Synthesis and Characterization of Thiosemicarbazides

NANDHINI.M

(21PCH014)

Thesis Submitted to

Avinashilingam Institute for Home Science and Higher Education for Women

Coimbatore-641043

In partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE IN CHEMISTRY

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Signature of the Supervisor

19/5/23 for

Signature of the Head of the Department

ACKNOWLEDGEMENT

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It is with choice of blessings and the divine grace of **LORD ALMIGHTY** that any human endeavour is achieved.

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Nandhini.M

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LIST OF ABBREVIATION

TSC	**ThioSemiCarbazide**
TLC	**Thin Layer Chromatography**
MC	**Mandelic Acid**
CA	**Coumaric Acid**
FT-IR	**Fourier Transform Infra Red**
NMR	**Nuclear Magnetic Resnance**
ADME-Tox	**Absorption,Distribution,Metabolism,Excretion and Toxicity**
MTT Assay	**(3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide)**
ROS	**Reactive oxygen species**
SAR	**Structure-Activity Relationship**
PASS	**Power Analysis & Sample Size**

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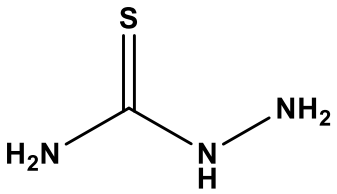
INTRODUCTION

1.INTRODUCTION

1.1.Thiosemicarbazide

Thiosemicarbazides play an essential role in the synthesis of a number of heterocycles, as evidenced by their use in organic synthesis. Their reactions with systems containing C=O and C=N groups is one of the methods for the preparation of biologically active compounds *viz*. pyrazole, thiazole, triazole, thiadiazole, oxadiazole, triazine and thiadiazine. The formation of C−N and C=N bonds as opposed to the N−N bond formation is reflected in their extensive use for the preparation of these heterocycles in excellent yields.Thiosemicarbazides are powerful chemical building blocks for the synthesis of pharmacological and bioactive compounds, and as a result, they were widely used in the field of medicinal chemistry.Thiosemicarbazides (TSC) having the -CO-NH-NHCS-NH- functional group were generally synthesized fromreactions of hydrazides with isothiocyanates in differentorganic solvents.

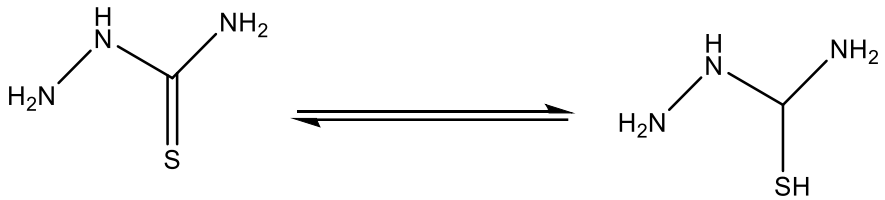
Thiosemicarbazideis used as a reagent for ketones and certain metals, for photography and as a rodenticide. It is also effective for control of bacterial leaf blight of rice.Thiosemicarbazide is the simplest hydrazinederivative of thiocarbamic acid. The chemical behaviour ofthiosemicarbazide is alike to its correspondent semicarbazide,however, is of superior chemical adaptability of the thione groupas compared with that of keto group and is liable for more diverse behaviour of thiosemicarbazide.Thiosemicarbazides are easily cyclized by the action of acids, bases or oxidants, therefore they are useful versatile building blocks for the preparation of heterocyclic ring systems.(**Patel, D. B.*et. al.,(2019))*** investigated the reactions of thiosemicarbazides with π-deficient compounds and synthesized many compounds such as thiazoles, thiazines, thiadiazoles, thiadiazines, pyrazines and indazoles. Semicarbazides are used in the synthesis of anti-tuberculosis drugs amidothiourea and sulfa drugs, used as pesticide intermediates and rubber additives (**Prachi T *et al.*,(2021)).**



hydrazinecarbothioamide

1.2.Reactivity of Thiosemicarbazide Derivatives

Thiosemicarbazides are polyfunctional compounds possessing nucleophilic properties. Typical nucleophilic positions were NH_2 – 1, NH – 2 and NH_2 – 4, with the reactivity order NH_2 – 1 > NH – 2 > NH_2 – 4. This nucleophilic behavior had been used to design different heterocyclic moieties with different ring sizes such as pyrazole, thiazole, triazole, oxadiazolethiadiazole, triazine and thiadiazine. Thiosemicarbazides also exist in the tautomeric thiol form.

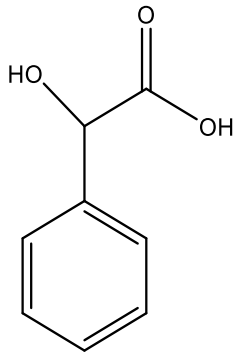


Thione form **Thiol form**

1.3.Mandelic acid

Mandelic acid is obtained from bitter almonds,it is an aromatic alpha hydroxy acid. It is a useful precursor for various drugs. The molecule was chiral. The racemic mixture is known as paramandelicacid.Mandelic acid is a 2-hydroxy monocarboxylic acid, which is acetic acid in which phenyl and hydroxyl groups have replaced two of the methyl hydrogens. It functions as a human xenobiotic metabolite and an antibacterial agent. It is a benzene and a 2-hydroxy monocarboxylic acid. It is similar to an acetic acid in terms of function. It is a mandelate's conjugate acid.

Mandelic acid is an alpha-hydroxy acid and it belongs to one of the most popular acids used in dermatology, cosmetology and aesthetic medicine **(Marzena Matejczyk*et al.,*).**

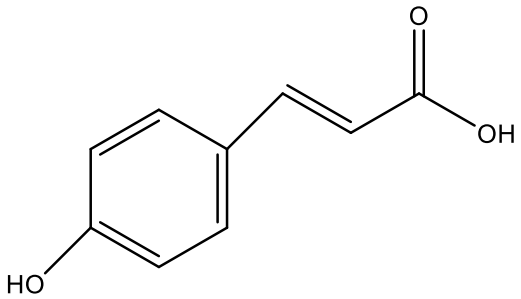


2-hydroxy-2-phenylacetic acid

1.4.Coumaric acid

It is a phenolic acid of the hydroxycinnamic acid family and is biologically synthesised through the shikimate path-way with phenylalanine and tyrosine as precursors.In plants andmushrooms, tyrosine ammonia-lyase converts tyrosine into p-coumalicacid.p-coumaric acid plays a central role in secondary metabolism because it canbe subsequently transformed to phenolic acids (e.g. caffeic acid,ferulic acid, chlorogenic acid and sinapic acid), flavonoids, ligninprecursors and other secondary metabolites**.(Kehan Pei.*et al.*,2015**).

p-coumaric acidcan be found in either free or bound form in all plants and mushrooms. Fruits and vegetables, including beans, potatoes, and onions, as well as cereals made from maize, oats, and wheat, are abundant sources of free or bound p-coumaric acid conjugates have been shown to have a variety of bioactivities, including anti-oxidant, anti-inflammatory, antimutagenic, anti-ulcer, anti-platelet, and anti-cancer activities, in addition to reducing the risk of atherosclerosis, oxidative cardiac damage, UV-induced damage to ocular tissues, neuronal injury, anxiety, gout, and diabetes.p-coumaric acidwithin the group of phenolic acids giving color, odorand taste to the plants The p-coumaric acid is aphenolic compound derived from cinnamic acid .**(SinerayKoç*et.al.*,2016).**



(*E*)-3-(4-hydroxyphenyl)acrylic acid

1.5.Applicaions of Thiosemicarbazide

1.5.1.Synthesis of Heterocycle Compounds Using Thiosemicarbazide

Five member heterocycles containing nitrogen and sulfur atoms are potential compounds for development of chemotherapeutic and pharmacotherapeutic agents**.(Prabhakar*, et. al.,2019)*** investigated the combination of two active pharmacophores in one molecule as the new method of drug design and discovery. 1,3,4-Thiadiazole derivatives have been reported to possess wide spectrum of biological activities. The molecular manipulation of promising lead compounds result in gradual change in the physicochemical properties and biological activity of compounds. Based on these observations, it was concluded worthwhile to synthesize novel substituted 1,3,4-thiadiazole derivatives and evaluate their antimicrobial, antifungal and anthelmintic properties to explore the spectrum of activities.

1.5.2.In Pharmaceutical

Thiosemicarbazides and their derivatives display interesting biological activities, including anti-cancer, anti-microbial, anti-HIV, anti-viral, insecticidal, anti-sclerotic, antioxidant, and anti-parasitic activities. They play an important role in the regulation of plant growth.On the other hand, nitro group is a structural moiety that isoften found in biologically active compounds. Nitroheterocyclicderivatives have a wide spectrum of activity including antibacterial, antifungal or anticancer properties.Thesesulfur and nitrogen donor ligands and their coordination complexes have extendedsingular attention due to their activity against smallpox virus, andprotozoa influenza**(Prachi T *et.al.,(*2021)).**

1.5.3.In Quantitative Analysis:

It isused as an analytical reagent for quantitative determination of chromium and identification of aldehydes and ketones. Its used fordetection of certain metals and sugars, aldehydes, and ketones. Used in the preparation of rodenticides. Thiosemicarbazide isan intermediate for organic synthesis, used in the synthesis of anti-tuberculosis drugs, ammonia thiourea and sulfa drugs, as well as rodenticides. It can also be used as an analytical reagent for the quantification of chromium and the identification of aldehydes and ketones. In addition, thiosemicarbazide was also used as pesticide intermediates, rubber additives and synthetic resin additives.**Zhang-Xu He *et.al.*,(2020)**

Hence the present work was carried out with the following objectives.

OBJECTIVES

To synthesis of hydrazinecarbothioamide from aromatic hydroxy acids,

- Mandelic acid
- p-coumaric acid

- To Synthesis carboxylic esters of mandelic acid and p-Coumaric acid
- To Synthesis aromatic carbohydrazides of mandelic acid and p-Coumaric acid
- To Synthesis Hydrazinecarbothioamides of mandelic acid and p-Coumaric acid.
- To characterize the compounds by

  FT-IR

  ^{1}H NMR

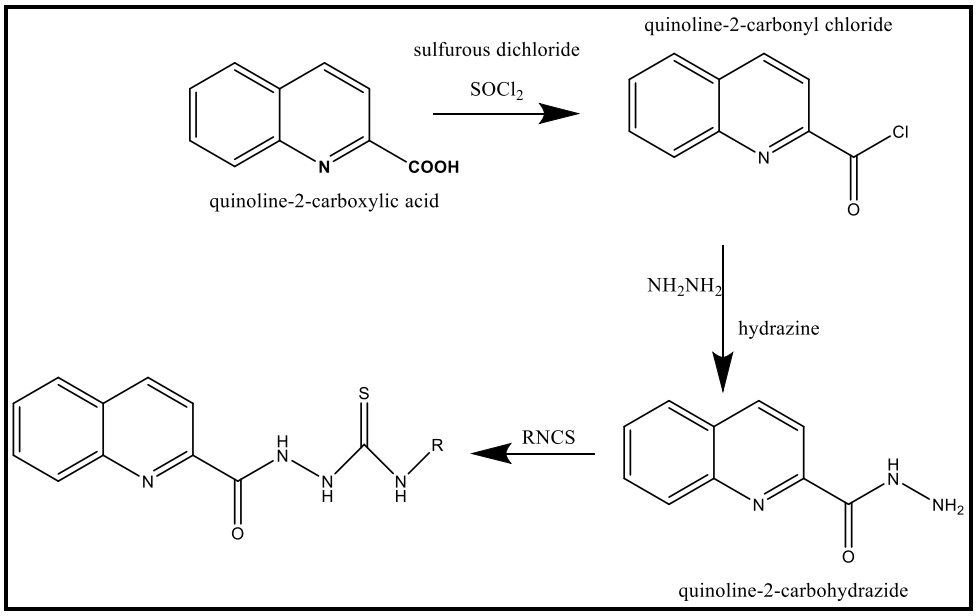
REVIEW

OF

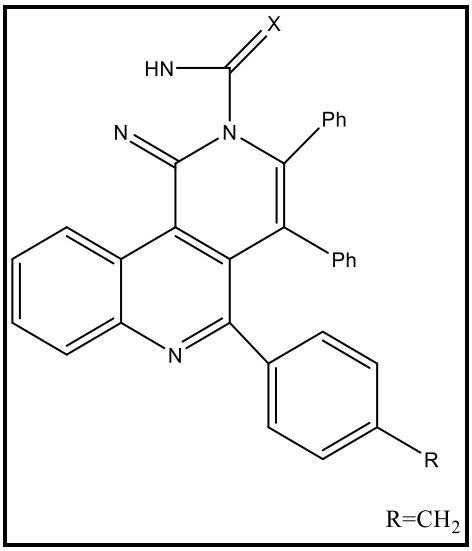
LITERATURE

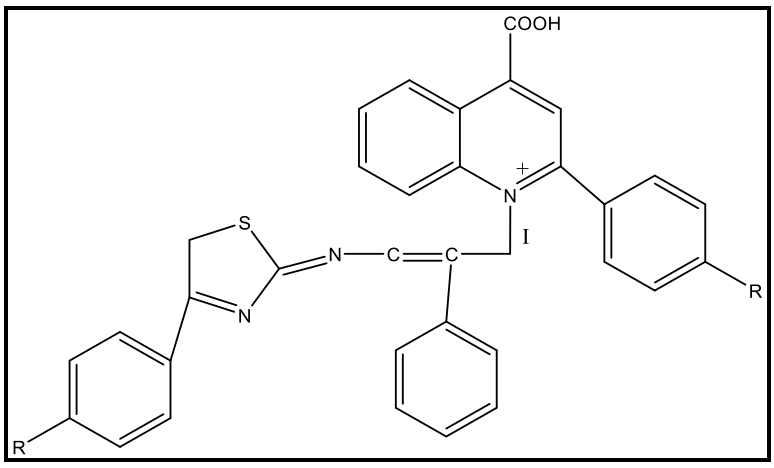
2.REVIEW OF LITERATURE

E. M. Keshk *et al.*,(2012) synthesized the new quinoline thiosemicarbohyrazidesderivatives, quinoline-2-carbohydrazideby the reactionof aryl or alkyl isothiocyanates to give the corresponding quinoline thiosemicarbazides. the newly synthesized compounds were tested and evaluated against gram positive bacteria (*Staphylococcus aureus)*, gram negative bacteria (*Escherichia coli*) and yeast (*Candida)*, and compared with respect to some reference antibiotics (Tetracycline and Ketoconazole). The structures of the products were conformed by elemental analyses, IR, ^{1}H NMR, and ^{13}C NMR spectra.

