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Thiosemicarbazone Complexes as Versatile Medicinal Chemistry Agents: A Review

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ABSTRACT

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Objective: Thiosemicarbazones are Schiff based ligands of significant biological importance and their biological relevance has been studied for a considerable amount of time period. When the thiosemicarbazones bind with metal ions, they have shown an array of potential anticancer, antimicrobial and antioxidant activities etc. They have also found numerous applications in Analytical Chemistry. This present review summarizes some of the medicinal benefits of thiosemicarbazone based complexes especially with transition metals.

Data Sources: The studies cited in the present review were sourced from journals, books and conference proceedings preferentially written and published in English. Literature from the past 15 years or so has been included in the article. Papers indexed in known databases such as PUBMED, SCOPUS, INDEX COPERNICUS, CHEMICAL AND BIOLOGICAL ABSTRACTS, MEDLINE, EMBASE, EBSCO, DOAJ, and THOMSON REUTERS have been reviewed and included.

Summary of the contents of the article: The study unravels the mechanistic action of these compounds on *in vitro* living beings viz. cell culture as well as animal models. An elaborate review of the available literature on thiosemicarbazones has shown that the modifications in the ligand moiety leads to enhancement in its activity and some of the best structural alterations have been cited in the review. Some of the potential future applications and uses of the complexes have also been discussed. Structure optimization of the compounds may result in path breaking finding of potential anticancer and antimicrobial drugs.

Conclusion: Latest advances in medicinal inorganic chemistry have given considerable importance to the development of metal based drugs with thiosemicabazones. The presence of metal ion in the drug moiety usually mitigates the ill effects of the compounds, this may lead to the production of new metal based drugs. The key factors identified for their action has been the inhibition of RR, topo II and the production of ROS, but identification of other probable targets need to be explored.

Keywords: Thiosemicarbazone, medicinal, applications, transition metal.

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1.0 Introduction

Cancer causes serious threat to human beings and the death rate due to tumours is found to be on rise in the recent years [1]. In spite of the decreasing smoking rate and detection in the initial stages in the last two decades, the four major cancers including lung, bronchus, bronchus, breast and colorectum account for 46% of the total deaths [2]. According to World Health Organization (WHO) around 7.7 million people died due to cancer in 2008 and the toll may extend to 11 million by the end of 2030 [3]. Cancer is thus our society's major main health concern and is considered as the primary aim in connection with medicinal chemistry [4].Treating tumour cells which have developed MDR (multiple drug resistance) displaying a large spectrum of changes in biochemistry and cytogeny such as increased expression of p-glycoprotien, enhanced level of glutathione related enzymes, down regulation of monooxygenases and changed expression of protienkinase C remains a challenge [3]. In recent years, researchers have been more focused on the discovery of precise target drugs, overseeing the generality of cancer cells, such as the uncontrolled multiplication caused by the need for more nutrients and trace elements [5-6]. Studies have shown that metal complexes possess a considerable range of biological and chemical properties same when bind with organic moieties

[7] so the synthesis of antitumour and antimicrobial drugs by forming metal complexes linked with organic ligands has been a new strategy [8]. Schiff bases are the class of compounds that display a range of biological activities such as antifungal, antipyretic, antitumour, antiproliferative and antimicrobial [9]. Metal based compounds came into light after the success of cisplatin [10-13]. Cisplatin is an antitumour compound which is widely used since it was discovered in 1960, but some tumor cells have developed internal resistance to it, thus the discovery of metal complexes with biological activity became the new interest for more researches [14]. The general structure of a Schiff base is given as Fig. 1

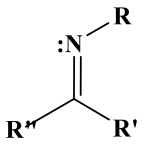

Fig. 1 General structure of Schiff base

Synthesis of Schiff based ligands is done by condensation reaction between primary amine and aldehyde and ketones [15] as presented in Fig. 2 and 3 [16].

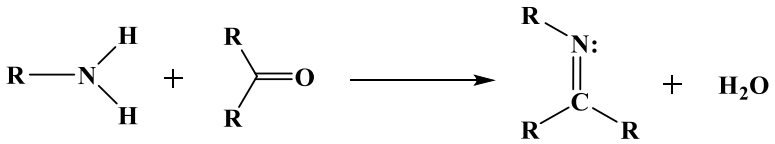

Fig. 2. Formation of Schiff base by condensation reaction

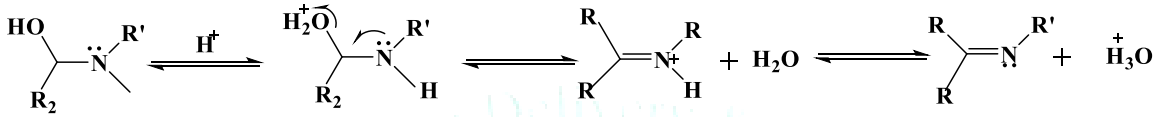

Fig. 3. Mechanism of formation of Schiff base

Schiff based thiosemicarbazone and its metal complexes shown array of activities such as antitumour, antibacterial and antigfungal. Antitumour activity of thiosemicarbazones has been found to be analogous to cisplatin [14]. The class name "thiosemicarbazone" was given to these compounds after the names of the respective aldehyde and ketone. Bis(thiosemicarbazones) was thus derived from di carbonyl compounds and two thiosemicarbazone moieties [17]. Thiosemicarbazones are synthesized by the condensation reaction between aldehyde or ketone with thiosemicarbazide [15]. General structure of thiosemicarbazone moiety is presented as Fig. 4.

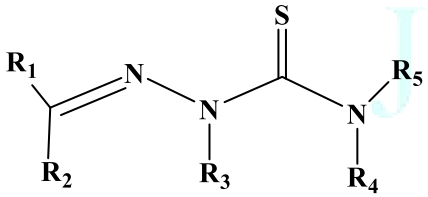

Fig. 4. General Structure of Thiosemicarbazone moiety. R^1, R^2, R^3, R^4 and R^5 may be H, or any organic substituents

Thiosemicarbazones (TSCs) are a very significant group of compounds used for the treatment of several diseases including cancer [18-20].Thiosemicarbazones and their complexes with metals have wide applications in nuclear medicine and analytical chemistry as well [21-23]. 2-formylpyridine is a TCS whose anticancer activity was examined in 1956 [3]. TCS also possess antiviral as well as anti-HIV properties [24-26]. The antiviral activity of amino acid based thiosemicarbazides has been screened by MIT and plaque formation reduction assays and the results stated that these compounds inhibited dengue virus infection in vero cells. Bz-Trp-TSC is a well-known thiosemicarbazide derivative which is used to treat dengue fever [27].There is an abrupt change in biological property of the ligands as seen in case of coordination of salicylaldehyde semicarbazone and thiosemicarbazone with metals which increased its antitumour activity and they have a range of applications in pharmacological clinical as well as biological areas [29-34].

When thiosemicarbazones interact with a charged metal ion, due to its polar nature the entry of the metal complex inside the cell membrane is facilitated as the hydrophobic part of the molecule gets exposed to outside resulting is increased activity of the overall compound, Fig. 5. [15].

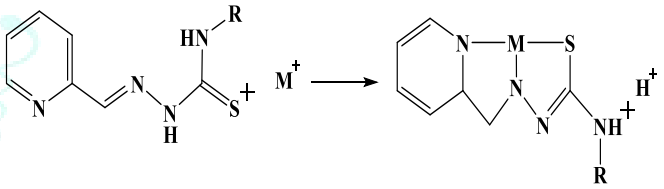

Fig.5 Metal ion coordination to a thiosemicarbazone moiety induces structural changes in the complex

This chelating ability of thiosemicarbazones with metal ions is a major reason of their anticancer activity [35, 36]. Tridentate ligands have better chelating ability as compared to bidentate ligands during the formation of stable chelates with metals such as Fe, Cu, Mn, Zn and Ga [37]. An extensive study has been done on tridentate ligand with NNS structure, their ability of chelation and also their pharmacological significance [38,39]. Covalent character in the bond between metal and ligand increases due to the coupled chromophore of quinone-thiosemicarbazone[40]. Owing to their high affinity with first transitional row metals they are known as potential chelators [41,42]. According to recent studies it has been found that the effects produced by central metal as Cu, Zn and Ga enhance whereas Fe, Mn and Ni decrease activity of the thiosemicarbazone ligand [43-46]. Platinum compounds possess antineoplastic potential, but at the same time they are toxic, so they cannot be used for clinical applications whereas ruthenium complexes are well suited for various biological applications. Thota et al. studied a variety of ruthenium(II) arene complexes with thiosemi carbazone and isonicotinylhydrazone ligands, their biological activity and structure activity relationship. The complexes possessed anticancer potential. The cytotoxic activity of these complexes has been checked against Molt $4/C_8$, L1210, CEM, HL60 and BEL7402 cell lines and the compounds

displayed significant inhibitory activity against many cell lines with IC_{50} in the micro molar range [47]. A range of bisthiosemicarbazone copper complexes have antitumour properties [48-50]. Copper complexes also have a limitation in terms of poor solubility and high toxicity *in vivo* [51,52]. Numerous attempts have been to modify thiosemicarbazone complexes in order to improve hydrophobicity and reduce its toxicity [53].

1.1 Derivatives of thiosemicarbazone:

Anticancer activity has been observed against HCT116 tumour cells in novel quinolene derivatives which are considered as iron chelators and structurally bind with the active moieties of identified quinoline and thiosemi-carbazonebio effectors. Palladium complex of phenylanthrenequinone thiosemicarbazone has been synthesized and found to have antiproliferative properties against breast cancer cells [15]. Chandra et al. synthesized novel macrocyclic ligands with Mn, Co, Ni, Pd and Cr in +2 oxidation state as $M(L)Cl_2$ and Pt(L) viz 1,3,4,8,9,11-hexaza-5,7,12,14-tetraphenyl-2,10-dithiocyclotetradecane(L).
Characterization of the complexes was done using elemental analysis, molar conductance, magnetic susceptibility, mass, H^1 NMR,IR,UV-visible and spectral studies and their screening was done in lab and they were found to possess activity against a class of bacteria and plant pathogenic fungi [54]. A group of MIZCA-TSC ligands were synthesized by the reaction of MIZCA(methyl-imidazole-2-carboxaldehyde) with common methyl substituted thiosemicarbazone and the NMR characterization confirmed the proposed structure of the ligands. These ligands formed chelates with Cu(II) and Pd (II) salts and the Pd (II) complexes were found to possess maximum antiproliferative activity[55]. Milligan et al. synthesized novel compounds through the reaction of 2-Acetyl-6-bromopyridine (ABrPy) with thiosemicarbazides to form a range of new 2-acetyl-6-bromopyridine thiosemicarbazone (ABrPy-TSC) ligands which were recrystallized and analyzed via ^1H NMR and ^{13}CNMR spectroscopy. They formed metal complexes of the ligands with Cu(II) and their MIC (minimum inhibitory concentration) studies were performed to confirm the anti-microbial properties of each TSC compound and it was found that the Cu metal complexes of the ligands exhibited potential anti-proliferation activities[56]. J.R. Pawar et al. synthesized heterocyclic base adducts of cobalt (III) complexes by the reaction of cobalt (II) chloride with 5-chloro-2-hydroxy acetophenonethiosemicarbazone and N(4) Me-thiosemicarbazone with heterocyclic base like 2,2'-bipyridine (bipy), 1,10-phenanthroline (Phen) and 8-amino quinolone, which were characterized by ^{13}C, ^1H NMR as well as IR, electronic spectra. The octahedral geometry for six coordinate complexes was confirmed by magnetic and spectroscopic data. The thiosemicarbazones and its cobalt(III) complexes displayed inhibitory activity against *Pseudomonas putida*, *Escherichia coli*, *Aspergillusniger and Candida albicans*. [57]. 2-butanone thiosemicarbazone and their 11 complexes of the type ML_2X_2, ML_2X', where M = Cu(II), Cd(II), Co(II), Zn(II), Hg(II); L=2-butanone thiosemicarbazone; X = Cl^-, NO_3^- or CH_3COO^-, X'= SO_4^{2-} have been synthesized and characterized using infra-red and ultra-violet spectroscopy which confirmed the bidentate nature of the ligand utilizing thionic sulfur and the azomethine nitrogen atom for co-ordination to the central metal atom and some of the complexes displayed activity against Gram positive bacteria *Staphylococcus aureus*, *Staphylococcus epidermidis* and Gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. [58]. Heterocyclic thiosemicarbazones have also been studied for their inhibitory action against gliomas which are tumours present in human central nervous system [59]. (N)-heterocyclic thiosemicarbazones resulting from 2-formyl, 2-acetyl, and 2-benzoylpyridine have also been investigated for their activity against gliomas [60]. Complexes of transition metals with the condensation products of 3-acetylpyridine (3-Acpy) with hydrazines and thiosemicarbazide have been synthesized and characterized [61]. Complexes of derivatives of 3-Acpy with semicarbazide, semioxamazide and thiosemicarbazide [62] have also been investigated in which it was found that 3-Acpy derivative coordinated in a monodentate manner via carbonyl oxygen or via pyridine nitrogen [63]. Mariasa et al. synthesized pyridoxal-thiosemicarbazone copper(II) and cobalt(III) complexes with nitroprusside and investigated antileukemic activity of three of these complexes against U937 and CEM [64].A series of new nopinone-based thiosemicarbazone derivatives have been designed and synthesized by Yunyun et al. as potential antitumour agents. In the *in vitro* antitumour activity, most derivatives showed significant cytotoxic activity against MDA-MB-231, SMMC-7721 and Hela cell lines. Some of the compounds exhibited good anticancer activity against the tested cancer cell lines with the IC_{50} values 2.79 ± 0.38, 2.64 ± 0.17 and 3.64 ± 0.13 M, respectively. Furthermore, the cell cycle analysis indicated that the compounds caused cell cycle arrest of MDA-MB-231 cells at G2/M phase. The Annexin V-FITC/7-AAD dual staining assay also showed that some compounds induced early apoptosis of MDA-MB-231 cells [65]. Two new Cu(II) mixed-ligand complexes with octadentate N,N',N'',N'''-tetrakis(2-pyridylmethyl)-1,4,8,11 tetraazacyclotetradecane (tpmc) and pentadentate ligands 2.6-diacetylpyridine bis(semicarbazone) ($DAPsc_2$) or 2,6-diacetylpyridine bis(thiosemicarbazone) ($DAPtsc_2$) have been synthesized by Tanaskovic. The general formulae $[Cu_4DAPsc_2(tpmc)_2]$ $(ClO_4)_8{\cdot}5CH_3COCH_3{\cdot}H_2O$ and $[Cu_2DAPtsc_2(tpmc)](ClO_4)_4$ ·7EtOH were proposed from elemental analyses and conductometric measurements. For the dinuclear complex, an exo-coordination of Cu(II) with four nitrogens from tpmc and μ-bonded $DAPtsc_2$ through sulfurs and probably terminal hydrazinic (azomethine) nitrogens was assumed. For the tetranuclear complex, one $DAPsc_2$ bridged two $[Cu_2tpmc]^{4+}$ units using oxygens and terminal hydrazinicnitrogens as ligators. The antibacterial activity of the complexes was also established [66]. A zinc complex of the 2-benzoylpyridine thiosemicarbazone(Hbpt) viz. $Zn(bpt)_2{\cdot}$DMF, has been synthesized and characterized by elemental analysis, IR spectra and single crystal X-ray diffraction by Li et al. The molecular structure showed that Zn(II) cation bonded to two perpendicular bpt ligand in a distorted octahedral geometry through two sulfur and four nitrogen atoms. The crystal contained a disordered DMF solvate molecule. Adjacent molecules were found to be interconnected by means of hydrogen bonding generating a one dimensional chain structure. The cytotoxic activity dimension indicated that the complex exhibited higher anticancer activity against lung cancer A549 cell lines than the free ligand [67]. Twelve cobalt(II) and nickel(II) complexes, $[M(L)(H_2O)_2(Y)]$ (M =Co(II) or Ni(II); Y= Cl^-, Br^- or NO_3^-) containing the Schiff-bases 4-hydroxycoumarin-3-carbaldehyde semicarbazone and thiosemicarbazone, HL^1 and HL^2 respectively were synthesized. The metal complexes were checked for their antifungal and antibacterial activities on different species of pathogenic fungi and bacteria [68]. Thiosemicarbazones of citronellal and menthone and their nickel(II), copper(II) complexes were synthesized and characterized by PhanThi Hong using IR,UV-VIS, MS and NMR spectroscopies. The results indicated the formation of 1:2 metal to ligand complexes with empirical formulas $[CuL_2]$ and $[NiL_2]$ (HL:thiosemicarbazone). The Cu(II) and Ni(II) complexes were four coordinate and square planar in geometry in which the ligands behaved as bidentate

