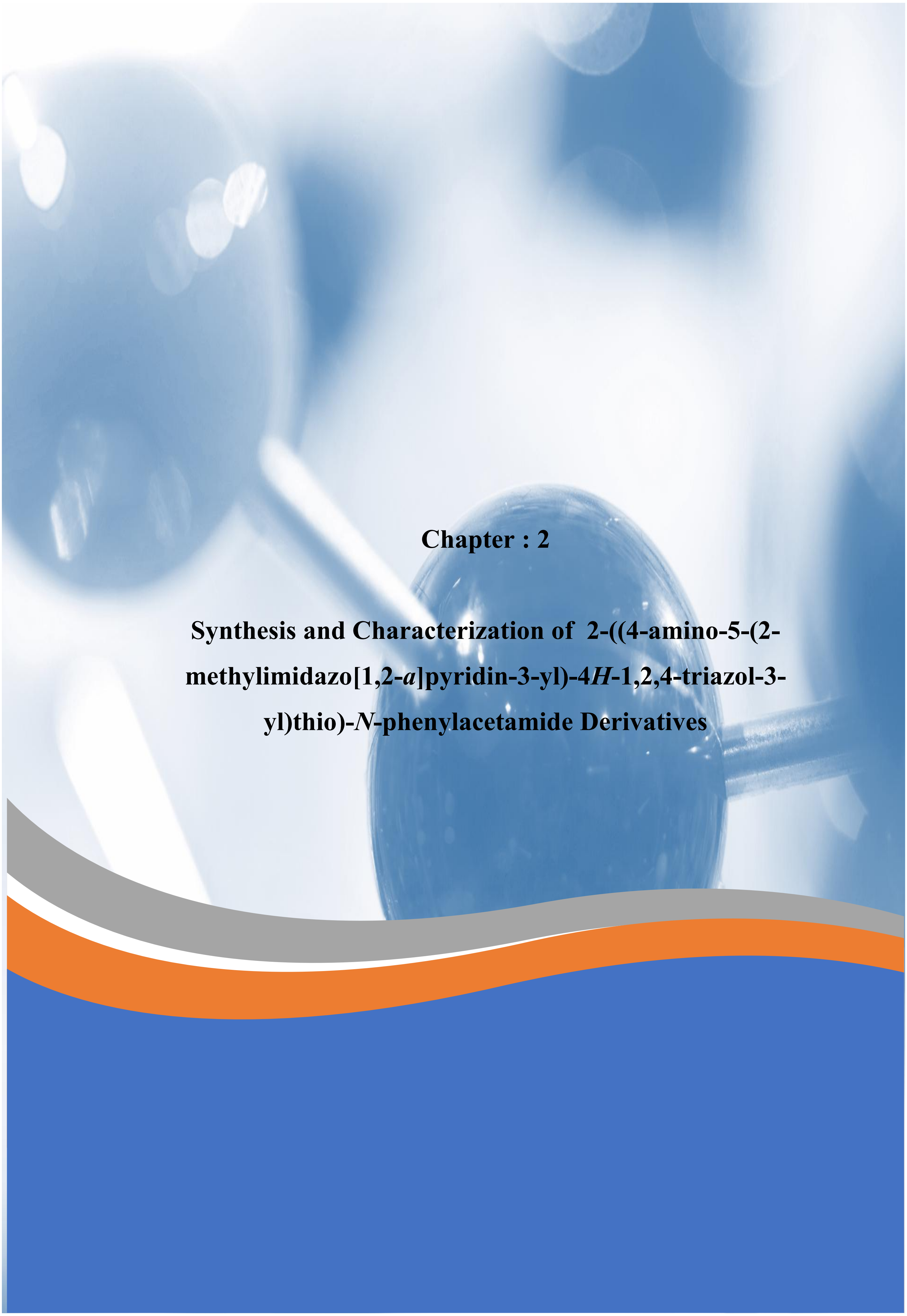


Chapter : 2

Synthesis and Characterization of 2-((4-amino-5-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-phenylacetamide Derivatives

2. Study on 1,2,4 triazole:

2.1 Introduction:

Ongoing and notable apprehension persists within the field of chemistry regarding five-member *N*-heterocycle compounds, specifically tetrazole (CH_2N_4), triazoles ($C_2H_3N_3$), and their various substituted derivatives. [73] Nitrogen heterocycles with five-membered rings are crucial structural components and are recognized for their significance as biologically active compounds [74] Triazoles exhibit isomeric forms based on the positions of nitrogen atoms. These isomers manifest as 1,2,3-triazoles and 1,2,4-triazoles in two tautomeric states. Notably, 1*H* and 4*H*-1,2,4-triazoles are recognized for their pharmacological importance within the nucleus.[75]

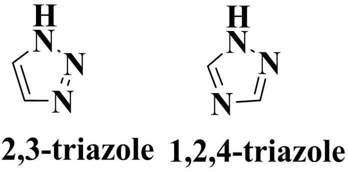


Fig.2.1: Two tautomeric forms of triazole

Triazoles, a class of nitrogen-containing heterocyclic compounds, have attracted substantial interest in the realms of chemistry, pharmacology, and materials science due to their diverse structural motifs and versatile properties. Among the various triazole isomers, the 1,2,4-triazoles stand out as a distinct subgroup, characterized by a five-membered ring structure and the specific arrangement of three nitrogen atoms at positions 1, 2, and 4. [76]

This structural arrangement imparts distinct chemical and physical properties to these isomers, influencing their reactivity and interactions with other molecules. [77] The pharmacological importance of 1,2,4-triazoles is underscored by their incorporation into numerous biologically active compounds. The diverse biological activities exhibited by these molecules have spurred extensive research in medicinal chemistry. [78] 1*H*-1,2,4-triazoles have demonstrated significant pharmacological potential. Various derivatives of this isomer have been explored for their antimicrobial[79][80][81][82], antifungal[83], antitumor[84][85], antituberculosis[86] and anti-inflammatory [87] properties. The presence of the triazole ring in these molecules often enhances their bioavailability and metabolic stability, contributing to their efficacy as pharmaceutical agents.

- **Medications incorporating the 1,2,4-triazoles nucleus are currently available in the market:**

➢ **Fluconazole:** An antifungal medication commonly used to treat fungal infections.[88]

➢ **Voriconazole:** Used to treat serious fungal infections, especially in people with compromised immune systems.[89]

➢ **Itraconazole:** Another antifungal agent used to treat a variety of fungal infections.[90]

➢ **Triazolam:** belongs to the drug class of benzodiazepines, acting as a short-acting hypnotic and anxiolytic medication**.**[91]

➢ **Alprazolam:** belongs to the benzodiazepine class of drugs, recognized for its anxiolytic properties in the treatment of anxiety disorders and panic attacks.[92]

➢ **Estazolam:** benzodiazepine medication primarily prescribed as a short-acting hypnotic for the treatment of insomnia.[93]

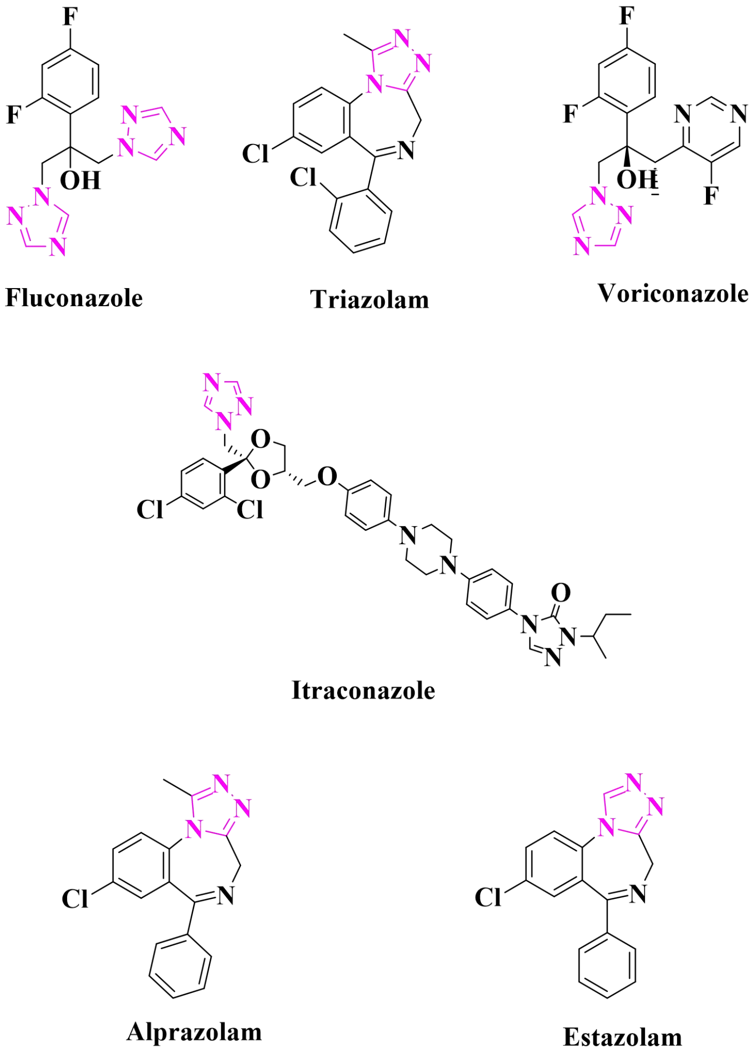
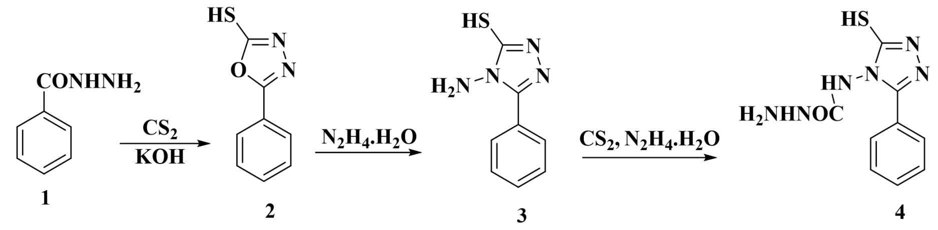


Fig.2.2: 2,4-triazole nucleus are currently available in the market

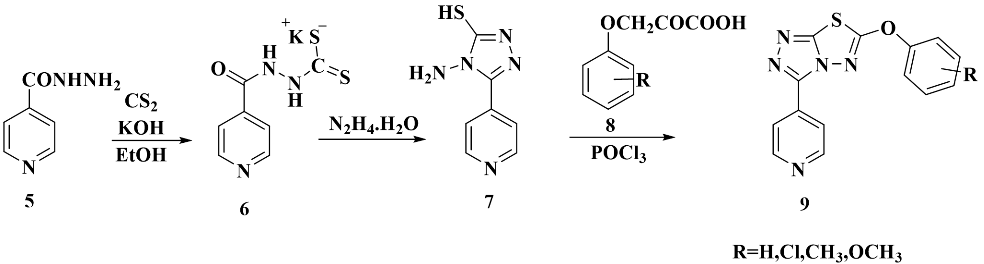
2.2 Common Procedures for 1,2,4 triazoles:

Aday et al., [94] reported series on triazole initiated from Benzohydrazide **1** was reacted with carbon disulfide and potassium hydroxide in ethanol to yield 5-phenyl-1,3,4-oxadiazol-2-ylamine **2**. Additionally, treating it with hydrazine hydrate in ethanol produced 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol **3**. Furthermore, the reaction with carbon disulfide and sodium hydroxide in DMF, followed by hydrazine hydrate, resulted in the formation of *N*-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)hydrazinecarbothioamide **4.(Scheme2.1)**



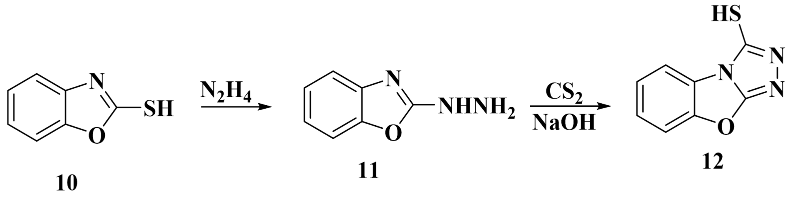
scheme2.1

Bolakatti et al., [95] reported series initiated from Isonicotinic acid hydrazide **5** was reacted with alcoholic KOH and carbon disulfide to form potassium salt of 2-isonicotinoylhydrazine-1-carbodithioate **6**. This intermediate **6** was then treated with hydrazine hydrate to produce 4-amino-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol **7**. The resulting thiol compound **7** was refluxed with substituted phenoxyaceticacid **8** in $POCl_3$, yielding 6-((substituted phenoxy)methyl)-3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-*b*]thiadiazole **9**. Compounds **9** shows good antimicrobial activity and antimycobacterial activity. **(Scheme2.2)**



Scheme2.2

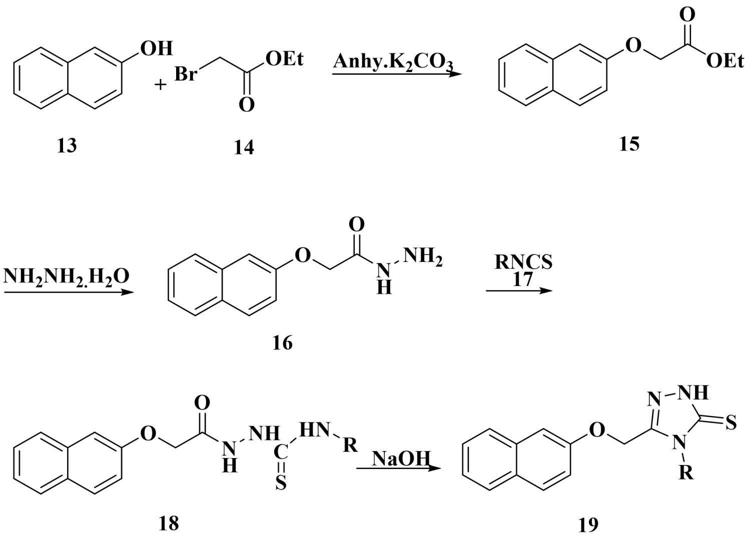
Askar et al., [96] reported the transformation of the mercapto group in 2-mercapto benzoxazole to a hydrazino group was achieved through reaction Benzo[*d*]oxazole-2-thiol **10** was reacted with hydrazine hydrate to form 2-hydrazinylbenzo[*d*]oxazole **11**. This intermediate was then treated with carbon disulfide in the presence of sodium hydroxide, resulting in the formation of benzo[4,5]oxazolo[2,3-*c*][1,2,4]triazole-3-thiol **12**. **(Scheme2.3)**



Scheme2.3

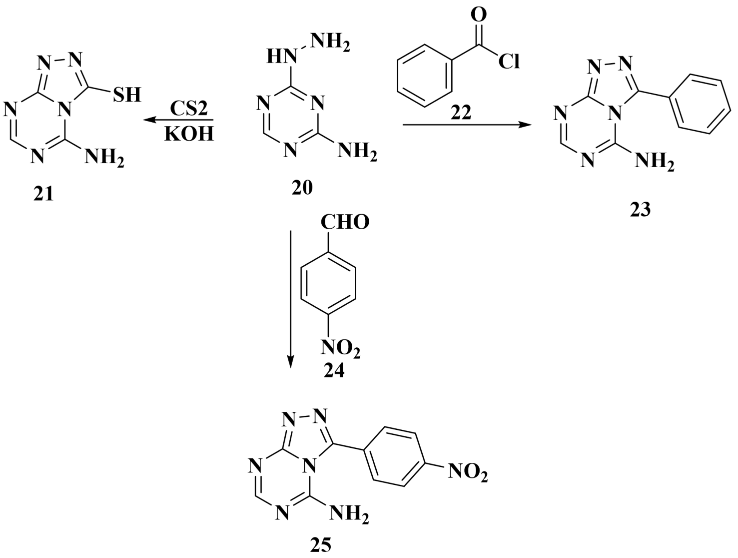
Palaska et al., [97] reported the synthesis of derivatives containing 5-(2-

naphthyloxymethyl)-4-substituted-1,2,4-triazole-3-thione **19** has been conducted though Naphthalen-2-ol **13** was reacted with ethyl 2-bromoacetate **14** in the presence of potassium carbonate to yield ethyl 2-(naphthalen-2-yloxy)acetate **15**, which was then treated with hydrazine hydrate to produce 1-naphthyloxyacetylhydrazine **16**. This compound **16** was condensed with substituted isothiocyanates **17** to form 2-naphthyloxyacetyl-4-substituted thiosemicarbazides **18**. The ring closure of these acylthiosemicarbazides in the presence of sodium hydroxide, a well-known method for synthesizing 1,2,4-triazoles, yielded 5-(2-naphthyloxymethyl)-4-substituted-1,2,4-triazole-3-thiones **19**. these compounds **19** were assessed for their potential as orally active anti-inflammatory activity. **(Scheme2.4)**



Scheme2.4

Salih et al.,[98] reported series from 4-Hydrazinyl-1,3,5-triazin-2-amine **20** underwent cyclocondensation reactions with CS_2, benzoyl chloride **22**, p-nitrobenzaldehyde **24** leading to the formation of 5-amino[1,2,4]triazolo[4,3-*a*][1,3,5]triazine-3-thiol **21**, 5-amino-3-phenyl[1,2,4]triazolo[4,3-*a*][1,3,5]triazine **23**, 5-amino-3-(p-nitrophenyl)[1,2,4]triazolo[4,3-*a*][1,3,5]triazine **25** respectively. **(Scheme2.5)**



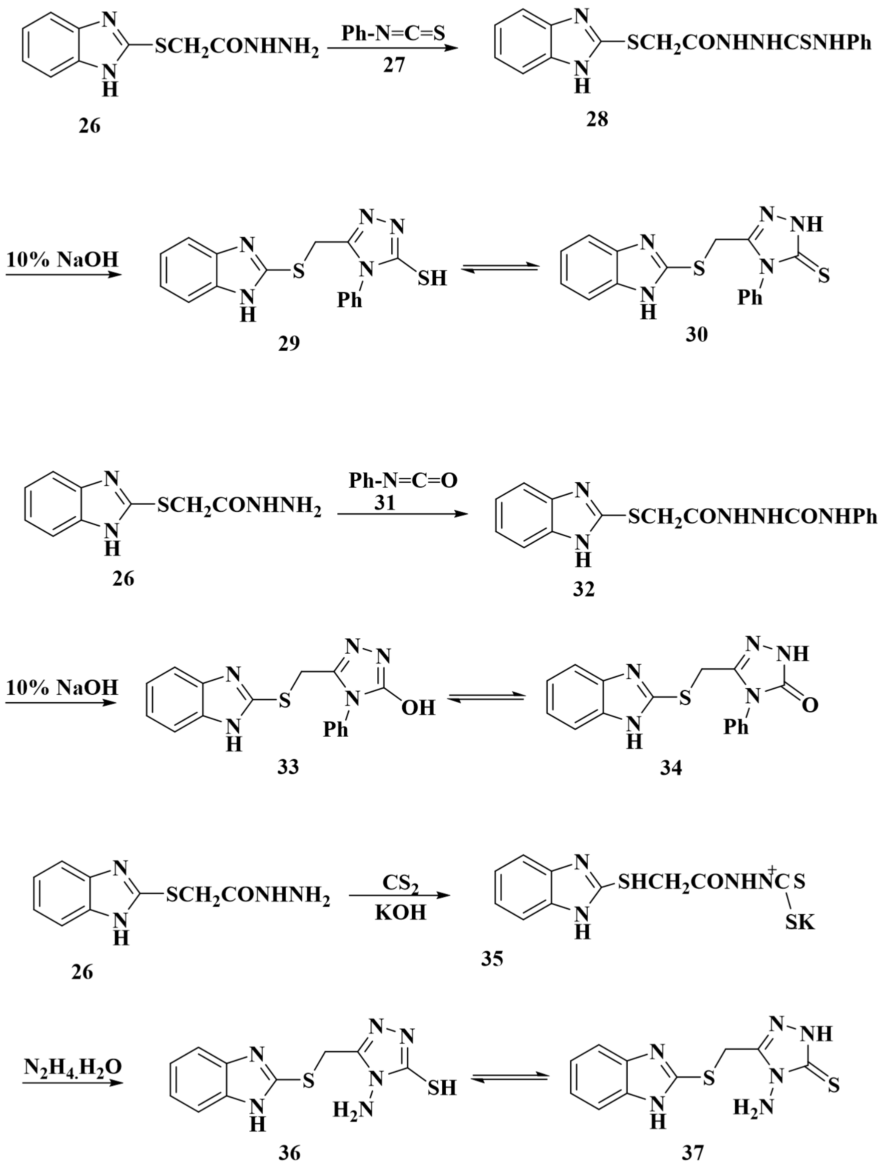
Scheme2.5

Al-Messri et al., [99] reported Novel derivatives of 1,2,4-triazole originating from 2-mercaptobenzimidazole (MB) have been synthesized using ((1*H*-benzo[*d*]imidazol-2-yl)thio)acetohydrazide **26** reacts with phenyl isothiocyanate **27** to form 2-(2-((1*H*-benzo[*d*]imidazol-2-yl)thio)acetyl)-*N*-phenylhydrazine-1-carbothioamide **28**. In the presence of an alkaline medium, this compound undergoes thiol-thione tautomerism to yield either 5-(((1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol **29** or 5-(((1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **30**. **(Scheme2.6)**

Similarly, ((1*H*-benzo[*d*]imidazol-2-yl)thio)acetohydrazide **26** reacts with phenyl isocyanate **31** to form 2-(2-((1*H*-benzo[*d*]imidazol-2-yl)thio)acetyl)-*N*-phenylhydrazine-1-carbothioamide **32**, which in the presence of an alkaline medium, undergoes keto-enol tautomerism to produce either 5-(((1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-4-phenyl-4*H*-1,2,4-triazol-3-ol **33** or 5-(((1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one **34**. **(Scheme2.6)**

((1*H*-benzo[*d*]imidazol-2-yl)thio)acetohydrazide **26** reacts with CS_2 in the presence of potassium hydroxide, it forms potassium 2-(2-((1*H*-benzo[*d*]imidazol-2-yl)thio)acetyl)hydrazine-1-carbodithioate salt **35**. Further treatment with hydrazine hydrate leads to thiol-thione tautomerism, resulting in either 5-(((1*H*-benzo[*d*]imidazol-2-yl)thio)methyl)-4-amino-4*H*-1,2,4-triazole-3-thiol **36** or 5-(((1*H*-