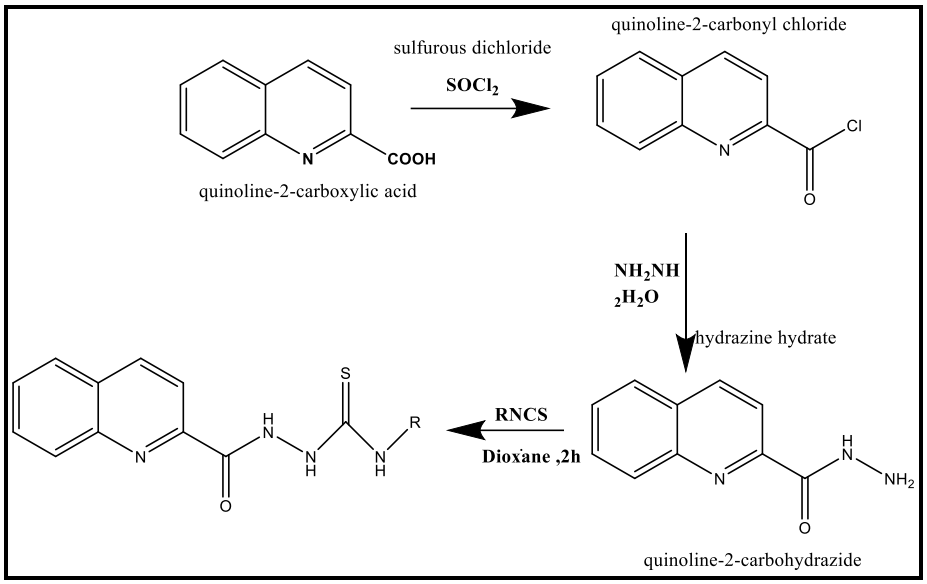


Abha Bishnoi *et al.*, (2012)synthesized thioazole derivatives of quinoline carboxylic acid and tested antimicrobial activity against a gram-positive bacteria [*Staphylococcus aureus* and *Bacillus subtilis*] and gram-negative bacteria *[Pseudomonasaeruginosa*), and *Escherichia coli*and fungal strains [*Candida albicansAspergillusniger,and Aspergillus fumigatus*)]. The structures of newly synthesized compounds were characterized by elemental analysis, Infrared (IR), ^{1}H NMR, ^{13}C-NMRand Mass-spectroscopy.the higher antimicrobial activity structure was shown below.

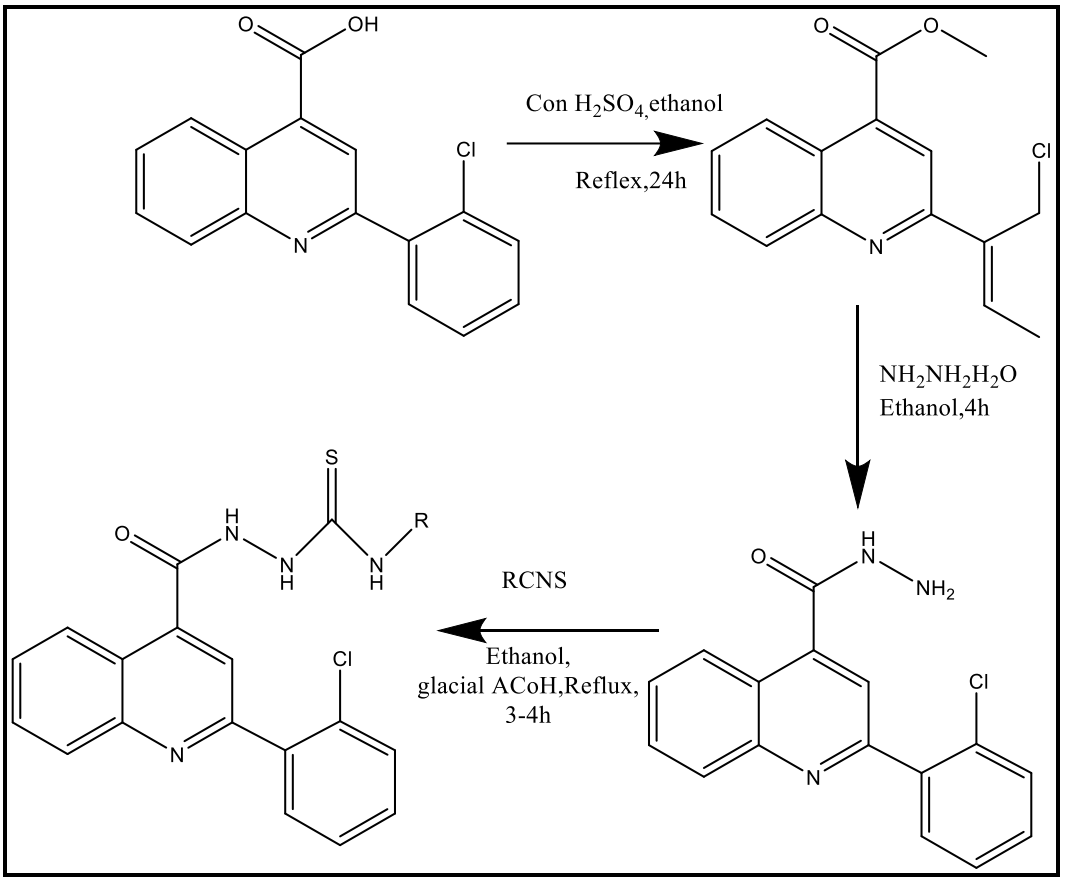




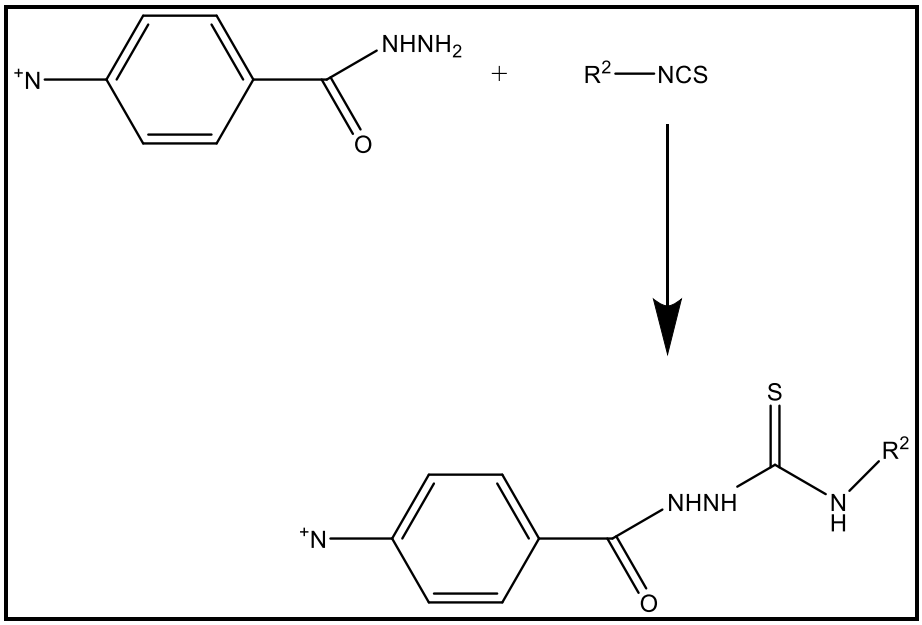
Prachi T. Acharya *et al., (*2021) developed the bio-active thiosemicarbazide derivatives .In recent years, the developed novel thiosemicarbazide compounds with a variety of biological functions had received a great deal of attention. In order to evaluate their biological activity, numerous scientists have produced this class of derivatives as target structures. Recent studies mostly focused on a significant collection of thiosemicarbazide analogues with a variety of biological functions that are extremely selective and effective. This report's main focus is on the synthesis of heterocyclic compounds known as hybrid thiosemicarbazides, their biological profiles, and studies of the structure-activity relationship (SAR), which can help expand the number of thiosemicarbazide derivatives with a variety of therapeutic uses.



Dhaval B *et al.*,(2018)synthesized,2-(2-(2-Chlorophenyl)quinoline-4-carbonyl)-N-substituted hydrazinecarbothioamide derivative. The synthetic compounds were tested against common medications for their *invitro* antibacterial, antifungal, antimalarial, and antituberculosis activities. Gram-positive and gramme-negative bacteria were used in the study on bacteria. These substances were found to have a wide range of activity against the screening microorganisms, but *Pseudomonas aeruginosa* and *Escherichia coli* showed weak activity. The structures of the compounds were elucidated with the aid of an elemental analysis, IR, ESI-MS, ^{1} H-NMR, and ^{13}C-NMR spectral data.

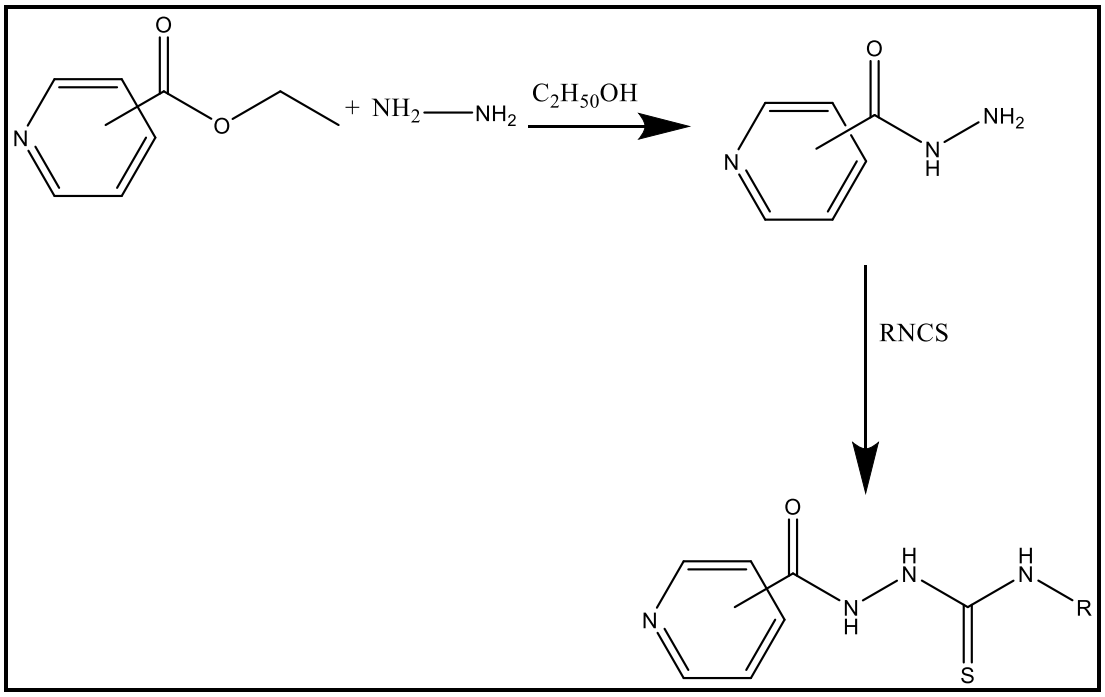


Maciej Wos *et al.,*(2017)developed a series of thiosemicarbazides having 4-nitrophenyl group by there action of carboxylic acid hydrazides with isothiocyanate. According to the investigation the respective structure shown good therapeutic activity. *In vitro* mild cytotoxicity, and antibacterial efficacy against *S. aureus, S. epidermidis, S. mutans, and S. sanguinis*. Each substance had its antibacterial and antiproliferative properties tested. Newly acquired product may be possible a-glucosidase inhibitors, according to PASS software. This was confirmed by *in vitro* studies.

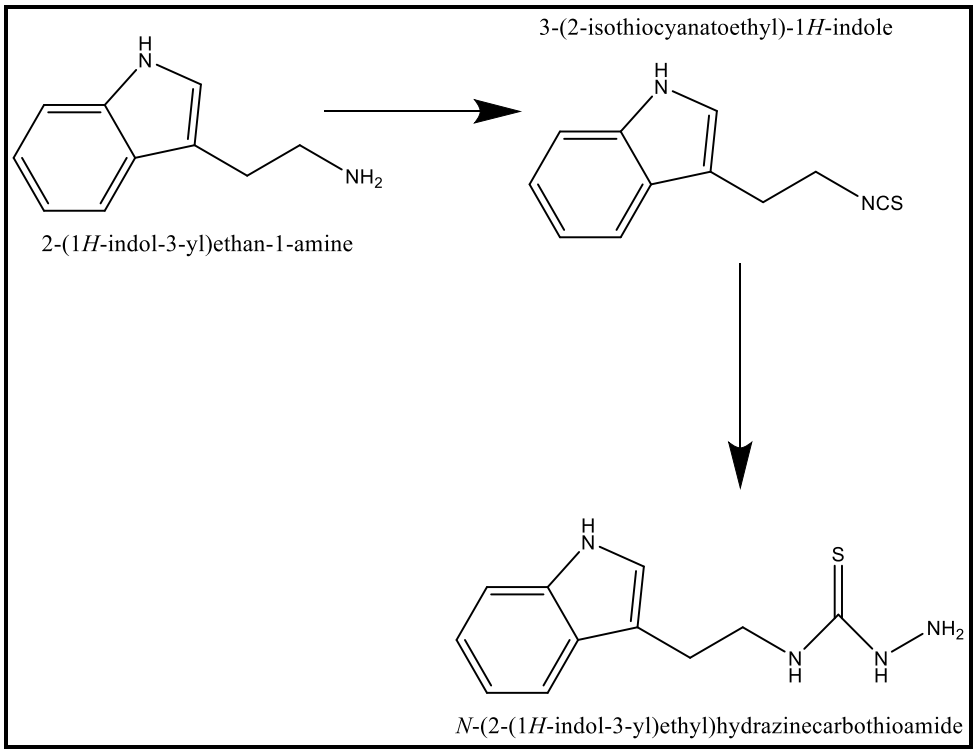


Magda A *et al.,* (2017)Synthesized a new family of 4,6-disubstituted quinolinesby the reaction of 2-(4-(dimethylamino) styryl) quinoline with 2-(4-(dimethylamino)styryl)quinoline.quinoline replaced by -6Thiosemicarbazide, p-hydroxybenzaldehyde, ethylcyanoacetate, and 2,4-pentandione with -4-carboxylic acids.The target compounds' structures were determined using information from the elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, 2-(4-(dimethylamino) styryl)-6-substituted quinoline, the precursorsFour-carboxylic acids were created by the Pfitzinger reaction, which provides an extremely practical synthetic entry to quinoline heating 4-(4-(dimethylamino) phenyl) but-3-en-2-one (1) and 5-substituted satins in an aqueous/alcoholic KOH solution to get the -4-carboxylic acid derivatives.biological evaluation of 2-styrylquinolines as antitumour agents and EGFR kinase inhibitors

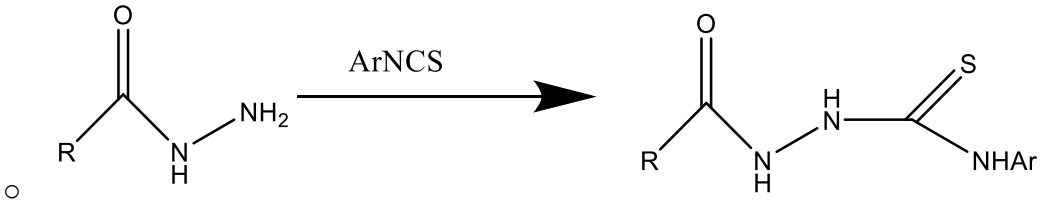
Monika Pitucha *et al.,(*2019)synthesized, a number of thiosemicarbazide derivatives by the interaction of carboxylic acid hydrazide with isothiocyanates.The *mycobacterium tuberculosis glutamine synthetase* (MtGS) was used as the molecular target in the molecular docking investigations for the drugs under investigation. Spectroscopic examination verified and provided details about the molecular structures of the examined thiosemicarbazides. X-ray analysis was used to describe the intra- and intermolecular interactions as well as the conformational preference of the carbonyl thiosemicarbazide chain in the crystalline state.For all compounds developed,*in vitro* tested were conducted using the four *Mycobacterium strains M. H37Ra, M. phlei, M. smegmatis, and M. timereck.*



Zhang-Xu He *et al.*,(2020)synthesized a variety of new thiosemicarbazone-indole analogues in an effort to find powerful and low-toxic anticancer drugs.The majority of substances showed moderate to strong anticancer activity against the five tumour cells (PC3, EC109, DU-145, MGC803, and MCF-7) that were evaluated.IC_{50} value of 0.054 M for PC3 cells compared to 19.470 M for normal WPMY-1 cells, demonstrating great antiproliferative efficacy and good selectivity. Overall, based on the biological activity evaluation, analogue 16f can be viewed as a potential lead compound for further developed novel anti-prostate cancer drug.

