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REVIEW

An Updated Review on Synthesis and Biological Activities of Thiosemicarbazide Analogs

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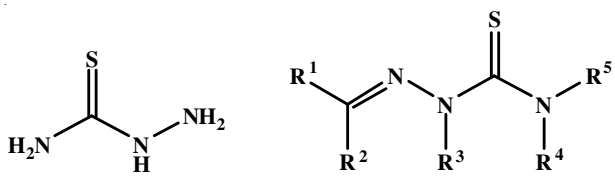
This review paper focuses on the different synthetic methodologies that researchers have adopted to synthesize various thiosemicarbazide derivatives with different biological activities of synthesized compounds in the last 20 years. Most of the investigations available in the literature are directed to the biological activities of thiosemicarbazide derivatives with less discussion on its synthetic schemes. This review article presents various reaction scheme, which has been adopted for thiosemicarbazide derivative synthesis along with the reported pharmacological activities of synthesized analogs. The available literature in the article aims to encourage more studies on the synthesis of thiosemicarbazide derivatives, which will help for drug discovery having thiosemicarbazide nucleus.

Keywords: Thiosemicarbazide, Drug discovery, Synthetic schemes, Biological activities, Pharmacological activities.

INTRODUCTION

The knowledge of the chemistry of thiosemicarbazide and its analogs is of utmost importance as they are used for the synthesis of a large number of new organic compounds [1-3]. Within the last few decades, extensive research studies on the chemistry of thiosemicarbazide have been done, which suggests that the thiosemicarbazide derivatives can undergo a wide variety of reactions leading to the synthesis of many useful drugs [4,5]. Thiosemicarbazones is one of the fundamental subgroups of hydrazine [6] and it can be obtained through the reaction of thiosemicarbazide with aldehydes or ketones [7,8]. Thiosemicarbazide (NH_2-NH-$CSNH_2$) is the simplest hydrazine analog of thiocarbamide acid [9,10]. Both thiosemicarbazide and thiosemicarbazones (Fig. 1) are strong intermediates for the combination of drug and bioactive materials and in this manner, they are utilized widely in the field of medicinal chemistry. The imine bond (-N=CH-) in these compounds is helpful in organic synthesis, specifically for the arrangement of heterocycles and non-characteristic β-amino acids [11-14]. These compounds and their derivatives show a large number of potential pharmacological activities like antifungal [15,16], antibacterial [17-19], anti-Alzheimers [20], anti-Trypanosoma [21], anti-inflammatory [22], antituberculosis [23,24], anti-urease [25,26], antioxidant [27,28], antiprotozoal [29], antiviral [30], anticancer [31], anticonvulsant [32], tyrosinase inhibitory activities [33]. From the pharmacological point of view, thiosemicarbazide derivatives are useful intermediates and subunits for the development of drugs or molecules of significant biological interest [34].



Thiosemicarbazide **Thiosemicarbazone**

Fig. 1. Structure of thiosemicarbazide and thiosemicarbazone

The application of these analogs in organic synthesis has developed a traditional method for the research of a wide variety of heterocyclic compounds [35]. Because of the presence of some reactive centers, these compounds are suitable precursors for the synthesis of nitrogen and sulfur-containing heterocyclic compounds, for example, triazoles, triazines, pyrazoles, thiazoles, thiadiazoles, pyrimidines, *etc*. [36-38]. Thiosemicarbazide can

easily incorporate other chemically biological active molecules which may increase the functionality and optimization of its the structure also for the discovery of a new class of therapeutic agents [39,40]. A large number of pharmacologically active drugs containing the moiety of thiosemicarbazide and thiosemicarbazone in their structure are shown in Table-1 and also several reported ligands are there, which shows different biological activities are listed in Table-2. The literature shown in this article is the compilation and systematic presentation of last 20 years, synthetic schemes that were used for the synthesis of thiosemicarbazide derivatives having a wide variety of biological actions.

Synthesis and biological activities of thiosemicarbazide analogs: Various synthetic schemes giving a large number of novel thiosemicarbazide and its derivatives with a different type of biological activities are discussed below:

Anticancer activity: Sibuh *et al.* [87] synthesized a novel series of thiosemicarbazones derivatives by the reaction with

TABLE-1
CLASS AND NAME OF DRUGS CONTAINING THIOSEMICARBAZONE AND THIOSEMICARBAZIDE ANALOGS

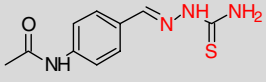
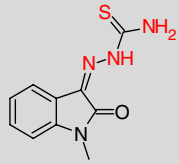
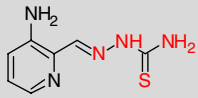
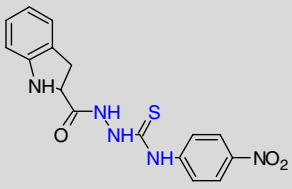
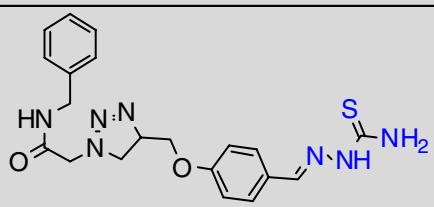
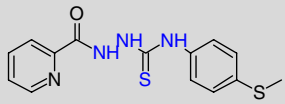
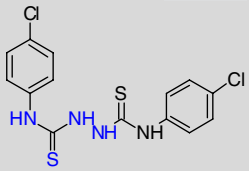
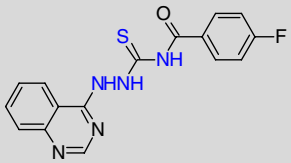
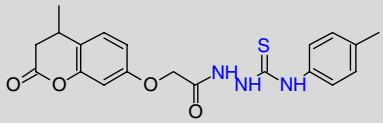
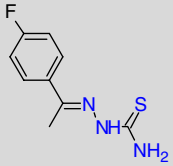
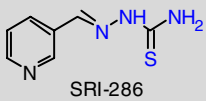
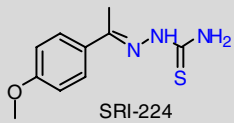
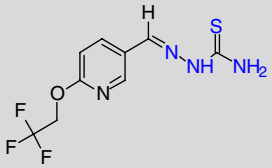
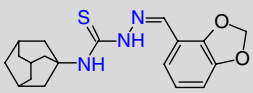
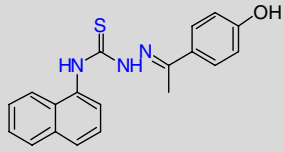
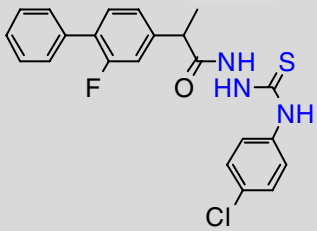
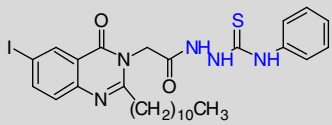
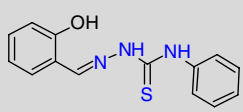
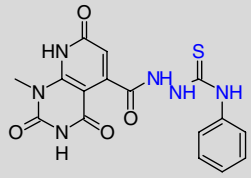
 Thioacetazone	 Methisazone	 Triapine
Antitubercular drug [Ref. 41,42]	Antiviral drug [Ref. 43]	Anticancer drug [Ref. 44]

TABLE-2
TABLE SHOWS PHARMACOLOGICALLY ACTIVE REPORTED COMPOUNDS WITH THIOSEMICARBAZIDE NUCLEUS AND HAVING DIFFERENT ACTIVITY

 Antibacterial [Ref. 45]	 Tyrosinase inhibitor [Ref. 46]	 Antitubercular [Ref. 47]
 Anticonvulsant [Ref. 48]	 Antitumor [Ref. 49]	 Antioxidant [Ref. 50]
 Antimalarial [Ref. 51]	 SRI-286 Antitubercular [Ref. 52]	 SRI-224 Antitubercular [Ref. 53]
 Antitumor [Ref. 54]	 Antitumor [Ref. 55]	 Antitumor [Ref. 56]
 Antitumor [Ref. 57]	 Antitumor [Ref. 58]	 Antileukemia [Ref. 59]



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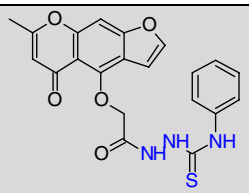
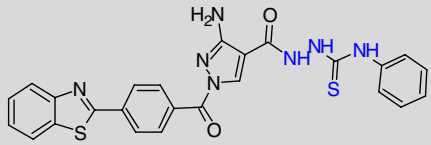


Antitumor [Ref. 61]



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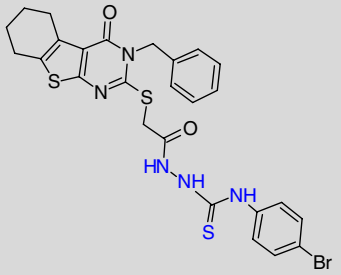
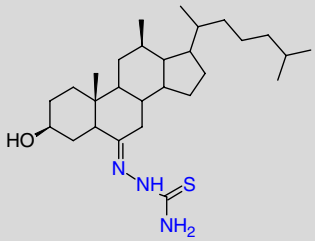
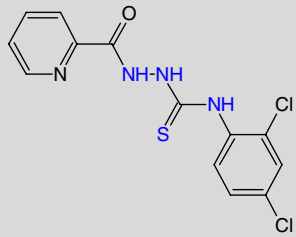


Antitumor [Ref. 63]



Antiproliferative [Ref. 64]



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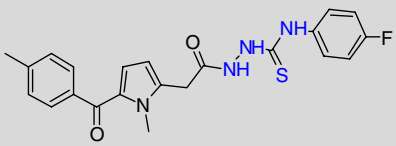

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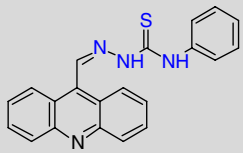
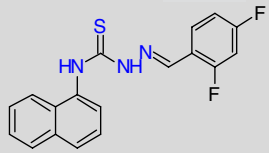


Antiproliferative [Ref. 67]



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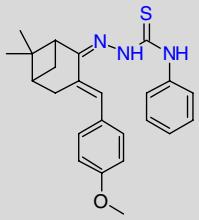
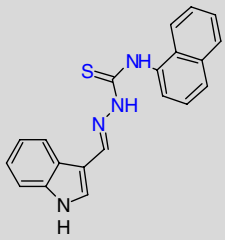
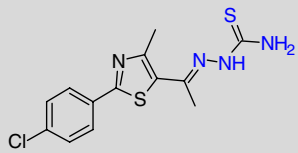


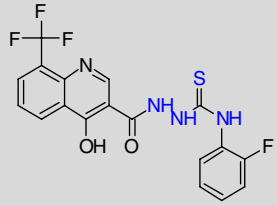
Antitumor [Ref. 69]



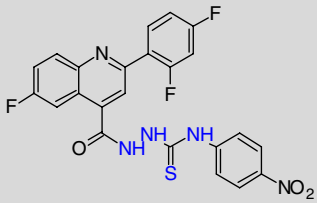
Antitumor [Ref. 70]



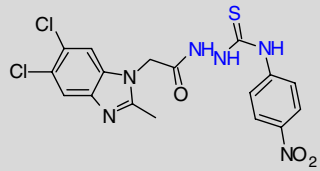
Antitubercular [Ref. 71]



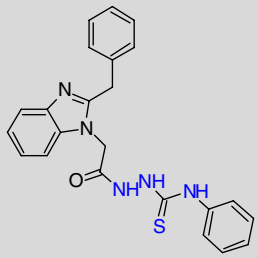
Antimicrobial [Ref. 72]



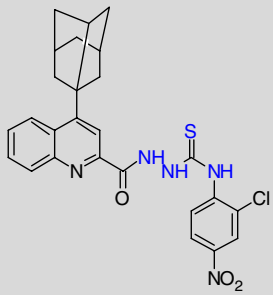
Antimalarial [Ref. 73]



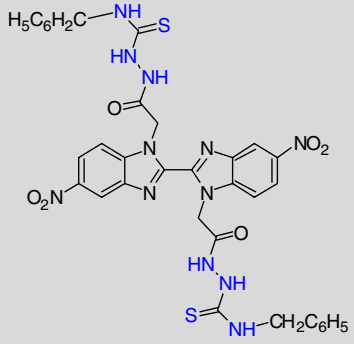
Anti-urease [Ref. 74]



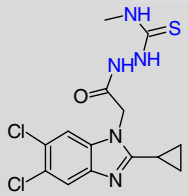
Antioxidant [Ref. 75]



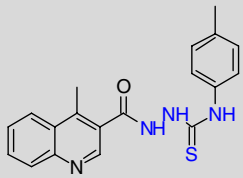
Antituberculosis [Ref. 76]



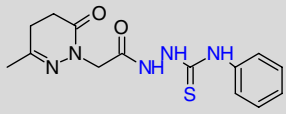
α-Glucosidase [Ref. 77]



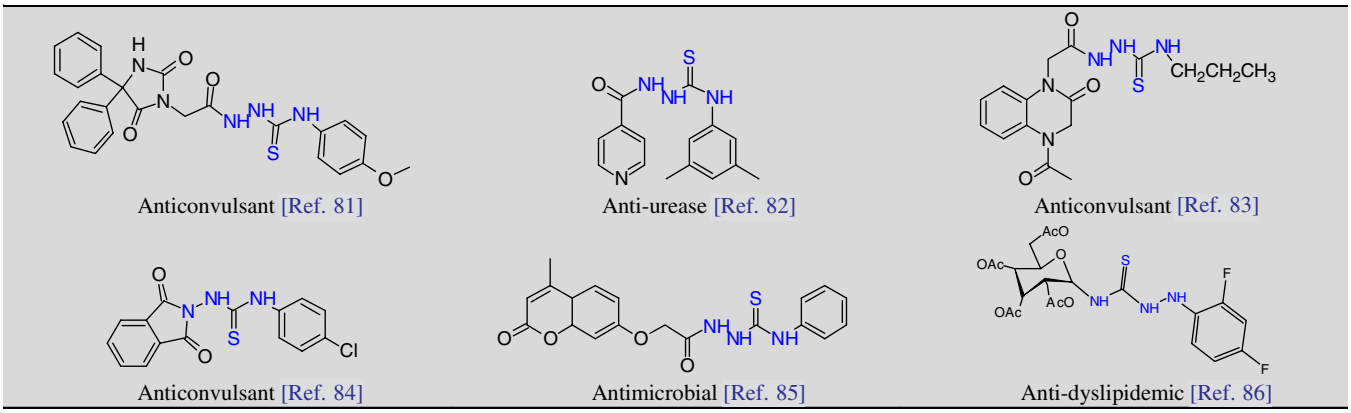
Anti-urease [Ref. 78]



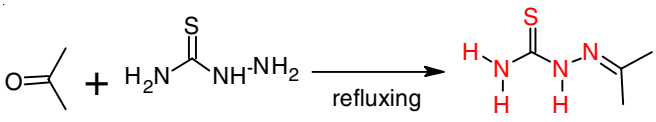
Antimalarial [Ref. 79]



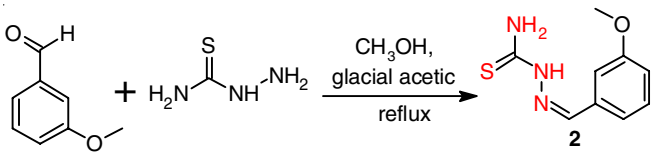
Antimycobacterial [Ref. 80]



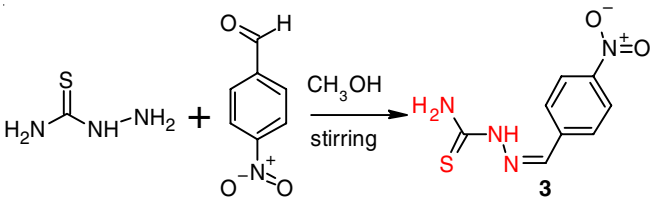
acetone, 3-methoxy benzaldehyde and 4-nitro benzaldehyde (**Schemes I-III**) which were further checked for their *in vitro* anticancer activity against human breast cancer cell line MCF-7 and normal cell MCF-10. It was observed that acetone thiosemicarbazone (**1**) and 3-methoxy benzaldehyde thiosemicarbazone (**2**), were more active against MCF-7 breast malignancy cells with IC_{50} estimation of 2.271 and 2.743 µg/mL, respectively. Yousef & El-Reash [88] synthesized 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde 4*N*-(2-pyridyl)thiosemicarbazone (**4**) (Fig. 2) and it was noted that the metal complexes of Mn(II), Zn(II), Cd(II), Cu(II), Ni(II), Co(II) showed the antioxidant and antitumor activities. The reported range of antioxidant activity was between 0.542 to 2.356 µg/mL and the antitumor activity with IC_{50} range was between 57.42 to 74.84%.



