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A REVIEW ON POTENTIAL BIOLOGICAL ACTIVITIES OF THIOSEMICARBAZIDES

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ABSTRACT

Heterocycles have contributed to the development of society from a biological and industrial point of view as well as to improve the quality of life. During the past few decades, interest has been rapidly growing in gaining insight into the properties and transformation of these heterocycles. As a result, variety of new compounds is being added to this field every year. Among the sulfur and nitrogen containing heterocyclic compounds, thiosemicarbazides and thiosemicarbazones have potential pharmacological activities. The hydrazides addition to various isothiocyanates is one of the convenient methods of the synthesis of substituted thiosemicarbazides, which are of great interest not only in terms of a possible study of biological activity, but also as the starting compounds for the synthesis. Thiosemicarbazides is a unique class of organic compounds which is not known only for its various biological activities but also as metal-chelating and anticorrosion agents. This review is focused on the current rapid proliferation of a huge amount of biological data which led to a set of bioinformatics application and their use in the process of drug discovery. It also provides an insight of the significance of computational studies, becoming important for the support of activities reported.

Key Words: Thiosemicarbazides, antimicrobial, biological, docking studies.

INTRODUCTION

Traditionally, small molecules have been a reliable source for discovering novel biologically active compounds. Organo-nitrogen and sulfur compounds dominate much of synthetic, analytical and medicinal chemistry. Several small molecules, like triazole, thiadiazole and oxadiazole based heterocycles have also been reported to possess potential bioactivity, including anti-inflammatory, anticancer, analgesic, antimicrobial, anticonvulsant, antiallergic etc. [1-4]. Compared to their natural counterparts with complex structures, these molecules are easily synthesized and their smooth structural optimization would usually lead to a feasible candidate compound. Through utilization of combinatorial chemistry large libraries of small molecules have been generated and screened for specific biological activities. Various research on the synthesis and biological evaluation of small bioactive heterocyclic molecules series of aryl containing thiosemicarbazides and thiosemicarbazones were reported [5].

Thiosemicarbazides have occupied an important place in drug industry. Use of these compounds in organic synthesis has become a classical strategy for the synthesis of several heterocycles. Their reactions with compounds containing C=O and C=N groups is an improtant method for the synthesis of biologically active compounds, viz triazoles and thiazoles. A better understanding of their biological activity can be derived from their oxidation mechanisms. It is widely accepted that the prerequisite for thio compounds to express their physiological effects is through S-oxygenation [6]. Oxidation of organo-sulfur compounds appears to be involved in many cellular functions [7], including the reductive degradation of polypeptide hormones and proteins, regulation of protein synthesis, maintenance of intracellular redox potential, protection of cell from oxidative damage, etc. The chemistry of hydrazine derivatives, such as thiosemicarbazide and its hydrazones is of immense interest owing to their wide synthetic and analytical applications and biological activities [8]. Thiosemicarbazides and their derivatives display interesting biological activities, including anticancer [9], antiHIV [10], antibacterial [11], antiviral [12] and antifungal [5] owing to their ability to diffuse through the semipermeable membrane of cell lines [13-16]. They play an important role in the regulation of plant growth [17]. Due to their abundance in plants and ease of synthesis, this class of compounds has generated great interest for possible therapeutic uses. These sulfur and nitrogen donor ligands and their co-ordination complexes have gained special attention due to their activity against protozoa,

influenza, small pox virus, fungi and cancer. Some industrially important activities, such as anticorrosion and antifouling effects [18] have also been observed for these compounds.

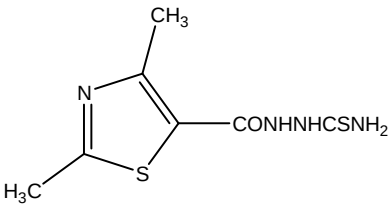
Thiosemicarbazide is a useful structural moiety that has the potential to display chemical functionality in biologically active molecules and optimization of this structure can result in ground breaking discovery of new class of therapeutic agents.

POTENTIAL BIOLOGICAL ACTIVITIES OF THIOSEMICABAZIDES AND THEIR DERIVATIVES

Thiosemicarbazide (NH_2-NH-$CSNH_2$) is the simplest hydrazine derivative of thiocarbamic acid. The chemical behavior of thiosemicarbazide is similar to its analogue semicarbazide, however is of greater chemical versatility of thione group as compared with that of keto group and is responsible for more varied behavior of thiosemicarbazide. Among the increasing number of heterocyclic sulfur and nitrogen containing compounds, being pursued in both industry and academia, thiosemicarbazide derivatives are also interesting targets for drug design. During the past few decades, interest has been rapidly growing in gaining insight into the properties and transformations of thiosemicarbazides and their derivatives due to their appreciable pharmacological activities [19-21]. Significant biological activities exhibited by thiosemicarbazides and their derivatives are discussed below.

Antibacterial Activity

Derivatives of thiosemicarbazides and thiosemicarbazones have been found to have excellent antibacterial activities. Antibacterial activity of 1-(2,4-dimethylthiazole-5-carboxyl)-N-4-ethylthiosemicarbazide (**I**), 1-(4-fluorobenzoyl)-N-4-ethylthiosemicarbazide (**II**), 2-pyridine-aldehyde-4-N-methylthiosemicarbazone (**III**) and 2-acetyl pyridine-4-N,N'-dimethylthiosemicarbazone (**IV**) has been reported by Sheikhy et al. [22]. They synthesized the molecules and studied their in vitro antibacterial activities. It was observed that all the four compounds were exhibiting inhibitory effect against *E. coli* at 0.4-0.5µM concentration. Compound **II** had been reported to be most lipophilic having an ability to influence the penetration through lipophilic LPS gram negative organisms, such as *E.* coli. Compounds **III** and **IV** demonstrated specific antibacterial effects on both *E. coli* and *S. aureus* samples at 0.1mg/ml. Also compounds **I** and **II** demonstrated specific antibacterial effects on *E. coli* at 0.1mg/ml concentration.