chelating agents in the uni-negatively charged form. The biological activity of thiosemicarbazones and its complexes against bacteria, fungi and cancer cell lines was also assessed [69]. Hitesh et. al. synthesized a series of thiosemicarbazones of 1-(5-chloro-1H-benzimidazol-2-yl)ethanone and studied their*in vitro*antitumor activity against 60 human cell lines derived from nine clinically isolated cancer types viz. Leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast, according to a standard protocol established at the National Cancer Institute, Bethesda, MD, USA [70]. Some of the important derivatives of thiosmeicarbazones along with their biological activity have been summarized in table 1.

Table 1. Some recent important derivatives of thiosemicarbazones and their activity spectru

S.No.	Year	Derivative	Coordinating metal	Activity tested	Ref.
1	2018	(E)-N-ethyl-2-[1-(thiazol-2-yl)-propylidene] hydrazinecarbothioamide. (E)-N-tert-butyl-2-[1-(thiazol-2-yl)-propylidene]hydrazinecarbothioamide	Cu(II)	Anticancer	71
2	2017	$C_{18}H_{20}N_6O_6$	Cu(II)	Anti-microbial	72
3	2017	Izatiton-izatinthiosemicarbazone derivative	-	Antiviral, antitumour	73
4	2016	di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT)	-	Anticancer	74
5	2016	3-acetyl coumarin thiosemicarbazone	-	Neuroprotective	75
6	2016	Thiosemicarbazone and Chloroethanol	Cu(II)	Antibacterial, Antifungal, Anticancer	76
7	2016	Benzoin Thiosemicarbazone	Co(II), Ni(II)	Antibacterial	77
8	2016	Benzaldehydesemicarbazone, Benzaldehyde thiosemicarbazone	As(III)	Antimicrobial	78
9	2016	8-ethyl-2 hydroxytricyclo(7.3.1.02,7)tridecan-13-one-thio-semicarbazone	Cu(II),Pd(II), Pt(II)	Antimicrobial, Antiproliferative	79
10	2015	Acetylcyclohexanthiosemicarbazone (ACHTSC)		Antibacterial	80
11	2015	Acetyl acetone semicarbazone, acetyl acetone thiosemicarbazone, benzoyl acetone semicarbazone, benzoyl acetone thiosemicarbazone, glyoxalsemicarbazoneglyoxal thiosemicarbazone.	Sn(II)	Antimicrobial	81
12	2015	5-allyl-2-hydroxy-3-methoxybenzaldehyde-4-thiosemicarbazone [H2L,1], [MeSnCl(L)] (2), [BuSnCl(L)] (3) [PhSnCl(L)] (4) [Me_2Sn(L)] (5)	Sn(IV)	Antibacterial	82
13	2015	1) 2–methoxybenzaldehyde semicarbazone/ thiosemicarbazone (mbsc, mbtsc) 22–bromobenzaldehydesemicarbazone/ thiosemicarbazone (bbsc, bbtsc)	Cu(II)		**83**
14	2015	Gallium(III)thiosemicarbarbazone	Ga (III)	Antiproliferative	84
15	2015	1)6-(3-thienyl) pyridine-2-carboxaldehyde-4N-ethyl thiosemicarbazone 2)6-(3-thienyl) pyridine-2-carboxaldehyde-4N-phenyl thiosemicarbazone	Cu(II)	Antibacterial, Antifungal, Antioxidant	**85**
16	2014	Quercetinthio semicarbozone(QTSC)	Cu(II)	Antioxidant, Antitumor, Anticancer	86
17	2014	1-methylpyrazole-3-aldehyde-4-(2-pyridyl) thiosemicarbazone	Cu(II)	Antimicrobial	87
18	2014	Acetylpyrazine-thiosemicarbazone	Cu(II), Pd(II), Pt(II)	Antimicrobial	88
19	2014	2(E)-2-[1-(4-pyridinyl)ethylidene]hydrazinecarbothioammidehydrochloride	Cu(I)	Anticancer	89
20	2013	1-TSCND (2-hydroxy-1,4-naphthalenedione-1-thiosemicarbazone)	Ni(II)	Anticancer	**90**

21	2013	1)4-phenyl-1-(acetone)-thiosemicarbazone 2)4-phenyl-1-(2'- chloro-benzaldehyde)-thiosemicarbazone 3)4-phenyl-1-(3'-hydroxy-benzaldehyde)-thiosemicarbazone 4)4-phenyl-1-(2'-naphthaldehyde)-thiosemicarbazone 5)4-phenyl-1-(1'-nitro-2'-naphthaldehyde)-thiosemicarbazone,	Pd(II)	Antiproliferative, Antitumor	91
22	2013	SalicylaldehydeThiosemicarbazone	Fe(II), Co(II)	Antimicrobial	92
23	2012	4-R-benzaldehyde thiosemicarbazones (denoted as H2L-R, where H2 stands for the two dissociable protons and R (R = -OCH_3, CH_3, H, Cl^- and NO_2^-)	Pt (II)	Antitumor	93
24	2011	4-(2-pyridyl)-3-thiosemicarbazide with phenyl isothiocyanate, benzoyl isothiocyanate, phenyl isocyanate and 4-pyridyl isothiocyanate. The products were N1-phenyl-N2-(pyridin-2-yl) hydrazine-1,2-bis (carbothioamide) (H2PPS), N-phenyl -2-(pyridine-2-ylcarbamothioyl) hydrazine carboxamide (H2PBO), 1-(amino (thioformyl)-N-phenylformyl)-4-(pyridine-2-yl)thiosemicarbazide (H2APO) and 1-(aminoN-(pyridine-3-yl)methanethio)-4-(pyridine-yl)thiosemicarbazide (H2PPY) respectively.		Antiproliferative, Anticancer	94
25	2011	Chalcone thiosemicarbazide derivatives		Anticancer, Antiproliferative	95
26	2011	Thiosemicarbazide derivatives of 4-(3-(Benzofuran-2-yl)-1-phenyl-1H-pyrazol-4-yl)-2-hydrazinyl-1,6-dihydro-6-oxopyrimidine-5-carbonitrile		Antitumor	96
27	2011	2-phenylcarbonylquinoxaline thiosemicarbazone	Co(II), Ni(II), Cu(II)	Antibacterial, Antifungal	97
28	2010	Triapine (3-aminopyridine-2-carbaldehyde thiosemicarbazone)	Cu(II), Zn(II),Fe (II)	Antitumor	98
29	2010	6-hydroxy chromone-3-carbaldehyde thiosemicarbazone	Ni (II)	Anticancer	99
30	2010	bis(phenylthiosemicarbazone)	Cu(II), Ni(II)	Antioxidant, Antibacterial	100
31	2009	2-pyridinecarboxaldehyde thiosemicarbazone	Mn(II), Co(II)	Antibacterial	101
32	2008	2-acetylpyridine thiosemicarbazones and aniline	Co(II), Ni(II), Cu(II)	Antimicrobial	102
33	2007	N(4)-o-, N(4)-m- and N(4)-p-tolylthiosemicarbazones	Cu(II)	Antimicrobial	103
34	2007	6-methyl-2-pyridylformamide semicarbazone and 6-methyl-2-pyridylformamide thiosemicarbazone	Co(II), Ni(II) Cu(II)	Antifungal	104
35	2005	4-aminoantipyrine thiosemicarbazone	Co(II), Ni(II)	Antibacterial, Antifungal	105
36	2001	5-methyl 2-furfural thiosemicarbazone	Ni(II)	Antifungal	106

2.0 Mechanism of action of thiosemicarbazones

Thiosemicarbazones work by the following mechanisms-

2.1.Inhibition of RibonucleosideDiphosphateReductase(RR)

The conversion of ribonucleotide to deoxyribonucleotide which forms DNA in all the cell types is done by Ribonucleotide reductase (RR) [107]. The total rate of DNA synthesis is regulated by RR such that the DNA to cell mass can be maintained at a constant rate ratio during DNA repairing and cell multiplication [108]. The anticancer activity and ribonucleotidereductase inhibitory activity of a thiosemcarbazide derivative 3AP has been advanced to clinical trials [109,110]. Antiproliferative activity on different cancer cells is found in thiosemicarbazoness a NNS-thiodentate ligand through chelation[111] and TCS inhibits an iron dependent enzyme ribonucleotidereductase[112]. The activity of this enzyme is initiated by tyrosyl radical and its inhibition leads to the death of the cell (apoptosis) due to the blockage in the S phase of the cell cycle [15]. QSAR analysis of 21 compounds which are thiosemicarbazone derivative showing RNR inhibitory activity was performed.The inhibitory concentration (IC_{50}) in the IM range was reported for 13 of them. The inhibitory concentration of those compounds was converted into -log IC_{50} before being correlated with structural features [113]. Due to the tetradentate nature the Pyrazinecarboxaldehydethiosemicarbazones and 1-formylisoquinolene thiosemicarbazone which are alpha (N) heterocyclic thiosemicarbazonethey are better chelators due to their tridentate nature [114]. 5-HP(5 hydroxyl 2-formylpyridine) is one of the earliest known inhibitors of RR that showed high activity in animals but its activity decreased in humans due to rapid excretion. This molecule acts on tyrosyl radical and destroys it[115]. In 1960s certain formylpyridylthiosemicarbazones were discovered to be powerful inhibitor of RR [116,117] and RR maintains the process of DNA synthesis and repair. Triapine also causes ribonucleotide reduction and is the most investigated ligand [118-119] Drugs belonging to this group class have undergone phase I and II trials as an anticancer agent