Scheme-I: Synthesis of acetone thiosemicarbazone



Scheme-II: Synthesis of 3-methoxybenzaldehyde thiosemicarbazone



Scheme-III: Synthesis of 4-nitrobenzaldehyde thiosemicarbazone

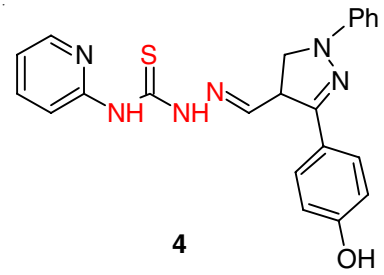
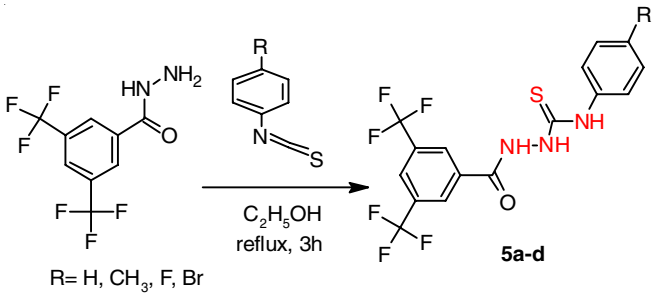


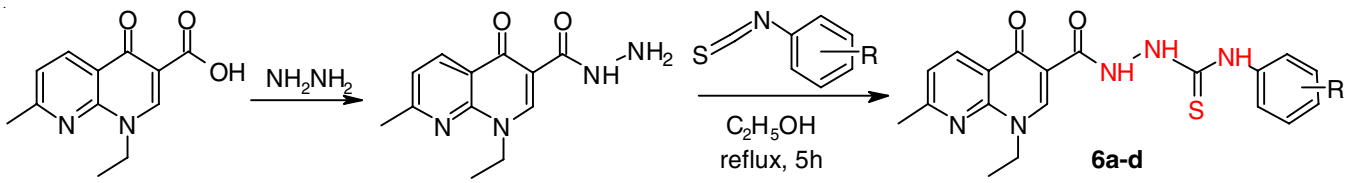
Fig. 2. Structure of 3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde 4*N*-(2-pyridyl)thiosemicarbazone

Dincel & Guzeldemirci [89] synthesized a series of thiosemicarbazide derivatives (**5a-d**) (**Scheme-IV**) and carried there *in silico* study for anticancer activity. The synthesized ligands showed the potential activity by affecting and hitting various targets like epidermal growth factor receptor, tubulin receptor and also carbonic anhydrase receptors displaying their anticancer action.

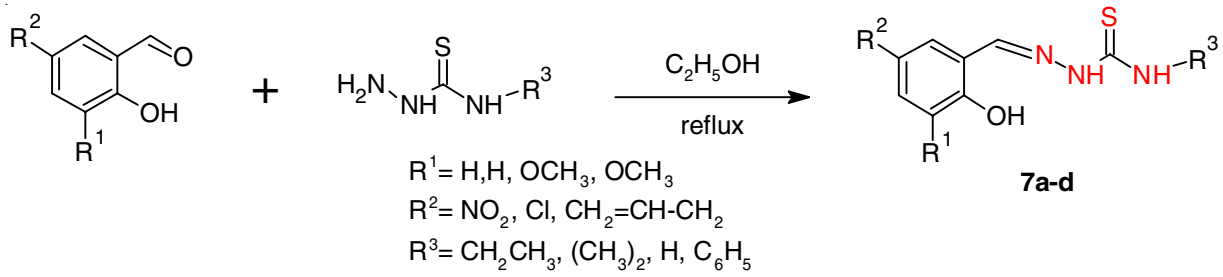


Scheme-IV: Synthesis of 3,5-*bis*(trifluoromethyl)benzothiosemicarbazide derivatives

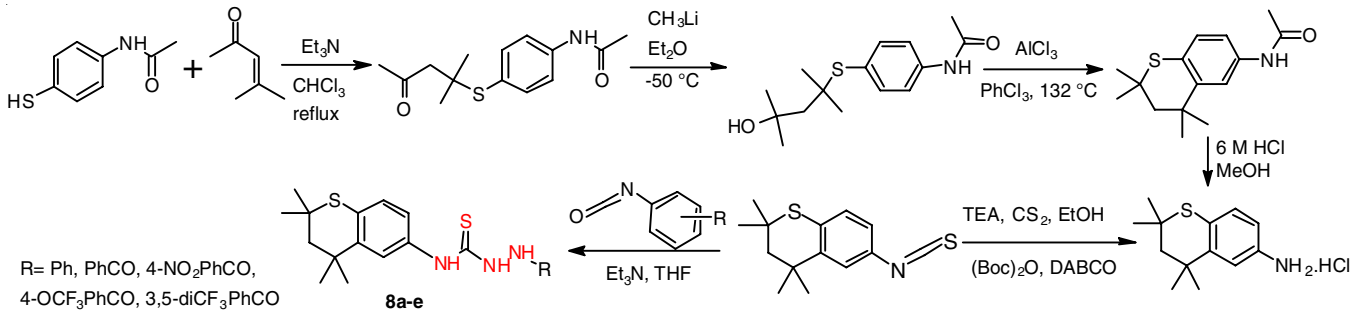
Khalil *et al.* [90] synthesized thiosemicarbazide analogs (**6a-d**) fused with nalidixic acid (**Scheme-V**). Nalidixic acid on condensation with hydrazine gives the intermediates which further were made to react with isothiocyanate in the presence



Scheme-V: Synthesis of nalidixic acid fused thiosemicarbazide analogs



Scheme-VI: Syntheses of thiosemicarbazone derivatives



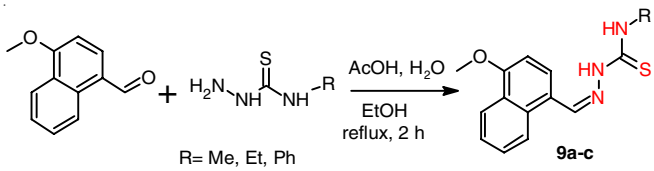
Scheme-VII: Synthesis of flexible hetroarotinoid derivatives

of absolute ethanol to obtain the desired derivatives which further were evaluated for anticancer activity. Among all these tested analogs, compound having 3-methyl phenyl ring showed good results against leukemia of cell line K-562 and SR sub-panels with IC_{50} 35.29 µM and 13.85 µM. The compound with 3-methyl phenyl ring substituent also gives good inhibitory activity against topoisomerase IIα and topoisomerase IIβ when compared to the standard inhibitors like doxorubicin and topotecan with IC_{50} 1.30 µM and 0.017 µM correspondingly.

Hussein *et al.* [91] synthesized and reported the cytotoxic activity of thiosemicarbazone analogs (**Scheme-VI**). They showed their cytotoxicity activity against three cancer cell lines PANC-1, HCT-116, MCF-7 and one normal cell line NIH/3T3. All these synthetic compounds showed cytotoxicity activity against cancerous cells with IC_{50} values range between 0.7-212.8 µM.

Nammalwar *et al.* [92] reported for the synthesis of novel series of flexible heteroarotinoid (Flex-Het) derivatives (**Scheme-VII**) and evaluated their anticancer activity against the A2780 ovarian cancer cell lines. Compounds were synthesized from isothiocyanate and they showed high action with an IC_{50} value in the range of 1.86 to 4.70 µM with 85.6 and 95.9% efficacies, which are similar to or better than the lead compound of IC_{50} 3.17 µM, 84.3% viability. Rajendran *et al.* [93] synthesized the thiosemicarbazone analogs copper (II) complex on *N*(4)-substituents (**Scheme-VIII**). The ligands and its metal complexes were screened by *in vitro* cytotoxicity activity against the Hela cell line. All tested ligands and their metal complexes showed percentages of cytotoxicity between 43 ± 0.12 to 89 ± 0.07 as compared with standard positive control cisplatin 96 ± 0.01.

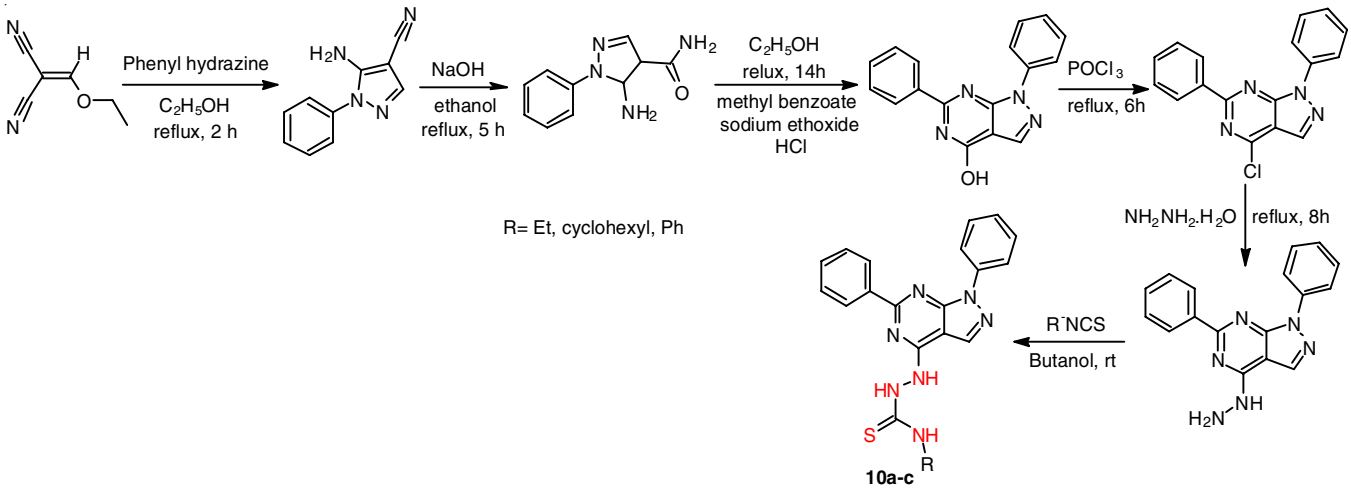
Gaber *et al.* [94] synthesized thiosemicarbazide derivatives fused with 1*H*-pyrazolo[3,4-*d*]pyrimidine hybrid (**Scheme-IX**). Ethoxy methylene malononitrile was refluxed with phenylhydrazine, followed by hydrolysis with alcoholic NaOH to



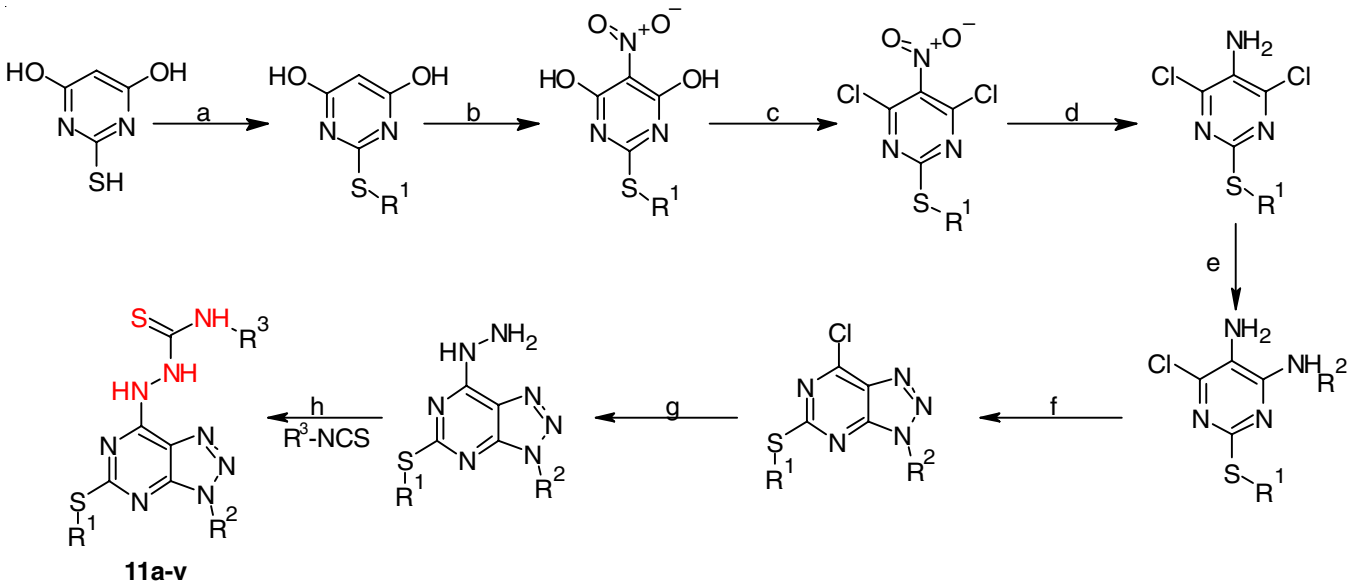
Scheme-VIII: Synthesis of *N*(4)-substituted thiosemicarbazone derivatives

produce carboxamide derivative, which was then reacted with methyl benzoate to give the intermediate compound and finally reacted with hydrazine hydrate and isothiocyanates. The obtained product was further screened for their inhibitory activity against $EGRF^{WT}$ by *in vitro* method. All the tested compounds exhibited significant antiproliferative activities against $EGRF^{T790M}$ containing cells with the IC_{50} value ranging between 0.35 ± 0.21 µM to 0.56 ± 0.19 µM, respectively. Geng *et al.* [95] synthesized a novel series of thiosemicarbazide moieties containing [1,2,3]-triazolo[4,5-*d*]pyrimidine derivatives (**Scheme-X**). They were also evaluated for the antiproliferative activity against different human cancer cell lines like PC-3, MGC-803, NCI-H1650. Among them, *N*-benzyl-2-(3-benzyl-5-(prop-2-yn-1-yl thio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-7-yl)hydrazine-1-carbothioamide compound showed potential inhibitory activity against MGC-803 malignant growth cells with IC_{50} value of 2.37 µM. The rest of the molecules showed moderate to good effects against three screened malignant growth cell lines.

Wos *et al.* [96] synthesized a novel series of thiosemicarbazide with a 4-nitrophenyl substitution (**Schemes XI** and **XII**) and also evaluated for antibacterial and antiproliferative activities. The *in vitro* antibacterial effects were evaluated against Gram-positive *Staphylococcus aureus*, *Staphylococcus epidermidis and* micro-aerobic Gram-positive *Streptococcus mutans*, *Streptococcus sanguinis* bacterial strains [97]. The antiproliferative activity was tested against different cell lines like HepG2, A549, MCF-7, BJ cell [98]. It was observed that 2-pyridine and 4-nitrophenyl derivatives exhibit antiproliferative



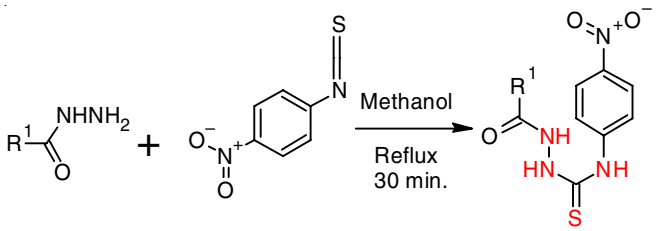
Scheme-IX: Synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidine hybrid thiosemicarbazide derivatives



(a) alkyl bromide, TEA, methanol, reflux, 2 h; (b) fuming nitric acid, AcOH, 25-45 °C, 1 h; (c) $POCl_3$, DMA, reflux, 2 h; (d) Fe, AcOH, methanol, rt~reflux; (e) proper amine, DIEA, DMF, reflux, 3 h; (f) $NaNO_2$, AcOH, H_2O, 10 °C, 1 h; (g) hydrazinehydrate, ethanol, rt, 2 h; (h) ethanol, reflux, 2 h.

