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REVIEW

1st Heterocyclic Update

Synthesis and biological significances of 1,3,4-thiadiazolines and related heterocyclic compounds

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Thiosemicarbazones;
Bisthiadiazolines;
Biological activity;
Heterocyclic compounds

Abstract This review article describes the survey of literature regarding the variety of synthetic methods of 1,3,4-thiadiazoline and related compounds in the last seven years (2004–2010). The aim of the review is to find out different methods for the synthesis of thiadiazolines. These heterocyclics are majorly obtained from the cyclization reactions of thiosemicarbazone under the various conditions. From the literature studies it was found that major importance was given to their pharmaceutical significance i.e., regarding their biological activity against different fungal and bacterial strains.

Contents

1. Introduction

Heterocyclic chemistry is an integral part of the chemical sciences and constitutes a considerable part of the modern researches that are occurring presently throughout the world. The chemistry of heterocyclic compounds is as logical as the chemistry of aliphatic or aromatic compounds. The study of heterocyclic systems is of great interest both from the theoretical and practical point of view. Heterocycles also play an important role in the design and discovery of new physiologi-

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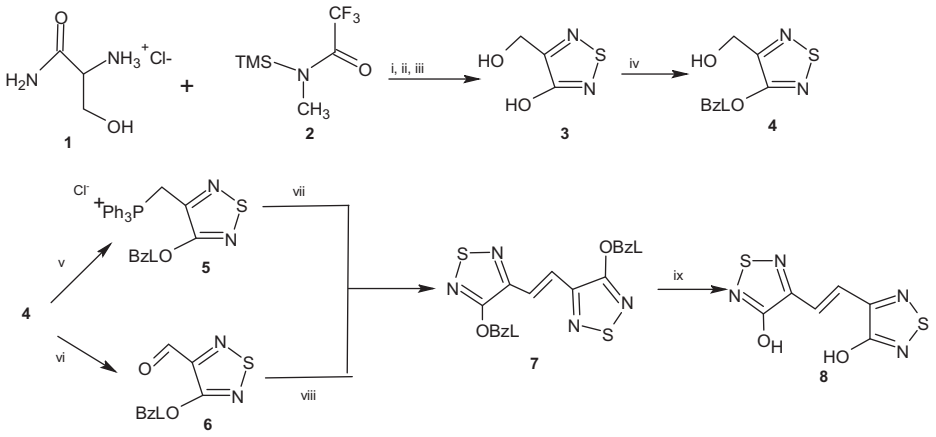
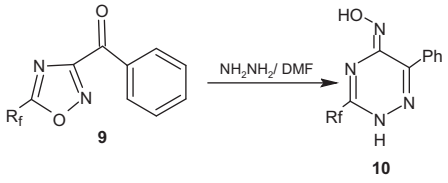
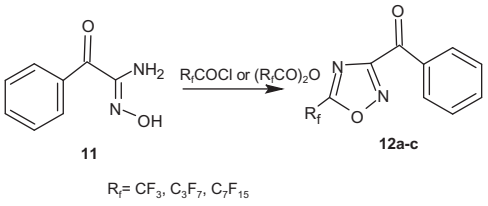


Reagents and conditions: i) MeCN, 1h ambient temp.; ii) 0 ^{0}C, Et_3N; iii) SO_2 in MeCN, ambient temp.; iv) dioxane, HMPA, BzlCl, K_2CO_3, reflux for 3.5h; v) $CHCl_3$, $SOCl_2$,reflux for 1h; vi)CH_2Cl_2, Bobbitt's reagent; vii) THF, -40 ^{0}C, K^+-N(TMS)$_2$, ambient temp.; viii) -40 ^{0}C, ambient temp. for 90 min. ix) DCM, -78 ^{0}C, 1M BBr_3

Scheme 1



Scheme 2

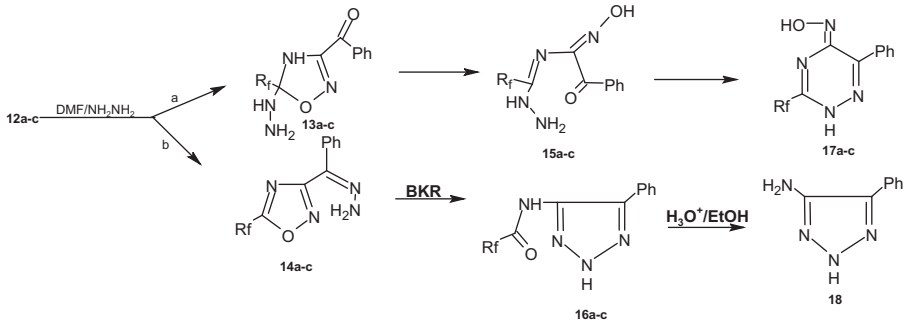


Scheme 3

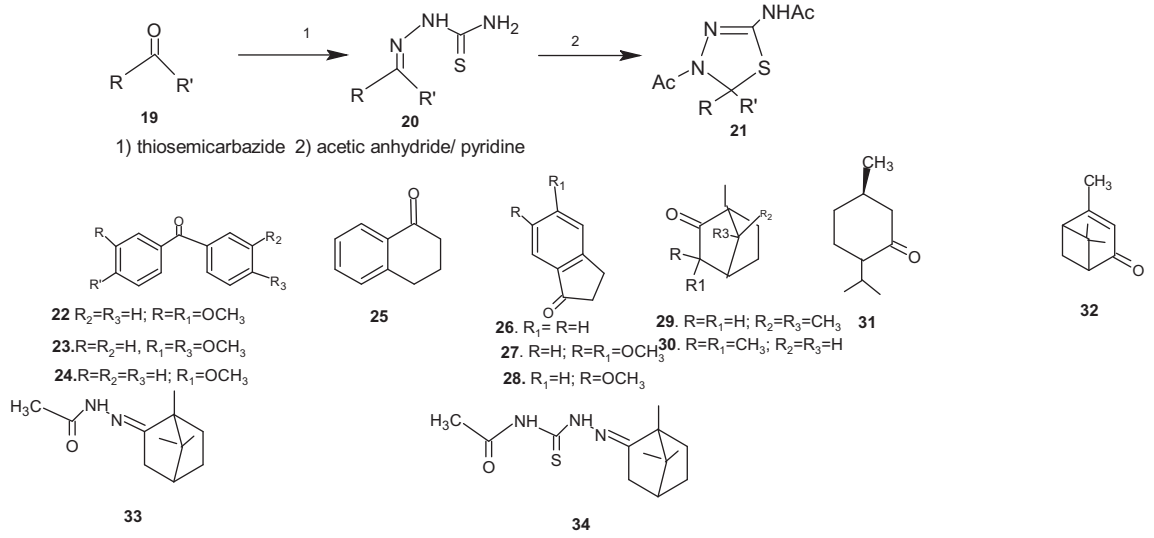
cal/pharmacologically active compounds. Five membered aromatic systems having three heteroatoms at the symmetrical positions have been studied because of their interesting physiological properties (Hetzhein and Mockel, 1996). In the recent decades, the synthesis of substituted thiadiazolines (Wilkins, 2008; Shih and Wu, 2005; Ogurtsov et al., 2005) and related compounds has attracted considerable attention because these compounds constitute the structural frameworks of several naturally occurring alkanoids that show a wide range of pharmaceutical and industrial importance (Kornis, 1996). The technological uses of these compounds include dyes, optically active liquid crystals and photographic materials. Thiadiazolines, thiadiazoles and oxadiazolines possess a wide range of biological properties and they act as anthelmintics (Chen and Xiao, 2004; Xiong et al., 2002; Wang et al., 2003), antihypertensive (Oh et al., 2002), antitumour (Ilies et al., 2003; Masereel et al., 2002; Supuran and Scozzafava, 2000), analgesic, anticancer, anti-inflammatory and antibacterial (Amir and Shikha, 2004; Demirbas et al., 2004; Palaska et al., 2002; Holla et al., 2002; Awad and El Ashry, 1998), tyrosinase inhibitory activity (Khan et al., 2005). The macrocycles containing thiadiazoline and thiadiazole subunits are found to be interesting host guest complexation characteristics (Bradshaw et al., 1990) and also exhibit antibacterial activities (Collier et al., 2000; Elizabeth et al., 2003; Jian et al., 2008; Huang et al., 2002). Some synthetic routes for the synthesis of 1,2,3-thiadiazolines had been reported in literature (Vasiliy and Wim, 2004).

2. Discussion

The compounds **8** bearing two symmetrical 1,2,5-thiadiazole (Philipp et al., 2004) ligands had been synthesized (Scheme 1) in order to investigate the co-ordination catalyst for the co-



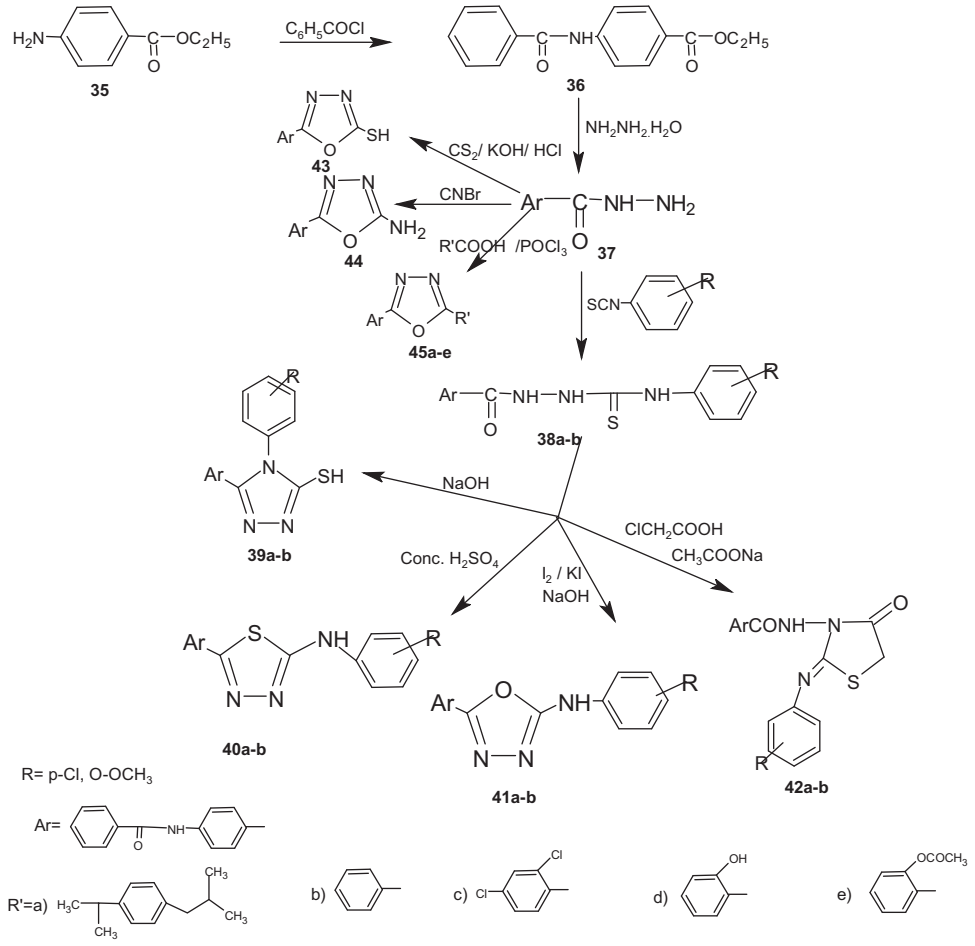
Scheme 4



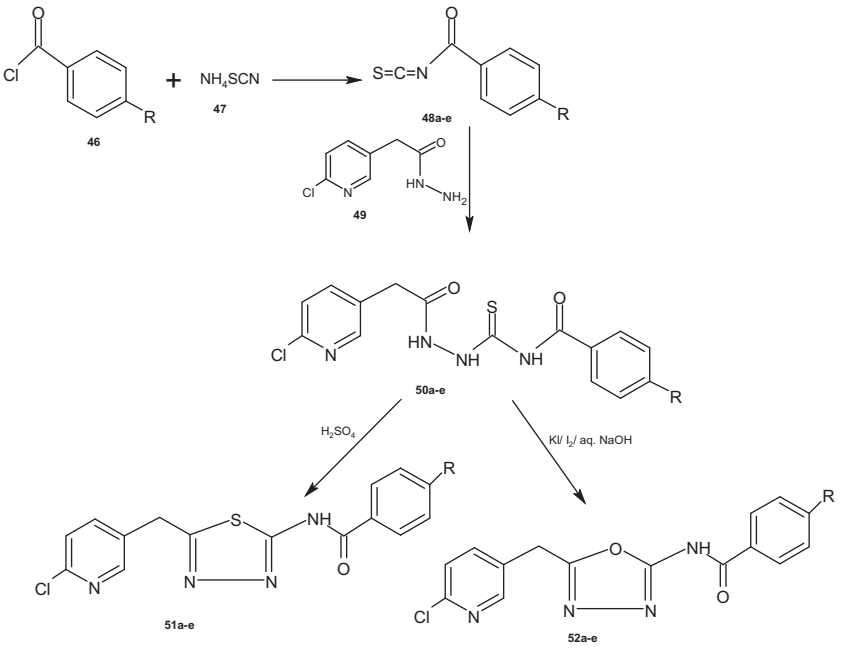
Scheme 5

polymerization of polar monomer (such as vinyl chloride and vinyl acetate) with ethylene. Here major investigations had been carried out on the complexes of transition metals with heterocyclic ligands **8**.