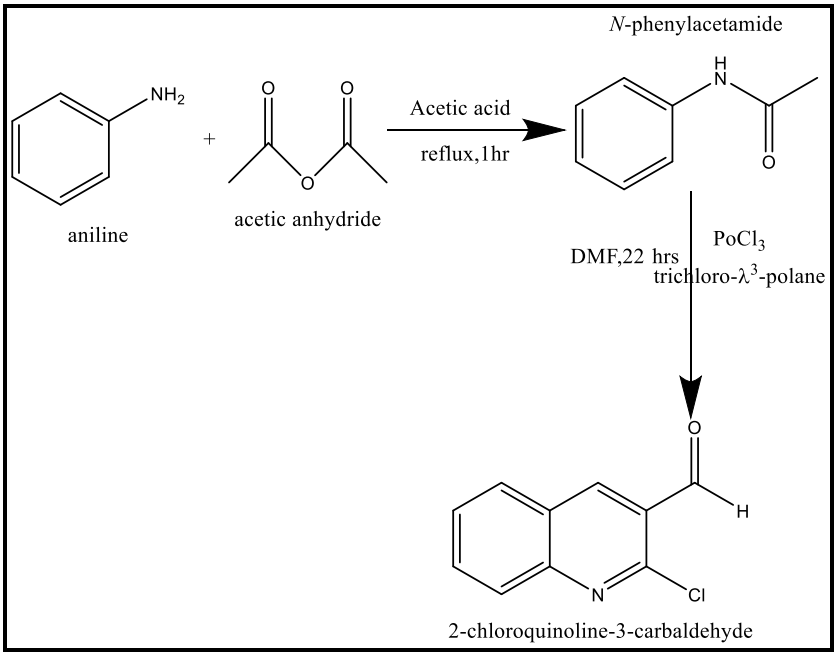


Mohamed A. Metwally *et al.*, (2011).Thiosemicarbazides play an essential role in the synthesis of a number of heterocycles, as evidenced by their use in organic synthesis. Their reactions with systems containing C=O and C=N groups is one of the methods for the preparation of biologically active compounds *viz*. pyrazole, thiazole, triazole, thiadiazole, oxadiazole, triazine and thiadiazine. The formation of C−N and C=N bonds as opposed to the N−N bond formation is reflected in their extensive use for the preparation of these heterocycles in excellent yields.

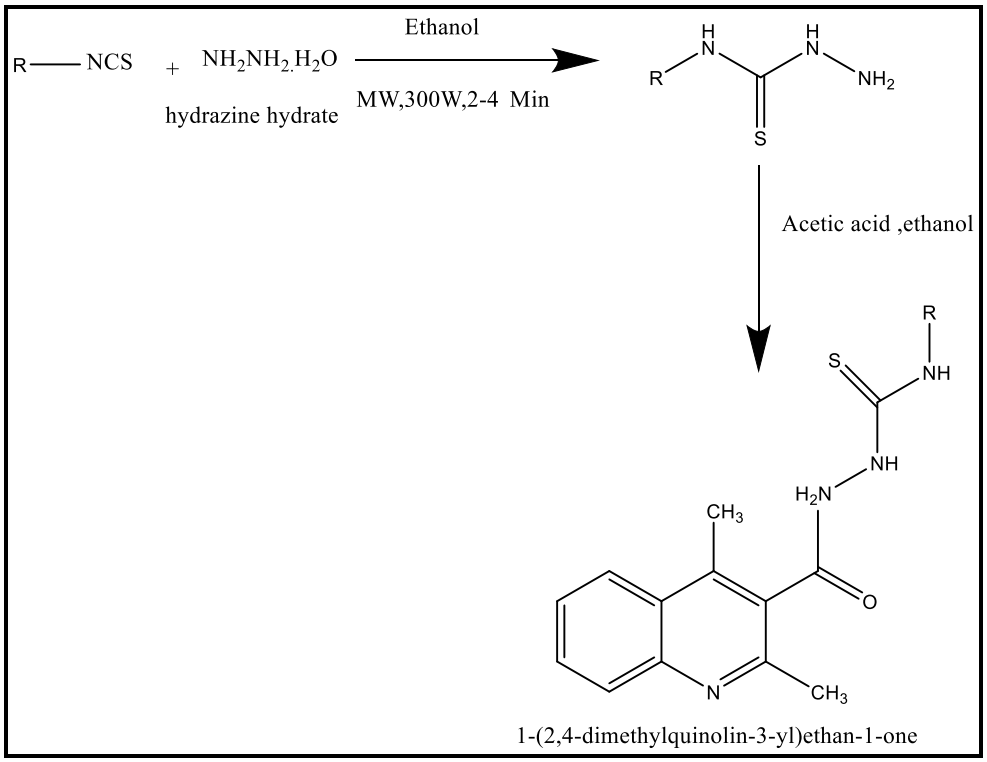


DigafieZeleke *et al.*, (2020)Synthesized acetamide derivatives of acetanilide and N-(o-tolyl) resulted in the creation of 2-chloroquinoline-3-carbaldehyde and 2-chloro-8-methylquinoline-3-carbaldehyde by the Vilsmeier reaction. The carbaldehyde group was oxidised by permanganate method and reduced with metallic sodium in methanol and ethanol. synthesized compounds were characterized by UV-Vis, IR, and NMR. antibacterial activity of the synthesized compounds was screened against two

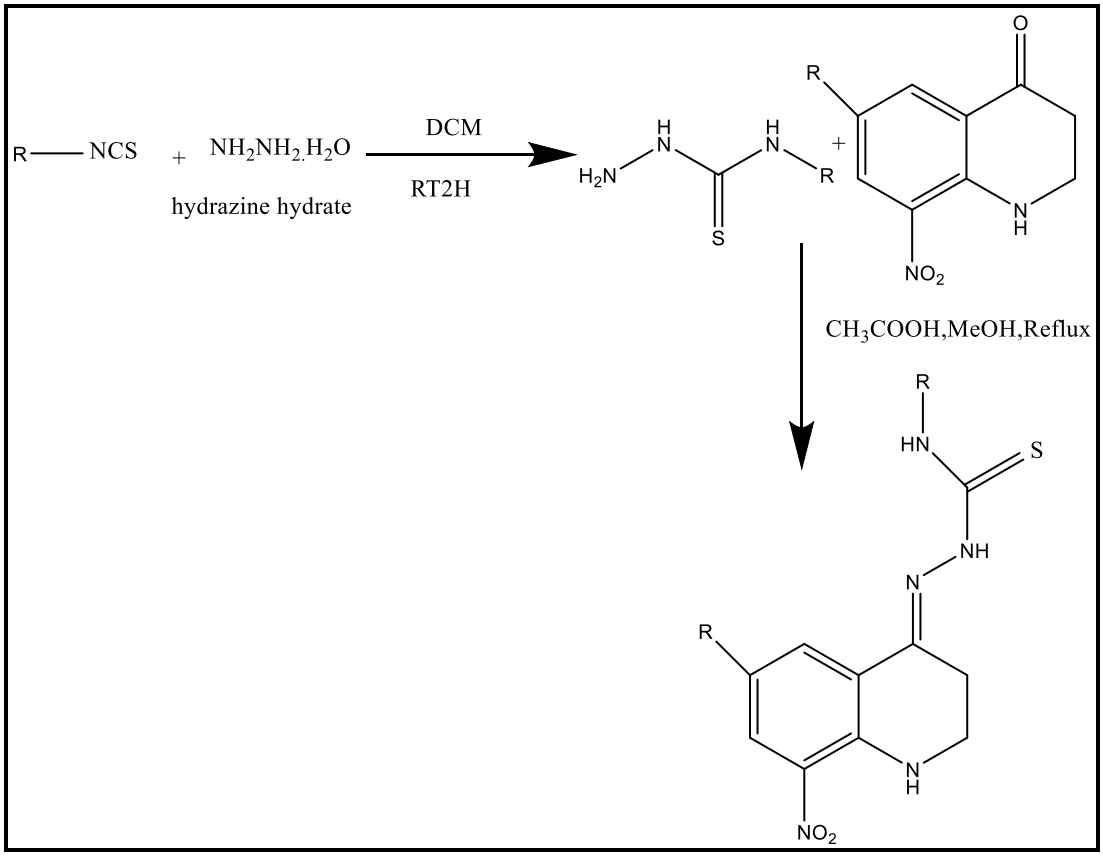
Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginos*a).potential lead compound for further developed novel anti-prostate cancer drug Using 1,1-diphenyl-2-picryl hydrazyl (DPPH), these compounds' ability to scavenge free radicals was assessed. All of them showed moderate antioxidant activity, the respective compound having the most potent action.



Dhaval B. Patel *et al.*, (2019) developed a novel series of N-((substituted)carbamothioyl)-2, 4-dimethylquinoline-3-carboxamide using a microwave-assisted technique. These derivatives' structures were investigated using spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, FT-IR, and ESI-MS. Additionally, the unique synthetic compounds were assessed for their *in-silico* research and *in-vitro* biological properties against antibacterial, antifungal, antimalarial, and antituberculosis activity. The synthesized compounds' computed ADME-Tox descriptors supported their favourable pharmacokinetic characteristics, indicating that they might be employed as a starting point for the creation of novel active drugs.



Selvaraj Shyamsivappan *et al.*,(2020)synthesised 8-nitro quinoline-based thiosemicarbazone analogues were created and examined using a variety of spectroscopic and single crystal X-ray methods. The molecular mechanistic studies of cell death have demonstrated that the treated potent compound 3a induced G1/S & G2/M phase cell cycle arrest and induced apoptosis via mitochondrial dysfunction and increased the production of cytotoxic ROS levels. The potent antitumor effects of synthesized compounds towards the cancer cells were evaluated by MTT assay. Amongst, the compound 3a exhibited the highest inhibitory activity and the compounds 3f and 3b were also showed significant activity. Furthermore, molecular docking studies were used to determine the molecular binding affinity of substances with oestrogen receptor alpha. Novel 8-nitro quinoline-thiosemicarbazone analogues thus offer a special tool for breast cancer treatment strategies.



Dhaval B. Patel *et al.*,(2019) Synthesized a novel series of N-((substituted)carbamothioyl)-2, 4-dimethylquinoline-3-carboxamide was created in the current work by using a microwave-assisted technique. To test the stability of the docked complex and their molecular interaction, we also ran a molecular dynamics simulation on the best dock compound 7e complex with PDB: 3JSU. Good pharmacokinetics features for the synthesised compounds were corroborated by the computed ADME-Tox descriptors, indicating that these compounds might be employed as a starting point for the creation of novel active medicines. Structure of these derivatives was examined by spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, FT-IR, and ESI-MS. Further, the novel synthesized compounds were evaluated for their *in-vitro* biological activities against antibacterial, antifungal, antimalarial, and antituberculosis activity as well as for *in silico* study.

Sumesh Eswaran *et al.*, (2009) developed a quinoline derivatives of 1,2,4-triazole moiety were created from derivatives of 4-hydroxy-8-(trifluoromethyl) quinoline-3-carbohydrazide by the multistep reaction. According to preliminary findings, the majority of the compounds showed excellent antibacterial activity. The most active substances have shown activity at MICs of 6.25 mg/mL. The final step, a

nucleophilic substitution reaction, was accomplished using a microwave-induced method, which, when compared to traditional heating, substantially cut the reaction time and increased yield. The effectiveness of the newly synthesised final compounds against four strains of each of four different microorganisms was assessed *in -vitro*.