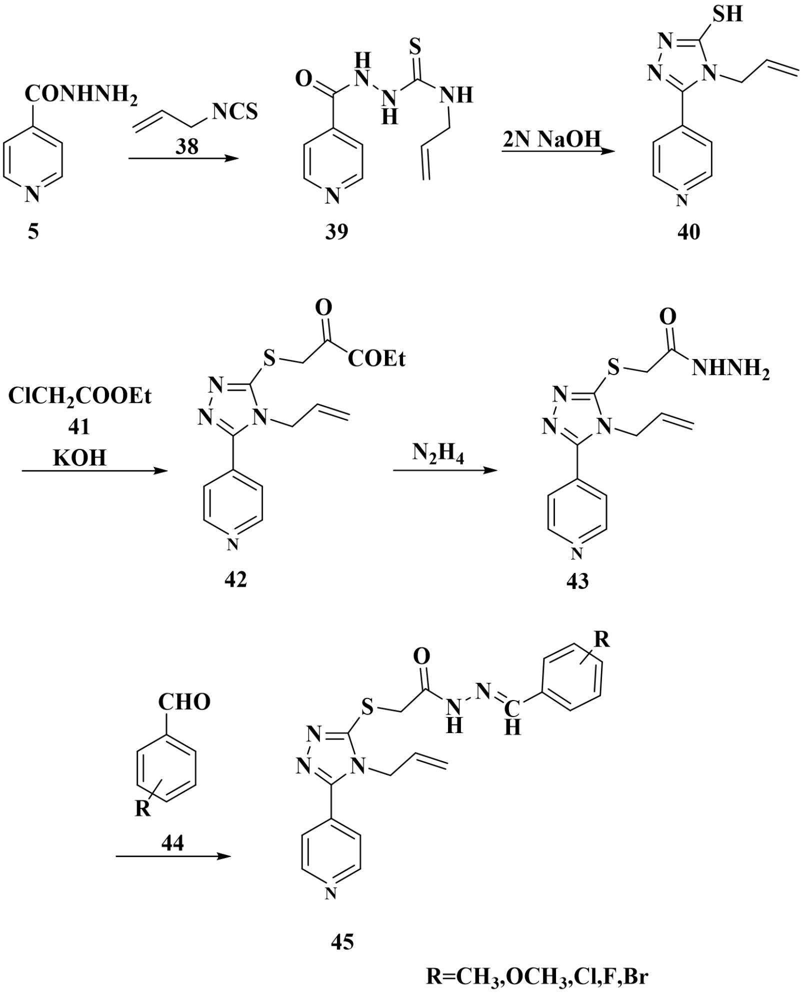
benzo[*d*]imidazol-2-yl)thio)methyl)-4-amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **37**. **(Scheme2.6)**



Scheme2.6

Mobinikhaledi et al., [100] reported novel schiff bases formation using Isonicotinohydrazide **5** with 3-isothiocyanatopropene **38** to produce *N*-allyl-2-isonicotinoylhydrazine-1-carbothioamide **39**. This intermediate **39** is then treated with sodium hydroxide to yield 4-allyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-3-thiol **40**. Subsequent reaction of compound **40** with ethyl 2-chloroacetate and potassium hydroxide forms 1-((4-allyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl)thio)pentane-2,3-

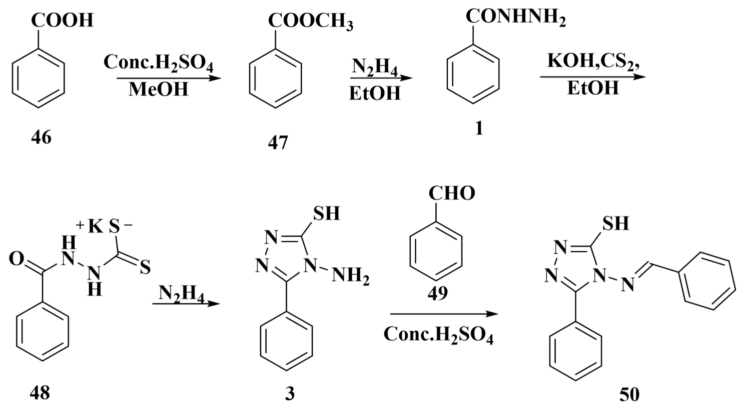
dione **41**. Treatment with hydrazine hydrate produces 2-((4-allyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl)thio)acetohydrazide **42**, which can then form a Schiff base upon reacting with various substituted aldehydes **43**, resulting in (E)-2-((4-allyl-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*'-(substituted benzylidene)acetohydrazide **44**. **(Scheme2.7)**



Scheme2.7

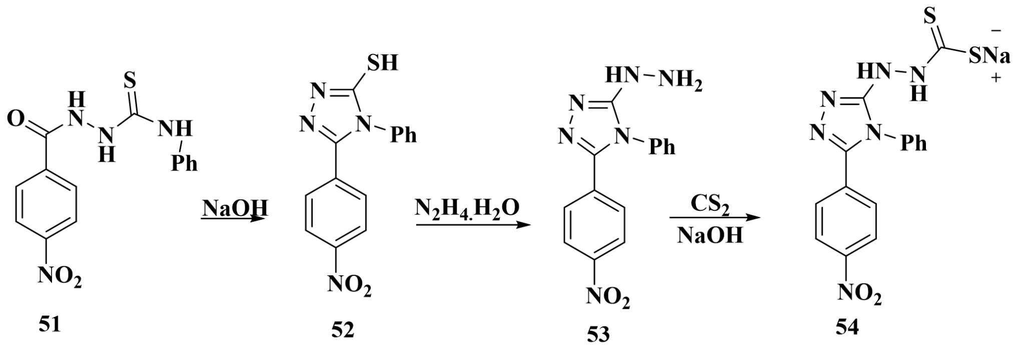
Kumar Singh et al.,[101] reported series initiated from Benzoic acid **46**, when treated with an acidic medium, yields methyl benzoate **47**. This ester is then converted into benzohydrazide **1** using hydrazine hydrate. The resulting hydrazide **1** reacts with carbon disulfide and potassium hydroxide to form potassium 2-benzoylhydrazine-1-carbodithioate **48**. This salt **48**, when treated with hydrazine hydrate, produces 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol **3**. compound **3** underwent condensation with benzaldehyde **49** to yield 4-(benzylideneamino)-5-phenyl-4*H*-1,2,4-triazole-3-

thiol **50**, commonly referred to as a Schiff base. **(Scheme2.8)**



Scheme2.8

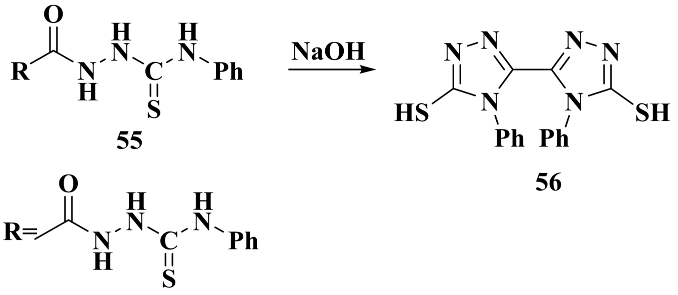
Hashim et al., [102] reported series to synthesize sodium 2-(5-(4-nitrophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)hydrazine-1-carbodithioate **54**, the process begins by reacting (4-nitrobenzoyl)-*N*-phenylhydrazine-1-carbothioamide **51** with sodium hydroxide solution to yield 5-(4-nitrophenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol **52**. This intermediate **52** is then treated with hydrazine hydrate in ethanol to produce 3-hydrazineyl-5-(4-nitrophenyl)-4-phenyl-4*H*-1,2,4-triazole **53**. Finally, an excess of carbon disulfide is added in the presence of sodium hydroxide in an ethanolic solution to complete the formation of sodium 2-(5-(4-nitrophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl)hydrazine-1-carbodithioate **54**. Compound **54** Shows the cytotoxicity effect. **(Scheme2.9)**



Scheme2.9

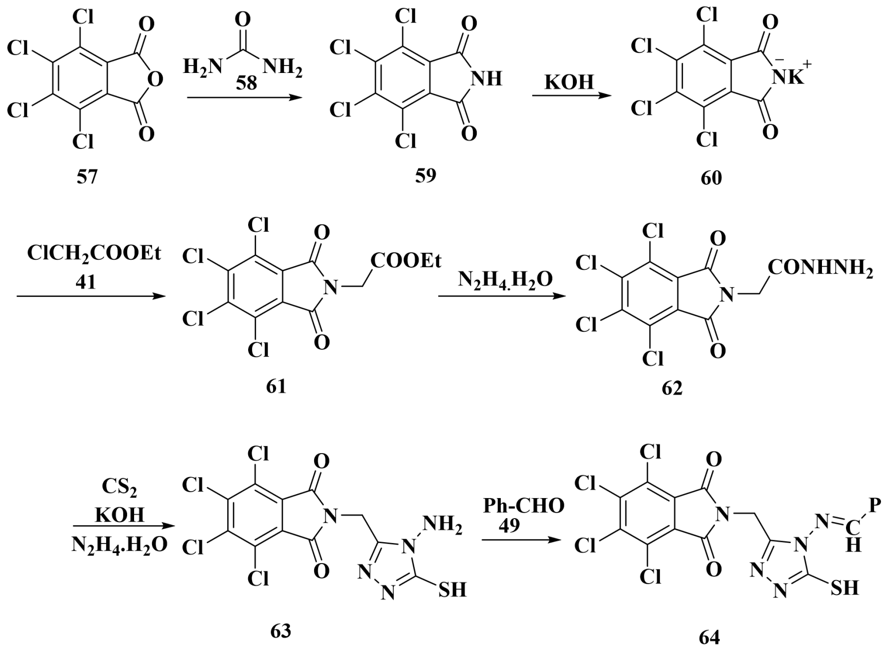
Jassim et al., [103] reported the synthesis of 4,4'-diphenyl-4*H*,4'*H*-[3,3'-bi(1,2,4-

triazole)]-5,5'-dithiol **56** involved the preparation of thiol-triazole through the intermolecular cyclization reaction of a thiosemicarbazide derivative **55** with NaOH. Shows antibacterial activity against bacteria like E. Coli and S.aureus. **(Scheme2.10)**



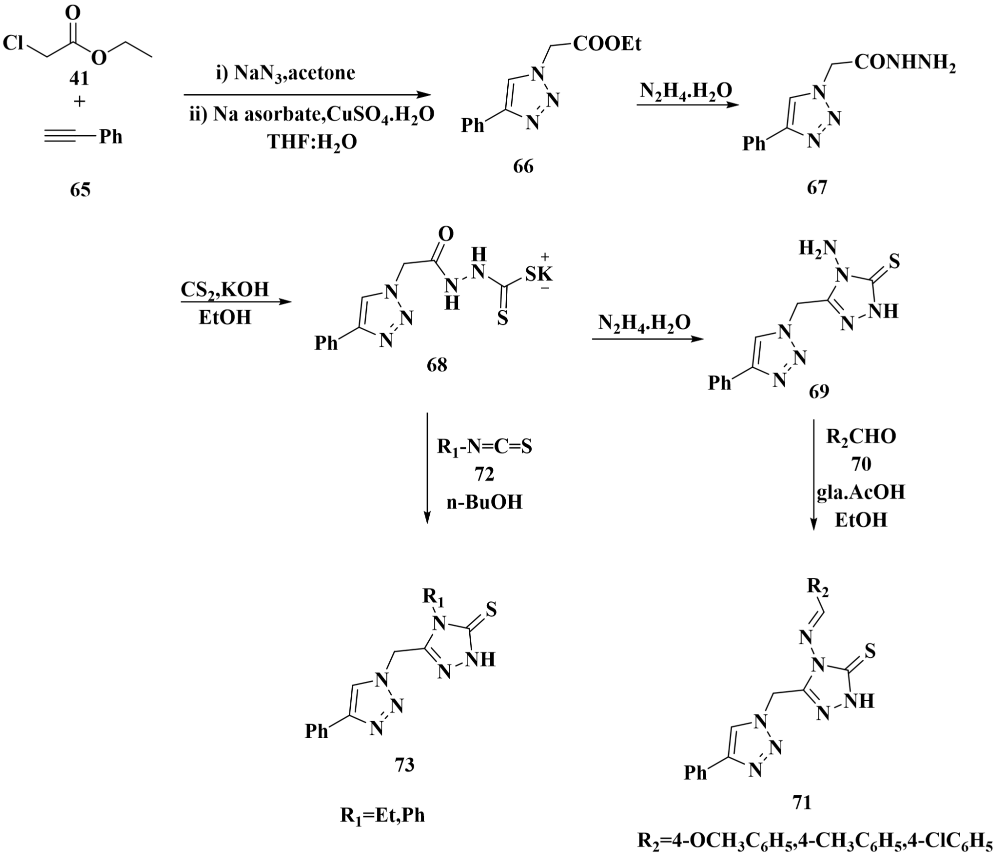
Scheme2.10

Marouf Al-Azzawi et al., [104] reported Novel derivatives of 1,2,4-triazoles, connected to a 3,4,5,6-tetrachlorophthalimide **58** moiety, were successfully synthesized through a multistep process. The initial step involved synthesizing unsubstituted 3,4,5,6-tetrachlorophthalimide **58** by reacting 3,4,5,6-tetrachlorophthalic anhydride **57** with an excess of urea, yielding 3,4,5,6-tetrachlorophthalimide **58**. This phthalimide **58** was then dissolved in DMF with potassium hydroxide as the base, forming the potassium salt of 3,4,5,6-tetrachlorophthalimide **59**. This salt **59** subsequently reacted with ethyl chloroacetate **41** in DMSO, resulting in ethyl 2-(*N*-(3,4,5,6-tetrachlorophthalimidyl))acetate **60**. The acetate derivative **60** was further treated with hydrazine hydrate to produce 2-(*N*-(3,4,5,6-tetrachlorophthalimidyl))acetohydrazide **61**. This hydrazide **61**, when reacted with carbon disulfide, potassium hydroxide, and additional hydrazine hydrate, formed 4-amino-5-(*N*-(3,4,5,6-tetrachlorophthalimidyl)methylene)-2,3-dihydro-1,2,4-triazole-3-thiol **62**. The resulting thiol **62** was dissolved in ethanol with benzaldehyde **49** and a few drops of glacial acetic acid, leading to the formation of the Schiff base: 4-*N*-benzylidene-5-(*N*-(3,4,5,6-tetrachlorophthalimidyl)methylene)-2,4-dihydro-1,2,4-triazole-3-thiol **64**. **(Scheme2.11)**



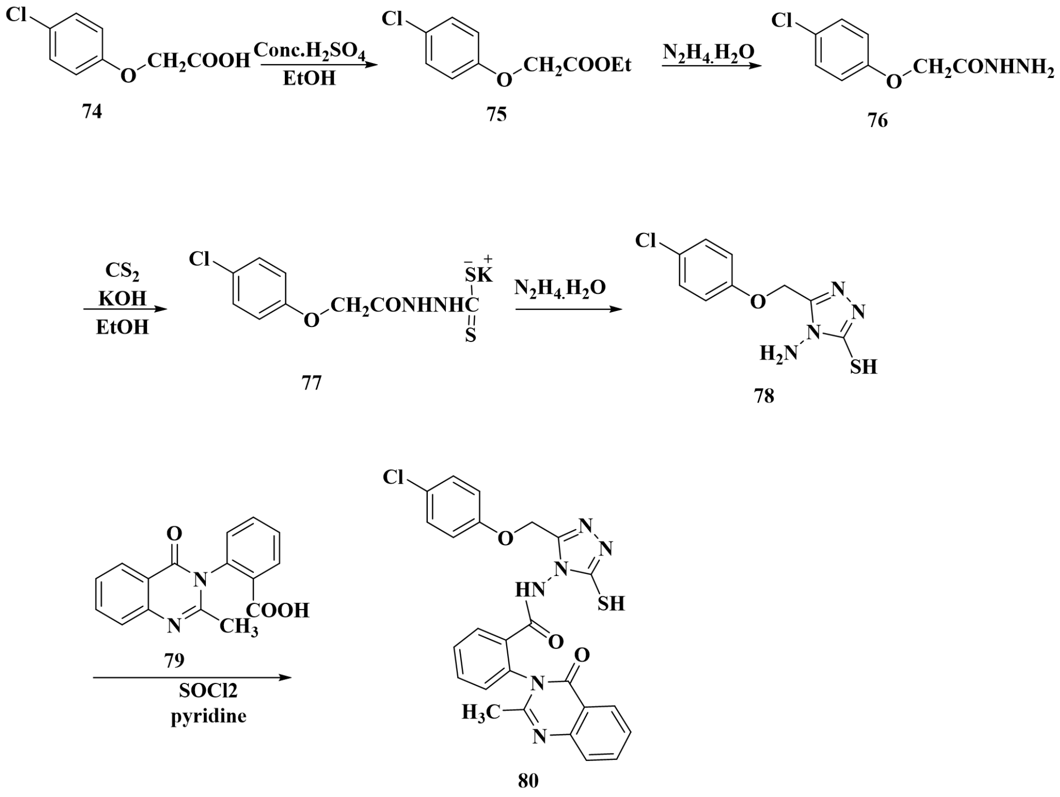
Scheme2.11

Maghraby et al.,[105] reported derivatives from Ethyl 2-azidoacetate was synthesized by reacting ethyl 2-chloroacetate **41** with sodium azide in acetone. The product, obtained after extraction with ethyl acetate, underwent a subsequent reaction with phenylacetylene **65**, $CuSO_4·5H_2O$, and sodium ascorbate in a THF:H_2O mixture at room temperature, yielding ethyl 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate **66**. This acetate was then treated with an excess of 99% hydrazine hydrate in ethanol to produce 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetohydrazide **67**. The hydrazide **67** was further reacted with CS_2 in the presence of potassium hydroxide to form potassium 2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetyl)hydrazine-1-carbodithioate **68**. This potassium salt **68** reacted with substituted isothiocyanate **72** in n-butanol to yield substituted 5-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **73**. Additionally, the salt **68** was treated with hydrazine hydrate to give 4-amino-5-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **69**. Furthermore, reaction of the salt **69** with substituted aldehyde **70** to form the Schiff base (E)-4-((4-methylbenzylidene)amino)-5-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **71**. These compounds **71** were tested for antiproliferative activity against different types of cancer cells. **(Scheme2.12)**



Scheme2.12

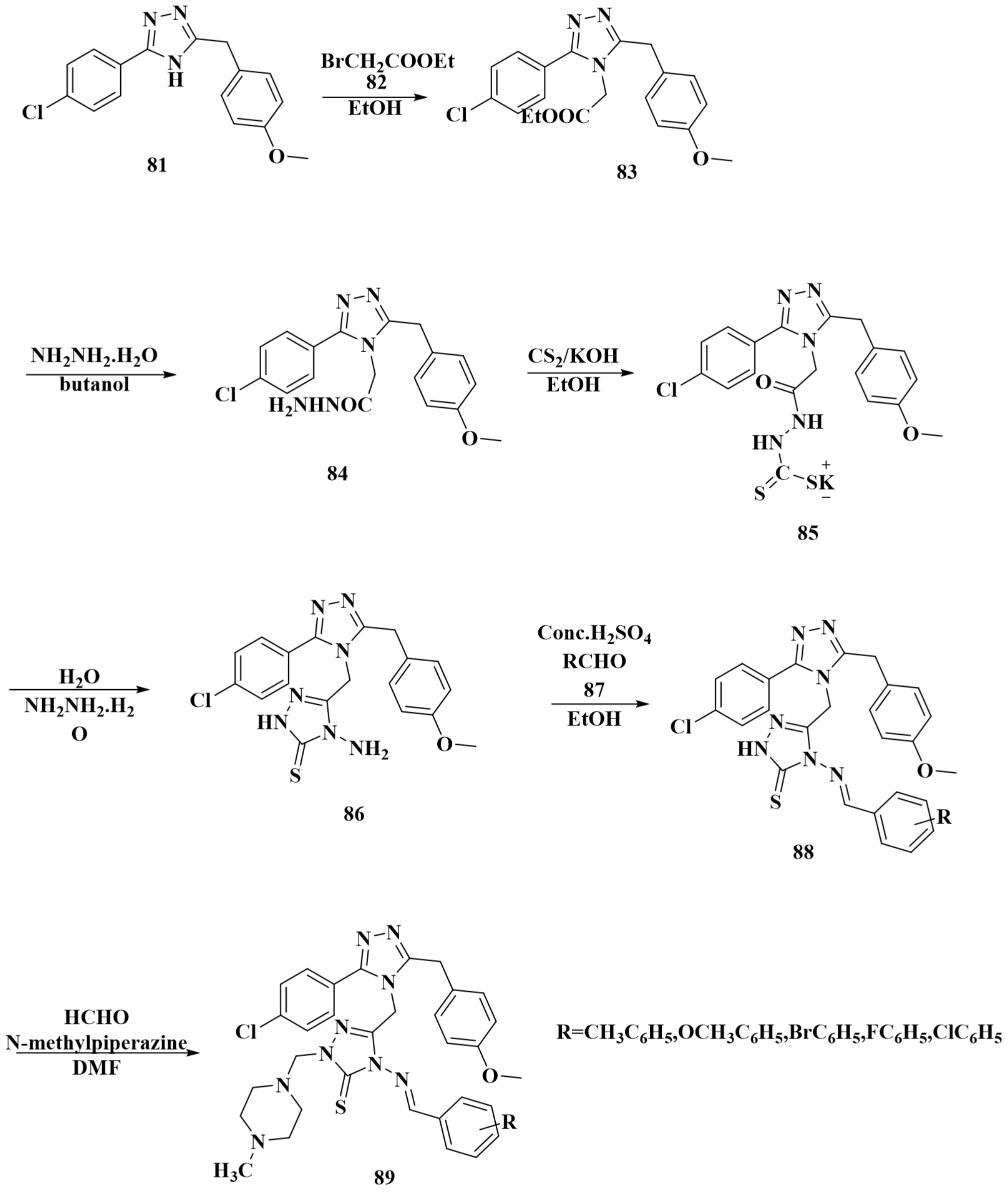
Sahoo et al., [106] reported Substituted 1,2,4-triazoles exhibit diverse biological activities, including anti-inflammatory and antifungal properties which is synthesized from the acetylation of 2-(4-chlorophenoxy)acetic acid **74** in an acidic medium to produced ethyl 2-(4-chlorophenoxy)acetate **75**. Compound **75** when treated with hydrazine hydrate, produces 2-(4-chlorophenoxy)acetohydrazide **76**. The hydrazide **76**, in the presence of carbon disulfide and potassium hydroxide, forms potassium 2-(2-(4-chlorophenoxy)acetyl)hydrazine-1-carbodithioate **77**. Salt **77** undergoes cyclization with hydrazine hydrate to generate 4-amino-5-((4-chlorophenoxy)methyl)-4*H*-1,2,4-triazole-3-thiol **78**. This intermediate **78** is then reacted with 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzoic acid **79**, thionyl chloride ($SOCl_2$), and pyridine to produce *N*-(3-((4-chlorophenoxy)methyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)-2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzamide **80**. **(Scheme2.13)**



