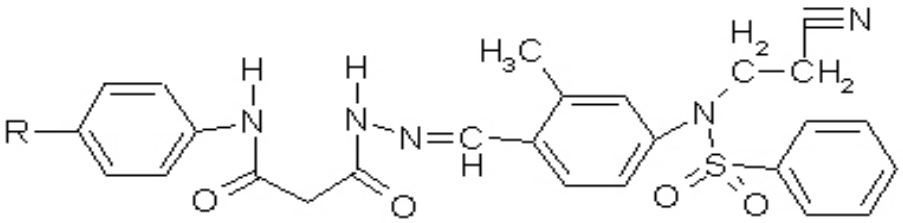
Hydrazones play an important role in inorganic chemistry as they easily form stable complexes with most transition metal ions in the periodic table the development of the field of bioinorganic chemistry has increased the interest in hydrazone complexes, as they have been recognized that many of these complexes may serve as models for biologically important species. The remarkable biological activity of acid hydrazides R-CO-NH-NH_2, their corresponding hydrazones, R-CO-NH-N=CH-R' and the dependence of their mode of chelation with transition metal ions present in the living system, have been of significant interest in the past[3-6]. The coordination compounds of aroylhydrazones have been reported to act as enzyme inhibitors[7] and are useful due to their pharmacological application[8-10]. Isonicotinic acid hydrazide is a drug of proven therapeutic importance and used against a wide spectrum of bacterial ailments, as tuberculosis[11].

Hydrazones have been studied as a group of the most useful spectrophotometric reagents[2, 12, and 13]. Combining appropriate starting materials (carbonyl compounds and hydrazine), the sensitivity as an analytical reagent and / or solubility of the hydrazones could be improved and the donating environment could be changed. The shortcoming of hydrazones was their lack of selectivity[2] for metal ions. Much effort has been devoted to developing masking agents for use with hydrazones[14, 15].

High-performance liquid chromatography (HPLC) of metal chelates[16] is a promising alternative approach for overcoming the lack of selectivity of the chelating reagents[2]. Hydrazone ligands and their complexes have been studied for their antifungal and antibacterial activity, as iron chelators in the treatment of anemias and as antiviral drugs[1].

The coordination chemistry of oxovanadium (IV) with multidentate ligands is important due to its growing application in catalysis[17] and therapeutics[18].Vanadium in traces has multiple biological roles, therapeutic value in small doses and toxic in excess. Vanadium containing compounds have their utility as insulin mimetic[19] and antiamoebic agent[20].

It is also suggested that vanadium could be considered as a representative of a new class of non-platinum metal antitumor agents[21]. In the present investigation we describe the synthesis and characterization of some new hydrazones and their oxovanadium (IV) complexes.



Where **R = -Cl and –NO_2**

Fig. 1: Structure of new synthesized Hydrazone

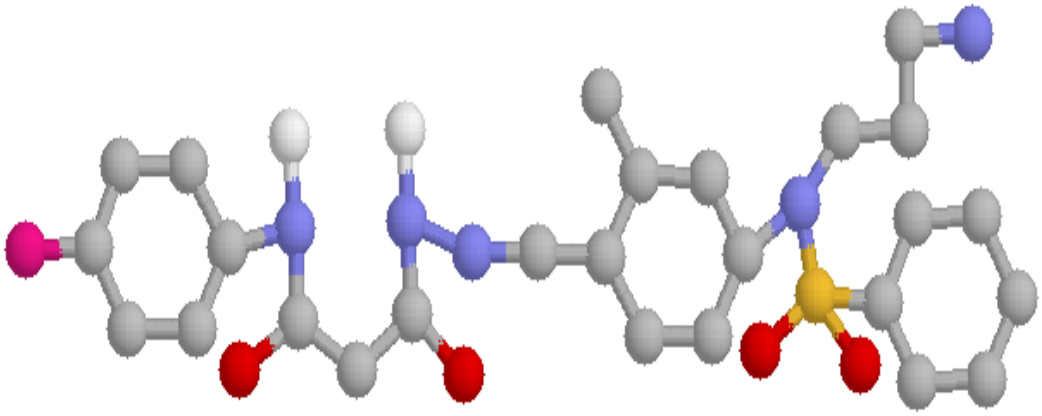


Fig. 2: Ball Stick modal of new synthesized Hydrazone

II. RESULTS AND DISCUSSION

All compounds gave satisfactory results for elemental analysis, IR and ^{1}H-NMR spectra. The physical and analytical data of synthesized new hydrazones and their metal complexes are presented in table-1.

