ISSN 2321-807X

Recent Developments In Chemistry Of 1,3,4-Thiadiazoles

Mahmoud Refaee Mahmoud, Mahmoud Fawzy Ismail*

*E-mail: fawzy2010@sci.asu.edu.eg

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt, post code 11566.

ABSTRACT

The methods of preparation, structure and biological activities of 1,3,4-thiadiazoles are reported.

Council for Innovative Research

Peer Review Research Publishing System

Journal: Journal of Advances in Chemistry

Vol. 10, No. 6

editorjaconline@gmail.com

www.cirjac.com

ISSN 2321-807X

INTRODUCTION

1,3,4-Thiadiazole are important because of their versatile biological actions. They have extensive applications as structural units of various biologically important molecules and as useful intermediates in medicinal chemistry. It is well established that various 1,3,4-thiadiazole derivatives exhibit a broad spectrum of pharmacological properties such as antibacterial, antifungal [1-61], Analgesic [11-14,36,62-65], antitumor [66-82], anxiolytic [83], antidiabetic [84,85], anti-inflammatory [34,62,86-101], antimicrobial [1,102-118], anesthetic [119], anthelmintic [120], carbonic anhydrase inhibitor [121], cytotoxic [122], antimycotic [3,34,123,124], antidepressant [125], antiviral [126-128], antileakemic [129-131], antituberculosis [12,55,132-134], antihypertensive [135,136], diuretic [137,139], calcium chanal blocker [140], anticonvulsant [97,140-148], herbicidal [149], cardiotonic [150], antileshmanial [151-153], antiparasitic [154-156], antioxidant [157], antisecretory [158], antihepatitis [2] and anti HIV [159].

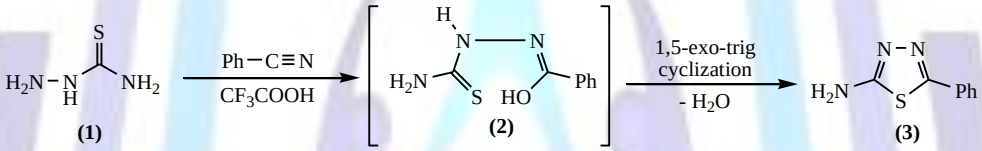
Many reviews have been published regarding the chemistry of this compound the synthetic versatility of thiadiazoles has stemmed from the interest in the biological and pharmacological properties of its derivatives. These properties are more fully detailed in the supplementary material. The review compiles published data on the synthesis and biological action of new thiadiazole derivatives until 2012.

SYNTHESIS OF 1,3,4-THIADIAZOLES AND FUSED 1,3,4-THIADIAZOLES

1) From thiosemicarbazide

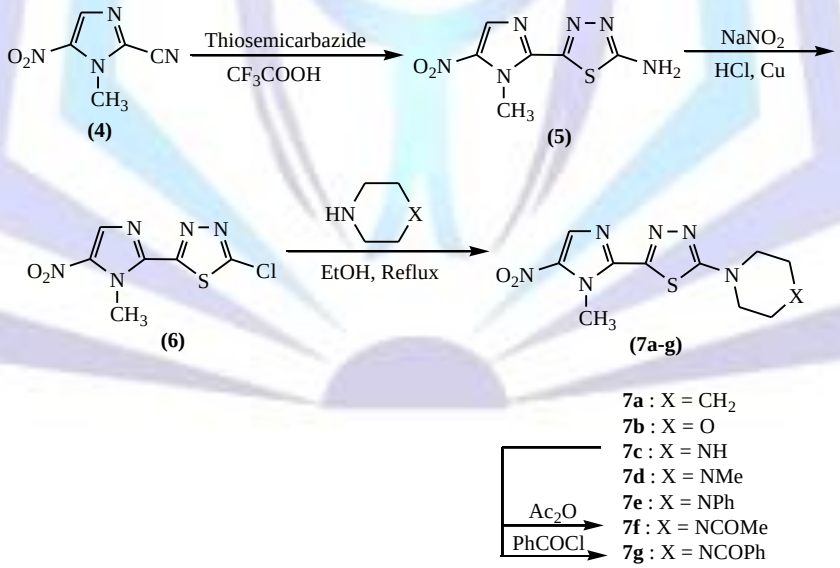
a-With nitriles

The reaction of thiosemicarbazide **1** with benzonitrile in the presence of trifluoroacetic acid afforded 2-amino-5-phenyl-1,3,4-thiadiazole **3** through the formation of the intermediate **2** which indicates the hydrolysis of benzonitrile followed by condensation with thiosemicarbazide and finally undergoes intramolecular cyclization [160]. **(Scheme 1)**



Scheme 1

The synthesis of 2-(1-methyl-5-nitro-1*H*-2-imidazol- yl)-5-substituted-1,3,4-thiadiazoles **7a-g** was achieved [161] with a versatile and efficient synthetic route outline in **(Scheme 2)**.



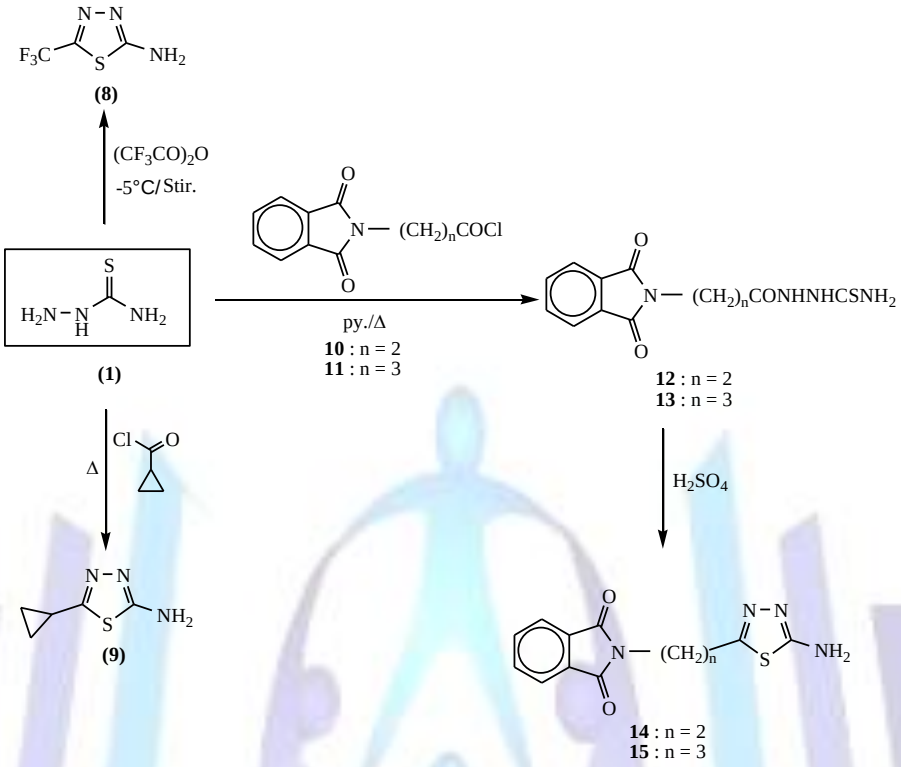
Scheme 2. Synthetic pathway to compounds **7a-g**

b-With acid anhydride and acid chloride

Stirring thiosemicarbazide with trifluoroacetic anhydride at -5°C for 2h yielded 2-amino-5-trifluoro-methyl-1,3,4-thiadiazole **8** (81%) [162].

2-Amino-5-cyclopropyl-1,3,4-thiadiazole **9** was prepared by refluxing cyclopropane carbonyl chloride and thiosemicarbazide [163].

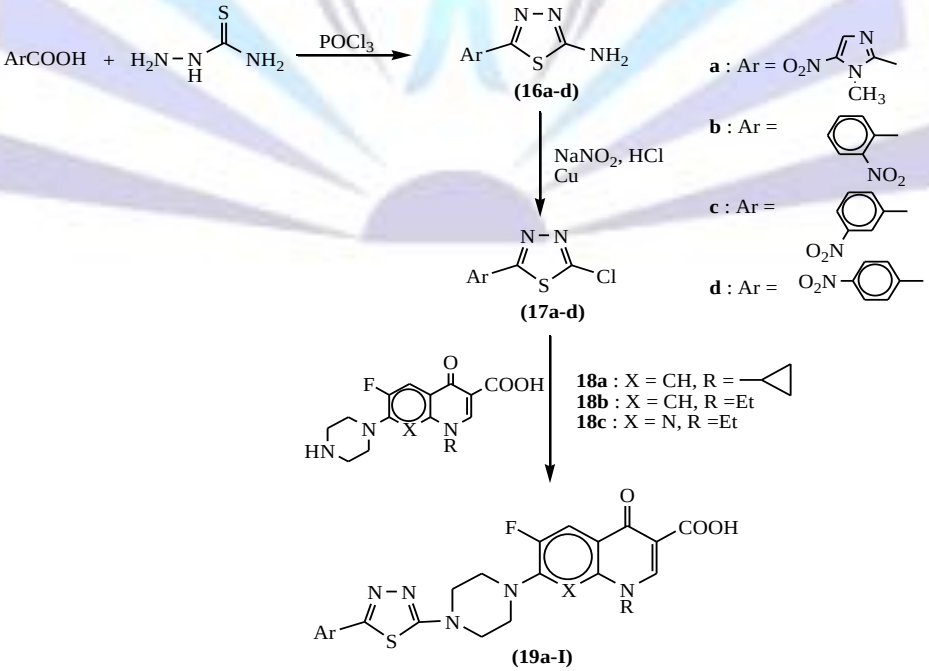
Acylation of thiosemicarbazide with acid chloride **10** and **11** in the presence of pyridine afforded compounds **12** and **13** which were cyclized in concentrated sulfuric acid and gave the thiadiazoles **14** and **15**, respectively [164]. **(Scheme 3)**



Scheme 3

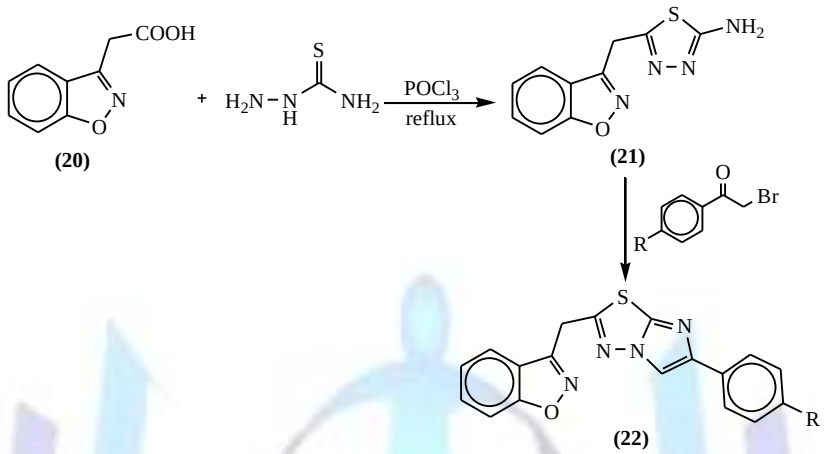
c-With acid in presence of $POCl_3$

The fact that 2,5-disubstituted-1,3,4-thiadiazole derivatives [37-39] and 5-nitro-2-imidazolyl analogues (e.g. metronidazole) [40,41] have antibacterial activity, a new series of *N*-substituted piperazinyl quinolinones carrying a 5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole moiety **19a-c** were designed and synthesized as potential antibacterial agents. Also, some *N*-[5-(nitropheny1)-1,3,4-thiadiazol-2-yl]piperazinyl quinolones **19** were synthesized for their antibacterial activity [165]. **(Scheme 4)**



Scheme 4

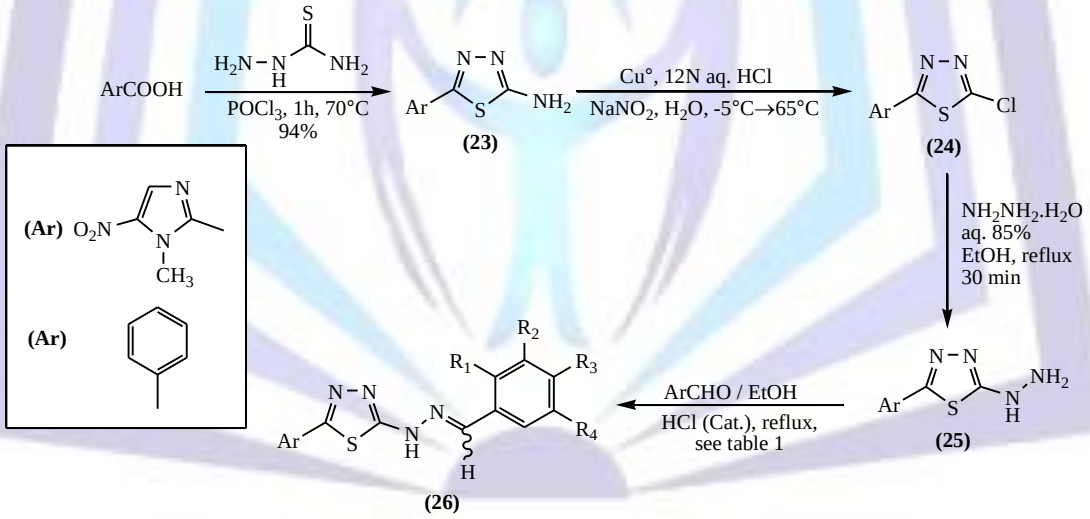
The formation of 1,3,4-thiadiazole derivative **21** by the reaction between 1,2-benzisoxazole-3-acetic acid **20** and thiosemicarbazide [166]. 2-Amino-5-benzo[*d*]isooxazol-3-ylmethyl-[1,3,4]thiadiazole **21** upon condensation with α-haloaryl ketones yielded the imidazothiadiazoles **22**. It is well established that this reaction proceeds via the intermediate iminothiadiazole [18] which under reflux temperature spontaneously undergoes dehydrocyclisation to form the desired fused heterocycle. The electronic and steric factors at 5th position of 2-amino-5- substituted-1,3,4-thiadiazole are crucial in determining the course of its reaction with substituted α-haloarylketones. The strongly electronegative groups imparts less nucleophilic character to the nitrogen at 4th position of the 1,3,4-thiadiazole. **(Scheme 5)**



Scheme 5

Condensation of benzoic acid and thiosemicarbazide in $POCl_3$ afforded 2-amino-5-phenyl-1,3,4-thiadiazole **23** in 94% yield [167].

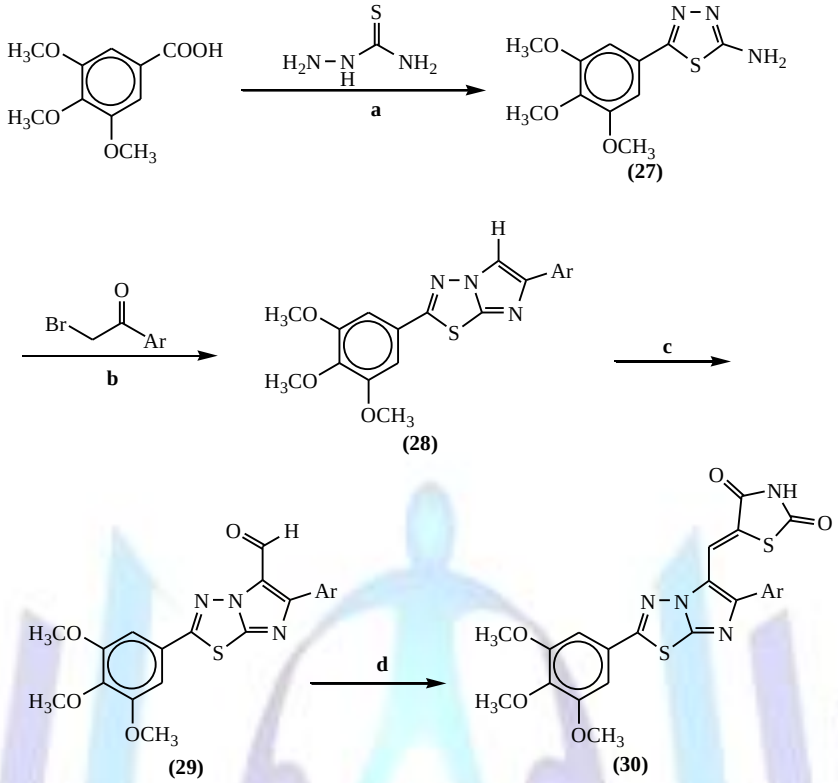
The compound **23** were employed as starting material for synthesis of new 1,3,4-thiadiazole-2-arylhydrazone derivatives [167] **26** according the synthetic rout in **(Scheme 6)**.



Scheme 6. Synthetic route for the preparation of the new 1,3,4-thiadiazole-2-arylhydrazone derivatives **26**.

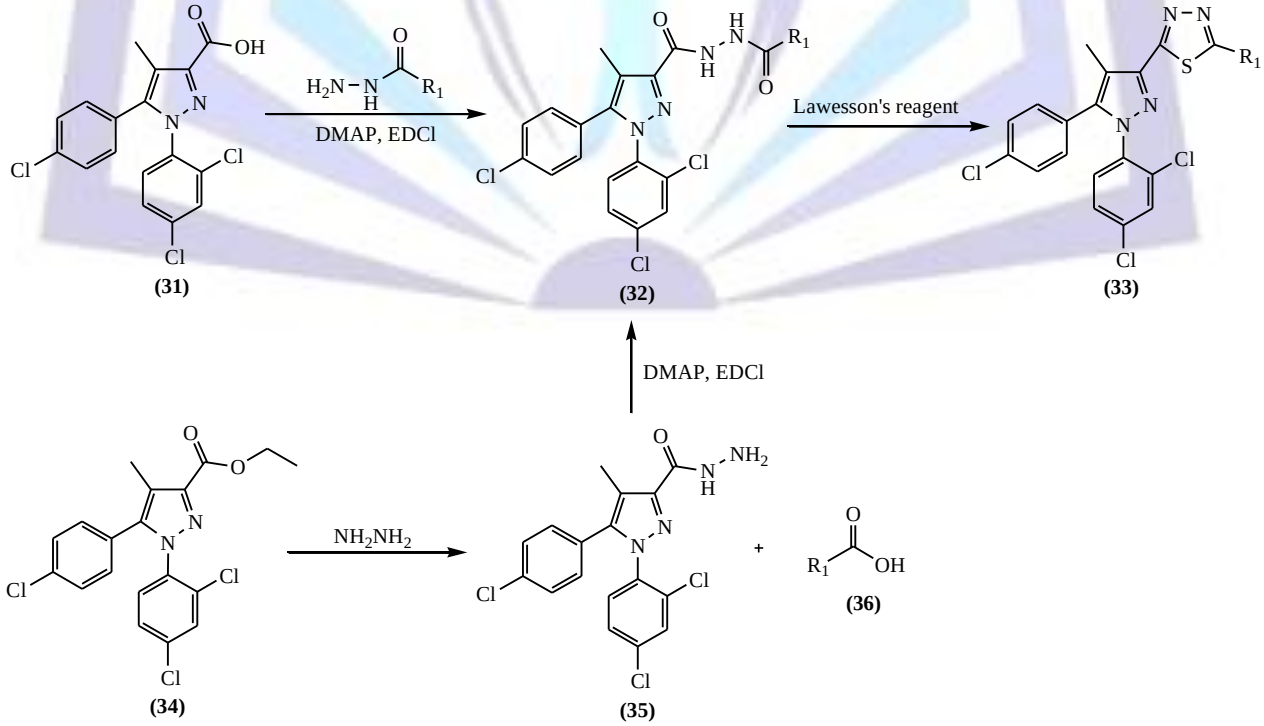
2-Amino-5-(3,4,5-trimethoxypheny1)-1,3,4-thiadiazole **27** was obtained by direct cyclisation of 3,4,5-trimethoxy benzoic acid and thiosemicarbazide in the presence of phosphorus oxychloride, the latter refluxed with substituted α-haloaryl ketones in dry ethanol yielded the imidazothiadiazoles [168] **28**.