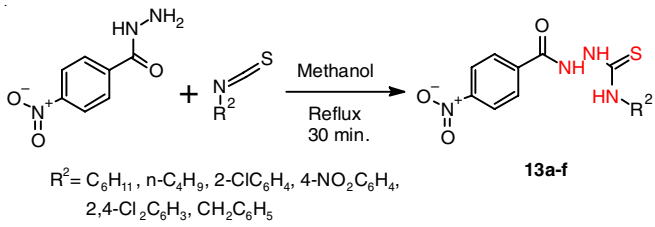
R^1=$CH(CH_3)_2$, propargyl, Bn; **R^2**=Bn, 4-OH-Bn, 4-Br-Bn, 3-Mefuran, C_5H_{10}, CH_2C-$(CH_3)_2$, 2-Et-thiopene, 3-Et-indol, C_2H_4OH; **R^3**=4-BrPh, 2-ClPh, 3-ClPh, 4-ClPh, 4-butyl Ph, 3-MeOPh, 1-napthyl, 3,4,5-tri-OMePh, Bn, $C(Ph)_2$

Scheme-X: Synthesis of thiosemicarbazide-triazolo-pyrimidine derivatives



R^1= 2-pyridine, 3-pyridine, 4-pyridine

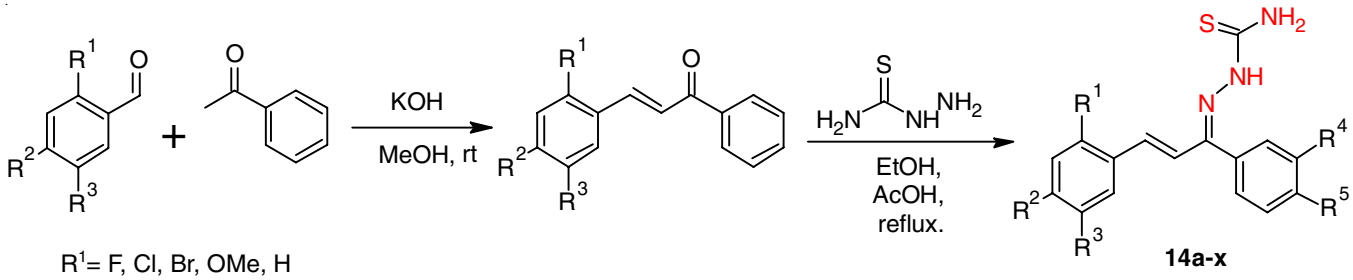
Scheme-XI



R^2= C_6H_{11}, n-C_4H_9, 2-ClC_6H_4, 4-$NO_2C_6H_4$, 2,4-$Cl_2C_6H_3$, $CH_2C_6H_5$

Scheme-XII: Synthesis of 4-nitrophenyl hybrid thiosemicarbazide derivatives

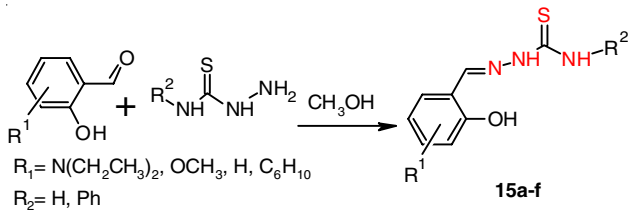
effectiveness with IC_{50} range 2.53 ± 1.21 to 11.88 ± 3.91 µg/mL. Among all of these synthetic compounds 2-chlorophenyl, 4-nitrophenyl and 2,4-dichloro phenyl substituents showed good antibacterial effects and compounds with 2,4-dichlorophenyl substituents showed inhibitory impact against *S. mutants* with MIC esteem 7.81 µg/mL, respectively. Zhang *et al.* [99] evaluated the anticancer effect and anti-proliferative action against human hepatocellular liver carcinoma (HepG2) for the a novel



R^1= F, Cl, Br, OMe, H
R^2= H, F, Cl, Br, Me, OMe, NO_2, Ph, OCH_2Ph
R^3= H, F, OMe, NO_2
R^4= H, Cl
R^5= H, Br, Me, OMe, Cl

Scheme-XIII: General synthesis of chalcone thiosemicarbazide derivatives

series of chalcone thiosemicarbazide analogs (**Scheme-XIII**). The *para*-substituted methyl group at ring B showed the most powerful inhibitory effect, which hindered the development of HepG2 cells with IC_{50} of 0.78 µM and inhibited the action of EGFR kinase with IC_{50} of 0.35 µM, respectively [99]. Đilovic *et al.* [100] also synthesized unique thiosemicarbazone derivatives (**Scheme-XIV**) and evaluated their anti-proliferative activity using the MTT test on five tumor cells like HeLa, Hep-2, MCF-7, MiapaCa-2, SW-620. It was observed that all compounds display potential antiproliferative activity against all cancerous cells, the IC_{50} values range between 0.2 ± 0.2 to 4.7 ± 0.3 µM.

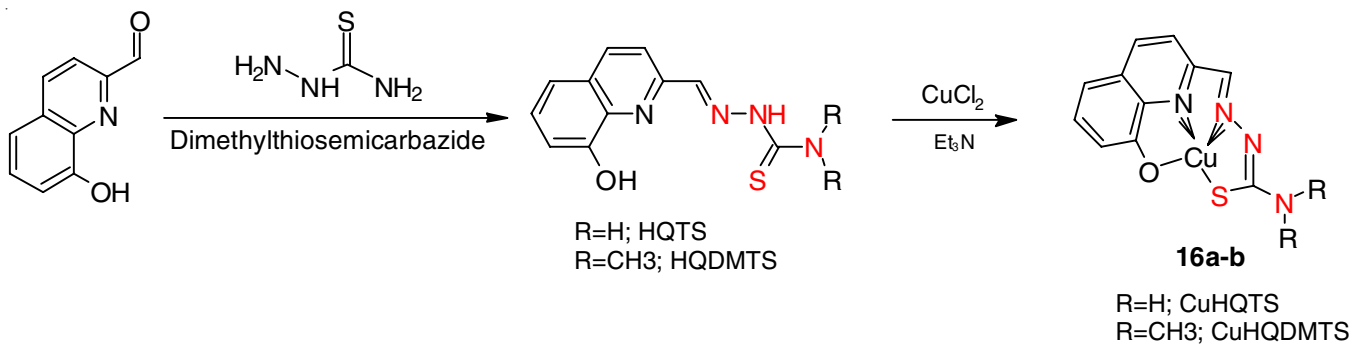


R_1= $N(CH_2CH_3)_2$, OCH_3, H, C_6H_{10}
R_2= H, Ph

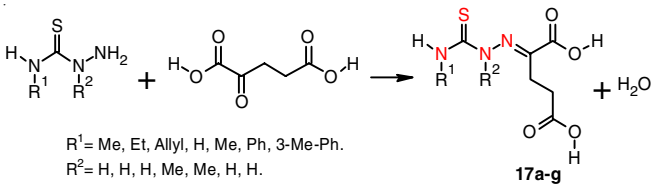
Scheme-XIV: General synthetic procedure of thiosemicarbazone derivatives

Zhang *et al.* [101] synthesized and evaluated the anticancer activity against cisplatin-resistant neuroblastoma cells of the two copper complexes *viz*. substituted 8-hydroxyquinoline-2-carboxaldehyde-4,4-dimethyl-3-thiosemicarbazide copper(II) (CuHQDMTS) and unsubstituted 8-hydroxyquinoline-2-carboxaldehyde thiosemicarbazide copper(II) complexes (CuHQTS). Moreover, the terminal amino-subbed complex, CuHQDMTS, indicated more potent anticancer activity than that of the unsubstituted complex, CuHQTS. In correlation, free HQDMTS and HQTS ligands demonstrated no noteworthy development restraint action on the SK-N-DZ cells. The IC_{50} values of CuHQDMTS and CuHQTS reported were 0.13 ± 0.03 µM to 0.64 ± 0.03 µM, separately. Baldini *et al.* [102] synthesized R-ketoglutaric acid thiosemicarbazone derivatives (**Scheme-XVI**) and reported that their copper(II) complexes were more potent inhibitors of cell growth of human leukemia cell line U937. The derivatives with copper complex showed the inhibition activity of 35% with the inhibition of cell proliferation at the various phase of the cell cycle like G1-53.5%, S-31.5% and G2-15.4%. Further, 48 h treatment on leukemic cell line (U937) demonstrated a delay in the cell cycle movement with a 28% decrease of the DNA amalgamation (stage S) and with an expansion of cell populace in the G1 and G2/M stages.

Antibacterial activity: Bisceglie *et al.* [103] synthesized cinnamaldehyde thiosemicarbazone derivatives (Fig. 3) and also reported their antibacterial activity against *E. coli* and *K. pneumonia* strains. Among all the derivatives, compound *bis*-(*E*)-cinnamaldehyde thiosemicarbazonate of Cu(II) (**18**) and *bis*-(*E*)-cinnamaldehyde thiosemicarbazonate of Zn(II) (**19**) showed minimum bactericidal concentration (MBC) in the range of 8-30 µM. Lapasam *et al.* [104] synthesized and evaluated *in vitro* antibacterial activity of a novel series of 4-phenyl-1-(pyridine-4yl)ethylidene thiosemicarbazide with



Scheme-XV: Synthesis of copper 8-hydroxyquinoline-2-carboxaldehyde thiosemicarbazide (CuHQTS) and copper 8-hydroxyquinoline-2-carboxaldehyde–4,4-dimethyl-3-thiosemicarbazide (CuHQDMTS)



Scheme-XVI: Synthesis of R-ketoglutaric acid thiosemicarbazone (H3ct) derivatives

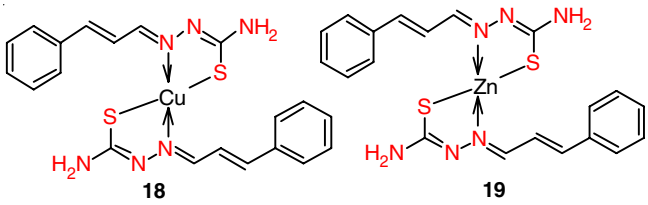
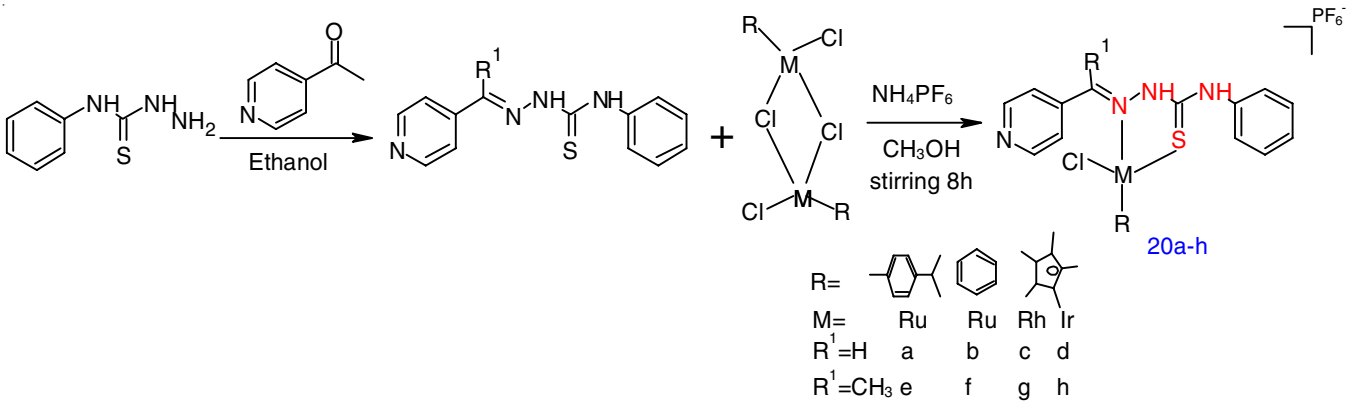


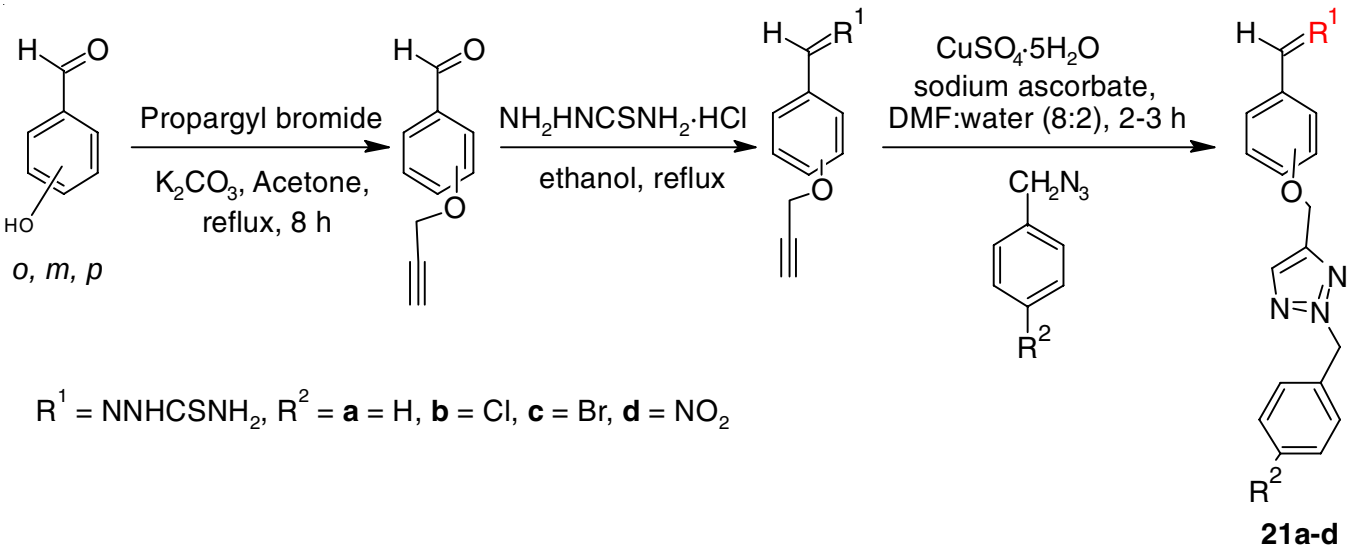
Fig. 3. Structure of metal complex of cinnamaldehyde thiosemicarbazone

complexes of rhodium, ruthenium and iridium metal ions (**Scheme-XVII**). The antibacterial activity was done by using the agar well diffusion method against Gram-negative bacteria *E. coli*, *K. pneumonia* and Gram-positive bacteria *S. aureus*. Antimicrobial action assessment uncovered that rhodium complexes have a huge antibacterial activity for all three strains, iridium and *p*-cymene ruthenium complexes have demonstrated directed action against the microorganisms yet none of the complexes outperform the action of their reference drugs. Tittal *et al.* [105] synthesized a novel hybrid molecules of 1,4-disubstituted-1,2,3-triazole with thiosemicarbazone derivatives (**Scheme-XVIII**) and also evaluated their *in vitro* antibacterial activity with a serial dilution method on Gram-negative bacteria *P. aeruginosa* and *E. coli* and Gram-positive bacteria like *B. subtilis*, *S. enteric* and *S. aureus*. All the tested compounds (**21a-d**) showed good results against the bacterial strains with a MIC value range between 0.0141 to 0.1366 µm/mL. Moreover, compound **21c** demonstrated the better effect for both *S. aureus* and *S. enteric* with MIC 0.0281 µmol/mL, compared with standard drug ciprofloxacin (MIC 0.0366 and 0.0732 µmol/mL) [105].