Table 1: Analytical Data of Synthesized hydrazones and their Metal Complexes

Compounds	Mol. Formula (Mol. Wt.)	M.P (^{0}C)	Colour (yield %)	Elemental Analysis (%) Calculated/ Found)			
				C	H	N	M
MCPH	$C_{26}H_{24}N_5O_4SCl$ (538.03)	207	Brown (71)	58.04 (58.00)	04.50 (04.48)	13.02 (13.00)	- -
MNPH	$C_{26}H_{24}N_6O_6S$ (548.58)	212	Yellow (75)	56.93 (56.87)	04.41 (04.35)	15.32 (15.28)	- -
[VO(IV)-(MCPH)$_2$]	VO(IV)-($C_{52}H_{48}N_{10}O_8S_2Cl_2$) (1143.00)	223	Light Blue (68)	54.59 (54.50)	04.19 (04.11)	12.24 (12.19)	04.45 (04.38)
[VO(IV)-(MNPH)$_2$]	VO(IV)-($C_{52}H_{48}N_{12}O_{12}S_2$) (1164.10)	230	Dark Blue (70)	53.60 (53.55)	04.12 (04.08)	14.43 (14.37)	04.37 (04.30)

Infrared Spectra: Comparative study of the IR of hydrazones and metal complexes are helpful in evaluating the results.
Spectral interpretation of new hydrazones show characteristic bands i.e. ν (N-H) stretching : 3320-3060 cm^{-1}, ν (C =O) stretching : 1750-1650 cm^{-1} and azomethine nitrogen : 1640-1610 cm^{-1}.
A strong band around 1630 cm^{-1} indicates the formation of new hydrazone because this band appears due to condensation of hydrazide with aldehyde, when these hydrazones chelate with metals, the normal frequency of ν (C=O) stretching band is shifted towards lower frequency region.
The lowering by 10-30 cm^{-1} in ν (C=N) azomethine nitrogen babd frequency around 1700-1600 cm^{-1} suggests the coordination of hydrazone ligand to the metal ion through imino nitrogen of the amido group and azomethine nitrogen. Some new bands present in far infrared region (690-650 cm^{-1} & 980-900 cm^{-1}) shows the formation of some new [ν (V-N) and ν (V-O)] bands in the spectra of metal complexes.
In all the complexes of VO^{2+}, the V = O (oxovanadium) stretching frequency occurs in the range 975-960 cm^{-1}. These values are in the range observed for monomeric VO^{2+} complexes[22]. The dπ –pπ orbital overlap involved in a multiple bond. This strong multiple bonding with the oxygen appears to be responsible for the trans influence of the oxo ligand, which disfavors attachment of a ligand trans to O[23].

Table-2 Infrared absorption frequencies (cm^{-1}) of Hydrazones and their Metal Complexes

Compounds	ν (NH)	ν (C=N)	ν (V=O)	ν (V-N)
MCPH	3230 m	1620 s	-	-
MNPH	3225 m	1627 s	-	-
[VO(IV)-$(MCPH)_2$]	3210 m	1600 s	975 m	665 m
[VO(IV)-$(MNPH)_2$]	3210 m	1605 s	978 m	673 m