Scheme2.13

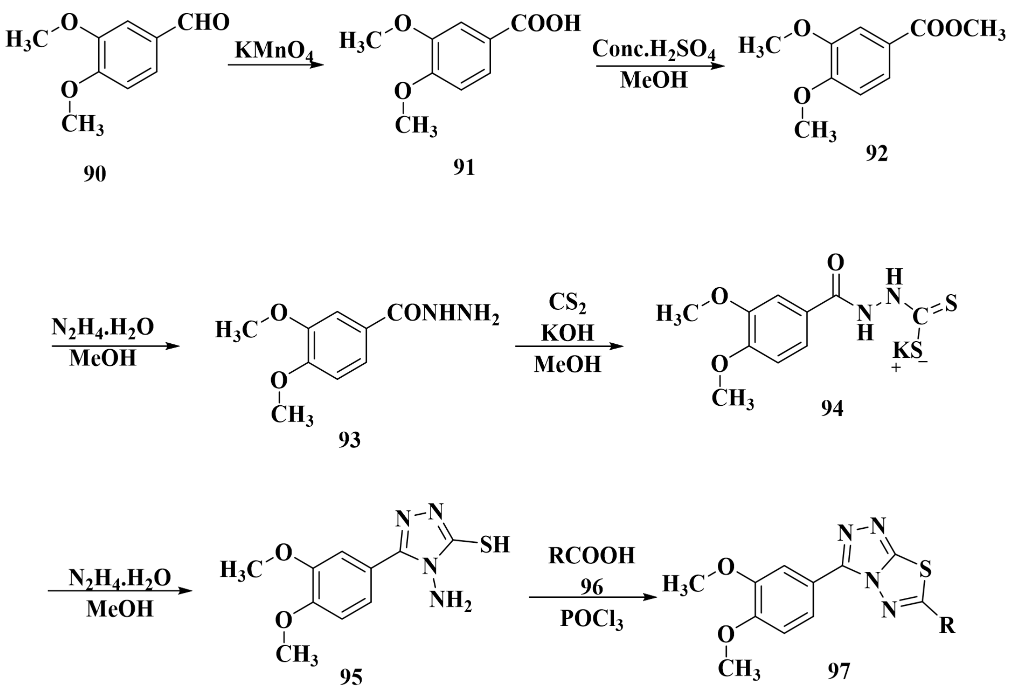
Bekircan et al., [107] reported Ethyl bromoacetate **82** was used to treat 3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazole **81**, yielding ethyl [3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-4-yl]acetate **82**. This compound **83** was then reacted with hydrazine hydrate to form 2-[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-4-yl]acetohydrazide **84**. The hydrazide derivative **83** was subsequently treated with carbon disulfide (CS_2) in the presence of potassium hydroxide (KOH), followed by cyclization with hydrazine hydrate, resulting in 4-amino-5-{[3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-4-yl]methyl}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **86**. Condensation of compound **86** with various aldehydes **87** led to the formation of Schiff bases (E)-4-(benzylideneamino)-5-((3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-4-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione derivatives **88**. These Schiff bases **88** were then treated with formaldehyde to produce Mannich bases (E)-4-(benzylideneamino)-5-((3-(4-chlorophenyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-4-yl)methyl)-2-((4-methylpiperazin-1-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **89**. The resulting compounds **89** were screened for their anti-lipase and anti-urease activities.

(Scheme2.14)



Scheme2.14

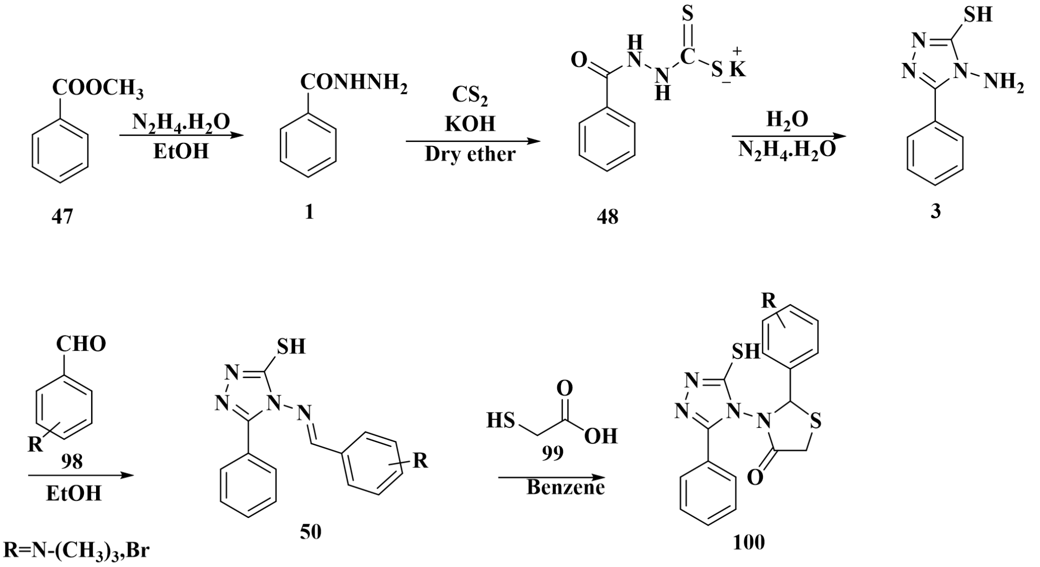
Sahu et al., [108] reported through a one-pot reaction, a series of 6-aryl-3-(3,4-dialkoxyphenyl)-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazole derivatives **97** was successfully synthesized and shows antimicrobial activity against a diverse range of microorganisms. This synthetic approach involved the condensation of 4-amino-5-(3,4-dialkoxyphenyl)-4*H*-[1,2,4]-triazole-3-thiol **96** with various aromatic carboxylic acids **96** in the presence of phosphorous oxychloride and for thiol **95** formation though Following the synthesis, 3,4-Dimethoxybenzaldehyde **90** was oxidized to 3,4-dimethoxybenzoic acid **91** using potassium permanganate ($KMnO_4$). The resulting 3,4-dimethoxybenzoic acid **91** was then esterified in the presence of an acidic medium to form methyl 3,4-dimethoxybenzoate **92**. This ester **92** was subsequently reacted with hydrazine hydrate to yield 3,4-dimethoxybenzohydrazide **93**. The hydrazide **93** was treated with carbon disulfide (CS_2) and potassium hydroxide (KOH) to produce the potassium salt of 2-(3,4-dimethoxybenzoyl)hydrazine-1-carbodithioate **94**. Finally, this potassium salt was reacted with hydrazine hydrate to form 4-amino-5-(3,4-dimethoxyphenyl)-4*H*-1,2,4-triazole-3-thiol **95**. **(Scheme2.15)**



R=Ph,$CH_2C_6H_5$,o-Br-C_6H_5,m-Br-C_6H_5,p-Br-C_6H_5

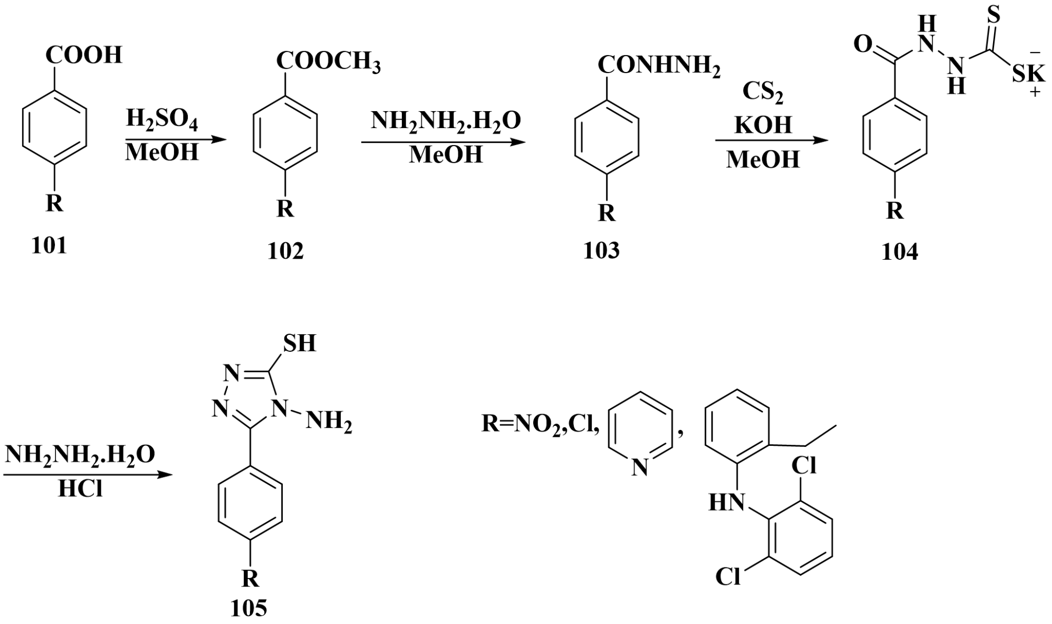
Scheme2.15

Hassan et al.,[109] reported a novel series of triazole derivatives **100** was synthesized through a cyclization reaction. The synthesis process commenced with the preparation of benzoic acid hydrazide **1** by reacting methyl benzoate **47** with hydrazine hydrate. Subsequently, this hydrazide **1** was subjected to a reaction with CS_2 in an alkali ethanol solution, resulting in the formation of the potassium dithiocarbazinate salt **48**. The fundamental nucleus, 4-amino-5-phenyl-1,4*H*-1,2,4-triazole-3-thiol **3**, was then obtained by cyclizing the potassium salt with hydrazine hydrate, utilizing water as a solvent. The next step involved addition reactions with various aldehydes **98** to synthesize Schiff bases **50**, which were further cyclized by treatment with thioglycolic acid **99** and give 2-(4-bromophenyl)-3-(3-mercapto-5-phenyl-4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one **100**. **(Scheme2.16)**



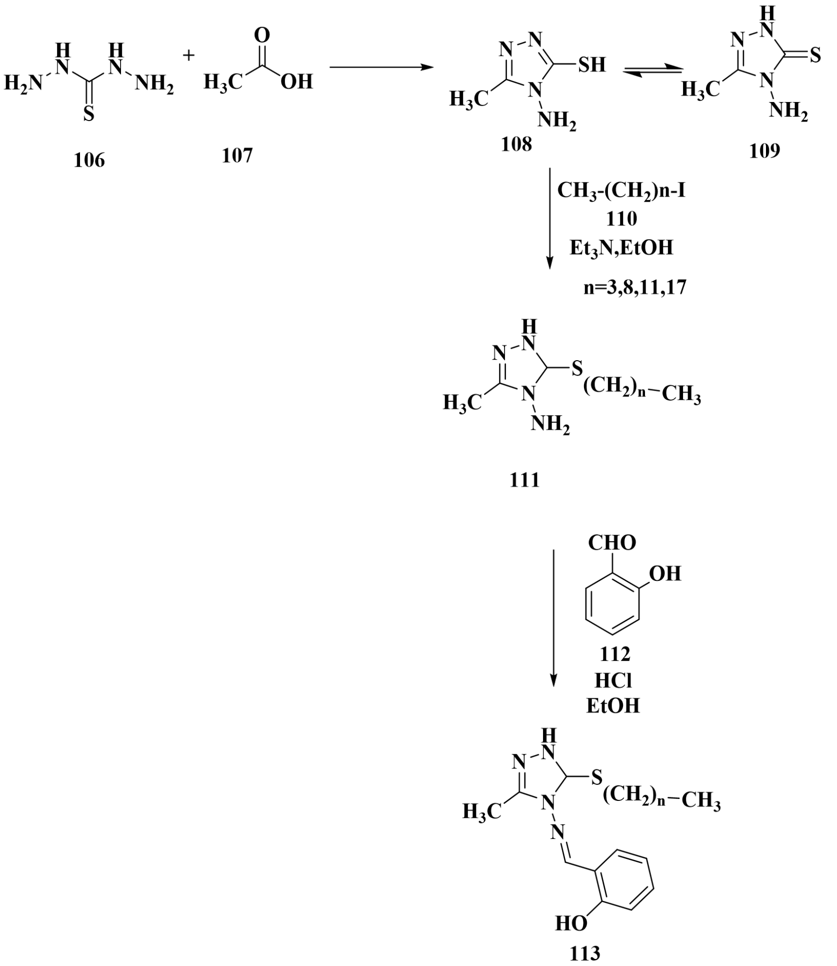
Scheme2.16

Kumar Shukla et al.,[110] reported a novel series of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol derivatives **105** was synthesized and subjected to comprehensive antimicrobial screening against both Gram-positive and Gram-negative bacteria, as well as various fungal strains. The majority of these compounds demonstrated significant antimicrobial activity. The synthesis of the **105** derivatives involved several steps. Substituted carboxylic acids **101** were first oxidized to 4-substituted methyl benzoates **102**, which were then reacted with hydrazine hydrate to form substituted benzohydrazide **103**. These benzohydrazide **103** were treated with carbon disulfide and potassium hydroxide (KOH) to yield the potassium salts of substituted 2-(4-methylbenzoyl)hydrazine-1-carbodithioates **104**. Finally, these potassium salts were cyclized with hydrazine hydrate to produce the 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol derivatives **105**. **(Scheme2.17)**



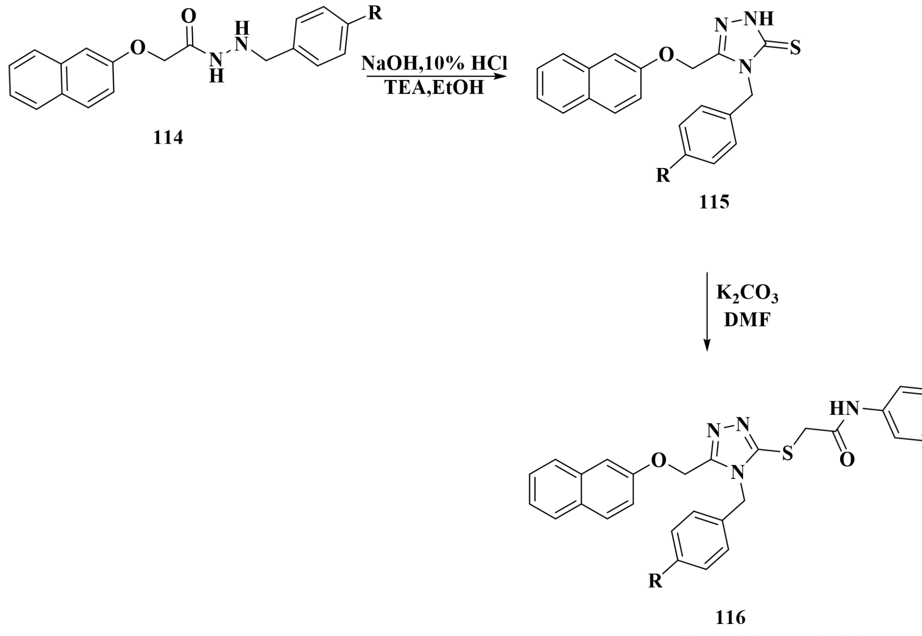
Scheme2.17

Boceiri et al.,[111] reported Thiocarbohydrazide **106** was reacted with acetic acid **107** to produce 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol **108**. This thiol **108** compound was then treated with iodoalkanes **109** (such as iodobutane, iodononane, iodododecane, or iodooctadecane) in the presence of an excess of triethylamine and ethanol, yielding 4-amino-5-methyl-3-alkylthio-1,2,4-triazole **110**. These triazole **111** were subsequently reacted with salicylaldehyde **112** in ethanol to form 4-(2-hydroxybenzylidene)amino-5-methyl-3-alkylthio-1,2,4-triazole derivatives **113**. **(Scheme2.18)**



Scheme2.18

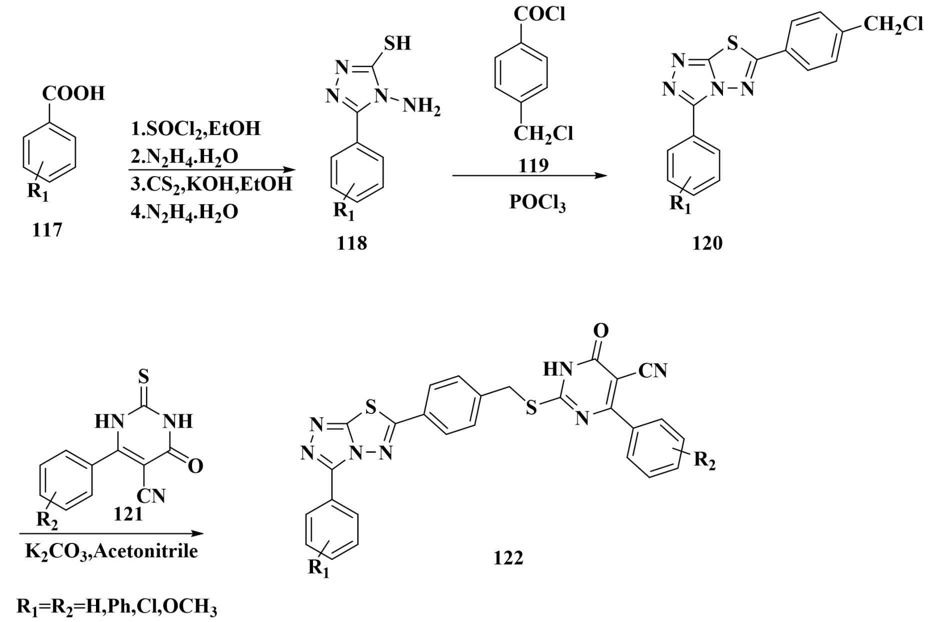
Kulabas et al., [112] reported in this study, a series of thiosemicarbazide derivatives, 1,2,4-triazol-3-thione derivatives, and compounds featuring the 2-(4*H*-1,2,4-triazole-3-ylthio)acetamide **116** structure were synthesized. The process began with the reaction of benzyl-2-(naphthalen-2-yloxy)acetohydrazide **114** in the presence of a base, yielding 4-(4-substituted benzyl)-5-((naphthalen-2-yloxy)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **115**. Subsequently, treatment with potassium carbonate produced *N*-(4-substituted phenyl)-2-((4-(4-chlorobenzyl)-5-((naphthalen-2-yloxy)methyl)-4*H*-1,2,4-triazol-3-yl)thio)acetamide derivatives **116**. synthesized compounds **116** were then evaluated for their anti-HIV activity. **(Scheme2.19)**



R=Cl,Br,OCH_3,NO_2,SO_2NH_2

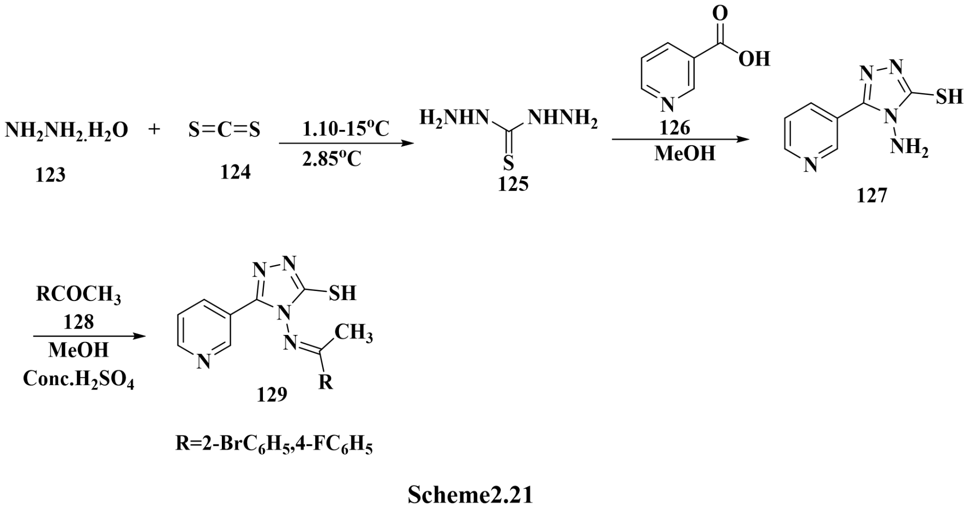
Scheme2.19

Cui et al., [113] reported Novel thiouracil derivatives **121**, featuring a triazolo-Thiadiazole moiety **122**, were synthesized in this study. This synthesis initiated with 4-amino-5-(4-substituted phenyl)-4*H*-1,2,4-triazole-3-thiol **118** was achieved through a four-step process starting from 4-substituted benzoic acid **117**. Initially, substituted benzoic acid **117** was reacted with thionyl chloride, followed by hydrazine hydrate, then carbon disulfide and a base, and finally another reaction with excess of hydrazine hydrate, yielding 4-amino-5-(4-substituted phenyl)-4*H*-1,2,4-triazole-3-thiol **118**. This thiol **118** compound was then reacted with 4-(chloromethyl)benzoyl chloride **119** in the presence of phosphorus oxychloride ($POCl_3$) to form 6-(4-(chloromethyl)phenyl)-3-(4-substituted phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **120**. The resulting thiadiazole **120** was subsequently reacted with 6-(4-substituted phenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **121** in the presence of potassium carbonate (K_2CO_3) and acetonitrile to produce 4-(4-substituted phenyl)-2-((4-(3-(4-substituted phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)benzyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **122**. The antibacterial activity of the synthesized compounds **122** was then evaluated. **(Scheme2.20)**