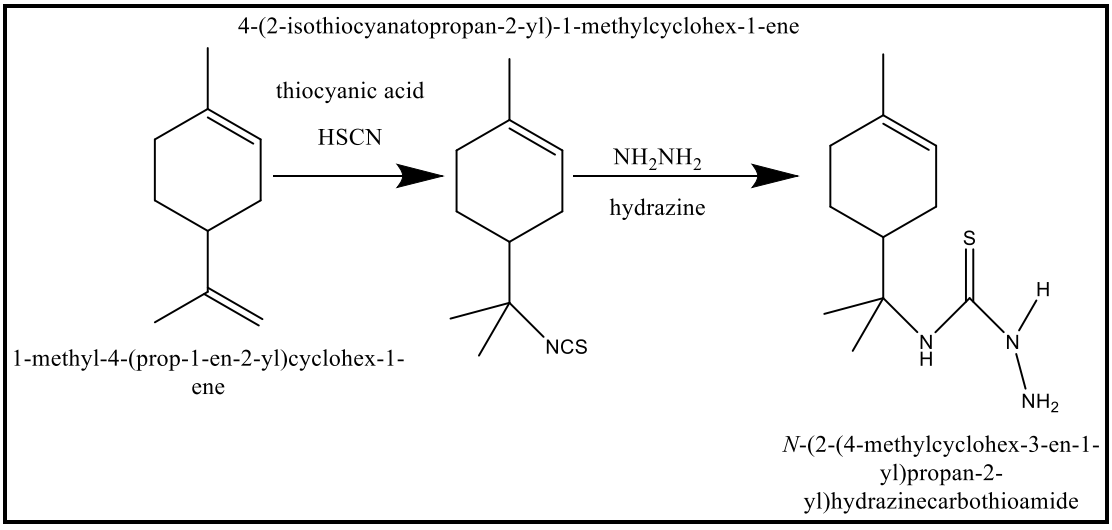
Shefai arora *et al.*, (2014)developed the new and more effective drugs to combat cancer disease. Thiosemicarbazides and thiosemicarbazone possess a wide range of biological applications. This key biological role is often related with their capability to inhibit the enzyme ribonucleotide reductase, similar to what is observed with potent anticancer drugs such as triapine and methisazone. Recent studies have revealed that thiosemicarbazones can inhibit topoisomerase II enzyme. This review discusses current advances of an emerging 'new wave' of thiosemicarbazide/thiosemicarbazone and their metal complexes as potent anticancer agents, mode of action and toxicity caused by them.

M. Botoshanskii, *et al.*, (2009)determined that the quinoline-8-aldehyde S-methyl thiosemicarbazone dihydrochloride's thiosemicarbazide fragment exhibits a cis-configuration of terminal nitrogen atoms, similar to that seen in its coordination compounds with copper(II) and palladium(II).The[S-Me-H2QATSC]+conformation does not undergo structural rearrangements, as demonstrated by a comparison between it and the free-state structure of quinoline-8-aldehyde thiosemicarbazone.

Atukuri Dorababu (2020)synthesized only a small subset of heterocycles, specifically quinoline derivatives, have demonstrated the best biological activities, despite the fact that the majority of them have been found to have considerable pharmacological activity. Despite the basic quinoline molecule having only a few therapeutic benefits, its derivatives have a wide range of pharmacological benefits, including anticancer, anti-inflammatory, antibacterial, antiviral, antifungal, and antiprotozoal activity. The decades of research on the quinoline compounds have demonstrated their potential antibacterial capabilities. These medications have lost their effectiveness in recent years due to drawbacks such drug resistance, high cost, severe side effects, and low absorption of previously synthesised antimicrobial agents. Therefore, the creation of antimicrobial medications that are more effective must be

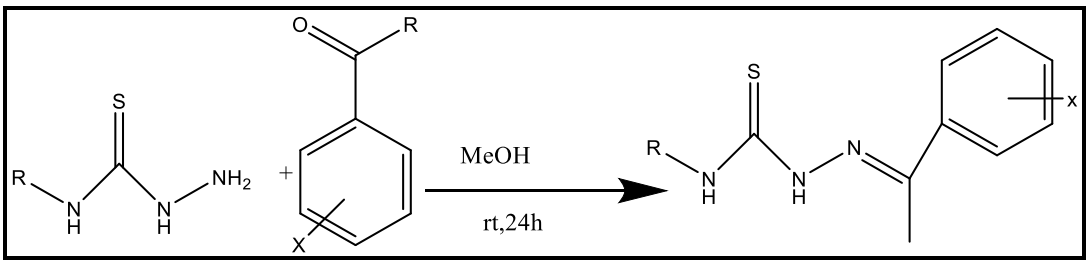
prioritised above everything else. To stop malicious behaviour, a drug discovery breakthrough is necessary.

Mirian Ueda Yamaguchi *et al.*, (2009)developed the biological activity of thiosemicarbazides is well recognised, and they are particularly well known for their antibacterial activities, which include activity against fungi.For the creation of these novel thiosemicarbazide derivatives, they choose the natural chemicals limonene and camphene as sources.Trichophyton mentagrophytes, the chemical N(4)-[2,2-dimethyl-3-methylnorbornane]-thiosemicarbazide (TIO C) demonstrated an antifungal activity with MIC = 55 mol L-1 and MFC = 110 mol L-1 values.Mentagrophytes cell walls and dividing cross-walls were demonstrated by the observed reduction in the fluorescence of tissues stained with calcofluor white, a specific marker for fungal chitin. This observation suggests that the compound can affect and damage the cell-wall structure or may interfere with its formation, during cell division, growth, and morphogenesis. This method for creating novel derivatives may result in intriguing substances with higher biological activity for use in pharmaceutical research



Soroush Sardari *et al.*, (2015)synthesized some new thiosemicarbazide derivatives by condensation reaction of various aldehydes or ketones with 4-phenylthiosemicarbazide or thiosemicarbazide is reported.High yields and strong bioactivity are two benefits of this synthesis technique.Thiosemicarbazides are powerful chemical building blocks for the synthesis of pharmacological and bioactive compounds, and as a result, they are widely used in the field of medical chemistry**.**All of these compounds were tested for their *in-vitro* anti-mycobacterial activity.The

structures of these compounds were confirmed by IR, mass, ^{1}H NMR, ^{13}C NMR, and single-crystal X-ray diffraction studies.



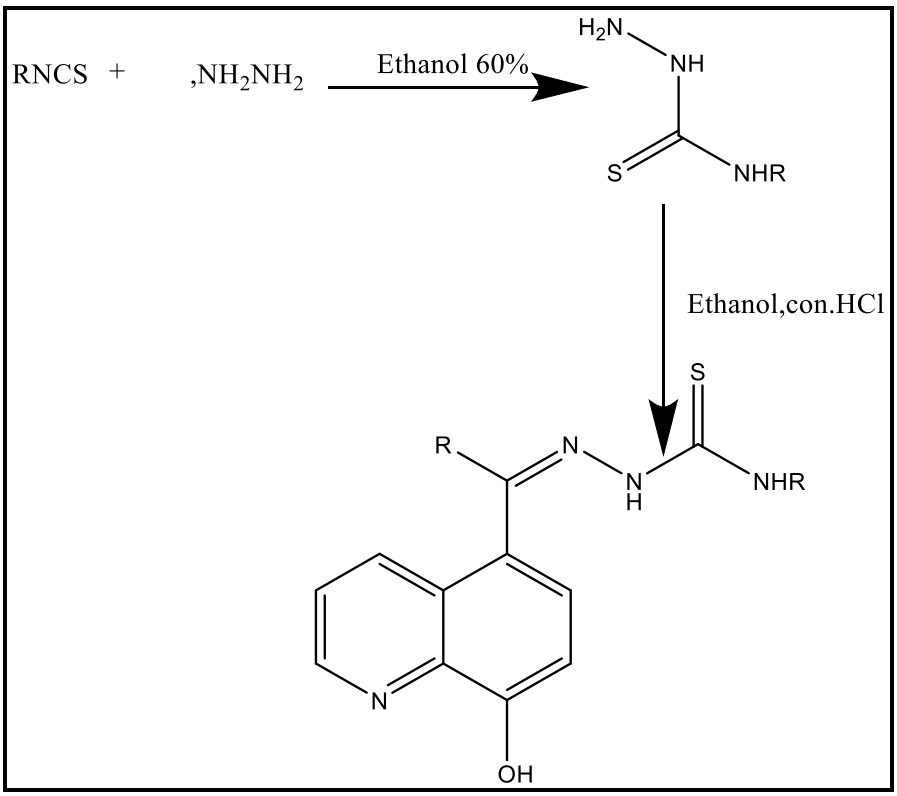
Nuha Ahmed Wazzan (2015) determined three different types of compounds, including thiosemicarbazide, phenylisothiocyanates, and 1-phenyl-2,5-dithiohydrazodicarbonamides, were subjected to DFT with three functionals. These molecules were employed as corrosion inhibitors for copper in chloride solutions. The majority of the computed quantum chemical parameters (QCPs) were in the same order as the experimental%IEs. The calculations of the complex energies and the inhibitor-copper bond lengths were utilised to forecast the most active site(s) in the inhibitor to be adsorbed on the copper surface, supported by the Mulliken population analysis and molecular electrostatic potential plots. The calculations determined a relationship between the molecular structures and the experimental inhibition efficiencies (%IEs).

A. RIONDEL *et al.*, (1963) estimated the measurement of testosterone in 10 ml of human peripheral plasma using a double isotope technique is discussed. The reagent is S35-thiosemicarbazide (100 mc/mM), and the indicator is 1,2-H3-testosterone (137 nc/jug).With the probable exception of 17-epitestosterone (5% of any initial amount of this compound would be evaluated as testosterone), no known product or endocrine gland metabolites were identified to be likely to affect the specificity of the estimation. In contrast to the plasma of five ovariectomized-adrenal-ectomized women (0.013 + 0.002 (SE) Mg/100 ml), a highly significant higher value of testosterone was discovered in the eight ovariectomized women (0.032 + 0.003 (SE) Mg/100 ml). In the progestational phase of the menstrual cycle, two normal women (ages 0.059 and 0.079) and eleven normal men (ages 21-36) had mean plasma concentrations of 0.080 0.225 (SD) jug/100 ml and 0.80 0.205 (SD) jug/100 ml, respectively.

Mohamed Abass *et al.*, (2015) synthesized, under various reaction conditions, the reactivity of 3-acetyl-4-methylthioquinolin-2(1H)-one (1) towards 1,2- and/or 1,4-

diazanucleophiles had been investigated. In various media, key component 1 was condensed with hydrazine, phenyl hydrazine, hydroxylamine hydrochloride, semicarbazide, and thiosemicarbazide**.** Accordingly, the reaction regioselectivety lead to different [1,2]diazolo and or [1,2,4]triazepino quinoline derivatives in addition to open chain condensates which were transformed to either annellated heterocyclo[b or c] quinolines, in good yield**s.** According to their analytical and spectral data, new products' structures were established.

Samia G. Abdel-Moty *et al.*, (2005)synthesized 5-Acetyl (or5-Benzoyl)-8-hydroxyquinolineBy condensation of 5-acetyl (or 5-benzoyl), -4-substituted thiosemi-carbazones have been created.when combined with the suitable 4-substituted-3-thiosemicabazide.Thethiosemicarbazones were subjected to cyclization into the corresponding thiazolidinones by the reaction with ethyl bromoacetate in the presence ofanhydrous sodium acetate.The structures of the thiosemicarbazones as well as the corresponding thiazolidinones were assigned based on both elemental and spectroscopic evidences. The prepared compounds were also evaluated for antibacterial and antifungal activities.



Maciej Wosa *et al.,* (2017) developed the reaction of carboxylic acid hydrazides with isothiocyanates produced a series of thiosemicarbazides having a 4-nitrophenyl group. Molecular docking for most active compounds to yeast a-glucosidase was performed and molecular interactions were determined. According to our findings, derivatives selected compound had good therapeutic safety in vitro, mild cytotoxicity, and antibacterial efficacy against S. aureus, S. epidermidis, S. mutans, and S. sanguinis.Additionally, A549, HepG2, and MCF-7 cell division was markedly reduced by selected compounds. Additionally, the PASS programme revealed that recently discovered compounds have the potential to be a-glucosidase inhibitors. This was confirmed by *in- vitro* studies.

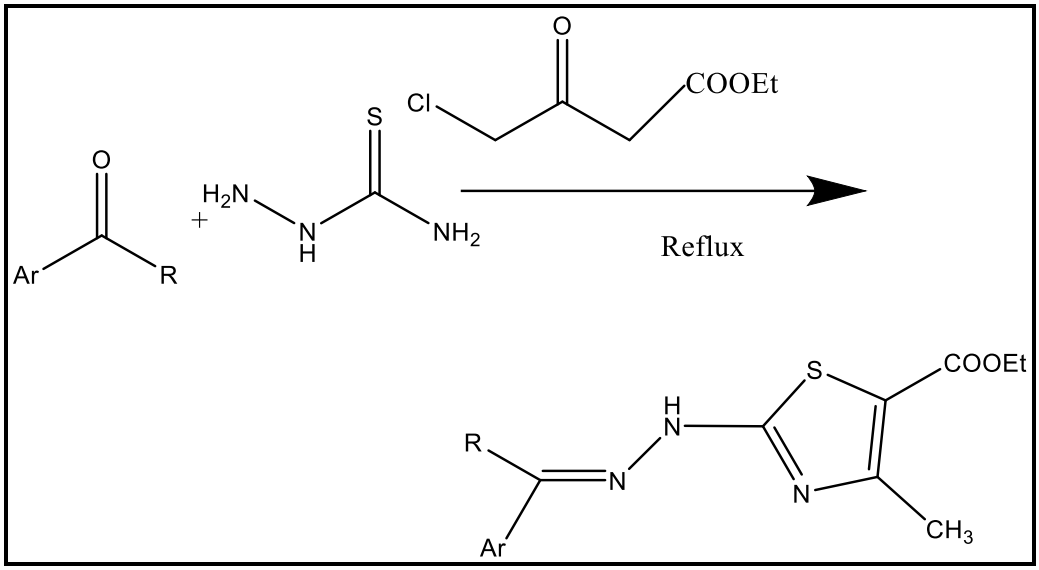
SHEFALI ARORA *et al.,* (2014) developed the chemotherapeutic treatment of cancer had advanced significantly, and scientists are still working to create new, more potent medications to treat the condition. Wide-ranging biological uses can be made of thiosemicarbazides and thiosemicarbazone. Similar to what is seen with powerful anticancer medications like triapine and methisazone, this important biological activity is frequently connected to their capacity to block the enzyme ribonucleotide reductase. Thiosemicarbazones have the ability to block the topoisomerase II enzyme, according to recent investigations. developing "new wave" of thiosemicarbazide/thiosemicarbazone and their metal complexes as effective anticancer treatments, as well as their mechanisms of action and potential side effects, are covered in this study.

K.D. Thomas *et al.,* (2011)synthesized a number of steps, three new series of 4-hydroxy-8-trifluoromethyl-quinoline compounds. Spectral and elemental studies were used to characterized each of the newly synthesized substances**.**The newly synthesized title compounds were evaluated for their antimicrobial activities including antimycobacterial activity.The structure of selected compound was evidenced by X-ray crystallographic study.