The reaction of 3-benzoyl-5-perfluoroalkyl-1,2,4-oxadiazoles **12a–c** with hydrazine had been initiated via the electrophilic C-5 addition of later on 1,2,4-oxadiazole ring (Buscemi et al., 2005), followed by ring opening and ring closure with enlargement to yield *Z*-oximes of 3-perfluoroalkyl-6-phenyl-2*H*-1,2,4-triazin-5-ones **17a–c** as the major products of reaction under the mild experimental conditions (Scheme 4). In turn, the hydrazine can also



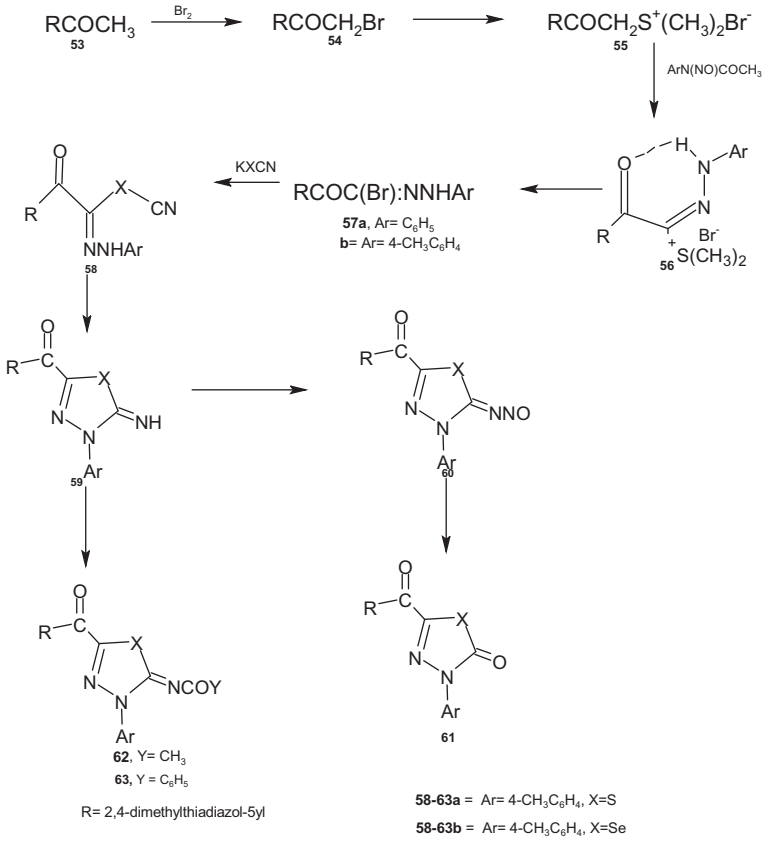
Scheme 6



Scheme 7

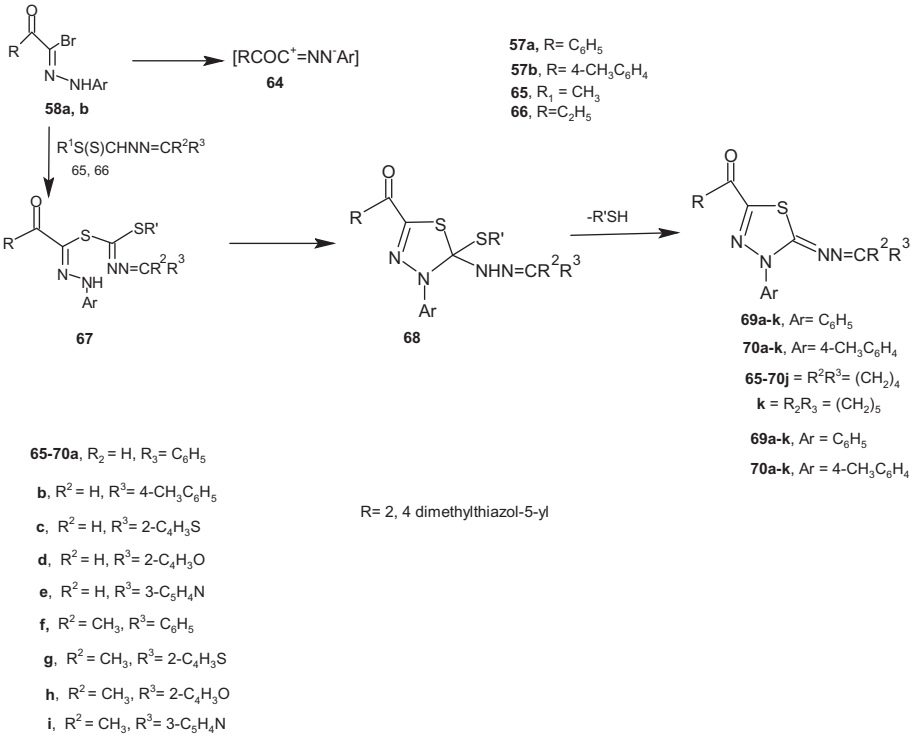
attack upon the carbonyl carbon giving 4-perflouro-acylamino-5-phenyl-2*H*-1,2,3-triazoles **16a–c** through the well-known Boulton–Katritzky rearrangement of the intermediate hydrazones (Schemes 3 and 4). Five membered oxadiazoles **9** react with hydrazine to provide six membered compound **10** (Scheme 2).

The researches are also carried out on the synthesis and biological activities of thiosemicarbazone **20** and thiadiazolines

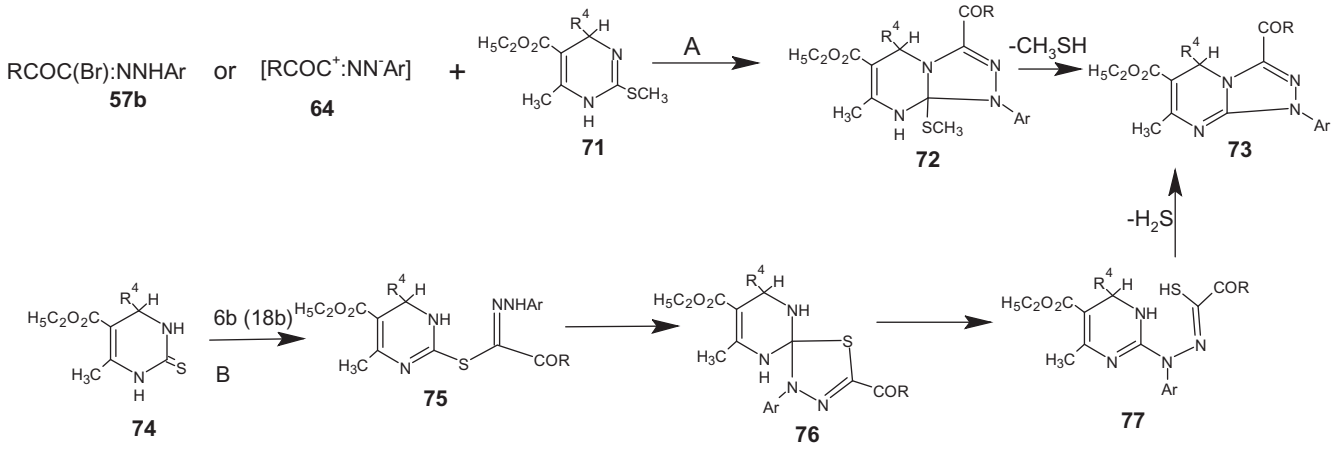


Scheme 8

(Brousse et al., 2004) **21** (Scheme 5). It had been observed that thiosemicarbazone have stronger activity than thiadiazoline and thiosemicarbazone of aromatic ketones **22–25** and indanones **26–28** were associated with interesting antifungal



Scheme 9



71-77a, $R^4 = C_6H_5$

b, R^4= 4-FC_6H_4

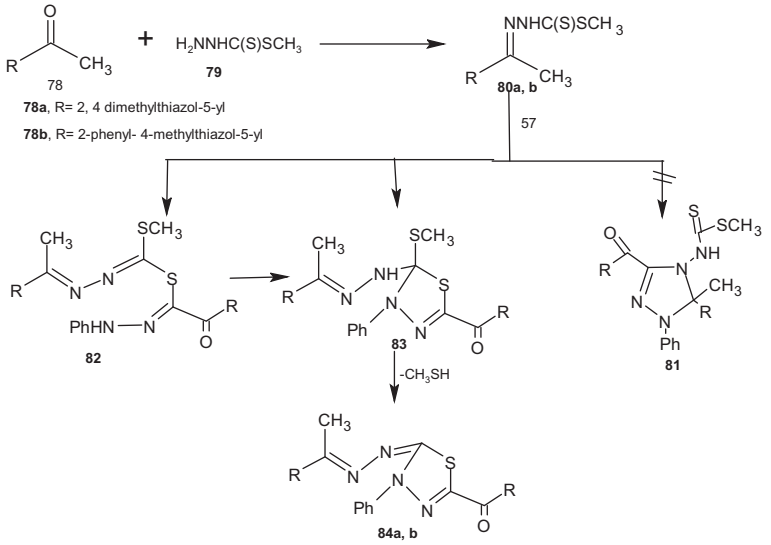
c, R^4= 3-BrC_6H_4

d, R^4= 2-C_4H_3S

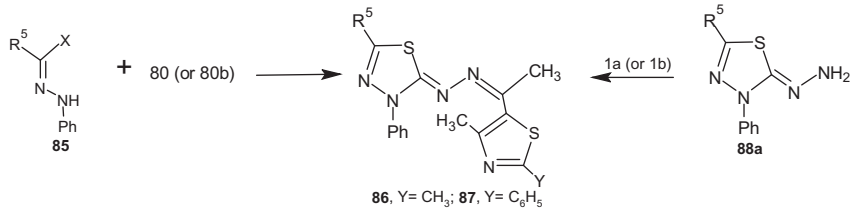
e, R^4= 4-$(CH_3)_2CHC_6H_4$

f, R^4= piperonylidene

Scheme 10



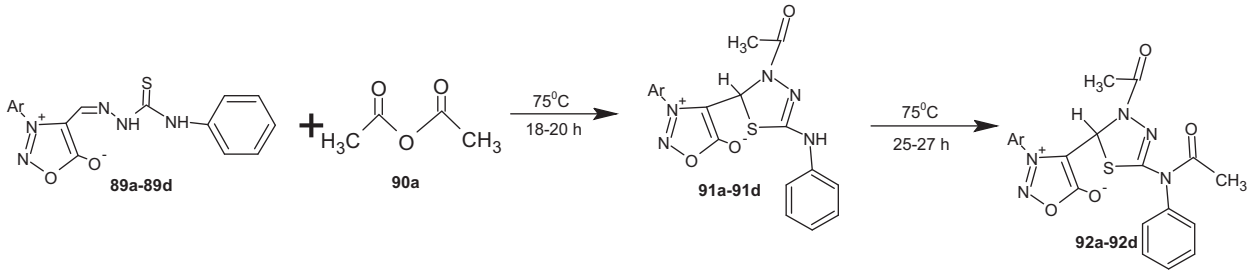
Scheme 11



85a, R^5= $CO_2C_2H_5$, X=Cl; **85b**, R^5= C_6H_5NHCO, X=Cl, **85c**, R^5=$COCH_3$, X=Cl, **85 d**, R^5=C_6H_5CO, X=Br

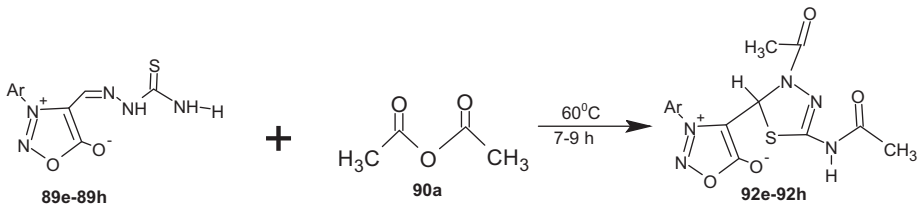
86-88a, R^5= $CO_2C_2H_5$; **b**, R^5= C_6H_5NHCO; **C**, R^5= $COCH_3$; **d**, R^5= C_6H_5CO