Vilsmeier-Haack reaction of imidazothiadiazoles **28** in dimethylformamide and phosphorus oxychloride provided 6-aryl-2-(3,4,5-trimethoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carboxaldehyde derivatives **29** which subjected to Knoevenagel condensation with 2,4-thiazolidinedione in the presence of catalytic amount of piperidine and acetic acid to afford 5-substituted-2,4-thiazolidinediones [168] **30**. **(Scheme 7)**



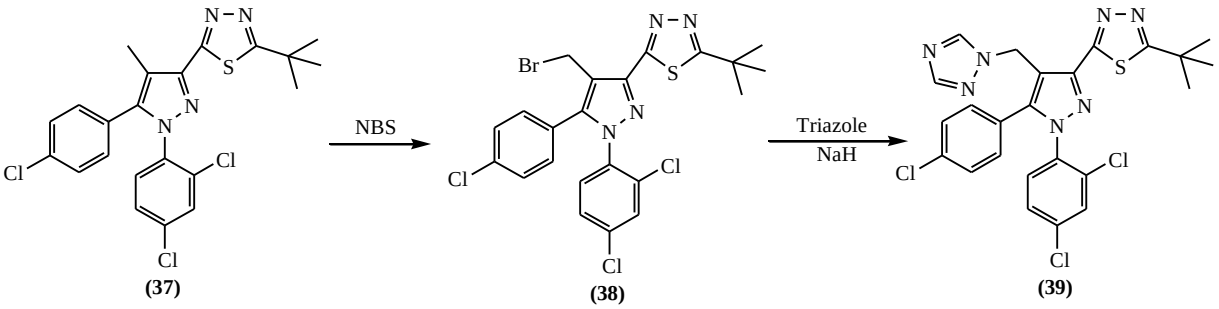
Scheme 7. Reagents a) $POCl_3$; b) dry ethanol, 10h; c)Vilsmeier-H, 10h, 85- 92%; d) thiazolidin-2,4-dione, piperidine, acetic acid, toluene.

Compounds of the general structure **33** were prepared [169-175] by (i) reaction of carboxylic acid **31** with a hydrazide compound in the presence of coupling reagents (EDCI, DMAP) and (ii) thionation-cyclization of the resulting product **32** using Lawesson's reagent [176]. Alternatively, the acylhydrazide intermediate **32** was also available through the coupling of the hydrazide **35** with a corresponding acid **36** mediated by coupling reagents such as DMAP, EDCI or EDCI, HOBt, NMM. For this sequence, the requisite hydrazide **35** was prepared by treating the known ester **34** with hydrazine in refluxing EtOH [177]. **(Scheme 8)**



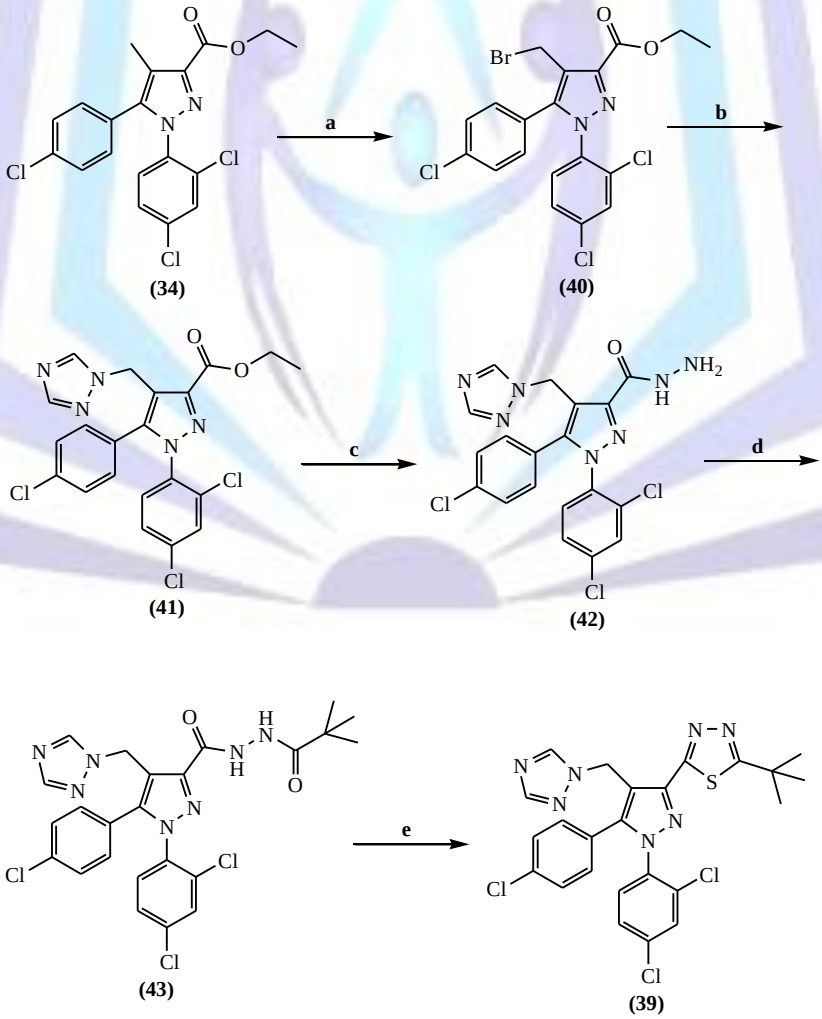
Scheme 8. Preparation of thiadiazole **33.**

The preparation of thiadiazole **39** was initiated with the activated 4-pyrazole intermediate **38**, which was prepared from **37** via a benzylic bromination-type reaction [178-182] as illustrated in **(Scheme 9)**. The triazole group of **39** was then introduced by treating bromide **38** with triazole in the presence of a suitable base such as sodium hydride or cesium carbonate.



Scheme 9. Preparation of thiadiazole **39.**

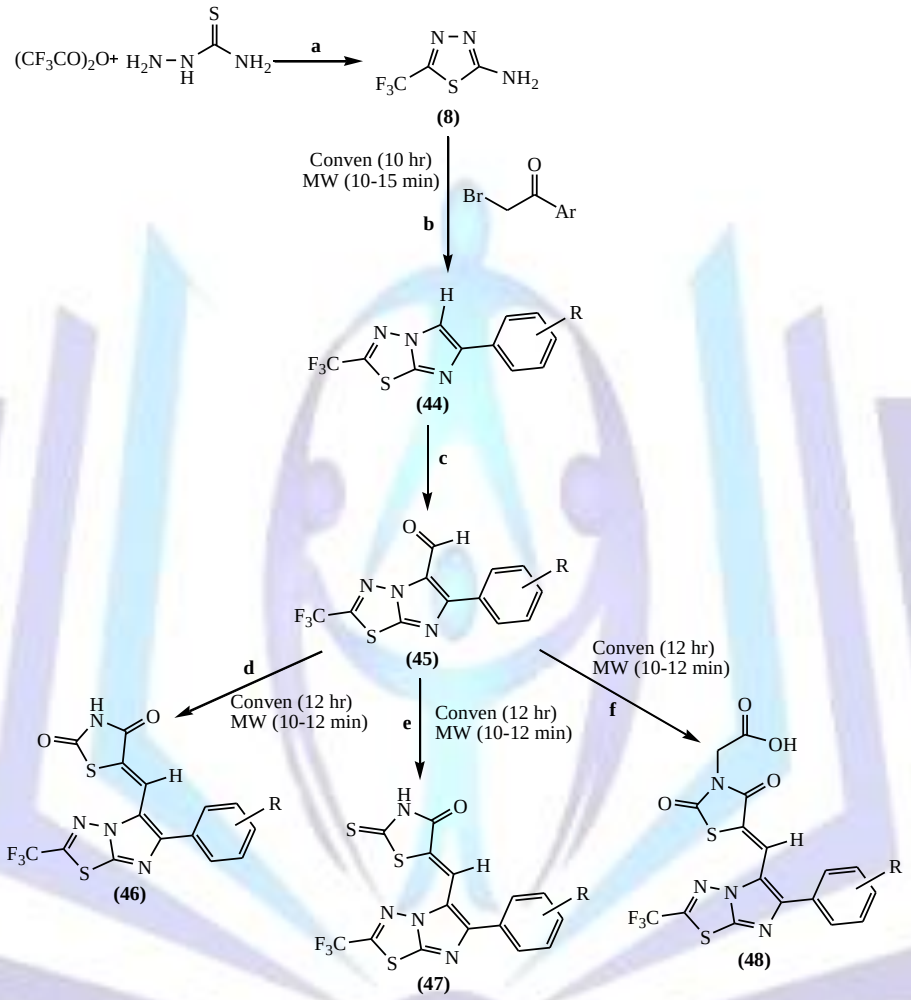
The thiadiazole containing the 1,2,4-triazole could also be obtained by a reaction sequence involving the key intermediate bromide **40**. Thus, bromide **40** obtained by reaction of pyrazole **34** with NBS in the presence of catalytic AIBN, was reacted with 1,2,4-triazole sodium derivatives to provide **41**. Hydrazinolysis of ester **41** produced the corresponding hydrazide **42**, which could then be coupled with an acid to give acyl hydrazide **43**. Alternatively, hydrolysis of ester **41** and activation of the acid followed by coupling with a hydrazide in the presence of triethyl amine then afforded acyl hydrazide **43**. Thionation-cyclization was then performed using Lawesson's reagent under microwave irradiation to give thiadiazole [177] **39**. **(Scheme 10)**



Scheme 10. Preparation of thiadiazole **39**. Reagents and conditions: a) NBS, AIBN, CCl_4; b)1,2,4-triazole.Na, DMF; c) hydrazine.H_2O, EtOH, 65ºC; d) pivalic acid, EDCI, HOB*t*, NMM, DMF; e) Lawesson's reagent, THF, reflux or microwave.

2-Amino-5-trifluoromethyl-1,3,4-thiadiazole **44** was prepared by treating of thiosemicarbazide with trifluoroacetic anhydride [162].

The microwave assisted reaction between 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **8** and various substituted α-haloaryl ketone. In the next step, imidazo[2,1-*b*][1,3,4]-thiadiazoles **44** were subjected in to Vilsmeier-Haack reaction to afford 2-(trifluoromethyl)-6-arylimidazo [2,1-*b*][1,3,4]-thiadiazole-5-carbaldehydes **45** which subjected to Knoevenagel condensation [183,184] with thiazolidine-2,4-dione, 2-thioxothiazolidin-4-one (rhodanine) and 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid (rhodanine acetic acid) in the presence of catalytic amount of piperidine acetate to afford 6-arylimidazo[2,1-*b*][1,3,4]-thiadiazole derivatives **46-48**, respectively. **(Scheme 11)**



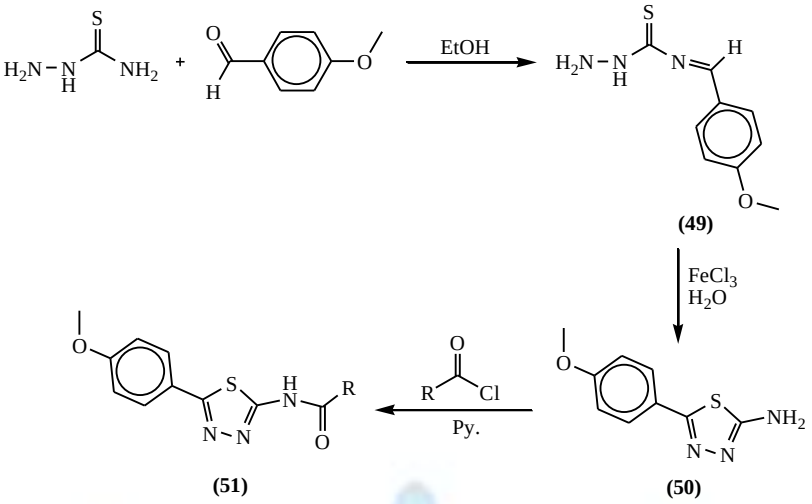
Scheme 11. Reagents and conditions: a) -5 to 0ºC, 2h, 81%; b)M.W. (600 watts) 10-15 min, 65-71%; c) Vilsmeiere-Haack reagent, 8h, 50-66%; d) thiazolidine-2,4-dione, M.W. (600 watts) 10 min, 69-72%; e) rhodanine, M.W. (600 watts) 12 min, 69-75%; f) rhodanine acetic acid, M.W. (600 watts) 12 min, 68-76%.

d-With aldehydes

Another regioisomer, 5-amino-[1,3,4]thiadiazole derivatives **50** was prepared from the reaction of *p*-anisaldehyde with thiosemicarbazide to give intermediate **49**, followed by cyclization in the presence of ferric chloride in aqueous solution [185,186]. **(Scheme 12)**

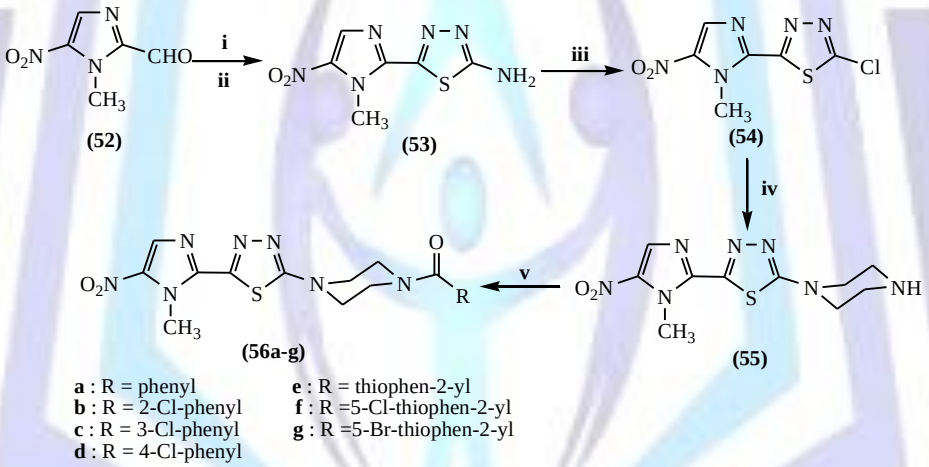
Aminothiadiazole **50** was subjected in the standard acylation protocols including coupling reagents with acids or anhydride or acid chloride with pyridine as base to afford **51**. **(Scheme 12)**

ISSN 2321-807X



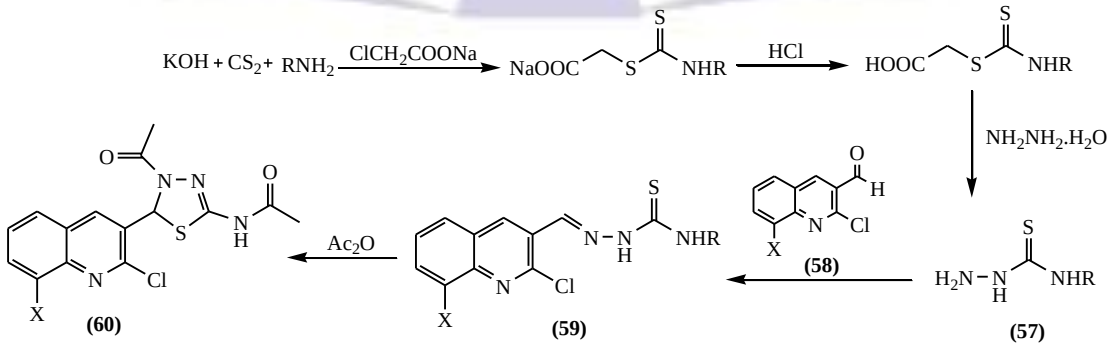
Scheme 12

1-Methyl-5-nitroimidazole-5-carboxaldehyde [53,187-190] **52** upon treatment with thiosemicarbazide yielded the corresponding thiosemicarbazone which cyclized with ammonium ferric sulphate to give the thiadiazole derivative **53**. Diazotization of amine **53** followed by reaction with piperazine afforded **55** which with aroyl chloride gave *N*-aroylation 1,3,4-thiadiazole derivative [191-194] **56**. **(Scheme 13)**



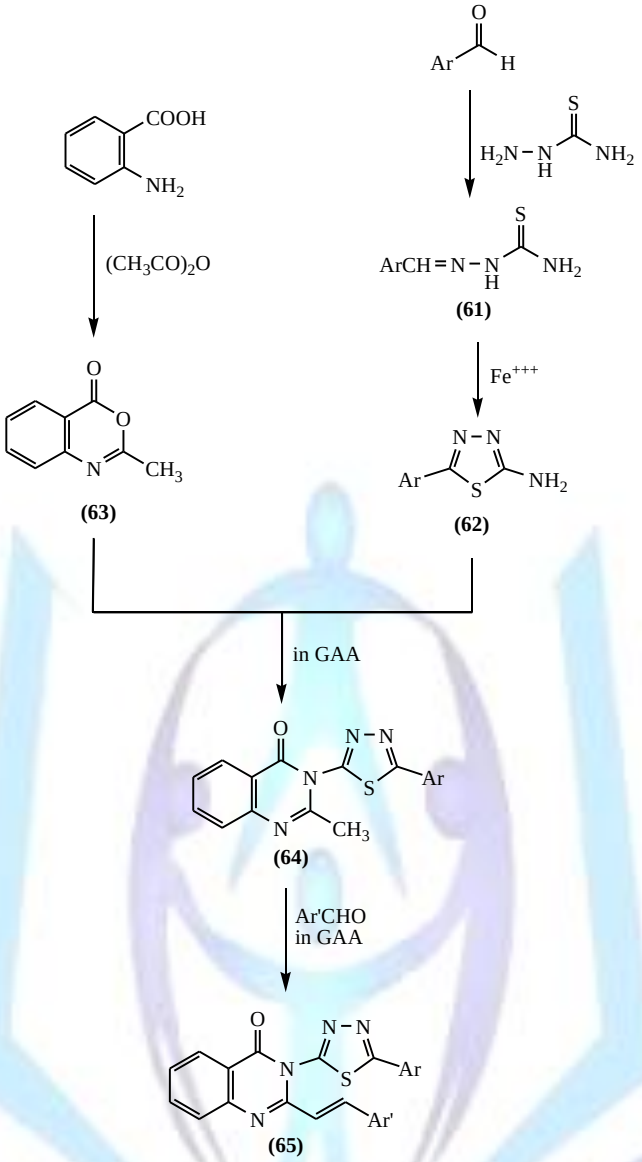
Scheme 13. Reagents and conditions: i) thiosemicarbazide, EtOH, HCl, reflux; ii) ammonium ferric sulfate, H_2O, reflux; iii) $NaNO_2$, HCl, Cu; iv) piperazine, EtOH, reflux; v) appropriate thiophen-2-carbonyl chlorides or benzoyl chlorides, benzene, pyridine, rt.