Mohammed A *et al.,* (2020)Identified the 6-substituted quinolin-2-one thiosemicarbazides represent a novel class of compounds**.**All the developed fnal compounds were tested for their effectiveness in vitro against the bacterial pathogen Proteus mirabilis and the fungus R. mucilaginosa, which both produce urease.The

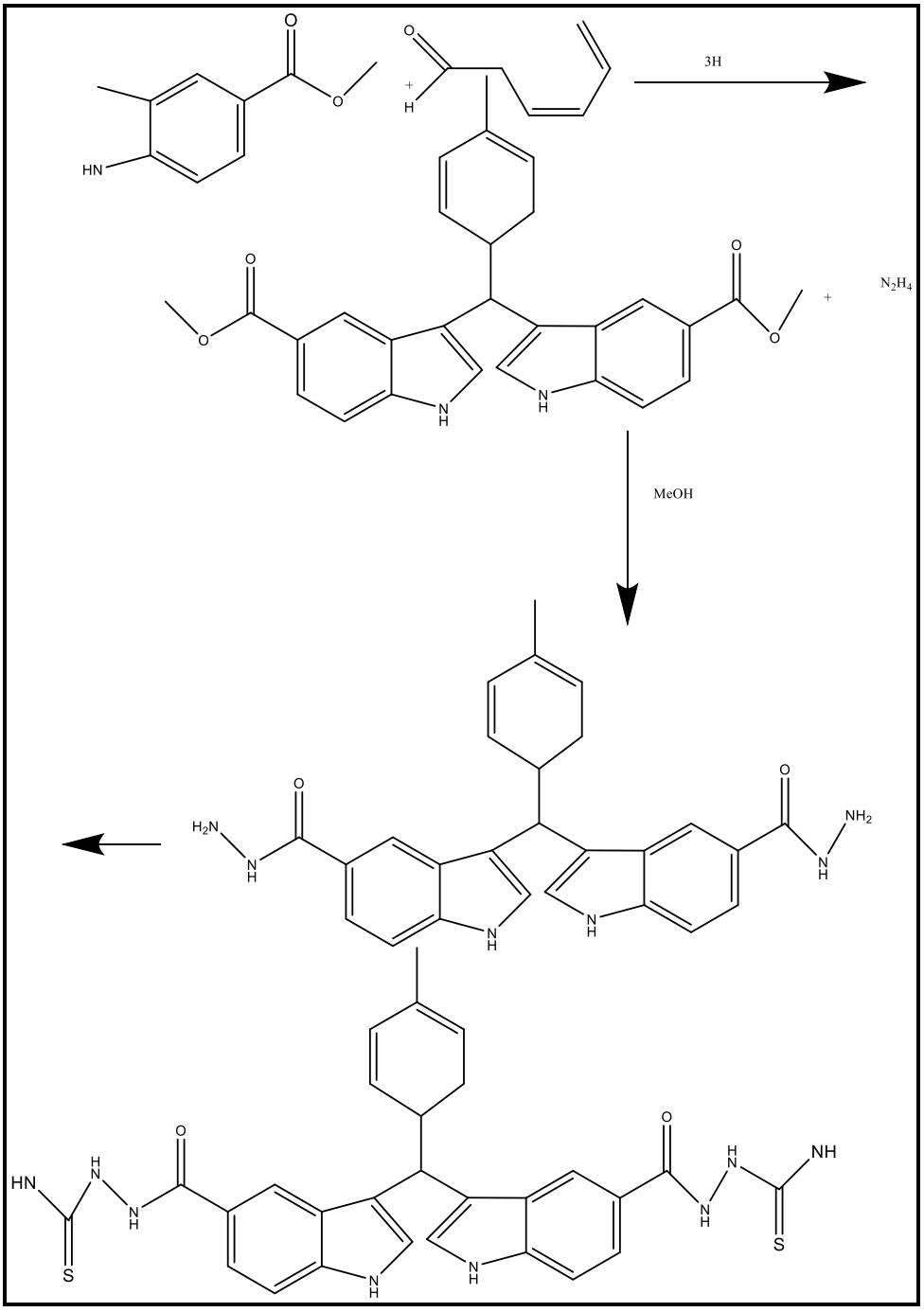
docking results showed that many powerful hydrogen bonds can be used by the proposed chemicals to engage with the enzyme's active region. In order to comprehend the 3D QSAR of synthetic compounds as urease inhibitors, a quick overlay of chemical structure analysis was presented.The structure of the target compounds was proved by diferent spectroscopic and elemental analyse.

Ma Xiabing *et al.*, (2009) synthesizedhydrazone derivatives of thiazole compounds, *via* one-pot three-component reaction of aldehyde/ketone, thiosemicarbazide and chlorinated β-keto ester catalyzed by anhydrous sodium acetate. The reactions had excellent yields in EtOH solvent. The synthetic method and reaction mechanism were discussed**.** It was reported that the method had a number of benefits, including high yields, a wider range of substrates, and a safe, inexpensive, and environmentally friendly process, which make it a useful method for the synthesis of comparable types of compounds.



Muhammed Taha et al.,(2018) synthesized the Bisindolyl methane thiosemicarbazides then their capacity to inhibit urease was assessed using ^{1}H NMR and ESI MS**.** When compared to the conventional inhibitor thiourea, which has an IC_{50} value of 21.25 0.90 lM, all analogues demonstrated exceptional urease inhibitory potentials with IC_{50} values ranging between 0.14 0.01 and 18.50 0.90 lM. Analogue 9 (0.14 0.01 lM), which had a dichloro substitution on the phenyl ring, was found to be the series' most effective urease inhibitor. On the basis of the binding interactions of the active analogues, the

structure-activity link had also been established. Studies using molecular docking helped to identify these binding connections.



MATERIALS

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METHODS

3.Materials and Methods

All organic chemical were purchased from Sigma-aldrich.

The solvents and reagents used for the synthesis were of reagent grade and were purified by standard methods.

TLC has been performed using glass plates coated with silica gel.Hexane,chloroform,ethylacetate,ethanol,aceticacid,pet ether(60-80℃) were used as the developing solvents.spots were detected with UV light and iodine chambaer.

Melting points have been determined on SAFIRE apparatus and were uncorrected.

The Fourier transform infrared (FT-IR) spectrum was recorded using SHIMADZU PRESTIGE 20 FT-IR spectrometer.

^{1}H NMR was recorded using 400 MHZ BRUKER spectrometer; chemical shifts are given in δ units (ppm) relative to internal standard tetramethylsilane (Me4Si) and refer to $CDCl_3$ solutions.

3.1.Preparation of Mandelothiosemicarbazide from Mandelic acid

3.1.1.Preparation of mandelo carboxylate from Mandelic acid

1g of mandelic acid was dissolved in 5 ml of ethanol.To this solution added 3 drops of con.H_2SO_4, This reaction mixture was kept in a waterbath under reflux at 70℃ for 3 hours.The reaction was monitored by TLC. After completion of reaction the mixture was worked up with ice cold water. The solution was separated with ethyl acetate using separatory funnel. Organic layer and water layer was collected and evaporated to yield the compound as powder.This was recrystallized with ethanol.

3.1.2. Preparation of Mandelo carbohydrazide from mandelo carboxylate

1g of mandelo carboxylate was dissolved in 5 ml of ethanol.To this solution added 1 ml of Hydrazine hydrate, This reaction mixture was kept in a water-bath under reflux at 70℃ for 5 hours. The reaction was monitored by TLC .After completion of the reaction, the mixture was worked up with ice cold water the solution was separated with di-ethyl ether using separatory funnel .Organic layer was collected and evaporated to yield the compound as powder. This was recrystallized with ethanol.

3.1.3.Preparation of mandelothiosemicarbazide from mandelo carbohydrazide

0.5g of mandelocarbohydrazide was dissolved in 10 ml of water.To this solution added 0.5g of(dissolved in 3 ml of water) potassium thiocyanate(KSCN), This reaction mixture was kept in a waterbath under reflux at 80℃ for 10 hours.The reaction was monitored by TLC.After completion of the reaction mixture was worked up with ice cold water.The solution was separated with diethylether using separatory funnel.Organic layer and water layer was collected and evaporated to yield the compound as powder.This was recrystallized with methanol.

3.2.Preparation of coumarothiosemcarbazide from coumaric acid

3.2.1.Preparation of coumaro carboxylate from coumaric acid

1g of coumaric acid was dissolved in 5 ml of ethanol.To this solution added 3 drops of con.H_2SO_4, This reaction mixture was kept in a waterbath under reflux at 70℃ for 3 hours.The reaction was monitored by TLC .After completion of the reaction mixture is worked up with ice cold water. The solution was separated with ethyl acetate using separatory funnel. Organic layer and water layerwas collected and evaporated to yield the compound as powder.This was recrystallized with ethanol.

3.2.2Preparation of coumaro carbohydrazide from coumaro carboxylate

1g of coumaro carboxylate was dissolved in 5 ml of ethanol.To this solution added 1 ml of Hydrazine hydrate, This reaction mixture was kept in a water-bath under reflux at 70℃ for 5 hours.The reaction will monitored by TLC .After completion of reaction the reaction mixture was worked up with ice cold water.The solution was separated with di-ethyl ether using separatory funnel.Organic layer and water layer was collected and evaporated to yield the compound as powder. This was recrystallized with ethanol

3.2.3.Preparation of coumarothiosemicarbazide from coumaro carbohydrazide

0.5g of mandelocarbohydrazide was dissolved in 10 ml of water.To this solution added 0.5g of(dissolved in 3 ml of water) potassium thiocyanate(KSCN), This reaction mixture was kept in a water-bath under reflux at 80℃ for 10 hours.The reaction was monitored by TLC After completion of the reaction mixture was worked up with ice cold water.The solution was separated with di-ethyl ether using separating

funnel.Organic layer and water layer was collected and evaporated to yield the compound as powder.This was recrystallized with methanol.

RESULTS

&

DISCUSSION

4.RESULT AND DISCUSSION

The result pertaining to the present study on synthesis of Thiosemicarbazide derivatives is reported and discussed in the light of the objectives set forth.

Synthesis of thiosemicarbazide involves three steps.

- To Synthesis carboxylic esters of mandelic acid and p-Coumaric acid
- To Synthesis aromatic carbohydrazides of mandelic acid and p-Coumaric acid
- To Synthesis Hydrazinecarbothioamides of mandelic acid and p-Coumaric acid.

4.1 .Synthesis of esters

Esters of mandelic acid & coumaric acid were prepared by condensation of corresponding acids with ethyl alcohol using concentrated sulphuric acid as catalyst.the esters were obtained in good yields..The yield and melting points of the compound are given in table-I.

TABLE-I

Ester	Melting point	Yield
2	80°C	77%
6	120°C	65%

4.2. Synthesis of carbohydrazide

The prepared esters were condensed with hydrazine hydride by reflux on water bath to give carbohydrazides. The yield and melting points of carbohydrazides are given in table-II.

TABLE-II

Carbohydrazides	Melting point	Yield
3	151°C	58
7	153°C	51

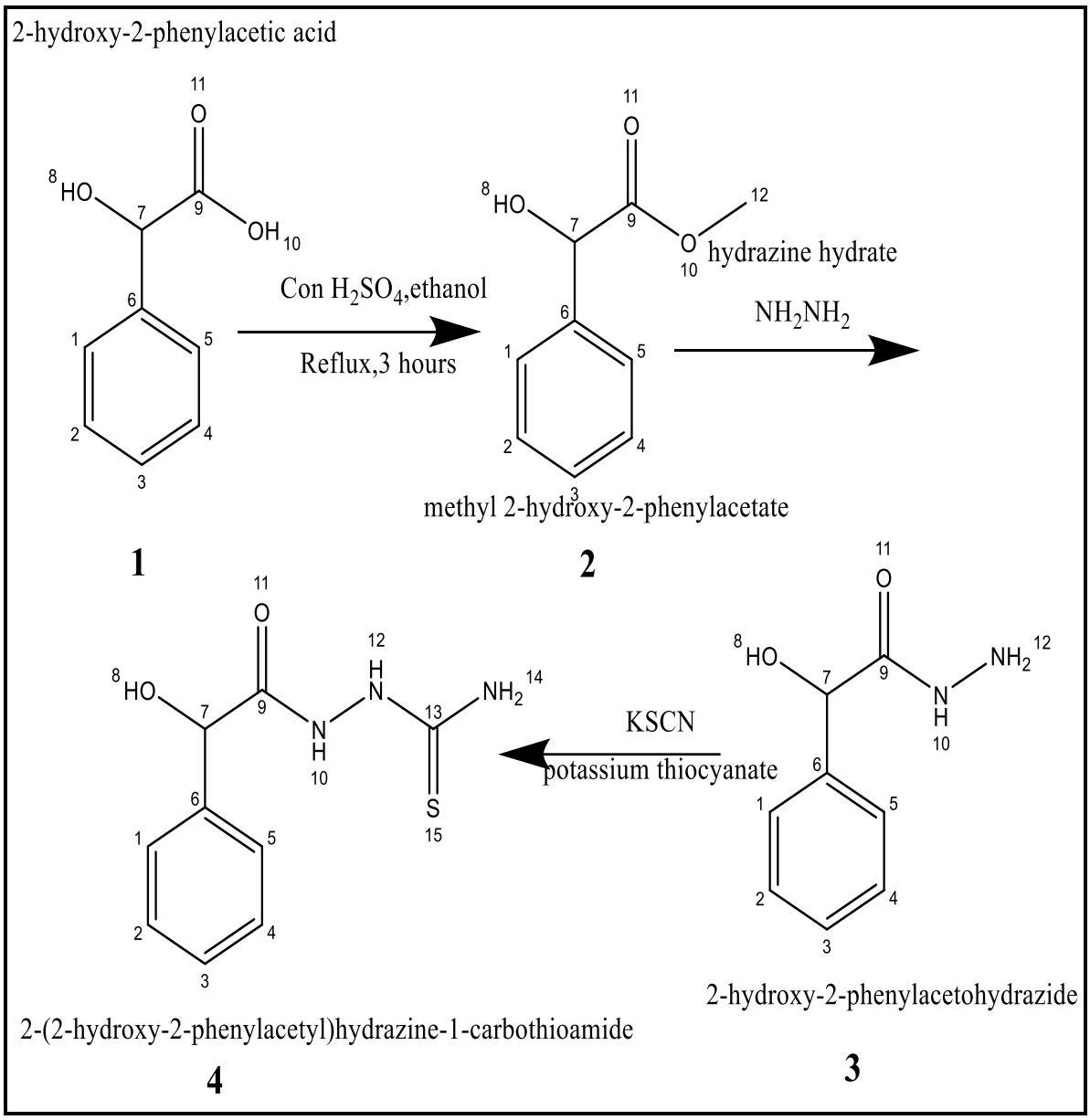
4.3. Synthesis of thiosemicarbazide

The prepared carbohydrazides condensed with potassiumthiocyanate by refux on water bath to give thiosemicarbazides. The yield and melting points of the thiosemicarbazide are given in table-III.

