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Biological Activities Of Thiosemi-Carbazone, And Use Of Their Metal Complexes.

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Abstract:

Schiff bases derived from various heterocyclic compounds displayed broad range of biological activities such as anticancer, antiviral, antimicrobial, anticonvulsant, antidepressant, an giotension-II receptor antagonist, anti-inflammatory and anti-glycation activity. So far, modifications of the Schiff bases have proven highly effective with improved potency and lesser toxicity. The present review highlights the recently synthesized Schiff bases possessing important biological activities. Schiff base are versatile ligands which are synthesized from the condensation of an amino compound with carbonyl compounds.

KEY WORDS- Spectral, Analytical and Physical studies, biological activities, chalcone thiosemicarbazones, metal complexes.

INTRODUCTION:

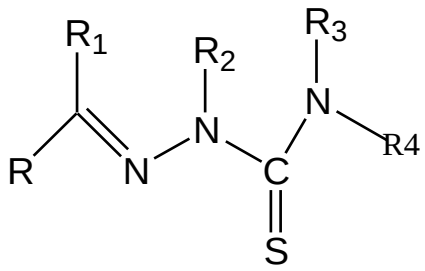
Domagk et al synthesis 4-acetylaminobenzal-thiosemi-carbazone, which are used for the treatment of pulmonary tuberculosis.

Antitumor Activity

Activity against Plasmodium falciparum and Plasmodium berghei[1], Trypanosoma cruzi[2-4], and Trypanosoma bruceirhodesiense[5], and Toxoplasma gondii[6]. They have also been found to be active against influenza, protozoa, small pox, and certain kinds of tumor, pesticides, and fungicides[7-10]. The thiosemicarbazones, an important class of synthetic compounds, have a variety of applications due to their wide spectrum of biological activities[11-12], which include antiviral [13], and antitumor [14-16], activities among others as well as parasiticidal Li et

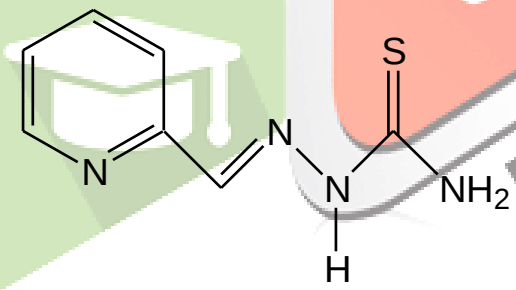
al[17]. Synthesized and characterized some new thiosemi-carbazones derived from natural aldehydes which were exhibited antiviral, antibacterial and antitumor properties.

The represents the general formula for thiosemicarbazones. R_1, R_2, R_3, R_4 = H,

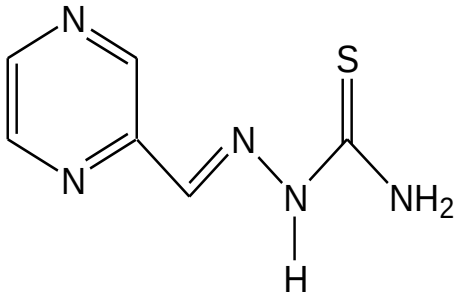


Ribonucleotide Reductase-

The anti-leukemic effect of 2-formylpyridine thiosemicarbazone (A) was first reported by Brockman *et al.*[18] in 1956. Almost ten years later, in 1965, French *et al.*[19] formulated hypotheses about the mode of action of the (N)-heterocyclic thiosemicarbazones: the active molecules shared a tridentate nature, that allows them to be effective chelators, and a better activity was obtained by modifying the aromatic system. Based on this principle they managed to predict the activity of pyrazine carboxaldehyde thiosemicarbazone (B) and 1-formylisoquinoline thiosemicarbazone (C).