Thiosemicarbazones of substituted quinoline **59** were prepared and cyclized in presence of acetic anhydride to get the final thiadiazole **60** [195]. **(Scheme 14)**



Scheme 14. Schematic Representation of the Synthetic route adopted for the synthesis N-4-acetyl-5-(2,8-substitutedquinolin-3-yl)4,5-dihydro1,3,4-thiadiazole-2-yl)acetamide derivative **60**.

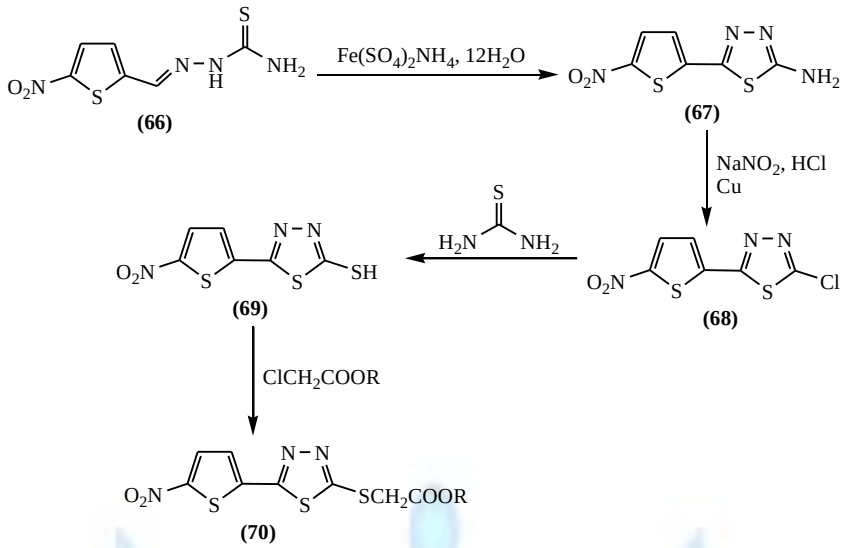
3-(1,3,4-Thiadiazoly1)-2-styryl-quinazoline-4(3*H*)-one **65** was synthesized by a three-step procedure [196]. **(Scheme 15)**



Scheme 15. Synthesis of 3-(1,3,4-thiadiazolyl)-2-styryl quinazolin-4(3*H*)one **65**.

The 2-amino-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole **67** was obtained by oxidative cyclization of 5-nitro-2-thiophene carboxaldehyde thiosemicarbazone **66**. Diazotation of **67** in hydrochloric acid in the presence of copper powder gave 2-chloro-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole **68**. The reaction of **68** with thiourea in refluxing ethanol afforded 2-mercapto-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole [197] **69**.

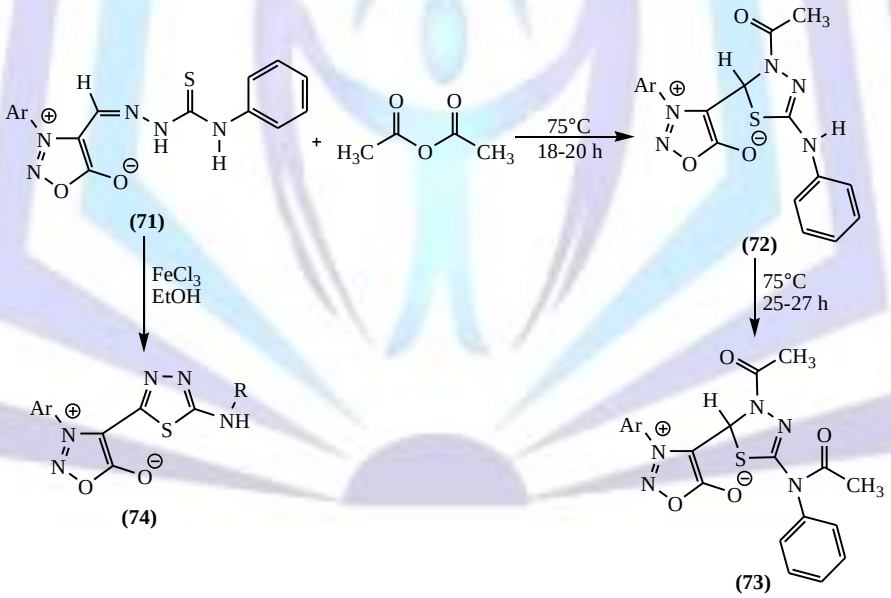
Treatment of the latter with alkyl chloroacetates gave alkyl-α-[5(5-nitro-2-thienyl)1,3,4-thiadiazole-2-yl thio] acetates **70** [197]. **(Scheme 16)**



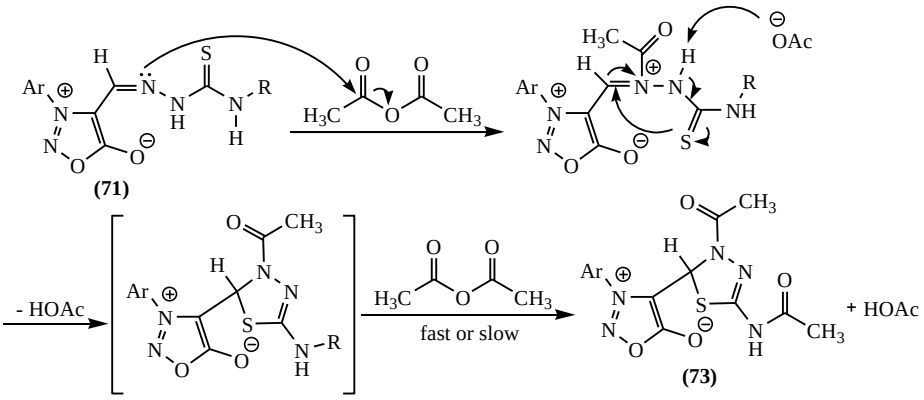
Scheme 16. Synthesis of alkyl α-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl thio]acetates **70**.

Substituted 1,3,4-thiadiazoles have attracted considerable attention due to their wide-ranging biological activities, including antimicrobial [19,28-37], antituberculosis [12,55,129-135], anesthetic, antithrombotic, anticonvulsant [97,145,147-150], antihypertensive [137,138], antiinflammatory [96] and antiulcer activities [106,107]. The treatment of 3-aryl-4-formylsydnone 4'-phenylthiosemicarbazones **71** with acetic anhydride in dichloromethane solution, following by heating at 75°C in an oil bath for 18-20h, produced the monoacetyl sydnonyl 1,3,4-thiadiazoline derivatives **72** and heating for a longer period the monoacetyl completely converted to the diacetyl substituted thiadiazolines **73** [198]. **(Scheme 17)**

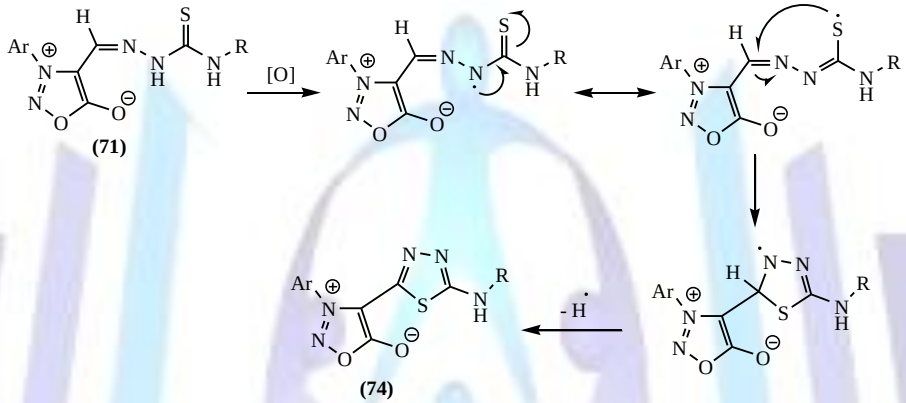
However, treating **71** with acetic anhydride without any other solvent produced the diacetyl-substituted thiadiazolines **73**. Stirring **71** with ferric chloride in aqueous ethanol yielded **74**.



Scheme 17



Scheme 18. The mechanism of reaction of compounds **71** with acetic anhydride.

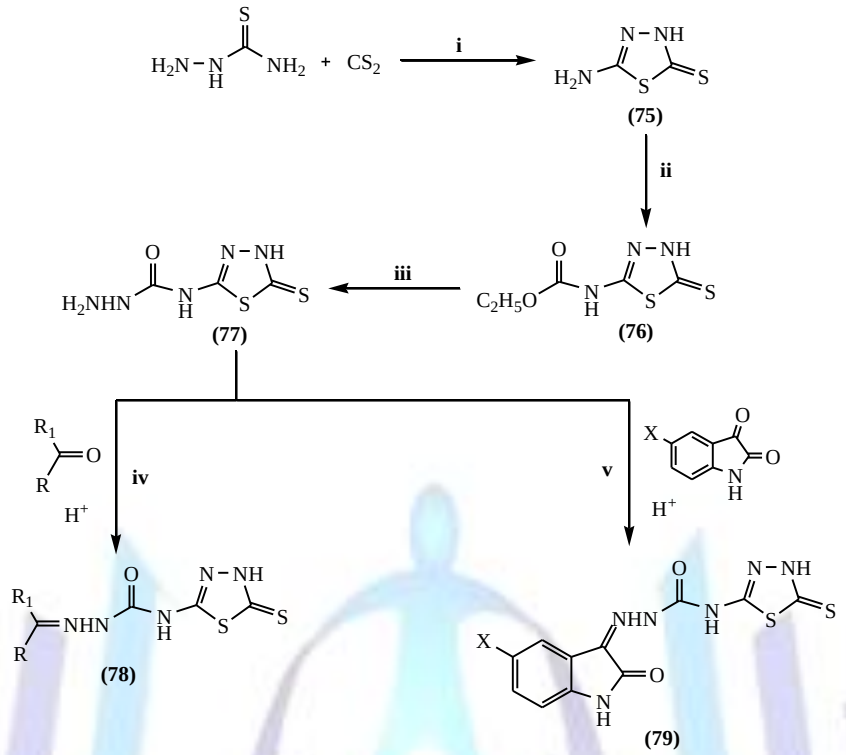


Scheme 19. The mechanism of reaction of compounds **71** with ferric chloride.

e-With carbon disulphide

It has been shown earlier by Supuran et al. that thiol carrying heterocycles can lead to the development of novel types of carbonic anhydrase inhibitors. [199-202] However the previously investigated heterocyclic thiols showed moderate inhibitory activities with no preferential inhibition against the tumor-associated isozyme CAIX.[203] Considering the 5-amino-3*H*-1,3,4-thiadiazole-2-thione **75** system as a scaffold. New class of semicarbazone derivatives of such system were synthesized and tested against the cytosolic as well as the tumor-associated CA isozymes I, II, and IX.

[1,3,4]Thiadiazoles **75-78** were synthesized using the reported Cho et al. method [204] via the reaction between thiosemicarbazide and carbon disulfide in alkaline medium to give the key intermediate **77** [205-212]. **(Scheme 20)**

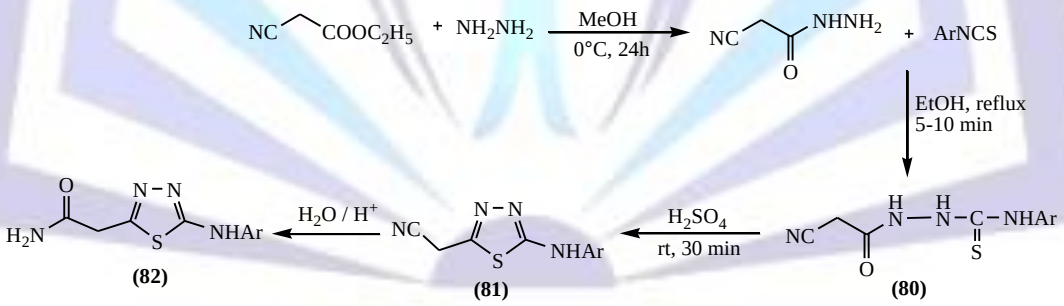


Scheme 20. Synthetic pathway of for intermediates **75-77** and target compounds **78**, **79**. Reagents and conditions: i) KOH, ethanol, reflux 6h; ii) $ClCOOC_2H_5$ / pyridine, stir 1h below 40 ºC; iii) hydrazine hydrate 80%, 60 ºC (1h), stir 48h at room temperature; iv) ethanol, reflux 1h, stir overnight; v) ethanol, reflux 3-5h, refrigerate overnight.

2) From Acid hydrazide

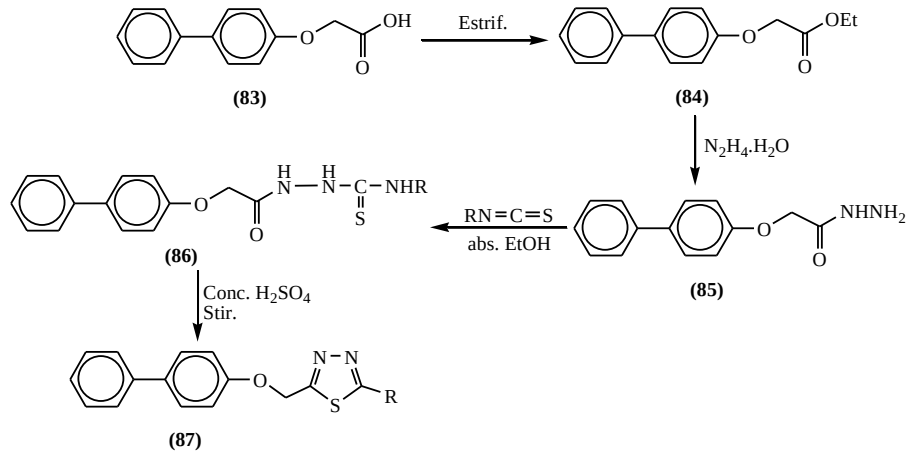
i-With Aryl isothiocyanate

5-Arylamino-1,3,4-thiadiazol-2-yl-acetamides **82** was accomplished by the synthetic sequences outlined in **(Scheme 21)**. [213]



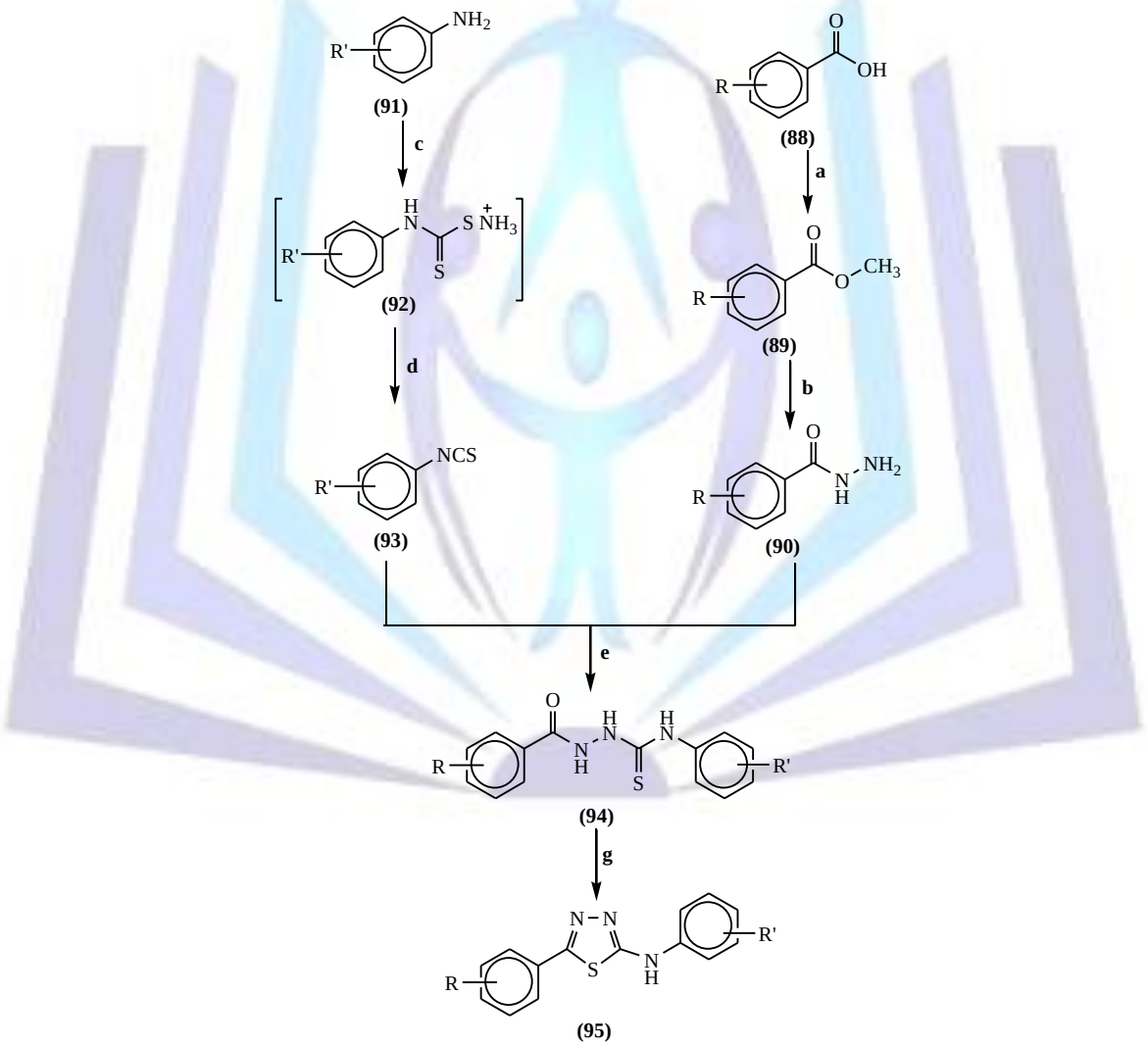
Scheme 21. Synthesis of 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides **82**.