[120,123,126-131].They exhibited promising properties *in vivo* but also caused some side effects which including diarrhea, nausea, neutropenia, thrombocytopenia, methemoglobinemia[132-133].A considerable amount of study on the biological, chemical and electrochemical properties of triapine and substituted variants and complexes with Fe and Ga has been performed by Kolinowski et al. [133]. N heterocyclic tridentate thiosemicarbazone play a significant role as iron chelator and are used for biomedical purposes [134]. Gallium complexes of triapine displayed an increase in toxicity than the iron complexes and RR inhibition was found to be responsible for cytotoxicity. The Fe(II)bis (triapine)complex has also been identified as a more effective RR inhibitor than the Fe(III) species and was found to attach itself to the tyrosyl radical present in the ribonucleotide reductase subunit [135]. The cellular disruption of triapine and its zinc complex was found out by confocal fluorescence microscopy displaying dispersion in the cytosol [136] which was found to be consistent with RR inhibition. The chelation with iron could play an important role by reducing the availability of Fe for RR and thereby reducing the RR activity which was measured by EPR of the quenching of the tyrosine radical [137]. It is evident that the Fe thiosemicarbazone complexes generate radical species on reduction and can carry out Fenton type of reaction to generate hydroxyl mediated by the presence of oxygen. The ROS can also degrade the DNA providing an additional mechanism for cytotoxicity. The reduced RR activity for analogues of Ga would stimulate the Fe based radical formation but it doesn't explain the greater cytotoxicity of Ga complexes than Fe complexes [138]

2.2 Inhibition of Topoisomerase II and DNA interactions

Topoisomerase is an enzyme found in eukaryotic cells that causes decatenation of DNA and is necessary for DNA replication. It also prevents supercoiling during replication [139,140]. Topoisomerase II plays important function in cell multiplication and is richly found in rapidly proliferating cancer cells. TCS are powerful antitumour agents that inhibit topoisomerase II activity. Relationship between *in vitro* and *in vivo* performance of 64Cu-labelledthiosemicarbazide complexes and the expression of Topo-II activity has been investigated [141]. Four 4N-azobicyclo [3.2.2] nonane thiosemicarbazideligands were prepared and radiolabelled with ^{64}Cu which leads to the formation of lipophilic cations. Of the four ligands investigated in the study three have been found to possess better growth inhibition property when compared with non-radioactive copper with IC_{50} value of 0.004µmol/l in HT29 cells. A wide range of tridentate TSCs with nitrogen based heterocycles have been tested.A ligand bearing aquinoline group has been identified to have particularly great cytotoxicity and ability to checkTopo-II activity. The mechanism of inhibition recommended that the blockage [142]. A succeeding paper has examined the Topo-II inhibition by Cu complexesof same ligand types and has revealed them to be effective inhibitors of Topo-II [143]. Cu-thiosemicarbazonecomplexes ha possess superior growth inhibitory activity than the uncomplexed ligand and have lesser IC_{50}values against tumor cells than the reported Topo-II inhibitors [144]. Anticancer property of 1,2 naphthoquinone-2-thiosemicarbazone and its metal complexes of Cu (II), Pd (II) and Ni (II) has been checked against breast cancer(MCF-7) cell line showing their potential anticancer activity. The Ni complex has been highly effective based onIC_{50} values [145]. Further investigation of the ligands and complexes has shown that they can only even out the single-strand DNA. The metal complexes of these ligands exhibit an antagonizing effect on Topo-II activity, as compared to the free ligands. In another study, Cu(II) complexes of 4-hydroxy-3-methyl-1,2 naphthoquinone-1-thiosemicarbazone have shown chief toxicity in the cell related to those of Fe(II), Ni(II), Pd(II) and Pt(II) metal complexes with the same ligand [146]. The binding doesn't allow the proper functioning of the protein complex during DNA and its interaction. Further studies on mechanism of action have shown that metal complexes could alleviate the cleavable complex formed by DNA and Topo-II. Studies have shown that iron and copper complexes perform better cell destruction as well as in the prevention of DNA synthesis than the uncomplexed thiosemicarbazone [147]. 5-hydroxy-2-formyl thiosemicarbazone has been revealed to create lesions in DNA [148]. It has been proven that a tridentate nature and a high formation constant is a qualified for increased activity by comparing the activity of pyrazine thiosemicarbazone derivatives and an analog derived from acetophenone. These compounds alter the iron hemostasis by preventing the iron exchange from the serum transferrin. In a very current study, Topo-IIα inhibition and antiproliferative activity of α-heterocyclicthiosemicarbazones and their analogous copper(II) complexes has been found. Cu (II)(thiosemicarbazonato)Cl complexes has been shown to catalytically inhibit Topo-IIα at concentrations 0.3-7.2µM The copper complexes have also shown inhibitory action towards the proliferation of breast cancer cells (SK-BR-3) expressing high levels of Topo-IIα at lower concentrations than breast cancer cells (MCF-7) showing lower levels of the enzyme [149]. Copper complex of acetylpyridinemethyl thiosemicarbazone inhibits Topo-IIα enzyme and the palladium(II) and platinum(II) complexes of the same ligand also inhibits the enzyme due to the same structural geometry (square planar around the metal), a series of acetylpyridine thiosemicarbazone ligands, and their Cu(II) and Pd(II) metal complexes have been synthesized and characterized by NMR and the results proved that the Cu II complexes have better antiproliferative property than Pd II complexes[150].

2.3. *Reactive Oxygen Species Generation*

Redox metal complexes can operate as ROS generators. Since most thiosemicarbazone complexes possess redox metal ions, they potentially activate O_2 and produce OH^- radicals [15]. $[Cu(L)_2(pz)](ClO_4)$ and $\{[Cu(L)_2(dca)](ClO_4)\}$ complexes where L=2-formylpyridine TSC, pz=pyrazine and dca=dicyanamide have been tested for their biological activity on DNA. The oxidative breaking of DNA has been investigated in the presence of 3-mercaptopropionic acid as reducing agent by the process of gel electrophoresis using supercoiled pUC18 and these complexes have been found to produce single and double strand breaks in DNA [151]. Copper is a vital micronutrient and has significant biological functions such as cellular trafficking, redox regulation [152-153] and angiogenesis modulation etc. [154-155]. Cu (II) complex-mediated cytotoxicity studies are on the rise [156-157]. Four novel thiosemicarbazone metal complexes, $[Cu(Am_4M)(OAc)]\cdot H_2O$ (1), $[Zn(HAm_4M)Cl_2]$ (2), $[Zn_2(Am_4M)_2Br_2]$ (3) and $[Zn_2(Am_4M)_2(OAc)_2]\cdot 2MeOH$ (4) [HAm_4M=(Z)-2 (amino(pyridin-2-yl) methylene)-N-methylhydrazinecarbothioamide], have been investigated and tested against HepG-2 cell. IC_{50} value (11.2±0.9 µM) of complex 1 against HepG-2 cells has been found to be nearly 0.5 fold of that against human hepatic cell lines LO2, showing a reduction in the side effects to liver cells. It has been seen that to display a stronger inhibition on the viability of HepG-2 cells than cis-platin (IC_{50}=25±3.1µM), suggesting complex-1 might be a good anticancer agent. Copper(II) is very receptive to electron transfer, whereas zinc(II) is difficult to participate in redox reaction because of the non-availability of variable valency. Fluorescence microscopy inspection and

flow cytometry analysis has exposed that complex-1 cannot repress HepG-2 cell viability and encourage systematic cell death. Some indexes, such as DNA cleavage, ROS production, comet assay and cell cycle analysis have shown that the antitumor mechanism of complex 1 on HepG-2 cells might be *via* ROS-triggered apoptosis pathway [158]. Complexes 1-4 have been found to display different coordination geometries even in parallel synthetic conditions, which is accredited to the nature of metal ion and its ionic radius, coordination numbers, different counter anions (Cl^-, Br^- and OAc^-) etc. [15]. Non-Hodgkin's lymphoma and bladder cancer are treated by using gallium nitrate. [158-159]. Lymphomas are disrupted by Gallium nitrate by increasing intracellular reactive oxygen specie and up-regulating cyclin D1 [160]. Alkyl/aryl-1,2naphthoquinonesthiosemicarbazones were synthesized and characterized. The crystal structure of the free ligands viz. 4-Pyrrolidine-1-yl-[1,2] naphthaquinone thiosemicarbazone copper complexes showed their E' conformation which were checked for their DNA cleaving activities in case of circular double stranded plasmid DNA pBR322 in the presensence of oxygen. All Cu conjugates showed more pronounced interaction with DNA presence of the oxidant [161].

2.4. Inhibition of tyrosinase

For the process of melanognesis inhibition tyrosinase is chosen as a target since it catalyzes the rate-limiting step of melanin production tyrosinase and is used in the production of anti-hyperpigmentation agents. Thiosemicarbazones have been found to inhibit the action of tyrosinase [162].

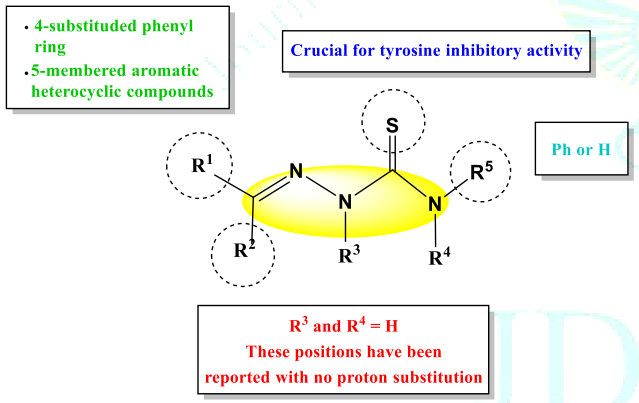

Fig. 6. Structure-activity relationship of thiosemicarbazones towards mushroom tyrosinase [162]

Since tyrosinase contains two copper atoms in its moiety, thiosemicarbazones usually containing S and N atoms as donors bind with the copper atoms. Sulfur atom particularly shows the ability to chelate copper ions in the active site of tyrosinase. Thiosemicarbazones and thiosemicarbazide are different only by one proton. There are few possibilities of proton substitution and a lot of compounds with at least one substitution of proton have been found to inhibit tyrosinase [163-164]. Benzaldehyde thiosemicarbazone has been to be a few times more effective in the inhibition of tyrosinase [165-166]. Xie et al. have reported the effect of thiophene, furan and pyrrole rings on the inhibitory potential of the synthesized compounds [167].

Yi

A group of mono-ligand trisubstituted benzaldehvde thiosemicarbazone derivatives containing hydroxy or methoxy groups on the benzene ring was synthesized by Yi et al. and the substitution at the 4th position of phenyl ring was found most effective for the inhibition of tyrosinase enzyme [168].The interaction kinetics of 4 hydroxy and 4 methoxy benzaldehyde thiosemicarbazones with tyrosinase was studied by Chen et al. [169]. Inhibition kinetics for 2-chlorobenzaldehyde thiosemicarbazone (A) and 4-chlorobenzaldehyde thiosemicarbazone (b) showed reversible inhibition when it was investigated by Lie et al. [170]. For 2-chlorobenzaldehyde thiosemicarbazone (A) IC_{50} was 15.4 and 1.22μM for mono- and diphenolase activity of the enzyme, respectively and for 4-chlorobenzaldehyde thiosemicarbazone (B) it was 6.7 and 1.82 μM respectively. A was noncompetitive inhibitor with K_i value of 1.20μM and B showed mixed-type inhibition with K_i and K_{is} of 1.25 and 2.49μM, respectively. For monophenolase activity, A and B (Fig.7) lowered reaction rate but did not control the lag time.

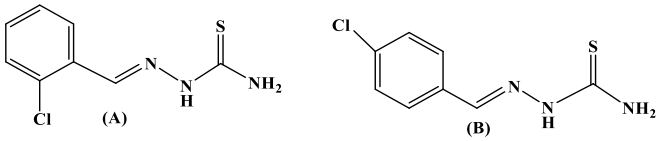

Fig. 7. Structures of 2-chlorobenzaldehyde thiosemicarbazone(A),4 –chlorobenzalde hydethiosemicarbazone(B)

Zhu et al. synthesized the derivative of cinnamaldehyde and thiosemicarbazide and proved it as a reversible mixed-typed inhibitor of diphenolase tyrosinase activity. It's K_i and K_{is} values were 4.45 and 8.85μM, respectively. For monophenolase activity, inhibitor not only lowered the steady-state rate but also lengthened the lag time [171]. The inhibition potential of two 4-dimethylaminobenzaldehyde thiosemicarbazone derivatives was studied by Yang et al. and the substitution of proton from thiosemicarbazide terminal group with phenyl moiety. In this case IC_{50} was calculated for both mono and diphenolasetyrosinase activity and it was 1.54 and 2.02μM for 4-dimethylbenzaldehyde thiosemicarbazone and 1.78 and 0.80μM for 4-dimethyl aminobenzaldehyde-N-phenyl-thiosemicarbazone respectively. Both compounds showed reversible mode of inhibition. Substitution of proton in position R5 with phenyl group changed the inhibitory action of 4-dimethylamino benzaldehyde-N-phenyl-thiosemicarbazone, as it inhibited tyrosinase in to non-competitive type, enhancing inhibitory potency (Ki 0.77μM).Both compounds inhibited tyrosinase activity but slightly prolonged the lag time [172].