^{1}H-NMR Spectra: The ^{1}H-NMR spectra of new synthesized hydrazones MCPH and MNPH were recorded (Table-3). The spectra in comparison to the corresponding hydrazide , show the disappearance of NH_2 group signal , while that of the NH protons are shows low field to the range δ 8.90 –11.80 ppm for the imino proton present in ligands[24] (hydrazones) .
The protin of azomethine group (CH = N) sharp peak is observed at δ 8.50 –8.80 ppm. Further two signals observed at δ 3.60 – 3.90 ppm are assigned to methylene protons[25]. The multiplet due to aromatic protons appears in the δ 7.03 –8.30 ppm region. The appearance of two doublets in the region δ 11.11 –12.96 ppm coupled with signals at δ 3.60 – 3.90 ppm suggests enolization of hydrazones involving active methylene group with keto-enol equilibrium in the solution. Thus, the signal at δ 3.60 ppm may be attributed to methylene (-CH_2-) and that at δ 3.90 ppm to methane proton (=CH-).
The bonding of ligand to metal is further supported by ^{1}H-NMR spectral studies and NMR spectra (Table 3) recorded for [VO-$(MCPH)_2$] and [VO-$(MNPH)_2$]. The signals in the δ 11 – 13 ppm region are medium, broad and shifted upfeild by about 0.38 – 0.45 ppm in the complex as compared to that in the free hydrazone in which they are relatively intense indicating that they arise due to secondary (imino) – NH protons [25]. This suggests coordination of the imino nitrogen (amido group) atoms to the metal center. In the spectrum of oxovanidium complex of hydrazones (MCPH and MNPH) position of δ – CH=N- signal shifts down field by 0.49 – 0.65 ppm suggesting coordination of azomethine nitrogen atoms to the metal center.[25].

Table-3 ^{1}H-NMR Spectral data of hydrazones and their metal complexes

Compounds	-N-H	-CH=N-	-CH_2-	Ar-H
MCPH	11.2 (1H,m)	8.5 (1H,s)	3.6 (2H,m)	7.10-8.00 (12H,m)
MNPH	11.5 (1H,m)	8.7 (1H,s)	3.8 (2H,m)	7.15-8.10 (12H,m)
[VO(IV)-$(MCPH)_2$]	11.6 (1H,m,bro.)	7.9 (1H,s)	3.5 (2H,m)	7.05-7.90 (12H,m)
[VO(IV)-$(MNPH)_2$]	11.9 (1H,m,bro.)	8.1 (1H,s)	3.7 (2H,m)	7.09-8.00 (12H,m)

III. BIOLOGICAL ACTIVITY

Anticonvulsant Action

Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been achieved during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity.

The biological results revealed that in general, the 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-chloro-1-phenyl) propanamido] hydrazone (MCPH) (Ia) provided good protection against convulsions while the 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-nitro-1-phenyl) propanamido] hydrazone (MNPH) were significantly less active. [Ib)].
Two new Vanadium metal complexes of 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-chloro-1-phenyl) propanamido] hydrazone (MCPH) (Ia) and 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-nitro-1-phenyl) propanamido] hydrazone (MNPH) (Ib) were synthesised and their antiepileptic activity was tested in scPTZ test. Both metal complexes were found to be more active than parent Hydrazones [MCPH and MNPH].
2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-nitro-1-phenyl) propanamido] hydrazone (MNPH) (Ib) is the principal inhibitory neurotransmitter in the mammalian brain. MNPH (Ib) hydrazones was designed and synthesized and evaluated for their anticonvulsant properties in different animal models of epilepsy such as MES, scPTZ, subcutaneous strychine (scSTY) and intraperitonal picrotoxin (ipPIC) induced seizure tests. The metal complex of Hydrazone [VO(IV)-$(MNPH)_2$] was effective in these models.

Anti-inflammatory Action

Non-steroidal anti-inflammatory drugs (NSAIDs) have a wide clinical use for the treatment of inflammatory and painful conditions including rheumatoid arthiritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. The two isoforms of cyclooxygenase (COX) are poorly distinguishable by most of the classical NSAIDs and these agents actually inhibit COX-1 extensively, besides COX-2, leading to gastrointestinal injury, suppression of TXA2 formation and platelet aggregation. The combination of these interactions is probably the reason for gastrointestinal bleeding as the most serious complication of these drugs. Some evidences suggest that the hydrazone moiety present in some compounds possess a pharmacophoric character for the inhibition of COX.