Scheme 12



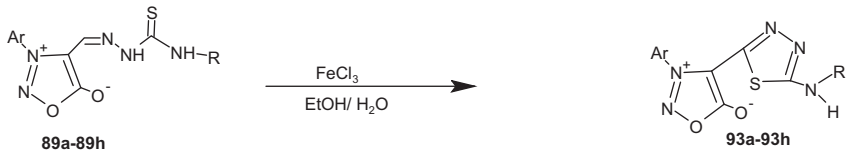
89a, 92a: Ar=C_6H_5; 89b, 92b: Ar= p-$CH_3C_6H_4$; 89c, 92c: Ar= p-$CH_3OC_6H_4$; 89d, 92d: Ar= p-$C_2H_5OC_6H_4$

Scheme 13



89e, 92e: Ar=C_6H_5; 89f, 92f: Ar= p-$CH_3C_6H_4$; 89g, 92g: Ar= p-$CH_3OC_6H_4$; 89h, 92h: Ar= p-$C_2H_5OC_6H_4$

Scheme 14

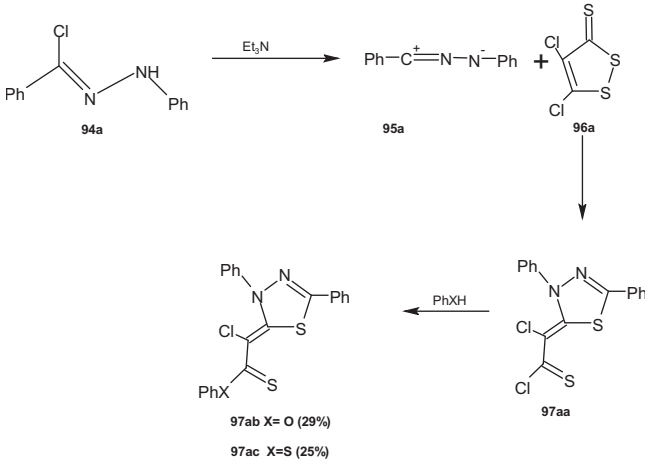


89a-89h

93a-93h

89a, 89e: Ar=C_6H_5; 89b, 89f: Ar= p-$CH_3C_6H_4$; 89c, 89g: Ar= p-$CH_3OC_6H_4$; 89d, 89h: Ar= p-$C_2H_5OC_6H_4$; 89a-89d: R=C_6H_5; 89e-89h: R=H

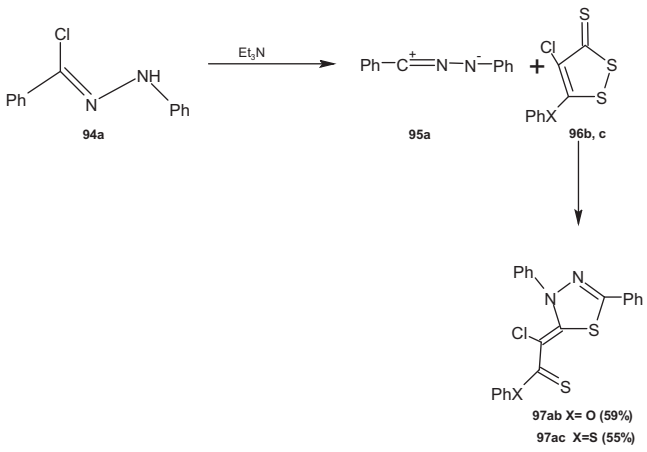
Scheme 15



94a 95a 96a 97aa

97ab X= O (29%)
97ac X=S (25%)

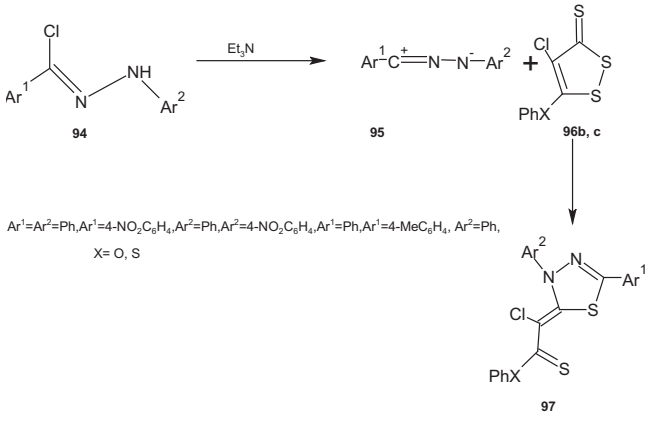
Scheme 16



94a 95a 96b, c

97ab X= O (59%)
97ac X=S (55%)

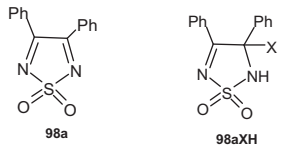
Scheme 18



94 95 96b, c 97

Ar^1=Ar^2=Ph,Ar^1=4-$NO_2C_6H_4$,Ar^2=Ph,Ar^2=4-$NO_2C_6H_4$,Ar^1=Ph,Ar^1=4-MeC_6H_4, Ar^2=Ph,
X= O, S

Scheme 17



98a 98aXH

X= RO, RS, ArNH, RC(O)NH, ArC(O)NH, NEt_2

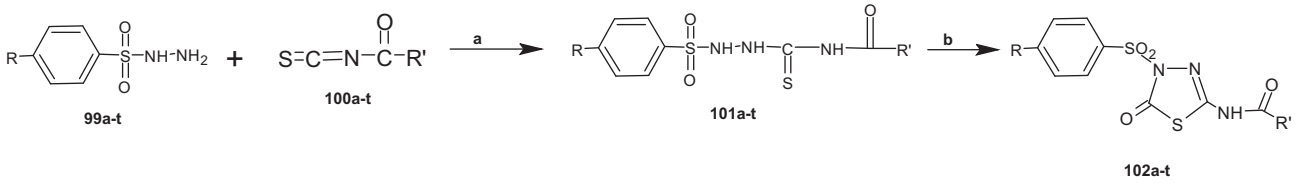
Scheme 19

activity. The terpenones based thiosemicarbazones **29–32** showed activity against the large numbers of bacteria than the aromatic derivatives **22–28**.

Amir et al. (2004) have studied the synthesis and antibacterial/anti-inflammatory examinations of new trizoles **39a–b**, thiadiazoles **40a–b,** oxadiazoles **41a–b** and 4-thiazolidinone derivatives **42a–b** (Scheme 6). It was observed that in oxadiazole derivatives, the maximum activity (72.34%) was shown by compound **45a** having a α-methyl-4-isobutyl benzyl group at position 2 but the replacement of this group by a simple phenyl group lead to a sharp decrease in the activity (22.34%). When phenyl group is replaced by mercapto group as in **43**, 2′-hydroxy phenyl group as in **45d** and 2′-acetoxyphenyl group as in **45e** then activity was found to be increased. When these groups are further replaced by 2,4-dichlorophenyl as in **45c** and amino groups as in **44** the activity was found to be decreased. On the basis of these results it was concluded that alkyl substituted phenyl rings were more preferable for the anti-inflammatory behaviours.

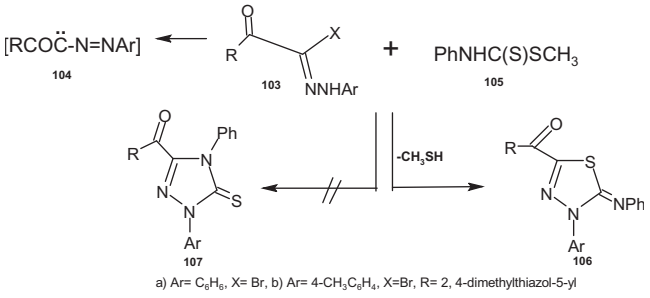
The reaction (Holla et al., 2004) of 2-chloropyridine-5-acetic hydrazide **49** with aroyl isothiocyanates **48a–e** yielded 4-aroyl-1-(2-chloropyridine-5-acetyl)thiosemicarbazides **50a–e**. The cyclization of later with conc. sulfuric acid and I_2 + KI afforded 2-chloro-5-(5-aroylamino-1,3,4-thidiazol-2-yl-methyl)-pyridines **51a–e** and 2-chloro-5-(5-aroylamino-1,3,4-oxadiazol-2-yl-methyl)pyridines **52a–e,** respectively as the final heterocyclic products (Scheme 7).

Some of new compounds like thiadiazolines **69** and **70**, seleniumdiazolines **60b–63b** and triazolino[4,3-*a*]pyrimidines **73** (Abdelhamid et al., 2004) have been obtained in the past starting from 3-aza-[2,4-dimethyl(1,3-thiazol-5-yl)-2-bromo-3-substituted-amino]prop-2-en-1-one under the reaction condition as shown in Schemes 8–12.



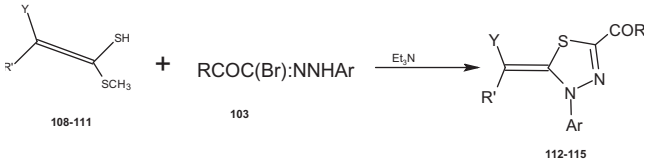
Reagents and Conditions: a) THF anhyd, rt, 3 days; b) CH3COONa anhyd, posgene, THF anhyd, 12h, rt

Scheme 20



a) Ar= C_6H_5, X= Br, b) Ar= 4-$CH_3C_6H_4$, X=Br, R= 2, 4-dimethylthiazol-5-yl

Scheme 21

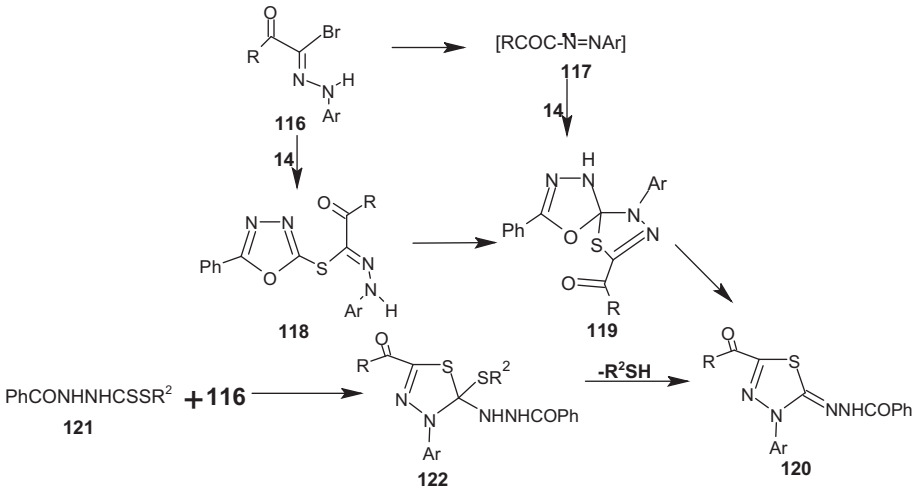


Scheme 22

Shih and Wu (2005) have studied the reaction of thiosemicarbazones **89a–d** with acetic anhydride **90a** in the presence of ferric chloride to give 4-acetyl-2-phenylamino-5-(3-arylsydnon-4-yl)-4,5-dihydro-[1,3,4]thiadiazoles **91a–d** and 4-acetyl-2-(*N*-phenylacetamido)-5-(3-arylsydnon-4-yl)-4,5-dihydro[1,3,4]thiadiazoles **92a–d** (Scheme 13). However under similar conditions thiosemicarbazones **89e–h** produced only 4-acetyl-2-acetamido-5-(3-arylsydnon-4-yl) 4,5-dihydro-[1,3,4]thiadiazoles **92e–h** in high yield (Scheme 14). The sydnonyl-substituted thiadiazole derivatives **93a–h** were also prepared successfully by the cyclization of 3-aryl-4-formylsydnone thiosemicarbazone **89a–h** in the presence of ferric chloride (Scheme 15). The cyclization reaction of thiosemicarbazones **89a–d** could occur easily than thiosemicarbazones **89e–h**.