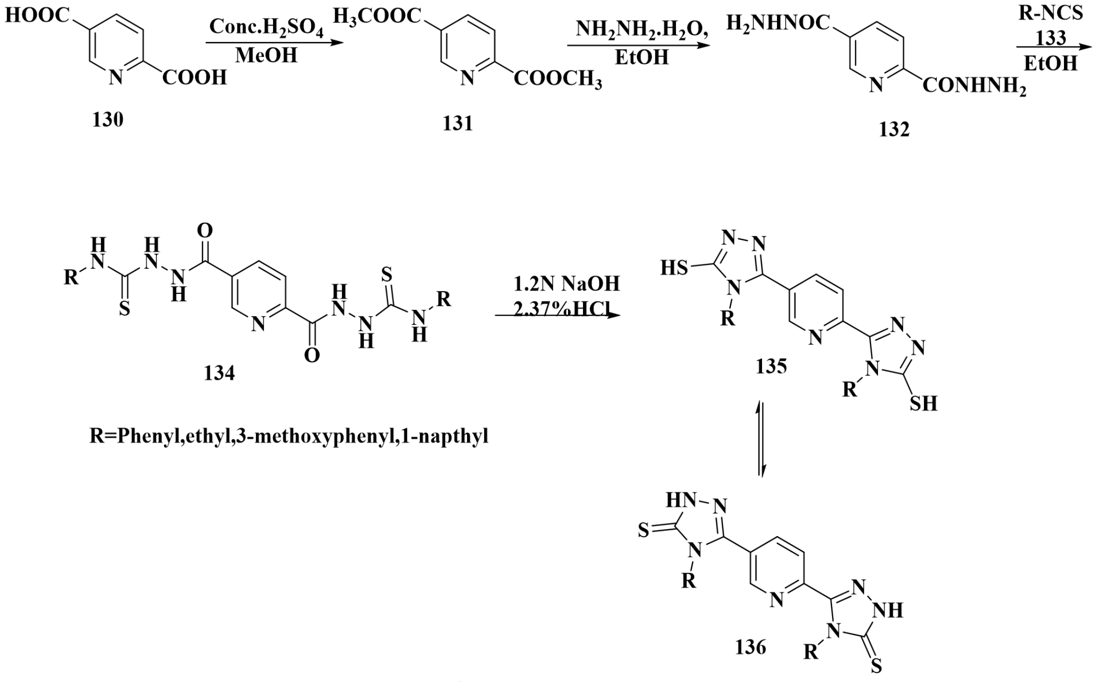
Scheme2.20

Praveen et al., [114] reported on the temperature of hydrazine hydrate **123** was lowered to 10°C, and carbon disulfide **124** was added dropwise under reflux conditions to produce thiocarbohydrazide **125**. This thiocarbohydrazide **125** was then reacted with nicotinic acid **126**, resulting in the formation of 4-amino-5-pyridin-3-yl-4*H*-[1,2,4]triazole-3-thiol. This compound was further reacted with the corresponding substituted acetophenone **127** in the presence of methanol to yield 4-[1-(2-substituted-phenyl)-ethylideneamino]-5-pyridin-3-yl-2,4-dihydro-[1,2,4]triazole-3-thione derivatives **128**. The newly synthesized compounds **128** were initially evaluated for their anticonvulsant activity, followed by screening through various phases of the maximal electroshock seizure (MES) model. **(Scheme2.21)**



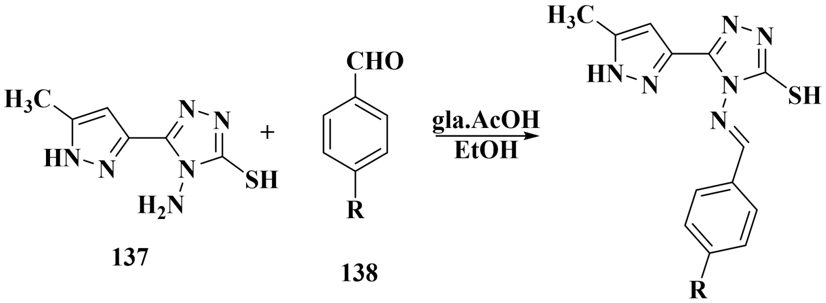
Scheme2.21

Bulut et al., [115] reported through the utilization of pyridine-2,5-dicarboxylic acid **130**, a set of innovative derivatives involving thiosemicarbazide **134** and 1,2,4-triazole-3-thiol **135** was successfully synthesized. Initially, the reaction of pyridine-2,5-dicarboxylic acid **130** with absolute ethanol yielded the corresponding dimethyl pyridine-2,5-dicarboxylate **131**. Subsequently, reacting dimethyl-2,5-pyridinedicarboxylate **131** with hydrazine hydrate efficiently produced pyridine-2,5-dicarbohydrazide **132**. This **132** was further synthesized by refluxing with substituted isothiocyanate derivatives **133**. The base-catalyzed intramolecular dehydrative cyclization of these intermediates resulted in the formation of 4-substituted-5-(6-(4-substituted-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)pyridin-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **135** and **136** derivatives in good yield. **135** and **136** compounds confirmed through spectral data These compounds were investigated for their antioxidant properties, as well as their inhibition profiles against carbonic anhydrase and acetylcholinesterase enzymes. **(Scheme2.22)**



Scheme2.22

Pillai et al., [116] reported the synthesis and evaluation of Schiff bases incorporating 4-amino-5-(5-methyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol **137** and aldehyde derivatives **138** were conducted using a few drops of glacial acetic acid and ethanol to specific compound 4-((4-substituted benzylidene)amino)-5-(5-methyl-1*H*-pyrazol-3-yl)-4*H*-1,2,4-triazole-3-thiol **139**. Derivative of schiff base **139** shows an antioxidant and α-glucosidase inhibitory properties. **(Scheme2.23)**



137

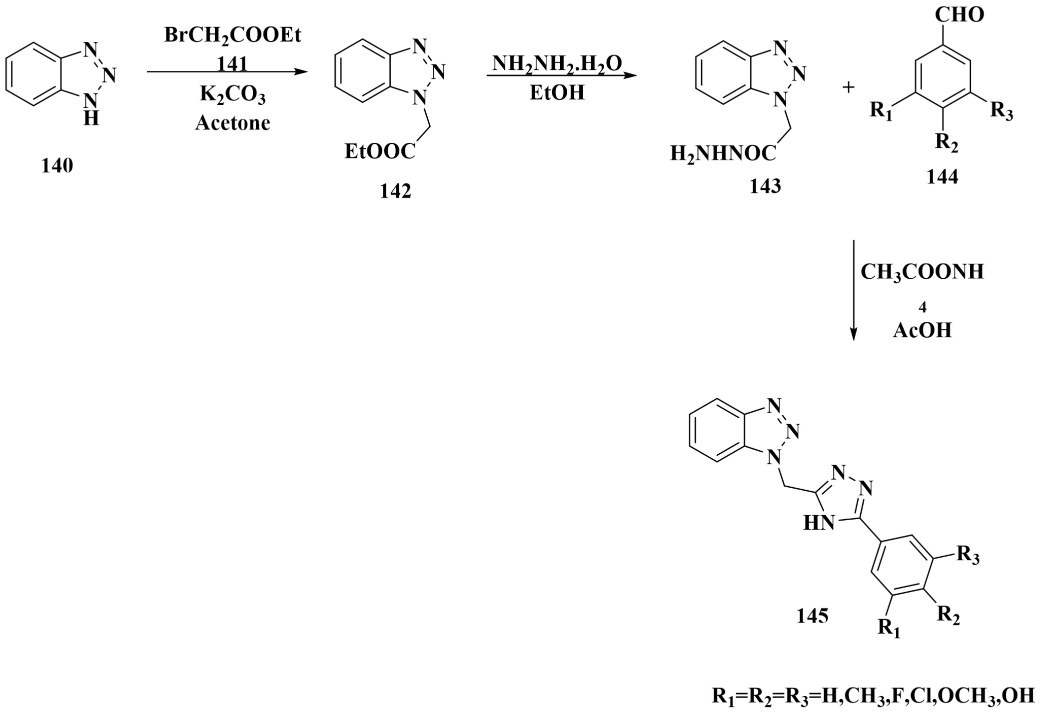
138

$R=OCH_3,N(CH_3)_2$

139

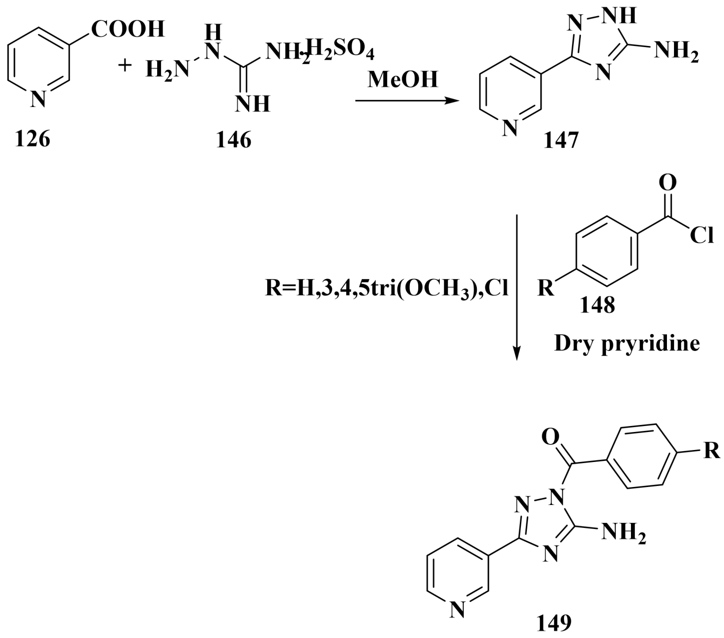
Scheme2.23

Chand et al., [117] reported the alkylation of 1*H*-benzo[d][1,2,3]triazole with ethyl bromoacetate in the presence of potassium carbonate in acetone at room temperature yielded 1-(ethoxycarbonylmethyl)-1*H*-benzotriazole. This product was then refluxed with hydrazine hydrate in ethanol to form 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole. Subsequently, this intermediate was reacted with an equimolar amount of substituted benzaldehyde in the presence of ammonium acetate in acetic acid at room temperature, resulting in 1-(3-substituted phenyl-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole derivatives. These derivatives were evaluated for their in vitro antimicrobial activity against bacteria and fungi, as well as their antioxidant activity. **(Scheme2.24)**



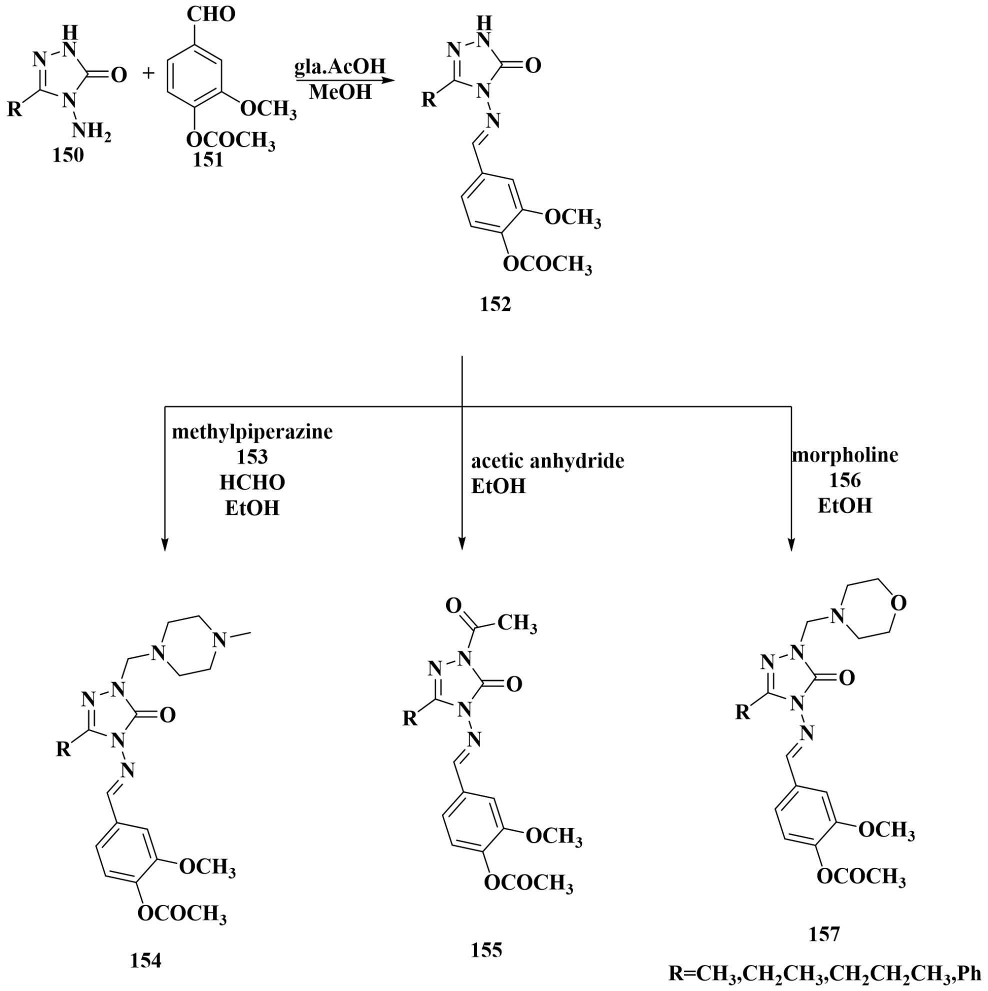
Scheme2.24

Osman et al., [118] reported a synthesis of Nicotinic acid **126** reacts with hydrazinecarboximidamide acid salt **146** in the presence of methanol to produce 3-(pyridin-3-yl)-1*H*-1,2,4-triazol-5-amine **147**. This compound **147** is then reacted with substituted benzoyl chloride **148** in dry pyridine to form (5-amino-3-(pyridin-3-yl)-1*H*-1,2,4-triazol-1-yl)(substituted)methanone derivatives **149**. The antioxidant activity of these novel compounds **149** was evaluated by assessing their scavenging activity against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. **(Scheme2.25)**



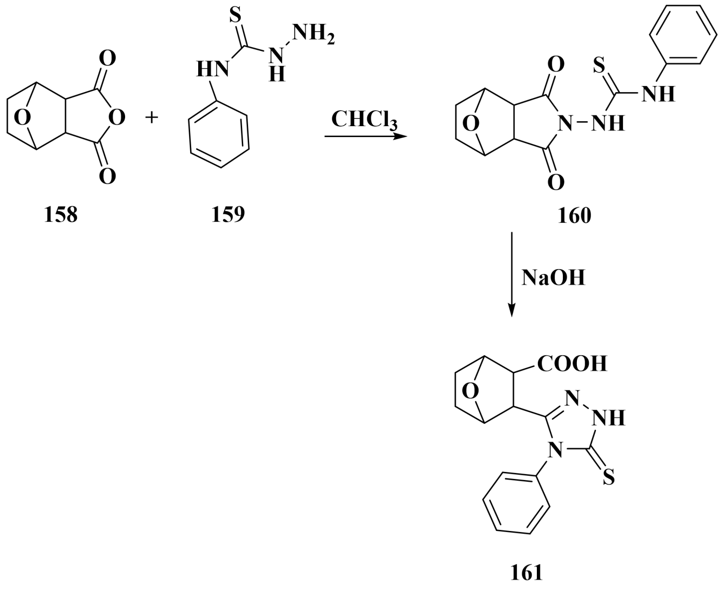
Scheme2.25

Manap et al., [119] reported in this investigation, 3-alkyl(aryl)-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **150** underwent reaction with 3-methoxy-4-isobutyryloxybenzaldehyde **151**, yielding the corresponding 3-substituted-4-(3-methoxy-4-isobutyryloxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **152**. Subsequently, the acetylation reactions of these compounds were explored. Treatment of 3-substituted-4-(3-methoxy-4-isobutyryloxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **152** with 1-methylpiperazine **153** or morpholine **156** in the presence of formaldehyde, following the Mannich reaction, led to the synthesis of 1-(1-methylpiperazin-4-yl-methyl)-3-substituted- 4-(3-methoxy-4-isobutyryloxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **154** Or 1-(morpholine-4-yl-methyl)-3-alkyl(aryl)-4-(3-methoxy-4-isobutyryloxy-benzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **157** respectively. **152** further with acetic anhydride to give 4-(((1-acetyl-3-substituted-5-oxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)imino)methyl)-2-methoxyphenyl acetate **155**. Additionally, the antimicrobial activities were assessed for **154**, **155** and **157** derivatives. **(Scheme2.26)**



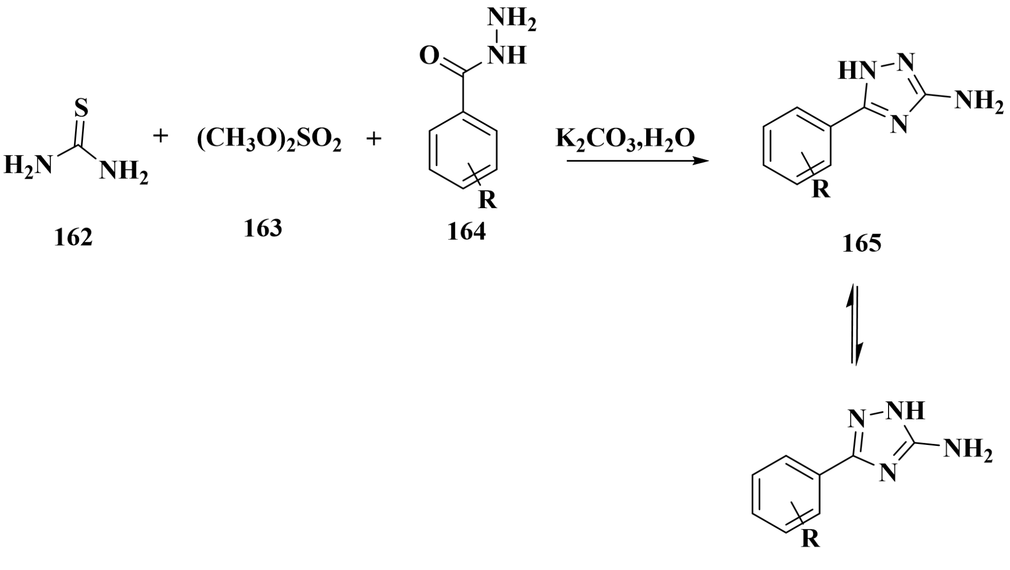
Scheme2.26

Pachuta-Stec et al., [120] reported synthesis on Hexahydro-4,7-epoxyisobenzofuran-1,3-dione **158** is refluxed with *N*-phenylhydrazinecarbothioamide **159** in dry chloroform, resulting in the formation of 1-(1,3-dioxooctahydro-2*H*-4,7-epoxyisoindol-2-yl)-3-phenylthiourea **160**. This intermediate **160** is then treated with sodium hydroxide, yielding 3-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid **161**. These synthesized compounds **161** are subsequently evaluated for their antioxidant properties. **(Scheme2.27)**



Scheme2.27

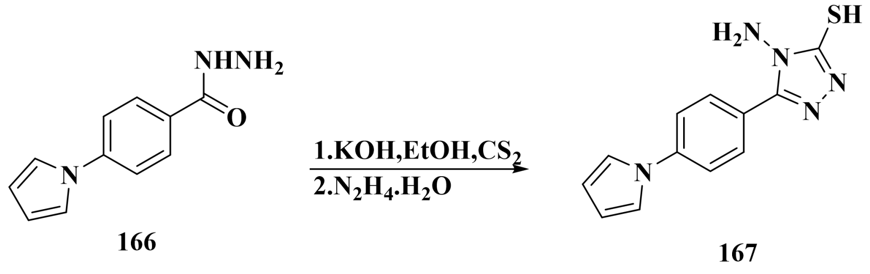
Beyzaei et al., [121] reported an efficient method was developed for synthesizing novel 5-substituted-1*H*-1,2,4-triazol-3-amines **165** using a one-pot reaction that combines thiourea **162**, dimethyl sulfate **163**, and substituted benzohydrazide **164**. This process, conducted in an aqueous medium under mild conditions, aligns with key principles of green chemistry. The derivatives of 1,2,4-triazoles **165** produced were readily isolated in good yields without the need for further purification. The antimicrobial activities of all synthesized derivatives **165** were assessed against various Gram-positive and Gram-negative bacteria, as well as certain fungal pathogens. **(Scheme2.28)**



$R=CH_3,OCH_3,Cl,Br,F$

Scheme2.28

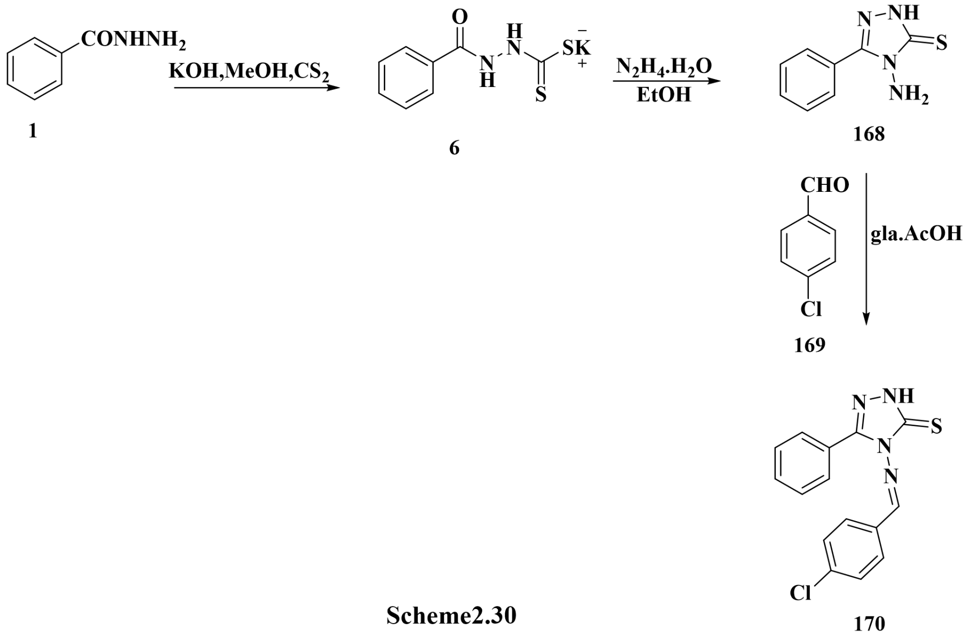
Mustafa et al., [122] reported the synthesis of 5-(4-(1*H*-pyrrol-1-yl)phenyl)-4-amino-4*H*-1,2,4-triazole-3-thiol **167** was accomplished by reacting 4-(1*H*-pyrrol-1-yl)benzohydrazide **166** with potassium hydroxide in an alcoholic solution, along with CS_2 and hydrazine hydrate. This compound **167** was then evaluated for its effectiveness in inhibiting steel corrosion in acidic environments. **(Scheme2.29)**



Scheme2.29

Hassan et al., [123] reported the synthesis commenced with the reaction of benzohydrazide **1** with carbon disulfide under basic conditions, yielding dithiocarbazinate **6**. Subsequent cyclization with hydrazine to give 4-amino-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione **168**. The targeted Schiff base, 4-(4-chlorobenzylideneamino)-5-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione **170**, was successfully produced in acetic acid under mild acidic conditions. This synthesis involved the treatment of 4-amino-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

168 with chlorobenzaldehyde **169**. Compound **170** shows anticancer activity. **(Scheme2.30)**



Scheme2.30

The thorough literature review concludes by highlighting the critical function that compounds containing 1,2,4-triazole moieties play in medicinal chemistry and highlighting their unique significance as powerful bioactive agents. It is clear that five-membered nitrogen-containing heterocycles, in particular 1,2,4-triazoles, are frequently used in the synthesis and design of molecules with intriguing biological features. These compounds show a wide variety of pharmacological properties, such as antioxidant, antiviral, antibacterial, anticancer, and anti-inflammatory abilities. The methods of synthesis, chemical attributes, and structural features clarified in the literature review offer crucial insights into the optimization of compound designs for medicinal uses. Furthermore, the investigation of structure-activity relationships (SAR) has made it easier to comprehend the molecular processes that underlie the bioactivity of 1,2,4-triazole derivatives, opening the door to the creation of new therapeutic possibilities.