The most important antiinflammatory derivative 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-chloro-1-phenyl) propanamido] hydrazone (MCPH) (Ia) presented a 79 % inhibition of pleurisy at a dose of 80.1 µmol/kg. The authors also described the results concerning the mechanism of the action of these series of Hydrazones in platelet aggregation that suggests a VO^{2+} scavenger mechanism. MCPH (Ia) was able to complex VO^{2+} in in-vitro experiments at 100 µM concentration, indicating that these series of compounds can act as VO^{2+} scavenger depending on the nature of imino nitrogen of the amido group and azomethinic-nitrogen atoms present at the synthesized hydrazones.

IV. CONCLUSION

In this paper coordination chemistry of a newly synthesized hydrazone ligands , obtained from the reaction of 3-oxo-[N-(substituted –1-phenyl) propanamido] hydrazide and 2- methyl-4-(N-cyanoethyl)-N-benzenesulphonyl benzaldehyde , is described . Oxovanadium (IV) complexes have been synthesized using the above newly hydrazone ligands and characterized on the basis of analytical, IR ^{1}H-NMR spectral data. The observation of newly hydrazone ligand to the metal ion through imino nitrogen of the amido group and azomethine nitrogen and acts as a bidentate ligand. In all the synthesized metal complexes of vanadium metal attached oxygen atom to monomeric (VO^{+2}) form because of the dπ-pπ orbital overlap involved in a multiple bond. This strong multiple bonding with the oxygen appears to be responsible for the trans-influence of the oxo-ligand, which disfavors attachment of a ligand Trans to oxygen.

The biological screening data of indicare that the metal chelates are more potent than the parent ligands.

V. EXPERIMENTAL

Materials and Instrumentation: All reagents used were purchased from Merck and used as received. Melting points were taken in open capillary and are uncorrected. Elemental analyses, ^{1}H-NMR spectra were obtained on a Bruker FT-400 spectometer using $CDCl_3$ as solvent and TMS as an internal standard. IR spectra were recorded on KBr disks, using a Jasco-410 FTIR spectrometer. All the hydrazides were prepared by the reaction of hydrazine hydrate with different esters. 3-oxo-[N-(4-chloro-1-phenyl) propanamido] hydrazide, 3-oxo-[N-(4-nitro-1-phenyl) propanamido] hydrazide[26] and 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzaldehyde[27] were prepared by reported methods.

(A) Preparation of Hydrazones : Synthesis of 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-chloro-1-phenyl) propanamido] hydrazone (MCPH) (Ia) : 3-oxo-[N-(4-chloro-1-phenyl) propanamido] hydrazide (0.227gm , 0.001mol) and 2-methyl-4- (N-cyanoethyl)-N-benzenesulphonyl benzaldehyde (0.328gm , 0.001mol) were dissolved in ethanol and added a drop of concentrated H_2SO_4 . Mixture was stirred for 5 min. The resulting solid was recrystallised from ethanol as brown crystals (71%).

Synthesis of 2-methyl-4-(N-cyanoethyl) –N-benzenesulphonyl benzylidene-3-oxo-[N-(4-nitro-1-phenyl) propanamido] hydrazone (MNPH) (Ib) [yellow crystals (75%)] was prepared similarly .

Preparation of the metal complexes of MCPH and MNPH: To a hot solution of the respective metal salt [0.173gm vanadyl chloride (VOCl2.2H2O)] in methanol was added a sufficient amount of the MCPH (0.538 gm) or MNPH (0.548 gm). The solution was mixed with a required stoichiometric amount of the respective ligand in hot methanol. The resulting mixture was refluxed for four hours and then concentrated to half of its volume. On cooling, a colored crystalline product was obtained , which was filtered , washed with organic solvents and dried in a vaccum oven.

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