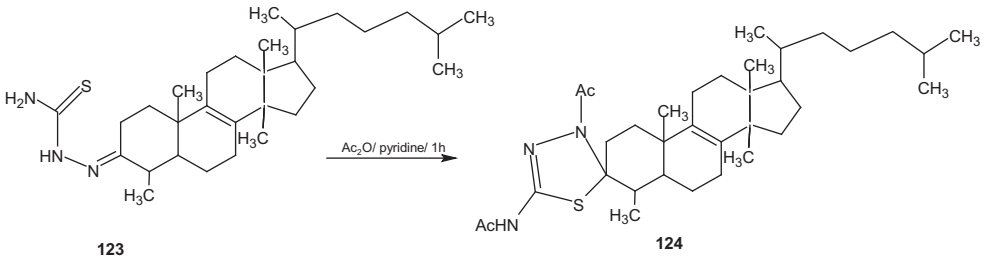
Ogurtsov et al. (2005) prepared 1,3,4-thiadiazolines **97** of 1,2-dithiole-3-thiones (Schemes 16–18). The thiocarbonyl group of 4,5-dichloro-1,2-dithiole-3-thione reacts as a dipolarophile towards dicarbonyl nitrile imines by 1,3-dipolar cycloaddition followed by opening of the dithiole ring with loss of sulfur to give 5-methylene-1,3,4-thiadiazolines. This reaction together with nucleophilic displacement of the selectively reactive 5-chloro group provides a rapid access to stable 5-methylene-1,3,4-thiadiazolines. Here compound **97aa** was obtained by 1,3-dipolar cycloaddition followed by the loss of sulfur, but it was too unstable to be isolated. The reaction of **95a** and **94a** with triethylamine in benzene solvent at room temperature followed by addition of phenol or thiophenol led to the formation of thiadiazolines **97ab** and **97bc**, (X = O and S) in low yields.

The reactions (Caram et al., 2006) of *n*-butylamine, 2-aminoethanol, diethylamine and phenylhydrazine with **98a** were studied by cyclic voltammetry. The course of the reactions was dependent on the nucleophile-substrate combination: Et_2NH added to **98a**, forming the

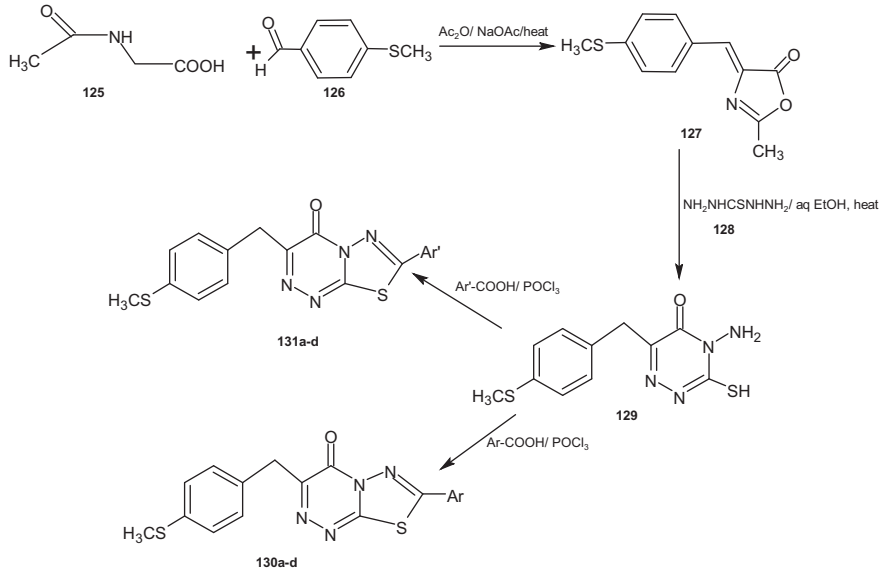


R=2,4-dimethylthiazol-5yl, 14=5-phenyl-1,3,4-thiadiazol-2-thione, a) Ar=C_6H_5, b) Ar= 4-C_6H_4

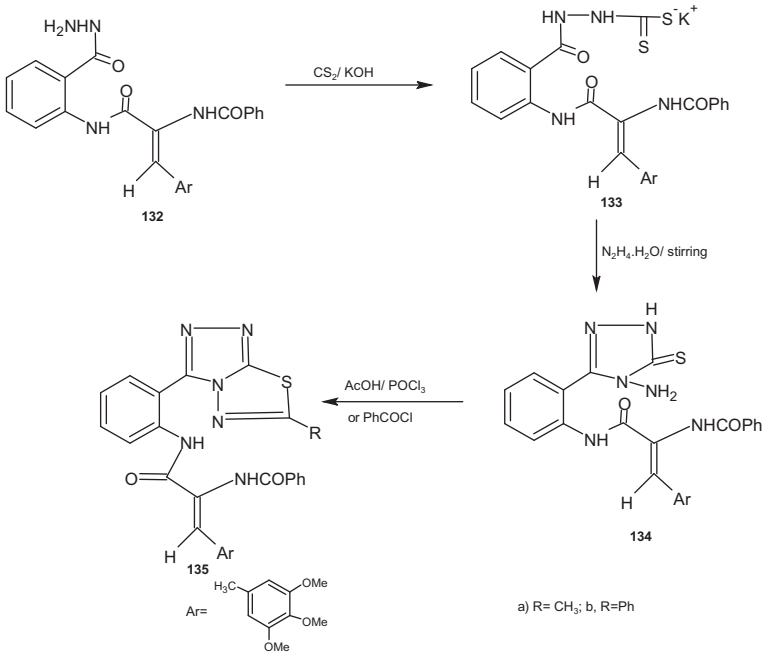
Scheme 23



Scheme 24



Scheme 25



Scheme 26

corresponding thiadiazolines in an equilibrium mono addition reaction. The equilibrium constants were evaluated and compared. With primary amines and PhN_2H_3, the nucleophile added to both C=N double bonds of **98a** and displayed the sulfamide moiety. $BuNH_2$ and $H_2N(CH_2)_2OH$ reacted with **98a** to give bis-imines, while **98a** with PhN_2H_3 gave the α-bis-hydrazone (Scheme 19). The configuration of benzil-bis(ethanolamine) and benzilosazone were determined by single X-ray diffraction analysis as Z, Z.

The synthesis of new 1,3,4-thiadiazole (Schenone et al., 2006) **102** derivatives endowed with analgesic and anti-inflammatory activities have been reported. Two series of *N*-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides **102a–t** (Scheme 20) were synthesized and tested in vivo for their analgesic and anti-inflammatory activities. All the new compounds were found to exhibit good analgesic action and some compounds also showed fair anti-inflammatory activity in the carrageenan rat paw oedema test. Ulcerogenic and irritative action on the gastrointestinal mucose, in comparison with indomethacin was observed to be low.

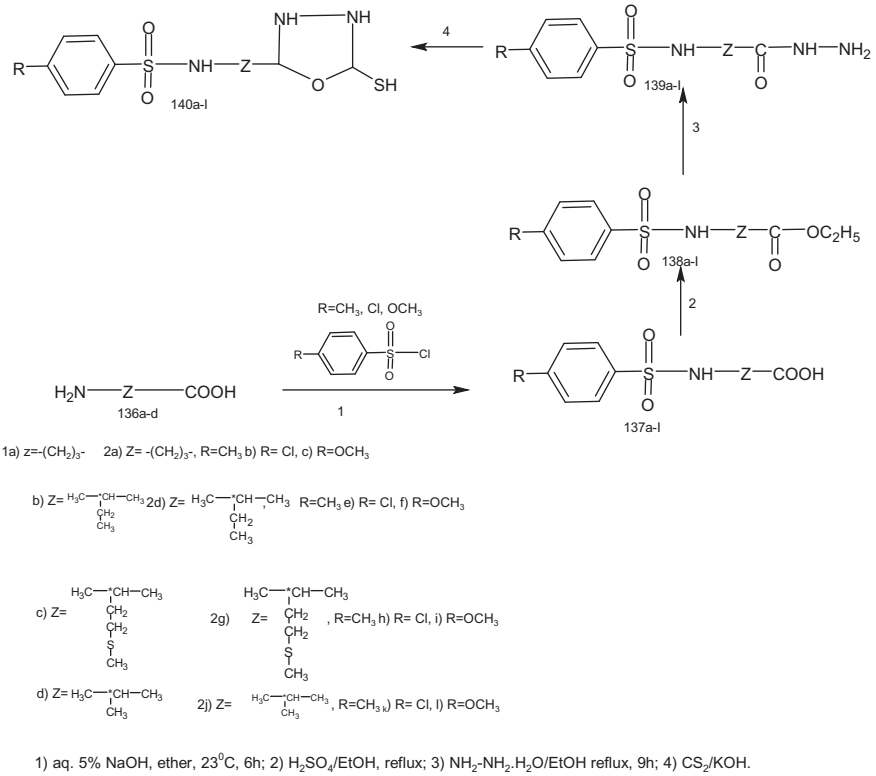
Zaki et al. (2006) have prepared 2,3-dihydro-1,3,4-thiadiazoles **112–115** and **120**, in good yields from the reactions of hydrazonoyl halides with alkyl carbodithioates, pyrimidine-2-thione and substituted prop-2-ene-1-one, respectively (Schemes 21–23). Some of these compounds were also tested against the bacteria and fungi strains.

Mazoir et al. (2006) synthesized some steroidal based spirocyclic thiadiazolines under the ordinary conditions as shown in Scheme 24.

The heterocyclic derivatives (Mithun and Holla, 2007) 7-(substituted aryl/aryloxy methyl-3-(4-methylthiobenzyl)-4*H*-1,3,4-thiadiazolo [2,3-*c*]-1,2,4-triazin-4-ones **130a–d** and **131a–d** were prepared by reacting 4-amino-6-(4-methylthiobenzyl)-3-mercapto-1,2,4-triazin-5(4*H*)-one **129** with substituted benzoic acids/aryloxy acetic acids in the presence of phosphorus oxychloride. 4-Amino-6-(4-methylthiobenzyl)-3-mercapto-1,2,4-triazin-5(4*H*)-one **129** was prepared by reacting 4-(4-methylthiobenzylidene)-2-methyl-oxazol-5-one(3) with thiocarbohydrazide **128** by refluxing in aq. EtOH (Scheme 25). The antibacterial and antifungal activities were carried out for **130a–d** and **131a–d** and all the tested compounds were possessing moderate activity for both microbes.

The treatment of **132** with carbon disulfide in the presence of potassium hydroxide resulted in the formation of 1,3,4-thiadiazole (Mahmoud et al., 2007) **135** (Scheme 26).

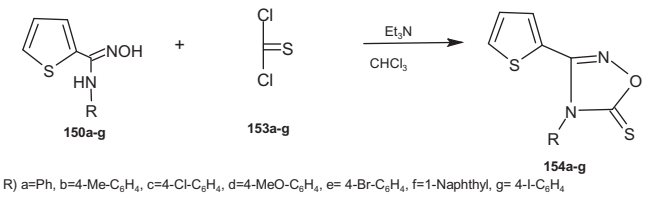
The literature (Zareef et al., 2007) also describes the synthesis of a series of novel chiral and achiral *N*-[1-(1,3,4-oxadiazol-2ylthiol alkyl]-4-methyl/chloro/methoxy benzenesulfonamides **140a–l** (Schemes 27 and 28). These compounds were prepared by the reaction of 4-[4-methyl, chloro, methoxyphenylsulfonamido) alkyl carboxylic acid hydrazides **139a–l** with CS_2 and KOH. Another series of new secondary benzenesulfonamides **145a–j** and bis-benzenesulfonamides **146a–j** have also been synthesized by a new approach using Et_3N and dimethylaminopyridine. The compounds **136a–d** were converted into their corresponding sulfonamides **137a–l**. Esterification of **137a–l** with ethanol in an acidic medium afforded esters **138a–d** and reaction of later with 80% hydrazine hydrate furnished hydrazides **139a–l** in good yields. The products **140a–l** were then prepared by the reaction of hydrazides **139a–l**. The hydrazides **141a–e** were converted into **142a–e** by treatment with 4-nitrobenzoylchloride in dry MeCN. Compounds **142a–e** were subjected