2.3 Result and Discussion:

The synthesis of the target molecules followed a systematic procedure outlined in the provided schematic diagram. The first step involved the reaction of 2-amino pyridine (1) with ethyl acetoacetate (2), facilitated by N-bromosuccinimide (NBS) in situ, resulting in an excellent yield of compound (3). Subsequently, compound (3) underwent transformation into its corresponding carbohydrazide (4) through a reaction with hydrazine hydrate. Further cyclization of compound (4) was achieved by utilizing carbon disulfide (CS2) in the presence of a basic medium. The formed salt was carefully washed with methanol and diethyl ether to avoid hydrolysis, followed by treatment with 99% hydrazine hydrate, leading to the formation of a five-membered heterocyclic ring with three nitrogen atoms, resulting in compound (5). The use of CS2 proved to be an effective cyclizing agent, yielding the desired product in good efficiency.

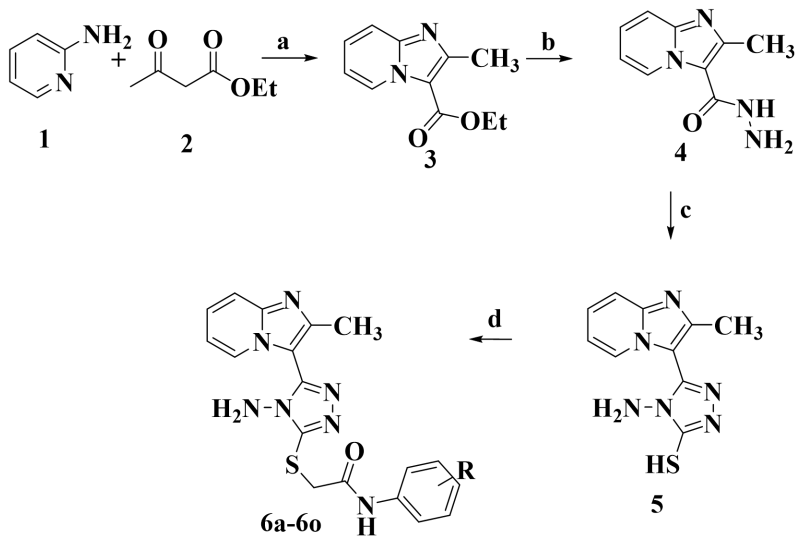
The final step involved coupling of compound (5) with various derivatives of 2-chloro-N-phenylacetamide in basic medium, furnishing a series of final target compounds (6a–6o). This synthetic strategy was found to be consistently high-yielding and reliable across all stages. The purity and structural identity of the synthesized compounds were validated through detailed spectral characterization.

The infrared (IR) spectra of the synthesized compounds revealed characteristic absorption bands typically ranging between 3050–3776 cm^{-1} for N–H and C–H stretching, 1600–1670 cm^{-1} for C=N and C=O stretching, and 1300–1400 cm^{-1} corresponding to C–N stretching vibrations. The ^{1}H NMR spectra (recorded in DMSO-d_6) showed singlets for methyl protons between δ 2.26–2.40 ppm, methylene protons at δ 4.19–4.23 ppm, aromatic and heteroaromatic protons spanning δ 6.05–8.34 ppm, and a distinct downfield signal for the amide –NH proton appearing between δ 10.33–10.60 ppm. The ^{13}C NMR spectra confirmed the presence of key functional groups, with chemical shifts ranging from δ 14.99–166.70 ppm. The presence of methyl, aromatic, imidazo[1,2-a]pyridine, and oxadiazole carbons were all clearly identified, consistent with the proposed structures.

Mass spectrometry further supported the structural assignments, with molecular ion peaks appearing in the expected range (m/z 378–457), confirming the calculated molecular weights of the compounds. Elemental analysis also demonstrated excellent agreement between calculated and experimental values, thereby validating the proposed molecular compositions.

Overall, the synthetic methodology provided robust access to the desired heterocyclic scaffolds with reproducible and well-defined spectral features, establishing a sound basis for further development and potential biological evaluation.

2.4 Reaction Scheme:



a) NBS, MeOH, 80°C; b) $NH_2NH_2.H_2O$, MeOH, 80-90°C;
c) KOH, CS_2, $NH_2NH_2.H_2O$, MeOH, 80°C;
d) K_2CO_3, DMF, Substituted 2-chloro-N-phenylacetamide, RT

2.5 Physical Characteristics:

Table:2.1 Physical examination of the synthesized compounds

Entry	Compound code	R	Molecular Formula	Molecular Weight	M.P. in °C	Yield %
1	6a	4-CH_3	$C_{19}H_{19}ON_7S$	393.14	186-188	85
2	6b	4-OCH_3	$C_{19}H_{19}O_2N_7S$	409.13	184-186	79
3	6c	4-Cl	$C_{18}H_{16}OClN_7S$	412.88	191-193	72
4	6d	4-Br	$C_{18}H_{16}OBrN_7S$	457.03	201-203	63

5	6e	4-F	$C_{18}H_{16}OFN_7S$	397.11	195-197	67
6	6f	H	$C_{18}H_{17}ON_7S$	379.12	185-187	86
7	6g	2,4-CH_3	$C_{20}H_{21}ON_7S$	407.15	181-182	80
8	6h	3-Cl	$C_{18}H_{16}OClN_7S$	413.88	188-190	71
9	6i	2-OCH_3	$C_{19}H_{19}O_2N_7S$	409.13	192-194	64
10	6j	2-CH_3	$C_{19}H_{19}ON_7S$	393.14	193-195	81
11	6k	3-CH_3	$C_{19}H_{19}ON_7S$	393.14	183-185	64
12	6l	3-OCH_3	$C_{19}H_{19}O_2N_7S$	409.13	188-190	85
13	6m	3-Cl,4-F	$C_{18}H_{15}OClFN_7S$	431.07	197-199	66
14	6n	2,4-F	$C_{18}H_{15}OF_2N_7S$	415.10	196-198	68
15	6o	3,4-Cl	$C_{18}H_{15}OCl_2N_7S$	447.04	199-201	70

All compound either amorphous or crystal white.

2.6 Conclusion:

In this study, we have successfully synthesized novel 2-((4-amino-5-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(p-tolyl)acetamide derivatives. The synthetic pathway employed demonstrated high efficiency and yielded substantial amounts of the target compounds at each step, highlighting the effectiveness and reliability of the methodology. Comprehensive spectral analysis, including ^{1}H NMR, ^{13}C NMR, and mass spectrometry, confirmed the structural integrity and composition of the synthesized compounds. The presence of the 2-methylimidazo[1,2-*a*]pyridine and 1,2,4-triazole moieties, along with the p-tolyl group, was verified, ensuring the successful formation of the desired derivatives. The incorporation of the 1,2,4-triazole and imidazo[1,2-*a*]pyridine scaffolds into the acetamide framework potentially enhances the pharmacological profile of these compounds. The structural novelty and functional diversity of these derivatives suggest their significant potential for further investigation in medicinal chemistry.

Overall, the successful synthesis and detailed characterization of these novel acetamide derivatives underscore their promise as valuable candidates for future studies and applications in drug discovery and development. Further exploration of their biological activities and therapeutic potential is warranted to fully realize their applicability in medical science.

2.7 Experimental Section:

2.7.1 Materials and Methods:

In our experiment, we utilized reagents sourced from reputable suppliers like Sigma-Aldrich and Spectrochem chemicals to ensure the reliability and quality of our materials. These reagents were used directly without purification, preserving the integrity of our experimental process and conserving time and resources. To monitor the progress of our reactions, we employed thin-layer chromatography (TLC) using silica gel-G plates (G60 F254, E-Merck Co.). By visualizing under UV light, we could observe the reaction progress in real-time, aiding in efficient optimization of reaction conditions. Melting points of synthesized compounds were determined in open capillaries, offering preliminary insights into their purity and identity, serving as useful indicators despite remaining uncorrected.

For structural analysis, infrared (IR) spectra were recorded using an FT-IR-8400 instrument with potassium bromide (KBr) as the matrix, enabling the identification of functional groups based on their absorption patterns. Nuclear magnetic resonance (NMR) spectroscopy, including both ^{1}H and ^{13}C NMR, was conducted on Bruker Avance spectrometers, with chemical shifts reported in δ ppm relative to the solvent DMSO-d^6 and using tetramethylsilane (TMS) as the internal reference, providing detailed structural information crucial for compound characterization.

Additionally, mass spectra were obtained using ultraperformance liquid chromatography coupled with mass spectrometry (LC/MS), employing electrospray ionization in positive ion mode. Covering a mass range from 100 to 1500 Da with a cone voltage set at 30 V, LC/MS analysis facilitated the determination of molecular weights and fragmentation patterns of the synthesized compounds, enriching our comprehension of their chemical composition.

2.7.2 General Procedures:

General procedure for ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate(3):

Ethylacetoacetate (2) (10 mmol) was dissolved in 40 mL of methanol and stirred at a temperature range of 0-50°C for 10-15 minutes. *N*-bromosuccinimide (NBS) (10 mmol) was added portion-wise and the mixture was stirred at the same temperature for 15-20 minutes. Subsequently, the mixture was stirred at room temperature for 45-50 minutes until the solution became clear. Then, 2-aminopyridine (1) (10 mmol) was added portion-wise, and the reaction mixture was refluxed for 2-3 hours at 80°C. The progression of the reaction was monitored via TLC until the starting material was consumed. Upon completion, the solvent was evaporated under reduced pressure, and the residue was poured onto crushed ice. The resulting solid was recrystallized using methanol to obtain the product.[50]

General procedure for 2-methylimidazo-[1,2-*a*]pyridine-3-carbohydrazide(4):

Ethyl 2-methylimidazo[1,2-a]pyridine-3-carboxylate (3)(10 mmol) was dissolved in 10 mL of methanol. Hydrazine hydrate (99%) (10 mmol) was added dropwise, and the reaction mixture was refluxed for 2-3 hours at 80°C. The progress of the reaction was monitored via TLC until the starting material was consumed. After completion, the reaction mixture was cooled to room temperature and poured into ice-cold water. The resulting solid was recrystallized using ethyl acetate to obtain the product.[32]

General procedure for 4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol(5):

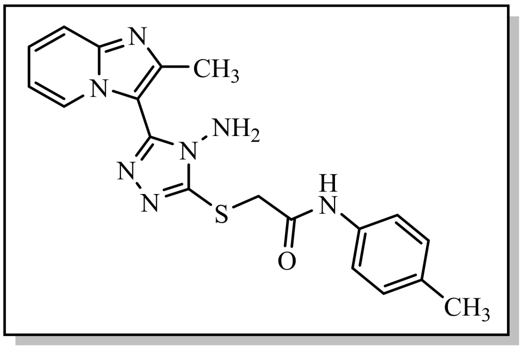
A solution of 2-methylimidazo-[1,2-a]pyridine-3-carbohydrazide(4) (10 mmol) and KOH (10 mmol) in methanol (20 mL) was stirred at 0°C until the solution became clear. CS_2 (10 mmol) was then added dropwise. After the addition of CS_2, the reaction mixture was refluxed and stirred at room temperature for 3-4 hours. The formed salt was washed with methanol and diethyl ether (avoiding water). Hydrazine hydrate (99%) (10 mmol) was added dropwise, and the reaction mixture was refluxed for 2-3 hours at 80°C. The progression of the reaction was monitored via TLC until the starting material was consumed. After completion, the reaction mixture was cooled to room temperature and poured into ice-cold water. The resultant solid was recrystallized using ethyl acetate to obtain the product.

General procedure for 2-((4-amino-5-(2-methylimidazo[1,2-*a*]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-phenylacetamide derivatives(6a-6o):

A mixture of 4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazole-3-thiol (5, 1 gm, 0.004 mol, 1 eq) and K_2CO_3 (1.12 gm, 0.004 mol, 2 eq) in DMF (10 mL) was agitated for 15 minute until a color change was observed. Then, 2-chloro-*N*-phenylacetamide derivative (0.75 gm, 0.004 mol, 1.1eq) was applied in portions When the mixture of reactions was agitated for 2-3 hours at ambient temperature. Using TLC, the reaction's progress was tracked until it was finished. Following the completion of the reaction, the mixture was poured into ice, resulting in a hazy solution. Then addition of few drops of aqueous HCl to the solution, causing the formation of a solid precipitate. The solid was gathered by vacuum filtration and dried in a refrigerator overnight. Through the process of recrystallization, newly formed chemical compounds were refined. using either methanol or ethanol as solvents. The reactions proceeded smoothly, yielding goods with yields that range from 63% to 86%. (6a-6o)

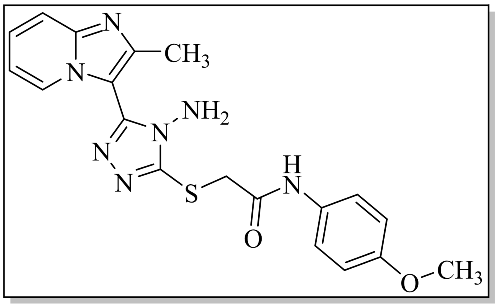
2.7.3 Spectral Characterization:

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(p-tolyl)acetamide(6a):



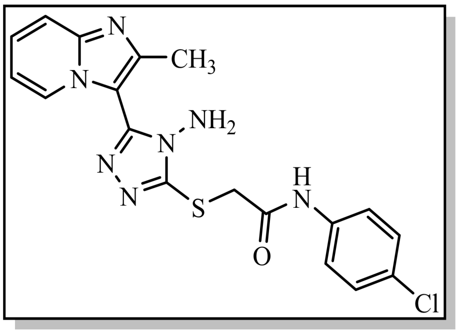
White; Yield: 85%; M.P.: 186-188°C; IR(KBr,υ_{max},cm^{-1}): 3776, 3460, 3128, 2920, 1662, 1546,1604 & 1658, 1373, 817; ^1H NMR (400 MHz, DMSO-d^6) δ 2.26 (s, 3H), 2.40(s, 3H), 4.19 (s, 2H), 6.05 (s, 2H), 6.93 (t, *J* = 6.5, 6.5 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.39 (m, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d^6) δ 15.00, 20.92, 37.19, 108.64, 112.84, 116.64, 116.63, 126.14, 126.26, 129.67, 133.00, 136.77, 145.41, 145.56, 147.88, 153.28, 166.22; MS(*m/z*): 394.8 (m^+). Anal. Calcd. For $C_{19}H_{19}N_7OS$: C, 58.00; H, 4.87; N, 24.92; O, 4.07; found: C, 57.98; H, 4.83; N, 24.90; O, 4.01.

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(4-methoxyphenyl)acetamide(6b):



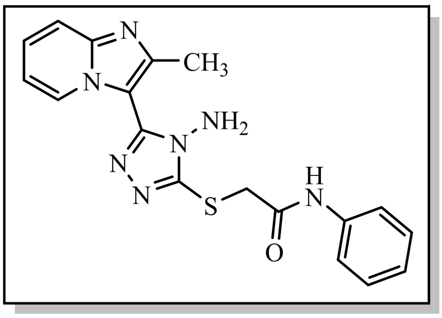
White; Yield: 79 %; M.P.: 184-186°C; IR(KBr,υ_{max},cm^{-1}): 3710, 3614, 3196, 2924, 1670, 1615, 1557, 1382, 817; ^{1}H NMR (400 MHz, DMSO-d^6) δ 2.40 (s, 3H), 3.72 (s, 3H), 4.19 (s, 2H), 6.08 (s, 2H), 6.92 (t, *J* = 8.8, 8.8 Hz, 3H), 7.30 – 7.38 (m, 1H), 7.49 – 7.62 (m, 3H), 8.34 (d, *J* = 6.6 Hz, 1H), 10.33 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d^6) δ 14.99, 37.19, 55.64, 108.67, 112.86, 114.41, 116.63, 121.23, 126.14, 126.29, 132.39, 145.43, 145.57, 147.90, 153.28, 155.92, 166.00; MS(*m/z*): 410.85 (m^+). Anal. Calcd. For $C_{19}H_{19}N_7OS$: C, 55.73; H, 4.68; N, 23.95; O, 7.81; found: C, 54.91; H, 4.52; N, 23.82; O, 7.01.

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(4-chlorophenyl)acetamide (6c) :



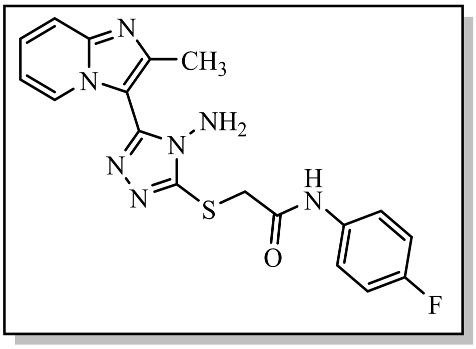
White; Yield: 72%; M.P.: 191-193°C; IR(KBr,υ$_{max}$,cm^{-1}): 3772, 3275, 2931, 1662, 1543, 1600 , 1392, 825; ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ 2.40 (s, 3H), 4.23 (s, 2H), 6.07 (s, 2H), 6.91 (t, *J* = 6.6, 6.6 Hz, 1H), 7.32 – 7.40 (m, 3H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 8.34 (d, *J* = 6.6 Hz, 1H), 10.60 (s, 1H); ^{13}C NMR (101 MHz, DMSO-*d*^{6}) δ 15.00, 37.10, 108.62, 112.85, 116.62, 121.18, 126.14, 126.28, 127.63, 129.22, 138.23, 145.43, 145.57, 147.92, 153.28, 166.70; MS(*m/z*): 412.3 (m$^+$). Anal. Calcd. For $C_{18}H_{16}N_7ClOS$: C, 52.24; H, 3.90; N, 23.69; found: C, 52.21; H, 3.88; N, 23.65.

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-phenylacetamide (6d):



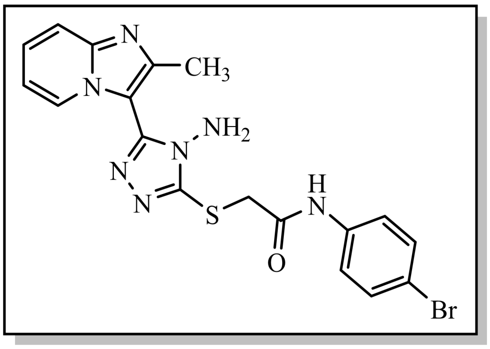
White; Yield: 86 %; M.P.: 185-187°C; IR(KBr,υ$_{max}$,cm^{-1}): 3776, 3309, 3074, 1670, 1489, 1597 , 1334, 898; ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ 2.40 (s, 3H), 4.22 (s, 2H), 6.05 (s, 2H), 6.93 (t, *J* = 6.7, 6.7 Hz, 1H), 7.08 (t, *J* = 7.3, 7.3 Hz, 1H), 7.34 (q, *J* = 7.7, 6.6, 6.6 Hz, 3H), 7.60 (t, *J* = 8.0, 8.0 Hz, 3H), 8.33 (d, *J* = 6.7 Hz, 1H), 10.41 (s, 1H); ^{13}C NMR (101 MHz, DMSO-*d*^{6}) δ 14.99, 37.22, 108.64, 112.87, 116.62, 119.66, 124.09, 126.13, 126.30, 129.31, 139.25, 145.43, 145.58, 147.90, 153.34,166.53; MS(*m/z*): 378.1 (m$^+$). Anal. Calcd. For $C_{19}H_{17}N_7OS$: C, 56.98; H, 4.52; N, 25.84; found: C, 56.91; H, 4.51; N, 25.81.

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(4-fluorophenyl)acetamide(6e):



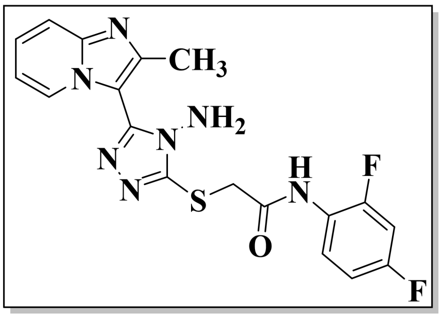
White; Yield: 67 %; M.P.: 195-197°C; IR(KBr,υ_{max},cm^{-1}): 3776, 3267, 3070, 2951, 1662, 1512, 1612 , 1334, 833; ^{1}H NMR (400 MHz, DMSO-*d*^{6}) δ 2.40 (s, 3H), 4.21 (s, 2H), 6.05 (s, 2H), 6.93 (t, *J* = 6.6, 6.6 Hz, 1H), 7.18 (t, *J* = 8.7, 8.7 Hz, 2H), 7.30 – 7.39 (m, 1H), 7.55 – 7.67 (m, 3H), 8.33 (d, *J* = 6.7 Hz, 1H), 10.48 (s, 1H); ^{13}C NMR (101 MHz, DMSO-*d*^{6}) δ 14.99, 37.04, 108.62, 112.85, 115.80, 116.01, 116.64, 121.37, 121.45, 126.13, 126.27, 135.65, 135.68, 145.42, 145.57, 147.90, 153.30, 159.42, 166.43; MS(*m/z*): 398.3 (m$^+$). Anal. Calcd. For $C_{18}H_{16}N_7FOS$: C, 54.40; H, 4.06; N, 24.67; found: C, 54.37; H, 4.01; N, 24.64.

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(4-bromophenyl)acetamide(6f):



White; Yield: 63%; M.P.: 201-203°C; IR(KBr,υ_{max},cm^{-1}): 3772, 3279, 3059, 1662, 1539, 1597 , 1388, 821; MS(*m/z*): 457.1 (m$^+$). Anal. Calcd. For $C_{18}H_{16}N_7BrOS$: C, 47.17; H, 3.52; N, 21.39; found: C, 47.14; H, 3.50; N, 21.37.

2-((4-amino-5-(2-methylimidazo[1,2-a]pyridin-3-yl)-4*H*-1,2,4-triazol-3-yl)thio)-*N*-(2,4-difluorophenyl)acetamide(6n):



White; Yield: 68 %; M.P.: 196-198°C; MS(*m/z*): 417.3(m^+); Anal. Calcd. For $C_{18}H_{15}F_2N_7OS$: C, 52.04; H, 3.64; N, 23.60; found: C, 52.00; H, 3.51; N, 23.01.

