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# Studies on Hydrazones Complexes of Ti (Ii) for Antimicrobial Activities

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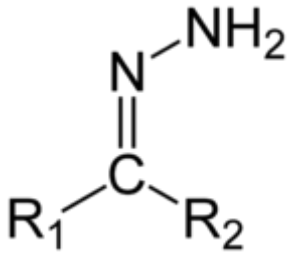
**ABSTRACT:** Hydrazones complexes of Ti (II) possess a wide spectrum of bioactivity, including antibacterial, antitubercular, antifungal, anticancer, anti-inflammatory, anticonvulsant, antidepressant, antiviral, and antiprotozoal properties. This review is focused on the latest scientific reports regarding antibacterial, antimycobacterial, and antifungal activities of Hydrazones complexes of Ti (II) published in different books. The molecules and their chemical structures presented in this article are the most active derivatives, with discussed activities having a hydrazide–hydrazone moiety as the main scaffold or as a side chain. Presented information constitute a concise summary, which may be used as a practical guide for further design of new molecules with antimicrobial activity.

**KEYWORDS:** hydrazones, complexes, Ti(II), antimicrobial, antibacterial, antimycobacterial, activities

## I. INTRODUCTION




**Structure of hydrazone functional group**

Hydrazones complexes of Ti (II) are the basis for various analyses of ketones and aldehydes. For example, dinitrophenylhydrazine coated onto a silica sorbent is the basis of an adsorption cartridge. The Hydrazones complexes of Ti (II) are then eluted and analyzed by HPLC using a UV detector.The compound carbonyl cyanide-p-trifluoromethoxyphenylhydrazone (abbreviated as FCCP) is used to uncouple ATP synthesis and reduction of oxygen in oxidative phosphorylation in molecular biology.Hydrazones are the basis of bioconjugation strategies.[6][7] Hydrazone-based coupling methods are used in medical biotechnology to couple drugs to targeted antibodies (see ADC), e.g. antibodies against a certain type of cancer cell. The hydrazone-based bond is stable at neutral pH (in the blood), but is rapidly destroyed in the acidic environment of lysosomes of the cell. The drug is thereby released in the cell, where it exerts its function.[8]

Hydrazones are susceptible to hydrolysis:

$$R_2C{=}N{-}NR'_2 + H_2O \rightarrow R_2C{=}O + H_2N{-}NR'_2$$

Alkyl hydrazones are $10^2$- to $10^3$-fold more sensitive to hydrolysis than analogous oximes.[9]

When derived from hydrazine itself, hydrazones condense with a second equivalent of a carbonyl to give azines:[10]

$$R_2C{=}N{-}NH_2 + R_2C{=}O \rightarrow R_2C{=}N{-}N{=}CR_2 + H_2O$$

Hydrazones are intermediates in the Wolff–Kishner reduction.

Hydrazones are reactants in hydrazone iodination, the Shapiro reaction, and the Bamford-Stevens reaction to vinyl compounds. Hydrazones can also be synthesized by the Japp–Klingemann reaction via β-keto-acids or β-keto-esters and aryl diazonium salts. Hydrazones are converted to azines when used in the preparation of 3,5-

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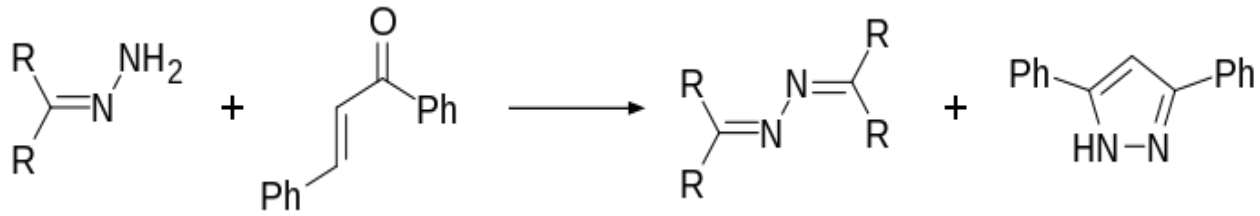
disubstituted 1H-pyrazoles,[11] a reaction also well known using hydrazine hydrate.[12][13] With a transition metal catalyst, hydrazones can serve as organometallic reagent surrogates to react with various electrophiles.[14]