Treatment of hydrazide **85** with various alkyl/aryl isothiocyanates in ethanol gave corresponding thiosemicarbazides **86**. Cyclization of **86** by treating with cold concentrated sulphuric acid gave the 1,3,4-thiadiazole **87**. [90] **(Scheme 22)**



Scheme 22

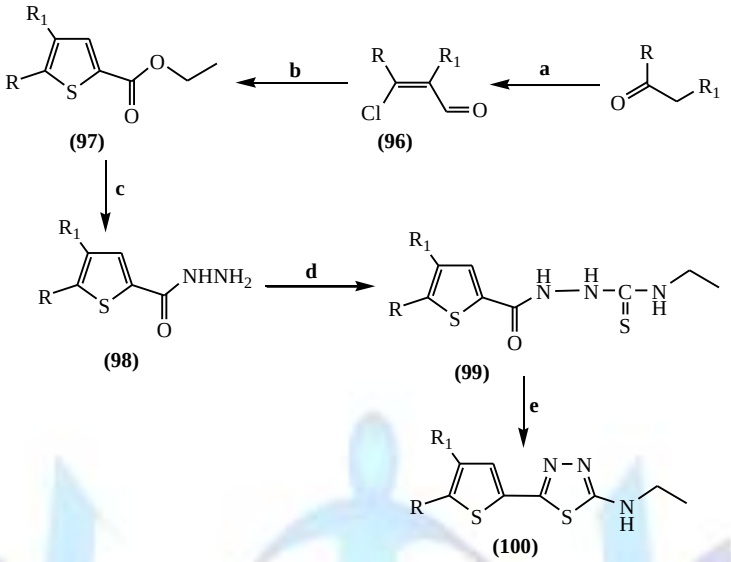
The synthetic route for the newly synthesized, 1,3,4-thiadiazole derivatives **95**, is illustrated. [80,155,214-220] **(Scheme 23)**



Scheme 23. Synthesis of 1,3,4-thiadiazole derivatives. a) dry methanol, conc. H_2SO_4, reflux; b) dry methanol, hydrazine hydrate 80%, reflux; c) CS_2, NH_4OH 33%, dry methanol; d) $Pb(NO_3)_2$; e) dry methanol, reflux; f) 4N NaOH, reflux; g) PPA, stirring.

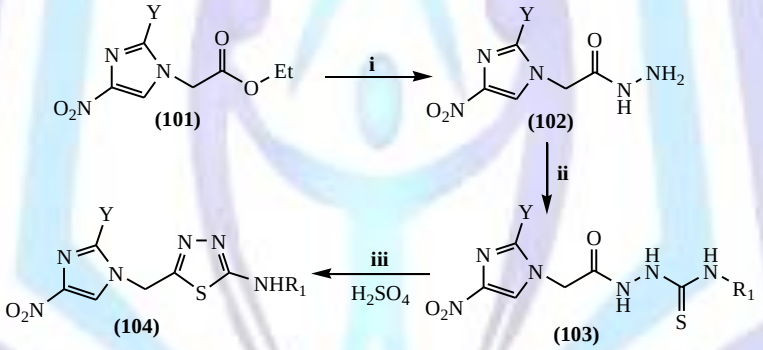
The interaction of ethyl thioglycolate with 3-chloroacrylaldehydes [221] **96** in pyridine in the presence of triethylamine led to ethyl thiophene-2-carboxylates **97** [222].

Hydrazinolysis of **98** followed by reaction with ethyl isothiocyanate then cyclization using sulfuric acid afforded *N*-ethy1-5-substituted-1,3,4-thiadiazol-2-amines **100** [223]. **(Scheme 24)**



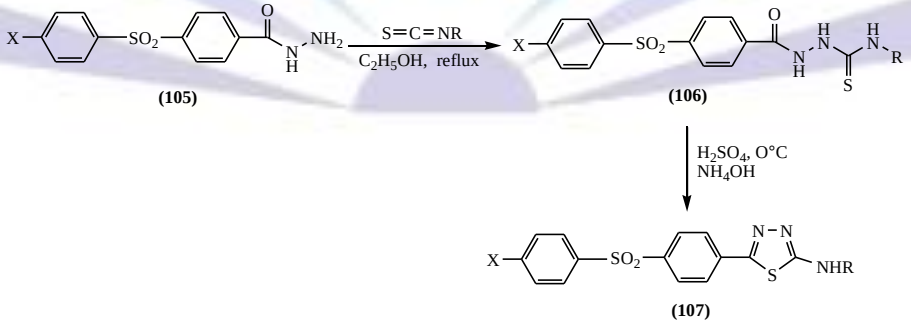
Scheme 24. Synthesis of 1,3,4-thiadiazole derivatives. Reagents and conditions: a) DMF, $POCl_3$, trichloroethylene; b) thioglycolate, triethylamine, pyridine, 10-15 ºC; c) hydrazine hydrate, ethanol, reflux; d) ethyl isothiocyanate, ethanol, reflux; e) concentrated sulfuric acid, 0 ºC.

A series of 1,3,4-thiadiazoles **104** were prepared [224] as shown in **(Scheme 25)**.



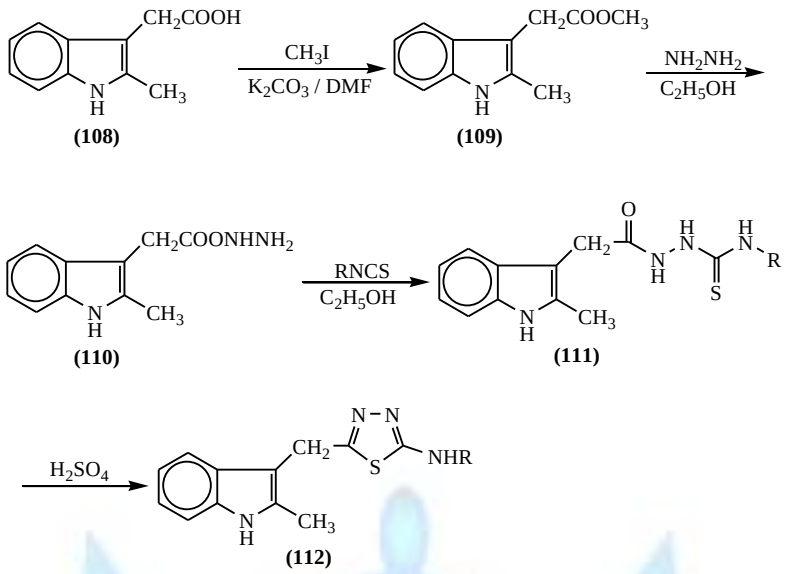
Scheme 25. Reagents: i) $NH_2NH_2.H_2O$; ii) $R_1N=C=S$; iii) H_2SO_4.

The synthesis 1,3,4-thiadiazoles **107** [225,226] and their acylthiosemicarbazides intermedicy, is outlined in **(Scheme 26)**.



Scheme 26

Synthesis and biological evaluation of indole-containing derivatives of 1,3,4-thiadiazole of the type **112** was performed. [227] **(Scheme 27)**

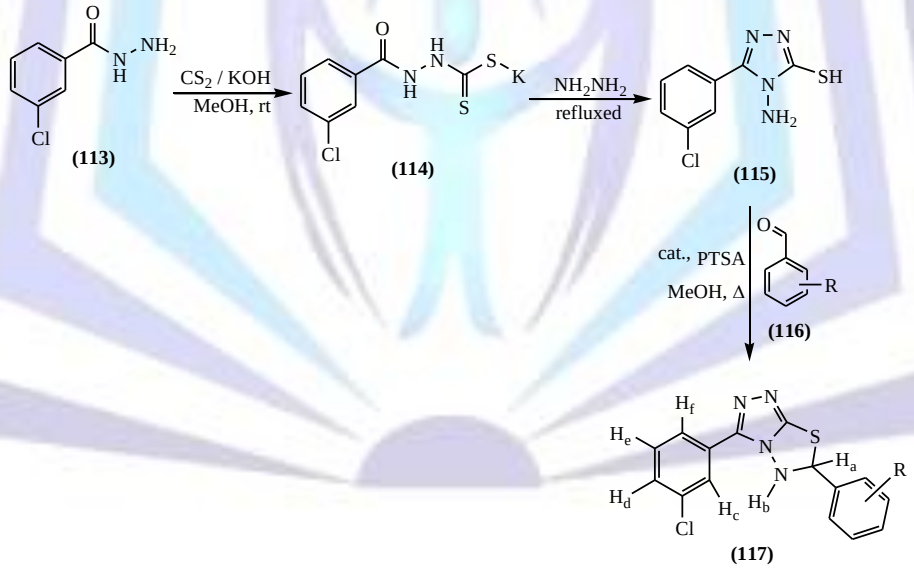


Scheme 27

ii- With CS_2

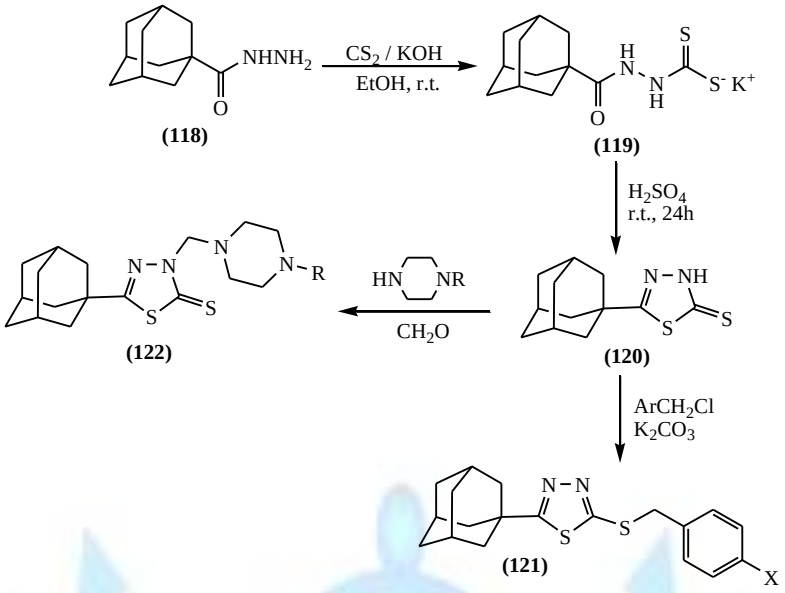
The starting 4-amino-5-(3-chloropheny1)-4*H*-1,2,4-triazole-3-thiol **115** was obtained in two steps. First, 3-chlorobenzohydrazide **113** reacted with carbon disulphide in the presence of KOH to form potassium 3-chlorobenzyl dithiocarbamate **114**. A cyclization reaction between hydrazine hydrate and **114** gave 4-amino-5-(3-chlorophenyl)-4*H*-[1,2,4]-triazole-3-thiol **115**.

The compounds **117** were synthesized by reacting 4-amino-5-(3-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol **115** with different aryl aldehydes in the presence of a catalytic amount of *p*-TsOH in dry DMF. [228] **(Scheme 28)**



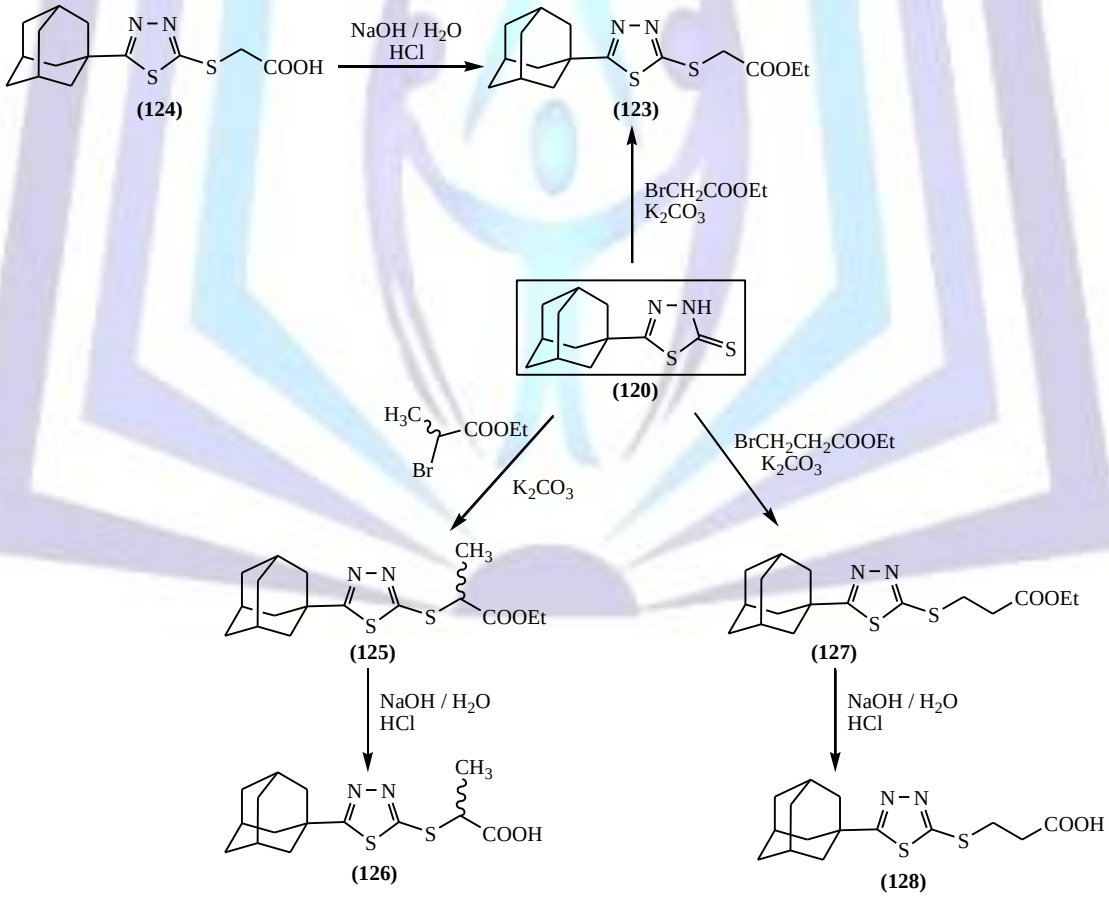
Scheme 28. Synthesis of 1,3,4-thiadiazoles **117**.

Adamantyl-1,3,4-thiadiazoles **120-122** were obtained via the reaction of hydrazide **118** with CS_2/KOH [229]. **(Scheme 29)**



Scheme 29. Synthesis of compounds **121** and **122**.

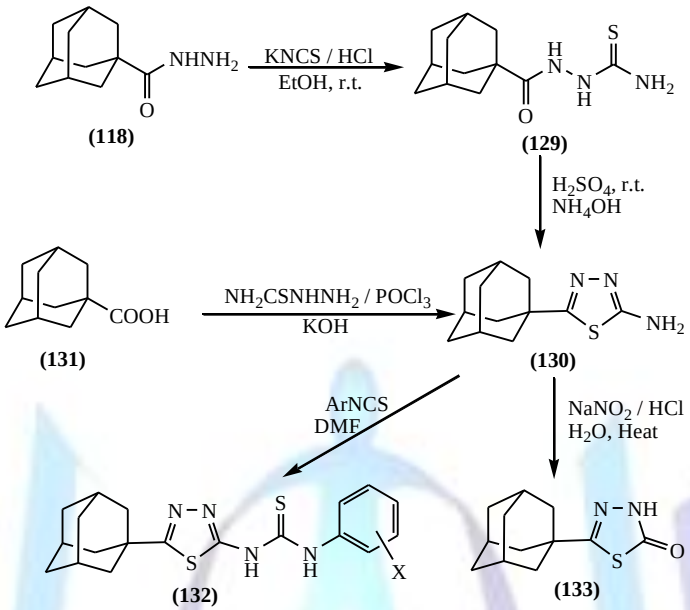
Moreover, the reaction of compound **120** with ethyl bromoacetate, ±-ethyl 2-bromopropionate or ethyl 3-bromopropionate, in ethanol, in the presence of anhydrous potassium carbonate yielded the corresponding ethyl esters **123**, **125** and **127**, which were hydrolyzed to afford the corresponding carboxylic acids **124**, **126** and **128**. **(Scheme 30)**



Scheme 30. Synthesis of [1,3,4]thiadiazole derivatives **120-128**.

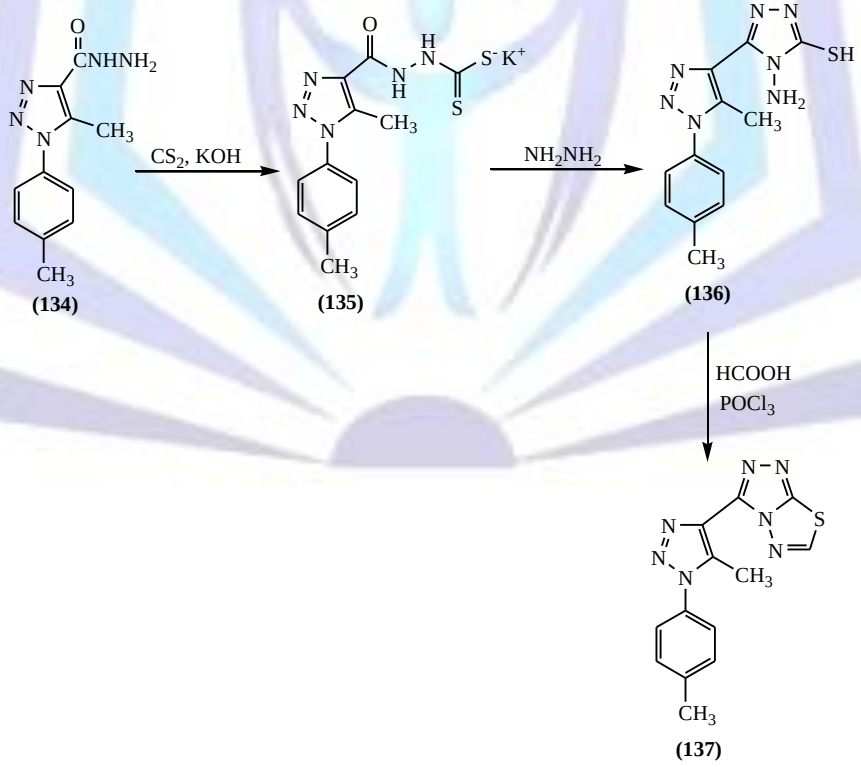
5-(1-Adamanty1)-2-amino-1,3,4-thiadiazole **130** was previously prepared in 48% yield from adamantane-l-carboxylic acid hydrazide **118** *via* reaction with potassium thiocyanate and hydrochloric acid to yield 1-(1-adamantyl carbony1)-3-thiosemicarbazide **129**, followed by dehydrative cyclization with sulphuric acid at room temperature. Compound **130** was also prepared in 59% yield *via* one-step three-component reaction of adamantane-1-carboxylic acid **137**, thiosemicarbazide and phosphorus oxychloride.

