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Biological Applications of Thiosemicarbazones and Their Metal Complexes†

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In this paper, we reviewed antimalarial, antibacterial, antitrypanosomal and antiviral properties of thiosemicarbazones and their metal complexes reported since 2008.

Key Words: Thiosemicarbazones, Transition metal complexes, Biological applications.

INTRODUCTION

Thiosemicarbazones (TSCs) are the condensed products of carbonyl compounds (aldehydes, ketones) and thiosemicarbazide. Thiosemicarbazones and their metal complexes attract both the analytical as well as biological researchers due to their vast applications in binding to the metal ions and also biological applications. Few authors reviewed the analytical applications of thiosemicarbazones[1-3]. The recent review[3] discussed the analytical and biological applications of thio and phenyl thiosemicarbazones, but mainly focused on the analytical applications. Wood *et al.*[4] reviewed the usage of Cu(II)-diacetyl-bis(N^4-methyl-thiosemicarbazones) as a radiotracer for tumor hypoxia. Garoufis *et al.*[5] reviewed antiviral, antifungal, antimicrobial and antitumor activities of Pd(II) coordination compounds including thiosemicarbazone complexes. Few authors[6,7] reviewed the therapeutic activities of transition metal complexes of thiosemicarbazones. Kathiravan *et al.*[8] reported the biology and chemistry of antifungal agents, including thiosemicarbazones. This present review extensively discusses the biological applications such as, antimalarial, antibacterial, antitrypanosomal and antiviral properties of thiosemicarbazones and their metal complexes reported since 2008.

RESULTS AND DISCUSSION

Antimalarial activity: The activity of compounds or agents, which will inhibit the growth and spread malarial parasites and the biological effect, is known as antimalarial activity. Various species of *Plasmodium* are the causative agents of malaria. *Plasmodium*, the parasite responsible for human malaria is among the most researched genera of parasites in the world. Cyclic-dependent kinesis play an important role in cell cycle progression and are conserved in all eukaryotic species. Cyclic-dependent kinesis have been investigated as possible drug[9]. Chellan *et al.*[10] reported the antimalarial activity properties of free ligands, such as 3,4-dichloroacetophenone thiosemicarbazone and 3,4-dichloropropiophenone thiosemicarbazone and their Pd(II) complexes. The authors tested the antimalarial activity against *Plasmodium falciparum* strains, 3D7 (chloroquine sensitive) and K1 (chloroquine and pyrimethamine resistant). They concluded that the palladium complexes of the above mentioned thiosemicarbazones have greater activity than the free ligands. Khanye *et al.*[11] reported *in vitro* antiplasmodial assays of the dendritic ferrocenyl thiosemicarbazones against the malaria parasite *P. falciparum*. Khanye *et al.*[12] reported that the significant improvement in antimalarial activity of thiosemicarbazones by chelating with Au(III) fragment.

Antibacterial activity: The activity of compounds or agents, which inhibit the growth and spread bacteria and the biological effect, is known as antibacterial activity. The bacteria are unicellular, microscopic prokaryotes and wide spread in nature being as autotrophic, heterotrophic and parasitic organisms. The parasitic bacteria using antibacterial agents work either by stopping bacterial growth or by killing the bacteria, without harming the human host. The main targets for antibacterial activity inhibit synthesis of peptidoglycan, alter the microbial cytoplasmic membrane, alter translation and inhibit nucleic acid replication by blocking topoisomerases and inhibit transcription[13]. Refat *et al.*[14] reported the antibacterial