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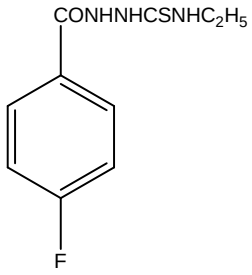

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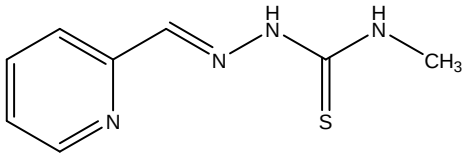
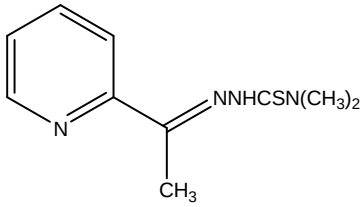
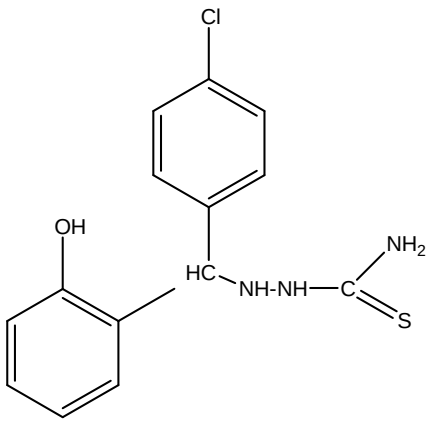


III

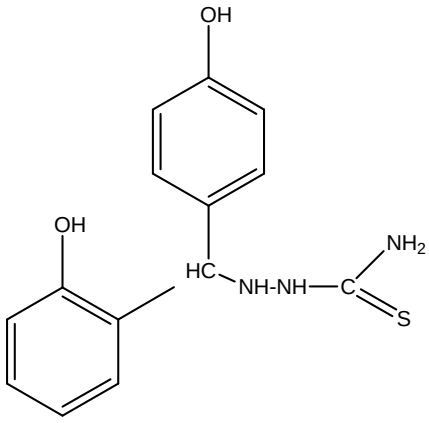


IV

Umadevi et al [23] reported the antibacterial activities of 2-(4-chlorophenyl)(2-hydroxyphenyl)methylthiosemicarbazide (**V**) and 2-(2-hydroxyphenyl)(4-hydroxyphenyl)methylthiosemicarbazide (**VI**) against gram positive *B. subtilis* & *S. aureus* and gram negative *S. typhi* & *S. dysentery* and specified the zone of inhibition in both the species.

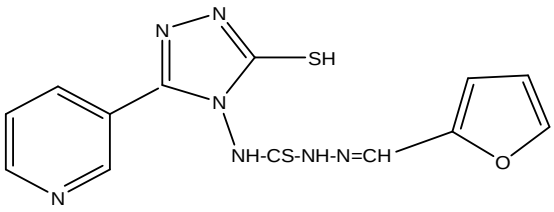


V

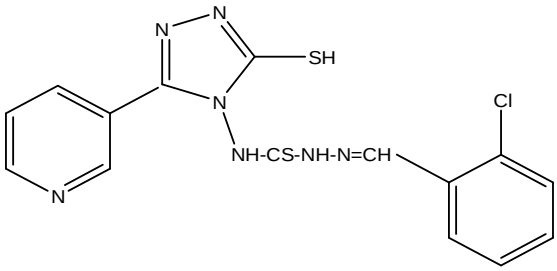


VI

Substituted N-(5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone have been synthesized [24] and evaluated for their antibacterial activities against *Staphylococcus aureus* and *Escherichia coli*. 2-furyl (**VII**) and 2-chlorophenyl derivatives (**VIII**) have been reported to be the most potent antibacterial agents with an inhibitory zone of 12 mm and 11 mm, respectively at a concentration of 100µg/ml.

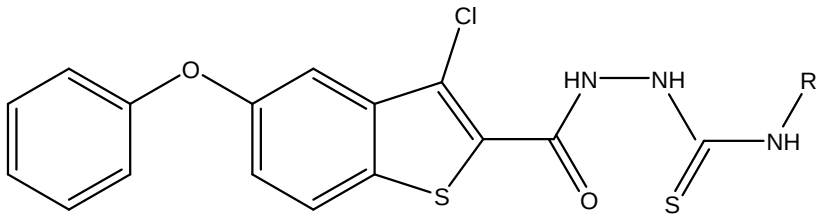


VII



VIII

N-substituted arylthiosemicarbazide derivatives were prepared by the reaction of 2-hydrazinocarbonyl-3-chloro-5-phenoxy-benzo[b]thiophene with different substituted phenyl isothiocyanate by Vasoya and co-workers [25]. All the compounds were assayed for their antimicrobial properties by cup-plate agar fusion method [26] and it was observed that N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(3-chlorophenyl)thiosemicarbazide (**IX**), N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-methylphenyl)thiosemicarbazide (**X**) and N1-(3'-chloro-5'-phenoxybenzo [b] thiophen-2'-yl) – N 4 - (4-methoxyphenyl) thiosemicarbazide (**XI**) were possessing good activities against *Escherichia coli*, while N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(3-chlorophenyl)thiosemicarbazide (**IX**), N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-methylphenyl)thiosemicarbazide (**X**), N1- (3'-chloro-5' -phenoxybenzo [b] thiophen -2'-yl) - N4 - (4-methoxyphenyl) thiosemicarbazide (**XI**), N1-(3'-chloro-5'- phenoxybenzo [b] thiophen-2'-yl)-N4-(4-methylphenyl) thiosemicarbazide (**XII**) and N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-methoxyphenyl)thiosemicarbazide (**XIII**) were active against *Bacillus megaterium*.