2.5. Multidrug resistance protein (MDR1) inhibition

Multidrug resistance is a major hurdle and clinical challenge, when it comes to development of anti-cancer drugs. Some tumour cells develop particular multidrug resistance (MDR), which makes the cells resistant to other classes of anticancer drugs to which the tumour cells have not been treated before [173]. Pd complexes with phenanthrenequinone thiosemicarbazone have been investigated for their anti-proliferative activity in the breast tumour cells and normal cells. The results revealed that the complex possessed potent anti neoplastic property having selective activity against tumour cells and found to be significant in curing breast tumour cells that has developed resistance to these drugs [174].

2.6. Other mechanisms

It has also been seen that substitution on terminal nitrogen increases the overall activity of the complex. 2-formyl- and 2-acetylthiosemicarbazone and their metal complexes with zinc have been tested against MCF7, T24 and L-929 [175]. Later acetyl derivative was modified by adding an ethyl group on terminal nitrogen and its Pt and Pd complexes were prepared with the formula, $[ML_2]$, M=Pd, Pt. The complexes showed activity towards cis-platin resistant tumour cell lines and role of metal was not found to be significant [176]. In another ssimilar study 8-hydroxy quinolone-2-

carboxaldehyde thiosemicarbazone and its 4,4-dimethyl derivative along with their Cu (II) complexes. The terminal amino substituted complex showed greater anticancer activity than the unsubstituted complex. The activity was checked on SK-N-DZ (a cisplatin resistant neuroblastoma cell lines). Improved expression of p53 protein was detected in the SK-N-DZ cells treated with the non- methylated complex suggesting that apoptosis was caused by DNA breakage [177]. Quinoline-2-carboxaldehyde thiosemicarbazone derivatives and their Cu (II) complexes have been found to generate apoptosis by inhibiting proteasome-ubiquitin pathway and not pass oxidative stress [178]. This shows an additional pathway of action. A zinc complex of 2-benzoylpyridine thiosemicarbazone (Hbpt), $Zn(bpt)_2 \cdot DMF$, has been synthesized and characterized by elemental analysis, IR spectra and single crystal X-ray diffraction. The molecular structure has a Zn(II) cation bound to two perpendicular bpt ligands in a distorted octahedral geometry through two sulfur and four nitrogen atoms. The crystal contains a disordered DMF solvate molecule. The cytotoxic activity measurement indicated that the complex exhibited superior antitumor activity against lung cancer A549 cell lines than the free ligand [179]. The ligand benzilbis(4-methyl-3-thiosemicarbazone), MeNHCSNHN:CPhCPh:NNHCSNHMe (LH_2) reacts with K_2PtCl_4 and Li_2PdCl_4forming cyclometalatedmesocates I (1, 4; M = Pt, Pd) and monomeric chelates II (2, 3; M = Pt, Pd), depending on the reaction conditions. Complexation of K_2PtCl_4 both in the presence and absence of $LiOH \cdot H_2O$, yielded a mixture of 1 and 2 (77:18) which could be easily separated by their different solubility. In contrast, reaction of Li_2PdCl_4 without base led to the formation of the monomeric [PdL] 3, while the use of $LiOH \cdot H_2O$ permitted the selective synthesis of the cyclometalatedmesocate $[Pd_2(\mu\text{-}L)_2]$ (4). All the complexes were characterized by the usual techniques, including x-ray single crystal diffraction that showed all the complexes to be four-coordinate in a square-planar arrangement, but 2 and 3 with a N_2S_2 environment while in 1 and 4 it was CNS_2. The cytotoxic activity has been evaluated against the human lung carcinoma cell line NCI-H460, but the results showed that the complexes were not vigorous against this cell line [180] Thiosemicarbazones and its copper complexes also cause membrane changes which is a characteristic of apoptosis [181].

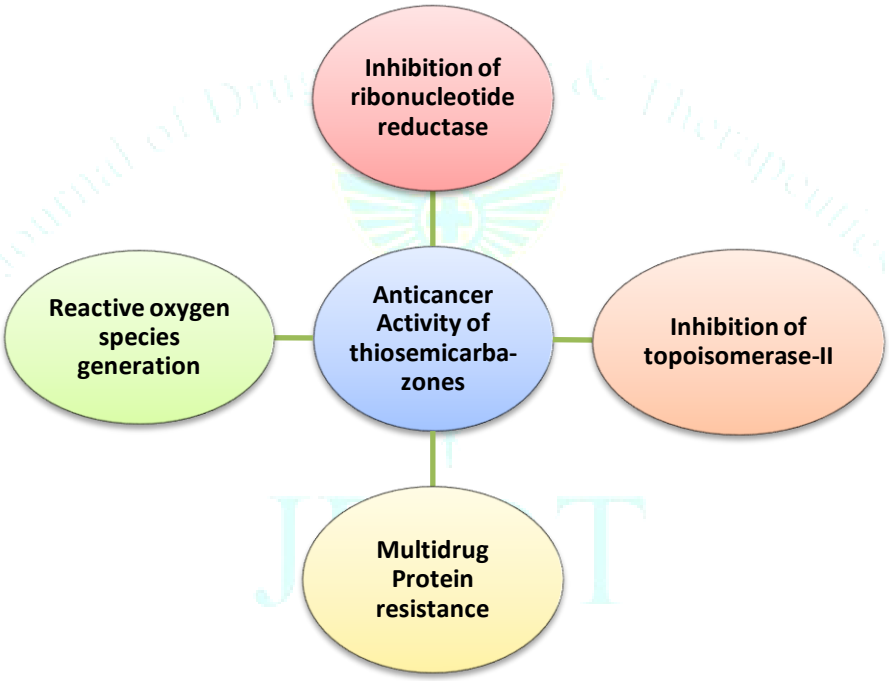

Fig.8. Anticancer Activity targets of thiosemicarbazones

2.7 Antimicrobial action of thiosemicarbazones and probable mechanisms-

2.7.1 Antibacterial action

The antibacterial agents usually act by disrupting bacterial growth or kill the bacteria without affecting the host. Antibacterial agents also inhibit the synthesis of peptidoglycan, change the microbial cytoplasmic membrane, alter translation and inhibit nucleic acid replication by blocking topoisomerases and transcription [182]. Antibacterial activity of Pt(II) and Pd(II) complexes of 2-acetylpyridinethiosemicarbazone has been assessed against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) [183]. Co(II) and Ni(II) complexes with benzilbisthiosemicarbazone have been tested against *B. macerans* and *P. striata*. Again in this case the metal complexes displayed better inhibitory effects than the parent ligand [184]. $[Ag(mtsc)_4]$ formed by the reaction of N-morpholyl-2-acetylpyridine thiosemicarbazone and silver(I) contained Ag-O bond. The chloroform solution of the complex showed moderate activity against several bacterial strains but the complex did not show any activity in a water suspension system. The lack of activity can be attributed to low solubility or the high stability of the complex [185]. Antibacterial activity of salicaldehyde4-phenyl thiosemicarbazone, 2-hydroxy-1-naphthaldehyde thiosemicarbazone (Fig. 9) and 2-hydroxy-1-naphthaldehyde 4-phenyl thiosemicarbazone complexes with Ru(II)-DMSO have been tested against several bacterial strains. The minimum inhibitory concentrations (MICs) of these complexes were greater when compared to standard as oxytetracyclin [186]. Literature has also revealed that the presence of some bulky groups at N^4 position of the thiosemicarbazones can enhance the activity.

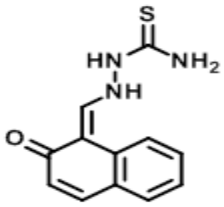

Fig. 9 2-hydroxy-1-naphthaldehyde thiosemicarbazone

2.7.2Antiviral activity

A series of isatin-β-thiosemicarbazones have been tested against herpes simplex virus type 1(HSV-1) and type 2 (HSV-2). From the structure-activity relationship confirmed the presence of thiourea group in thiosemicarbazone and the NH group in isatin were responsible for the activity of the compounds [187].

2.7.3 Antimalarial activity

Antimalarial activity of chimers of thiosmeicarbazones and ferroquine has been reported. The major contributor to the activity has been identified as aminoquinolinethiosemicarbazone[188]. Free ligand 3,4-dichloroacetophenone thiosemicarbazone and its Pd(II) complex have been tested against *P. falciparum* strains 3D7 (chloroquine sensitive) and K1(chloroquine and pyrimethamine resistant). Pd complex displayed greater activity than the free ligand [189].

2.7.4.Antitrypanosomal activity

Glycolysis, an important biochemical metabolic pathway has been identified as a promising target for trypanosomal activity of drugs. Sb(III) complexes of pyridine derived thiosemicarbazones have been tested against *Trypanosomacruzi* with better activity than the reference drugs benzimidazole and nifurtimox [190]. *In vitro* activity of Mn(II) complex obtained with N4-methyl-4-nitrobenzaldehyde, N4-methyl-4nitroacetophenone and N4-methyl-4-nitrobenzophenone thiosemicarbazones have been studied against *T. cruzi* [191].

2.7.5. Antifungal activity

The chelation theory can be used to study the antifungal activity of the complex [192]. In some instances the increased lipophilicity causes the breakdown of the permeability barrier of the cell. Pt complexes with 2-acetylpyridine thiosemicarbazone have shown effective antifungal activity towards yeast. Antifungicidal activity of heterocyclic thiosemicarbazone and their dimethylsilicone (IV) complexes has been demonstrated against several pathogenic fungi [193].

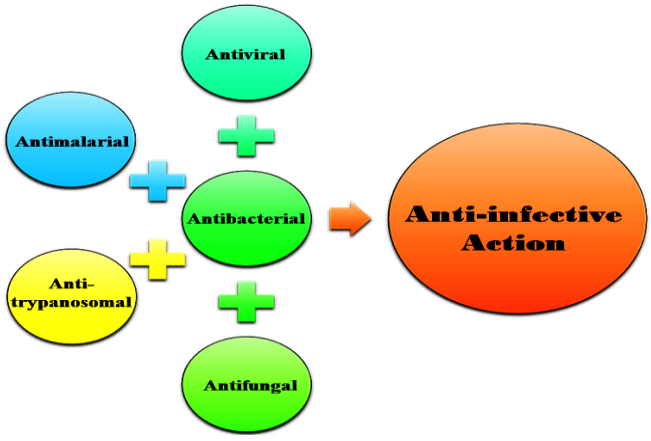

Fig. 10. Bio activity spectrum of thiosemicarbazones

3.0 Conclusion

Schiff bases are important organic ligands having potential tendency of complexation with transition metals and they have shown excellent pharmacological properties over the years. Thiosemicarbazones are well known Schiff based ligands which are usually neutral yet their anioninc forms are also known. Their bidentate, tridentate or in some cases polydentate nature is due to the presence of donor atoms like sulphur, nitrogen or in some instances oxygen. As transition metals can exhibit an array of coordination power, they easily form stable complexes with Schiff based thiosemicarbazone ligands. Latest advances in medicinal inorganic chemistry have given considerable importance to the development of metal based drugs. Since the presence of metal ion in the drug moiety usually mitigates the ill effects of carbon-based compounds, this may lead to the production of new metal based drugs. The key factors identified for their action has been the inhibition of RR, topo II and the production of ROS, but identification of other probable targets need to be explored. The main action of the metal chelates when compared to free ligand is the prevalence of diffusive mechanism over the active transport mechanism across the membrane. The chelation of the metal ion by the polar regions of the ligands facilitates easy uptake by the cell. Just a limited number of *in vivo* studies have been done indicating the need of further deliberations. Attempts have been made to enhance the hydrophilicity and decrease the side effects of the parent moiety by suitable modifications in the thiosemicarbazone frameworks. Another area which needs attention is metal ion sequestering, as thiosemicarbazones are versatile chelators, they sometimes deprive the cell of essential metal ions by forming stable chelates with them. Lack of water solubility is another drawback of the compounds that needs to be work upon because it leads to lesser *in vivo* activity. Detailed studies are required to explore new mechanistic actions and the specific role of metal ions and ligand inside the body. Ligands which have poor or moderate activity should be studied in combination with ligands of good biological significance for activity enhancement. Interaction of one metal with another can also be explored taking synergistic effect into consideration. Not only this, the fact that needs exploration is whether the complex acts in unison or metal and ligand act independently inside the body needs a greater depth of understanding by interlinking chemistry and molecular biology. The redox capability of transition metals also is a key factor affecting the activity enhancement and structure modification in their structures to favour *in vivo* activity warrant future studies.

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Conflict of Interest- The authors declare they have no competing interests.