Compound **130** was reacted with phenyl-, 4-fluorphenyl- or 4-chlorophenylisothiocyanate to yield the corresponding *N*-[5-(1-adamanty1)-1,3,4-thiadiazol-2-y1]-*N'*-arylthioureas **132a-c** in poor yields. 5-(1-Adamanty1)-1,3,4-thiadiazoline-2-one **133** was prepared through deamination of compound **130** *via* treatment with sodium nitrite in cold aqueous hydrochloric acid solution followed by boiling for 10 min. [229] **(Scheme 31)**



Scheme 31. Synthesis of 1,3,4-thiadiazole **130-133**.

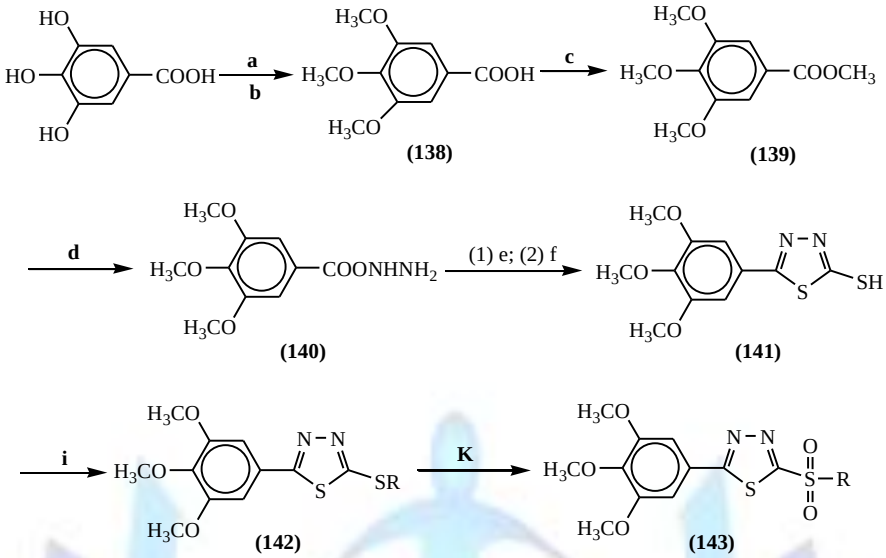
1,2,3-Triazolyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole **137** was obtained via a series of reactions involves the formation of the hydrazide [30,230-232] **134** which treated with CS_2/KOH followed by hydrazinolysis and treatment with formic acid in the presence of $POCl_3$ [233]. **(Scheme 32)**



Scheme 32

The synthetic route designed for the sulfone analogues **143** is summarized in **(Scheme 33)**. Following the reported method, [234] 5-(3,4,5-trimethoxypheny1)-1,3,4-thiadiazole-2-thiol **141** was synthesized from gallic acid in five steps: etherification, esterification, hydrazidation, salt formation, and cyclization. Phenylhydrazid **140**, potassium hydroxide, and carbon disulfide in absolute ethanol under reflux condition. Then, 5-(3,4,5-trimethoxypheny1)-1,3,4-thiadiazole-2-thiol **141**

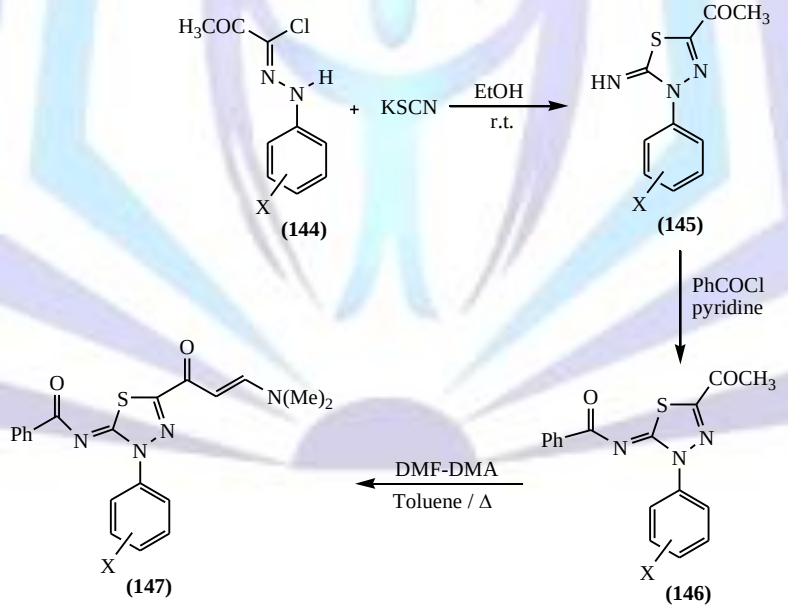
were converted to thioether derivatives containing thiadiazole **142** which when treated with ammonium molybdate in ionic liquid afforded the heterocyclic sulfones **143** [9].



Scheme 33. Synthetic rout to title compounds **143**. Reagents and conditions: a) $(CH_3)_2SO_4$, 10% NaOH; b) 35% HCl; c) CH_3OH, 98% H_2SO_4, reflux; d) $NH_2NH_2.H_2O$, CH_3OH, reflux 5h; e) KOH, CS_2, C_2H_5OH, rt; f) 98% H_2SO_4, 0-5 ºC; i) In, 3% NaOH, H_2O, RX (6), rt; k) 30% H_2O_2, $(NH_4)_6Mo_7O_{24}$ (1 mol%), ionic liquid, 40 ºC, 2h.

3) From Enaminones

Enaminones are polydentate reagents that have been utilized extensively in this decade as building blocks are organic synthesis [235-241]. A new series of thiadiazole-enaminones **147** were synthesized via reactions of 5-acetyl 1,3,4-thiadiazoles **146** with dimethyl formamide-dimethyl acetal (DMF-DMA) [242].

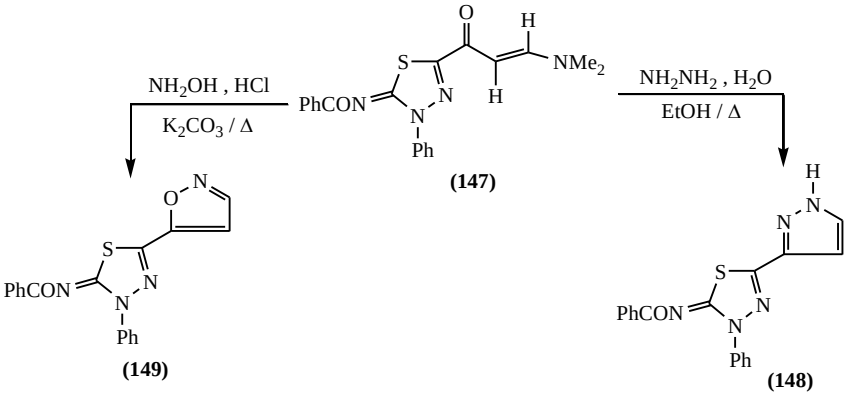


Scheme 34. Synthesis of enaminones **147**.

Reaction of enaminone **147** with hydrazine hydrate led to formation of the thiadiazole pyrazole linked product **148**.

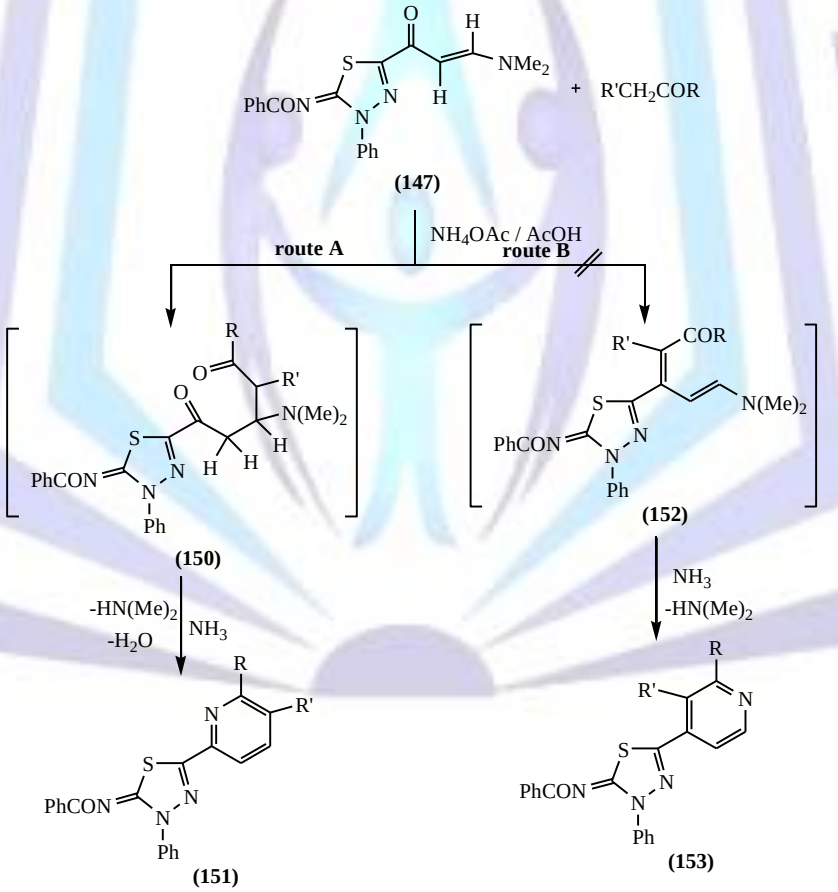
In a related manner, reaction of enaminone **147** with hydroxylamine hydrochloride in the presence of potassium carbonate led to formation of the thiadiazole isoxazole [242] **149**. **(Scheme 35)**

ISSN 2321-807X



Scheme 35. Reaction of enaminone **147** with hydrazine hydrate and hydroxylamine.

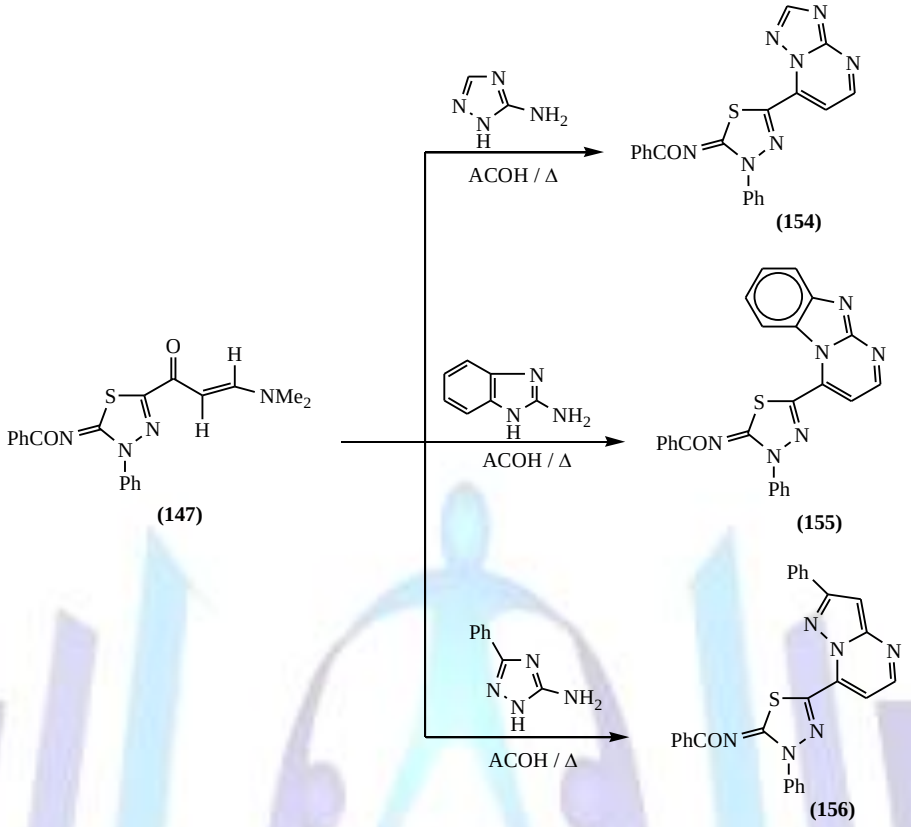
Compound **147** reacts with active methylene compounds and yielded the regioisomeric linked thiadiazole pyridine structures represented by either **151** or **153**. Two pathways are outlined in **(Scheme 36)** for this reaction. The reaction may proceed by initial Michael addition **(route A)** of the active methylene compound to the activated double bond of **147** to give the Michael adduct **150** followed by tandem elimination of dimethylamine and condensation with ammonia to give product or the other suggested pathway **(route B)** may proceed by initial condensation of active methylene compound with the carbonyl group of **147** which leads to formation of intermediate **152** that cyclizes in the presence of ammonium acetate to give **153**.



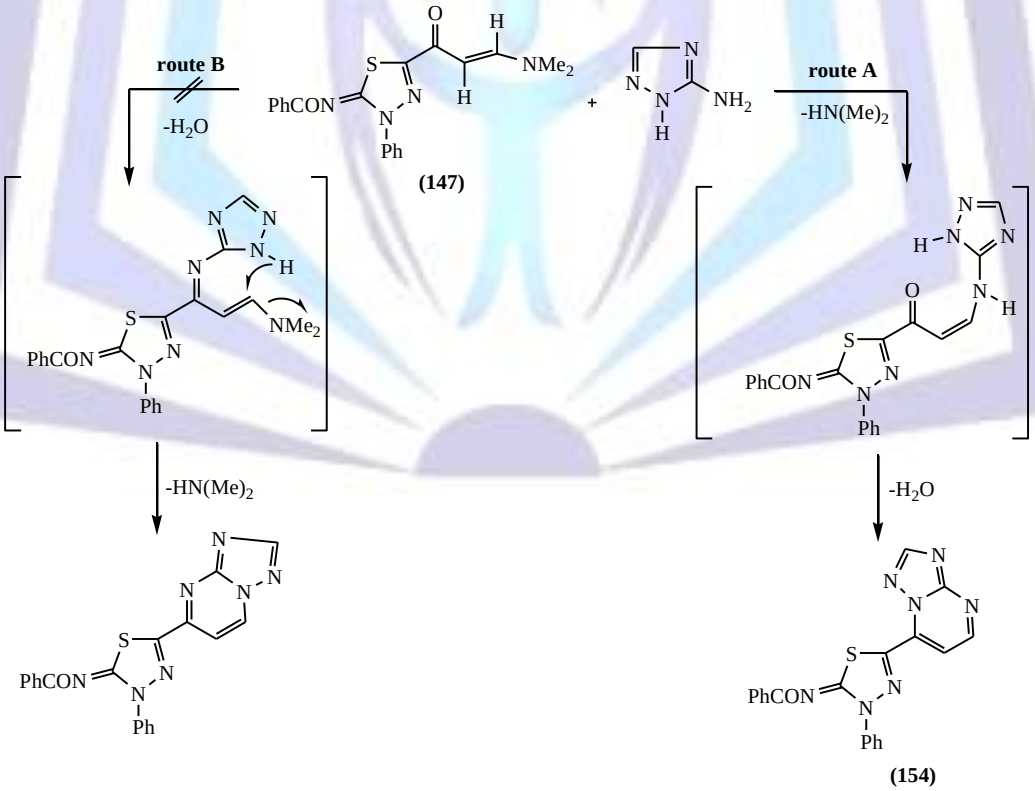
Scheme 36. Reaction of enaminone **147** with active methylene compounds.

Also, the reactivity of the enaminone **147** towards some heterocyclic amines was examined. For example, 5-amino-1,2,4-triazole was found to react with **147** in acetic acid to yield the 1,2,4-triazolo[1,5-*a*] pyrimidine derivative **154 (Scheme 37)**. Similarly, treatment of **147** with each of 2-aminobenzimidazole and 5-amino-3-phenylpyrazole under the same reaction conditions afforded the respective benzimidazo[1,2-*a*]pyrimidine **155** and pyrazolo[1,5-*a*] pyrimidine derivatives [242] **156**. **(Scheme 37)**

ISSN 2321-807X



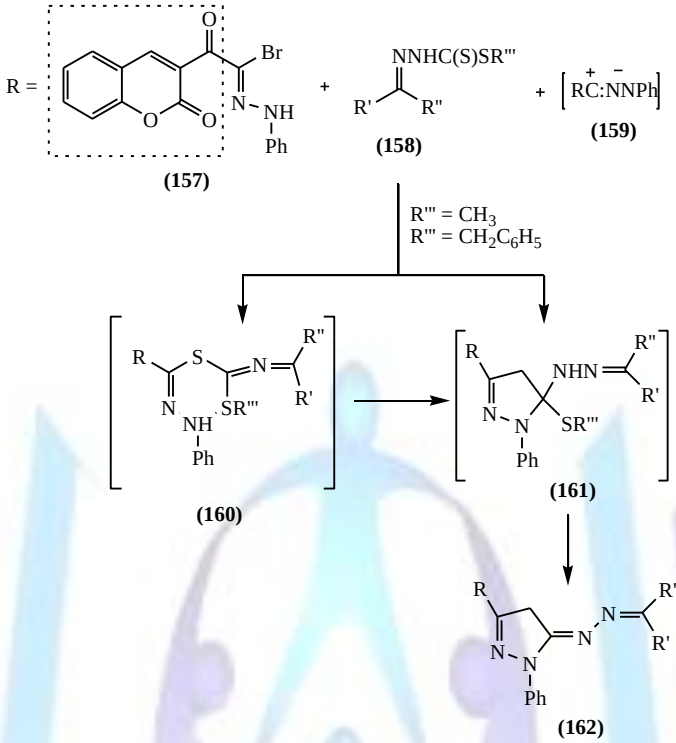
Scheme 37. Reaction of enaminone **147** with heterocyclic amine.



Scheme 38. The mechanism of reaction of enaminone **147** with heterocyclic amine.