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activity of ligands, such as (1E)-1-(1-(2-oxo-2H-chromen-3-yl)ethylidene) thiosemicarbazide (OCET) and (1E)-1-(1-(6-bromo-2-oxo-2H-chromen-3-yl)ethylidene) thiosemicarbazide (BOCET) and their metal complexes against *Bacillus subtili, Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. Their results reveal that the metal complexes have more potent activity against the tested bacteria than the free ligands. Antibacterial activity of Schiff bases derived from 4-(2-pyridyl)-3-thiosemicarbazide and pyruvic acid and its complexes with Co(II), Cu(II), Cd(II), Fe(III) and U(VI) against *Bacillus thuringiensis, S. aureus, P. aeuroginosa* and *E. coli* were reported by Yousef *et al*.[15]. Zahinos *et al*.[16] tested the antibacterial activity of 2-acetyl-2-thiazoline thiosemicarbazone and its complexes with the metal ions, such as Co(III), Ni(II), Zn(II) and Cd(II) tested against *S. epidermidis, S. aureus, Enterococcus faecalis, E. coli and B. subtilis*. Among the free ligand and its metal complexes, Cd(II) complex shows more activity against the tested bacterial stains. Silva *et al*.[17] found that the increase in antibacterial activity of Ga(III) against *P. aeruginosa* due to coordination with pyridine-derived thiosemicarbazones. Shebl *et al*.[18] studied the antibacterial activities of thiosemicarbazone, semicarbazone and thiocarbohydrazone ligands derived from 4,6-diacetylresorcinol and their metal complexes. Their results reveal that the thiosemicarbazone ligand has lower activity while the other ligands have more activity than their metal complexes against the *Rhizobium* bacteria. Mahalingam *et al*.[19] reported the antibacterial activity of free ligands, such as salicylaldehyde 4-phenyl thiosemicarbazone, 2-hydroxy-1-naphthaldehyde thiosemicarbazone and 2-hydroxy-1-naphthaldehyde 4-phenyl thiosemicarbazone and their Ru(II)-DMSO (dimethylsulphoxide) complexes against *E. coli, S. aureus, S. epidermidis, Klebsiella pneumoniae* and *Shigella sonnei*. The minimum inhibition concentrations of these complexes were so high compare to the standard antibiotics, such as oxytetracyclin and kanamycin.

Antibacterial activity of organotin(IV) complexes of 2-hydroxyacetophenone-N(4)-cyclo-hexyl thiosemicarbazone against *E. coli, Enterobacter aerogenes, S. aurues* and *Salmonella typhi* was reported by Affan *et al*.[20]. Their results showed that the organotin complexes have better activity than the free ligand. Among the organotin complexes, diphenyltin(IV) derivatives exhibits significantly better activity than the monoorganotin(IV) derivatives. Chandra *et al*.[21] synthesized and studied the antibacterial activity of Cu(II) and Ni(II) complexes of pyridinecarbozaldehyde thiosemicarbazone against *P. striata* and *B. macerans* and their results were comparable with the standard antibiotic, streptomycin. Beckford *et al*.[22] evaluated the antibacterial activity of diimine-piperonal thiosemicarbazone complexes of Ru(II). They concluded that the ruthenium complexes were more active against the Gram-positive bacteria than the Gram-negative bacteria strains. Santhakumari *et al*.[23] synthesized a semi-organic crystal, thiosemi -carbazide Cd(II) picrate and tested its antibacterial and antifungal activities. They found that this material had good antifungal activity. The antibacterial activities of Mn(II) and Co(II) complexes of benzyloxybenzaldehyde-4-phenyl-3-thiosemicarbazone were reported by Prathima *et al*.[24]. Anti-*Myco bacterium tuberculosis* activity of oxovanadium(IV) and *cis*-dioxovanadium (V) complexes of thiosemicarbazone derivatives was reported by Maia *et al*.[25].