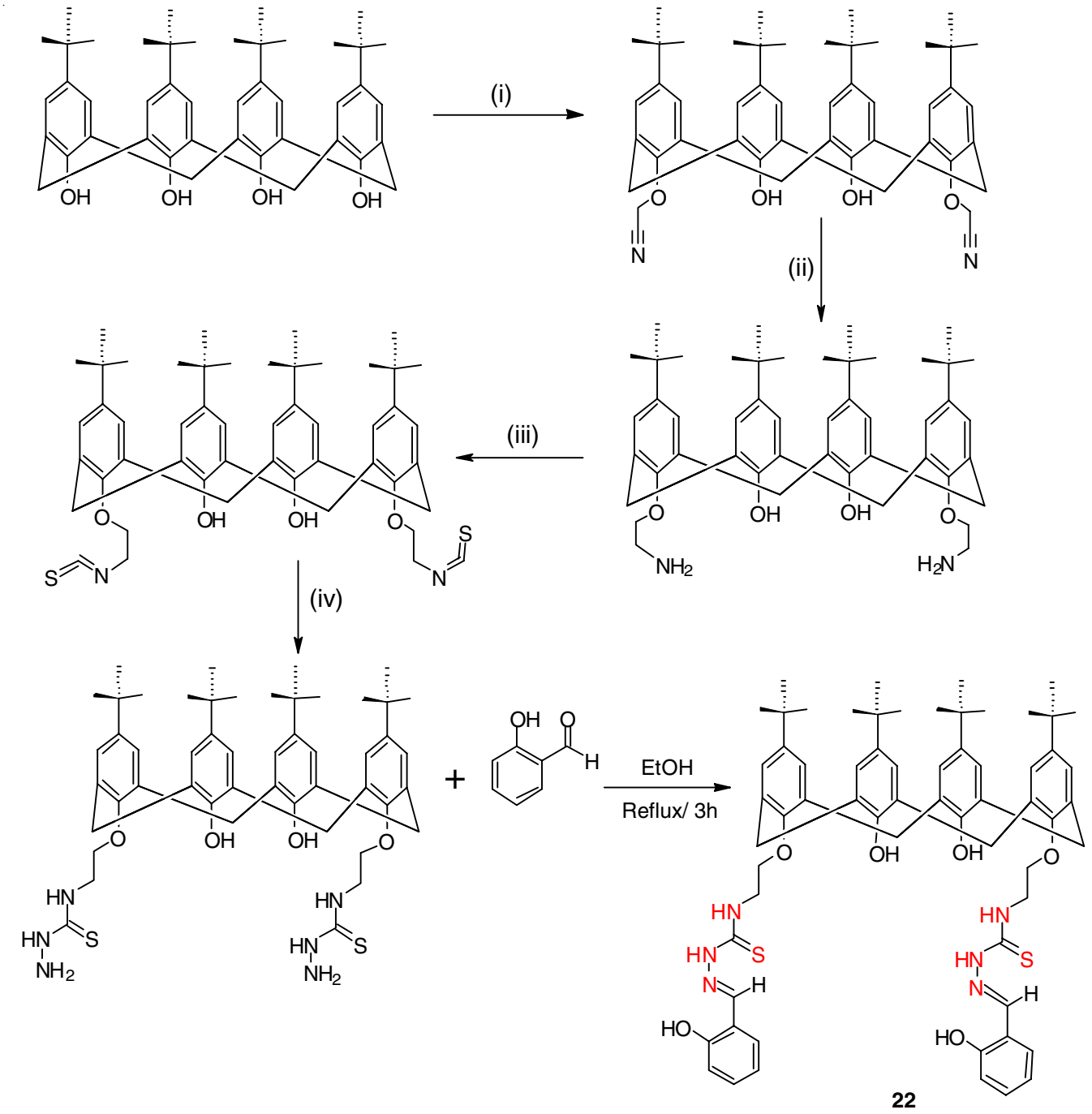
Bahojb-Noruzi *et al.* [106] synthesized a novel series of *t*-butylcalixarene based thiosemicarbazone derivatives (**Scheme-XIX**) and evaluated antifungal, antibacterial, anticancer activities. An impressive antibacterial potential effect (specifically against *E. coli*, MIC and MBC = 31.25 µg/mL) was observed for the compounds. The antifungal activity was evaluated against fungi strains like *C. albicans* and *C. glabrata*. Good antifungal activity was observed against yeast *C. albicans* for the ligand with values of MIC = 31.25 µg/mL and MBC =



Scheme-XVII: Synthesis of 4-phenyl-1-(pyridine-4-yl)ethylidene thiosemicarbazide complexes



Scheme-XVIII: Synthesis of triazole thiosemicarbazone hybrid molecules

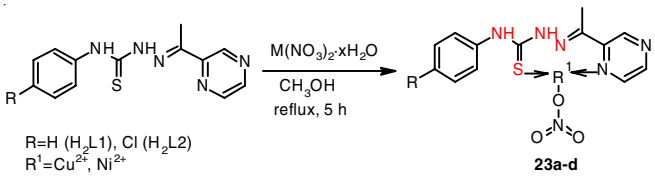


(i) Chloroacetonitrile, K_2CO_3, NaI, reflux, 7 h (ii) $LiAlH_4$ (0 °C), 4 h (iii) $CSCl_2$, $BaCO_3$, 24 h (iv) Hydrazine hydrate, room temperature, 3 h

Scheme-XIX: Synthesis of *tert*-butyl-calix arene-based thiosemicarbazone analogous

125 µg/mL and MIC value of 62.5 µg/mL for its Co(II) complex was higher when compared with the ligand. The *in vitro* cytotoxicity activity was investigated with the help of an MTT reduction assay against two different human bone cancer cell lines (Saos-2 and MG-63). All compounds show cytotoxicity against the malignant cells. For Saos-2 cell line, the promising anticancer action of ligand (IC_{50} < 25 µg/mL) was higher when compared with the value of its metal complexes. Polo-Ceron [107] synthesized and evaluated *in vitro* antibacterial activity of a new series of copper(II) and nickel(II) complexes with tridentate thiosemicarbazone ligands H_2L1 and H_2L2 synthesized from 2-acetyl pyrazine (**Scheme-XX**). The result showed that best outcomes were acquired for copper complexes with MIC estimations of 3.9 µg mL^{-1} for *S. aureus* and *B. cereus strains*.

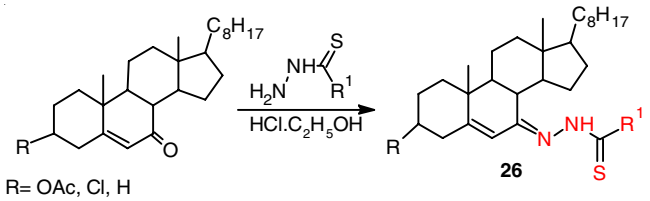
Patel *et al.* [108] reported for the synthesis and antibacterial activity of novel series of 2-(4-morpholino quinoline-7-yl)-*N*-substituted phenyl hydrazinyl carbothioamide analogs



Scheme-XX: Synthesis of a metal complex of tridentate thiosemicarbazone derivatives

(**Scheme-XXI**). All the synthesized compounds display a good antibacterial activity against all pathogen strains with MIC values in the range of 62.5-500 µg/mL. Among all the synthesized analogs, one containing methyl-substitution in its phenyl ring showed incredible action against Gram-negative strains, while analogs with electron-withdrawing substituents like chloro, fluoro and also the unsubstituted phenyl ring showed moderate action against Gram-negative strains. Kaplanciki *et al.* [109] synthesized and evaluated the antibacterial activity of a novel series of thiosemicarbazone analogs (**Scheme-XXII**). Among all the tested compounds, the 4-trifluoro, 4-fluoro and 4-nitro substituted derivatives showed the most effective inhibitory effect against *S. aureus* and *E. faecalis* pathogen with a MIC value of 100 µg/mL, respectively.

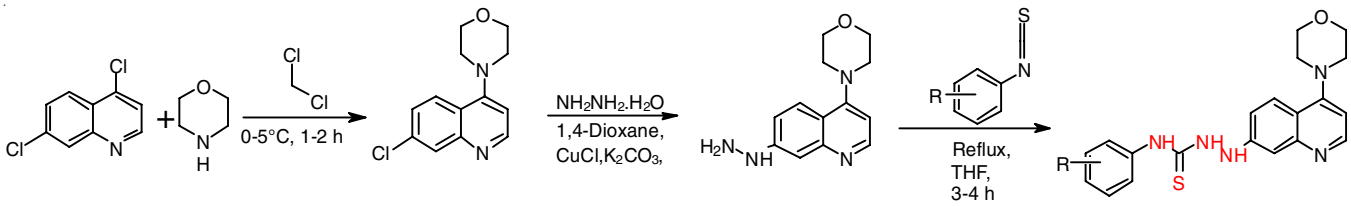
Khan *et al.* [110] synthesized thiosemicarbazone derivatives fused with steroidal rings (**Scheme-XXIII**) and also reported for their *in vitro* antibacterial activity. The synthesized compounds showed the minimum inhibitory concentration (MIC) value in the range of 32-256 µg mL^{-1}. The *in vitro* examination results also demonstrated that the compounds with chloro and acetoxy subordinates were found to be more effective among all the derivatives of thiosemicarbazone synthesized. Abou-Melha [111] evaluated the antibacterial and antifungal activity of synthesized metal complex of compound N^4-(7-chloroquinoline-4-ylamino)-N^1-(2-hydroxy-benzylidene)thiosemicarbazone (**Scheme-XXIV**). It was observed that the metal complexes of these compounds exhibited significant biological activity.



R= OAc, Cl, H

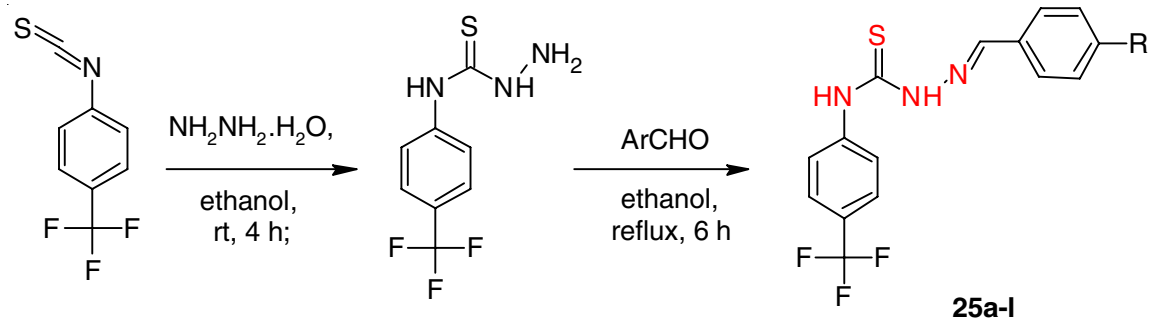
R^1= Cyclopentyl amine, cyclohexyl amine, cyclooctyl amine

Scheme-XXIII: Synthesis of steroidal rings contains thiosemicarbazone derivatives



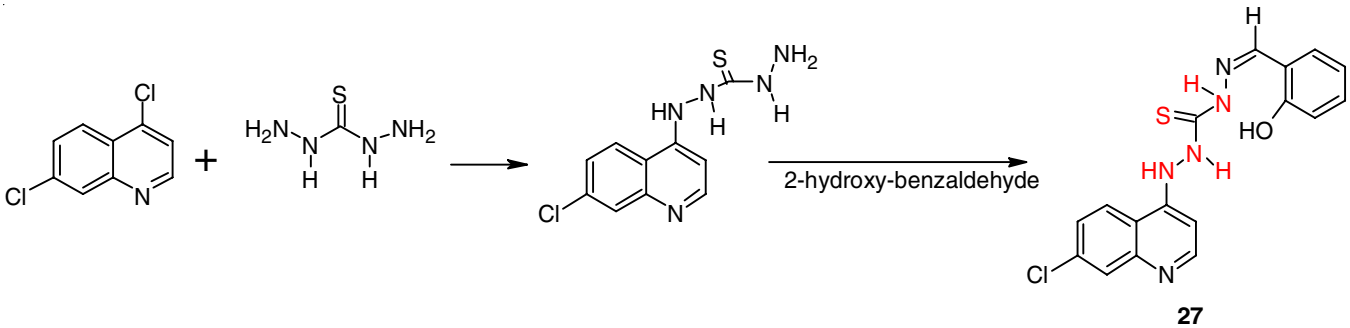
R= H, 2-Cl, 3-Cl, 4-Cl, 2-CH_3, 3-CH_3, 4-CH_3, 2-F, 3-F, 4-F

Scheme-XXI: Synthesis of 4,7-dichloroquinoline hybrid thiosemicarbazide derivatives

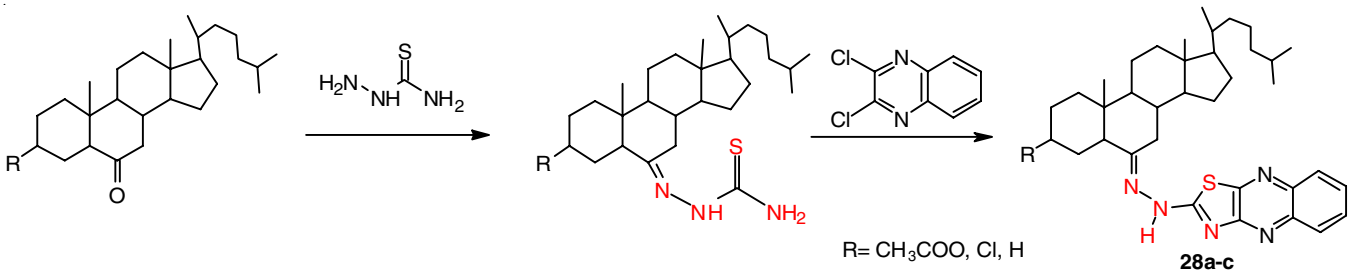


R= H, F, Cl, Br, NO_2, OH, OCH_3, CH_3, $CH(CH_3)_2$, $N(CH_3)_2$, CF_3, CN

Scheme-XXII: Synthesis of the thiosemicarbazone derivatives



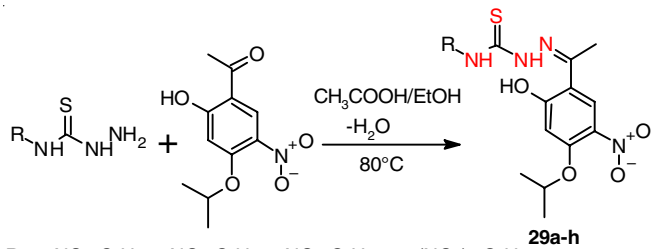
Scheme-XXIV: Synthesis of N^4-(7-chloroquinoline-4-ylamino)-N^1-(2-hydroxy-benzylidene) thiosemicarbazone (HL)



Scheme-XXV: Synthesis of steroidal thiazolo quinoxaline derivatives

Saleem *et al.* [112] synthesized a novel series of steroidal thiazolo quinoxaline derivatives (**Scheme-XXV**). All these synthetic derivatives were screened by *in vitro* method for antibacterial activity against *E. coli* with the help of the disk diffusion method. Compound having 3β-chloro substituent showed antibacterial effects having a zone of inhibition of 1.6 mm. Parekh *et al.* [113] synthesized a series of 1-[(2-hydroxy-4-isopropoxy-5-nitrophenyl)-ethanone]-4-(aryl)-3-thiosemicarbazones derivatives (**Scheme-XXVI**). Compound having fluorine substitution showed the maximum antibacterial effects against all the species of pathogen, the observed zone of inhibition for the same was found to be 13 mm. Agarwal *et al.* [114] synthesized analogs of Schiff bases having 4-aminoantipyrine and different aromatic aldehyde with the help of condensation reaction with thiosemicarbazide and further evaluated for the antibacterial and antifungal activities. Copper(II) complexes of 4[*N*-(benzylidene)amino]antipyrine thiosemicarbazone (**30**) and 4[*N*-(4-methoxybenzalidene)aminoantipyrine thiosemicarbazone (**31**) (Fig. 4) were also evaluated for antibacterial activity against Gram-positive bacteria *B subtilis* and *S aureus* and Gram-negative bacteria *E. coli* and *S. typhi*. Copper(II) complexes of 4[*N*-(4-methoxybenzalidene)aminoantipyrine thiosemicarbazone (**31**) showed the best antibacterial activity than the copper(II) complex of 4[*N*-(benzylidene)amino]antipyrine thiosemicarbazone (**30**) . All derivatives showed almost similar antifungal activity but less than salicylic acid, a standard drug. El-Dissouky & Jeragh [115] reported the antibacterial activity of 1-acetylferrocene thiosemicarbazone (**32**) and 1,10-diacetylferrocene dithiosemicarbazone (**33**) (Fig. 5). It was found that the inhibition effects of compound **33** were higher than the inhibition effect of compound **32** both in bacterial as well as in fungal.