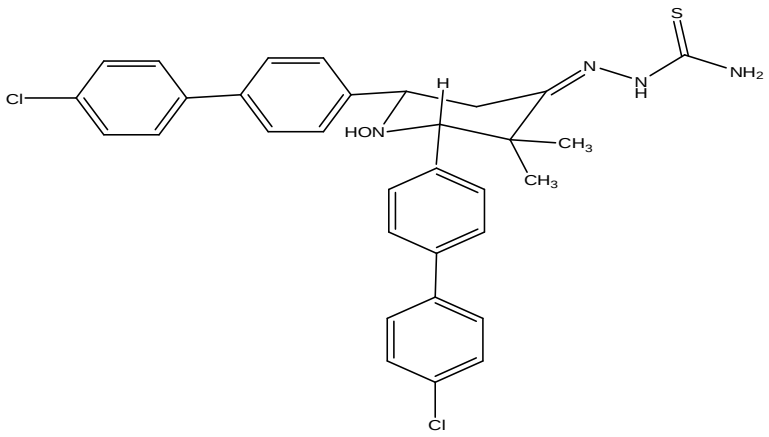


IX-XIII

IX : R = 3-Cl,C_6H_4 **X** : R = 2-CH_3,C_6H_4 **XI** : R = 4-OCH_3,C_6H_4

XII : R = 4-CH_3,C_6H_4 **XIII** : R = 2-OCH_3,C_6H_4

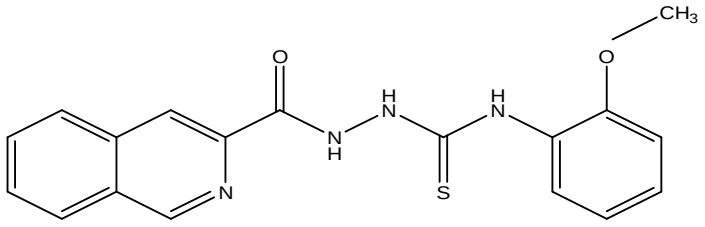
A series of novel N-hydroxy-3,3-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazones was synthesized and evaluated for their *in vitro* antibacterial and antifungal activities. Of all the compounds synthesized, N-hydroxy-3,3-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone (**XIV**) exerted a wide range of antibacterial activities against the entire tested gram-positive and gram-negative bacterial strains viz. *Staphylococcus aureus*, β-*haemolytic streptococcus*, *Vibreo cholerae*, *Salmonella typhii*, *Escherichia coli*, *Klebsiella pneumonia* and *Pseudomonas* [8].



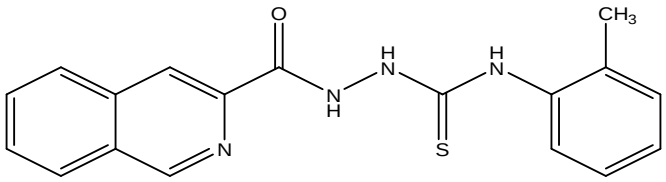
XIV

Antifungal Activity

The in-vitro antifungal potency of isoquinoline derivatives of 4-aryl thiosemicarbazides has been studied [5]. Six series of the derivatives were synthesized and evaluated against *Candida albicans*. Two isoquinoline derivatives with an o-methoxy and o-methyl group at phenyl ring (**XV** and XVI**)** were found to be the most potent antifungals:



XV



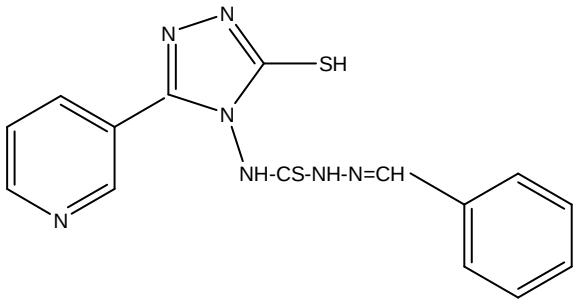
XVI

Molecular modeling studies and docking of these derivatives into active sites of sterol 14α-demethylase (CYP51), topoisomerase II (topo II), L-glutamine: D-fructose-6-phosphate

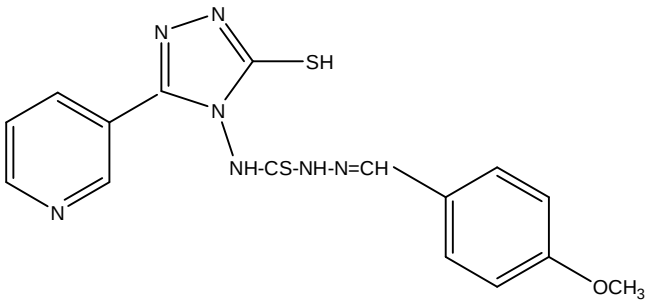
amidotransferase (GlcN-6-P), secreted aspartic proteinase (SAP), N-myristoyltransferase (NMT) and UDP-N-acetylmuramoyl-L-alanine: D-glutamate ligase (MurD) indicated the importance of both structural and electronic factors in ligand recognition and thus for antifungal effectiveness. A possible antifungal target was identified (NMT) and isoquinoline-thiosemicarbazides showed better affinity than the native ligand.

4-benzylamidothiosemicarbazide and its 2-furyl & 2-thinyl- derivatives have been synthesized and reported to be very much effective against *Alternaria solani*, *Cunninghmella blakesleema* and *Sclerotium rolfsii* [27], toxicity being comparable with that of 8-hydroxyquinoline sulfate. The effect of substituents in benzene ring was observed and phenolic group was suggested to be the most effective according to the order: dimethyl aminophenyl ~ amino < methyl ~ chloro < nitro < phenolic.

2-chlorophenyl (**VIII**), phenyl (**XVII**) and 4-methoxyphenyl derivatives (**XVIII**) of N-(5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone have been observed to exhibit good antifungal activity against *Candida albicans* [24].