Antitrypanosomal activity: The activity of compounds or agents, which inhibit the growth and spread trypanosome and the biological effect, is known as antitrypanosomal activity. The trypanosomes are unicellular microscopic protozoan's that are widely present in nature and parasitize on insects, plants, birds, aquatic animals and other mammals. Recent days the biochemical metabolic pathway *i.e.*, glycolysis is perceived as a promising target for new drugs against parasitic trypanosomatid protozoa because this pathway plays an essential role in their ATP supply[26]. Perez-Rebolledo *et al*.[27] was tested the antitrypanosomal activity of thiosemicarbazones obtained form N^4-methyl-4-nitroacetophenone, N^4,N^4-dimethyl-4-nitroacetophenone and N^4-piperidyl-4-nitroacetophenone and their Cu(II) complexes. Antitrypanosomal activity of Sb(III) complexes of pyridine-derived thiosemicarbazones against the epimastigote and trypomastigote forms of *Trypanosoma cruzi* was reported by Lessa *et al*.[28]. These complexes were found to be more active against the *Trypanosoma cruzi* than the reference drugs benzemidazole and nifurtimox. Ru(II) complexes of nitro thiosemicarbazones, such as N^4-methyl-4-nitrobenzaldehyde thiosemicarbazone, N^4-methyl-4-nitroacetophenone thiosemicarbazone[29] and N^4-methyl-4-nitrobenzophenone thiosemicarbazone[30] were also tested as antitrypanosomal agents against Trypanosoma cruzi. Ru(II) complexes were most active than the free ligands against the *Trypanosoma cruzi*. Soares *et al*.[31] reported the antitrypanosomal activity of 4-N-(2'-methoxy styryl)-thiosemi-carbazone against *Trypanosoma cruzi* trypomastigotes obtained from LLC-MK2 cell cultures. *In vitro* antitrypanosomal activity of Mn(II) complexes obtained from N^4-methyl-4-nitrobenzaldehyde, N^4-methyl-4-nitroacetophenone and N^4-methyl-4-nitrobenzophenone thiosemicarbazones against *Trypanosoma cruzi* was reported by Batista *et al*.[32].

Antiviral activity: A virus particle, also known as a virion, is essentially a nucleic acid (DNA or RNA) enclosed in a protein shell or coat. Viruses are extremely small, approximately 15-25 nano meters in diameter. A virus is a small infectious agent that can replicate only inside the living cells of an organism. Viruses can infect all types of living organisms, such as animals and plants to bacteria. For many years virus diseases have been considered as intractable to selective antiviral drugs because the replicative cycle of the virus was assumed to be too closely interwoven with normal cell metabolism so that any attempt to suppress virus reproduction would be doomed to kill (or severely harm) the uninfected cell as well. With the elucidation of virus-specific events as targets for chemotherapeutic attack and the advent of a number of specific antiviral agents, it has become increasingly clear that a selective chemotherapy of virus infections can be achieved and that virus reproduction can be suppressed without deleterious effects on the host[33]. Kang *et al*.[34] evaluated a series of isatin-β-thiosemicarbazones for antiviral activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). The isatin-β-thiosemicarbazones were found more selective against the tested virus. From their structure-activity relationship

(SAR) studies, it was concluded that thiourea group in thiosemicarbazone and the NH group in isatin were the responsible for antiherpetic activity. Vitamin A derived (retinoid) thiosemicarbazone was found as a good antiviral agent by Kesel[35]. In his studies, he tested the inhibitor activity of cytopathic effect caused by human varicella-zoster virus and / or human cytomegalovirus with the proposed thiosemicarbazones. The retinoid thiosemicarbazone derivative was also active against human immunodeficiency virus type 1. Karakucuk-iyidogan *et al*.[36] were synthesized Pd(II) and Pt(II) complexes of 5-substituted thiophene-2-carboxaldehydes thiosemicarbazones and tested their antivirus activity. They found that the Pd(II) complex shows slight and selective activity against cytomegalovirus.

Conclusion

This mini review reveals that in recent years so many researchers were concentrated on the biological applications of thiosemicarbazones and their metal complexes. But the potentiality of thiosemicarbazones is not fully utilized. In most cases the biological applications were enhanced by chelating the thiosemicarbazones with the metal ions, but their mechanisms were not fully discovered. In future, the researchers have to concentrate on mechanism, which enhances the biological applications of thiosemicarbazones.

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