Antiurease activity: Shehzad *et al.* [116] reported the synthesis and urease inhibitory activity of a novel series of



R= 2-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2,4-$(NO_2)_2$-C_6H_3, 4-$CH(CH_3)_2$-C_6H_4, 2,5-$(Cl)_2$-C_6H_3, 4-F-C_6H_4, -$C_{10}H_7$(a)

Scheme-XXVI: Synthesis of 1-[(2-hydroxy-4-isopropoxy-5-nitrophrnyl)-ethanone]-4-(aryl)-3-thiosemicarbazones derivatives

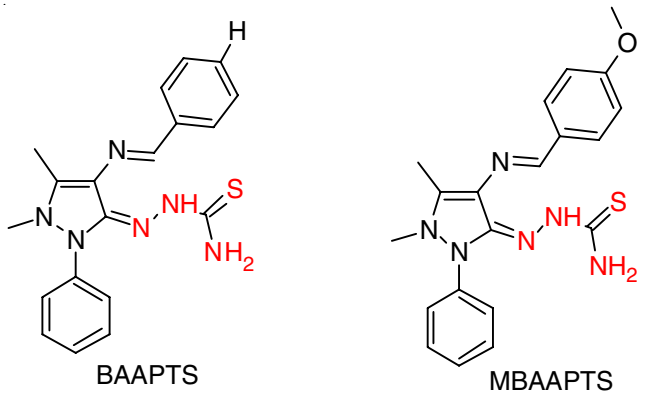


Fig. 4. Structures of BAAPTS and MBAAPTS compounds

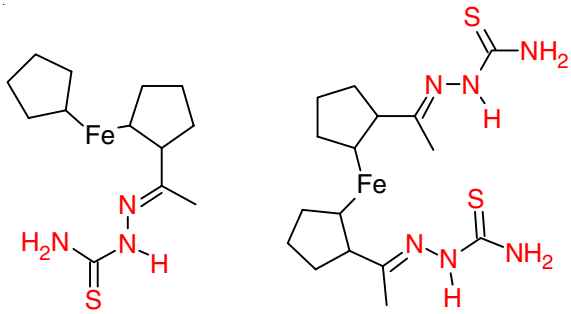
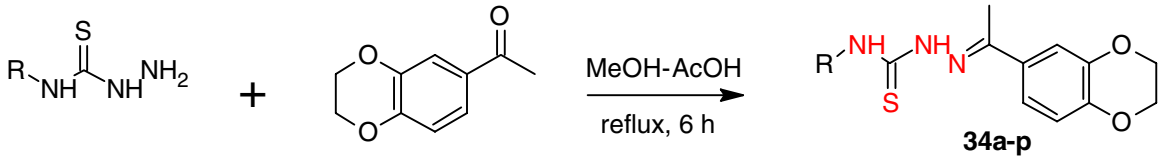


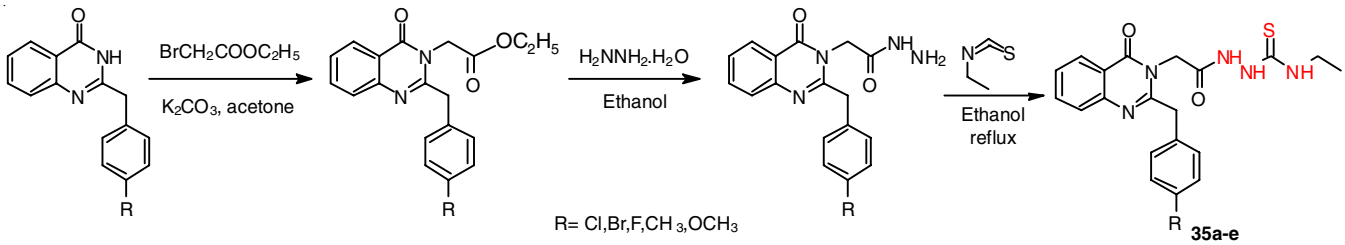
Fig. 5. Structures of molecules HL^1 and H^2L^2

1,4-benzodioxane-based thiosemicarbazone derivatives (**Scheme-XXVII**). It was reported that the urease enzyme gives a reasonable climate to *Helicobacter pylori* at low pH in the stomach, a causative specialist of peptic and ulcer gastric that may prompt disease [117,118]. The tested molecules showed maximum intense inhibitory potential with IC_{50} esteems extending between 3.65 ± 2.64 to 31.9 ± 1.094 µM, when compared to the value of reference compound, thiourea with the value of IC_{50} as 20.8 ± 0.75 µM. Mentese *et al.* [119] synthesized a novel series of thiosemicarbazide containing quinazolinone analogs (**Scheme-XXVIII**). The tested compounds showed good potential inhibition effect against urease enzyme, the IC_{50} value ranged in between 6.00 ± 0.25 to 6.42 ± 0.23 µg/mL, values were also compared to standard reference thiourea (IC_{50} = 15.06 ± 0.68 µg/mL) and acetohydroxamic acid (IC_{50} = 21.03 ± 0.94 µg/mL).



R= C_6H_5, 3-ClC_6H_4, 3-BrC_6H_4, 3-O$CH_3C_6H_4$, 2-$CH_3C_6H_4$, $C_{10}H_7$, 4-FC_6H_4, 4-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, C_6H_{11}, $C_6H_5CH_2CH_2$, 3,5-$(CF_3)_2C_6H_3$, H, $C_6H_5CH_2$, 2,6-$(CH_3)_2C_6H_3$

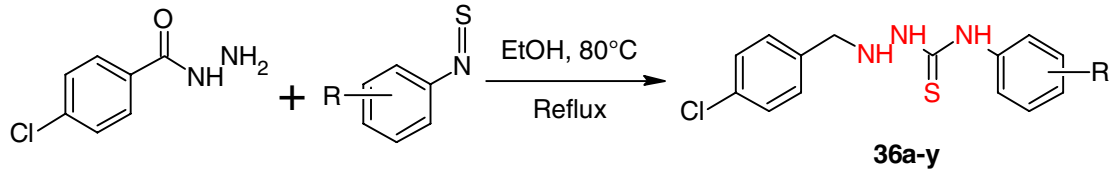
Scheme-XXVII: Synthesis of 1,4-benzodioxane-based thiosemicarbazones



Scheme-XXVIII: Synthesis of quinazolinone hybrid thiosemicarbazide derivatives

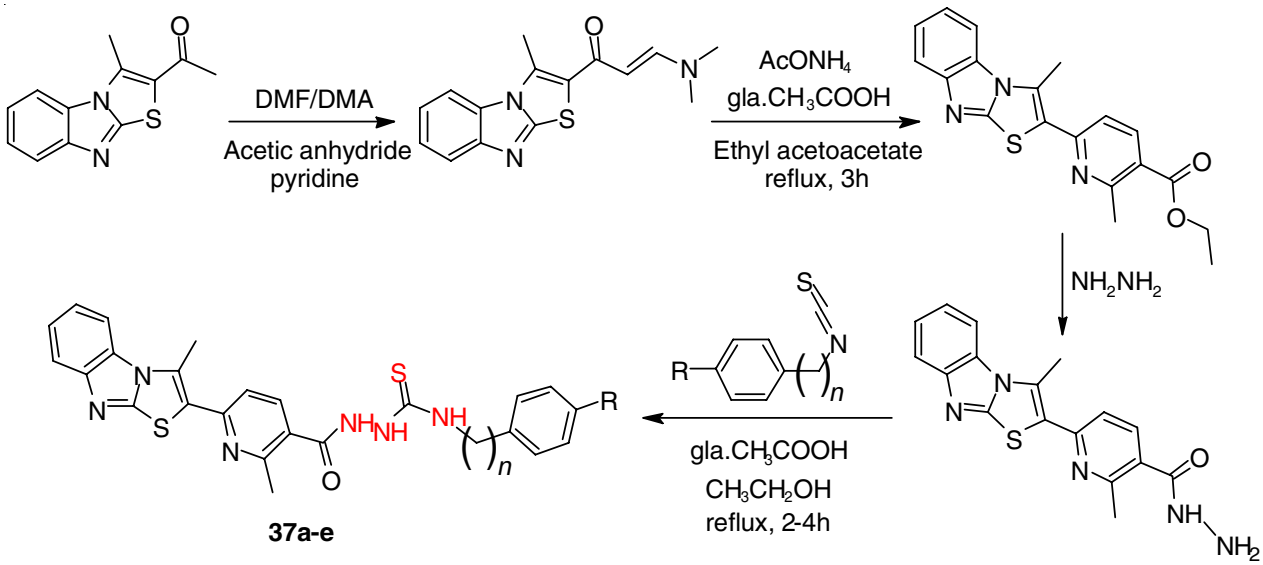
Ali *et al.* [120] synthesized and evaluated the *in vitro* urease inhibitory activity of a novel series of 1-[(4′-chlorophenyl)-carbonyl-4-(aryl) thiosemicarbazide analogs (**Scheme-XXIX**). The majority of the synthesized compounds showed incredible inhibitory effects in the scope of IC_{50} 0.32 ± 0.01 µM to 25.13 ± 0.13 µM when contrasted with the standard thiourea (IC_{50} 21.25 ± 0.13 µM). Out of all analogs, 2,4-dimethoxyphenyl substituted compounds showed remarkable strength with an IC_{50} value of 0.32 ± 0.01 µM.

Anti-inflammatory activity: El-Kerdawy *et al.* [121] synthesized thiosemicarbazide derivatives fused with benzimidazole and thiazole ring (**Scheme-XXX**). Synthesized comp-



R= 2-Br, 3-Br, 2-Cl, 3-Cl, 4-Cl, 2,3-diCl, 2,5-diCl, 3,4-diCl, 2-CH_3-5-Cl, 2-F, 3-F, 2,4-diCl, 2,6-diCl, 2-CF_3, 3-CF_3, 2-CH_3-5-F, 4-NO_2, 2,6-diMe, 3,5-diMe, 2-OMe, 3-OMe, 4-OMe, 4-OEt, 2,4diOMe.

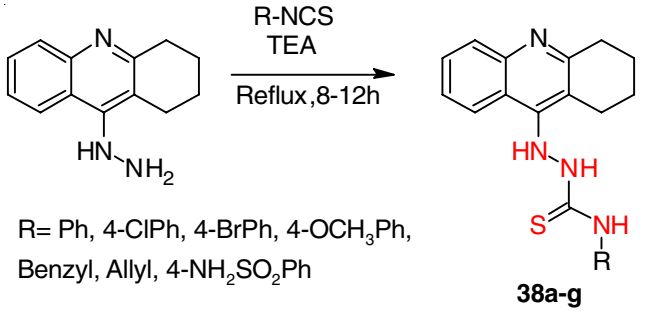
Scheme-XXIX: Synthesis of 1-[(4-chlorophenyl)carbonyl-4-(aryl)thiosemicarbazide derivatives



R = H, Cl, OCH_3, C_6H_5O, H
n = 0,1

Scheme-XXX: Synthesis of benzimidazothiazole fusion thiosemicabazide analogs

ounds were also screened for anti-inflammatory properties by the *in vitro* method through the cyclooxygenase enzyme inhibition test, or *in vivo* through carrageenan paw edema procedure. The result observed was % hindrance of 72.19 %, 72.07% for the COX-1 enzyme and value of 87.46%, 87.38% for COX-2, individually. Alfadly *et al.* [122] synthesized a novel series of tacrine hybrid thiosemicarbazide derivatives (**Scheme-XXXI**) and evaluated their anticholinesterase and anti-inflammatory activities. Among the synthesized ligands, a compound having benzyl substituent was found to have the value of IC_{50} as 0.218 ± 0.035 µg/mL as with higher inhibitory effect than the reference inhibitors tacrine (for hBChE hindrance), celecoxib (for COX2 restraint) and both NDGA and Zileuton (for 15-LOX restraint). Moreover, benzyl derivatives indicated a sub-micromolar blended sort inhibitory effect against human acetylcholinesterase (hAChE) also.



Scheme-XXXI: Synthesis of tacrine hybrid thiosemicarbazide derivatives

Anti-HIV activity: Patel *et al.* [123] synthesized a novel series of quinazolinyl-triazinyl semicarbazides and quinazolinyl-triazinyl thiosemicarbazides derivatives (**Scheme-XXXII**). 4-(4-Chloro-6-hydrazinyl-*s*-triazin-2-yl)morpholine was reacted with *N*-(2-aminoethyl)-6,8-dibromoquinazolin-4-amine in the presence of dry acetonitrile for 12-20 h, which further were reacted with isothiocyanates in the presence of ethanol for 4-6 h for obtaining the desired products. All these synthetic compounds were then evaluated for anti-HIV activity against HIV-1 (lll_B) and HIV-2 (ROD) cell cultures, for which obtained IC_{50} values ranges between 49.13 to 125 µg/mL. It was observed that compounds having 4-fluoro phenyl substituents displayed utmost activity with IC_{50} of 49.13 µg/mL.

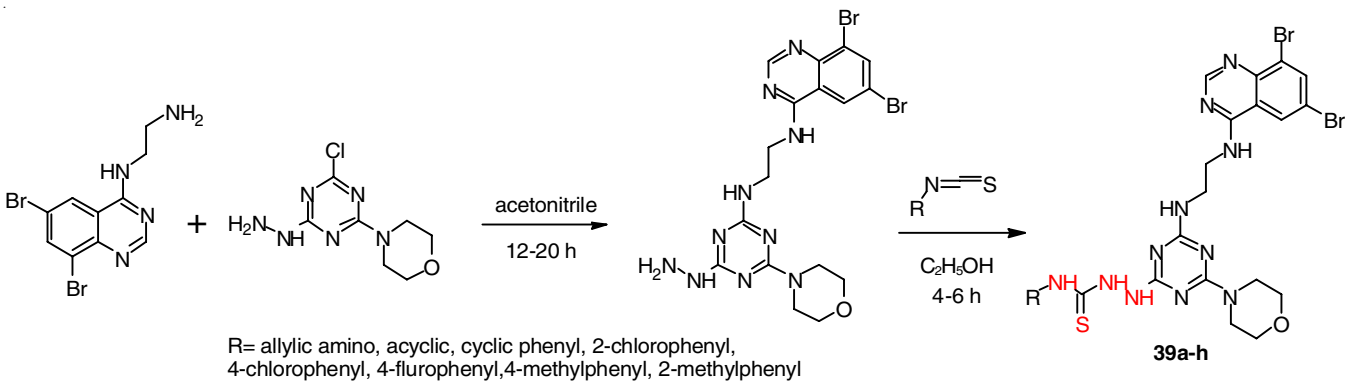
Antituberculosis activity: Trotsko *et al.* [124] synthesized a novel series of thiazolidine-2,4-dione (TZD) based thiosemicarbazone analogs (**Scheme-XXXIII**). All the synthesized compounds were evaluated for antimycobacterial activity against *Mycobacterium tuberculosis* with the help of the broth microdilution process. 4-Aryl substituted derivative showed moderate effect when compared to 4-unsubstituted thiosemicarbazone substituents with TZD. All compounds showed inhibitory effects with the concentration range of 0.031-64 µg/mL. The 4-unsubstituted thiosemicarbazone substituents with TZD showed the maximum antimycobacterial effects with MIC of 0.031-0.125 µg/mL.

Antifungal activity: Hicks *et al.* [125] synthesized a novel series of thiosemicarbazones containing boronic acids and cyclic 2,3,1-benzodiazaborines (**Schemes XXXIV** and **XXV**). The synthetic compounds were further evaluated for antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans* and *Saccharomyces cerevisiae.* Among all of these synthetic derivatives, compounds **41a**, **41b** and non-cyclized imine derivatives **42d** displayed an effective antifungal activity.

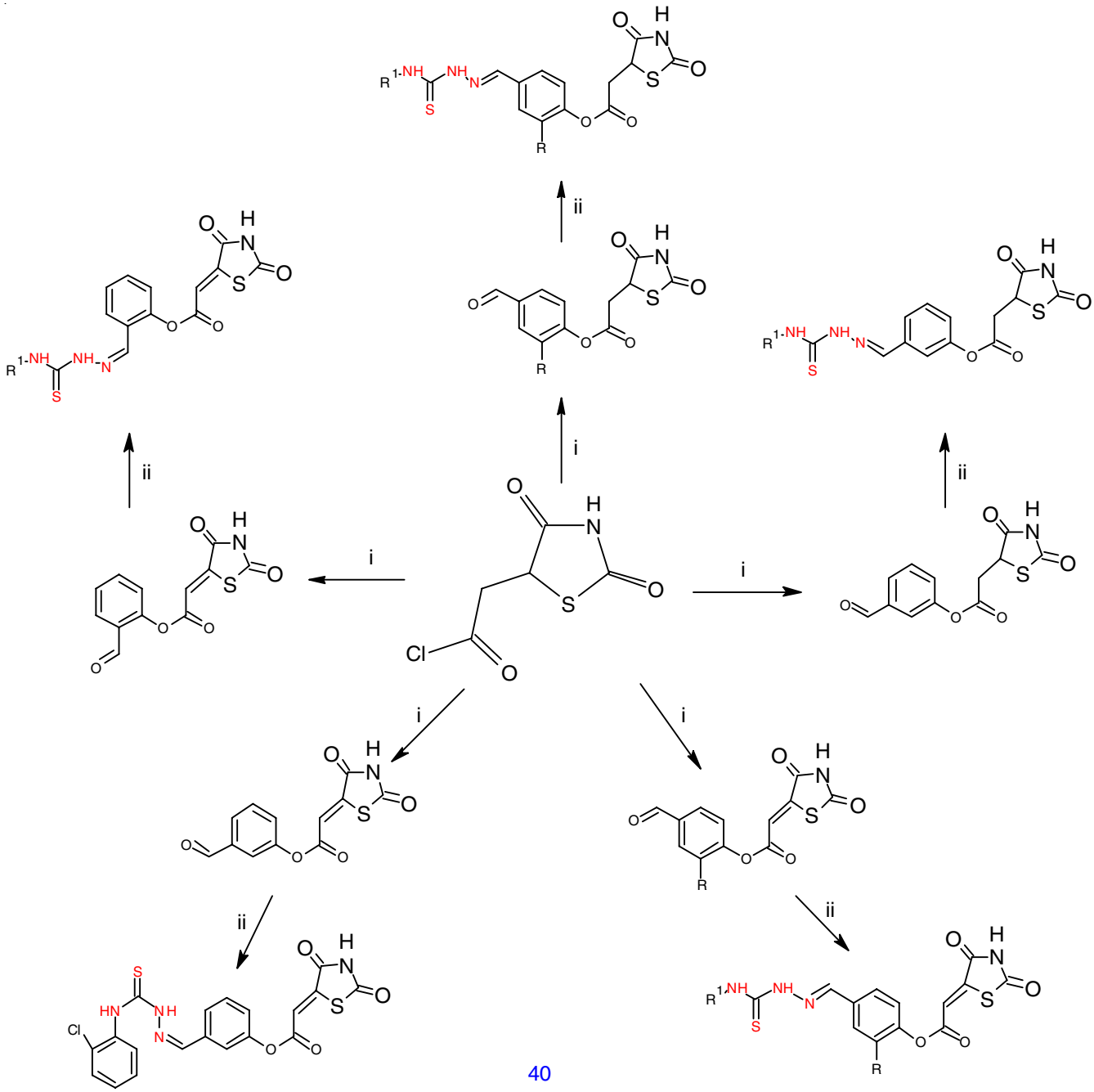
Antiplatelet activity: Al-Saad *et al.* [126] synthesized a novel series of thiosemicarbazide derivatives of captopril (**Scheme-XXXVI**). These ligands were obtained by the reaction of hydrazide of captopril with different substitutions of phenyl isothiocyanate. The captopril shows a significant role in angiotensin converting enzyme inhibitors (ACE-I) and these synthetic derivatives were screened for antiplatelet effect utilizing multiple analyzers and adenosine diphosphate (ADP), arachidonic corrosive (AA) and collagen, as platelet total inducers. Among all of these screened compounds, 3-ethylthio and 3-mercapto substitutes were the most active inhibitors of platelet collection incited by arachidonic corrosive, with percent hindrances value of 97.14 ± 1.0 and 95.71 ± 2.02 and IC_{50} values as 2.7 and 1.21 µg/mL.