2.7.4 Representative Spectra:

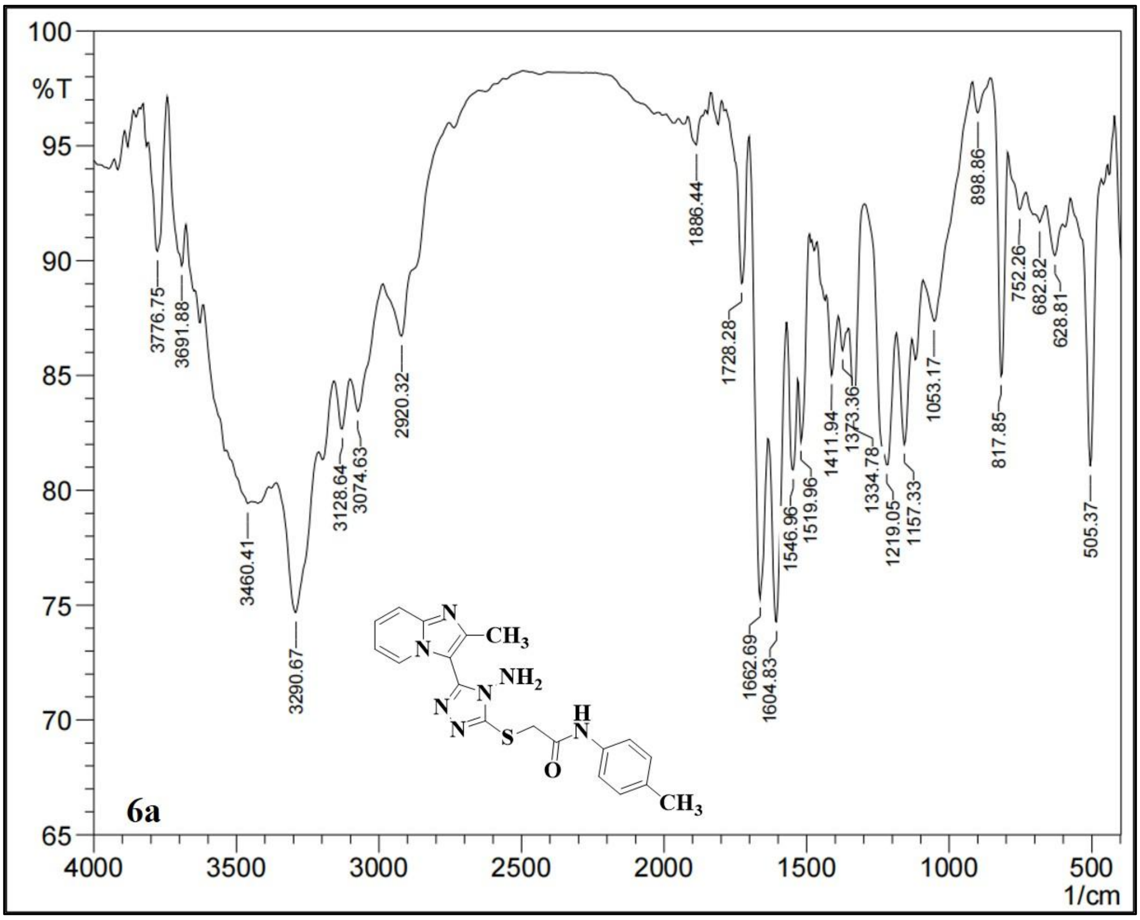


Fig.2.3: Representative IR spectrum of compound 6a

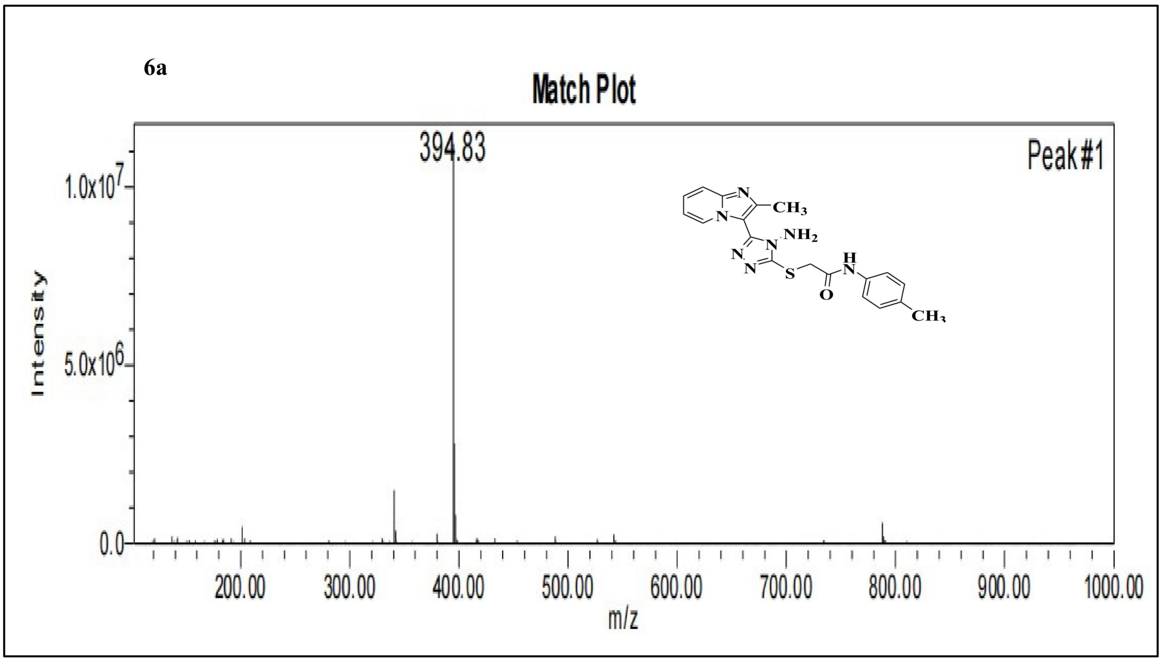


Fig.2.4: Representative mass spectrum of compound 6a

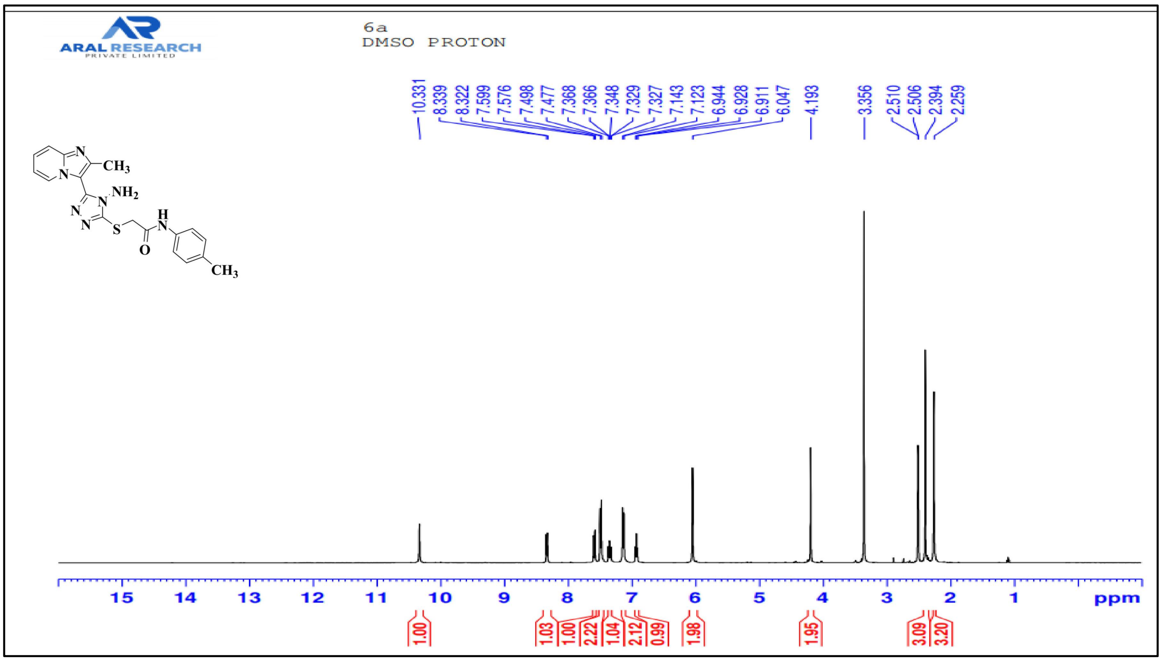


Fig.2.5: Representative ^{1}H NMR spectrum of compound 6a

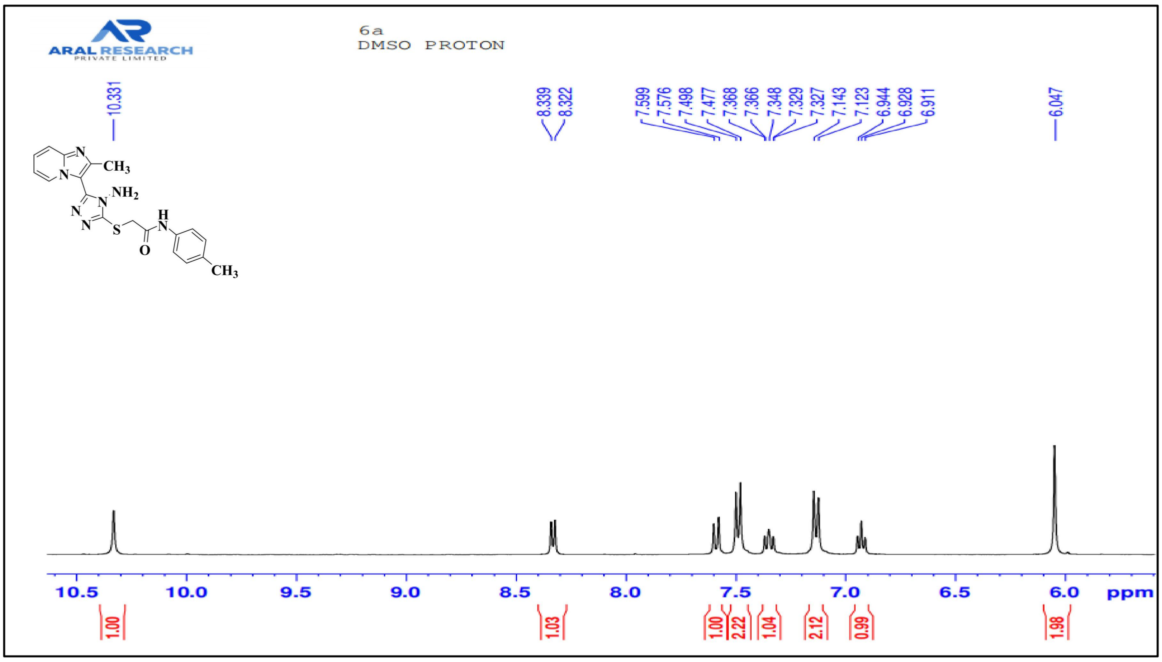


Fig.2.6: Representative Expanded ^{1}H NMR spectrum of 6a

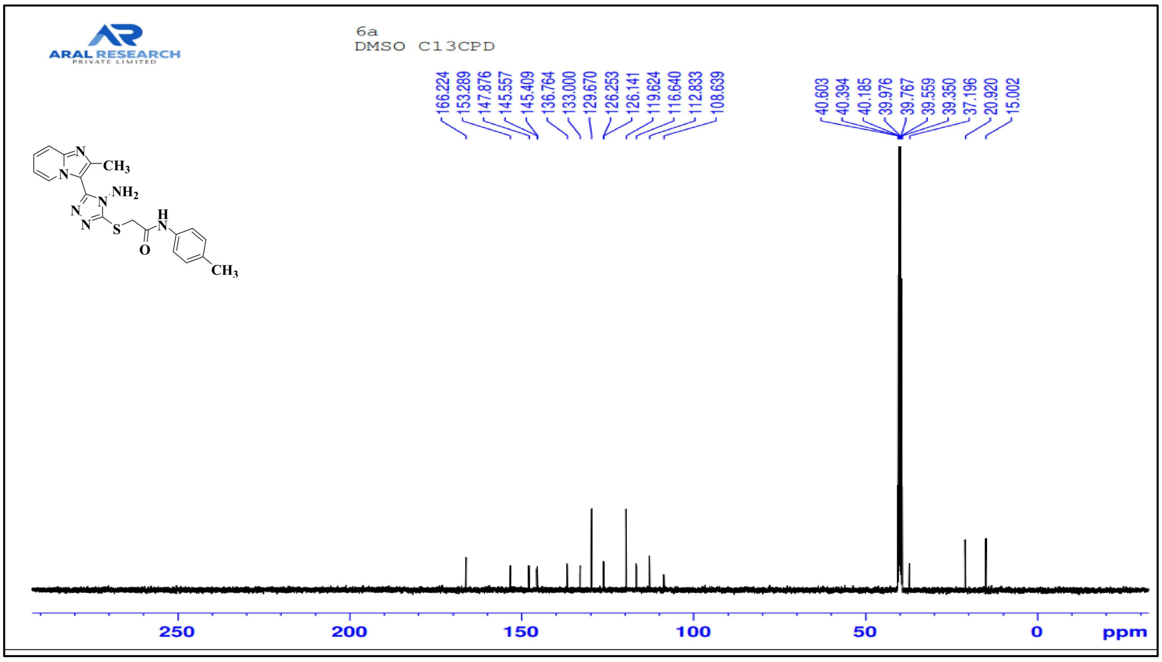


Fig.2.7: Representative ^{13}C NMR spectrum of compound 6a

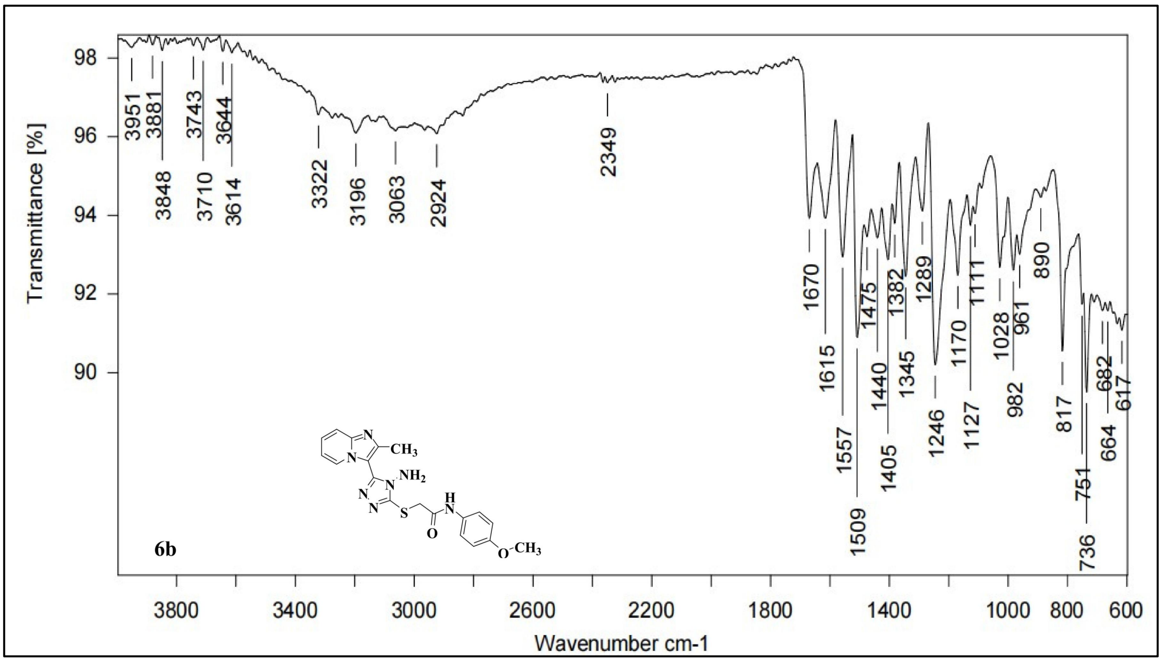


Fig.2.8: Representative IR spectrum of compound 6b

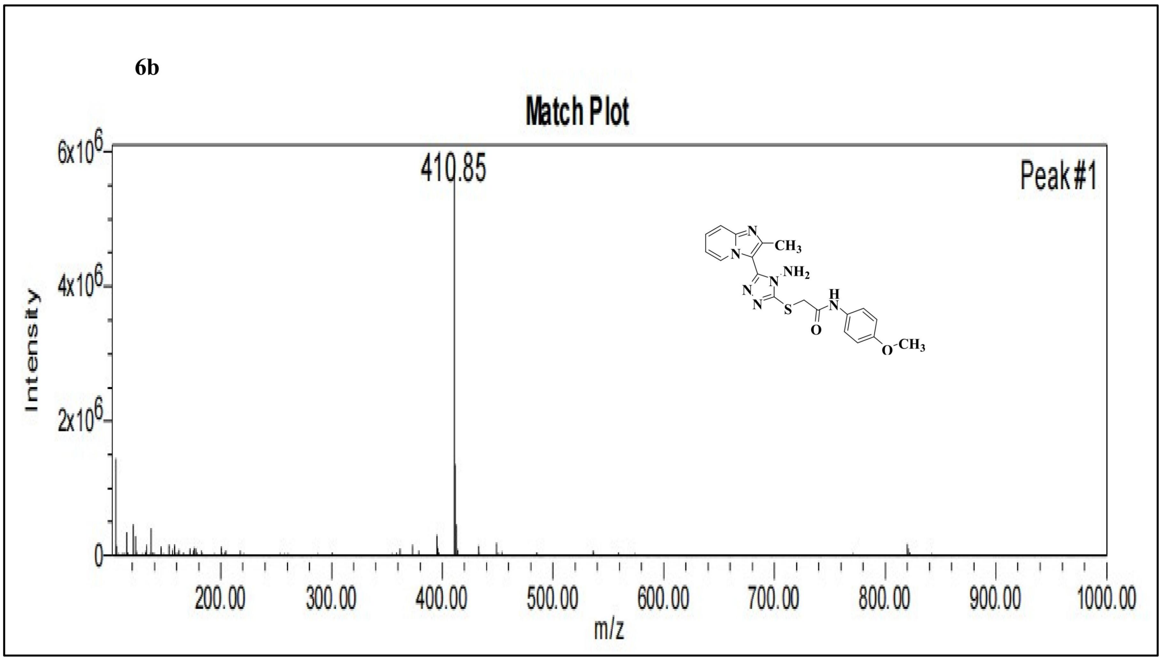


Fig.2.9: Representative mass spectrum of compound 6b

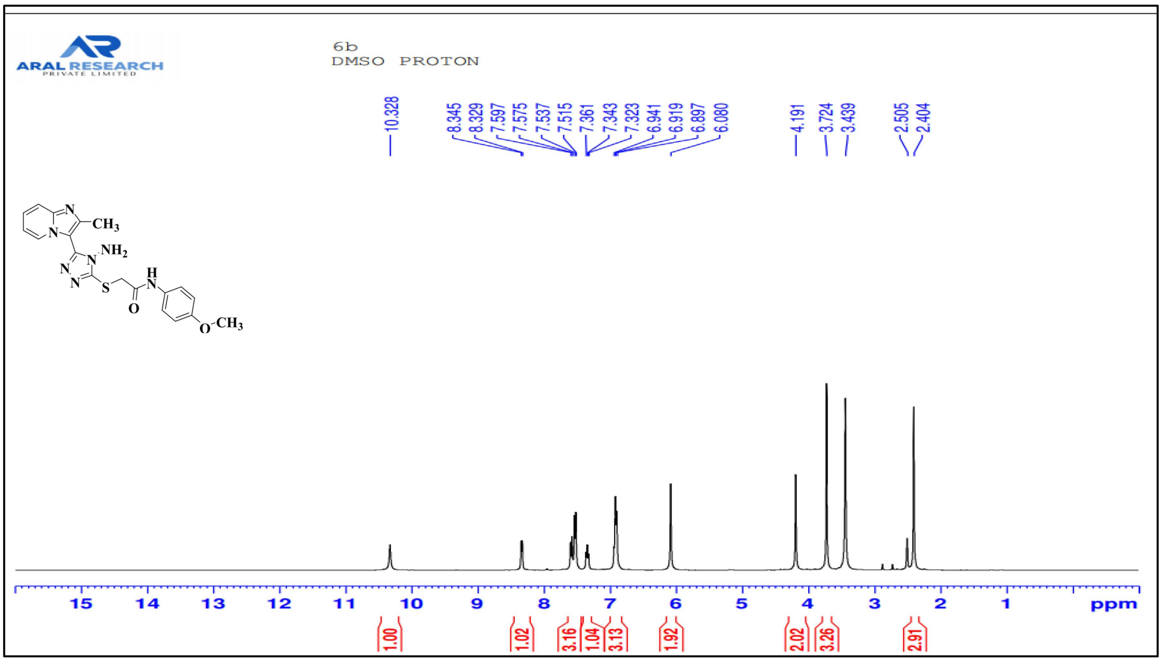


Fig.2.10: Representative ^{1}H NMR spectrum of compound 6b

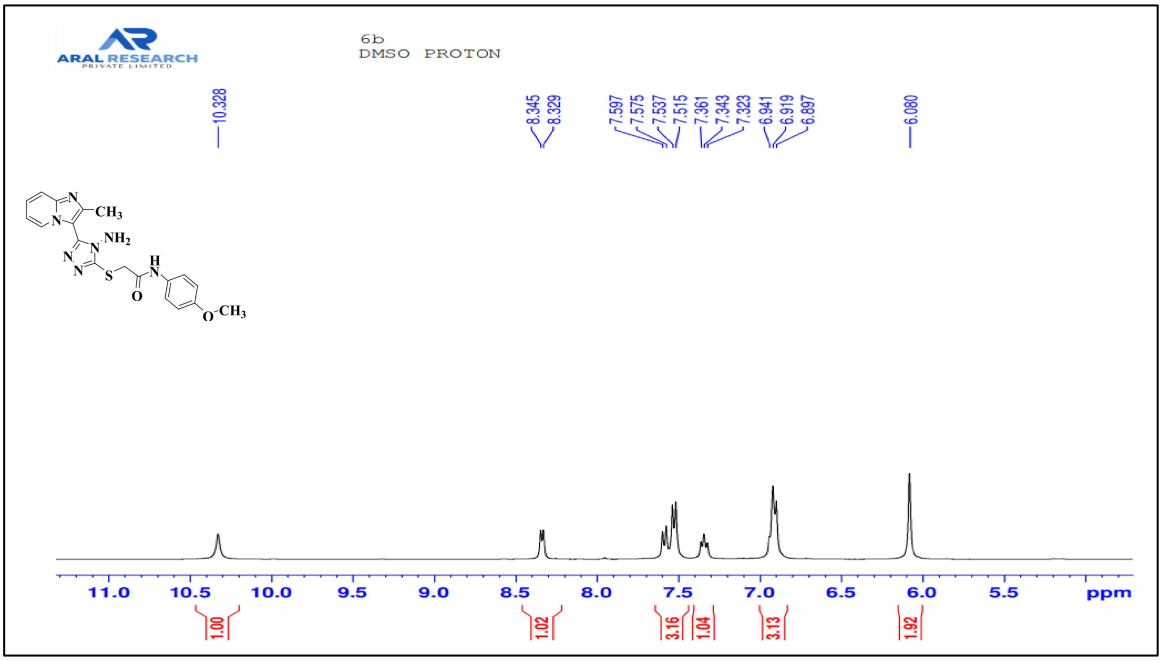


Fig.2.11: Representative Expanded ^{1}H NMR spectrum of 6b