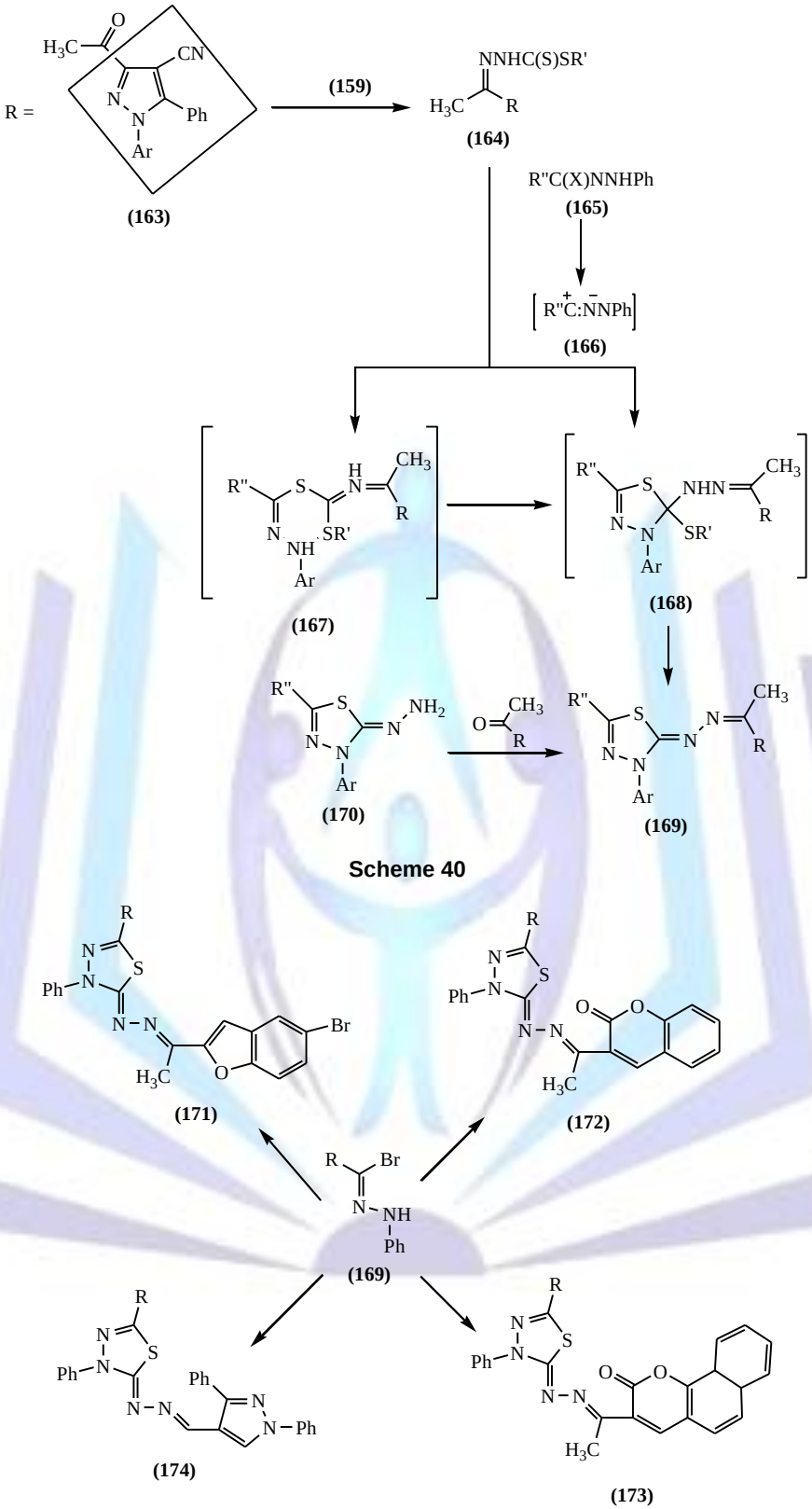
4) From Hydrazonyl halides

2,3-Dihydro-1,3,4-thiadiazole derivative containing coumarin moieties were synthesized from the reactions of methyl (or benzyl) carbodithioate with C-coumarinoyl-*N*-phenyl hydrazonoyl bromide [243] **157**. **(Scheme 39)**



Scheme 39

Furthermore, 2,3-dihydro-1,3,4-thiadiazoles containing pyrazole moieties were prepared from the reaction of alkyl-2-[1-(4-cyano-1,5-diphenyl-1*H*-pyrazol-3-yl)ethylidene]-hydrazine carbodithioate with appropriate hydrazonyl halides. [244] **(Scheme 40,41)**



Scheme 40

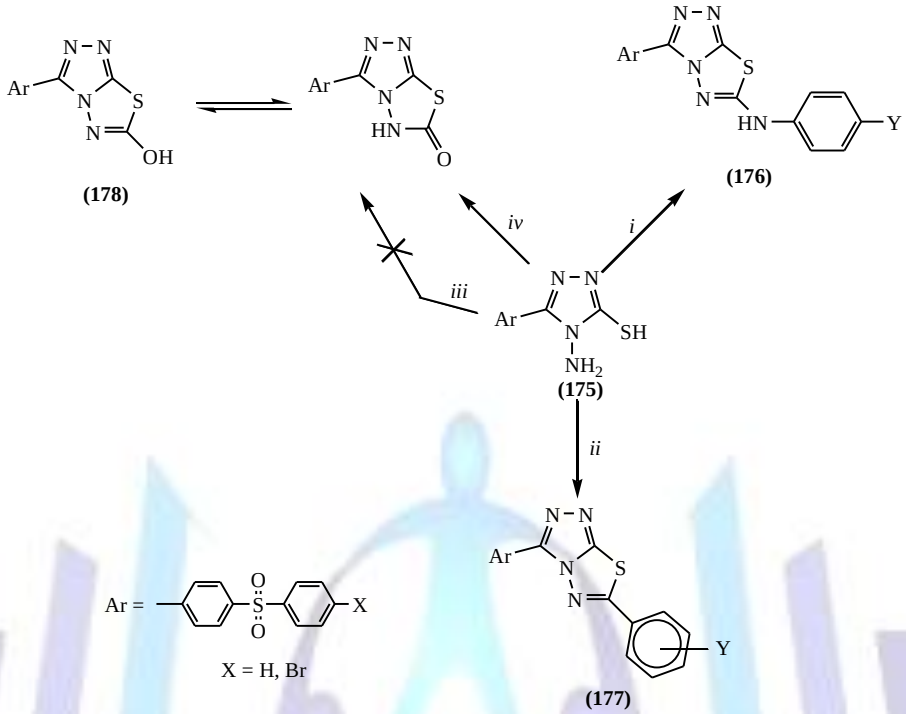
R = 5-phenyl-1-*p*-tolyl-1*H*-pyrazolyl-4-carbonitrile

Scheme 41

The ambient nucleophilic centers present in 3-substituted-4-amino-5-mercapto-1,2,4-triazoles render them as useful synthons for the synthesis of various *N*-bridged heterocycles. The key intermediates, 4-amino-5-[4-(4-X-phenylsulfonyl) phenyl]-4*H*-1,2,4-triazole-3-thiols **175** (X= H, Br) were prepared from corresponding substituted benzoic acid hydrazides according to literature [245]. The resulted triazoles **175** further converted to 3-[4-(4-X-phenylsulfonyl)

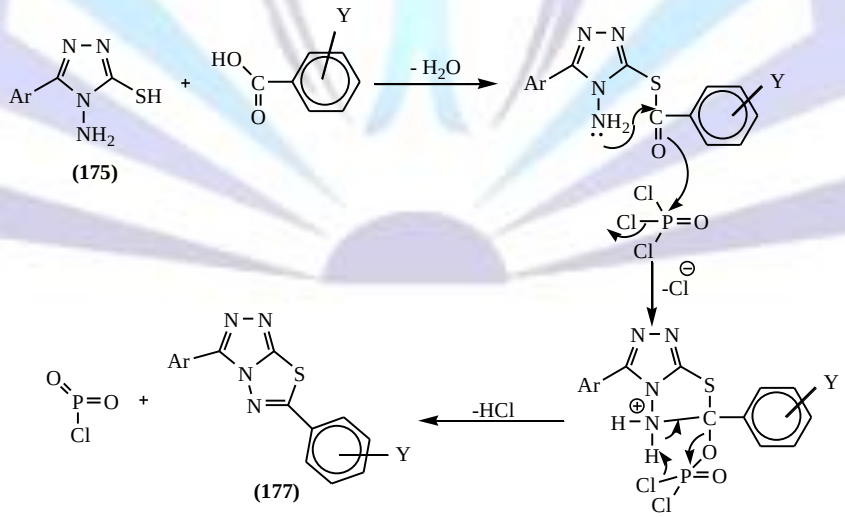
ISSN 2321-807X

pheny1]-6-*N*-(substituted phenyl) amino-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **176-178** by reacting with different reagents [246]. **(Scheme 42)**



Scheme 42. Synthesis of 1,2,4-triazolothiadiazoles **176-178**.

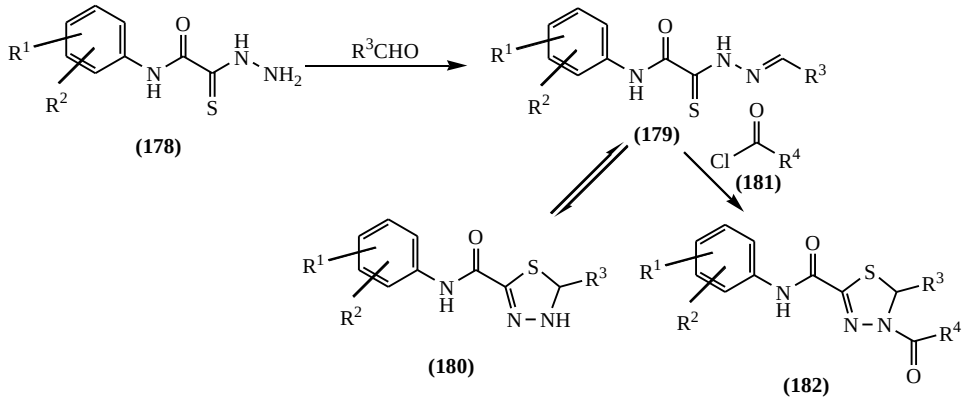
Cyclocondensation of the SH and NH_2 functions of **175** with various substituted aromatic acids in the presence of phosphorus oxychloride afforded a series of 3-[4-(4-X-phenylsulfonyl)pheny1]-6-(substituted phenyl)-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazoles **177**. The ring closure reaction with $POC1_3$ as the cyclization may have an esterification-addition-elimination mechanism [246]. **(Scheme 43)**



Scheme 43

5) From Oxamic acid thiohydrazide

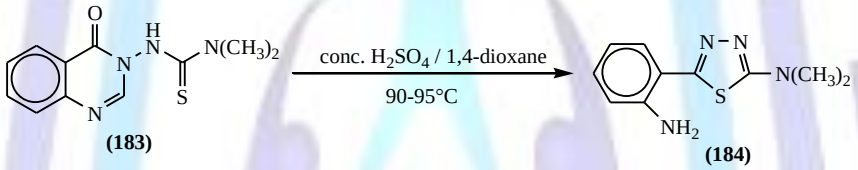
Oxamic acid thiohydrazides **178** and aldehydes, gave the corresponding hydrazones **179**, based on which the previously undescribed 4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **180** and 2-carbamoy1-4,5-dihydro-1,3,4-thiadiazole-1-oxides **182** [247] were obtained. **(Scheme 44)**



Scheme 44

6) From 3-Substituted amino quinazolin-4(3*H*)one

Derivatives of 3-aminoquinazolin-4(3*H*)-one are widely used in organic synthesis and exhibit a wide spectrum of physiological properties [248-250]. Heating of 3-*N*,*N*-dimethylthioureidoquinazolin-4(3*H*)-one **183** with concentrated sulfuric acid in 1,4-dioxane at 90-95°C results in a new compound, 5-(2'-aminopheny1)-2-dimethylamino1,3,4-thiadiazole [251,252] **184**.



REFERENCES

1. Demirbas, N.; Karaoglu, S. A.; Demirbas, A. *Eur. J. Med. Chem.* **2004**, *39,*793-804.
2. Foroumadi, A.; Emani, S.; Hassanzadeh, A. *Bioorg. Med. Chem. Lett.* **2005**, *15,* 4488-4492.
3. Mamolo, M. G.; Vio, L.; Banfi, E. *Farmaco* **1996**, *51,* 71-74.
4. Sabir, H.; Jyoti, S.; Mohd, A. *E-J. Chem.* **2008**, *5,* No.4, 963-968.
5. Aly, A. A.; El-Sayed, R. *Chem*. *Pap*. **2006**, *1,* 60 56-60.
6. Rajiv, D.; Srivastava, S. K. *Int. J. Pharma and Bio. Sci.* **2010**, V1(2).
7. Farzin, H.; Rahil, V. *J. Hetero. Chem.* **2008** *45,* 1-3.
8. Jumat, S.; Nadia, S.; Ayad, H.; Hiba, I.; Emad, Y. *J. Appl. Sci. Res.* **2010**, *6(7),* 866-870.
9. Cai-Jun, C.; Bao-An, S.; Song, Y.; Guang-Fang, X.; Pinaki, S. B.; Lin-Hong, J.; De-Yu, H.; Qian-Zhu, L.; Fang, L.; Wei, X.; Ping, L.; Zhuo, C. *Bioorg. Med. Chem.* **2007**, *15,* 3981-3989 .
10. Han, S. C.; Zheng, M. L.; Yu, F. H.; Zhong, W. W. *Chinese Chem. Lett.* **1999**, *10,* No. 5, 365-366.
11. Varvaresou, A.; Siatra-Papastaikoudi, T.; Tsotinis, A.; Tsantili-Kakoulidou, A.; Vamvakides, A.; *Farmaco* **1998**, *53,* 320-326.
12. Foroumadi, A.; Mirzaei, M.; Shafiee, A. *Pharmazie* **2001**, *56,* 610-612.
13. Zou, X. J.; Jin, G. Y.; Zhang, Z. X. *J. Agric. Food Chem*. **2002**, *50,* 1461-1454.
14. Zou, X. J.; Lai, L. H.; Jin, G. Y.; Zhang, Z. X. *J. Agric. Food Chem*. **2002**, *50,* 3757-3760.
15. Desai, K.; Baxi, A. *Indian J. Pharm Sci.* **1992**, *54,*183.
16. Gawande, N. G.; Shingare, M. S. *Indian J. Chem.* **1987**, *26B,* 387.
17. Atta, K. M. F.; Farahat, O. O. M.; Ahmed, A. Z. A.; Maria, M. G. *Molecules* **2011**, *16,* 5496.
18. Gadad, A. K.; Mahajanshetti, C. S.; Nimbalkar, S.; Raichurkar, A. *Eur.J. Med.Chem*. **2000**, *35,* 853-857.
19. Andotra, C. S.; Langer, T. C.; Kotha, A. *J. Indian Chem. Soc*. **1997**, *74(2),* 125.
20. Shams El-Dine, S. A.; Hazzaa, A. A. B. *Pharmazie* **1974**, *29,* 761-768.

21. Misato, T.; Ko, K.; Honma, Y.; Konno, K.; Taniyama, E. *Jpn. Kokai* **1977**, *77,* 25-28 [CA: **1977**, *87,* l4705a].
22. Reisdorff, J. H.; Brandes, W.; Scheinpflug, H.; Homeyer, B.; Roessler, P.; *Ger. Offen*. **1977**, *2,* 533- 604. [CA: **1978**, *88,* 137064b].
23. Van Reet, G.; Heeres, J.; Wals, L.; *US Patent* **1979**, *4,* I60, 838. [CA: **1979**, *91,* 175361z].
24. Habib, N. S.; Abdel-Hamid, S.; El-Hawash, M. *Farmaco* **1989**, *44,* 1225-1232.
25. Fujikawa, F.; Yamashita, I.; Seno, T.; Sasaki, M.; Naito, M.; Tsukuma, S. *Yakugaku Zasshi* **1966**, *86 (a),* 861-864 [CA: **1966**, *65,* 20086hl].
26. Canoira, L.; Rodriguez, J. G.; Subirats, J. B.; Escario, J.-A.; Jimenez, I.; Martinez-Fernandez, A. R. *Eur. J. Med. Chem*. **1989**, *24,* 39-42.
27. Masanori, S.; Toshiharu, O.; Hiroko, T.; Yoshitoku, Y.; *Jpn. Kokai, Tokyo Koho JP* **1989**, 01 31 762 [89 31 762]. [CA: **1989**, *111*, 153624s].
28. Omar, E.; Mohsen, A.; Aboul, W.; Omainma, M. *J. Heterocycl. Chem*. **1986**, *23,* 1339.
29. Bano, Q.; Tiwari, N.; Nizamudolin, G. S. *Indian J. Chem*. **1992**, *31B,* 714.
30. Zhang, Z.-Y.; Dong, H.-S.; Zhu, Y.; *Acta Chim. Sci*. **1996**, *54,* 1054.
31. Trost, B. M. *Chem. Rev.* **1978**, *78,* 363-382.
32. Ganellin, R. *J. Med. Chem*. **1981**, *24,* 913-920.
33. Dogan, H. N.; Rollas, S.; Erdeniz, H. *Farmaco* **1998**, *53,* 462-467.
34. Dogan, H. N.; Duran, A.; Rollas, S.; Sener, G.; Uysal, M. K.; Gülen, D. *Bioorg. Med. Chem*. **2002**, *10,* 2893-2898.
35. Gadad, A.K.; Nayak, R.; Khazi, I. M.; Mahajanshetti, C. S. *Indian Drugs* **1993**, *30,* 252-257.
36. Khazi, I. M.; Mahajanshetti, C. S.; Gadad, A. K.; Tarnalli, A. D.; Sultanpur, C. M. *Arzneim-Forsch./Drug Res*. **1996**, *46,* 949–952.
37. Foroumadi, A.; Ashraf-Askari, R.; Moshafi, M. H.; Emami, S.; Zeynali, A. *Pharmazie* **2003**, *58,* 432-433.
38. Ashour, F. A.; Habib, N. S.; Taibbi, M.; Dine, S.; Dine, A. *Farmaco* **1990**, *45,* 134-139.
39. Rollas, S.; Karakus, S.; Durgun, B. B.; Kiraz, M. Erdeniz, H. *Farmaco* **1996**, *51,* 811-814.
40. Freeman, C. D.; Klutman, N. E.; Lamp, K. C.; *Drugs* **1997**, *54,* 679-708.
41. Lau, A. H.; Lam, N. P.; Piscitelli, S. C.; Wilkes, L.; Danziger, L. H. *Clin. Pharmacokinet*. **1992**, *23,* 328-364.
42. Güzeldemirci, N. U.; Küçükbasmaci, Ö. *Eur. J. Med. Chem*. **2010**, *45,* 63-68.
43. Küçükgüzel, S. G.; Küçükgüzel, I.; Tatar, E.; Rollas, S.; Ahin, F. S.; Güllüce, M.; De Clercq, E.; Kabasakal, L. *Eur. J. Med. Chem*. **2007**, *42,* 893-901.
44. Abdel-Aal, M. T.; El-Sayed, W. A.; Abdel Aleem, A. H.; El Ashry, E. S. H. *Pharmazie* **2003**, *58,* 788-792.
45. Küçükgüzel, I.; Küçükgüzel, S. G.; Rollas, S.; Kiraz, M. *Bioorg. Med. Chem. Lett*. **2001**, *11,* 1703-1707.
46. Kadi, A. A.; El-Brollosy, N. R.; Al-Deeb, O. A.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. *Eur. J. Med. Chem.* **2007**, *42,* 235-242.
47. Plech, T.; Wujec, M.; Siwek, A.; Kosikowska, U.; Malm, A. *Eur. J. Med. Chem*. **2011**, *46,* 241-248.
48. Siddiqui, A. A.; Arora, A.; Siddiqui, N.; Misra, A. *Indian J. Chem*. **2005**, *44B,* 838-841.
49. Camoutsis, C.; Geronikaki, A.; Ciric, A.; Sokovi, M.; Zoumpoulakis, P.; Zervou, M. *Chem. Pharm. Bull*. **2010**, *58,* 160-167.
50. Elslager, E. F.; Gavrilis, Z. B.; Phillips, A. A.; Worth, D. F.; *J. Med. Chem*. **1969**, *12,* 357-363.
51. Wolf, R.; Matz, H.; Orion, E.; Tuzun, B.; Tuzun, Y. *Dermatol. Online J*. **2002**, *8,* 2.
52. Al-Deeb, O. A.; Al-Omar, M. A.; El-Brollosy, N. R.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. *Arzneim-Forsch./Drug Res*. **2006**, *56,* 40-47.
53. Foroumadi, A.; Mansouri, S.; Kiani, Z.; Rahmani, A. *Eur. J. Med. Chem*. **2003**, *38,* 851-854.
54. Thomasco, L. M.; Gadwood, R. C.; Weaver, E. A.; Ochoada, J. M.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Stapert, D.; Moerman, J. K.; Schaadt, R. D.; Yagi, B. H. *Bioorg. Med. Chem. Lett*. **2003**, *13,* 4193-4196.
55. Karaku, S.; Rollas, S. *IL Farmaco* **2002**, *57,* 577-581.