New potentially Hydrazones complexes of Ti (II) were prepared by the condensation of 2,4-dihydroxybenzophenone with furoylhydrazide. Reaction of this ligand with titanium trichloride, chromium chloride hexahydrate, anhydrous ferric chloride, uranyl nitrate hexahydrate gave mononuclear metal complexes. The ligand and its complexes have been characterized by a variety of physico-chemical techniques. An octahedral geometry has been proposed for all the complexes.[1,2,3] The ligand acts as a tridentate molecule coordinating through deprotonated phenolic/enolic oxygen atoms and azomethine nitrogen atom. Thermogravimetric analyses confirm coordination of water/methanol molecule in complexes. The antibacterial and antifungal activities of ligand ($H_2L$) and its complexes have been studied against various bacteria and fungi using the disc diffusion technique. All complexes exhibit good biological activity as compared to free ligand. New series of Hydrazones complexes of Ti (II) [4,5] were designed and synthesized. The targed compounds were obtained in yields of 51 to 96% and their structures were elucidated by FTIR, $^{1}$H NMR, $^{13}$C NMR, MS and microanalyses. All of the compounds were found to be “drug-like” as they fulfill the criteria of drug-likeness, which includes the MDDR-like rule. The tested compounds were subjected to in silico prediction of substrate/metabolite specificity and Drug Induced Liver Injury (DILI). The prediction for indicated that the evaluated compounds would most probably act as CYP1A2 substrates. The performed in vitro studies didn’t reveal statistically significant hepatotoxicity of the tested compounds, probably due to the pro-oxidant effects expressed on sub-cellular (isolated rat liver microsomes) level.[6,7] The obtained experimental results confirmed the predicted low hepatotoxicity for the tested structures. Based on these results the compounds may be considered as promising structures for design of future molecules with low hepatotoxicity.[8]

## II. DISCUSSION

The Hydrazones complexes of Ti (II) have synthesized and characterized by elemental analysis, magnetic measurement data, molar conductance, TGA,UV-visible and IR spectra data. Hydrazones complexes of Ti (II) have octahedral geometry while VO (IV) and MoO(V) have distorted octahedral geometry due to the presence of M=O moiety. 5-Bromo-2-hydroxy-3-methoxybenzaldehyde-p-hydroxybenzoichydrazone reacts with Hydrazones complexes of Ti (II) forming thick orange coloured soluble complex in aqueous dimethyl formamide in the pH range 2.0-7.0. It has a λmax at 390 nm. Studies were carriedout at pH-4.0.The method obeys Beer’s law in the range 0.241 to 2.87 µg /ml. The molar absorptivity is 1.44×104 l mol-1cm-1 and Sandell’s sensitivity is 0.0033 µg/cm2. The standard deviation of the method for ten determinations of 1.197 µg/m l o f Hydrazones complexes of Ti (II) i s 9.04×10-3. T h e correlation coefficient (γ) of the calibration equation of the experimental data is 0.9998. The effect of various diverse ions is studied. The formula of the complex is 1:1 and its stability constant is 2.25×105.[9,10] Based on the above , a rapid, simple, sensitive and selective direct spectrophotometric method has been developed. The method developed was used for the determination of Hydrazones complexes of Ti (II) in alloy and steel samples. The results are in good agreement with the certified values. A series of novel mono and bishydrazones each bearing a 2-oxindole moiety along with substituted phenylaminopropanamide, pyrrolidin-2-one, benzimidazole, diphenylmethane, or diphenylamine fragments were synthesized, and their anticancer activities were tested by MTT assay against human melanoma A375 and colon adenocarcinoma HT-29 cell lines. In general, the synthesized compounds were more cytotoxic against HT-29 than A375. 3-((4-Methoxyphenyl)(3-oxo-3-(2-(2-oxoindolin-3-ylidene)hydrazinyl)propyl)amino)-N′-(2-oxoindolin-3-ylidene)propanehydrazide and (N′,N‴)-1,1′-(methylenebis(4,1-phenylene))bis(5-oxo-N′-(2-oxoindolin-3-ylidene)pyrrolidine-3-carbohydrazide) were identified as the most active compounds against HT-29 in 2D and 3D cell cultures. The same compounds showed the highest antioxidant activity among the synthesized compounds screened by ferric reducing antioxidant power assay (FRAP). Their antioxidant activity is on par with that of a well-known antioxidant ascorbic acid.[11,12]