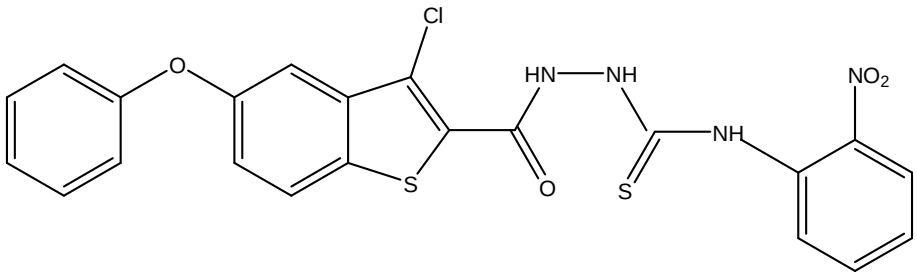


XVII



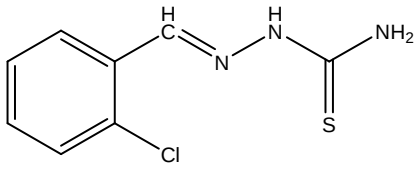
XVIII

Besides their excellent antibacterial activity, compounds **X-XIII** have been found to be active against *Staphylococcus aureus* whereas compounds **IX-XI** and N1-(3'-chloro-5'-phenoxybenzo[b]thiophen-2'-yl)-N4-(2-nitrophenyl)thiosemicarbazide (**XIX**) have been found to be active against *Aspergillus niger* [25].

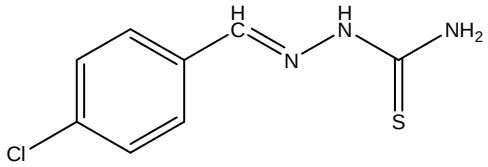


XIX

Cong et al [28] synthesized 2-chlorobenzaldehyde thiosemicarbazone (2-Cl-BT) (**XX**) & 4-chlorobenzaldehyde thiosemicarbazone (4-Cl-BT) (**XXI**) and investigated their inhibitory kinetics on the activity of mushroom tyrosinase. Results showed that these compounds reveal significant inhibitory potency on both monophenolase activity and diphenolase activity of tyrosinase. Such tyrosinase inhibition may have broad applications in cosmetics, medicinal, food preservation and insect control area.



XX

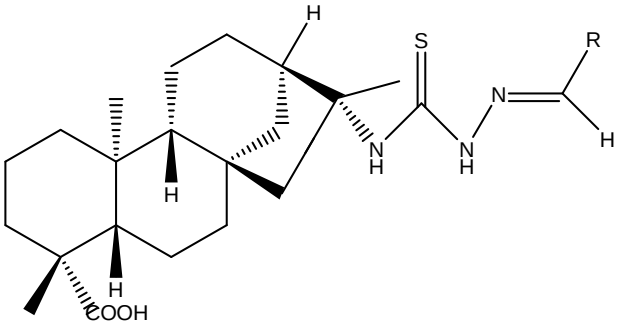


XXI

Compound **XIV** also exerted strong antifungal activities against *Aspergillus flavus*, *Mucor* and *Microsporum gypseum.*

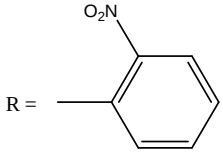
Antihelminthic Activity

A series of new thiosemicarbazones derived from natural diterpene kaurenoic acid had been synthesized and tested against the epimastigote forms of *Trypanosoma cruzi* to evaluate their antitrypanosomal potential. Five of the synthesized thiosemicarbazones had been reported to be more active than kaurenoic acid with IC_{50} values between 2-24.0µM. Out of different compounds synthesized, o-nitro (**XXII**), o-chloro (**XXIII**), p-methyl (**XXIV**), p-methoxyl (**XXV**) and m-nitrobenzaldehyde-thiosemicarbazone (**XXVI**) were found to be most effective with selectivity index values 9.0, 8.4, 7.3, 5.7 and 5.6, respectively. Further o-nitrobenzaldehyde-thiosemicarbazone (**XXII**) was the most active compound, with an IC_{50} of 2.0µM [29].

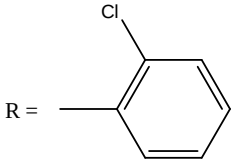


XXII-XXVI

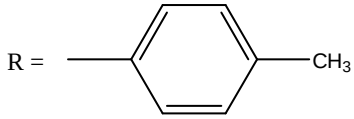
XXII



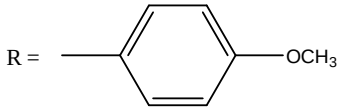
XXIII



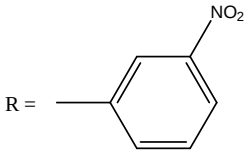
XXIV



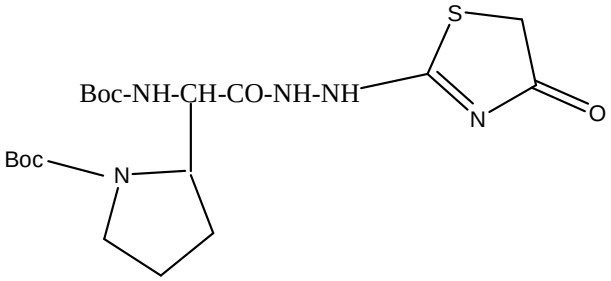
XXV



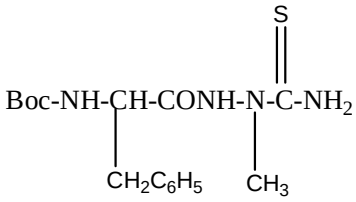
XXVI



A novel series of thiosemicarbazides and thiosemicarbazones was synthesized by Leite et al [30] and was studied for biological studies against *Trypanosoma cruzi*. Among various compounds synthesized and examined, following (**XXVII, XXVIII**) have been reported to have appreciable anti-*Trypanosoma cruzi* activity in concentrations non-cytotoxic to mammalian cells:



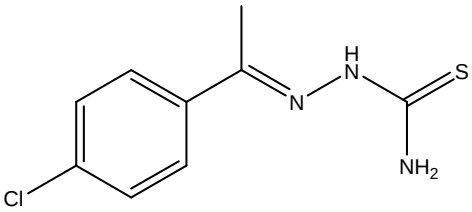
XXVII



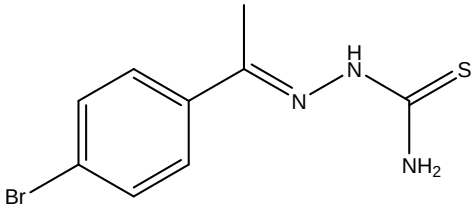
XXVIII

Docking studies of the compounds were carried out in order to investigate the binding pattern of these compounds for the *T. cruzi* cysteine protease cruzain (TCC) protein (1U9Q) which showed a significant correlation with the experimental data. A detailed analysis of the binding characteristics of these ligands in *T. cruzi* cysteine protease cruzain revealed important and specific interactions, important for describing the affinity of such molecules to the cruzain. Fatondji and co-workers [31] synthesized six aromatic thiosemicarbazones and

tested these compounds in vitro on *Trypanosoma brucei brucei* according to the "LILIT, Alamar Blue" method [32-34] for the comparison of their trypanocidal activity. All the compounds were found to be active against *T. brucei brucei*, but 4'-chloroacetophenone thiosemicarbazone (**XXIX**), 4'-bromoacetophenone thiosemicarbazone (**XXX**) and acetonaphtone thiosemicarbazone (**XXXI**) were found to be appreciably active with IC_{50} values of 11.07, 17.02 and 9.62µM, respectively.



XXIX



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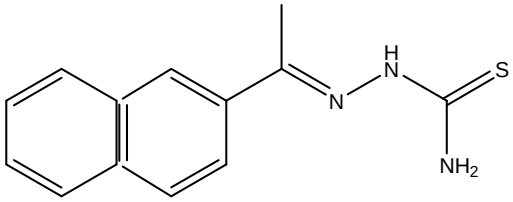
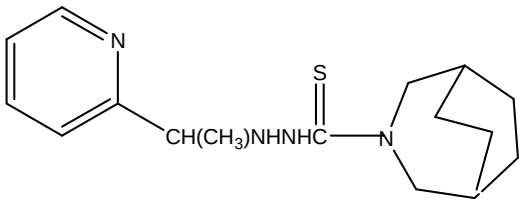


XXXI

Effect of various substituents has been discussed on trypanosidal activity. It has been observed and reported that compounds with no substituent on the nucleus has highest IC_{50} value (212.50µM). Substitutions at position 2 and 3 respectively with chlorine (IC_{50} = 199.97µM) and bromine (IC_{50} = 70.44µM) were reported to be less interesting than substitution at position 4 by chlorine (IC_{50} = 11.07µM) or bromine (IC_{50} = 17.02µM). The substitution of phenyl with naphthyl in thiosemicarbazone (IC_{50} = 9.62µM) was found to increase the trypanocidal activity.

Antimalarial Activity

Klayman et. al. [35] synthesized and investigated substituted 1-[l-(2-pyridyl)ethyl]-3-thiosemicarbazides as potential antimalarial agents. These compounds were somewhat more active as antimalarial agents in *Plasmodium berghei* infected mice than the corresponding thiosemicarbazones; however, the enhancement of activity was accompanied by an increase in toxicity. 3-azabicyclo[3.2.2]nonane-3-carbothioic acid 2-[1-(2-pyridyl)ethyl]hydrazide (**XXXII**) has been reported to be the most potent antimalarial agent which could cure two test animals at a dose of 10mg/kg.

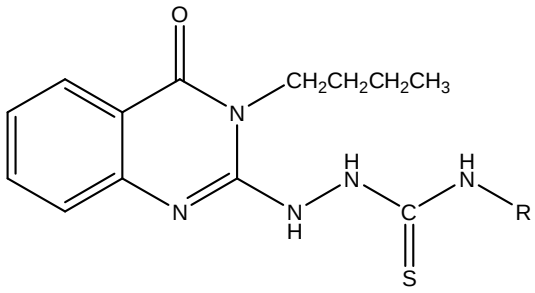


XXXII

Antitubercular Activity

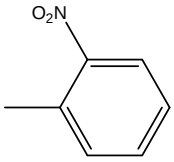
The antitubercular activity of the a series of compounds [25] was evaluated at 6.25µg/ml concentration against *Mycrobacterium tuberculosis* H37RV in BACTEC 12B medium using the ALAMAR radiometric system. Compound **XXX** was reported to have good activity having MIC > 6.25µg/ml with 21% inhibition.

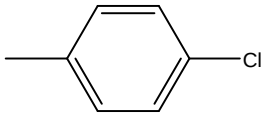
A new series of novel 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(substituted) thiosemicarbazides were synthesized by the reaction of 3-butyl-2-hydrazino quinazolin-4(3H)-one with various methyl esters of dithiocarbamic acid [36]. In vitro antitubercular activity of all the tested compounds using H37RV strain on Middle brook 7H11 agar slants with OADC growth supplement, illustrated the inhibited growth of *Mycrobacterium tuberculosis* at microgram concentration. Among the test compounds, 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(2-nitrophenyl) thiosemicarbazide (**XXXIII**), 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(4-chlorophenyl) thiosemicarbazide (**XXXIV**) and 1-(4-oxo-3-butyl-3,4-dihydroquinazolin-2-yl)-4-(2-pyridyl) thiosemicarbazide (**XXXV**) were found to be appreciably active against *M. tuberculosis* with MIC of 6 µg/ml.