Scheme 27

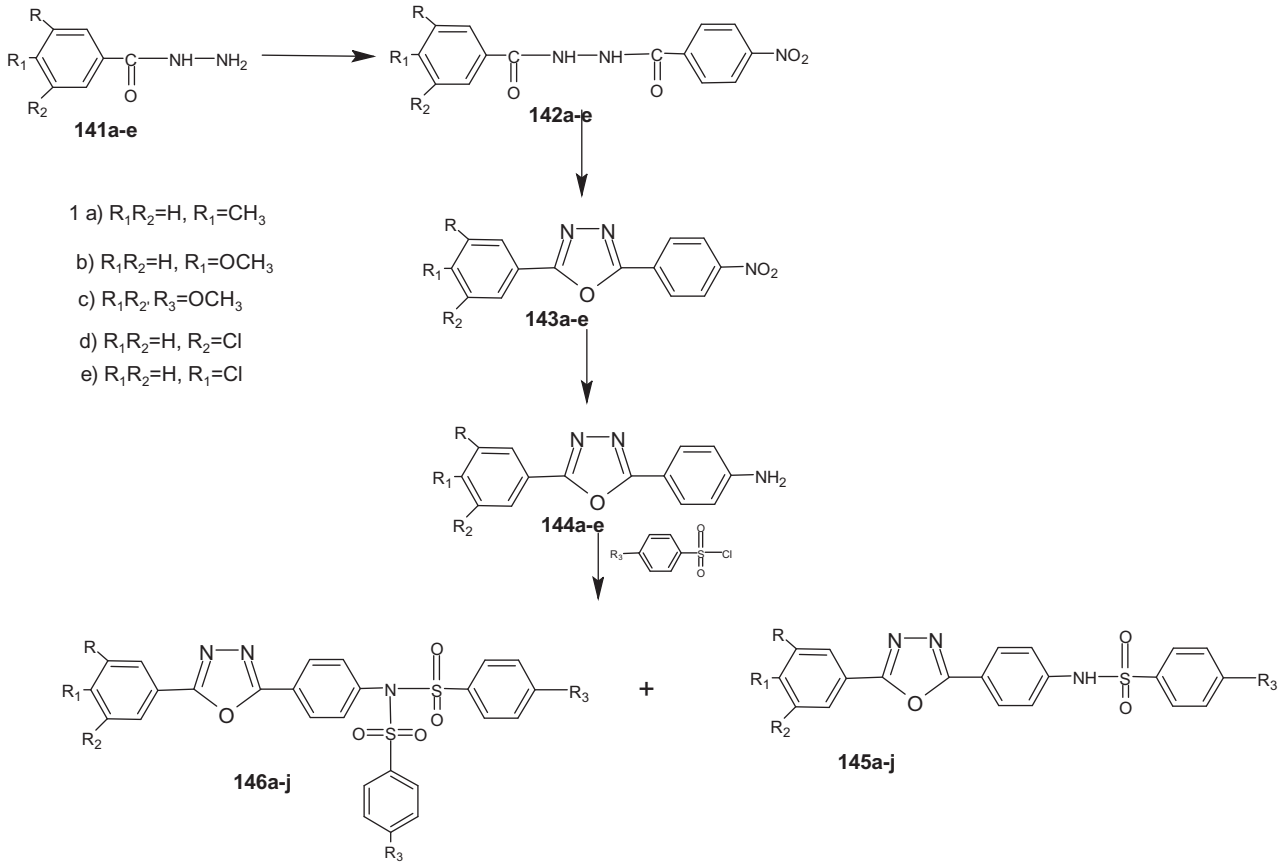
to dehydrative cyclization in the presence of thionyl chloride to give **143a–e**. The reduction of **143a–e** with Pd/C and hydrazine hydrate produced **144a–e** in good yields. The treatment of **144a–e** with Et_3N and dimethylaminopyridine furnished the sulfonamides **145a–e** and **146a–e** (Scheme 28). The prepared compounds were also checked for their anti-HIV activity.

Twenty one new thiophene substituted 1,2,4-oxadiazol-5(4*H*)-ones (Durust et al., 2007) **152a–g**, 1,2,4-oxadiazol-



R) a=Ph, b=4-Me-C_6H_4, c=4-Cl-C_6H_4, d=4-MeO-C_6H_4, e= 4-Br-C_6H_4, f=1-Naphthyl, g= 4-I-C_6H_4

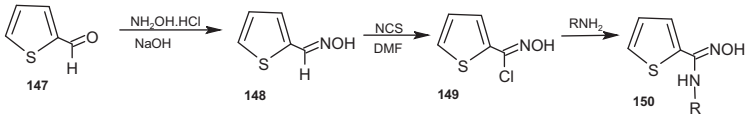
Scheme 30



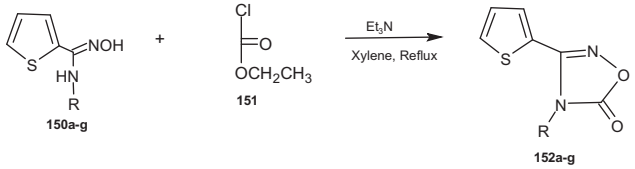
Conditions: 1) p-NO_2-PhCOCl, CH_3CN, 23 ^{0}C, 6h; ii) $SOCl_2$, reflux, 2h; iii) Pd/C, ethanol, reflux, 9h;

iv) Et_3N, DMAP, $CHCl_3$, 70^0 C, reflux, 11h

Scheme 28

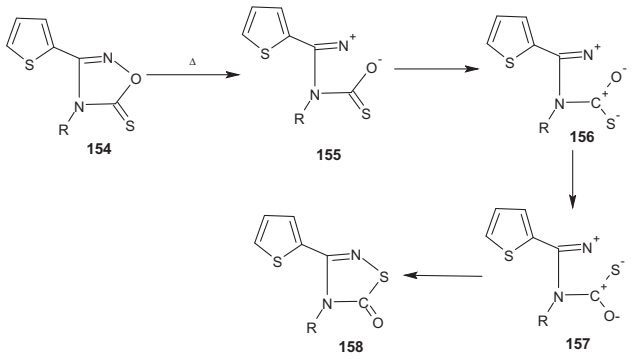


R) a=Ph, b=4-Me-C_6H_4, c=4-Cl-C_6H_4, d=4-MeO-C_6H_4, e= 4-Br-C_6H_4, f=1-Naphthyl, g= 4-I-C_6H_4

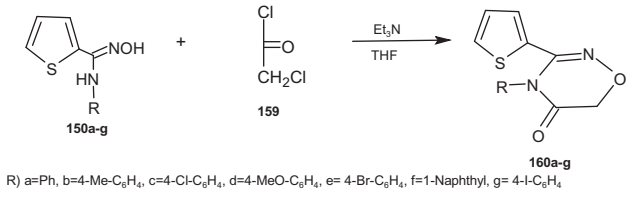


R) a=Ph, b=4-Me-C_6H_4, c=4-Cl-C_6H_4, d=4-MeO-C_6H_4, e= 4-Br-C_6H_4, f=1-Naphthyl, g= 4-I-C_6H_4

Scheme 29



Scheme 31



Scheme 32

5(4*H*)-thiones **154a–g** and 1,2,4-oxadiazin-5(6*H*)-ones **160a–g** were synthesized by the reaction of thiophene ring substituted amidoximes with ethyl chloroformate, thiophosgene and chloroacetylchlorine, respectively according to the protocol as described in Schemes 29–32.

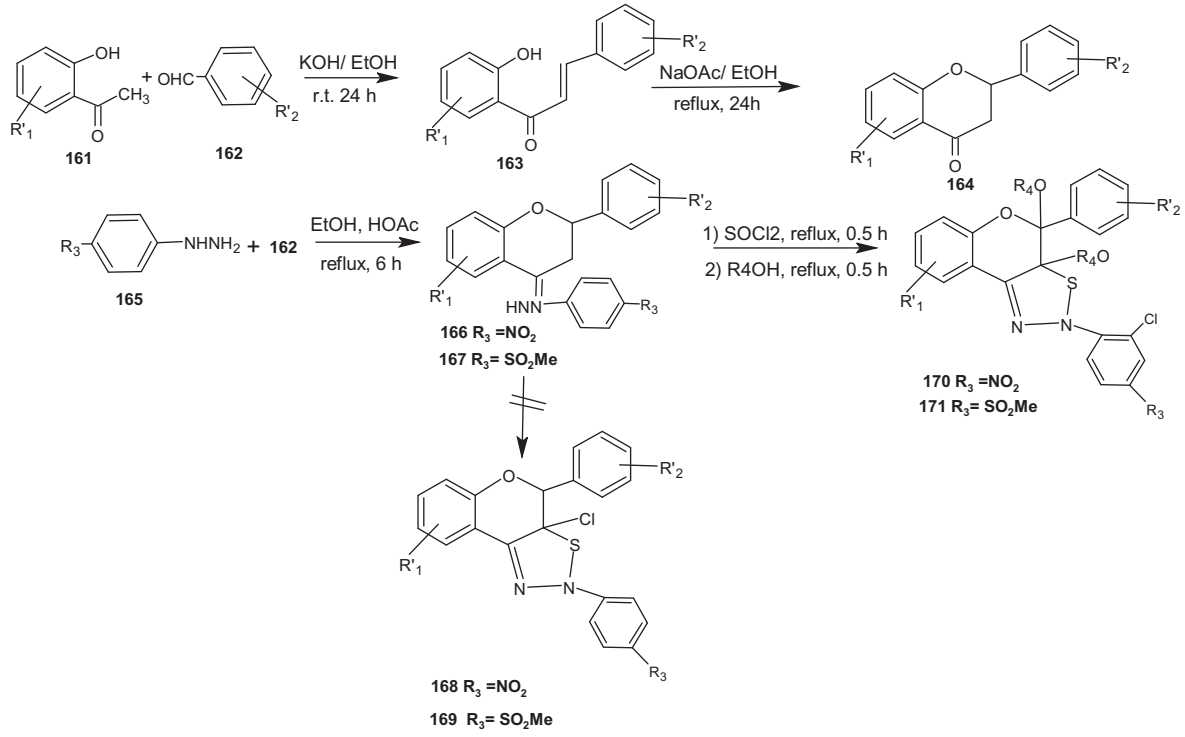
Ying et al. (2007) have investigated the synthesis of a series of flavanoid based thiadiazoline **170** and **171**. These heterocycles were synthesized by the cyclization of the corresponding 2-arylchroman-4-one-arylhydrazones **166** and **167** with $SOCl_2$ followed by treatment with alcohol (Schemes 33 and 34). The resulting compounds **170** and **171** were also examined for their antiproliferative activity in vitro against six human tumour cell lines and the derivative **171a** was found to have higher inhibitory effect upon the growth of tumour cell.

The spirocyclic oxadiazole (Islam and Mohsin, 2007) **179** were synthesized successfully starting from *p*-chloroaniline through the sequence of reactions as shown in Scheme 35.

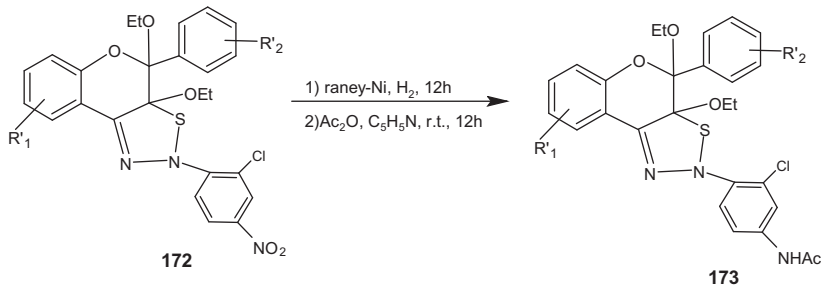
The cyclization (Li et al., 2007) reactions of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **181a–o** with hexanedioic acid in the presence of $POCl_3$ and $Bu_4N^+I^-$ as a catalyst provided 1,4-bis(3-aryl)-1,2,4-triazolo[3,4-*b*]–[1,3,4]thiadiazole-6-yl]butanes **182a–o** (Scheme 36). The compounds **182a–o** were screened for their anti-bacterial and compounds **182d**, **182n** and **182o** showed better antibacterial activity.

The inhibition activity on carbonic anhydrase I of some substituted thiadiazole and thiadiazoline-disulfonamides (Bolboala, and Jantschi, 2007) have been studied. The structure activity relationships based upon an original molecular descriptors family method has been developed and applied on a sample of substituted 1,3,4-thiadiazole and 1,3,4-thiadiazoline-disulfonamides. Forty compounds were studied for their inhibition activity on carbonic anhydrase I. The results revealed that the molecular descriptions family on structure activity relationships is a useful approach in the characterization of inhibition activity on carbonic anhydrase I of studied substituted 1,3,4-thiadiazole and 1,3,4-thiadiazoline-disulfonamides.