Anthelmintic activity: Dziduch *et al.* [127] synthesized a novel series of 1-[(1-methyl-4-nitroimidazol-2-yl)carbonyl]-4-substituted thiosemicarbazides derivatives (**Scheme-XXXVII**) and also evaluated for *in vitro* anthelmintic activity against *Rhabditis* sp. Most of the compounds showed the anthelmintic activity, but derivatives with phenyl, *ortho*-chlorophenyl and *meta*-chlorophenyl substituents were more potent than the reference drug, albendazole.

Antimalarial activity: Matsa *et al.* [128] synthesized different types of thiosemicarbazone derivatives (**Scheme-XXXVIII**) and evaluated for *in vitro* antimalarial activity



Scheme-XXXII: Synthesis of quinazoline triazinyl thiosemicarbazides analogs



40

R= H, OCH_3, Cl, Br

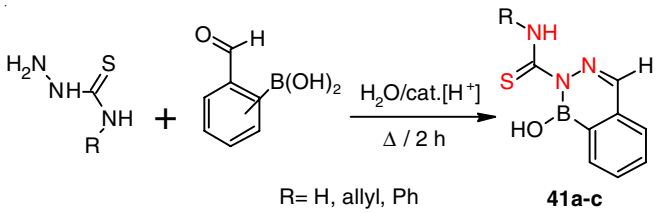
R^1= H, C_6H_5, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2,4-diCl-C_6H_3, 2,6-diCl-C_6H_3, C_6H_5, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2,4-diCl-C_6H_3, 2,6-diCl-C_6H_3, H, H, C_6H_5, 4-CH_3-C_6H_4, H, C_6H_5, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2,4-diCl-C_6H_3, H, C_6H_5, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 3-Cl-C_6H_4, H, H, 2-Cl-C_6H_4, 3-Cl-C_6H_4

(i) corresponding hydroxybenzaldehyde, pyridine, 1,4-dioxane, rt, after 2 h acidified of solution of hydrochloric acid; (ii) thiosemicarbazide or corresponding 4-arylthiosemicarbazide, anhydrous ethanol, reflux.

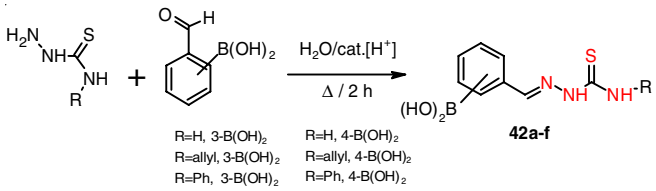
Scheme-XXXIII: Synthesis pathway of TZD-based thiosemicarbazone derivatives

against *Plasmodium falciparum*. The ligands containing 4-fluorophenyl, 3-bromophenyl and 3,4,5-trimethoxybenzylidene substituted demonstrated prominent antimalarial effects with EC_{50} estimations of 13.54, 15.83 and 14.52 μM, respectively.

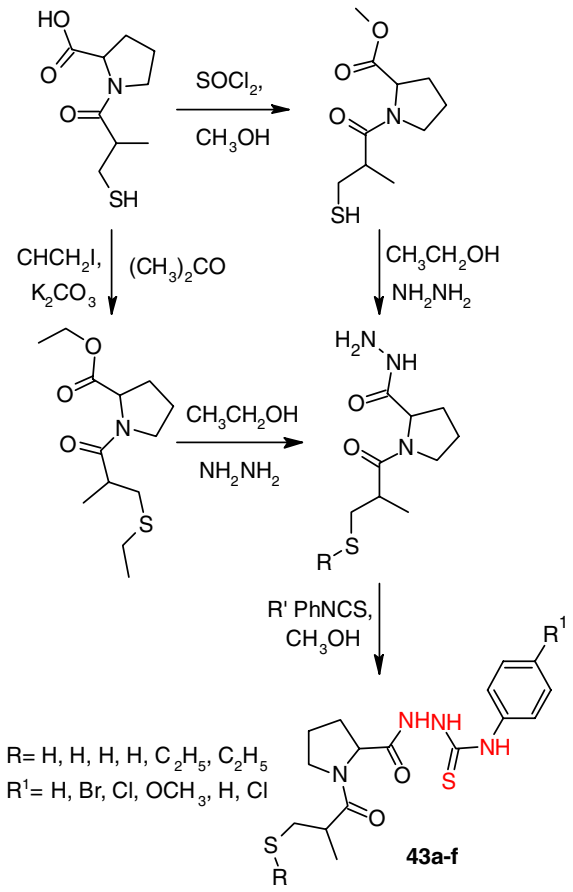
α-Glucosidase activity: Rahim *et al.* [129,130] synthesized and evaluated the α-glucosidase activity of a novel series of isatin-based thiosemicarbazide analogs (**Scheme-XXXIX**). All the synthesized compounds showed more potential α-glucosidase inhibitory effects the IC_{50} value range between 1.20 ±



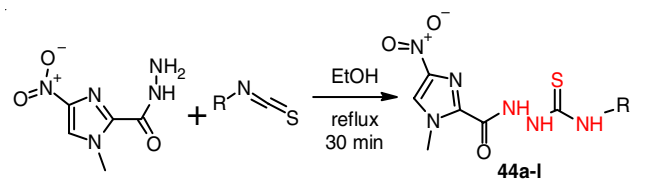
Scheme-XXXIV: Synthesis of thiosemicarbazones containing boronic acids and cyclic 2,3,1-benzodiazaborines derivatives



Scheme-XXXV: Synthesis of thiosemicarbazones containing boronic acids derivatives

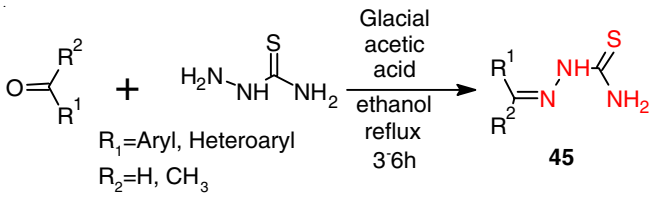


Scheme-XXXVI: Synthesis of captopril thiosemicarbazide derivatives

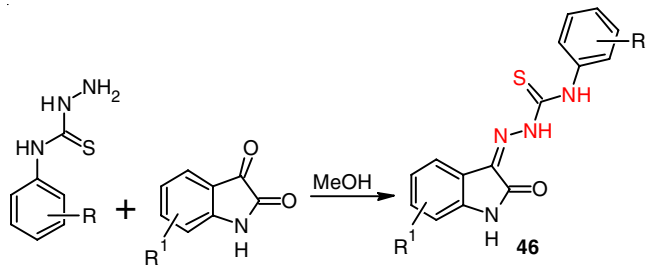


R= phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluoropheny, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylpheny

Scheme-XXXVII: Synthesis of 1-[(1-methyl-4-nitroimidazol-2-yl)carbonyl]-4-substituted-thiosemicarbazides derivatives



Scheme-XXXVIII: Synthesis of thiosemicarbazone derivatives



R= 2-Br, *p*-CH_3, 3,5-Cl, 2,3-Cl, *o*-CH_3, 3,4-Cl, *o*-Br
R^1= 5-Cl, 5-NO_2, 6-NO_2

Scheme-XXXIX: Synthesis of isatin-based thiosemicarbazide derivatives

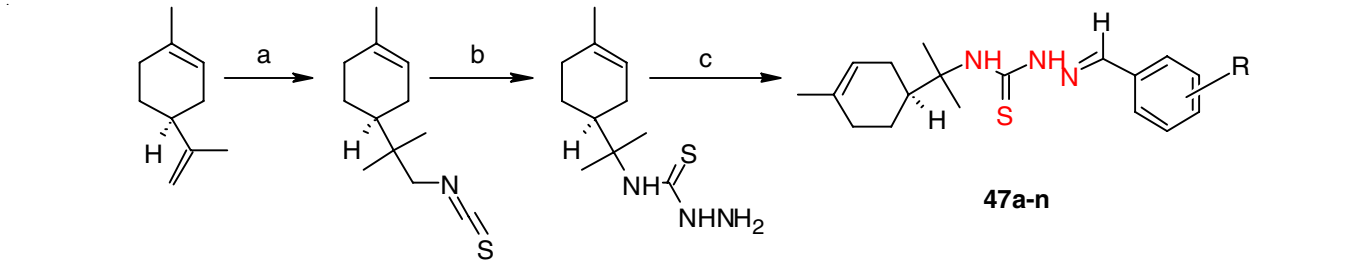
0.10 to 35.60 ± 0.80 µM, but among all of these the compound *N*-(2,3-dichlorophenyl)-2-(5-nitro-2-oxoindolin-3-ylidene)-hydrazine-1-carbothioamide displayed a significant role with IC_{50} = 1.20 ± 0.10 µM.

Antileishmanial activity: Almeida-Batista *et al.* [131] synthesized a novel series of *S*-(-) and *R*-(+) limonene-based benzaldehyde thiosemicarbazones derivatives (**Scheme-XL**). And these were further evaluated for antileishmanial activity against *in vitro* cultures of the promastigote forms of *L. amazonensis*. The compound 4-nitro derivative showed excellent antiprotozoal activity with IC_{50} of 2.4 µM.

Anti-trypanosoma cruzi activity: Leite *et al.* [132] synthesized a series of 4-thiazolidone-2-arylthiosemicarbazone derivatives (**Scheme-XLI**) and evaluated the *in vitro* anti-trypanosoma cruzi activity against epimastigote (Y and Colombian strain). Some derivatives can exhibit the anti-trypanosoma cruzi activity. Among all of these derivatives *N*-(4-oxo-5-methyl-2-thiazoline-2yl)-*N*-*p*-chlorophenylthioethylidenehydrazone (IC_{50} = 31.9) shows a potential effect against epimastigote *T. cruzi*.

Antiamoebic activity: Abid & Azam *et al.* [133] synthesized 1-N-substituted cyclized pyrazoline derivatives of thiosemicarbazones (**Scheme-XLII**). These were further evaluated for the antiamoebic activity against HM1:1MSS strain of *Entamoeba histolytica* with help of the microdilution method. The 3-chloro and 3-bromo substituents on the phenyl ring at position 3 of the pyrazoline ring were reported to show more potential effects of anti-amoebic activity than unsubstituted phenyl ring. The effective anti-amoebic activity was shown with IC_{50} = 0.6 µM when compared to IC_{50} = 1.8 µM of metronidazole.

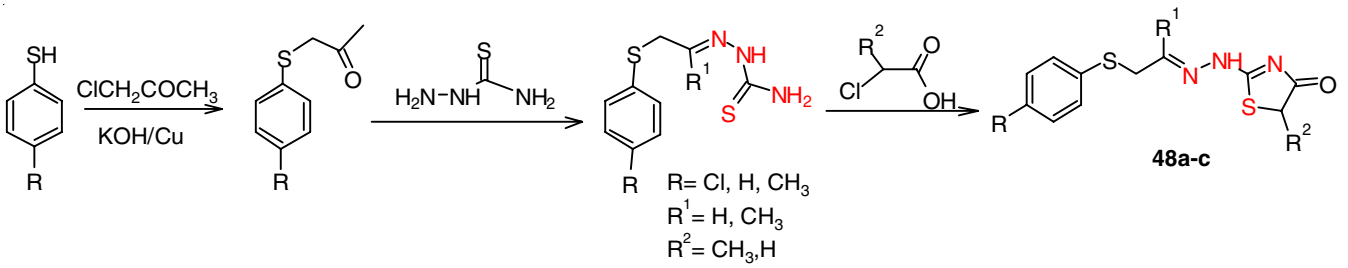
Antityrosinase activity: Chaves *et al.* [134] synthesized and evaluated tyrosinase inhibitory activity of a novel series of β-enamino thiosemicarbazide derivatives (**Scheme-XLIII**). Both compounds *i.e.* (Z)-2-(3-(phenethylamino)-but-2-enoyl)-hydrazine carbothioamide (ETS1) and (Z)-*N*-methyl-2-(3-



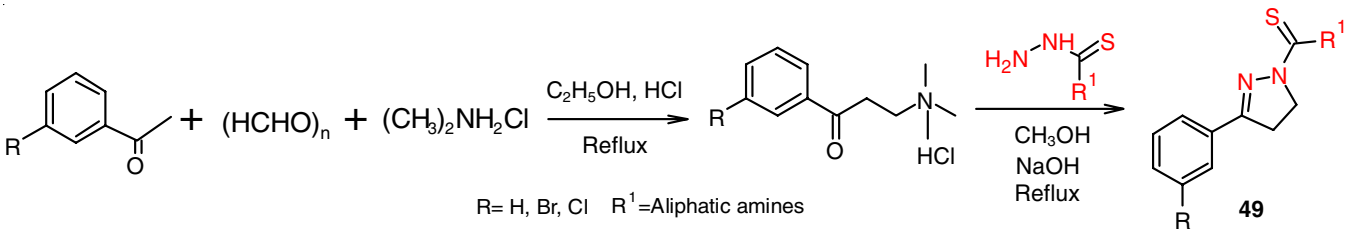
(a) $KHSO_4$, KSCN, $CHCl_3$, rt, 24 h; **(b)** $NH_2NH_2{\cdot}2HCl/NaHCO_3/H_2O$, EtOH, reflux, 3 h; **(c)** RCHO, SiO_2/H_2SO_4 5%, rt

R= H, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl, 4-Cl, 4-CH_3, 4-OCH_3, 4-$N(CH_3)_2$, 2-OH, 4-OH, 3-OCH_3, 4-OH

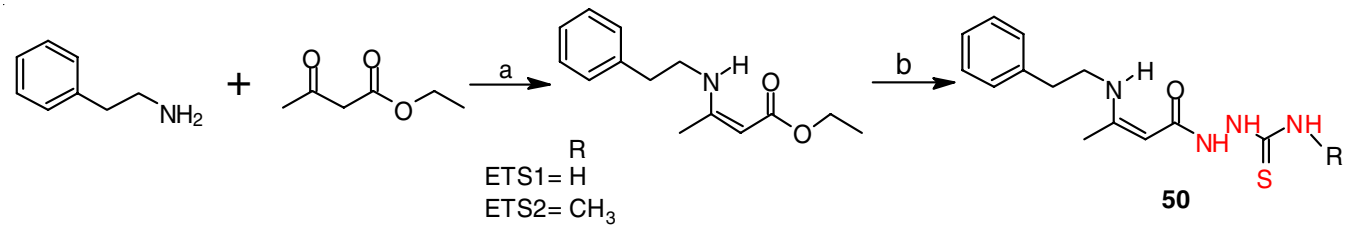
Scheme-XL: Synthesis of limonene-based benzaldehyde thiosemicarbazones derivatives



Scheme-XLI: Synthesis of 4-thiazolidone-2-arylthiosemicarbazone derivatives



Scheme-XLII: Synthesis of cyclized pyrazoline analogs of thiosemicarbazones



(a) ethanol, *p*-toluenesulfonic acid, rt., 18 h; (b) ethanol, 60 °C, thiosemicarbazide derivatives, 4–5 h

Scheme-XLIII: General synthesis of β-enamino thiosemicarbazide derivatives ETS1 and ETS2

(phenethylamino)-but-2-enoyl)hydrazine carbothioamide (ETS2) were tested for their activity against tyrosinase enzyme. Only one compound (ETS1) was found to have an excellent inhibition activity percentage (89%) of the tyrosinase enzyme, with an IC_{50} value of 49 μM.