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## III. RESULTS

Fifteen Hydrazones complexes of Ti (II)and sulfonyl hydrazones 5a–k were synthesized. They were characterized by $^{1}$H-NMR, $^{13}$C NMR, and HRMS. *Mycobacterium tuberculosis* strain H37Rv was used to assess their antimycobacterial activity. All compounds demonstrated significant minimum inhibitory concentrations (MIC) from 0.07 to 0.32 µM, comparable to those of isoniazid. The cytotoxicity was evaluated using the standard MTT-dye reduction test against human embryonic kidney cells HEK-293T and mouse fibroblast cell line CCL-1. Hydrazones complexes of Ti (II) demonstrated the highest antimycobacterial activity (MIC = 0.0730 µM) and minimal associated cytotoxicity against two normal cell lines (selectivity index SI = 3516, HEK-293, and SI = 2979, CCL-1).[13,14] The next in order were sulfonyl hydrazones 5g and 5k with MIC 0.0763 and 0.0716 µM, respectively, which demonstrated comparable minimal cytotoxicity. All compounds were subjected to ADME/Tox computational predictions, which showed that all compounds corresponded to Lipinski's Ro5, and none were at risk of toxicity. The suitable scores of molecular docking performed on two crystallographic structures of enoyl-ACP reductase (InhA) provide promising insight into possible interaction with the InhA receptor. The Hydrazones complexes of Ti (II) and sulfonyl hydrazones proved to be new classes of lead compounds having the potential of novel candidate antituberculosis drugs.

In this study, we present the synthesis and investigation of the Hydrazones complexes of Ti (II) scaffolds 5a–k and 4-methyl-1,2,3-thiadiazole-containing hydrazone derivatives 3a–d, looking for the most effective compounds as *M. tuberculosis* growth inhibitors with low cytotoxicity and a highly selective index, that would reduce or eliminate adverse effects. The new compound 3d displayed antimycobacterial activity at a submicromolar concentration level with the lowest MIC of 0.0730 µM against *M. tuberculosis* H37Rv and remarkably minimal associated cytotoxicity in the normal human embryonic kidney cell line HEK-293T and mouse fibroblast cell line CCL-1.[15,16] It was also found that the vanillin, cinnamyl, and p-nitrophenyl fragments in Hydrazones complexes of Ti (II) as well as 4-methyl-1,2,3-thiadiazole scaffolding in Hydrazones complexes of Ti (II) may be pharmacophores with antimycobacterial activity much higher than other compounds tested. The in silico ADME study revealed that all compounds had suitable bioavailability and fraction absorption at high levels of gastrointestinal absorption. All the compounds that form the collection seem to be suitable drug-like molecules in terms of their satisfactory membrane permeability and oral bioavailability. Their predicted toxicity properties are a prerequisite for considering the new compounds as effective and safe and with potential for TB treatment. The results of the molecular docking studies agree with experimental studies focused on the significance of the synthesized compounds as potential growth inhibitors of *M. tuberculosis*.[17,18]All most active compounds displayed interactions with critical residues. Thus, we consider that the 4-methyl-1,2,3-thiadiazole derivatives and sulfonyl hydrazones are promising scaffolds for antitubercular drug discovery that prompt further studies on their mechanism of action to completely validate InhA as the main molecular target.[19]

## IV. CONCLUSIONS

Hydrazones complexes of Ti (II) derived from benzhydrazide and salicylaldehyde (BSH), o-hydroxyacetophenone (BAH), o-hydroxypropiophenone (BPH), o-hydroxybutyrophenone (BBH) and 2-hydroxynaphthaldehyde (BNH) have been described.[20,21]These complexes have been characterised by elemental analyses, and by conductance, magnetic, infrared and electronic spectral measurements. The complexes have trans-octahedral stereochemistry as indicated by ν (M–N) and ν (M–O) vibrations in far infrared region.[22]

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