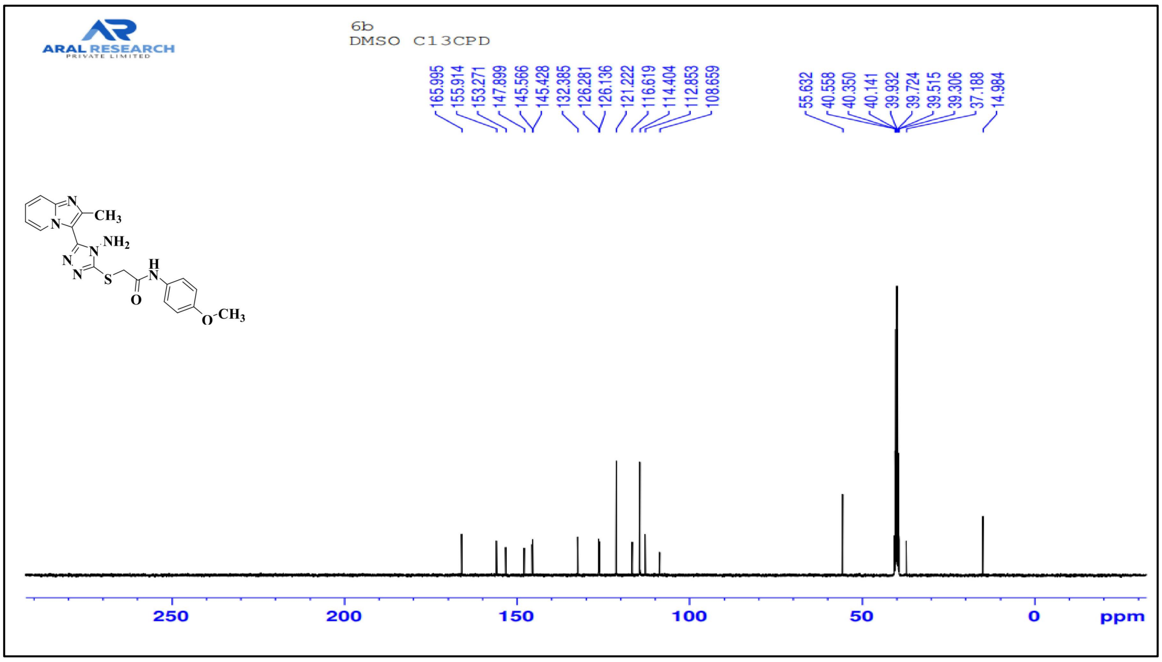


Fig.2.12: Representative ^{13}C NMR spectrum of compound 6b

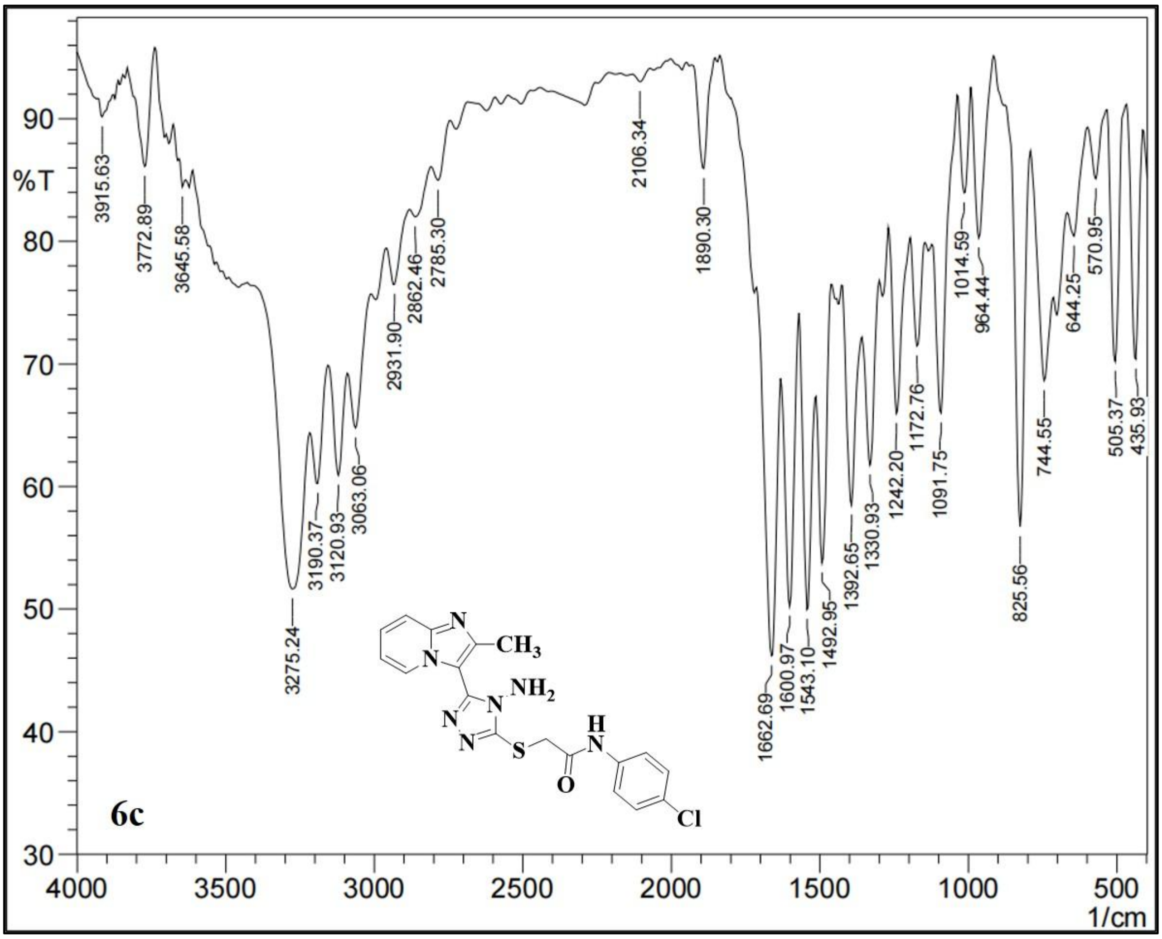


Fig.2.13: Representative IR spectrum of compound 6c

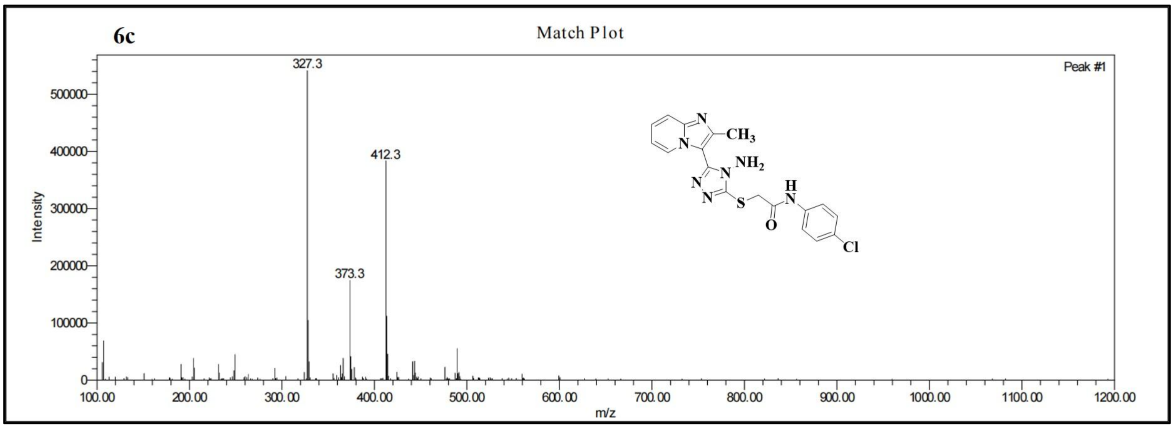


Fig.2.14: Representative mass spectrum of compound 6c

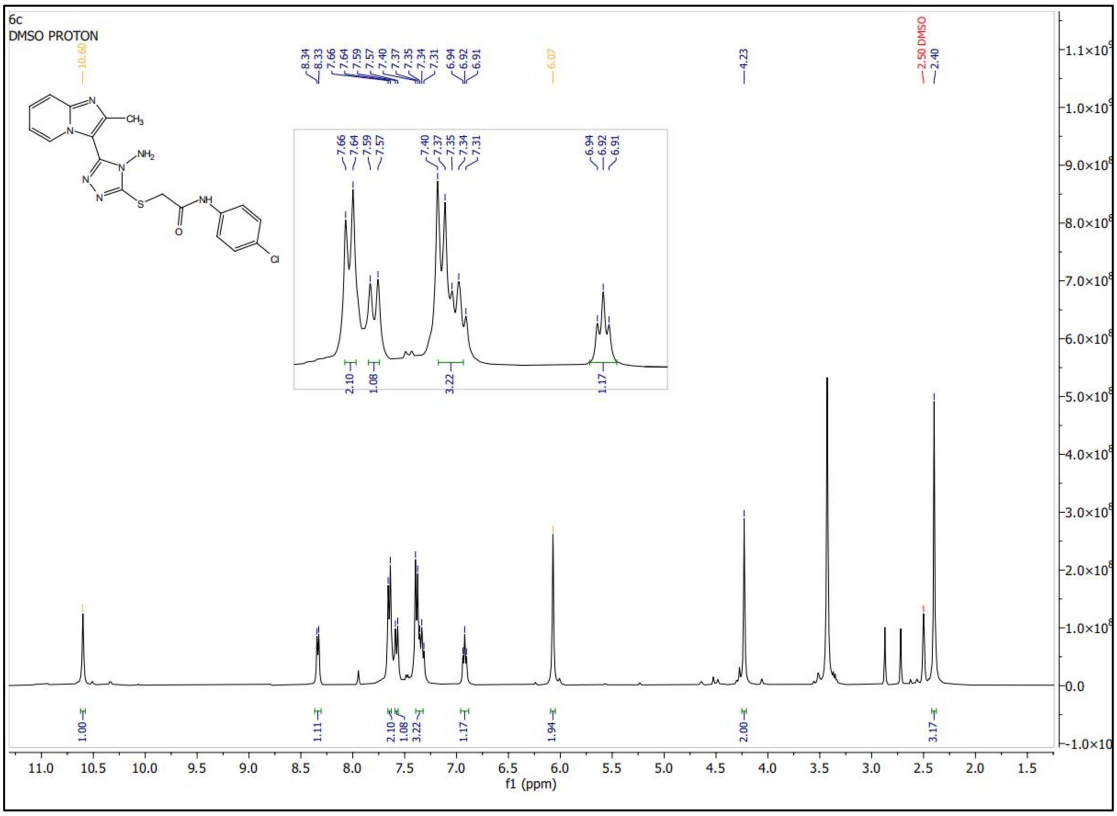


Fig.2.15: Representative ^{1}H NMR spectrum of compound 6c

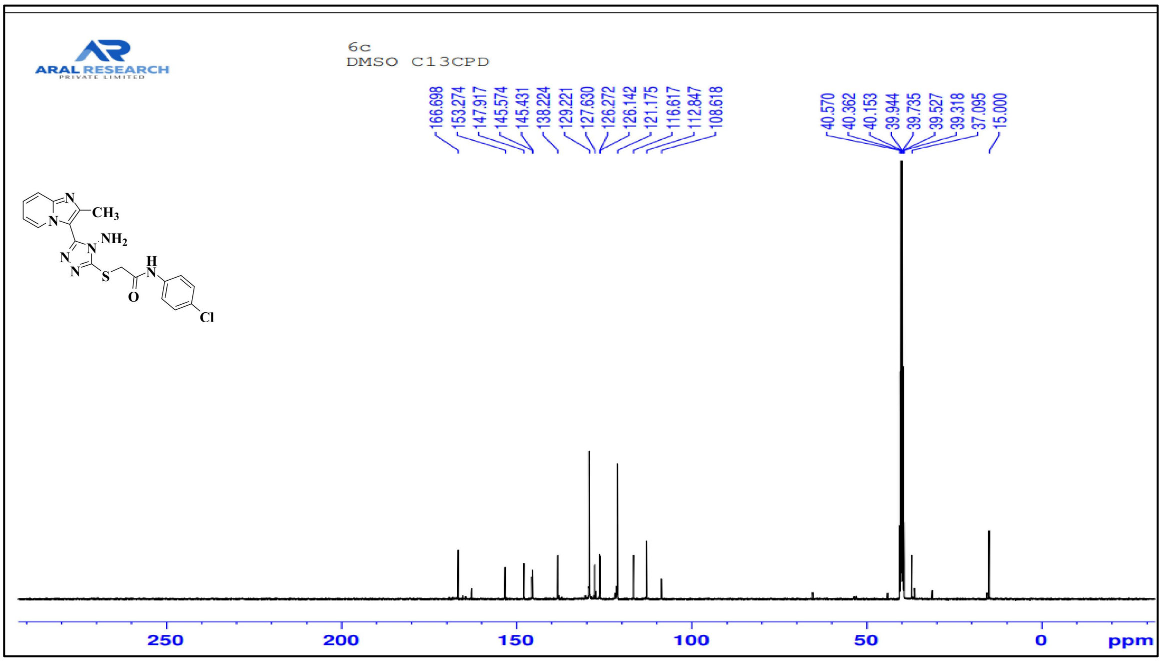


Fig.2.16: Representative ^{13}C NMR spectrum of compound 6c

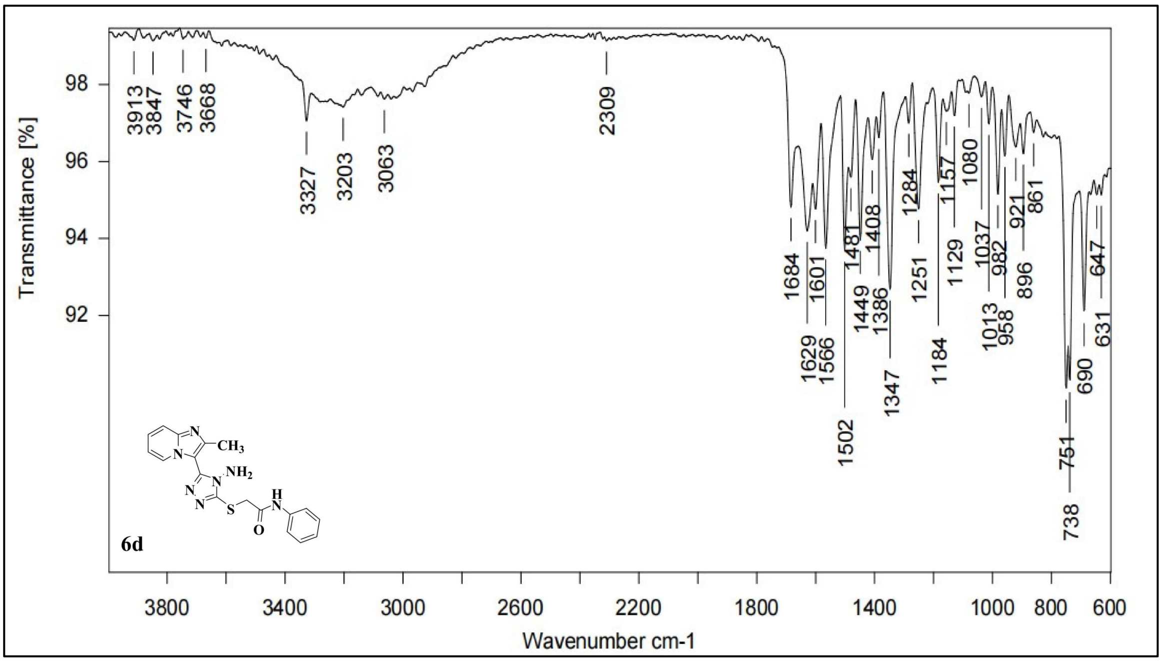


Fig.2.17: Representative IR spectrum of compound 6d

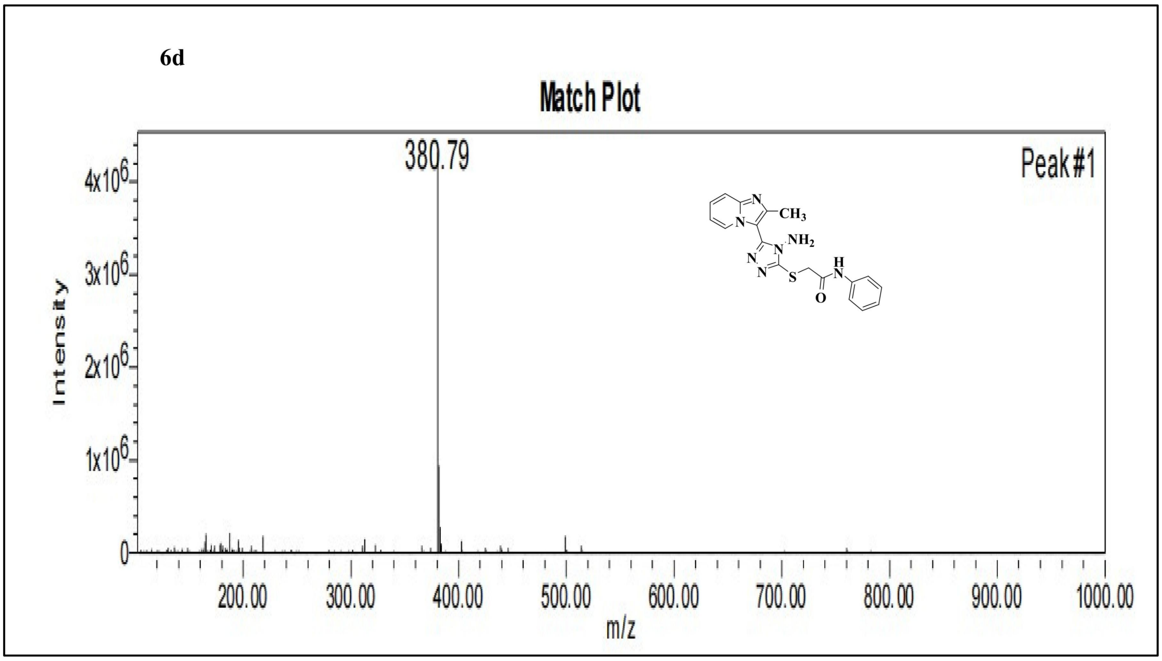


Fig.2.18: Representative mass spectrum of compound 6d

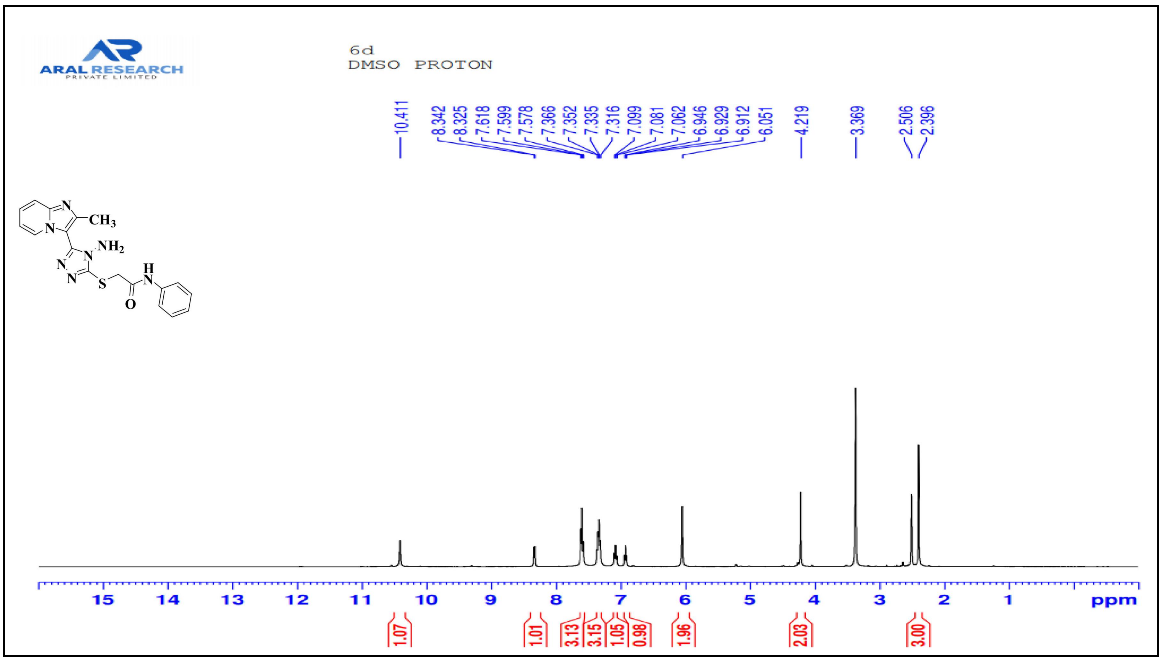


Fig.2.19: Representative ^{1}H NMR spectrum of compound 6d

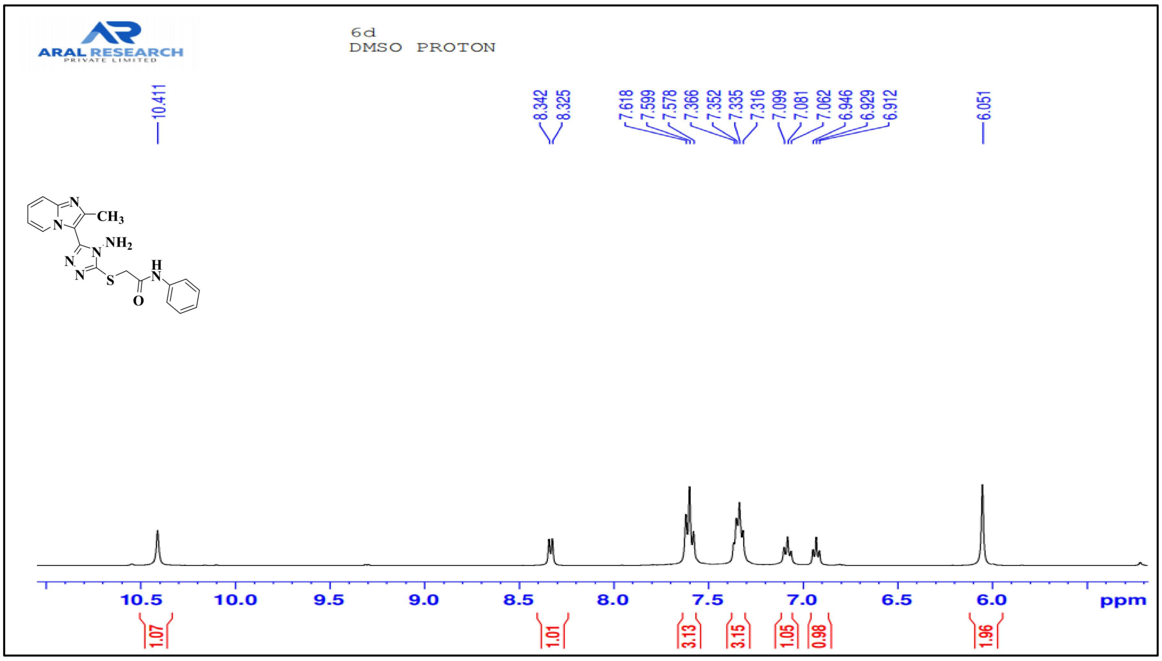


Fig.2.20: Representative Expanded ^{1}H NMR spectrum of 6d

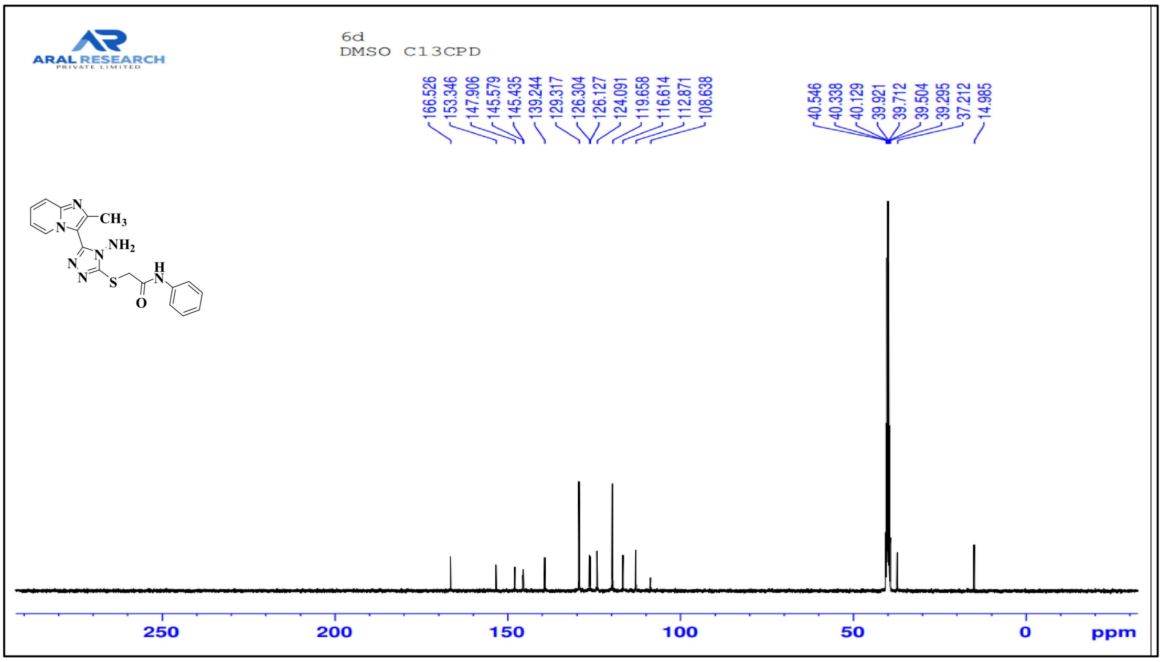