(A)



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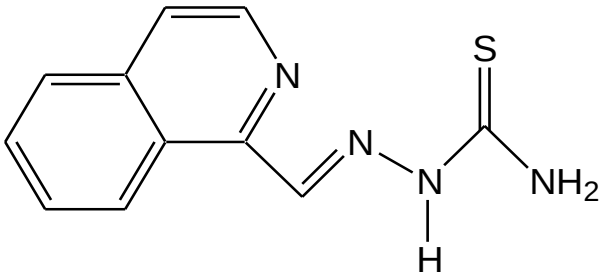
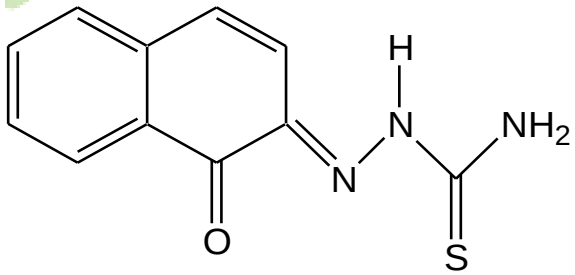


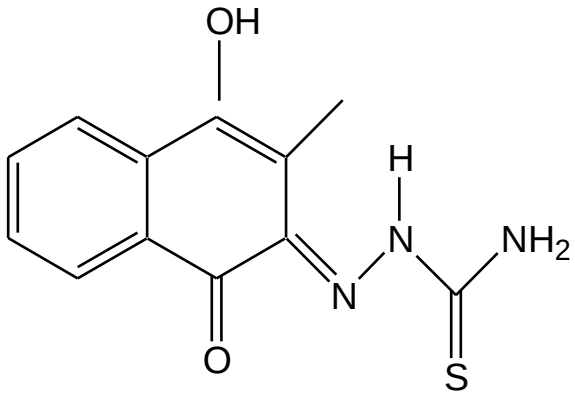
(C)

Topoisomerase II and DNA Interactions-

Copper-thiosemicarbazone complexes have significantly higher growth inhibitory activity than the uncomplexed ligand and have lower IC50 values against tumour cells than other reported topoisomerase-II inhibitors[20]. The antitumor activity of 1, 2-naphthoquinone-2-thiosemicarbazone (D) and that of its metal complexes of copper (II), palladium (II) and nickel (II) was investigated by Chen *et al*.[21] against MCF-7 human breast cancer cells. The results revealed that these complexes are effective antitumor chemicals in inhibiting MCF-7 cell growth. The nickel complex is the most effective among the complexes studied and, based on IC50 values; it is also more effective than etoposide, a commercial antitumor drug. Further data showed that 1, 2-naphthoquinone-2-thiosemicarbazonecopper (II), nickel (II) and platinum (II) complexes, 1, 2-naphthoquinone-2-thiosemicarbazone, and naphthoquinone can only stabilize the single-strand nicked DNA, but not double-strand breakage intermediates. The metal derivatives of these ligands, but not the parent ligand molecules, exerted an antagonizing effect on topoisomerase II activity. It had been previously shown that Cu (II) derivative of 4-hydroxy-3-methyl-1, 2-naphthoquinone-1-thiosemicarbazone (E) had the highest cytotoxicity compared to those of Fe (III), Ni (II), Pd (II), and Pt (II) metal derivatives; this was explained by the generation of Cu (I) species during intracellular enzymatic reduction or greater binding affinity of Cu (I) to an estrogens receptor protein complex[22].



(D)

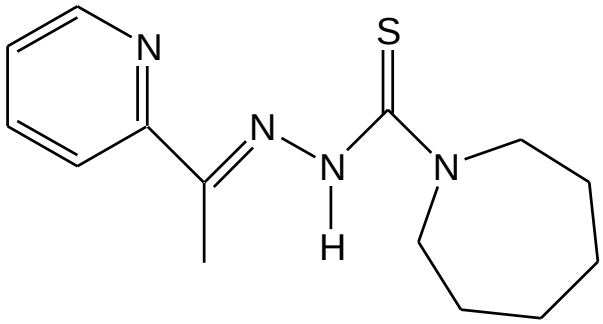


(E)