56. Pan, K.; Scott, M. K.; Lee, D. H. S.; Fitzpatrick, L. J.; Crooke, J. J.; Rivero, R. A.; Rosenthal, D. I.; Vaidya, A. H.; Zhao, B.; Reiz, A. B. *Bioorg. Med. Chem*. **2003**, *11,* 185-192.
57. Jung, K. Y.; Kim, S. K.; Gao, Z. G.; Gross, A. S.; Melman, N.; Jacobson, K. A.; Kim, Y. C. *Bioorg. Med. Chem*. **2004**, *12,* 613-623.
58. Foroumadi, A.; Asadipour, A.; Mirzaei, M.; Karimi, J.; Emami, S. *IL Farmaco* **2002**, *57,* 765-769.
59. Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M.; Daneshtalab, M.; Shafiee, A. *IL Farmaco* **2002**, *58,* 63-68.
60. Leung-Toung, R.; Wodzinska, J.; Li, W.; Lowrie, J.; Kukreja, R.; Desilets, D.; Karimian, K.; Tam, T. F. *Bioorg. Med. Chem*. **2003**, *11,* 5529-5537.
61. Desai, N. C.; Parekh, B. R.; Thaker, K. A. *J. Indian Chem. Soc*. **1987**, *64,* 491-493.
62. Schenone, S.; Brullo, C.; Bruno, O.; Bondavalli, F.; Ranise, A.; Filippelli, W.; Rinaldi, B.; Capuano, A.; Falcone, G. *Bioorg. Med. Chem*. **2006**, *14(6),* 1698-1705.
63. Varandas, L. S.; Fraga, C. A. M.; Miranda1, A. L. P.; Barreiro, E. J. *Letters in Drug Design & Discovery*. **2005**, *2,* 62-67**.**
64. Sughen, J. K.; Yoloye, T. *Pharm. Acta Helv*. **1978**, *58,* 64-68.
65. Kelarev, V. I.; Karakhanov, R. A.; Gasanvo, S. Sh. Morozova, G. V.; Kuatbekova, K. P. *J. Org. Chem. (USSR)* **1993**, *29,* 323-329.
66. Hirpara, S.B.; Parikh, K. A.; Merja, B. C. *Indian J. Chem.* **2003**, *42B,* 1172.
67. Matysiak, J.; Nasulewicz, A.; Pelczynska, M. *Eur. J. Med. Chem*. **2006**, *41,* 475-482.
68. Miyamoto, K.; Koshiura, R.; Mori, M.; Yokoi, H.; Mori, C.; Husegawa, T.; Takatori, K. *Chem Pharm Bull* **1985**, *33,* 5216.
69. Terzioglu, N.; Gursoy, A. *Eur. J. Med. Chem.* **2003**, *38,* 781-786.
70. Oleson, J. J.; Sloboda, A.; Troy, W. P.; Halliday, S. L.; Landes, M. J.; Angier, R. B.; Semb, J.; Cyr, K.; Williams, J. H. *J. Am. Chem. Soc*. **1955**, *77,* 6713-6714.
71. Gadad, A. K.; Karki, S. S.; Rajurkar, V. G.; Bhongade, B. A. *Arzneim.-Forsch./Drug*. *Rec.* **1999**, *49,* 858-863.
72. Andreani, A.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Recanatini, M.; Garaliene, V. *Bioorg. Med. Chem*. **2000**, *8,* 2359-2366.
73. Ibrahim, D.A. *Eur. J. Med. Chem*. **2009**, *44,* 2776-2781.
74. Noolvi, M. N.; Patel, H. M.; Bhardwaj, V.; Chauhan, A. *Eur. J. Med. Chem*. **2011**, *46,* 2327-2346.
75. Noolvi, M. N.; Patel, H. M.; Bhardwaj, B. *Dig. J. Nanomater. Bios*. **2010**, *5,* 387-401.
76. Duran, A.; Dogan, H. N.; Rollas, S. IL Farmaco **2002**, *57,* 559-564.
77. Rzeski, W.; Matysiak, J.; Kandefer-Szerszen, M. *Bioorg. Med. Chem*. **2007**, *15,* 3201-3207.
78. Mavrova, A. T.; Wesselinova, D.; Tsenov, Y. A.; Denkova, P. *Eur. J. Med. Chem*. **2009**, *44,* 63-69.
79. Kumar, H.; Javed, S. A.; Khan, S. A.; Amir, M. *Eur. J. Med. Chem*. **2008**, *43,* 2688-2698.
80. Amir, M.; Shikha, K. *Eur. J. Med. Chem*. **2004**, *39,* 535-545.
81. El-Moghazy, S. M.; Barsoum, F. F.; Abdel-Rahman, H. M.; Marzouk, A. A. *Med. Chem. Res.* **2011**. doi:10.1007/s00044-011-9691-4.
82. Chou, J. Y.; Lai, S. Y.; Pan, S. L.; Jow, G. M.; Chern, J. W.; Guh, J. H. *Biochem. Pharmacol*. **2003**, *66,* 115-124.
83. Clerici, F.; Pocar, D.; Guido, M. *J. Med. Chem.* **2001**, *44(6),* 931-936.
84. Arum, K. P.; Nag, V. L.; Panda, C. S. *Indian J. Chem*. **1999**, *38B,* 998.
85. Shashikant, R. P.; Prajact, K.; Nachiket, S. D.; Sunil, A. N.; Deepak, S. M.; Smita, K. P.; Aarti, V. D. *J. Chem. Pharm. Res.* **2009**, *1(1),* 191-198.
86. Pattan, S. R.; Desai, N. S.; Rabara, P. A. Indian J. Pharm. Edu. Res. **2008**, *42(4),* 314-318.
87. Mohd, A.; Harish, K.; Javed, S. A. *Eur. J. Med. Chem*. **2008**, *43,* 2056-2066.
88. Mohammad, A.; Harish, K.; Sadique, A. J. *Bioorg. Med. Chem. Lett*. **2007**, *17,* 4504-4508.
89. Mihaela, M.; Valeriu, S.; Lenuta, P.; Marcel, P.; Jacques, D.; Cristian, P. *Molecules* **2009**, *14,* 2621-2631.
90. Harish, K.; Sadique, A. J.; Suroor, A. K.; Mohammad, A. *Eur. J. Med. Chem*. **2008**, *43,* 2688-2698.

91. Holla, B. S.; Akberali, P. M.; Shivananda, M. K. *Farmaco* **2001**, *56*, 919-927.

92. Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem*. **1993**, *36,* 1090-1099.

93. Unangst, P. C.; Sbmm, G. P.; Connor, D. T.; Dyer, R. D.; Schrier, D. J. *J. Med. Chem*. **1992**, *35,* 3691-3698.

94. Boschelli, D. H.; Connor, D. T.; Bomemeier, D. A.; Dyer, R. D.; Kennedy, J. A.; Kuipers, P. J.; Okonkwo, G. C.; Schrier, D. J.; Wright, C. D.; *J. Med. Chem*. **1993**, *36,* 1802-1810.

95. Andreani, A.; Bonazzi, D.; Rambaldi, M.; Fabbri, G.; Rainsford, K. D. *Eur. J. Med. Chem*. **1982**, *17,* 271-274.

96. Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altinok, G. *Farmaco.* **2002**, *57,* 101-107.

97. Kane, J. M.; Staeger, M. A.; Dalton, C. R.; Miller, F. P.; Dudley, M. W.; Ogden, A. M. L.; Kehne, J. H.; Ketteler, H. J.; McCloskey, T. C.; Senyah, Y.; Chmielewski, P. A.; Miller, J. A. *J. Med. Chem*. **1994**, *37,* 125-132.

98. Sharma, R.; Misra, G. P.; Sainy, J.; Chaturvedi, S. C. *Med. Chem. Res*. **2011**, *20,* 245-253.

99. Santagati, M.; Modica, M.; Santagati, A.; Russo, F.; Amico-Roxas, M. *Pharmazie* **1994**, *49,* 880-884.

100. Song, Y.; Connor, D. T.; Doubleday, R.; Sorenson, R. J.; Sercel, A. D.; Unangst, P. C.; Roth, B. D. Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D.; *J. Med. Chem*. **1999**, *42,* 1161-1169.

101. Labanauskas, L.; Kalcas, V.; drenaite, E.; Gaidelis, P.; Brukstus, A.; Dauksas, A. *Pharmazie* **2001**, *56,* 617-619.

102. Swamy, S. N.; Basappa , B. S. P.; Prabhuswamy, B.; Doreswamy, B. H.; Shashidhara, J. P.; Kanchugarakoppal, S. R. *Eur. J. Med. Chem*. **2006**, *41,* 531-538.

103. Amjad. M. Q.; Haitham, N. T.; Mohammad, A. H. *Acta Pharm. Sci*. **2006**, *48,* 95-107.

104. Reddy, C. S.; Rao, L. S.; Nagaraj, A. *Acta Chim. Slov*. **2010**, *57,* 726-732.

105. Awas, M. A. *Acta Chim. Slov*. **2008**, *55,* 492-501.

106. Li, Z.; Wang, X.; Da, Y. *Syn. Commun*. **2001**, *31,* 1829-1836.

107. Supuran, C. T.; Brigantl, F.; Tilli, S.; Chegwidden, W. R.; Scozzafava, A. *Bioorg. Med. Chem*. **2001**, *9,* 703-714.

108. Liu, X.; Shi, Y.; Ma, Y.; Zhang, C.; Dong, W.; Pan, L.; Wang, B.; Li, B.; Li, Z. *Eur. J. Med. Chem*. **2009**, *44,* 2782-2786.

109. Holla, B. S.; Poorjary, K. N.; Rao, B. S.; Shivananda, M. K. *Eur. J. Med. Chem*. **2002**, *37,* 511-517.

110. Barbuceanu, S.-F.; Bancescu, G.; Cretu, O. D.; Draghici, C.; Bancescu, A.; Radu-Popescu, M. *Rev. Chim. (Bucharest)* **2010**, *61,* 140-145.

111. Aramet, I. S.; Alm_ajan, G.-L.; B_arbuceanu, S.; Dr_aghici, C.; Banciu, M. D. *Rev. Roum. Chim*. **2005**, *50,* 19-27.

112. Barbuceanu, S. F.; Almajan, G. L.; Saramet, I.; Draghici, C.; Socoteanu, R.; Barbuceanu, F. *J. Serb. Chem. Soc*. **2009**, *74,* 1041-1049.

113. Barbuceanu, S. F.; Almajan, G. L.; Saramet, I.; Draghici, C.; Tarcomnicu, A. I.; Bancescu, G. *Eur. J. Med. Chem*. **2009**, *44,* 4752-4757.

114. Almajan, G. L.; Barbuceanu, S. F.; Bancescu, G.; Saramet, I.; Saramet, G.; Draghici, C. *Eur. J. Med. Chem*. **2010**, *45,* 6139-6146.

115. Almajan, G. L.; Barbuceanu, S. F.; Almajan, E.-R.; Draghici, C.; Saramet, G. *Eur. J. Med. Chem*. **2009**, *44,* 3083-3089.

116. Al-Omar, M. A.; Al-Abdullah, E. S.; Shehata, I. A.; Habib, E. E.; Ibrahim, T. M.; El-Emam, A. A. *Molecules* **2010**, *15,* 2526-2550.

117. Vikani, H. J.; Parekh, H. *Indian J. Chem. Soc*. **1990**, *67,* 859-861.

118. Poorrajab, F.; Ardestani, S. K.; Foroumadi, A.; Emami, S.; Kariminia, A.; Fardmoghadam, M. B.; Shafiee, A. *Exp. Parasitol*. **2009**, *121,* 323-330.

119. Mazzone, G.; Pignatello, R.; Mazzone, S.; Panico, A.; Penisi, G.; Castana, R.; Mazzone, P. *Farmaco* **1993**, *48,* 1207.

120. Marin, A.; Valls, N.; Javier, B. F.; Alonson, M. T.; Ramon, M. A.; Mercedes, M. M.; Elguero, J. *Farmaco* **1992**, *47,* 63.

121. Barnish, I. T.; Cross, P. E.; Dickinson, R. P.; Gadsby, B.; Parry, M. J.; Randall, M. J.; Sinclair, I. W. *J. Med. Chem*. **1980**, *23,* 117.

122. Sevgi, K.; Ufuk, Ç.; Bilgehan, B.-D.; Ezequiel, M. V.-L.; Suna, Ö.-T.; Jülide, A.; Sevim, R. Marmara *Pharmaceutical Journal* **2010**, *14,* 84-90.

123. Zamani, K.; Faghifi, K.; Tefighi, I.; Sharlatzadeh, M. R. *Turk. J. Chem*. **2004**, *28,* 95-101.

124. Chen, H.; Li, Z.; Han, Y. *J. Agric. Food Chem*. **2000**, *48,* 5312–5315.

125. Clerici, F.; Pocar, D.; Guido, M.; Loche, A.; Perlini, V.; Brufani, M. *J. Med. Chem*. **2001**, *44,* 931-936.

126. Jones, D. H.; Slack, R.; Squires, S.; Wooldridge, K. R. H. *J. Med. Chem*. **1965**, *8,* 676-680.

127. Sidwell, R. W.; Robins, R. K.; Hillyard, I. W. *Pharmacol. Ther*. **1979**, *6,* 123-128.

128. Küçükgüzel, I.; Tatar, E.; Küçükgüzel, S. G.; Rollas, S.; De Clercq, E. *Eur. J. Med. Chem*. **2008**, *43,* 381-392.

129. Sandstrom, J.; *Adv. Heterocycl. Chem*. **1969**, *9,* 165-177.

130. Ovsesyan, T. R.; Gushoglyan, L. A.; Mirzoyan, V. S.; *Arm. Khim. Zh*. **1988**, *41,* 3, 1363142.

131. Adam, F. A.; *J. Chin. Chem. Soc*. **1987**, *34,* 1113115.

132. Shucla, M. D.; Desai, N. C.; Astik, R. R.; Thaker, K. A. *J. Ind. Chem. Soc*. **1984**, *61,* 168-171.

133. Kolavi, G.; Hegde, V.; Khan, I.; Gadad, P. *Bioorg. Med. Chem*. **2006**, *14,* 3069-3080.

134. Orucu, E. E.; Rollas, S.; Kandermirli, F.; Shvets, N.; Dimoglo, A. S. *J. Med. Chem*. **2004**, *47,* 6760-6767.

135. Turner, S.; Myers, M.; Gadie, B.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. *J. Med. Chem*. **1988**, *31,* 902-906.

136. Turner, S.; Myers, M.; Gadie, B.; Hale, S. A.; Horsley, A.; Nelson, A. J.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. *J. Med. Chem*. **1988**, *31,* 907-913.

137. Andreani, A.; Rambaldi, M.; Locatelli, A.; Malandrino, S.; Pifferi, G. *Arzneim.-Forsch*. **1994**, *44,* 618.

138. Andreani, A.; Rambaldi, M.; Mascellani, G.; Rugarli, P. *Eur. J. Med. Chem*. **1987**, *22,* 19-22.

139. Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Dubinsky, B.; Moore, J. B. *J. Med. Chem*.**1988**, *31,* 2221.

140. Chapleo, C. B.; Myers, P. L.; Smith, A. C.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S. *J. Med. Chem*. **1988**, *31,* 7-11.

141. Gupta, A.; Mishra, P.; Kashaw, S. K.; Kashaw, V.; Stables, J. P. *Eur. J. Med. Chem*. **2008**, *43,* 749-754.

142. Mohammad, S. Y.; Mohammad, W. A. *Acta Poloniae Pharmaceutica and Drug Research* **2009**, *66,* 4, 393-397.

143. Bahar, A.; Mohd, Y. *Ind. J. Chem*. **2010**, *49B,* 241-246.

144. Varsha, J.; Pradeep, M.; Sushil, K.; Stables, J. P. *Eur. J. Med. Chem*. **2008**, *43,* 1945-1954.

145. Chapleo, C. B.; Myers, M.; Myers, P. L.; Saville, J. F.; Smith, A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S.; Welbourn, A. P. *J. Med. Chem*. **1986**, *29,* 2273

146. Stillings, M. R.; Welboum, A. P.; Walter, D. S. *J. Med. Chem.* **1986**, *29,* 2280-2284.

147. Ainsworth, C.; Easton, N. R.; Livezey, M.; Morrison, D. E.; Gibson, W. R. *J. Am. Pharm. Assoc*. **1962**, *5,* 383-389.

148. Andreani, A.; Rambaldi, M.; Locatelli, A.; Andreani, F. *Collect. Czech. Chem. Commun*. **1991**, *56,* 2436-2447.

149. Andreani, A.; Rambaldi, M.; Mascellani, G.; Bossa, R.; Galatulas, I. *Eur. J. Med. Chem*. **1986**, *21,* 451-453.

150. Edwards, D. I.; *Antimicrob. J. Chemother*. **1993**, *31,* 9-20.

151. Chauviere, G.; Bouteille, B.; Enanga, B.; De Aluquerque, C.; Croft, S. L. Dumas, M.; Perie, J. *J. Med. Chem*. **2003**, *46,* 427-440.