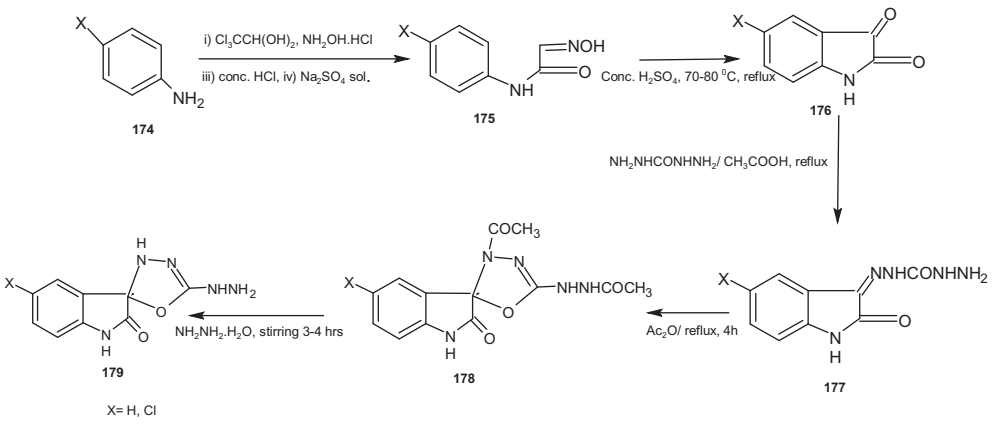
In order to investigate a better antimicrobial agent, 1,3,4-thiadiazoles (Banday and Rauf, 2008) **186a–d** bearing long alkenyl and hydroxyl-alkenyl chain have been synthesized



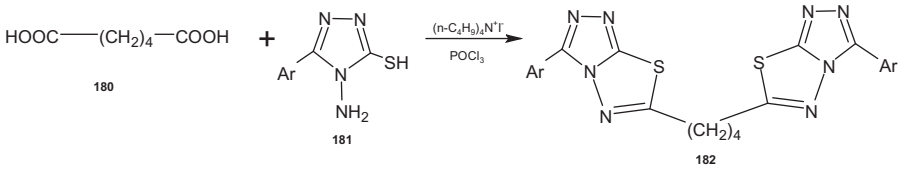
Scheme 33



Scheme 34



Scheme 35



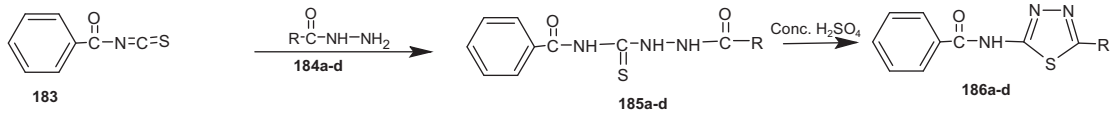
Ar=Ph, 2-Cl-Ph, 4-Cl-Ph, 3-CH_3-Ph, 3-CH_3-Ph, 3-Br-Ph, 4-Br-Ph, 2-I-Ph, 3-I-Ph, 4-I-Ph, 4-OCH_3-Ph, 4-pyridyl, 3-pyridyl

Scheme 36

(Scheme 37) and their antibacterial activity has also been examined.

Abdelhamid et al. (2008) have prepared 1,3,4-thiadiazolines containing a chromone moiety and 5-{1-[4-substituted-5-phenyldiazenyl)(1,3-thiazol-2-yl]-5-phenyl-2-pyrazoline-3-yl)}-4-methoxybenzo[*b*]-furan-6-ol. These compounds were prepared from the reaction of hydrazonoyl halide and alkyl carbodithioates and 5-[1-aminothiomethoxy)-5-phenyl-2-pyrazolin-3-yl)]-4-methoxybenzo[*b*]-furan-6-ol, respectively (Schemes 38–41).

Er et al. (2008) have investigated the cyclization reactions of new tetra-thiosemicarbazone. The tetra-aldehyde and ketone derivatives **205a–d** which were used in these syntheses were obtained via the reaction of ethane-1,1,2,2,tetra-yl-tetra-methylene-tetra-bromide with aldehydes and ketones. The

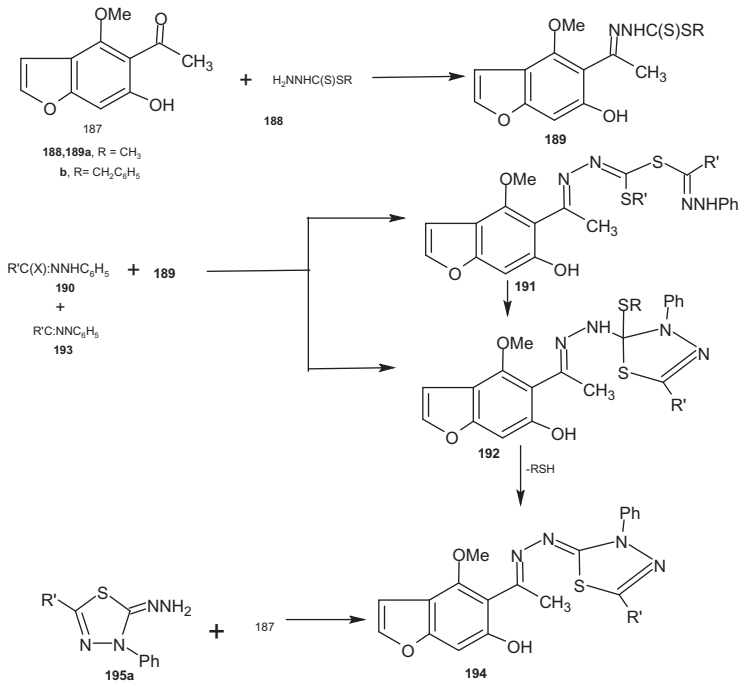


184a-186a $CH_2=CH(CH_2)_8$, **184b-186b** $CH_3(CH_2)_7CH=CH(CH_2)_7$

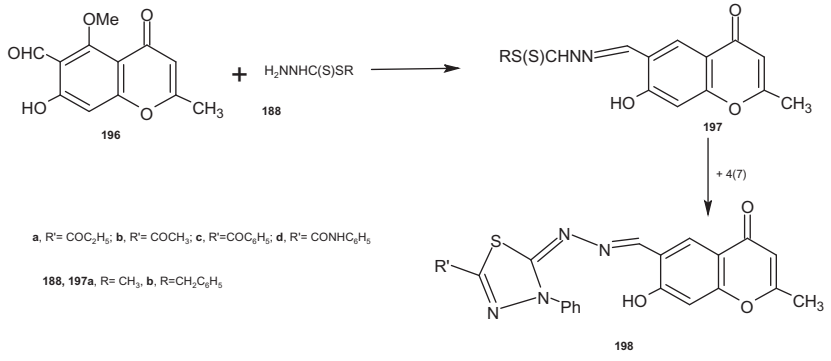
184c-186c $CH_3(CH_2)_5CH(OH)CH_2CH=CH(CH_2)_7$, **184d-186d** $CH_3(CH_2)_4CH=CH(CH_2)_2CH(OH)(CH_2)_7$

Scheme 37

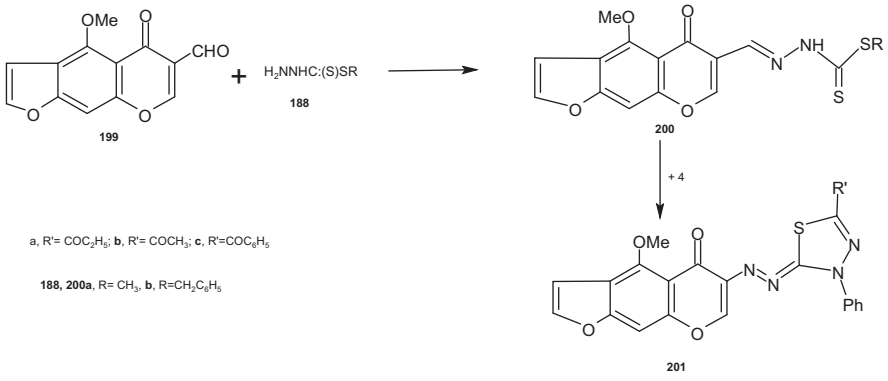
reactions of tetra-aldehydes and ketone derivatives **205a–d** with thiosemicarbazite and 4-methyl thiosemicarbazite led to the formation of **206a–h**. In the same way, tetra-4-methyl-5-ethoxycarbonyl 1-2,3-dihydro-1,3-thiazoles **207a–h** were synthesized via the reaction of tetra-thiosemicarbazone compounds **206a–h** with ethyl-2-chloroacetoacetate. Finally



Scheme 38



Scheme 39



Scheme 40

compounds **206a–h** were reacted with acetic-anhydride under refluxing to yield tetra-2-acetyl-amino-4-acetyl-4,5-dihydro-1,3,4-thiodiazol compounds **207a–d** and **208a–d** (Scheme 42).

The interaction of α,β-unsaturated ketones of furan series (Anis'Kov et al., 2009) with thiosemicarbazide under basic catalysis condition led to 3-furyl-2-thio-carbamoylpyrazolines and the intramolecular cyclization of thiosemicarbazones under conditions of acid activation of sulfurous nucleophile provided spirocyclic furylmethylene 1,3,4-thiadiazoline. These heterocycles are of potential biological activity and can be used in medicines.

The heterocyclization of **210a–d** under the acylation condition proceeded regioselectively to give 5-furfurylidene-1, 3,4-thiadiazoline including spirocyclic one. The use of basic catalysis in these reactions allows one to carry out region directed synthesis of *N*-thiocarbamoyl pyrazolines (Scheme 43).

A series of novel 2-(1-substituted-1,11-undecylidene)-5-aryl-imino-Δ-1,3,4 thiadiazolins (Jin et al., 2009) **218** had been synthesized and their solubility in polar and non polar solvents was significantly improved owing to the introduction of ethyl or methylthio group at cyclodecyl ring as compared with parent compounds [1,2-(1,11-undecylidene)-5-aryl imines-Δ-1,3,4-thiadiazolines] (Scheme 44). However their fungicidal activity against Rhizoctonia Solanu is less than that of parent compounds.

The [3 + 2] cycloaddition reaction (Jayashankar et al., 2009) of nitrile oxide with allyl alcohol followed by intramolecular 1,3-dipolar cycloaddition reaction of nitrile imine with carbonyl group could led to the formation of novel ether linked bis(heterocycles) (Scheme 45). These bisheterocycles were also tested for anti-inflammatory and analgesic activities and **225g** exhibited highest activity among the tested products **225a–e**.

The reaction of *trans*-1,4-dichloro-2-butene **226** with phenol afforded (*E*)-1,4-bis(aryloxy)-2-butene Er et al., 2009 **228a–d** which were converted into bis-thiosemicarbazones **229a–h** by reacting with thiosemicarbazide and 4-methyl thiosemicarbazide, respectively. Similarly, 4-methyl-5-ethoxycarbonyl-2,3-dihydro-1,3-thiazoles **231a–h** were synthesized via the reaction of bis-thiosemicarbazones **229a–h** with ethyl 2-chloroacetoacetate. *trans*-1,4-Dithiocyanato-2-butene **230** was obtained from the reaction of KSCN and *trans*-1,4-dichoro-2-butene **226**. Furthermore, the bis-2-amino-1,3,4-thiadiazoles **232k** and **I** were realized from the reaction of *trans*-1,4-dithiocyanato-2-butene **230** with thiosemicarbazide and 4-methyl thiosemicarbazide, respectively (Scheme 46). Finally the microbial activities of all the compounds **231a–h** were also determined.

The synthesis of some new heterocyclic compounds (Pawar et al., 2009) has been reported containing spiro-benzopyrans, thiadiazoles, selenadiazoles and thiadiazolines as the subunits (Scheme 47). The anti-microbial and anti-fungal analyses of the heterocycles have been carried out.

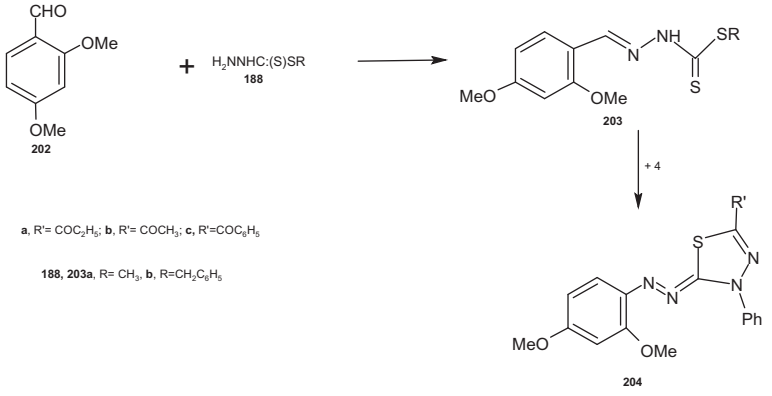
The condensation reaction of 4-amino-5-(aroyl)-4*H*-1,2,4-triazole-3-thiols **240a–b** or 2-amino-5-mercapto-1,3,4-thiadiazole with bis-aldehydes **239a–c** provided bis-schiff bases **241a–d** and **245a–c (**Foroughifar et al., 2009) which were further treated with dibromoalkanes to afford the new macrocycles **243a–f** and **247a–d,** respectively (Schemes 48 and 49).