References

1. Ali NA, O'Brien JM Jr, Blum W, Byrd JC, Klisovic RB, Marcucci G, Phillips G, Marsh CB, Lemeshow S, Grever MR, Hyperglycemia in patients with acute myeloid leukemia is associated with increased hospital mortality, Cancer, 2007;110(1):96-102.

2. Siegel RL, Miller KD, Jemal A, Cancer Statistics, 2017. CA-Can J Clin, 2017; 67 (1) 7-30.doi: 10.3322/caac.21387.

3. Arora S, Agarwal S, Singhal S, Anticancer activities of thiosemicarbazides/thiosemicarbazones: a review, Int J Pharm and Pharmac Sci, 2014;6(9):34-41.

4. Sharma B, Kothari R, Synthesis, characterization, anticancer, antibacterial and antioxidant evaluation of macrocyclic copper (II) complexes derived from thiosemicarbazide, Int J Pharm Bio Sci, 2015;6(1):1154-1169.

5. Lovejoy DB, Jansson PJ, Brunk UT, Wong J, Ponka P, Richardson DR, Antitumor Activity of Metal-Chelating Compound Dp44mT Is Mediated by Formation of a Redox-Active Copper Complex That Accumulates in Lysosomes, Cancer Res, 2011;71(5):5871-5880.

6. Johnstone TC, Suntharalingam K, Lippard SJ, The next generation of platinum drugs: targeted Pt(II) agents, nanoparticle delivery, and Pt (IV) prodrugs, Chem Rev, 2016;116 (5):3436-3486.

7. Padhye S, Afrasiabi Z, Sinn E, Fok J, Mehta K, Rath N, Antitumor Metallothio semi carbazonates: structure and antitumor activity of palladium complex of phenanthrene quinine thiosemi carbazone, Inorg Chem, 2005;44:1154-1156.

8. Laine A, Passirani C, Novel metal-based anticancer drugs: a new challenge in drug delivery. Current opinion in pharmacology, Curr Opin Pharmacol, 2012; 12(4):420-426.

9. Singh VK, Kumar D, Application of metal complexes of Schiff base with special reference to thiosemicarbazones: a review, Journal of Drug Discovery and Therapeutics, 2014;2(13):24-32.

10. Tanaka K, Tengeiji A, Kato T, Toyama N,Shiro M, Shionoya M, Efficient incorporation of a copper hydroxyl pyridine base pair in DNA, Journal of the American Chemical Society, 2002; 124 (42):12494-12498.

11. Kozikowski A P , Tuckmantel W, Powis G, Synthesis and biological activity of D-3-deoxy-3- fluoro phosphatidylinositol, A new direction in the design of non-DNA targeted anticancer agents, Angewandte Chemie, 1992; 31(10): 1379-1381.

12. Ming L-J, Structure and function of metalloantibiotics, Med Res Rev, 2003;23(6): 697-762.

13. Ma D-L, Che C-M, A bifunctional platinum(II) complex capable of intercalation and hydrogen bonding interactions with DNA:binding studies and cytotoxicity, Chemistry, 2003;9 (24): 6133-6144.

14.O'Rourke KA, Anderson BJ, Synthesis and investigation of novel thiosemicarbazone ligands and their metal complexes. Abstracts of Papers, 249th ACS National Meeting & Exposition, Denver, CO, United States, March 22-26, 2015 (2015), CHED-833.

15. Khan T, Ahmad A, Joshi S, Khan AR, Anticancer potential of metal thiosemicarbazone complexes: A review, Der Chem Sin, 2015;6(12):1-11.

16. Hossain MS, Roy PK, Zakaria CM, Zahan M, Selected Schiff base coordination complexes and their microbial application, A IJCS, 2018; 6(1):19-31.

17.Panico R, Powell WH, Richer JC. Eds. IUPAC, Nomenclature of Organic Compounds Blackwell: London. 1993;105.

18. Richardson DR, Iron chelators as therapeutic agents for the treatment of cancer, Crit Rev Oncol/Hematol, 2002;42:267-281.

19. Lovejoy DB, Richardson DR, Novel "hybrid" iron chelators derived from aroyl hydrazones and thiosemicarbazones demonstrate selective antiproliferative activity against tumor cells, Blood, 2002;100: 666-676.

20. Jutten P, Schumann W, Hartl A, Heinisch L, Grafe U, Werner W, Ulbricht HA, Novel type of nonsteroidal estrone sulfatase inhibitors, Bioorg Med Chem Lett, 2002;12:1339-1342.

21. West DX, Swearingen JK, Valdes-Martinez J, Hernandez-Ortega S, El-Sawaf AK, van Meurs F, et al, Spectral and Structural Studies of Iron(III), cobalt(II,III) and Nickel(II) complexes of 2-pyridineformamide N(4)-methylthiosemicarbazone, Polyhedron, 1999;18:2919-29.

22.Tarasconi P, Capacchi S, Pelosi G, Cornia M, Albertini R, Bonati A, et al, Synthesis, spectroscopic characterization and biological properties of new natural aldehydes thiosemicarbazones, Bioorg Med Chem, 2000;8:157-62.

23. Ghazy SE, Kabil MA, El-Asmy AA, Sherief YA, Sulfur containing reagent for ion flotation and spectrophotometric determination of palladium(II), Anal Lett, 1996;29:1215-1229.

24. Mishra V, Pandeya SN, Pannecouque C, Witvrouw M, De Clercq E, Anti-HIVactivity of thiosemicarbazone andsemicarbazone derivatives of (±)-3-Menthone, Archiv Pharmazie, 2002;335(5):183-186.

25. Bal TR, Anand B, Yogeeswari P, Sriram D, Synthesis and evaluation of anti-HIV activity of Isatin beta-thiosemicarbazonederivatives, Bioorg Med Chem, 2005;15(20):4451-4455.

26. Varadinova T, Kovala-Demertzi D, Rupelieva M, Demertzis M, Genova P, Antiviral activity of platinum (II) andpalladium (II) complexes of pyridine-2-carbaldehyde thiosemicarbazone, Actaologica, 2001;45(2):87-94.

27.Padmapriyaa P, Sheriffb K, Kaverib K, Gunasekaranb P, Ramanathana G, Thennarasuc S et al, Antiviral activity of Thiosemicarbazones derived from δ-amino acids against Dengue virus, P Coordin Chem Rev, 2015;284:329-350.

28. González-Álvarez M, Borrás J, García-Grandab S, Montejo-Bernardo J, Structural and functional models for the dinuclear copper active sitein catechol oxidases: Synthesis, X-ray crystal structures, magnetic and spectroscopic properties of μ-methoxo-brideged dinuclear copper(II) complexes with N-substituted sulfonamide ligands, J Inorg Biochem, 2003;99(2): 443-451.

29. Nobila P, Baran EJ, Otero L, Draper P, Cerecetto H, González, M, Sakurai H, New Vanadium (V) Complexes with Salicylaldehyde Semicarbazone Derivatives: Synthesis, Characterization, and in vitro Insulin-Mimetic Activity– Crystal Structure of [VvO2 (salicylaldehyde semicarbazone)], Eur J Inorg Chem, 2004 2004(2):322-328.

30. Leovac VM, Vojinovi lS, Mészáros Szécsényi K, Ljevi VE, Transition metal complexes with thiosemicarbazide-based ligands, part 46: Synthesis and physico-chemical characterization of mixed ligand cobalt(III)-complexes with salicylaldehyde semi-, thiosemi-an, J Ser Chem Soc, 2003; 68(12): 919-927.

31.Halder S, Peng SM, Lee GH, Chatterjee T, Mukherjee A, Dutta S, Bhattacharya S, Synthesis, structure, spectroscopic properties and cytotoxic effect of some thiosemicarbazone complexes of palladium, New J Chem, 2008;32(1): 105-114.

32. Singh RB, Garg BS, Singh RP, Analytical applications of thiosemicarbazones and semicarbazones: A review, Talanta, 1978;25(11-12): 619-632.

33. Gambino D, Fernández M, Santos D, Etcheverría GA, Piro OE, Pavan FR, Marques F, Searching for gallium bioactive compounds: Gallium (III) complexes of tridentate salicylaldehyde semicarbazone derivatives, Polyhedron, 2011;30(7):1360-1366.

34. Cindric M, Uzelac M, Cincic D, Halasz I, Pavlovic P, Hrenar T. et al, Three routes to nickel (II) salicylaldehyde 4-phenyl and 4-methylthiosemicarbazonato complexes: mechanochemical, electrochemical and conventional approach, Cryst Eng Comm, 2012;14: 3039-3045.

35. Kalinowski DS, Quach P, Richardson DR, Thiosemicarbazones: the new wave in cancer treatment. Fut Med Chem, 2009;1(6):1143-1151.

36. Thota S, Vallala S, Yerra R, Barreiro EJ, Design, synthesis, characterization, cytotoxic and structure activity relationships of novel Ru(II) complexes, Chi Chem Lett, 2015; 26(2):721-726. DOI:10.1016/j.cclet.2015.03.011.

37. Timerbaev AR, Hartinger CG, Aleksenko SS, Keppler BK, Interactions of Antitumor Metallodrugs With Serum Proteins: Advances in Characterization Using Modern Analytical Methodology, Chem Rev, 2006;106:2224-2248.

38. Merlot A M, Pantarat N, Lovejoy DB,Kalinowski DS, Richardson DR, Membrane Transport and Intracellular Sequestration of Novel Thiosemicarbazone Chelators for the Treatment of Cancer, Mol Pharmacol, 2010; 78: 675-684.

39. Stacy AE, Palanimuthu D, Bernhardt PV, Kalinowski DS, Jansson PJ, Richardson DR, Zinc(II)-Thiosemicarbazone Complexes Are Localized to the Lysosomal Compartment Where They Transmetallate with Copper Ions to Induce Cytotoxicity, J Med Chem, 2016; 59: 4965-4984.

40. Chikate RC, Belapure AR, Padhye SB, West DX, Transition metal quinone–thiosemicarbazone complexes 1: Evaluation of EPR covalency parameters and redox properties of pseudo-square-planar copper(II)–naphthoquinone thiosemicarbazones, Polyhedron, 2005;24(8): 889-899.

41. Yu Y, Kalinowski DS, Kovacevic Z, Siafakas AR, Jansson PJ, Stefani C, Richardson DR et al, Thiosemicarbazones from the Old to New: Iron Chelators That Are More Than Just Ribonucleotide Reductase Inhibitors, J Med Chem, 2009;52: 5271-5294.

42. Casas JS, Garcia-Tasende MS, Sordo J, Main group metal complexes of semicarbazones and thiosemicarbazones. A structural review, Coord Chem Rev, 2000;209:197-261.

43. Stacy AE, Palanimuthu D, Bernhardt PV, Kalinowski DS, Jansson PJ, Richardson DR, Zinc(II)-Thiosemicarbazone Complexes Are Localized to the Lysosomal Compartment Where They Transmetallate with Copper Ions to Induce Cytotoxicity, J Med Chem, 2016;59:4965-4989.

44. Kowol CR, Berger R, Eichinger R, Roller A, Jakupec MA, Schmidt PP, Arion VB, Keppler BK, Gallium (III) and iron (III) complexes of α-N-heterocyclic thiosemicarbazones: synthesis, characterization, cytotoxicity, and interaction with ribonucleotide reductase, J Med Chem, 2007;50 (3):1254-1265.

45. Qi J, Zhang Y, Gou Y, Zhang Z, Zhou Z, Wu X, Yang F, Liang H, Developing an anticancer Copper (II) pro-drug based on the His242 residue of the human serum albumin carrier IIA subdomain, Mol Pharma, 2016;13(5):1501-1507.

46. Qi J, Zheng Y, Qian K, Tian L, Zhang G X, Cheng Z, Wang Y, Synthesis, crystal structure and antiproliferative mechanisms of 2-acetylpyridine-thiosemicarbazones Ga(III) with a greater selectivity against tumor cells, J Inorg Biochem, 2017;177:110-117.

47. Siegel RL, Miller KD, Jemal A, Cancer Statistics, 2017. CA Cancer J Clin, 2017;67(1):7-30.

48. Chandra S, Gupta K, Chromium (III), manganese (II), iron (III), Cobalt (II), Nickel(II) and copper (II) complexes with a pentdentate, 5 membered new macrocyclic ligand, Trans Met Chem, 2002;27:196-199.

49. Liu J, Lu T-B, Deng H, Ji L-N, Qu L-H, Zhou H, Synthesis, DNA-binding and cleavage studies of macrocyclic copper (II)complexes, Transit Met Chem, 2003; 28:116-121.

50. Wang T, Guo ZJ, Copper in medicine:Homostasis, chelation therapy and antitumor drug design, Curr Med Chem, 2006;1315: 525-537.

51. Saryan LA, Ankel E, Krishnamurti C, Petering DH, Elford H, Comparative cytotoxic and biochemical effects of ligands and metal complexes of alpha–Nheterocyclic carboxaldehyde thiosemicarbazones, J Med Chem, 1979;22(10):1218-1221.

52. Antholine WE, Knight JM, Petering DH, Inhalation of tumor cell transplantability byiron and copper complexes of 5-substituted 2-formyl pyridine thiosemicarbazones, J Med Chem, 1976; 19(2): 339-341.