152. Carvalho, S. A.; Da Silva, E. F.; Santa-Rita, R. M. De Castro, S. L.; Fraga, C. A. M. *Bioorg. Med. Chem. Lett*. **2004**, *14,* 5967-5970.

153. Gosh, B. K.; Ray, D. H.; Chatterjee, A. N. *J. Trop. Med. Hyg*. **1989**, *92,* 383-386.

154. Bekircan, O.; Ozen, T.; Gumrukcuoglu, N.; Bektas, H. *Z. Naturfor*. **2008**, *63,* 548-554.

155. Aktay, G.; Tozkoparan, B.; Ertan, M. *J. Enz. Inh. Med. Chem*. **2009**, *24,* 898-902.

156. Khan, I.; Ali, S.; Hameed, S.; Rama, N. H.; Hussain, M. T.; Wadood, A.; Uddin, R.; Ul-Haq, Z.; Khan, A.; Ali, S.; Choudhary, M. I. *Eur. J. Med. Chem*. **2010**, *45,* 5200-5207.

157. Ayhan-Kilcigil, G.; Kus, C.; Çoban, T.; Can-Eke, B.; Iscan, M. *J. Enz. Inhib. Med. Chem*. **2004**, *19,* 129-135.

158. Andreani, A.; Leonia, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Simon, W. A.; Senn, J. *Arzneim.-Forsch./Drug. Res*. **2000**, *50,* 550-553.

159. Zhan, P.; Liu, X.; Cao, Y.; Wang, Y.; Pannecouque, C.; Clercq, E. D. *Bioorg. Med.Chem. Lett*. **2008**, *18,* 5368-5371.

160. Ishankhodzhaeva, M. M.; Kadyrova, A. Sh.; Surazhskaya, M. D.; Parpiev, N. A.; Koźmin, P. A. *Russian. J. Org. Chem*. **2001**, *37*, 5, 721-723.

161. Alireza, F.; Saeed, E.; Shirin, P.; Arsalan, K.; Abbas, S.; *Eur. J. Med. Chem.* **2005**, *40*, 1346-1350.

162. Shankar, G.; Kallanagouda, R. A.; Pranali, V. S.; Sagar, M. C.; Dilip, H. D.; Amol, S. S.; *Bioorg, Med. Chem. Lett*. **2012**, *43(29)*.

163. Malleshappa, N. N.; Harun, M. P.; Navjot, S.; Andanappa, K. G.; Swaranjit, S. C.; Arvind, B.; *Eur. J. Med. Chem.* **2011**, *46*, 4411-4418.

164. Supuran, C. T.; Barboiu, M.; Luca, C.; Pop, E.; Brewster, M. E.; Dinculescu, A. *Eur. J. Med. Chem.* **1996***, 31*, 597-606.

165. Alireza, F.; Fatemeh, S.; Mohammad, H. M.; Rogheeyeh, A. A. *IL Farmaco* **2003***, 58*, 1023-1028.

166. Ravi, S. L.; Nitinkumar, S. S.; Ravindra, R. K.; Imtiyaz, A. M. K. *Eur. J. Med. Chem.* **2009***, 44*, 2828-2833.

167. Samir,A. C.; Edson, F. d.; Ricardo, M. S. R.; Solange, L. d.; Carlos, A. M. F. *Bioorg. Med. Chem. Lett.* **2004***, 14*, 5967-5970.

168. Kallanagouda, R. A.; Shankar, G. A. *Arabian. J. Chem.* **2011***, 4*, 465-472.

169. Lin, L. S.; Lanza, T. J.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S.; Fong, T. M.; Shen, C.-P.; Lao, J.; Chen, J.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; Vander Ploeg, L.; Goulet, M. T.; Hagman,W. K. *J. Med. Chem*. **2006**, *49*, 7584.

170. Chen, C.-y.; Frey, L. F.; Shultz, S.; Wallace, D. J.; Marcantonio, K.; Payack, J. F.; Vazquez, E.; Springfield, S. A.; Zhou, G.; Liu, P.; Kieczykowski, G. R.; Chen, A. M.; Phenix, B. D.; Singh, U.; Strine, J.; Izzo, B.; Krska, S. W.; *Org. Process Res. Dev.* **2007***, 11,* 616.

171. Lin, L. S.; Ha, S.; Ball, R. G.; Tsou, N. N.; Castonguay, L. A.; Doss, G. A.; Fong, T. M.; Shen, C. P.; Xiao, J. C.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem.* **2008***,* 51, 2108.

172. Griffith, D. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; Carpino, P. A.; DaSilvaJardine, P.; Day, R.; DiBrino, J.; Dow, R. L.; Landis, M. S.; O'Connor, R. E.; Scott, D. O. *J. Med. Chem.* **2009***, 52,* 234.

173. Barth, F.; Casellas, P.; Congy, C.; Martinez, S.; Ridaldi, M. *U.S. Patent* **1995***, 5*, 462, 960.

174. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Frnando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, *J. Med. Chem.* **1999***,42,* 769.

175. Katoch-Rouse, R.; Pavlova, O. A.; Caulder, T.; Hoffman, A. F.; Mukhin, A. G.; Horti, A. G. *J. Med. Chem*. **2003**, *46*, 642.

176. Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Org. Chem.* **2001***, 66*, 7925.

177. Lee, J.; Seo, H. J.; Lee, S. H.; Kim, J.; Jung, M. E.; Lee, S.-H.; Song, K.-S.; Lee, J.; Kang, S. Y.; Kim, M. J.; Kim, M.-S.; Son, E.-J.; Lee, M. W.; Han, H.-K. *Bioorg. Med. Chem.* **2010***, 18*, 6377-6388.

178. Lee, J.; song, K. S.; Kang, J. H.; Lee, S. H.; Lee, J. *Curr. Top. Med. Chem*. **2009**, *9,* 564.

179. Barth, F.; Congy, C.; Martinez, S.; Rinaldi, M. *U.S. Patent,* 6,028,084, **2000**.

180. Amengual, R.; Marsol, C.; Mayeux, E.; Sierra, M.; Wagner,P. *PCT Patent WO.* **2006***,* 2006/133926 A1.

181. Cooper, M.; Receveur, J.-M.; Bjurling, E.; Norregaard, P. K.; Nielsen, P. A.; Skold, N.; Hogberg, T. *Bioorg. Med. Chem. Lett.* **2010***, 20,* 26.

182. Receveur, J.-M.; Murray, A.; Linget, J.-M.; Norregaard, P. K.; Cooper, M.; Bjurling, E.; Nielsen, P.; Hogberg, T. *Bioorg. Med. Chem. Lett.* **2010***, 20,* 453.

183. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994***, 37*, 3977.

184. Sortino, M.; Delgado, P.; Juarez, S.; Quiroga, J.; Abonia, R.; Insuasty, B.; Nogueras, L.; Garibotto, F. M.; Enriz, R. D.; Zacchino, S. A. *Bioorg. Med. Chem.* **2007***, 15*, 484.

185. Kwan-Young, J.; Soo-Kyung, K.; Zhan-Guo, G.; Ariel, S. G.; Neli, M.; Kenneth, A. J.; Yong-Chul, K. *Bioorg. Med. Chem.* **2004***, 12*, 613-623.

186. Bernstin, J.; Yale, H. L.; Losee, K.; Holsing, M.; Martins, J.; Lott, W. A. *J. Am. Chem. Soc.* **1951***, 73*, 906.

187. Foroumadi, A.; Mirzaei, M.; Shafiee, A. *Il Farmaco* **2001***, 56*, 621-623.

188. Croft, S. L.; Yardley, V. *Curr. Pharm. Des.* **2002***, 8*, 319-342.

189. Dutta, A.; Bandyopadhyay, S.; Mandal, C.; Chatterjee, M. *Parasitol. Int.* **2005***, 54*, 119-122.

190. Tanaka, A. K.; Valero, V. B.; Takahashi, H. K.; Straus, A. H. *J. Antimicrob. Chemother.* **2007***, 59*, 487-492.

191. Fatemeh, P.; Sussan, K. A.; Saeed, E.; Mina, B. F.; Abbas, S.; Alireza, F. *Eur. J. Med. Chem.* **2009***, 44*, 1758-1762.

192. Foroumadi, A.; Pournourmohammadi, S.; Soltani, F.; AsgharianRezaee, M.; Dabiri, S.; Kharazmi, A.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2005***, 15*, 1983-1985.

193. Foroumadi, A.; Emami, S.; Pournourmohammadi, S.; Kharazmi, A.; Shafiee, A*. Eur. J. Med. Chem.* **2005***, 40*, 1346-1350.

194. Behrouzi-Fardmoghadam, M.; Poorrajab, F.; Ardestani, S. K.; Emami, S.; Shafiee, A.; Foroumadi, A. *Bioorg. Med. Chem.* **2008***, 16*, 4509-4515.

195. Abdul, R. B.; Tazeem, Amir, A.; Inho, C.; Fareeda, A. *Eur. J. Med. Chem.* **2011***, 46*, 3158-3166.

196. Varsha, J.; Sushil, K.; Pradeep, M. *Med. Chem. Res.* **2008***, 17*, 169-181.

197. Alireza, F.; Zahra, K.; Fatemeh, S. *Il Farmaco* **2003***, 58*, 1073-1076.

198. Mei-Hsiu, S.; Cheng-Ling, W. *Tetrahedron* **2005***, 61*, 10917-10925.

199. Supuran, C. T.; Scozzafava, A.; Saramet, I.; Banciu, M. D. *J. Enzyme Inhib.* **1998**, *13,* 177-194.

200. Brezenau, M.; Olar, R.; Manole, G.; Supuran, C. T. *Rev.Roum. Chim.* **1992**, *37,* 425-431.

201. Supuran, C. T.; Lepadatu, C.; Olar, R.; Meghea, A.; Brenzenau, M. *Rev. Roum. Chim.* **1993**, *38,* 1509-1517.

202. Brezenau, M.; Olar, R.; Meghea, A.; Stanica, N.; Supuran, C. T. *Rev. Roum. Chim.* **1996**, *41,* 103-107.

203. Almajan, G. L.; Innocenti, A.; Puccetti, L.; Manole, G.; Barbuceanu, S.; Saramet, I.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2005**, *15,* 2347-2352.

204. Cho, N. S.; Kim, C. N. *J. Heterocyclic Chem.* **1993**, *30,* 397-401.

205. Petrow, V.; Stephenson, O.; Thomas, A. J.; Wild, A. M. *J. Chem. Soc.* **1958**, 1508-1513.

206. Mohammed, K. A.; Atef, A. A.; Nawal, A. E.; Nadia, M. M.; Alessio, I., Claudiu, T. S. *Bioorg. Med. Chem*. **2007**, *15*, 6975-6984.

207. Abbate, F.; Winum, J. Y.; Potter, B. V.; Casini, A.; Montero, J. L.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2004**, *14,* 231-234.

208. Abbate, F.; Casini, A.; Owa, T.; Scozzafava, A.; Supuran, C. T. *Bioorg. Med. Chem. Lett.* **2004**, *14,* 217-223.

209. Tripodi, S. A.; DelVecchio, M. T.; Supuran. C. T.; Scozzafava, A.; Gabrielli, M. G.; Pastorekova, S.; Rossie, R.; Fasolis, G.; Puccetti, L. *J. Enzyme Inhib. Med. Chem.* **2004**, *19,* 287-291.

210. Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. *Expert Opin. Ther. Patents* **2001**, *11,* 765-787.

211. Casini, A.; Scozzafava, A.; Supuran, C. T. *Environ. Health Perspect.* **2002**, *110,* 801-806.

212. Gough, J. D.; Lees, W. J. *Bioorg. Med. Chem. Lett.* **2005**, *15,* 777-781.

213. Georgeta, S.; Tunde, H. Clujul Medical **2011**, *84, 4,* 547-549.

214. Zheng, X.; Li, Z.; Wang, Y.; Chen, W.; Huang, Q.; Liu, C.; Song, G. *J. Fluorine Chem.* **2003**, *123,* 163-169.

215. Moise, M.; Sunel, V.; Profire, L.; Popa, M.; Desbrieres, J.; Peptu, C. *Molecules* **2009**, *14,* 2621-2631.

216. Shi, W.; Qian, X.; Zhang, R.; Song, G. *J. Agric. Food Chem*. **2001**, *49,* 124-130.

217. Gilman, H.; Blatt, A. H. *Organic Synthesis Coll.* 2nd ed. John Wiley Inc, New York, **1967**.

218. Turan-Zitouni, G.; Sivac, M.; Kilic, F. S.; Erol, K. *Eur. J. Med. Chem*. **2001**, *36,* 685-689.

219. Mukherjee, J.; Chatterjee, J. N.; Sengupta, C. *Ind. J. Chem*. **1975,** *13,* 859-860.

220. Imtiaz, K.; Sajid, A.; Shahid, H.; Nasim, H. R.; Muhammad, T. H.; Abdul, W.; Reaz, U.; Zaheer, U.; Ajmal, K.; Sajjad, A.; M. Iqbal, C. *Eur. J. Med. Chem*. **2010**, *45,* 5200-5207.

221. Bodendorf, K.; Mayer, R. *Chem. Ber*. **1965**, *98,* 3554-3563.

222. Hauptman, S.; Werner, E.-M. *J. Prakt. Chem*. **1972**, *314,* 499-506.

223. Anelia, T. M.; Diana, W.; Yordan, A. T.; Pavletta, D. *Eur. J. Med. Chem*. **2009**, *44,* 63-69.

224. Asal, F. T.; Tahmineh, A.; Parastoo, S.; Farideh, S.; Abbas, S.; Alireza, F. *Turk. J. Chem*. **2011**, *35,* 307-316.

225. Mavrodin, A.; Zotta, V.; Stoenescu, V. M.; Oteleanu, D. *Pharm. Zentr. Deutsch* **1956**, *95,* 353-361.

226. Stefania, F. B.; Gabriel, S.; Gabriela. L. A.; Constantin, D.; Florica, B.; Gabriela, B. *Eur. J. Med. Chem.* **2012**, 1-7.

227. Alhanasia, V.; Theodora, S. P.; Andrew, T.; Anna, T. K.; Alexandre, V. *IL Farmaco* **1998**, *53,* 320-326.

228. Dushyant, H. P.; Bhavesh, L. D.; Renish, M. G.; Piyush, B. V.; Hitendra, S. *J. Acta. Chim. Slov*. **2011**, *58,* 53-59.

229. Adnan, A. K.; Ebtehal, S. A.; Ihsan, A. S.; El-Sayed, E. N.; Tarek, M. I.; Ali, A. E. *Eur. J. Med. Chem*. **2010**, *45,* 5006-5011.

230. Zhang, Z.-Y.; Dong, H.-S. Guan, Z.-W.; Yang, S.-Y. *Chem. Res. Chin. Univ*. **1997,** *13,* 27.

231. Zhang, Z.-Y.; Dong, H.-S.; Yang, S.-Y. *Org. Chem*. **1996**, *16,* 430.

232. Zhang, Z.-Y.; Dong, H.-S.; Yang, S.-Y. *Org. Chem*. **1998**, *18,* 253.

233. Heng, S. D.; Bin, Q.; Duo-Wen, Z.; Wei-Dong, L. *J. Molecular Structure* **2002**, *613,* 1-5.

234. Song, B. A.; Chen, C. J.; Yang, S.; Jin, L. H.; Xue, W.; Zhang, S. M.; Zou, Z. H.; Hu, D. Y. *Acta. Chim. Sinica*. **2005**, *63,* 1720-1726.

235. Ferraz, H. M. C.; Goncalo, E. R. S.; *Quim. Nova* **2007**, *30,* 957-964.

236. Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67,* 207-215.

237. Stanovnik, B.; Svete, J. *Chem. Rev*. **2004**, *104,* 2433-2480.

238. Yermolayev, S. A.; Gorobets, N. Y.; Lukinova, E. V.; Shishkin, O. V.; Shishkina, S. V.; Desenko, S. M. *Tetrahedron* **2008**, *64,* 4649-4655.

239. Riyadh, S.M.; Farghaly, T.A.; Abdallah, M.A.; Abdalla, M.M.; Abdel-Aziz, M.R. *Eur. J. Med.Chem*. **2010**, *45*, 1042-1050.

240. Farghaly, T. A.; Abdalla, M. M. *Bioorg. Med. Chem*. **2009**, *17,* 8012-8019.

241. Abbas, E. M. H.; Farghaly, T. A. *Monatsh. Chem*. **2010**, *141*, 661-667.

242. Thoraya, A. F.; Magda, A. A.; Zienab, A. M. *Molecules* **2011**, *16,* 10420-10432.

243. Abdou, O. A.; Abdelgwad, A. F.; Abeer, B. A. *Eur. J. Chem*. **2011**, *2(4),* 544-551.

244. Abdou, O. A.; Abdelgwad, A. F.; Karema, N. M. H. *Eur. J. Chem*. **2011**, *2(3),* 317-323.

245. Almajan, G. L.; Barbuceanu, S. F.; Saramet, I.; Draghici, C. *Rev. Chim. (Bucharest)* **2005**, *56,* 1182-1187.

246. Gabriela, L. A.; Stefania, F. B.; Gabriela, B.; Ioana, S.; Gabriel, S.; Constantin, D. *Eur. J. Med. Chem*. **2010**, *45,* 6139-6146.

247. Yarovenko, V. N.; Shirokov, A. V.; Zavarzin, I. V.; Krupinova, O. N.; Ignatenko, A. V.; Krayushkin, M. M. *Chemistry of Heterocyclic Compounds* **2003**, *39, 12,* 1633-1638.

248. Smith, K.; El-Hiti, G. A.; Abdo, M. A.; Abdel-Megeed, M. F. *J. Chem. Soc., Perkin Trans* **1995**, *1, 8,* 1029.

249. Abdel-Megeed, M. F.; Saleh, M. A.; Abdo, M. A.; El-Hiti, G. A. *Collect. Czech. Chem. Commun*. **1995**, *60,* 1016.

250. Atkinson, R. S.; Barker, E. *J. Chem. Soc., Perkin Trans* **1995**, *1, 8,* 819.

251. Malinovskii, S. T.; Rusu, G. G.; Barba, N. A.; Krimer, M. Z.; Lipkowski, J. *Crystallography Reports* **2000**, *45, 3,* 453-456.

252. Noor, S. B.; Vasundhara, D. E.; Girija, C. R.; Kolavi, G. D.; Hegde, V. S.; Khazi, I. M. *J. Chem. Crystallogr*. **2007**, *37,* 561-565.