Recently, multistep synthesis of the steroidal based thiadiazolone derivatives (Khan and Yusuf, 2009) has been reported. The target compounds **254–256** were obtained from the cyclization of thiosemicarbazones **251–253** with bromoethylacetate in dioxane medium. The later were prepared from the reaction of steroidal ketones **248c–250c** with thiosemicarbazones (Scheme 50). The antibacterial analysis of the compounds **254–256** showed that steroidal thiozolidinone derivatives are better in inhibiting the growth as compared to steroidal thiosemicarbazones.

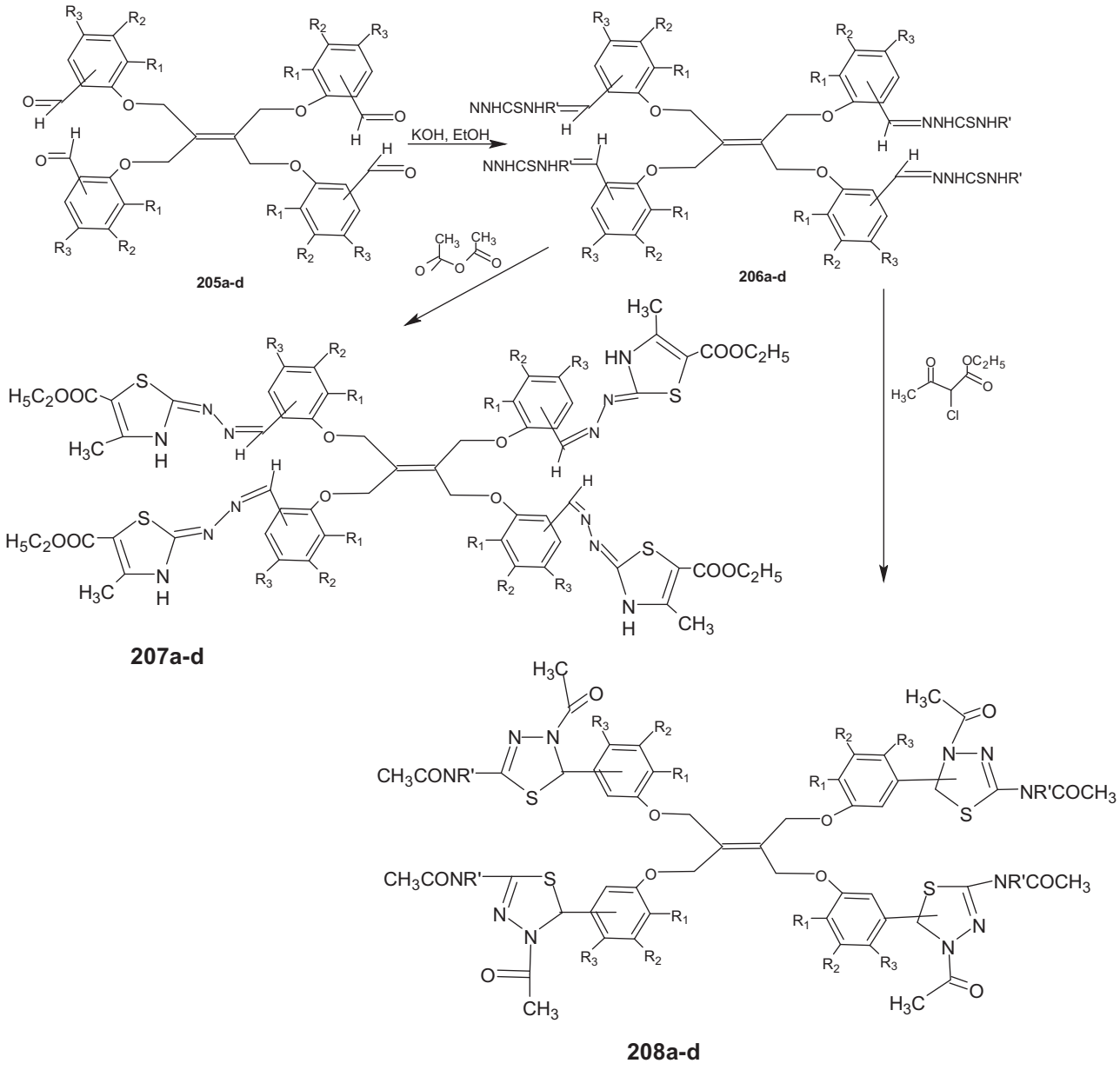
El-Sayed et al. (2009) have investigated the synthesis of a series of new disubstituted 2,5-thiazolidinone derivatives **260a–d**, **262a–d and 264a–d** (Scheme 51). The antimicrobial examination of these compounds has also been carried out against gram positive and gram negative bacteria strains and actinomycetes.

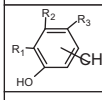
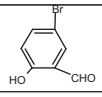
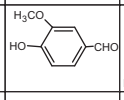
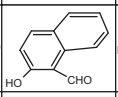
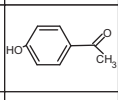
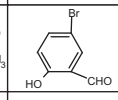
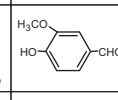
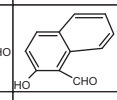
The 1,3,4-thiadiazoline (Umamatheswari and Kabilan, 2009) **267** had been obtained starting from 3-methyl-2,6-diphenyltetrahydrpopyran-4-one **265** which was treated with thiosemicarbazide to give **266.** The cyclization later with Ac_2O resulted in the formation of final product (Scheme 52). These results showed that the title compounds exist in chair conformation with equatorial orientations of phenyl group at C-2, C-6 methyl group at C-3 carbons and *N*-acetyl group of thiadiazoline moiety.

Some halogenated thiadiazoles and trizoles (Radhavane et al., 2010) were synthesized initially starting from acid hydrazine **268** under the conventional and ultra sound irradiation method (Scheme 53). These heterocyclic compounds **270** and **271** were also examined for their anti-microbial, antiviral and anti-oxidant activities.



Scheme 41

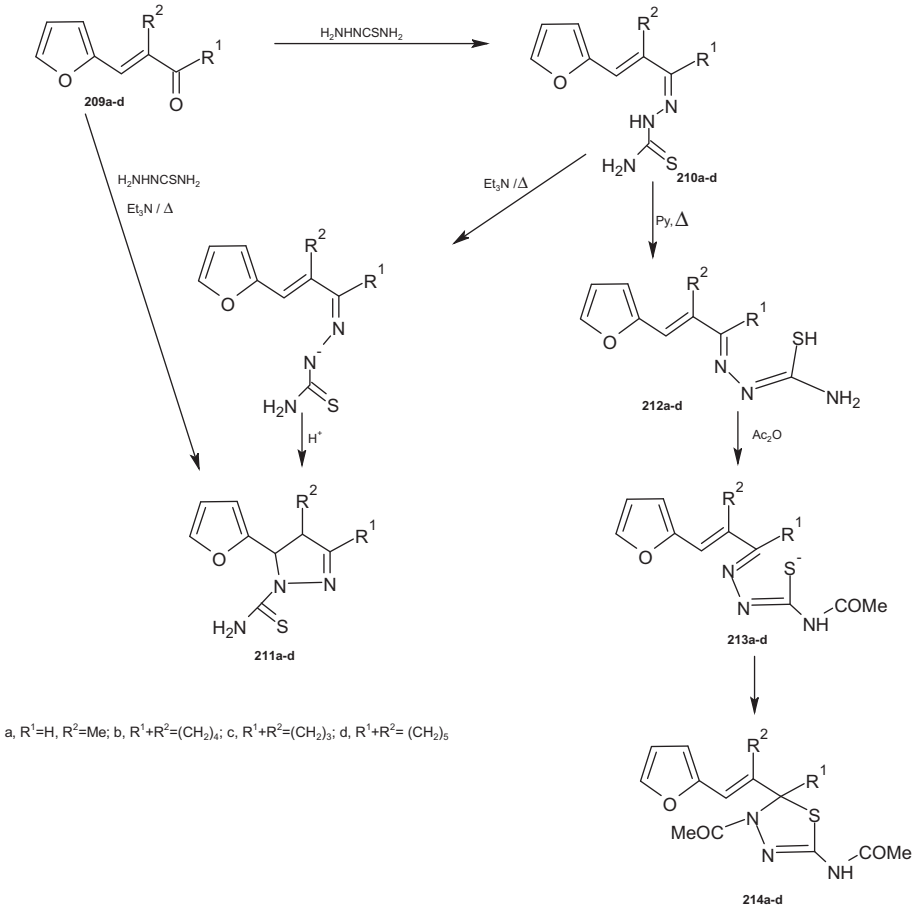


	a	b	c	d	e	f	g	h
								
R'	H	H	H	H	CH_3	CH_3	CH_3	CH_3

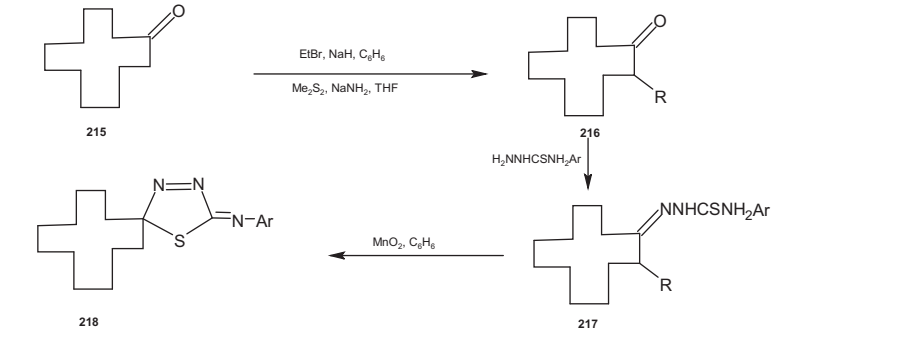
Scheme 42

A reaction of alkenoic acid hydrazides **272a–d** with phenylisocyanate and phenylthiocyanate yielded semicarbazides **273a–d** and thiosemicabazide (Farshori et al., 2010) **275a–d,** respectively, which were further refluxed with $POCl_3$ and Ac_2O to provide 1,3,4-oxadiazoles **274a–d** and thiadiazoles **276a–d,** respectively (Schemes 54 and 55). The anti-bacterial and anti-fungal analyses of the synthesized compounds have also been carried out.

A series of new 2-imino-5-[(*Z*)-1-(4-methylphenyl)methylidene]-3-[5-(2-oxo-2*H*-3-chromenyl)-1,3-oxazol-2-yl]-1,3-thiazolan-4-ones (Reddy et al., 2010) **281a–j** have been synthesized (Scheme 56) and assayed for their antibacterial activity.