Conclusion

The literature summarized in this review paper concludes that thiosemicarbazide derivatives with a variety of applications can be synthesized by a large number of novel synthetic schemes. A review on thiosemicarbazide has described that the modifications in the structure of ligand moieties can bring change and can also enhance particular activity possessed by the nucleus. The latest advances in the pharmaceutical domain have given a lot of consideration to the development of thiosemicarbazide ligands. Different synthetic schemes identified with a large number of biological activities may result in path-breaking exploration of potential derivatives of thiosemicarbazide with other new probable targets.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. J.S. Casas, M.S. Garcia-Tasende and J. Sordo, *Coord. Chem. Rev.*, **209**, 197 (2000); https://doi.org/10.1016/S0010-8545(00)00363-5
2. M.A. Metwally, S. Bondock, H. El-Azap and E.-E.M. Kandeel, *J. Sulfur Chem.*, **32**, 489 (2011); https://doi.org/10.1080/17415993.2011.601869
3. M.A. Metwally, M.E. Khalifa and M. Koketsu, *Am. J. Chem.*, **2**, 38 (2012); https://doi.org/10.5923/j.chemistry.20120202.09
4. N.P. Prajapati and H.D. Patel, *Synth. Commun.*, **49**, 2767 (2019); https://doi.org/10.1080/00397911.2019.1649432
5. M.A. Metwally, S. Bondock, H. El-Azap and E.-E.M. Kandeel, *J. Sulfur Chem.*, **32**, 489 (2011); https://doi.org/10.1080/17415993.2011.601869
6. S.A. Anand, K. George, N.S. Thomas and S. Kabilan, *Phosphorus Sulfur Silicon Rel. Elem.*, **195**, 821 (2020); https://doi.org/10.1080/10426507.2020.1757672
7. O.K. Nehar, R. Mahboub, S. Louhibi, T. Roisnel and M. Aissaouid, *J. Mol. Struct.*, **1204**, 127566 (2020); https://doi.org/10.1016/j.molstruc.2019.127566
8. A.A. Aly, A.A. Hassan and E.-S.S.M. Abd El-latief, *J. Heterocycl. Chem.*, **55**, 2196 (2018); https://doi.org/10.1002/jhet.3295
9. M.A. Bhat, A.A. Khan, H.A. Ghabbour, C.K. Quah and H.-K. Fun, *Trop. J. Pharm. Res.*, **15**, 1751 (2016); https://doi.org/10.4314/tjpr.v15i8.22
10. G.D. Andreetti, P. Domiano, G.F. Gasparri, M. Nardelli and P. Sgarabotto, *Acta Crystallogr. B*, **26**, 1005 (1970); https://doi.org/10.1107/S0567740870003497
11. T.S. Lobana, R. Sharma, G. Bawa and S. Khanna, *Coord. Chem. Rev.*, **253**, 977 (2009); https://doi.org/10.1016/j.ccr.2008.07.004
12. S. Padhye and G.B. Kauffman, *Coord. Chem. Rev.*, **63**, 127 (1985); https://doi.org/10.1016/0010-8545(85)80022-9
13. B. Prathima, Y.S. Rao, S.A. Reddy, Y.P. Reddy and A. Varada Reddy, *Spectrochim. Acta A Molecul. Biomol. Spectrosc.*, **77**, 248 (2010); https://doi.org/10.1016/j.saa.2010.05.016
14. T. Plech, M. Wujec, A. Siwek, U. Kosikowska and A. Malm, *Eur. J. Med. Chem.*, **46**, 241 (2011); https://doi.org/10.1016/j.ejmech.2010.11.010
15. V.K. Sharma and S. Srivastava, *J. Coord. Chem.*, **61**, 178 (2008); https://doi.org/10.1080/00958970701318426
16. N.D. Thanh, N.T. Giang, T.H. Quyen, D.T. Huong and V.N. Toan, *Eur. J. Med. Chem.*, **123**, 532 (2016); https://doi.org/10.1016/j.ejmech.2016.07.074
17. K.S. Abou-Melha, *J. Coord. Chem.*, **61**, 2053 (2008); https://doi.org/10.1080/00958970701862167
18. N. Trotsko, U. Kosikowska, A. Paneth, T. Plech, A. Malm and M. Wujec, *Molecules*, **23**, 1023 (2018); https://doi.org/10.3390/molecules23051023
19. A. Paneth, P. Staczek, T. Plech, A. Strzelczyk, K. Dzitko, M. Wujec, E. Kucœmierz, U. Kosikowska, A. Grzegorczyk and P. Paneth, *J. Enzyme Inhib. Med. Chem.*, **31**, 14 (2016); https://doi.org/10.3109/14756366.2014.1003214
20. B.M. Paterson and P.S. Donnelly, *Chem. Soc. Rev.*, **40**, 3005 (2011); https://doi.org/10.1039/c0cs00215a
21. S.K. Haraguchi, A.A. Silva, G.J. Vidotti, P.V. Dos Santos, F.P. Garcia, R.B. Pedroso, C.V. Nakamura, C.M.A. De Oliveira and C.C. Da Silva, *Molecules*, **16**, 1166 (2011); https://doi.org/10.3390/molecules16021166
22. G.R. Subhashree, J. Haribabu, S. Saranya, P. Yuvaraj, D.A. Krishnan, R. Karvembu and D. Gayathri, *J. Mol. Struct.*, **1145**, 160 (2017); https://doi.org/10.1016/j.molstruc.2017.05.054
23. S. Sardari, S. Feizi and A.H. Rezayan, *Iran. J. Pharm. Res.*, **16**, 1128 (2017).
24. S. Alegaon, K. Kashniyal, S. Kuncolienkar, R. Kavalapure, P. Salve, M. Palled, S. Suryawanshi and S. Jalalpure, *Futur. J. Pharm. Sci.*, **6**, 2 (2020); https://doi.org/10.1186/s43094-019-0016-7
25. M. Islam, A. Khan, M.T. Shehzad, A. Hameed, N. Ahmed, S.A. Halim, M. Khiat, M.U. Anwar, J. Hussain, R. Csuk, Z. Shafiq and A. Al-Harrasi, *Bioorg. Chem.*, **87**, 155 (2019); https://doi.org/10.1016/j.bioorg.2019.03.008
26. A. Hameed, K.M. Khan, S.T. Zehra, R. Ahmed, Z. Shafiq, S.M. Bakht, M. Yaqub, M. Hussain, A. de la Vega de León, N. Furtmann, J. Bajorath, H.A. Shad, M.N. Tahir and J. Iqbal, *Bioorg. Chem.*, **61**, 51 (2015); https://doi.org/10.1016/j.bioorg.2015.06.004
27. V.A. Kumar, Y. Sarala, A. Siddikha, S. Vanitha, S. Babu and A.V. Reddy, *J. Appl. Pharm. Sci.*, **8**, 71 (2018); https://doi.org/10.7324/JAPS.2018.8410
28. D.T. Nguyen, T.H. Le and T.T. Bui, *Eur. J. Med. Chem.*, **60**, 199 (2013); https://doi.org/10.1016/j.ejmech.2012.10.004
29. N. Bharti, K. Husain, M.T. Gonzalez-Garza, D.E. Cruz-Vega, J. Castro-Garza, B.D. Mata-Cardenas, F. Naqvi and A. Azam, *Bioorg. Med. Chem. Lett.*, **12**, 3475 (2002); https://doi.org/10.1016/s0960-894x(02)00703-5
30. E. Namiecińska, M. Sobiesiak, M. Malecka, P. Guga, B. Rozalska and E. Budzisz, *Curr. Med. Chem.*, **26**, 664 (2019); https://doi.org/10.2174/0929867325666180228164656
31. T. Khan, S. Dixit, R. Ahmad, S. Raza, I. Azad, S. Joshi and A.R. Khan, *J. Chem. Boil.*, **10**, 91 (2017); https://doi.org/10.1007/s12154-017-0167-y
32. A. Kshirsagar, M.P. Toraskar and V.M. Kulkarni, *Int. J. Chemtech Res.*, **1**, 696 (2009).
33. J. Liu, W. Yi, Y. Wan, L. Ma and H. Song, *Bioorg. Med. Chem.*, **16**, 1096 (2008); https://doi.org/10.1016/j.bmc.2007.10.102
34. P. Heffeter, V.F. Pape, É.A. Enyedy, B.K. Keppler, G. Szakacs and C.R. Kowol, *Antioxid. Redox Signal.*, **30**, 1062 (2019); https://doi.org/10.1089/ars.2017.7487
35. S. Singhal, S. Arora and S. Agarwal, *World J. Pharm. Pharm. Sci.*, **2**, 4661 (2013).
36. G.A. Gazieva, P.A. Poluboyarov, L.D. Popov, N. Kolotyrkina, A. Kravchenko and N. Makhova, *Synthesis*, **44**, 3366 (2012); https://doi.org/10.1055/s-0032-1317194
37. M.H. Abd ElAzim, M.G. Assy, M.I. Khalil and Y.A. Selim, *J. Heterocycl. Chem.*, **57**, 3153 (2020); https://doi.org/10.1002/jhet.4022
38. S.M. Mustafa, V.A. Nair, J.P. Chittoor and S. Krishnapillai, *Mini Rev. Org. Chem.*, **1**, 375 (2004); https://doi.org/10.2174/1570193043403082
39. A.S. Fouda, M.N. Moussa, F.I. Taha and A.I. Elneanaa, *Corros. Sci.*, **26**, 719 (1986); https://doi.org/10.1016/0010-938X(86)90035-1
40. S. Mohebbi, M. Hassan, R. Ghaffari, S. Sardari and Y.F. Farahani, *Res. Pharm. Sci.*, **15**, 281 (2020); https://doi.org/10.4103/1735-5362.288435
41. A.E. Grzegorzewicz, J. Korduláková and V. Jones, *J. Biol. Chem.*, **287**, 38434 (2012); https://doi.org/10.1074/jbc.M112.400994
42. A.E. Grzegorzewicz, N. Eynard, A. Quémard, E.J. North, A. Margolis, J.J. Lindenberger, V. Jones, J. Korduláková, P.J. Brennan, R.E. Lee, D.R. Ronning, M.R. McNeil and M. Jackson, *ACS Infect. Dis.*, **1**, 91 (2015); https://doi.org/10.1021/id500032q
43. G. Cihan-Üstündag, E. Gürsoy, L. Naesens, N. Ulusoy-Güzeldemirci and G. Çapan, *Bioorg. Med. Chem.*, **24**, 240 (2016); https://doi.org/10.1016/j.bmc.2015.12.008
44. A.M. Tsimberidou, Y. Alvarado and F.J. Giles, *Expert Rev. Anticancer Ther.*, **2**, 437 (2002); https://doi.org/10.1586/14737140.2.4.437
45. A. Siwek, P. St¹czek and J. Stefańska, *Eur. J. Med. Chem.*, **46**, 5717 (2011); https://doi.org/10.1016/j.ejmech.2011.09.034