Other Mechanisms

In the literature is also present thiosemicarbazones with a non aromatic substituent on the imino nitrogen. Baldini *et al*. report the synthesis and biological evaluation of α-ketoglutaric acid thiosemicarbazone linear and cyclic derivatives and their copper and zinc complexes[23-24].The role of the metals seems not to be relevant and moreover the newly synthesized compounds are active towards cisplatin-refractory tumour cell lines. In a recent paper[25], in an effort to further understand the influence of the terminal nitrogen atom, the 2-formyl and2-acetylpyridine thiosemicarbazones have been modified by incorporating the terminal nitrogen into an aliphatic azepane ring (F). Reaction with platinum (II) afforded the related complexes [Pt (L) Cl]. Ligands and complexes have been evaluated for ant proliferative activity *in vitro* against four cancer cell lines: MCF-7 (human breast cancer cell line), T24 (human bladder cancer cell line), A-549 (human non-small cell lung carcinoma) and L-929 (murine).The 2-acetylpyridine ligand exhibited high activity as anticancer agent against all four cancer cell lines, while the 2-formylpyridine derivative exhibited selectivity against MCF-7, L-929 and its platinum complex against A-549, T-24 cancer cell lines.

Zhang *et al*. have carried out a study on 8-hydroxyquinoline-2-carboxaldehyde thiosemicarbazone (G), on its 4, 4-dimethyl derivative and on their copper (II) complexes[26]. Adsule *et al*. reports studies about the activity of quinoline-2-carboxaldehyde thiosemicarbazone (H) derivatives and its copper (II) complex as proteasome inhibitors in human prostate cancer cell lines PC-3 and LNCaP[27].



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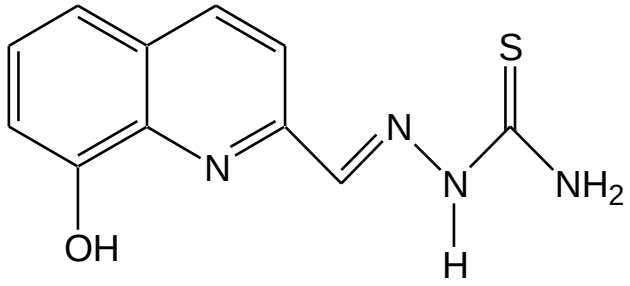
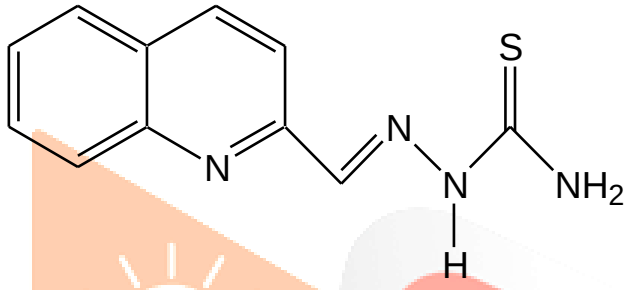


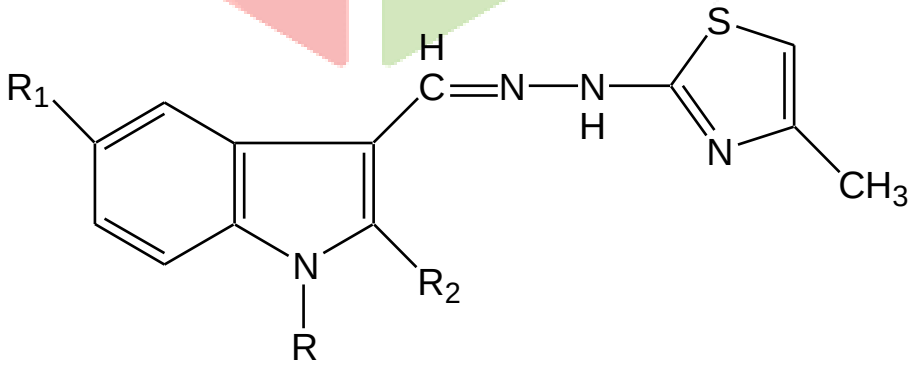
(G)



(H)

More recently the same group has reported on a series of thiosemicarbazones derived from natural aldehydes and in particular 9-cis-retinal thiosemicarbazone and its cobalt (III), nickel (II) and copper (II) complexes[28]. These complexes possess neither an aromatic ring nor a donor atom on the imino side of the thiosemicarbazone but a long hydrophobic chain.

Another field in which thiosemicarbazone metal complexes are receiving a great deal of attention is their use as carrier for radiotracers such as Cu[29]. Indole and its heterocyclic fused derivatives indole-3-aldehydes and their thiosemicarbazones (I) are found to be a potential anticancer and antitumor intermediates.



(I)

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