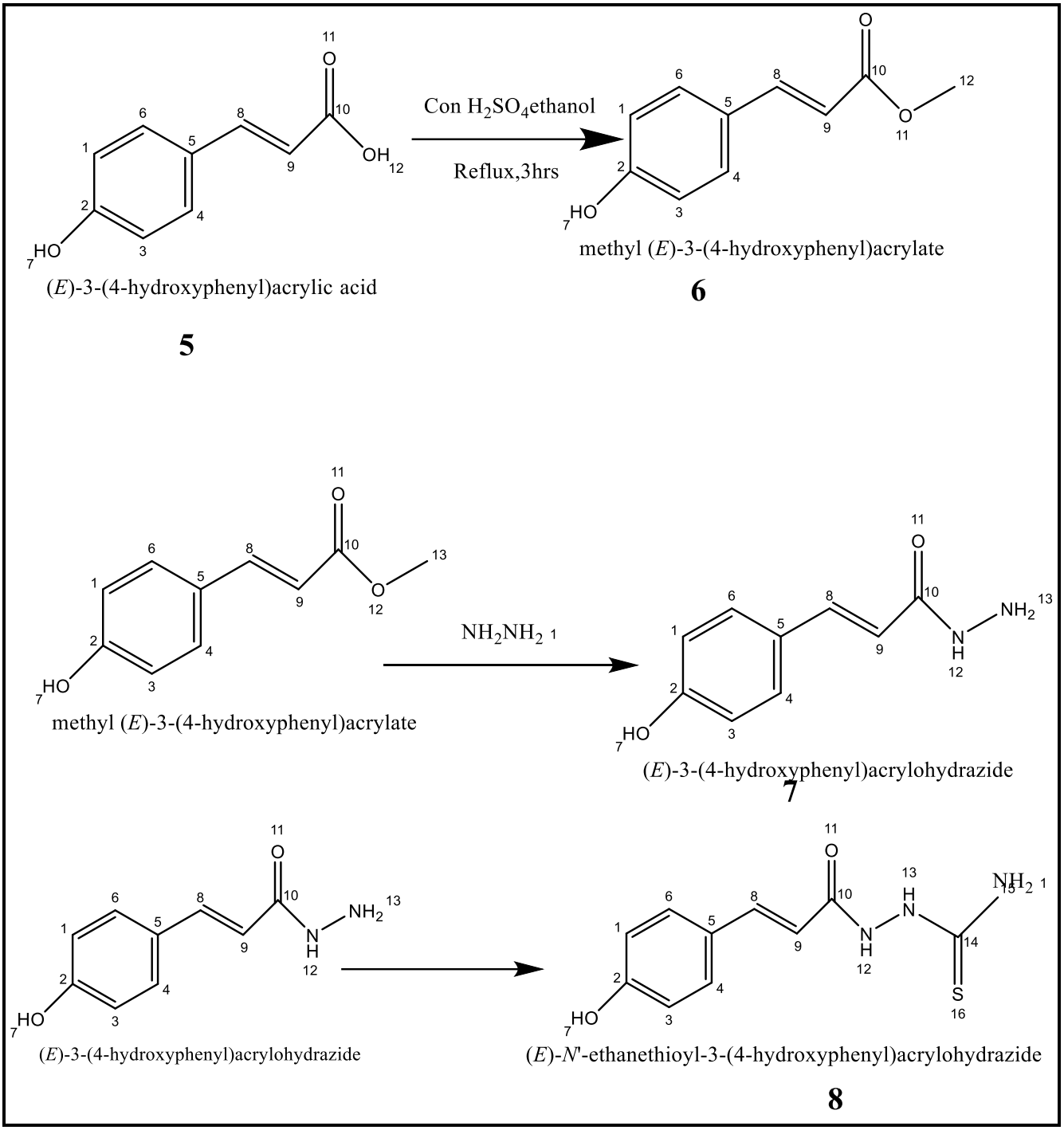
TABLE-III

Thiosemicarbazides	Melting point	Yield
4	181°C	47%
8	183°C	42%

4.4. The scheme reaction of the synthesized compound are given in below.



4.4.1. SCHEME-I



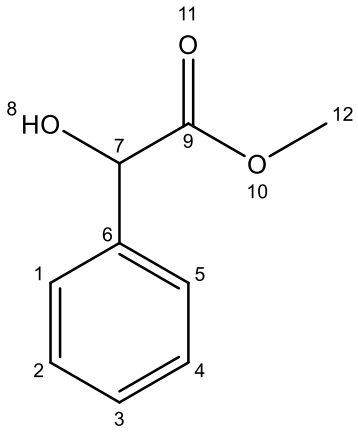
4.4.2. SCHEME-II

4.5. CHARACTERIZATION OF SYNTHESIS COMPOUND

4.5.1. FT-IR ANALYSIS

FT-IR spectrum analysis of compounds 2,3,4,6,7,8 are given in (**TABLE-IV,V,VI,VII,VIII,IX)** &[**FIGURE -I,II,III,IV,V,VI]** respectively.

4.5.1.1. Methyl 2-hydroxy-2-phenylacetate

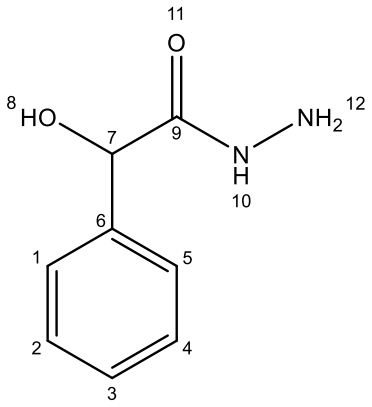


The FT-IR Spectrum of methyl 2-hydroxy-2-phenylacetate (**TABLE-IV) & [FIGURE-I]** showed a sharp band at 1728 cm^{-1} corresponding to C=O stretching,A peak observed at 3441 cm^{-1} indicated OH stretching,In addition,the stretching vibration of C-O stretch was observed at 1242 cm^{-1}.

TABLE-IV

Frequency(cm^{-1})	Functional group
1728	C=O stretch
3441	O-H stretch
1242	C-O stretch

4.5.1.2. 2-hydroxy-2-phenylacetohydrazide

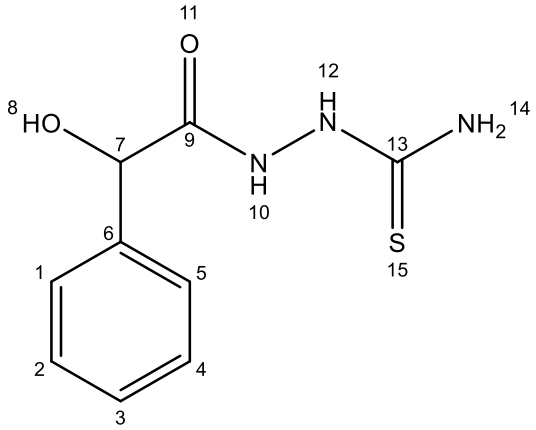


The FT-IR Spectrum of 2-hydroxy-2-phenylacetohydrazide **(TABLE-V) & [FIGURE-II]** showed a sharp band at 1890cm^{-1} corresponding to C=O stretching,A peak observed at 2854 cm^{-1} indicated OH stretching.A peak observed at 1589cm^{-1} indicated amide group. A peak observed at 1188cm^{-1} indicated C-N stretch.A sharp peak observed at 686cm^{-1} indicated C-H stretch.

TABLE-V

Frequency(cm^{1})	**Functional group**
1890	C=O
2854	O-H
1589	Amide group
1188	C-N stretch
686	C-H stretch

4.5.1.3. 2-(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide



The FT-IR Spectrum of 2-(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide **(TABLE-VI) &[FIGURE-III]** showed a sharp band at 1643cm^{-1} corresponding to C=O stretching.A peak observed in 3348cm^{-1} indicated (O-H) stretch, A peak observed at 1126cm^{-1} indicated (C-N) amines, A peak observed at 3811 cm^{-1} indicated (NH_2) secondary amine. A peak at observed 1180 cm^{-1} indicated C-N stretch, a sharp band observed at 887cm^{-1} C=S stretch. A peak observed at 1643cm^{-1} indicated C=C stretching.

TABLE-IV

Frequency(cm^{-1})	**Functional group**
1643	C=O
3348	O-H
1126	C-N
3811	NH_2group
1180	C-N stretch
887	C=S
1643	C=C Stretching