46. H. Hosseinpoor, S.M. Farid, A. Iraji, S. Askari, N. Edraki, S. Hosseini, A. Jamshidzadeh, B. Larijani, M. Attarroshan, S. Pirhadi, M. Mahdavi and M. Khoshneviszadeh, *Bioorg. Chem.*, 104979 (2021); https://doi.org/10.1016/j.bioorg.2021.104979
47. M. Pitucha, Z. Karczmarzyk, M. Swatko-Ossor, W. Wysocki, M. Wos, K. Chudzik, G. Ginalska and A. Fruzinski, *Molecules*, **24**, 251 (2019); https://doi.org/10.3390/molecules24020251
48. R.J. Nevagi, A.S. Dhake and H.I. Narkhede, *Bioorg. Chem.*, **54**, 68 (2014); https://doi.org/10.1016/j.bioorg.2014.04.002
49. J. He, X. Wang, X. Zhao, Y.J. Liang, H. He and L. Fu, *Eur. J. Med. Chem.*, **54**, 925 (2012); https://doi.org/10.1016/j.ejmech.2012.06.003
50. B. Šarkanj, M. Molnar, M. Èaèic and L. Gille, *Food Chem.*, **139**, 488 (2013); https://doi.org/10.1016/j.foodchem.2013.01.027
51. R. Matsa, P. Makam, M. Kaushik, S.L. Hoti and T. Kannan, *Eur. J. Pharm. Sci.*, **137**, 104986 (2019); https://doi.org/10.1016/j.ejps.2019.104986
52. L.E. Bermudez, P. Kolonoski, L.E. Seitz, M. Petrofsky, R. Reynolds, M. Wu and L.S. Young, *Antimicrob. Agents Chemother.*, **48**, 3556 (2004); https://doi.org/10.1128/AAC.48.9.3556-3558.2004
53. L.E. Bermudez, R. Reynolds, P. Kolonoski, P. Aralar, C.B. Inderlied and L.S. Young, *Antimicrob. Agents Chemother.*, **47**, 2685 (2003); https://doi.org/10.1128/AAC.47.8.2685-2687.2003
54. W. Hernández, F. Carrasco, A. Vaisberg, E. Spodine, J. Manzur, M. Icker, H. Krautscheid and L. Beyer, *J. Chem.*, **2020**, 2960165 (2020); https://doi.org/10.1155/2020/2960165
55. A.A. Al-Mutairi, M.A. Al-Alshaikh, F.A. Al-Omary, H.M. Hassan, A.M. El-Mahdy and A.A. El-Emam, *Molecules*, **24**, 4308 (2019); https://doi.org/10.3390/molecules24234308
56. M.D. Altintop, B. Sever, A. Özdemir, G. Kus, P. Oztopcu-Vatan, S. Kabadere and Z.A. Kaplancikli, *J. Enzyme Inhib. Med. Chem.*, **31**, 410 (2016); https://doi.org/10.3109/14756366.2015.1031126
57. K.S. Hmood, A.A.R.M. Kubba, R.I. Al-bayati and A.M. Saleh, *Indones. J. Pharm.*, **32**, 17 (2021); https://doi.org/10.22146/ijp.730
58. M.H. Hekal, F.S. Abu El-Azm and S.R. Atta-Allah, *Synth. Commun.*, **49**, 2630 (2019); https://doi.org/10.1080/00397911.2019.1637001
59. E. Pahontu, V. Fala, A. Gulea, D. Poirier, V. Tapcov and T. Rosu, *Molecules*, **18**, 8812 (2013); https://doi.org/10.3390/molecules18088812
60. O.A. Abdelaziz, W.M. El Husseiny and K.B. Selim, *Bioorg. Chem.*, **90**, 103076 (2019); https://doi.org/10.1016/j.bioorg.2019.103076
61. O.M. Abdelhafez, E.Y. Ahmed, N.A. Abdel Latif, R.K. Arafa, Z.Y. Abd Elmageed and H.I. Ali, *Bioorg. Med. Chem.*, **27**, 1308 (2019); https://doi.org/10.1016/j.bmc.2019.02.027
62. E.A.A. El-Meguid and M.M. Ali, *Res. Chem. Intermed.*, **42**, 1521 (2016); https://doi.org/10.1007/s11164-015-2100-8
63. S.B. Salib, O.M. Khalil, M.M. Kamel and Y. El-Dash, *Open Access Libr. J.*, **3**, e2876 (2016); https://doi.org/10.4236/oalib.1102876
64. C. Gan, J. Cui, S. Su, Q. Lin, L. Jia, L. Fan and Y. Huang, *Steroids*, **87**, 99 (2014); https://doi.org/10.1016/j.steroids.2014.05.026
65. M. Pitucha, M. Wos, M. Miazga-Karska, K. Klimek, B. Miroslaw, A. Pachuta-Stec, A. Gladysz and G. Ginalska, *Med. Chem. Res.*, **25**, 1666 (2016); https://doi.org/10.1007/s00044-016-1599-6
66. Y. Dadas, G.P. Coskun, Ö. Bingöl-Akpinar, *Marmara Pharm. J.*, **19**, 259 (2015); https://doi.org/10.12991/mpj.201519328306
67. S.M. De Almeida, E.A. Lafayette, L.P. Da Silva, C. Amorim, T. de Oliveira, A. Ruiz, J. de Carvalho, R. de Moura, E. Beltrão, M. de Lima and L. Júnior, *Int. J. Mol. Sci.*, **16**, 13023 (2015); https://doi.org/10.3390/ijms160613023
68. M.D. Altintop, Ö. Atli, S. Ilgin, R. Demirel, A. Özdemir and Z.A. Kaplancikli, *Eur. J. Med. Chem.*, **108**, 406 (2016); https://doi.org/10.1016/j.ejmech.2015.11.041
69. Y. Wang, W. Gu, Y. Shan, F. Liu, X. Xu, Y. Yang, Q. Zhang, Y. Zhang, H. Kuang, Z. Wang and S. Wang, *Bioorg. Med. Chem. Lett.*, **27**, 2360 (2017); https://doi.org/10.1016/j.bmcl.2017.04.024
70. J.F. de Oliveira, T.S. Lima, D.B. Vendramini-Costa, S.C.B. de Lacerda Pedrosa, E.A. Lafayette, R.M.F. da Silva, S.M.V. de Almeida, R.O. de Moura, A.L.T.G. Ruiz, J.E. de Carvalho and M.C.A. de Lima, *Eur. J. Med. Chem.*, **136**, 305 (2017); https://doi.org/10.1016/j.ejmech.2017.05.023
71. Y.K. Abhale, A. Shinde, K.K. Deshmukh, L. Nawale, D. Sarkar and P.C. Mhaske, *Med. Chem. Res.*, **26**, 2557 (2017); https://doi.org/10.1007/s00044-017-1955-1
72. K.D. Thomas, A.V. Adhikari, S. Telkar, I.H. Chowdhury, R. Mahmood, N.K. Pal, G. Row and E. Sumesh, *Eur. J. Med. Chem.*, **46**, 5283 (2011); https://doi.org/10.1016/j.ejmech.2011.07.033
73. D.B. Patel, K.D. Patel, N.P. Prajapati, K.R. Patel, D.P. Rajani, S.D. Rajani, N.S. Shah, D.D. Zala and H.D. Patel, *J. Heterocycl. Chem.*, **56**, 2235 (2019); https://doi.org/10.1002/jhet.3617
74. E. Mentese, M. Emirik and B.B. Sökmen, *Biol. Chem.*, **86**, 151 (2019); https://doi.org/10.1016/j.bioorg.2019.01.061
75. H. Bektas, B.B. Sökmen, S. Aydin, E. Mentese, A. Bektas and G. Dilekçi, *J. Heterocycl. Chem.*, **57**, 2234 (2020); https://doi.org/10.1002/jhet.3943
76. S.R. Patel, R. Gangwal, A.T. Sangamwar and R. Jain, *Eur. J. Med. Chem.*, **85**, 255 (2014); https://doi.org/10.1016/j.ejmech.2014.07.100
77. M. Özil, M. Emirik, A. Beldüz and S. Ülker, *Bioorg. Med. Chem.*, **24**, 5103 (2016); https://doi.org/10.1016/j.bmc.2016.08.024
78. E. Mentese, H. Bektas, B.B. Sokmen, M. Emirik, D. Çakir and B. Kahveci, *Bioorg. Med. Chem. Lett.*, **27**, 3014 (2017); https://doi.org/10.1016/j.bmcl.2017.05.019
79. D.B. Patel, D.G. Darji, K.R. Patel, D.P. Rajani, S.D. Rajani and H.D. Patel, *J. Heterocycl. Chem.*, **57**, 1183 (2020); https://doi.org/10.1002/jhet.3855
80. O. Unsal Tan, K. Ozadali, P. Yogeeswari, D. Sriram and A. Balkan, *Med. Chem. Res.*, **21**, 2388 (2012); https://doi.org/10.1007/s00044-011-9770-6
81. S. Botros, N.A. Khalil, B.H. Naguib and Y. El-Dash, *Eur. J. Med. Chem.*, **60**, 57 (2013); https://doi.org/10.1016/j.ejmech.2012.11.025
82. B. Ali, K.M. Khan, Arshia, Kanwal, S. Hussain, S. Hussain, M. Ashraf, M. Riaz, A. Wadood and S. Perveen, *Biol. Chem.*, **79**, 34 (2018); https://doi.org/10.1016/j.bioorg.2018.04.004
83. A.G. El-Helby, R.R. Ayyad, K. El-Adl, H. Sakr, A.A. Abd-Elrahman, I.H. Eissa and A. Elwan, *Med. Chem. Res.*, **25**, 3030 (2016); https://doi.org/10.1007/s00044-016-1723-7
84. P. Yogeeswari, D. Sriram, V. Saraswat, J.V. Ragavendran, M.M. Kumar, S. Murugesan, R. Thirumurugan and J.P. Stables, *Eur. J. Pharm. Sci.*, **20**, 341 (2003); https://doi.org/10.1016/j.ejps.2003.08.002
85. M. Zayane, A. Romdhane, M. Daami-Remadi and H.B. Jannet, *J. Chem. Sci.*, **127**, 1619 (2015); https://doi.org/10.1007/s12039-015-0927-6
86. S. Ghosh, A.K. Misra, G. Bhatia, M.M. Khan and A.K. Khanna, *Bioorg. Med. Chem. Lett.*, **19**, 386 (2009); https://doi.org/10.1016/j.bmcl.2008.11.070
87. B.Z. Sibuh, P. Taneja and S. Khanna, *Life Sci.*, **273**, 119305 (2020); https://doi.org/10.1016/j.lfs.2021.119305
88. T.A. Yousef and G.A. El-Reash, *J. Mol. Struct.*, **1201**, 127180 (2020); https://doi.org/10.1016/j.molstruc.2019.127180
89. E.D. Dincel and N.U. Guzeldemirci, *Med. Sci.*, **9**, 305 (2020).
90. O.M. Khalil, E.M. Gedawy, A.A. El-Malah and M.E. Adly, *Bioorg. Chem.*, **83**, 262 (2019); https://doi.org/10.1016/j.bioorg.2018.10.058
91. M.A. Hussein, M.A. Iqbal, M.I. Umar, R.A. Haque and T.S. Guan, *Arab. J. Chem.*, **12**, 3183 (2019); https://doi.org/10.1016/j.arabjc.2015.08.013
92. B. Nammalwar, R.A. Bunce, K.D. Berlin, D.M. Benbrook and C. Toal, *Eur. J. Med. Chem.*, **170**, 16 (2019); https://doi.org/10.1016/j.ejmech.2019.03.010

93. N. Rajendran, A. Periyasamy, N. Kamatchi and V. Solomon, *J. Coord. Chem.*, **72**, 1937 (2019); https://doi.org/10.1080/00958972.2019.1634806
94. A.A. Gaber, A.H. Bayoumi, A.M. El-morsy, F.F. Sherbiny, A.B.M. Mehany and I.H. Eissa, *Bioorg. Chem.*, **80**, 375 (2018); https://doi.org/10.1016/j.bioorg.2018.06.017
95. P.F. Geng, X.Q. Liu, T.Q. Zhao, C.C. Wang, Z.-H. Li, J. Zhang, H.-M. Wei, B. Hu, L.-Y. Ma and H.-M. Liu, *Eur. J. Med. Chem.*, **146**, 147 (2018); https://doi.org/10.1016/j.ejmech.2018.01.031
96. M. Wos, M. Miazga-Karska, A.A. Kaczor, K. Klimek, Z. Karczmarzyk, D. Kowalczuk, W. Wysocki, G. Ginalska, Z. Urbanczyk-Lipkowska, M. Morawiak and M. Pitucha, *Biomed. Pharmacother.*, **93**, 1269 (2017); https://doi.org/10.1016/j.biopha.2017.07.049
97. D. Morgan, *Trends Microbiol.*, **3**, 449 (1995); https://doi.org/10.1016/S0966-842X(00)89003-4
98. G.M. Sheldrick, SADABS Bruker Axs Inc. Madison, Wisconsin, USA. (2007).
99. H.J. Zhang, Y. Qian, D.D. Zhu, X.-G. Yang and H.-L. Zhu, *Eur. J. Med. Chem.*, **46**, 4702 (2011); https://doi.org/10.1016/j.ejmech.2011.07.016
100. I. Đilovic, M. Rubèic, V. Vrdoljak, S.K. Pavelic, M. Kralj, I. Piantanida and M. Cindric, *Bioorg. Med. Chem.*, **16**, 5189 (2008); https://doi.org/10.1016/j.bmc.2008.03.006
101. H. Zhang, R. Thomas, D. Oupicky and F. Peng, *J. Biol. Inorg. Chem.*, **13**, 47 (2008); https://doi.org/10.1007/s00775-007-0299-6
102. M. Baldini, M. Belicchi-Ferrari, F. Bisceglie, P.P. Dall'aglio, G. Pelosi , S. Pinelli and P. Tarasconi, *Inorg. Chem.*, **43**, 7170 (2004); https://doi.org/10.1021/ic049883b
103. F. Bisceglie, C. Bacci, A. Vismarra, E. Barilli, M. Pioli, N. Orsoni and G. Pelosi, *J. Inorg. Biochem.*, **203**, 110888 (2020); https://doi.org/10.1016/j.jinorgbio.2019.110888
104. A. Lapasam, V. Banothu, U. Addepally and M.R. Kollipara, *J. Chem. Sci.*, **132**, 34 (2020); https://doi.org/10.1007/s12039-019-1731-5
105. M.T. Shehzad, A. Khan, M. Islam, A. Hameed, M. Khiat, S.A. Halim, M.U. Anwar, S.R. Shah, J. Hussain, R. Csuk, S. Khan, A. Al-Harrasi and Z. Shafiq, *J. Mol. Struct.*, **1209**, 127922 (2020); https://doi.org/10.1016/j.molstruc.2020.127922
106. E. BahojbNoruzi, B. Shaabani, S. Geremia, N. Hickey, P. Nitti and H.S. Kafil, *Molecules*, **25**, 370 (2020); https://doi.org/10.3390/molecules25020370
107. D. Polo-Cerón, *Bioinorg. Chem. Appl.*, **2019**, 3520837 (2019); https://doi.org/10.1155/2019/3520837
108. J.J. Patel, A.P. Patel and K.H. Chikhalia, *Res. Chem. Int.*, **44**, 813 (2018); https://doi.org/10.1007/s11164-017-3136-8
109. Z.A. Kaplancikli, M.D. Altintop, B. Sever, Z. Cantürk and A. Özdemir, *J. Chem.*, **2016**, 1692540 (2016); https://doi.org/10.1155/2016/1692540
110. S.A. Khan, P. Kumar, R. Joshi, P.F. Iqbal and K. Saleem, *Eur. J. Med. Chem.*, **43**, 2029 (2008); https://doi.org/10.1016/j.ejmech.2007.12.004
111. K.S. Abou-Melha, *J. Enzyme Inhibit. Med. Chem.*, **23**, 493 (2008); https://doi.org/10.1080/14756360701631850
112. S.A. Khan, K. Saleem and Z. Khan, *Eur. J. Med. Chem.*, **42**, 103 (2007); https://doi.org/10.1016/j.ejmech.2006.07.006
113. A.K. Parekh and K.K. Desai, *Indian J. Chem.*, **45B**, 1072 (2006).
114. R.K. Agarwal, L. Singh and D.K. Sharma, *Bioorg. Chem. Appl.*, **2006**, 59509 (2006); https://doi.org/10.1155/BCA/2006/59509
115. B.J. Jeragh and A. El-Dissouky, *J. Coord. Chem.*, **58**, 1029 (2005); https://doi.org/10.1080/00958970500096975
116. P. Kosikowska and L. Berlicki, *Expert Opin. Ther. Pat.*, **21**, 945 (2011); https://doi.org/10.1517/13543776.2011.574615
117. H. Beraldo and D. Gambino, *Mini Rev. Med. Chem.*, **4**, 31 (2004); https://doi.org/10.2174/1389557043487484
118. E. Bayerdorffer and R. Ottenjann, *Scand. J. Gastroenterol.*, **23(sup142)**, 93 (1988); https://doi.org/10.3109/00365528809091721
119. E. Mentese, G. Akyüz, M. Emirik and N. Baltas, *Bioorg. Chem.*, **83**, 289 (2019); https://doi.org/10.1016/j.bioorg.2018.10.031
120. B. Ali, K.M. Khan, U. Salar, Kanwal, S. Hussain, M. Ashraf, M. Riaz, A. Wadood, M. Taha and S. Perveen, *Bioorg. Chem.*, **79**, 363 (2018); https://doi.org/10.1016/j.bioorg.2018.05.017
121. M.M. El-Kerdawy, M.A. Ghaly, S.A. Darwish, H.A. Abdel-Aziz, A.R. Elsheakh, R.S. Abdelrahman and G.S. Hassan, *Biol. Chem.*, **83**, 250 (2019); https://doi.org/10.1016/j.bioorg.2018.10.048
122. E.D. AlFadly, P.A. Elzahhar, A. Tramarin, S. Elkazaz, H. Shaltout, M.M. Abu-Serie, J. Janockova, O. Soukup, D.A. Ghareeb, A.F. El-Yazbi, R.W. Rafeh, N.-M.Z. Bakkar, F. Kobeissy, I. Iriepa, I. Moraleda, M.N.S. Saudi, M. Bartolini and A.S.F. Belal, *Eur. J. Med. Chem.*, **167**, 161 (2019); https://doi.org/10.1016/j.ejmech.2019.02.012
123. J.J. Patel, R.P. Modh, M. Asamdi and K.H. Chikhalia, *Mol. Divers.*, (2020); https://doi.org/10.1007/s11030-020-10117-y
124. N. Trotsko, J. Golus, P. Kazimierczak, A. Paneth, A. Przekora, G. Ginalska and M. Wujec, *Bio. Chem.*, **97**, 103676 (2020); https://doi.org/10.1016/j.bioorg.2020.103676
125. J.W. Hicks, C.B. Kyle, C.M. Vogels, S.L. Wheaton, F.J. Baerlocher, A. Decken and S.A. Westcott, *Chem. Biodivers.*, **5**, 2415 (2008); https://doi.org/10.1002/cbdv.200890206
126. H. Najeh Al-Saad, A.A. Razzak Mahmood and R. I. Al-Bayat, *Orient. J. Chem.*, **35**, 829 (2019); https://doi.org/10.13005/ojc/350246
127. K. Dziduch, P. Kolodziej, A. Paneth, A. Bogucka-Kocka and M. Wujec, *Molecules*, **25**, 2770 (2020); https://doi.org/10.3390/molecules25122770
128. R. Matsa, P. Makam, M. Kaushik, S.L. Hoti and T. Kannan, *Eur. J. Pharm. Sci.*, **137**, 104986 (2019); https://doi.org/10.1016/j.ejps.2019.104986
129. F. Rahim, F. Malik, H. Ullah, A. Wadood, F. Khan, M.T. Javid, M. Taha, W. Rehman, Ashfaq-Ur-Rehman and K.M. Khan, *Biol. Chem.*, **60**, 42 (2015); https://doi.org/10.1016/j.bioorg.2015.03.005
130. F. Rahim, M. Taha, N. Iqbal, S. Hayat, F. Qureshi, I. Uddin, K. Zaman,A. Rab, A. Wadood, N. Uddin, M. Nawaz, S.A.A. Shah and K.M. Khanj, *J. Mol. Struct.*, **1222**, 128922 (2020); https://doi.org/10.1016/j.molstruc.2020.128922
131. S.A. Almeida-Batista, F. Vandresen, H. Falzirolli, E. Britta, D.N. de Oliveira, R.R. Catharino, M.A. Gonçalves, T.C. Ramalho, F.A. La Porta, C.V. Nakamura and C.C. da Silva, *J. Mol. Struct.*, **1179**, 252 (2019); https://doi.org/10.1016/j.molstruc.2018.11.017
132. A.C. Leite, R.S. de Lima, D.R. Moreira, M.V.O. Cardoso, A.C. Gouveia de Brito, L.M. Farias dos Santos, M.Z. Hernandes, A.C. Kiperstok, R.S. de Lima and M.B.P. Soares, *Bioorg. Med. Chem.*, **14**, 3749 (2006); https://doi.org/10.1016/j.bmc.2006.01.034
133. M. Abid and A. Azam, *Bioorg. Med. Chem.*, **13**, 2213 (2005); https://doi.org/10.1016/j.bmc.2004.12.050
134. O.A. Chaves, M.R. de Lima Santos, M.C. de Oliveira, C.M.R. Sant'Anna, R.C. Ferreira, A. Echevarria and J.C. Netto-Ferreira, *J. Mol. Liq.*, **254**, 280 (2018); https://doi.org/10.1016/j.molliq.2018.01.083