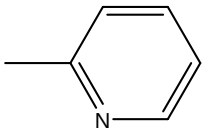


XXXIII-XXXV

R



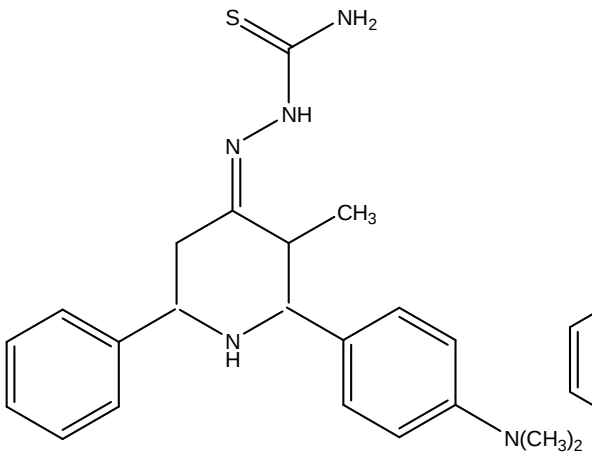




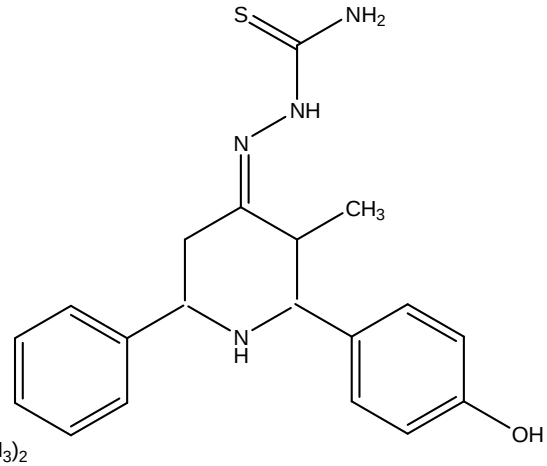
Compound	**XXXIII**	**XXXIV**	**XXXV**

Anticonvulsant Activity

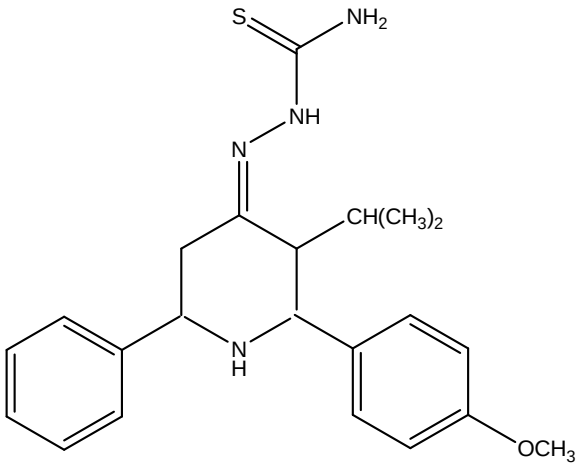
Thiosemicarbazone derivatives of 2,6-diaryl-3-methyl-4-piperidones were synthesized by reaction with thiosemicarbazide using microwave irradiation [37]. All the derivatives were evaluated for their in-vivo anticonvulsant activity by maximal electroshock (MES) method in rats, among which three, i.e. 2-[4-(dimethylamino)phenyl]-3-methyl-6-phenyl-piperidin-4-thiosemicarbazone (**XXXVI**), 2-(4-hydroxyphenyl)-3-methyl-6-phenylpiperidin-4-thiosemicarbazone (**XXXVII**) and 3-isopropyl-2-(4-methoxyphenyl)-6-phenylpiperidin-4-thiosemicarbazone (**XXXVIII**) showed maximum activity.



XXXVI



XXXVII



XXXVIII

Derivatives of 1-phthalazine thiosemicarbazide were also found to have potential anticonvulsant activity. In 1981, Soliman *et al.* converted 1- phthalazine thiosemicarbazide to 3-substituted-4-oxothiazolin-2-yl-(1-phthalazinyl)hydrazones (**XXXIX**, **XL**), 3-substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl)hydrazones (**XLI**) and 2-substituted-amino-

5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines (**XLII**) and observed their anticonvulsant activities on mice of both the sexes [38]. Composition of these compounds w.r.t. alkyl groups and their anticonvulsant activity is summarized in table-1.