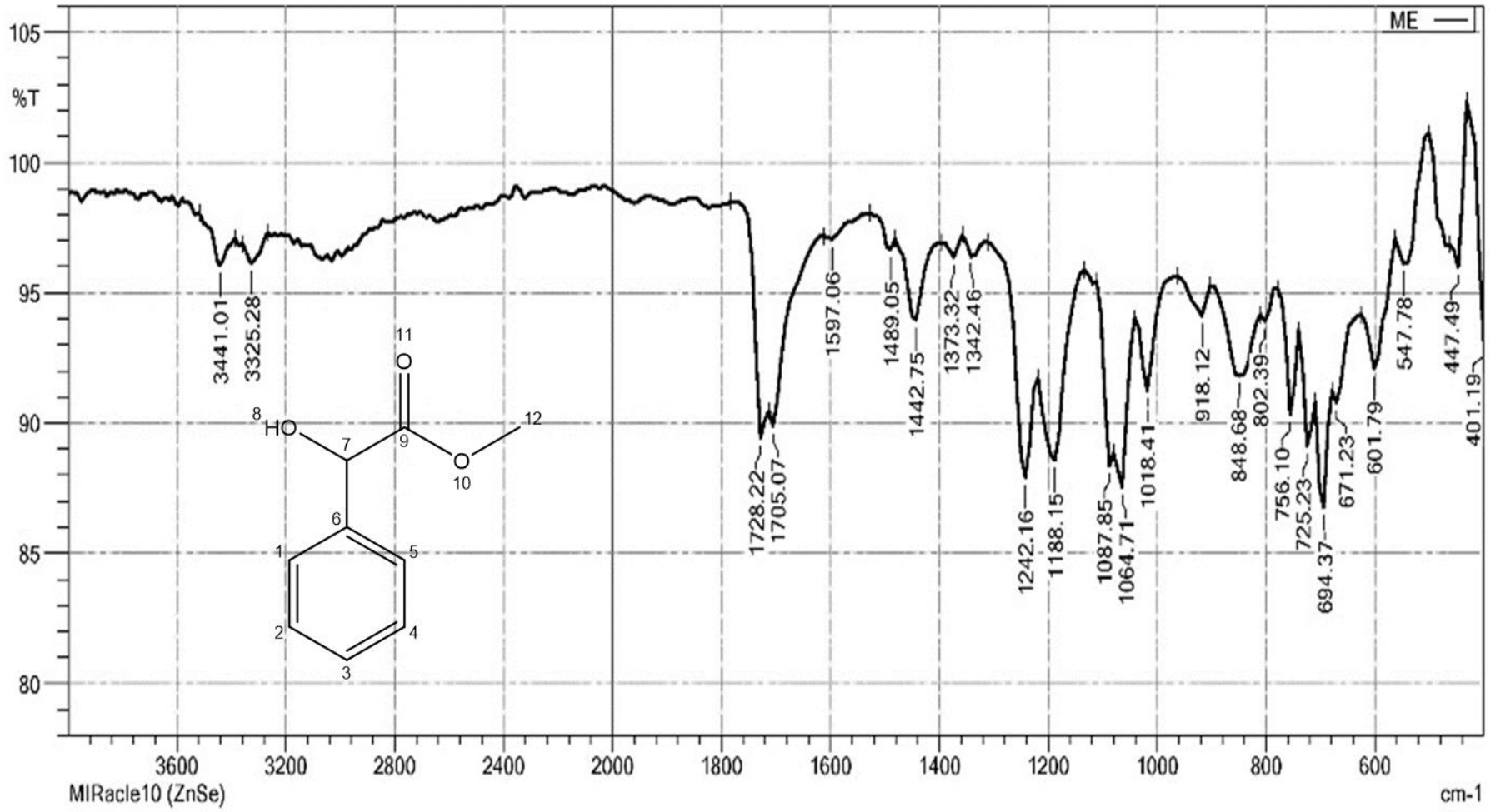


FIGURE-I :FT-IR SPECTRUM of methyl 2-hydroxy-2-phenylacetate

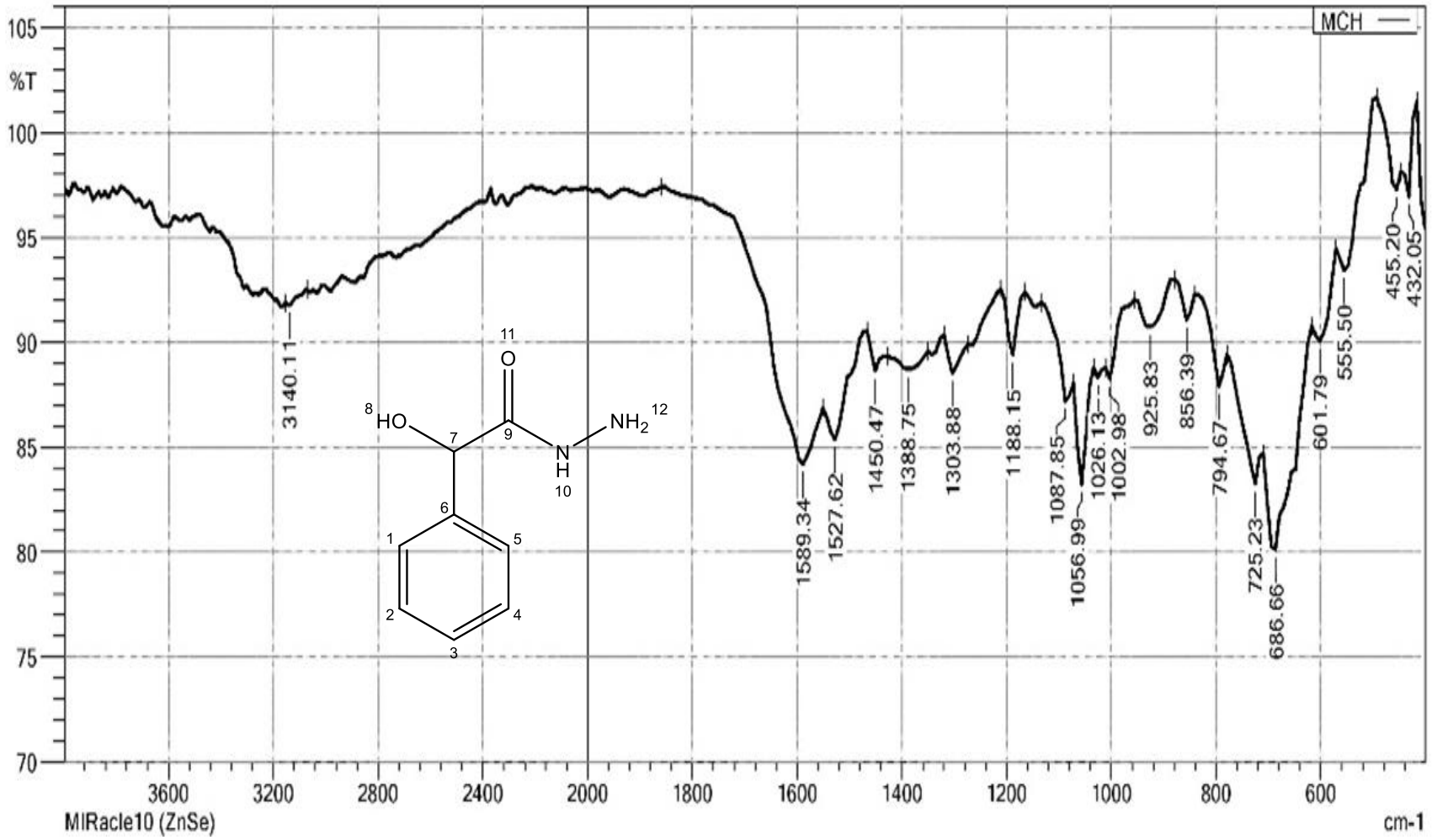


FIGURE-II:FT-IR SPECTRUM OF 2-hydroxy-2-phenylacetohydrazide

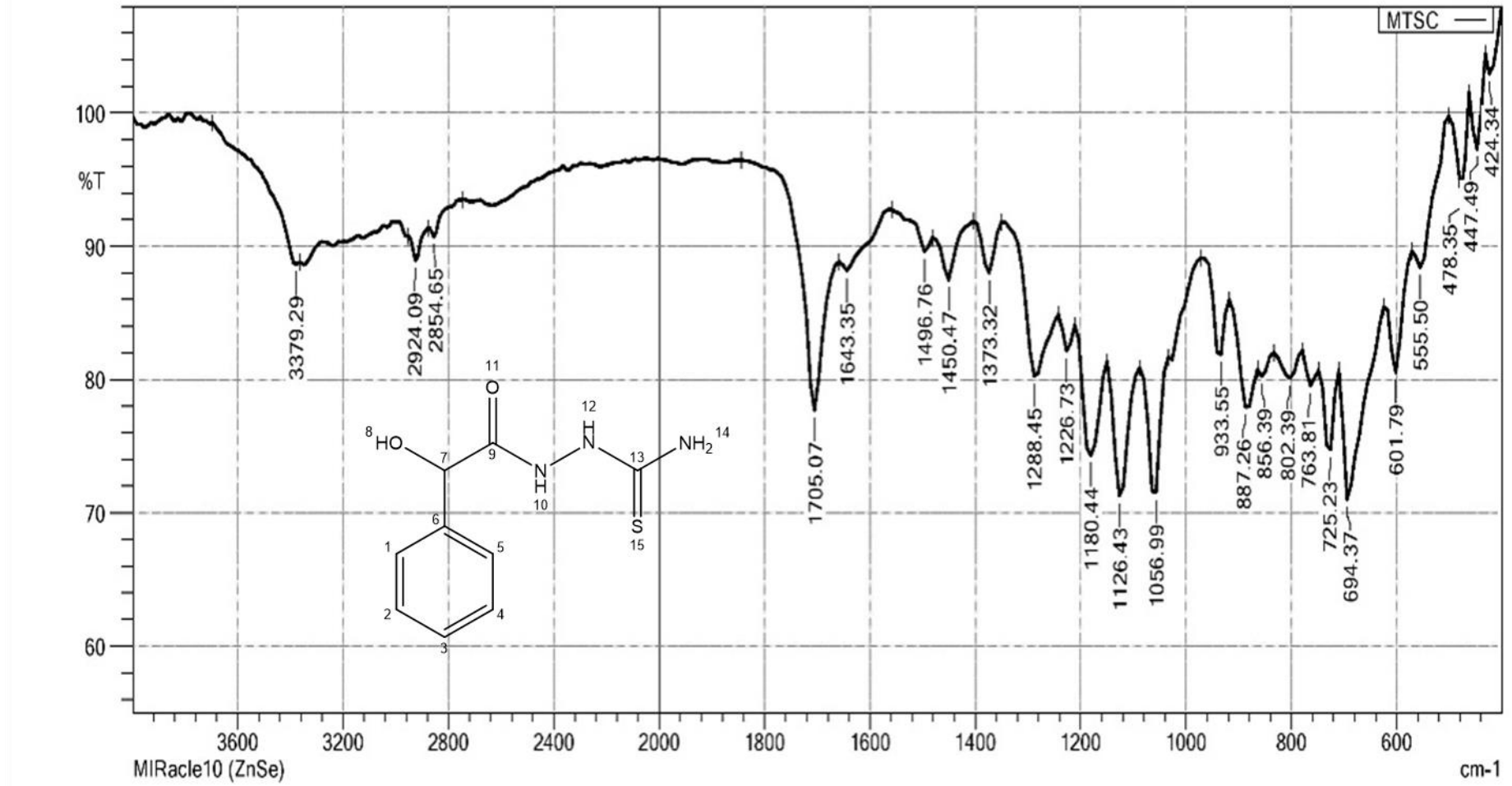


FIGURE-III:FT-IR SPECTRUM OF 2-(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamid

4.5.1.4. Methyl (*E*)-3(-4-hydroxyphenyl)acrylate

The FT-IR Spectrum of Methyl *(E)*-3(-4-hydroxyphenyl)acrylate **(TABLE-VII) & [FIGURE-IV]** showed a sharp band at 1705cm^{-1} indicated conjugation of C=O and 1512cm^{-1} for phenyl ring.A peak observed at 1249 cm^{-1} indicated for C-O stretching vibration .A peak observed at 925cm^{-1}indicated for O-H out of plane bending.

TABLE-VII

Frequency(cm^{-1})	Functional group
1705	C=O
1512	Phenyl ring
1249	C-O stretching
925	O-H bending vibration

4.5.1.5. Methyl (*E)*-3-(4-hydroxyphenyl)acrylohydrazide

The FT-IR Spectrum of(*E)*-3-(4-hydroxyphenyl)acrylohydrazide **(TABLE-VIII) &[FIGURE-V]** showed a sharp band at 1620cm^{-1} indicated C=O stretching,A peak observed at 1512cm^{-1}indicated (N-H) secondary amine. A peak observed at 956cm^{-1} indicated (NH_2) out of plane bending.

TABLE-VIII

Frequency(cm^{-1})	Functional group
1620	C=O stretching
1512	(N-H)Stretching
956	(NH_2) out of plane bending

4.5.1.6. Methyl (*E)-N*-ethanethioyl-3-(-4-hydroxyphenyl)acrylohydrazide

The FT-IR Spectrum of 2-(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide **(TABLE-IX) & [FIGURE-VI]** shows that the compound have a sharp band at 1643cm^{-1} corresponding to C=O stretching.A peak observed in 3348cm^{-1} indicated (O-H) stretch, A peak observed at 1126cm^{-1} indicated (C-N) amines,A peak observed at 3811 cm^{-1} indicated (NH_2) secondary amine.A peak at observed 1180 cm^{-1} indicated C-N stretch, a sharp band observed at 887cm^{-1} C=S stretch.1643cm^{-1} C=C stretching.

TABLE-IX

Frequency(cm^{-1})	**Functional group**
1643	C=O
3348	O-H
1126	C-N
3811	NH_2group
1180	C-N stretch
887	C=S
1643	C=C Stretching