Fig.2.21: Representative ^{13}C NMR spectrum of compound 6d

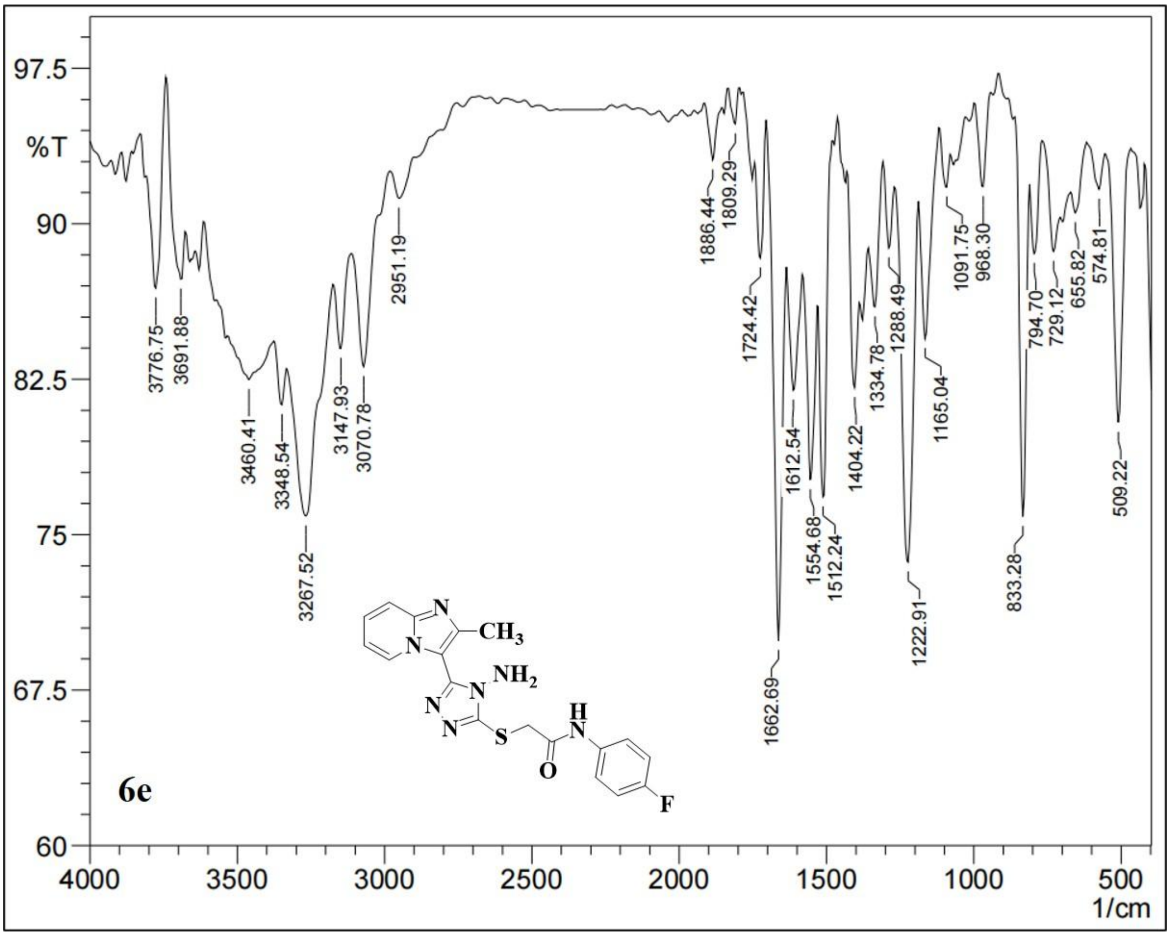


Fig.2.22: Representative IR spectrum of compound 6e

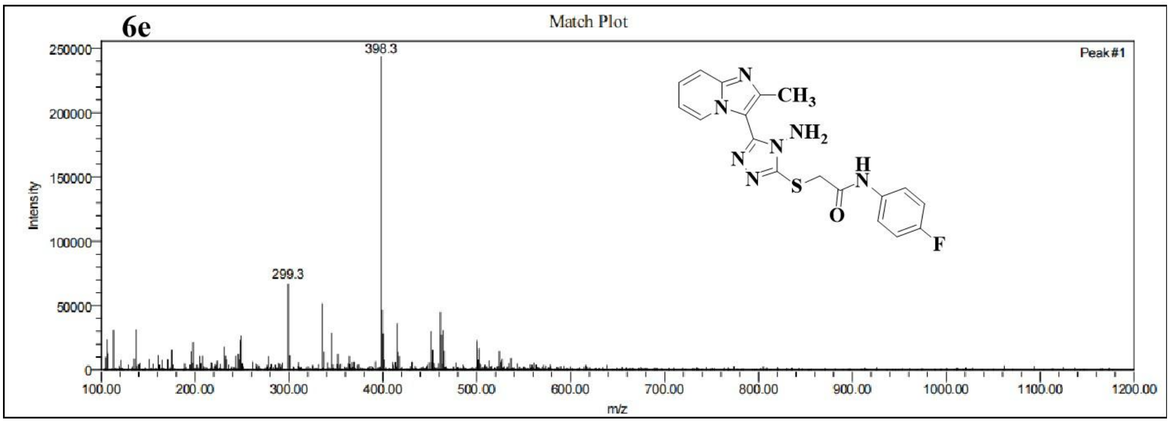


Fig.2.23: Representative Mass spectrum of compound 6e

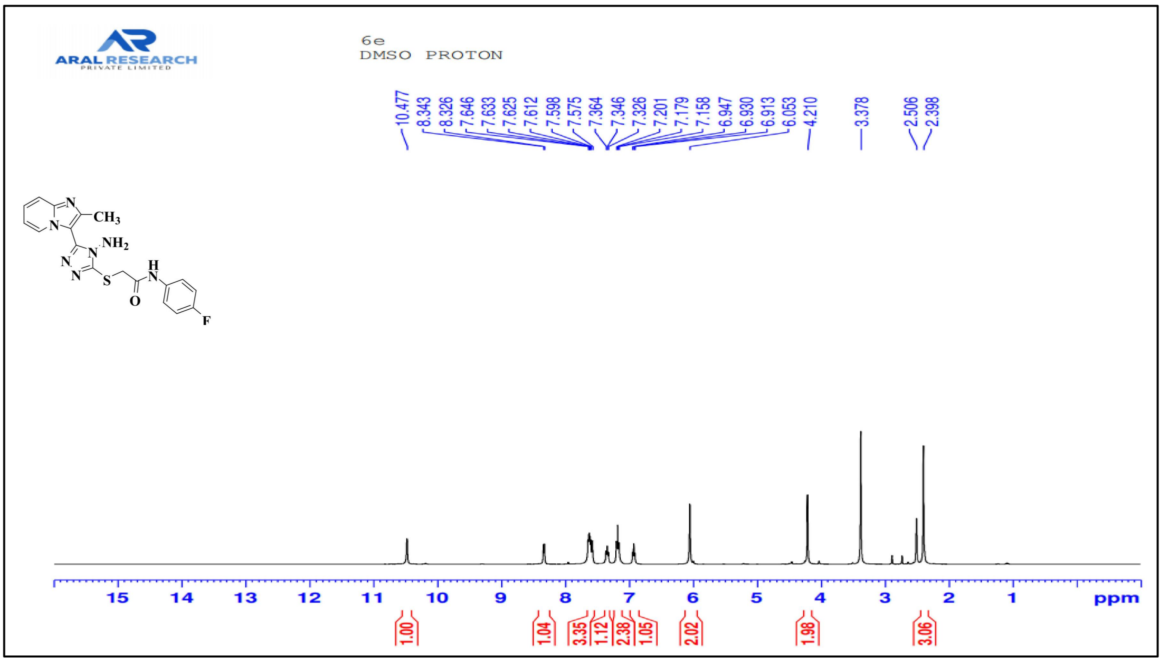


Fig.2.24: Representative ^{1}H NMR spectrum of compound 6e

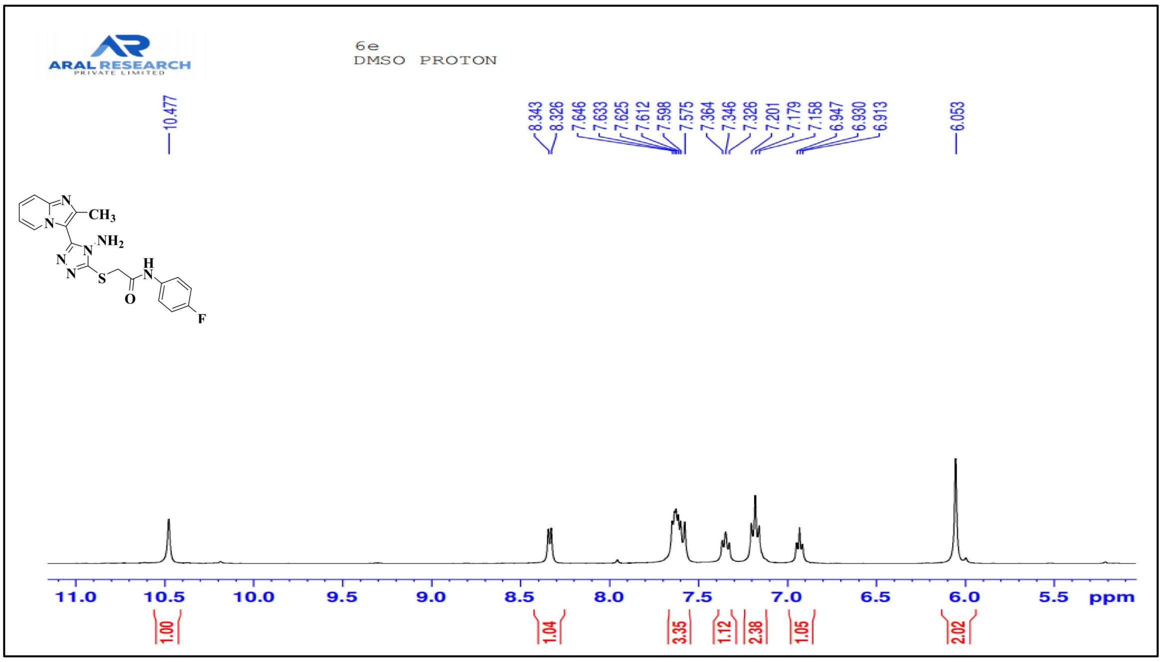


Fig.2.25: Representative Expanded ^{1}H NMR spectrum of compound 6e

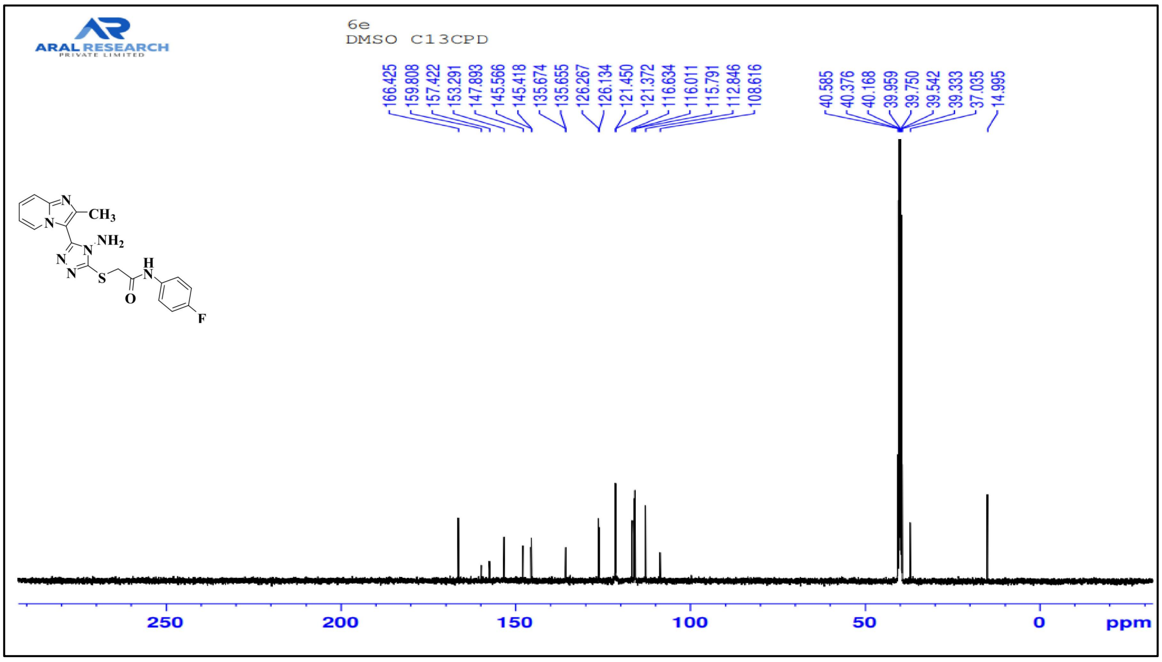


Fig.2.26: Representative ^{13}C NMR spectrum of compound 6e

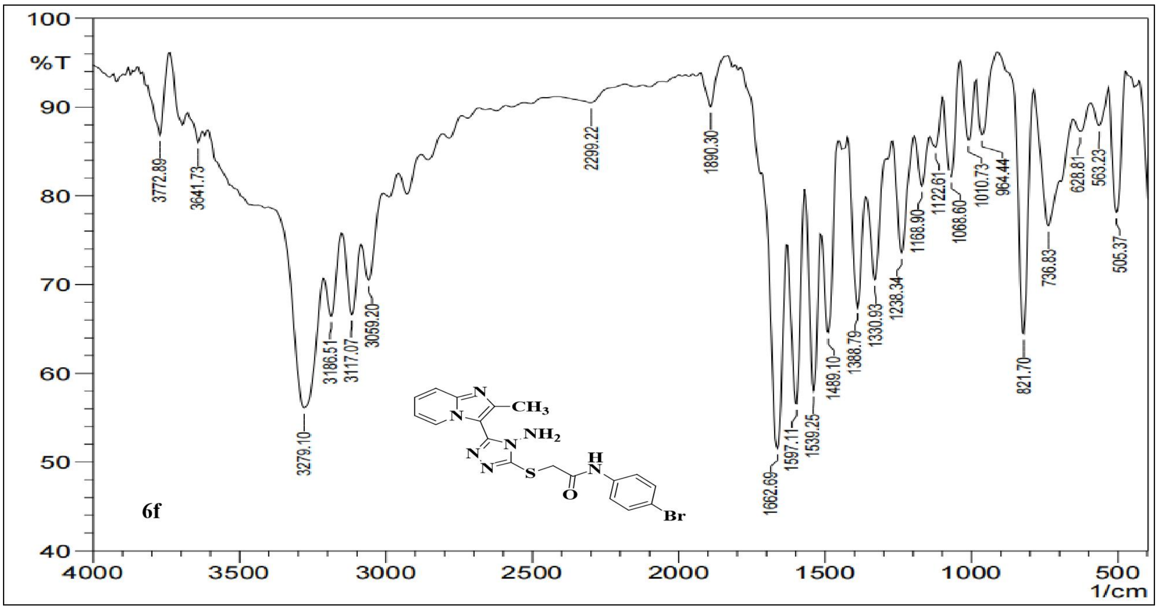


Fig.2.27: Representative IR spectrum of compound 6f

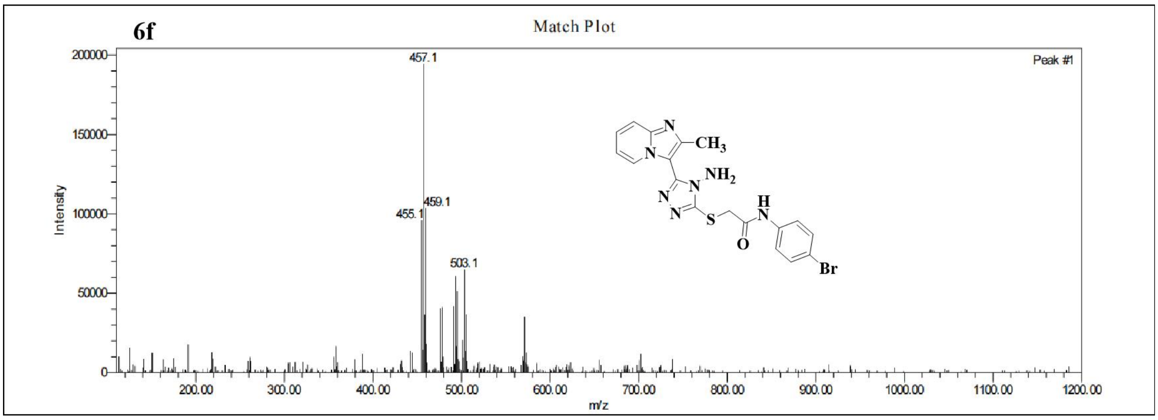
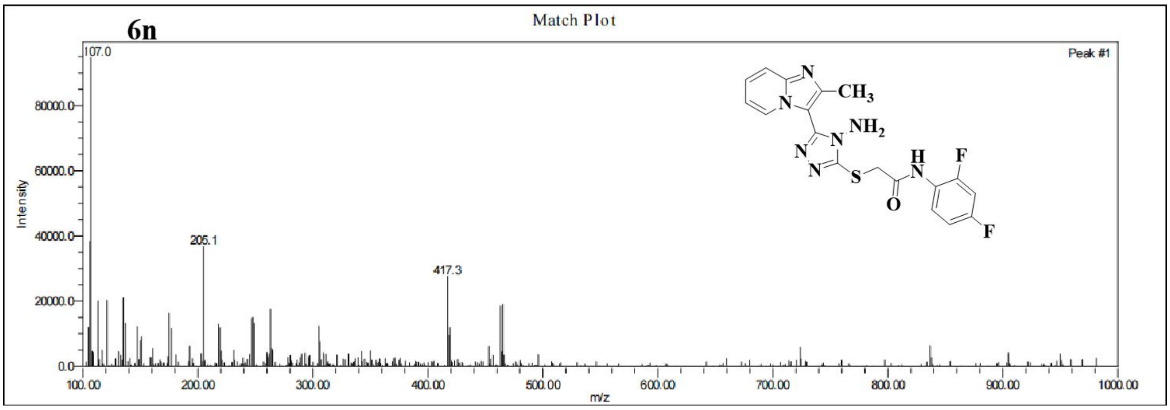


Fig.2.28: Representative mass spectrum of compound 6f



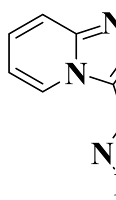


Fig.2.29: Representative mass spectrum of compound 6n