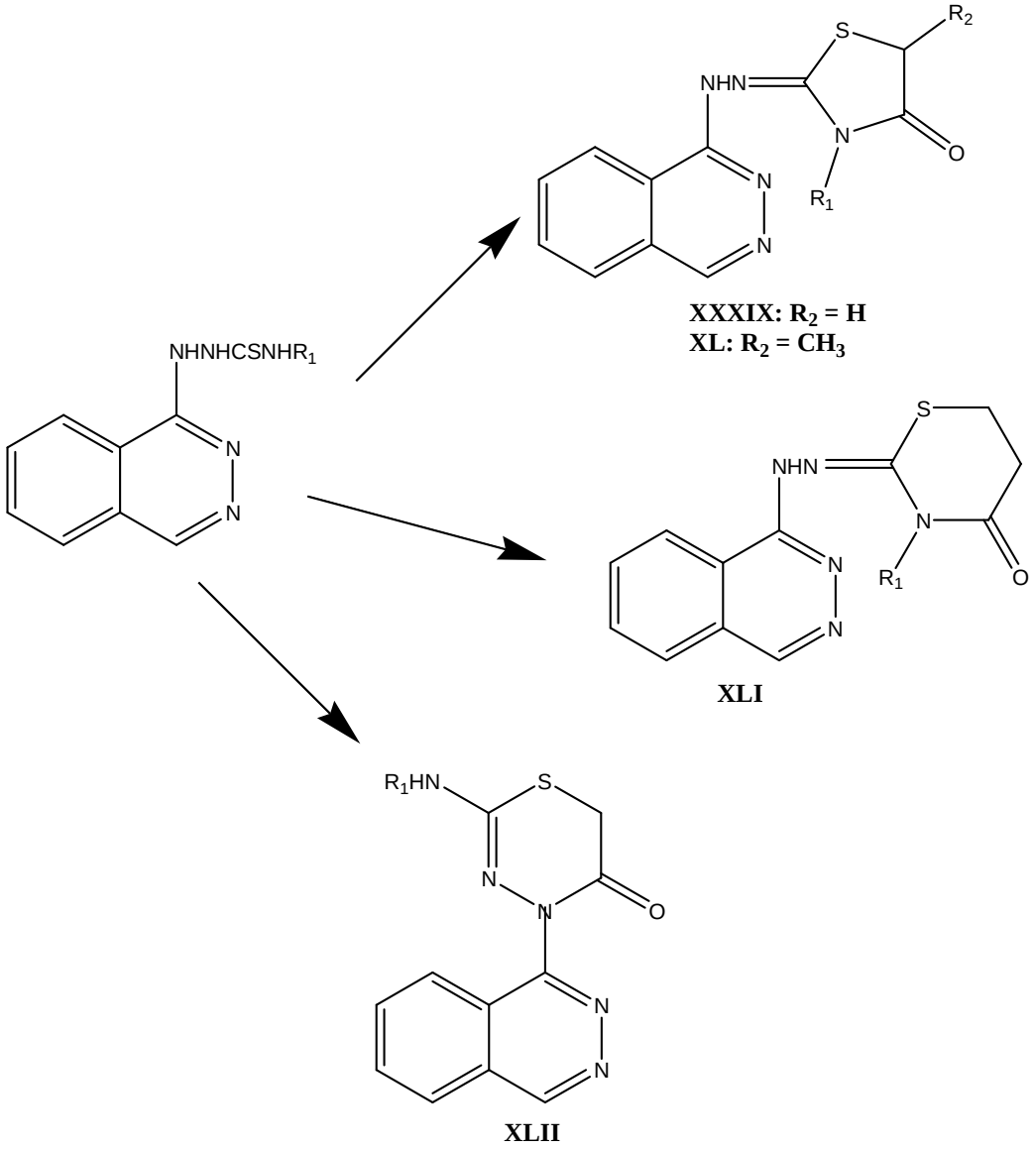


Table-1: Anticonvulsant Activity of Compounds XXXIX-XLII

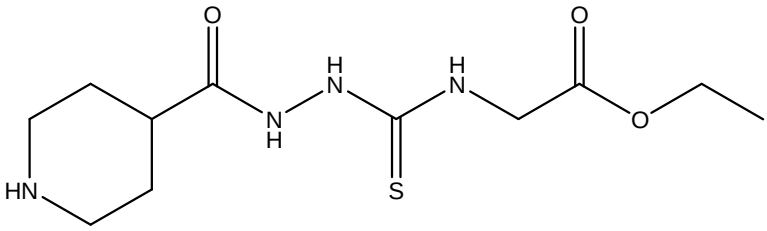
Compound	**R_1**	**R_2**	**Anticonvulsant Activity (% Protection)**
3-Substituted-4-oxothiazolin-2-yl-(1-phthalazinyl)hydrazones			
XXXIXa	C_6H_{11}	H	70
XXXIXb	$C_6H_5CH_2$	H	20
XLa	C_2H_5	CH_3	10
XLb	$C_6H_5CH_2$	CH_3	40
3-Substituted-4-oxo-5,6-dihydro-1,3-thiazin-2-yl-(1-phthalazinyl)hydrazones			

XLIa	C_2H_5	-	30
XLIb	CH_2=$CHCH_2$	-	0
XLIc	C_6H_{11}	-	20
XLId	C_6H_5	-	30
XLIe	$C_6H_5CH_2$	-	10
2-Substituted-amino-5-oxo-4-(1-phthalazinyl)-6-hydro-1,3,4-thiadiazines			
XLII	C_2H_5	-	50

Phenyl-N-(5-mercapto-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone (**XVII**) has shown potential anticonvulsant activity [24] with the time for hind limb extension recovery lesser than phenytoin used as reference drug at the dose of 30mg/Kg (observed to protect 100% against the induced convulsions).

Antitumor Activity

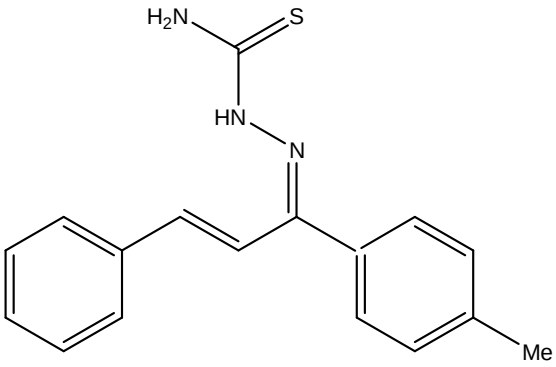
Cytotoxic effect of 4-ethoxycarbonylmethyl-1-(piperidine-4-ylcarbonyl)-thiosemicarbazide hydrochloride (**XLIII**) was measured using an MTT assay [39] and it was observed that the compound decreased the number of viable cells in both estrogen receptor-positive MCF-7 and estrogen receptor-negative MDA-MB-23 breast cancer cells, with IC_{50} values of 146±2 and 132±2µM, respectively [40].