53. Booth BA, Agrawal KC, Moore EC, Sartorelli AC, Alpha-N-heterocyclic carboxaldehyde thiosemicarbazone inhibition of ribonucleotide diphosphate reductase, Cancer Res, 1974;34(6):1308-1314.

54. Chandra S, Gautam A, Schiff base macrocyclic ligand derived from thiosemicarbazones with their spectroscopic and antimicrobial studies, J Ind Chem Soc, 2013;90(8):1053-1059.

55. Scott RE, McGill BC, Riggsbee NP, Carroll WF, Lisic EC, New methyl-imidazolecarboxaldehyde thiosemicarbazone ligands: NMR structural studies and complexation with Pd^{2+} to form [Pd(MIZCA-TSC)Cl] compounds. Abstracts of Papers, 249th ACS National Meeting & Exposition, Denver, CO, United States, March 22-26, 2015 (2015), CHED-1093.

56.Milligan TB, McGill BC, Hatmaker L, Lisic EC, New 2-acetyl-6-bromopyridine: NMR and complexation with Cu(II) to form [Cu(ABrPy-TSC)Cl] compounds. Abstracts of Papers, 249th ACS National Meeting & Exposition, Denver, CO, United States, March 22-26, 2015 (2015), CHED-962.

57. Gujarathi JR, Pawar NS, Bendre R, Cobalt (III) complexes with the O,N,S-tridentate ligand 5-chloro-2-hydroxy acetophenone thiosemicarbazone and N(4) methyl thiosemicarbazone, J App Chem, 2013; 2(5):1370-1381.

58. Kumar S, Kumar N, Synthesis and biological activity of butanone thiosemicarbazone and their metallic complexes, Int Res J Pharm, 2013;4(1):177-181.

59. Levin VA, Gutin PH, Leibel S,Vita VTD, Hellman S, Rosenberg AS, Cancer: Principles and practice of oncology, Lippincott, Philadelphia, 1993;1697-1737.

60. Liberta AE, West DX, Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: Current status, Biometals, 1992;5:121-26.

61. Cobeljic B, Pevec A, Turel I, Swart M, Mitic D, Milenkovic M, Markovic I, Jovanovic M, Sladic D, Jeremic M, Andelkovic K, Synthesis, characterization, DFT calculations and biological activity of derivatives of 3-acetylpyridine and the zinc(II) complex with the condensation product of 3-acetylpyridine and semicarbazide, Inorg Chim Acta, 2013;404: 5-12.

62. Khanpour M, Morsali A, Solid state crystal-to-crystal transformation from a monomeric structure to 1-D coordination polymers on anion exchange, Cryst Eng Comm, 2009;11: 2585-2587.

63. Hosli AP, Sappino N, De Tribolet, Dietrich PY, Malignant glioma: Should chemotherapy be overthrown by experimental treatments? Ann Oncol, 1996; 9:589-600.

64. Belicchi-Ferrari M, Bisceglie F, Casoli C, Durot S, Morgenstern-Badarau I, Pelosi G, Tarasconi P, Copper (II) and cobalt (III) pyridoxal thiosemicarbazone complexes with nitroprusside as counterion: syntheses, electronic properties, and antileukemic activity, J Med Chem, 2005; 48(5):1671-1675.

65. Wang Y, Gu W, Shan Y, Liu F, Xu X, Yang Y, Zhang Q et al, Design, synthesis and anticancer activity of novel nopinone-based thiosemicarbazone derivatives, Bioorg Med Chem Lett, 2017;27(11):2360-2363.

66.Tanaskovic, Sladjana B, Vuckovic, Gordana, The preparation and characterization of Cu(II) complexes with N,N',N'',N'''-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazacyclotetradecane and 2,6-diacetylpyridine bis(semi/thiosemicarbazones. J Serb Chem Soc, 2004;69(3):187-193.

67. Xue LM, Jing Z, Ling CC, Wang, Ping J, Synthesis, crystal structure and antitumor study of a zinc complex of the 2-benzoylpyridine thiosemicarbazone ligand, Chem Sci 2008; 63(3): 280-284.

68. Abou-Melha, Khlood S, Octahedral Co(II) and Ni(II) complexes of Schiff bases, semicarbazone and thiosemicarbazone, synthesis, biological, spectral, and thermal studies, J Coord Chem, 2008;61(13): 2053-2067.

69. Krishana PM. Shankara BS, Reddy NS, Synthesis, Characterization, and Biological Studies of Binuclear Copper(II) Complexes of (2E)-2-(2-Hydroxy-3-Methoxybenzylidene)-^{4}N-Substituted Hydrazinecarbothioamide, Int J Inorg Chem, 2013;2013:1-11. https://doi.org/10.1155/2013/741269.

70. Patel HD, Divatia SM, Clereq DE, Synthesis of some novel thiosemicarbazonederiatives having anti-cancer, anti-HIV as well as anti-bacterial activity, Ind J Chem, 2013;52:535-545.

71. Lisic EC, Rand VG, Ngo L, Kent P, Rice J, Gerlach D, Papish ET, Jiang X, Cu(II) Propionyl-Thiazole Thiosemicarbazone Complexes: Crystal Structure, Inhibition of Human Topoisomerase IIα ,and Activity against Breast Cancer Cells, Open J Med Chem, 2018;6;8(02):30.

72. Jayanthi K, Meena RP, Chithra K, Kannan S, Shanthi W, Saravanan R, Suresh M, Satheesh D, Synthesis And Microbial Evaluation of Copper(II) Complexes of Schiff Base Ligand Derived From 3-Methoxysalicylaldehyde With Semicarbazide and Thiosemicarbazide, J Pharm Chem Bio Sci 2017;5(3):205-215.

73. Bolsunova Ol'ha I, Zaika Leonid A., Potopalsky Anatoliy I, Voznyuk Anna V, Izatizon, As an Izatin-Thiosemicarbazone Derivative, Has Antiviral, Anti-Tumor Actions and No Side Effects, Int J Pharm Sci Inv 2017;6(5):07-09.

74. Nam SY, Han NR, Yoon KW, Kim HM, Jeong HJ, Di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT), an anticanceragent, exerts an anti-inflammatory effect inactivated human mast cells, Inflam Res, 2017; 66(10):871-879.

75. Ranade DS, Archika Bapat AM, Ramteke SN, Joshi BN, Roussel P, Tomas A, Deschamps P, Kulkarni PP, Thiosemicarbazone modification of 3-acetyl coumarin inhibits A β-peptide aggregation and protect against Aβ-induced cytotoxicity, Eur J Med Chem, 2015;121:803-809.

76. Brindha G, Vijayanthimala R, Complexes of Copper (II) with Thiosemicarbazone andChloroethanol - Synthesis, Characterization and Biological Studies, IOSR J App Chem, 2016;9(6):90-93.

77. Zakir HM, Antibacterial Activities of Benzoin Thiosemicarbazone andIts Complexes with Co(II) and Ni(II), Asian J Med Pharm Res, 2016;6(4):32-40.

78. Kamalpuria T, Chourey M, Bende N, Ghuraiya A, Bhardwaj A, Synthesis, Spectral studies and Antimicrobial activity ofArsenic (III) Benzaldehyde Semicarbazone, Thiosemicarbazone and their Derivatives, Int J Curr Res Chem Pharm Sci, 2016;3(5):30-35.

79. Pahonţu E, Paraschivescu C, Ilieş DC, Poirier D, Oprean C, Păunescu V, Bratu O, Synthesis and Characterization of Novel Cu(II), Pd(II) and Pt(II) Complexes with8-Ethyl-2-hydroxytricyclo(7.3.1.02,7)tridecan-13-onethiosemicarbazone:Antimicrobial and *in Vitro* Antiproliferative Activity, Molecules, 2016; 21(5):674.

80. Venkatesha K, Venkanna B, Chandra Sekhar, KB, Mukkantia K, Synthesis, characterization & biological activity of some newThiosemicarbazide derivatives and their transition metal complexes, J Chem and Pharm Res, 2015;7(8):437-445

81. Sharma S, Bedi M, Varshney S, Varshney AK, Some new organotin(IV) complexes of biologically important semicarbazones and thiosemicarbazones, J Ind Chem Soc, 2012;89:41-50.

82. Haque RA, Salam MA, Synthesis, structural characterization and biological activitiesof organotin(IV) complexes with 5-allyl-2-hydroxy-3-methoxybenzaldehyde-4-thiosemicarbazone, J Chem Sci, 2015;127(9):1589-1597.

83. Kumar B, Kumar A, Synthesis, Magnetic and Spectral Investigations of Copper Metal Ion Complexes of 2-Substituted Benzaldehyde Semicarbazones andThiosemicarbazones, Int J Sci Eng App Sci, 2015;1(5):405-410.

84. Qi J, Yao Q, Qian K, Tian L, Cheng Z, Yang D, Wang Y, Synthesis,antiproliferative activity and mechanism of gallium(III)-thiosemicarbazone complexes as potential anti-breast cancer agents, Eur J Med Chem, 2018;154:91-100.

85. Abdalla O, Farina Y, Ibrahim N, Synthesis, Characterization And Antibacterial Study Of Copper (II) Complexes Of Thiosemicarbazones, Mal J Anal Sci, 2015;19(6):1171-1178.

86.Subrahmanyam PVN, Prakash MMSK, Structure and biological activities of novel phytochemicals Cu(II)-quercetinthiosemicarbazone and its derivatives: potential anti-cancer drugs, Int J Pharm Med Bio Sci, 2012;1(2):55-65.

87. Aljahadali MS, Elmalik YH, El-Reash MAE, Synthesis of some transition metal of novel 1-methylpyrazole-3-aldehyde-4-(2-pyridyl)thiosemicarbazone: Spectroscopic and in vitro biological activity, Eur J Med Chem, 2014;5(2):201-208.

88. Beck C, Koch A, Conner J, Lisic E, Synthesis and antimicrobial studies of acetylpyrazine-thiosemicarbone ligands and their Cu(II), Pd(II) and Pt(II) metal complexes. Abstracts of Papers, 247th ACS National Meeting & Exposition, Dallas, TX, United States, March 16-20, 2014.

89. Fu Q, Zhi-Yu G, Jie Z, Han-Yu S, Chao L, Jin-Hong R, Copper thiosemicarbazones: Antiproliferative action against C6glioma cells, Bang J Pharmacol, 2014;9:466-473.

90. Gaikwad S, Nickel Complexes of Thiosemicarbazone Derivatives of Lawsone, Research and Reviews: Journal of Chemistry, 2013;2(3):10-15.

91. Shanmugapriya A, Dallemer F, Prabhakaran R, Synthesis, characterisation, crystal structures and biological studies of palladium(II) complexes containing 5-(2-hydroxy-3-methoxy-phenyl)-2,4-dihydro[1,2,4]triazole-3-thione derivatives, New J Chem, 2018;42:18850-18864.

92. Jain B, Malik S, Synthesis and Characterisation of Mixed Ligand Complexes of SalicylaldehydeThiosemicarbazone and Pyridine with Iron and Cobalt, Asi J Biochem Pharma Res, 2013; 4(3):91-96

93. Paul P, Seth DK, Richmond MG, Bhattacharya S, Unusual chemical transformations of acetone thiosemicarbazone mediated by ruthenium: C-H bond activation, thiolation, and C-N bond cleavage, RSC Adv, 2014;4:1432-1440.

94. Yousef TA, Badria FA, Ghazy SE, El-Gammal OA, Abu El-Reash GM, In vitro and In vivo antitumor activity of some synthesized 4-(2-pyridyl)-3-Thiosemicarbazides derivatives, Int J Med Med Sc,i 2011;3(2):37-46.

95. Zhang HJ, Qian Y, Zhu DD, Yang XG, Zhu HL, Synthesis, molecular modeling and biological evaluation of chalconethiosemicarbazide derivatives as novel anticancer agents, Eur J Med Chem, 2011;46:4702-4708.

96. El-Zahar MI, El-Karim SSA, Haiba ME, Khedr MA, Synthesis, antitumor activity nd molecular docking study of novel benzofuran-2-yl pyrazole pyrimidine derivatives, Acta Poloniae, Pharm Drug Res, 2011;68(3):357-73.

97. Kumar B, Rai BK, Ambastha N, Synthesis, characterization and antimicrobial screening of cobalt(II), nickel(II) and copper(II) complexes with schiff base derived from 2-phenylcarbonylquinoxalin thiosemicarbazone, Orie J Chem, 2011;27(3): 1173-1178.

98. Beckford F, In: Abstracts of Papers, 240th ACS National Meeting, 22-26Aug.2010, Boston, MA, United States, INOR 27.

99. Enyedy EA, Nagy NV, Zsigo E, Kowol CR, Arion VB, Keppler BK et al, Comparative solution equilibrium study of the interactions of copper(II), iron(II) and zinc(II) with Triapine (3-aminopyridine2-carbaldehyde thiosemicarbazone) and related ligands, Eur J Inorg Chem, 2010;11:1717-1728.