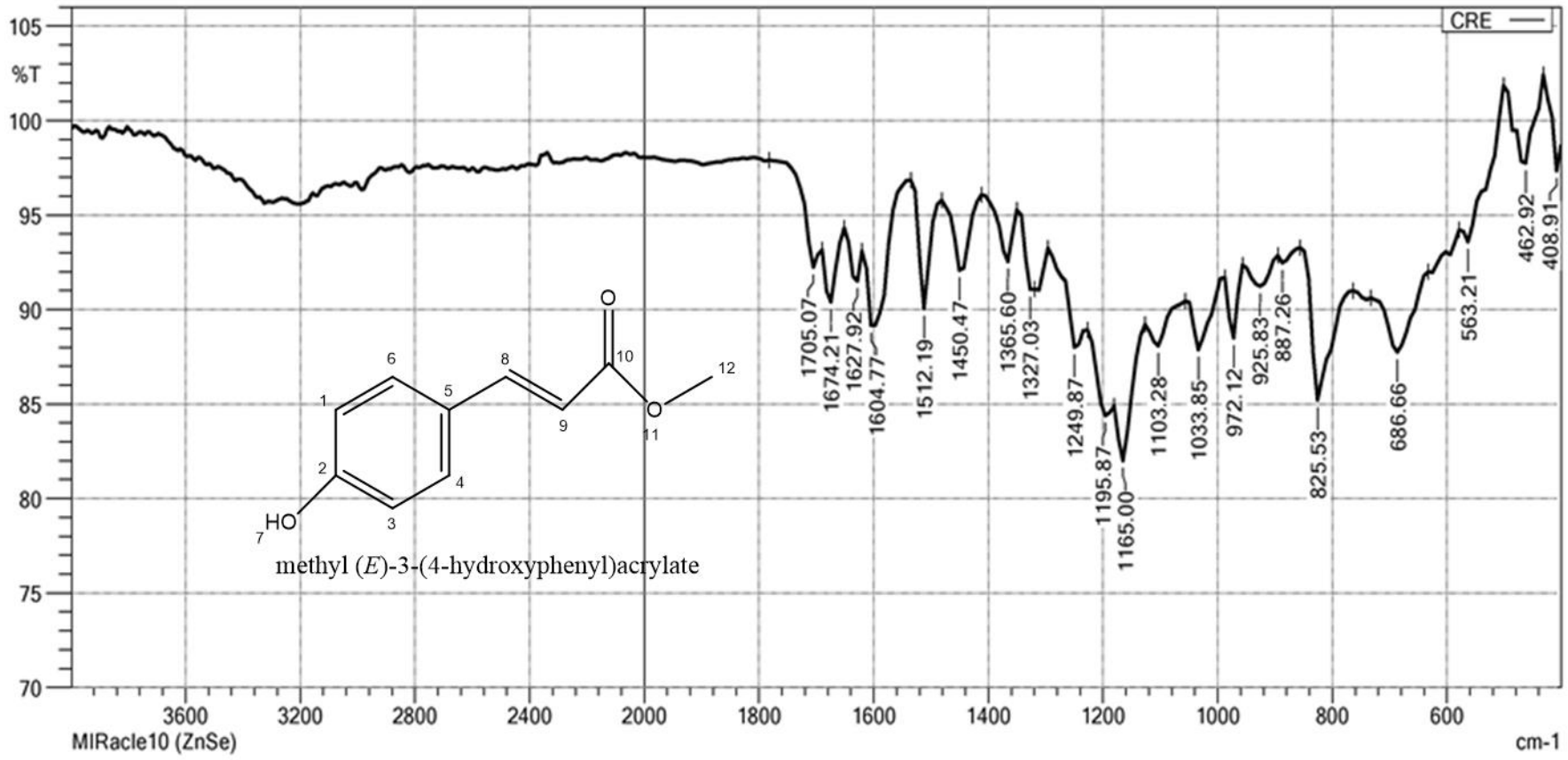


FIGURE-IV:FT-IR SPECTRUM OF Methyl (*E*)-3(-4-hydroxyphenyl)acrylate

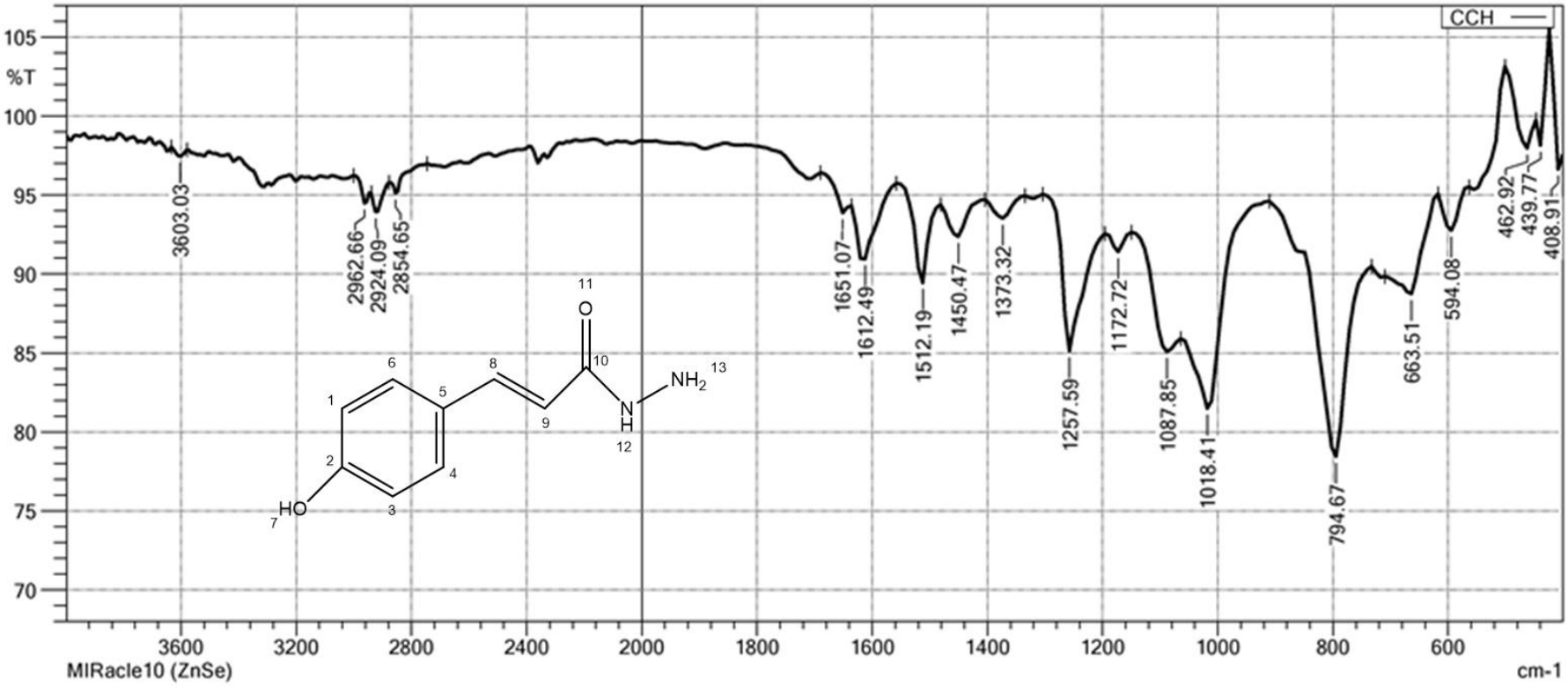


FIGURE-V:FT-IR SPECTRUM OF *E)*-3-(4-hydroxyphenyl)acrylohydrazid

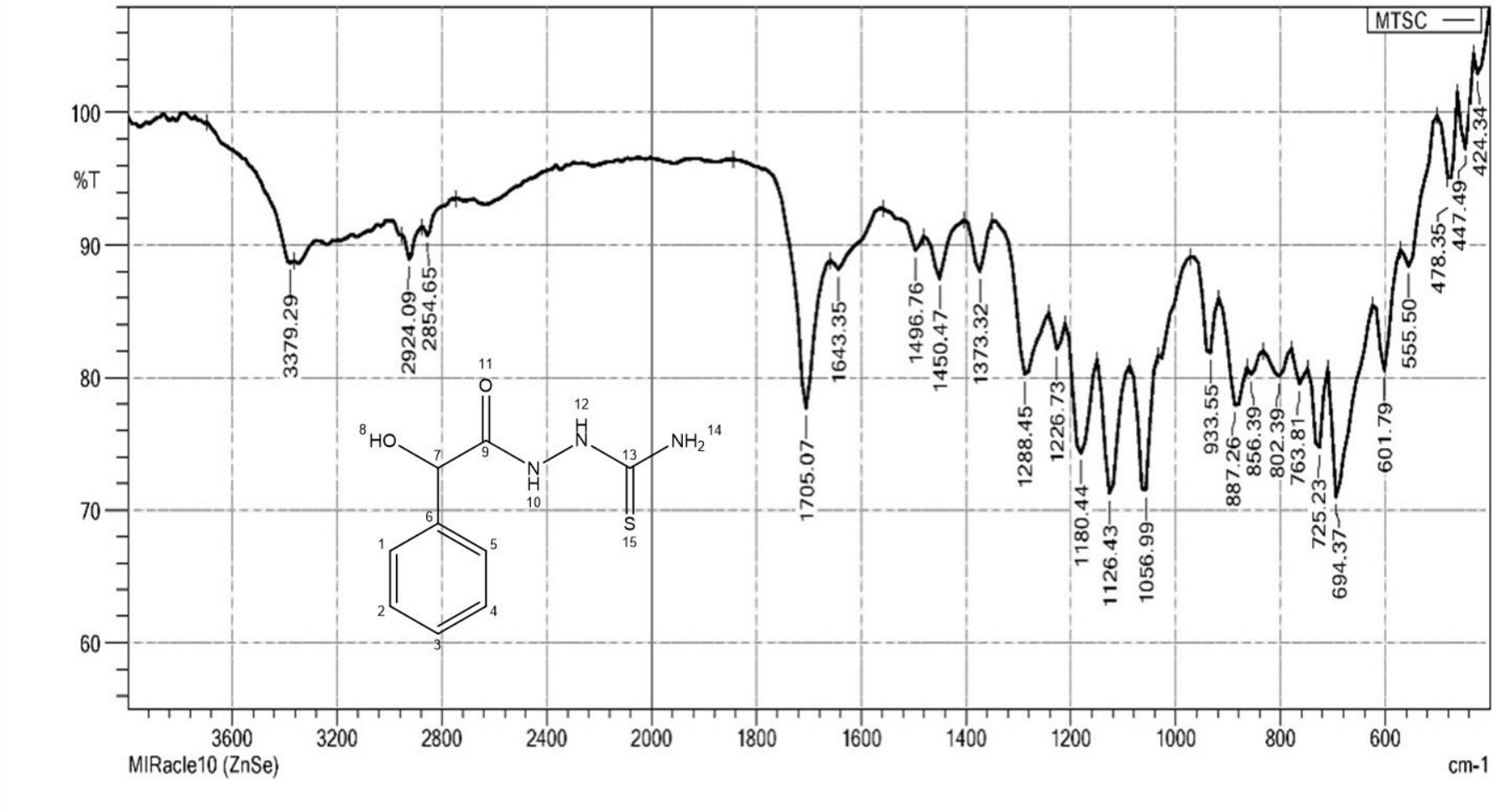


FIGURE-VI:Methyl (*E*)-*N*-ethanethioyl-3-(-4-hydroxyphenyl)acrylohydrazide

4.5.2. NMR ANALYSIS

4.5.2.1. ^{1}H NMR spectrum of (-**(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide)**

The NMR spectrum of compound -(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide)are

- In the aromatic region, three signals were observed for six protons,δ 7.45, δ 7.40 and δ 7.37.as multiplet.
- A signals observed at δ 5.25 accounted for OH proton.
- A signals observed at δ 5.98 indicated CH proton.
- A signal observed at δ 5.06(s) accounted for amide (O=C-NH) hydrogen.
- A signal observed at δ 4.10(S) was recorded for hydrogen attached to an amide nitrogen are variable in chemical shift.
- A signal observed at δ 3.60 accounted for amine hydrogens. This hydrogen is deshielded due to the anisotropy of the ring and the resonance that removes electron density from nitrogen and changes its hybridization.(**L.Pavia ,Gary M.Lampman,George S.Krish,2001).**

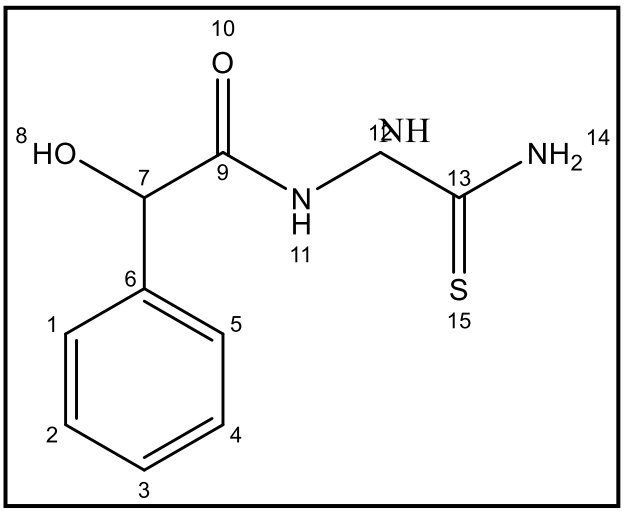


TABLE-X

^{1}H shift in ppm	**Multiplicity/no of ^{1}H**	**J value(Hz)**	**Assigned to**
7.45	^{2}H,^{4}H/dd	8.0	C_2&C_4
7.40	^{3}H/T	4.0	C_3
7.37	^{1}H,^{5}H/d	4.0	C_1&C_5
5.98	^{7}H/d	7.2	C_7
5.25	^{6}H/d	7.1	C_6
5.06	^{11}H/S		C_{11}
4.10	^{12}H/S		C_{12}
3.60	^{14}H/S		C_{14}

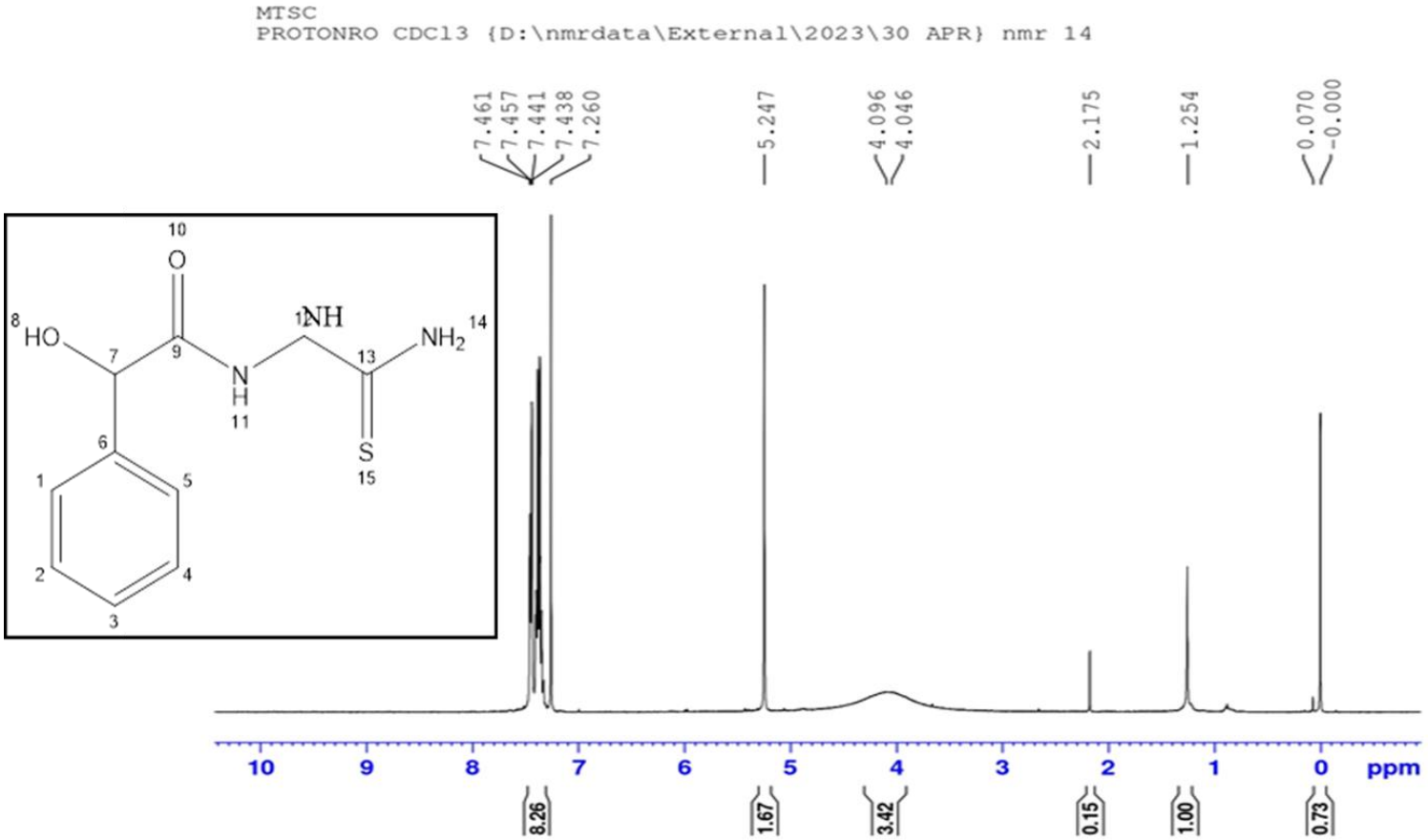


FIGURE-VII:^{1}H NMR OF (-(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide)

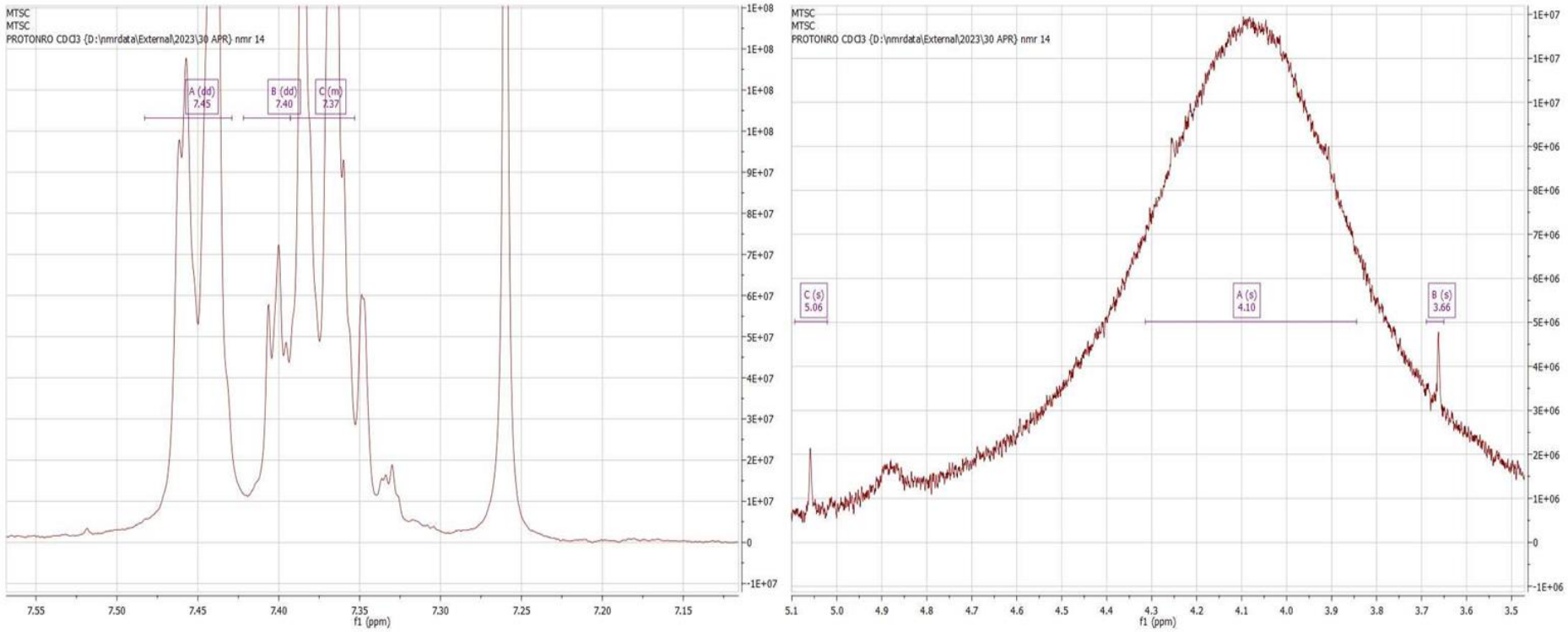


FIGURE -VIII :^{1}H NMR OF (-(2-hydroxy-2-phenylacetyl)hydrazine-1-carbothioamide)

SUMMARY
&
CONCLUSION

5.SUMMARY AND CONCLUSION

The results of the reaction of (-(2-hydroxy-2-phenylacetyl)hydrazine-1-) are summarized below.

- The reaction of Hydrazine carbothioamide by different aromatic hydroxy acids such as mandelic acid and p-coumaric acid in excellent yields at room temperature.
- The reaction was carried out using reflux in a steam bath to yield (-(2-hydroxy-2-phenylacetyl)hydrazine-1-).The yield of the compounds was moderate.
- The synthesized compounds were characterized by IR and ^{1}H NMR spectral studies.
- The IR and ^{1}H NMR data showed good correlation with the proposed structure.
- Thus an environmentally bengin synthesis of (-(2-hydroxy-2-phenylacetyl)hydrazine-1-) is developed.
- The method is simple and cost effective and does not require strong hazardous acids .
- Hence,this successful reaction may find important a application in the synthesis of thiosemicarbazide derivatives.

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