HCl

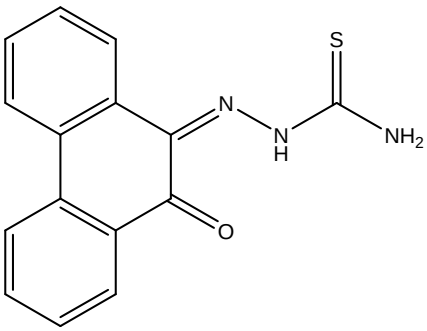
XLIII

A series of novel chalcone thiosemicarbazide derivatives were synthesized and evaluated for their biological activities as potential EGFR kinase inhibitors. Among the compounds, compound **XLIV** showed the most potent biological activity (IC_{50} ¼ 0.78- 0.05 mM for $HepG_2$ and IC_{50} ¼ 0.35 mM for EGFR), which is comparable to the positive controls. Docking simulation was also performed to position compound **XLIV** into the EGFR active site to determine the probable binding model. Antiproliferative assay results demonstrated that some of these compounds possessed good antiproliferative activity against human hepatocellular liver carcinoma cell (HepG2) [41].



XLIV

Padhye et. al. [42] reported the structure and antitumor activity of palladium complex of phenanthrenequinone thiosemicarbazone (**XLV**)**.** The crystal structure of potential antitumor metal compound, viz. chloro, mono(phenanthrenequinone thiosemicarbazonato) palladium(II) dimethyl formamide solvate was reported. The central palladium(II) atom was in a square planar environment provided by the tridentate, monoanionic thiosemicarbazone ligand and the ancillary chloride ion. The compound exhibited remarkable activity against drug-sensitive and drug-resistant breast cancer cell lines and was relatively nontoxic towards the normal mammary epithelial cells. The drug-induced killing effect against breast cancer cell lines was predominantly mediated via apoptosis, a physiologic form of cell death.

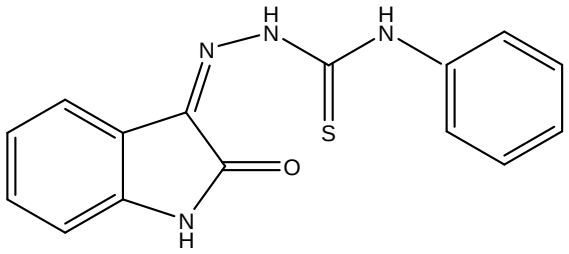


XLV

Antioxidant Activity

Barcelos and co-workers [43] tested for the antioxidant activity of isatin-3-N^4-benzilthiosemicarbazone (IBTC) (**XLVI**). They measured the conjugated diene formation in serum and LDL as well as the loss of tryptophan fluorescence in LDL induced by two oxidant agents, 2,2-azobis(2-amidinopropane dihydrochloride) (AAPH) and Cu^{2+}, which are responsible for increase in the formation of oxidized low density lipoprotein (LDL). LDL plays a crucial role in the initiation and progression of atherosclerosis. The results showed that IBTC significantly reduced the AAPH and Cu^{2+}-induced formation of conjugated dienes, increased in a dose-dependent manner the lag phase and the $t_{1/2}$ of tryptophan fluorescence,

and reduced the TBARS formation in LDL, plasma and rat tissues, showing no toxicity to aortic slices. These results indicated the good antioxidant nature of IBTC proposed it to be a promising antiatherogenic agent.



XLVI

OTHER APPLICATIONS

A very simple, highly sensitive and selective spectrophotometric procedure was developed to determine the presence of platinum (IV) in the sample by Attas et al [44]. It is based on the reaction at pH = 3 between the synthesized 1-phenyl-4-ethyl thiosemicarbazide (HPETS) and Pt(IV) forming a green complex, Pt(IV):PETS (1:2) that floats quantitatively with oleic acid surfactant. The molar absorptivities in aqueous and surfactant media were $0.14x10^5$ and $0.5x10^5$mol/l, respectively. Different analytical parameters affecting the floatation and determination processes were examined. The proposed procedure has been successfully applied to the analysis of Pt(IV) in natural waters, prepared solid complexes and simulated samples. The results obtained were in agreement with atomic absorption spectroscopy (AAS). Moreover, the floatation mechanism is suggested based on some physical and chemical studies on the solid complexes isolated from aqueous and surfactant layer.

COMPUTATIONAL STUDIES

Three dimensional quantitative structure-activity relationships (3D-QSARs) were performed with new thiosemicarbazone analogues as a substrate molecule [45] and their inhibitory activity against tyrosinase as a receptor was observed. They used CoMFA (comparative molecular field analysis) [46] and CoMSIA (comparative molecular similarity indices analysis) [47] methods for the quantitative discussion. Molecular docking was also performed which indicated that the inhibitory activation of the substrate molecules against tyrosinase (1WX2) would not take place via uncompetitive inhibition forming a chelate between copper atoms in the active site of tyrosinase and thiosemicarbazone moieties of the substrate molecules, but via competitive inhibition based on hydrogen bonding. 4-benzoyl-1-(4-methyl-imidazole-5-yl)-carbonylthiosemicarbazide and 4-benzoyl-1-(indol-2-yl)-carbonyl thiosemicarbazide were synthesized and compared for their activities against type II

topoisomerase by antimicrobial as well as by docking studies, wherein it was investigated that the inhibitory activity against topoisomerase originates in the preferential binding of indole derivative in the ATP binding pocket [48].

The mode of inhibitory action of 4-ethoxycarbonylmethyl-1-(piperidine-4-ylcarbonyl)-thiosemicarbazide hydrochloride (**XLIII**) was studied by docking simulations with ATP-binding domain of hTopoIIα (1ZXM) and DNA binding site of hTopoIIβ (3QX3) using the flex program [49]. It was concluded from the studies that the inhibitory action of compound **XLIII** is connected with the ATP binding pocket.

CONCLUSION

Studies indicate the variety and diversity in application areas of significant importance shown by thiosemicarbazides and their derivatives. Apart from the antimicrobial activities, these have been proved to be good antitumor, anticonvulsant and antioxidant agents. These compounds have been found to be effective against a wide range of bacteria, fungi and plasmodium species. They also showed significant role in the cure of CNS and cardio-vascular disorders. Effectiveness of the moiety has been improved by the presence of various aryl substituents. Further, computational studies support the effectiveness of the class and prove to be in accordance with the observations of wet lab.

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