100. Yakkate SR, Prathima B, Somala AR, Madhavi K, Complexes of Cu(II) and Ni(II) with bis(phenylthiosemicarbazone): synthesis, spectral, EPR and in vitro -antibacterial and antioxidant activity, J Chi Chem Soc, 2010;57:677-682.

101. Prathima B, Subba Rao Y, Adinarayana Reddy S, Reddy YP, Varada Reddy A, Spectroscopic, thermal and antibacterial studies on Mn(II) and Co(II) complexes derived from thiosemicarbazone. Spectrochim. Acta, Part A: Mol and Biomol Spect, 2010; 77A(1): 248-252.

102. Iniama GE, Offiong OE, Nfor E, Ayi A, Mixed-ligand complexes of nickel(II) with 2-acetylpyridine thiosemicarbazone and some N/S monodentate ligands: synthesis, structural characterization and biological activity, Glo J Pure App Sci, 2008;14(4):411-415. DOI:10.4314/gjpas.v14i4.16830.

103. Mendes, Isolda C, Moreira, Juliana P, Mangrich, Antonio S, Balena et al, Coordination to copper(II) strongly enhances the in vitro antimicrobial activity of pyridine-derived N(4)-tolyl thiosemicarbazones, Polyhedron, 2007; 26(13):3263-3270.

104. Rai BK, Kumar, Karunesh, Srivastava YP, Spectroscopic investigation and antifungal studies of some mixed ligand complexes of Co(II), Ni(II) and Cu(II) with 6-methyl-2-pyridyl formamide semicarbazone and thiosemicarbazone, Asi J Chem, 2005;17(3):1773-1779.

105. Agarwal RK, Prasad S, Synthesis, spectroscopic and physicochemical characterization and biological activity of Co(II) and Ni(II) coordination compounds with 4-aminoantipyrine thiosemicarbazone, Bioinorg Chem Appl, 2005;3(3-4):271-288. DOI:10.1155/BCA.2005.271.

106. Jouad M, Larcher G, Allain M, Riou A, Khan M, Than X D et al, Synthesis, structure and biological activity of nickel (II) complexes of 5- methyl 2-furfural thiosemikcarbazone, J Inorg Biochem, 2001;86(2-3):565-571.

107. Sharma S, Athar F, Maurya MR, Azam A, Copper(II) complexes with substitutedthiosemicarbazones of thiophene-2-carboxaldehyde: Synthesis, characterizationand antiamoebic activity against E. histolytica, Eur J Med Chem, 2005;40(12):1414-1419.

108. Herrick J, Sclavi B, Ribonucleotide reductase and the regulation of DNA replication an old story and an ancient heritage. Molecular Microbiology, 2007;63(1):22-34.

109. Feun L, Modiano M, Lee K, Mao J, Marini A, Savaraj N. et al, Phase I and pharmacokinetic study of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP) using a single intravenous dose schedule, Cancer Chemother Pharmacol, 2002;50:223-229.

110. Mackenzie MJ, Saltman D, Hirte H, Low J, Johnson C, Pond G, Moore MJ, A Phase II study of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP) and gemcitabine in advanced pancreatic carcinoma. A trial of the Princess Margaret hospital Phase II consortium, Invest New Drugs, 2007;25:553-558.

111. Pelosi G, Thiosemicarbazone Metal Complexes: From Structure to Activity, Open Crys J, 2010;3:16-18.

112. Elford HL, Freese M, Passamani E, Morris HP, Ribonucleotide reductase and cell proliferation. I. Variations of ribonucleotide reductase activity with tumor growth rate in a series of rat hepatomas, J Biol Chem1970;245(20):5228-5233.

113. Lawar M, Badwe S, Yalçin I, Bolelli K, Quantum Chemical Studies on SomeThiosemicarbazone Derivatives as Ribonucleotide Reductase inhibitor, Asi J Chem Sci, 2018;4(4):1-13.

114. Moore EC, Zedeck MS, Agrawal KC, Sartorelli AC, Inhibition of ribonucleoside diphosphate reductase by 1-formylisoquinoline thiosemicarbazone and related compounds, Biochem,1970;9:4492.

115. Antholine W, Knight J, Whelan H, Petering D. Studies of the reaction of 2-formylpyridine thiosemicarbazone and its iron and copper complexes with biological systems. Mol. Pharm.1977;13(1):89-98.

116. Shao J, Zhou B, Chu B, Yen Y, Ribonucleotide reductase inhibitors and future drug design, Curr Canc Drug Targ 2006;6(5):409-431.

117. Finch RA, Liu M, Grill SP, Rose WC, Loomis R, Vasquez KM, Cheng Y, Sartorelli AC, Triapine (3-aminopyridine-2-carboxaldehyde- thiosemicarbazone): A potent inhibitor of ribonucleotide reductase activity with broad spectrum antitumor activity, Biochem Pharmacol., 2000;59(8):983-9391.

118. Lee K, Noveroske J, Almassian B, Short term toxicological evaluation in Triapine (3-amino yridine-2-carboxaldehyde thiosemicarbazone or 3-AP), a ribonucleotide reductase inhibitor with potential antitumor activity, in dogs and rats, Int J Toxicol, 2000;19(2):85-93.

119. Wadler S, Makower D, Clairmont C, Lambert P, Fehn K, Sznol M, Phase I and pharmacokinetic study of the ribonucleotide reductase inhibitor, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, administered by 96-hour intravenous continuous infusion, J Clin Oncol, 2004;22(9):1553-1563.

120. Barker CA, Burgan WE, Carter DJ, Cerna D, Gius D, Hollingshead MG, Camphausen K, Tofilon PJ, In vitro and in vivo radiosensitization induced by the ribonucleotide reductase inhibitor Triapine (3-aminopyridine-2-carboxaldehyde-thiosemicarbazone),Clin Cancer Res, 2006;12(9):2912-2918.

121. Alvero AB, Chen W, Sartorelli A, Schwartz P, Rutherford T, Mor G, Triapine (3-aminopyridine-2 carboxaldehyde thiosemicarbazone) induces apoptosis in ovarian cancer cells, J Soc Gynecol Investig, 2006;13(2):145-152.

122. Mackenzie M, Saltman D, Hirte H, Johnson C, Pond G, Moore M, A Phase II study of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP) and gemcitabine in advanced pancreatic carcinoma. A trial of the Princess Margaret hospital Phase II consortium, Invest New Drugs, 2007;25(6):553-558.

123. Choi B, Alberti D, Schelman W, Kolesar J, Thomas J, Marnocha R, Eickhoff J, Ivy S, Wilding G, Holen K, The maximum tolerated dose and biologic effects of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP) in combination with irinotecan for patients with refractory solid tumors, Can Chemother Pharmacol, 2010;66(5):973-980. doi: 10.1007/s00280-010-1250.

124. Popovic-Bijelic A, Kowol CR, Lind MES, Luo JH, Himo F, Enyedy EA, Anion VB, Graslund A, Ribonucleotide reductase inhibition by metal complexes of Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone): a combined experimental and theoretical study, J Inorg Biochem., 2011;105(11):1422-1431. doi: 10.1016/j.jinorgbio.2011.07.003.

125. Kolesar J, Brundage R, Pomplun M, Alberti D, Holen K, Traynor A, Ivy P, Wilding G, Population pharmacokinetics of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine®) in cancer patients, Cancer Chemother Pharmacol, 2011;67(2):393-400. doi: 10.1007/s00280-010-1331-z. Epub 2010 May 4.

126. Atieh D, Modiano M, Shriberg L, Brafman L, Szno M, Vahdat L, A A phase II trial of 3-Aminopyridine-2-Carboxaldehyde Thiosemicarbazone (3-AP) in patients with metastatic breast cancer, J Clin Oncol, 2004;864. DOI: 10.1200/jco.2004.22.90140.

127. Attia S, Kolesar J, Mahoney M, Pitot H, Laheru D, Heun J, Huang W, Eickhoff J, Erlichman CK, Holen K, A phase 2 consortium (P2C) trial of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP) for advanced adenocarcinoma of the pancreas, Invest New Drugs, 2008;26(4):369-379. doi: 10.1007/s10637-008-9123-6.

128. Kolesar JM, Sachidanandam K, Schelman WR, Eickhoff J, Holen KD, Traynor AM, Alberti DB, Thomas JP, Chitambar CR, Wilding G, Antholine WE, Cytotoxic Evaluation of 3-Aminopyridine-2-Carboxaldehyde Thiosemicarbazone, 3-AP, in Peripheral Blood Lymphocytes of Patients with Refractory Solid Tumors using Electron Paramagnetic Resonance, Exp Ther Med, 2011;2:119-123.

129. Gojo I, Tidwell M, Greer J, Takebe N, Seiter K, Pochron M, Johnson B, Sznol M, Karp J, Phase I and pharmacokinetic study of Triapine, a potent ribonucleotide reductase inhibitor, in adults with advanced hematologic malignancies. Leuk Res. 2007 ;31(9):1165-1173.

130. Karp J, Giles F, Gojo L, Morris L, Greer J, Johnson B, Thein M, Sznol M, Low J. A phase I study of the novel ribonucleotide reductase inhibitor 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, Triapine) in combination with the nucleoside analog fludarabine for patients with refractory acute leukemias and aggressive myeloproliferative disorders, Leuk Res, 2008;32(1):71-77.

131. Kowol C, Berger R, Eichinger R, Roller A, Jakupec M, Schmidt P, Arion V, Keppler B, Gallium(III) and iron(III) complexes of alpha-N-heterocyclic thiosemicarbazones: synthesis, characterization, cytotoxicity, and interaction with ribonucleotide reductase, J Med Chem, 2007;22;50(6):1254-1265.

132. Kowol C, Reisner E, Chiorescu I, Arion V, Galanski M, Deubel D, Keppler B, An Electrochemical Study of Antineoplastic Gallium, Iron and Ruthenium Complexes with Redox Noninnocent α-N-Heterocyclic Chalcogensemicarbazones, Inorg Chem, 2008;47(23):11032-11047.

133. Kolinowski D, Richardson D, The evolution of iron chelators for the treatment of iron overload disease and cancer, Pharmacol Rev, 2005;57(4):547-583.

134. Shao J, Zhou B, Di Bilio A, Zhu L, Wang T, Qi C, Shih J, Yen , A Ferrous-Triapine complex mediates formation of reactive oxygen species that inactivate human ribonucleotide reductase, Mol Cancer Ther, 2006;5(3):586-592.

135. Kowol CR, Trondl R, Arion VB, Jakupec MA, Lichtscheidl I, Keppler BK, Fluorescence properties and cellular distribution of the investigational anticancer drug triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) and its zinc(II) complex, Dalton Trans, 2010; 21;39(3):704-716. doi: 10.1039/b919119b.

136. Cooper C, Lynagh G, Hoyes K, Hider R, Cammack R, Porter J, The relationship of intracellular iron chelation to the inhibition and regeneration of human ribonucleotide reductase, J Biol Chem, 1996;271(34):20291-20299.

137. Jonathan R, Dilworth, Hueting R, Metal complexes of thiosemicarbazones for imaging and therapy, Metallomics, 2015;7(5):795-804. doi: 10.1039/c4mt00330f.

138. Larsen AK, Skladanowski A, Cellular resistance to topoisomerase-targeted drugs: from drug uptake to cell death, Biochim Biophys Acta, 1998;1400(1-3):257-274.

139. Larsen AK, Skladanowski A, Bojanowski K, The roles of DNA topoisomerase II during the cell cycle, Prog Cell Cycle Res., 1996;2:229-239.

140. Easmon J, Pürstinger G, Heinisch G, Roth T, Fiebig HH, Holzer W et al, Synthesis, cytotoxicity, and antitumor activity of copper(II) and iron(II) complexes of (4)N-azabicyclo[3.2.2]nonane thiosemicarbazones derived from acyl diazines, J Med Chem, 2001;44(13):2164-2171.

141. Wei L, Easmon J, Nagi RK, Muegge BD, Meyer LA, Lewis JS, 64Cu-azabicyclo[3.2.2]nonane thiosemicarbazone complexes: radiopharmaceuticals for PET of topoisomerase II expression in tumors, J Nucl Med., 2006;47(12):2034-2041.

142. Huang H, Chen Q, Ku X, Meng L, Lin L, Wang X, Zhu C , Wang Y, Chen Z, Li M, Jiang H, Chen K, Ding J, Liu H, A series of alpha-heterocyclic carboxaldehyde thiosemicarbazones inhibit topoisomerase II alpha catalytic activity, J Med Chem, 2010;53(8):3048-3064.

143. Chen J, Huang YW, Liu G, Afrasiabi Z, Sinn E, Padhye S, Ma Y, The cytotoxicity and mechanisms of 1,2-naphthoquinone thiosemicarbazone and its metal derivatives against MCF-7 human breast cancer cells, Toxicol Appl Pharmacol, 2004;197(1):40-48.

144. Saha MT, Saha HH, Niskanen LK, Salmela KT, Pasternack AI, Time course of serum prolactin and sex hormones following successful renal transplantation, Nephron., 2002;92(3):735-747.

145. Satorelli AC, Agarwal KC, Tsftsoglou AS, Moore EC, Characterization of the biochemical mechanism of action of alpha-(N)-heterocyclic carboxaldehyde thiosemicarbazones, Adv Enzyme Regul,1977;15: 117-139.

146. Caron M, Benedict WF, Chromatid breakage: differential effect of inhibitors of DNA synthesis during G 2 phase, Science, 1972;178(4056):62.

147. Opletalová V, Kalinowski DS, Vejsová M, Kunes J, Pour M. Jampílek J. et al, Identification and characterization of thiosemicarbazones with antifungal and antitumor effects: cellular iron chelation mediating cytotoxic activity, Chem Res Toxicol, 2008;21:1878-1889.

148. McGill B, Snyder HM, Probasco M, Koch A, E.C. Lisic EC. In: Abstracts of Papers, 247th ACS National Meeting & Exposition, 16-20 March 2014, Dallas, TX, United States, CHED-823

149. Zeglis BM, Divilov V, Lewis JS, Role of metalation in the topoisomerase IIα inhibition and antiproliferation activity of a series of α-heterocyclic-N4-substituted thiosemicarbazones and their Cu(II) complexes, J Med Chem, 2011;54,:2391-2398.

150. Gómez-Saiz P, Gil-García R, Maestro MA, García-Tojal J, Structure, magnetic properties and nuclease activity of pyridine-2-carbaldehyde thiosemicarbazonecopper(II) complexes, J Inorg Biochem,2008;102:1910-1920.

151. Shao J, Ma ZY, Li A, Liu YH, Xie CZ, Qiang ZY, Xu JY, Thiosemicarbazone Cu(II) and Zn(II) complexes as potential anticancer agents: syntheses, crystal structure, DNA cleavage, cytotoxicity and apoptosis induction activity, J Inorg Biochem., 2014;136:13-23. doi: 10.1016/j.jinorgbio.2014.03.004.

152. Gourdon P, Liu XY, Skjørringe T, Morth JP, Møller LB, Pedersen BP, Nissen P, Crystal structure of a copper-transporting PIB-type ATPase, Nature, 2011;475:59-64.

153. Reddi AR, Culotta VC, SOD1 integrates signals from oxygen and glucose to repress respiration, Cell, 2013;152:224-235.

154. Khan GN, Merajver SD, Modulation of angiogenesis for cancer prevention: strategies based on antioxidants and copper deficiency, Curr Pharm Des, 2007;13(35): 3584-3590.

155. Pan Q, Bao LW, Merajver SD, Tetrathiomolybdate inhibits angiogenesis and metastasis through suppression of the NFkappaB signaling cascade, Mol Cancer Res., 2003;1(10):701-706.

156. Li MX, Zhang LZ, Chen CL, Niu JY, Ji BS, Synthesis, crystal structures, and biological evaluation of Cu(II) and Zn(II) complexes of 2-benzoylpyridine Schiff bases derived from S-methyl- and S-phenyldithiocarbazates, J Inorg Biochem., 2012;106(1):117-25. doi: 10.1016/j.jinorgbio.2011.09.034.

157. Singh S, Bharti N, Mohapatra PP, Chemistry and Biology of Synthetic and Naturally Occurring Antiamoebic Agents, Chem Rev,2009;109:1900-1947.

158. Chen D, Frezza M, Shakya R, Cui QC, Milacic V, Verani CN, Dou QP, Inhibition of the Proteasome Activity by Gallium(III) Complexes Contributes to Their Anti–Prostate Tumor Effects, Cancer Res, 2007;67: 9258-9265.

159. Einhorn L, Gallium nitrate in the treatment of bladder cancer, Semin Oncol, 2003;30:34-41.

160. Gogna R, Madan E, Keppler B, Pati U, Gallium compound GaQ(3)-induced Ca(2+) signalling triggers p53-dependent and -independent apoptosis in cancer cells, Br J Pharmacol, 2012;166 :617-636.

161. Afrasiabi Z, Sinn E, Kulkarni, Prasad P,Ambike V, Padhye S et al, Synthesis and characterization of copper(II) complexes of 4-alkyl/aryl-1,2-naphthoquinones thiosemicarbazones derivatives as potent DNA cleaving agents, Inorg ChimActa, 2005;358(6): 2023-2030.

162. Hałdys K, Rafał Latajka R, Thiosemicarbazones with tyrosinase inhibitory activity, Med Chem Comm 2019;10(3):378-89.

163. Arslan H, Duran N, Borekci G, Ozer CK, Akbay C, Antimicrobial Activity of Some Thiourea Derivatives and Their Nickel and Copper Complexes, Molecules, 2009;14:519-527

164. Zhu TH, Cao SW, Yu YY, Synthesis, characterization and biological evaluation of paeonol thiosemicarbazone analogues as mushroom tyrosinase inhibitors, Int J Biol Macromol, 2013;62:589-595.

165. Buitrago E, Vuillamy A, Boumendjel A, Yi W, Hardré G, Philouze C, Serratrice G, Jamet H, Regliér M, Belle C, Exploring the interaction of N/S Compounds with a Dicopper centre: Tyrosinase inhibitionand Model Studies, Inorg Chem, 2014;53(24):12848-12858.

166. Hałdys K, Goldeman KW, Jewgiński M, Wolińska E, Anger N, Rossowska J, R. Latajka R, Inhibitory properties of aromatic thiosemicarbazones on mushroom tyrosinase: Synthesis, kinetic studies, molecular docking and effectiveness in melanogenesis inhibition, Bioorg Chem, 2018;81:577-586.

167. Xie J, Dong H, Yu Y, Cao S, inhibitory effect of synthetic aromatic thiosemicarbazone derivatives on mushroom tyrosinase: Insights from fluorescence,(1)H NMR titration and molecular docking studies, Food Chem, 2016;190:709-716.

168. Yi W, Cao R-H,. Chen ZY, Yu L, Wen H, Yan Q, Ma L, Song H, ChemInform Abstract: Rational Design and Synthesis of 4-O-Substituted Phenylmethylenethiosemicarbazones as Novel Tyrosinase Inhibitors, Chem Pharm Bull, 2010;58:752-754.

169. Chen LH, Hu YH, Song W, Song KK, Liu X, Y. Jia L, Zhuang JX, Chen QX, Synthesis and Antityrosinase Mechanism of Benzaldehyde Thiosemicarbazones: Novel Tyrosinase Inhibitors, J Agric Food Chem, 2012;60, 1542-1547.

170. Li ZC, Chen LH, Yu XJ, Hu YH, Song KK, Zhou XW, Chen QX, Inhibition kinetics of chlorobenzaldehyde thiosemicarbazones on mushroom tyrosinase, J Agric Food Chem, 2010;58:12537-12540.

171. Pillaiyar T, NamasivayamV, ManickamM, Jung S-H, Inhibitors of Melanogenesis: An Updated Review, J Med Chem, 2018;61(17):7395-7418.

172. Haldys K, Latajka R, Thiosemicarbazones with tyrosinase inhibitory activity, Med Chem Commun, 2019;378-389.

173. Chen JSK, Agarwal N, Mehta K. Multidrug-resistant MCF-7 breast carcinoma cells contain deficient intracellular calcium pools, Bre Can Res Treat, 2002;71(3): 237-247.

174. Padhye S, Afrasiabi Z, Sinn e, Fork J, Mehta K, Rath N, (2005), Antitumor Metallothiosemicarbazonates: Structure and Antitumor Activity of Palladium Complex of Phenanthrenequinone Thiosemicarbazone. Inorganic Chemistry, 2005;44(5):1154-1156.

175. Kovala-Demertzi D, Yadav PN, Wiecek J, Skoulika S, Varadinova T, Demertzis MA, Zinc(II) complexes derived from pyridine-2-carbaldehyde thiosemicarbazone and (1E)-1-pyridin-2-ylethan-1-one thiosemicarbazone. Synthesis, crystal structures and antiproliferative activity of zinc(II) complexes, J Inorg Biochem, 2006;100:1558-1567.

176. Kovala-Demertzi D, Boccarelli A, Demertzis MA, Coluccia M, In vitro antitumor activity of 2-acetyl pyridine 4n-ethyl thiosemicarbazone and its platinum(II) and palladium(II) complexes, Chemotherapy, 2007; 53:148-152.

177. Zhang H, Thomas R, Oupicky D, Peng F, Synthesis and characterization of new copper thiosemicarbazone complexes with an ONNS quadridentate system: cell growth inhibition, S-phase cell cycle arrest and proapoptotic activities on cisplatin-resistant neuroblastoma cells, J Biol, Inorg Chem, 2008;13:47-55.

178. Adsule S, Barve V, Chen D, Ahmed F, Dou QP, Padhye S, Sarkar FH, Novel Schiff base copper complexes of quinoline-2 carboxaldehyde as proteasome inhibitors in human prostate cancer cells, J Med Chem, 2006;49: 7242-7246.

179. Li MX, Zhou JC, Chun WL, Jing P, Zeitschrift fuer Naturfor, B: Chem. Sci, 2008;63(3):280-284.

180. Torres EL, Mendiola, AM, Orthometallated versus coordination compounds for reactions of platinum(II) and palladium(II) with the ligand benzil bis(4-methyl 3-thiosemicarbazone, Inorg Chim Acta, 2010;363(8):1735-1740.

181. Qiang F, Zhi-Yu G, Jie Z, Han-Yu S, Chao L, Jin-Hong R, Copper thiosemicarbazones: Antiproliferative action against C6 glioma cells, Ban J Pharmacol, 2014;9:466-473.

182. Dhumwad SD, Gudasi KB, Gudar TR, Synthesis and structural characterization of biologically active metal complexes of N1-(N-morpholinoacetyl)-N4-phenyl thiosemicarbazide and 3,4-methylenedioxybenzaldehyde thiosemicarbazone with oxovanadium(lV) chromiumtlll), manganese(II), iron(III), cobalt(II), nickel(II), copper(II), cadmium(II), uranium(VI), thorium(IV) and silicon(IV), Ind J Chem, 1994;3A:320-324.

183. Demertzi DK, Demertzi MA, Filiou E, Pantazaki AA, Yadav PN, Miller, JR, Zheng Y, Kyriakidis DA, Platinum(II) and palladium(II) complexes with 2-Acetyl pyridine 4N-ethyl thiosemicarbazone able to overcome the cis-Platin resistance. Structure, antibacterial activity and DNA strand breakage, Biometels, 2003 ;16(3): 411-418.

184. Chandra S, Kumar A, Spectroscopic evaluation of Co(II), Ni(II), Cu(II) complexes derived from thiosemicarbazone and semicarbazone, Spectrochim Acta Part A, 2007; 68:1410-1415.

185. Kumar S, Dhar DN, Saxena PN, Applications of metal complexes of Schiff bases-A review, Journal of Scientific and Industrial Research, 2009;68(03):181-187.

186. Mahalingam V, Chitrapriya N, Fronczek, FR, Natarajan K, New Ru(II)-DMSO complexes of ON/SN chelates: Synthesis, behavior of Schiff bases towards hydrolytic cleavage of C=N bond, electrochemistry and biological activities, Polyhedron, 2011; 29(18) :3363-3371.

187. Kang IJ, Wang LW, Hsu TA, Yueh, Lee A, Chao YS, Shih YS et al, Isatin-β-thiosemicarbazones as potent herpes simplex virus inhibitors, Bioorg & Med Chem Lett, 2011; 21(7): 1948-1952.

188. Biot C, Pradines B, Sergent M-H, Gut J, Design, synthesis, and antimalarial activity of structural chimeras of thiosemicarbazone and ferroquine analogues, Bioorg Med Chem Lett, 2008;17(23):6434-6438.

189. Chellan P, Naser S, Vivas L, Chilbale K, Smith GS, Cyclopalladated complexes containing tridentate thiosemicarbazone ligands of biological significance: Synthesis, structure and antimalarial activity, J Organomet Chem, 2010; 695(19-20):2225-2232.

190. Lessa JA, Reis DC, Mendes IC, Speziali NL, Rocha LF, Pereira VRA, Melo VRA, Beraldo H, Antimony(III) complexes with pyridine-derived thiosemicarbazones: Structural studies and investigation on the antitrypanosomal activity, Polyhedron, 2011;30(2):372-380.

191. Batista D, Silva P, Lachter D, Silva R, Aucelio R, Louro R, Beraldo H, Soeiro N, Teixeira LR, Manganese(II) complexes with N4-methyl-4-nitrobenzaldehyde, N4-methyl-4-nitroacetofenone,and N4-methyl-4 nitrobenzophenonethiosemicarbazone: Investigation of in vitro activity against Trypanosoma cruzi, Polyhedron, 2010; 29(10): 2223-2232.

192. Prashanthi Y, Kiranmai K, Subhashini NJP, Shivaraj S, Synthesis, potentiometric and antimicrobial studies on metal complexes of isoxazole Schiff bases, Spectrochim Acta Part A: Mol. & Biomol Spect, 2008; 70(1): 30-35.

193. Singh RV, Chaudhary A, Biologically relevant tetra azamacrocyclic complexes of manganese. Spectral, antimicrobial, antifertility, and anti-inflammatory approach, J Inorg Biochem, 2004; 98(11): 1712-1721.