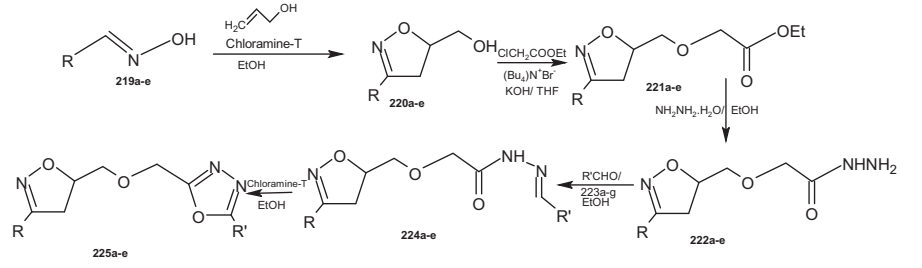


Scheme 43



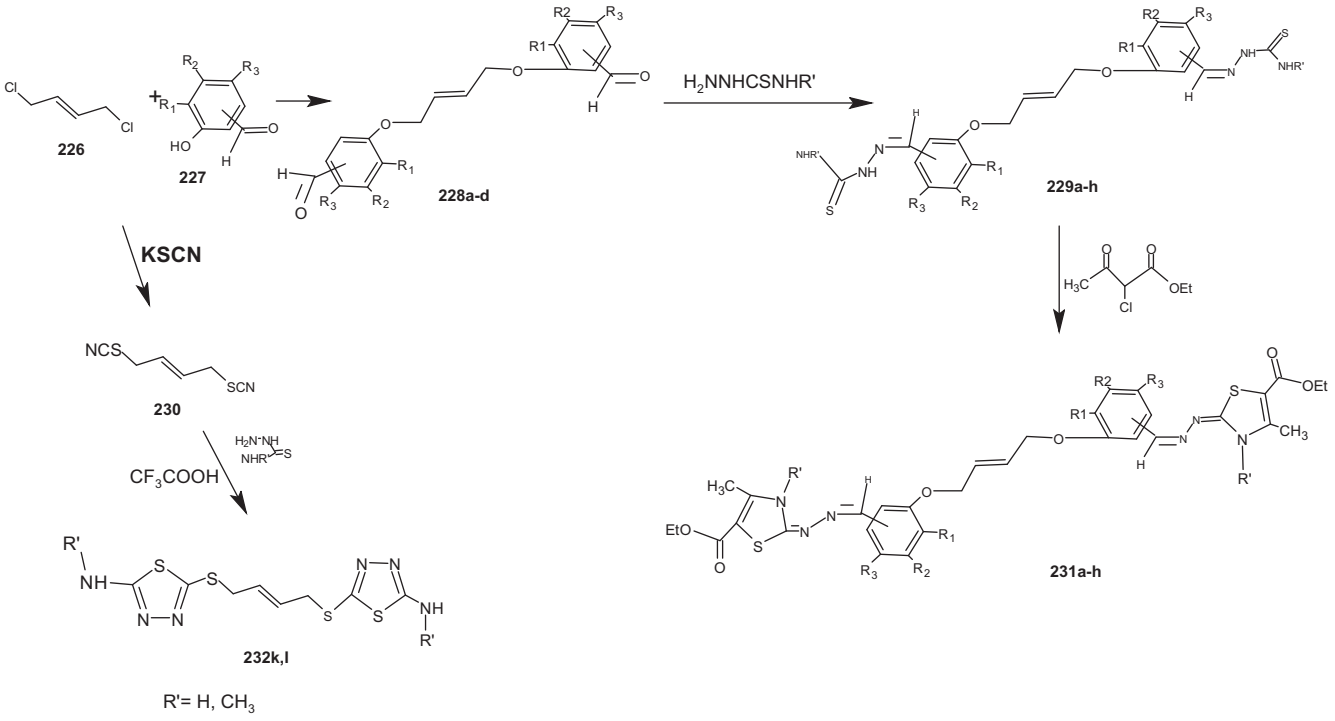
4a: R=Et, Ar= C_6H_5; 4b: R=Et, Ar=4-FC_6H_4; 4c: R= Et, Ar=2-ClC_6H_4; 4d: R=Et, Ar=4-MeC_6H_4; 4e: R=Et, Ar=2,4-$Me_2C_6H_3$; 4f: R=MeS, Ar=4-ClC_6H_4; 4g: R=MeS, Ar=4-MeC_6H_4

Scheme 44

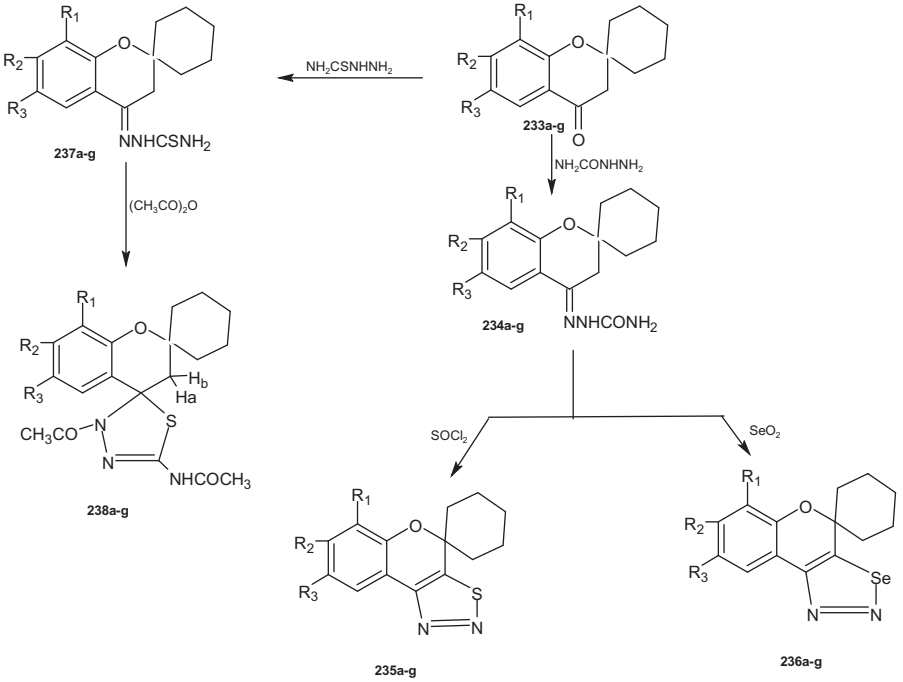


a = 4-MeC_6H_4, b=4-$OMeC_6H_4$, c= 3,4,5-$(OMe)_3C_6H_2$,d= 3-$O_2NC_6H_4$, e= 4-$O_2NC_6H_4$, f= 4-ClC_6H_4, g= 2,4-$Cl_2C_6H_3$

Scheme 45

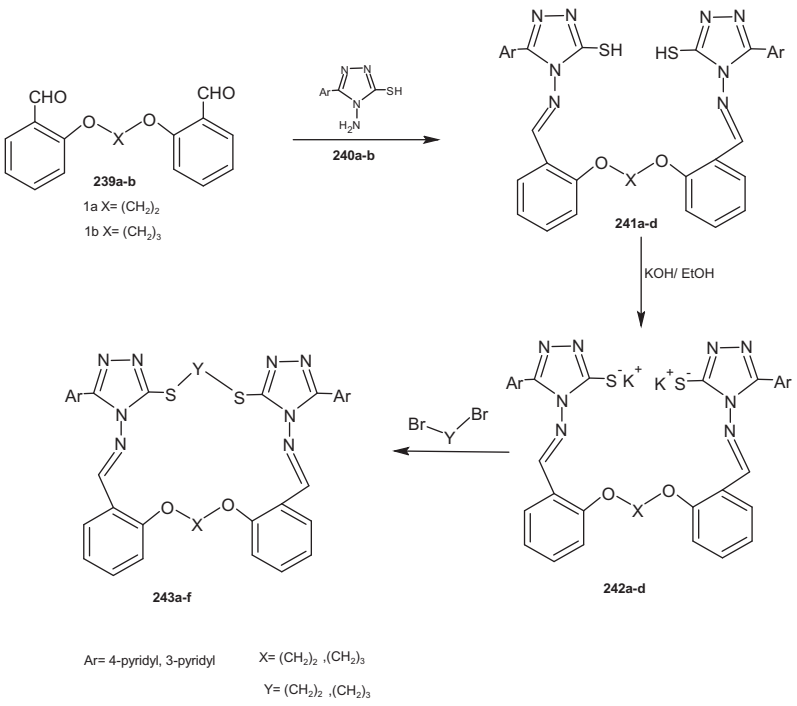


Scheme 46

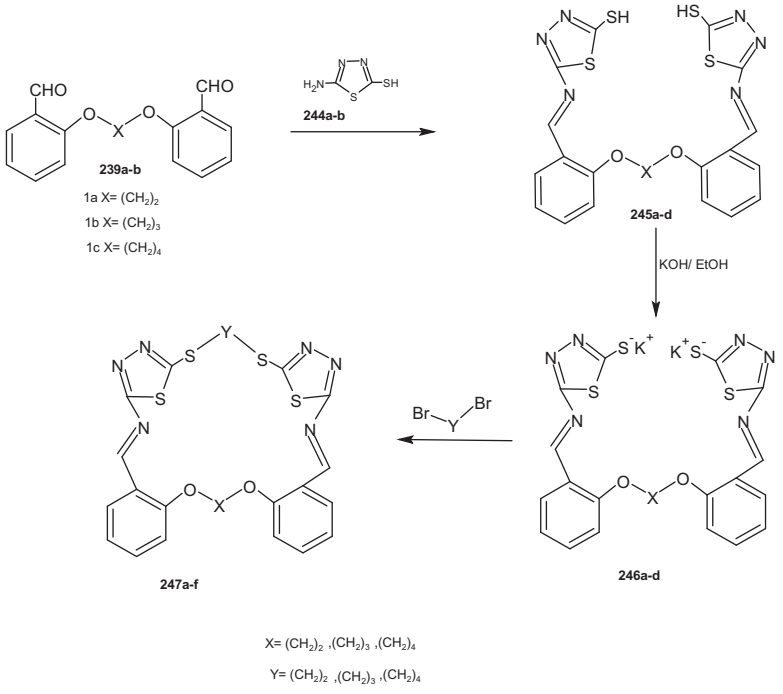


	a	b	c	d	e	f	g
R_1	H	H	H	H	Cl	H	H
R_2	H	H	H	H	H	CH_3	H
R_3	Cl	H	Br	CH_3	Cl	Cl	F

Scheme 47



Scheme 48

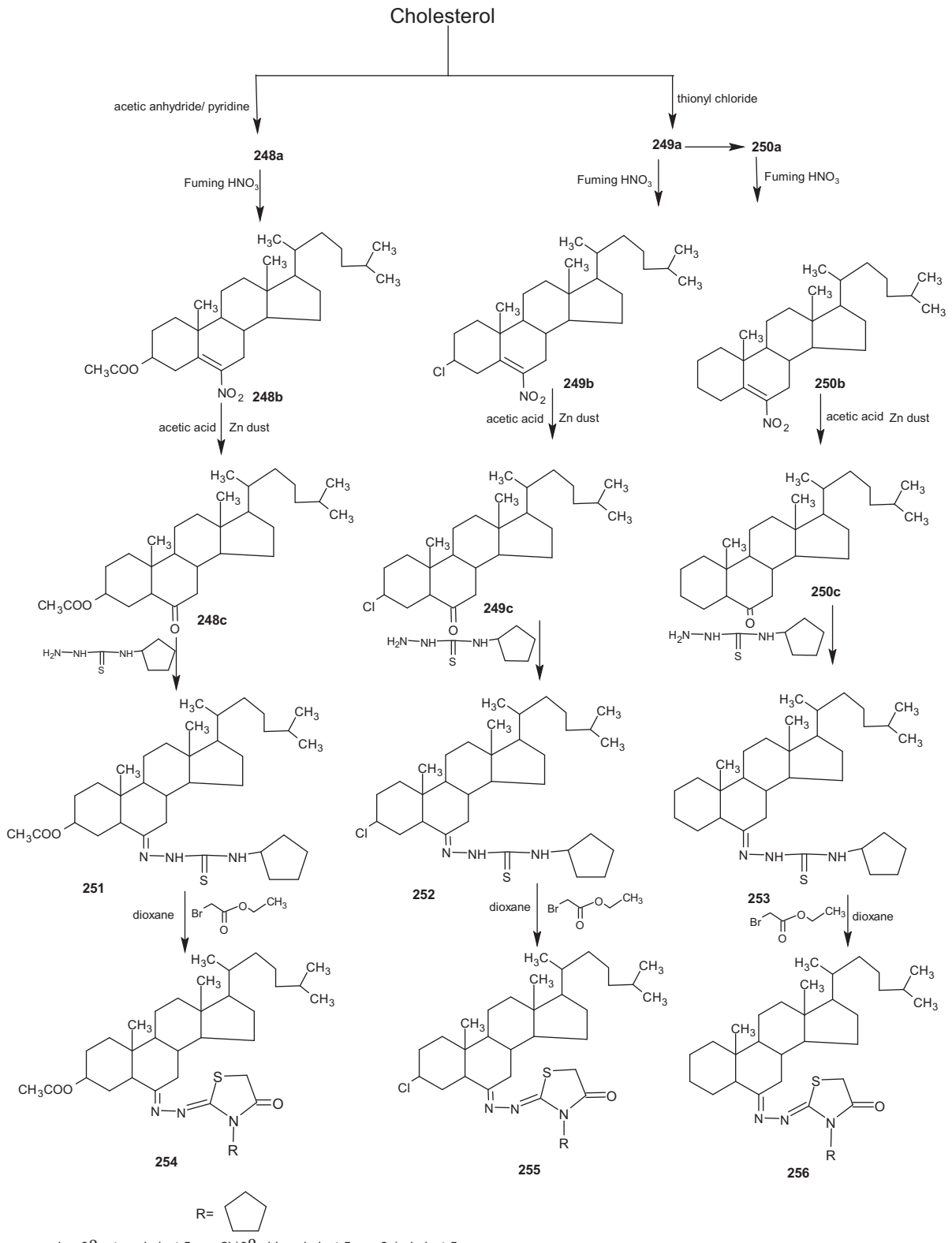


Scheme 49

Among the screened products, the compounds **281d**, **281e**, **281f**, **281g** and **281j** exhibited better activity as compared to the standard drug and emerged as potential derivatives for further researches.

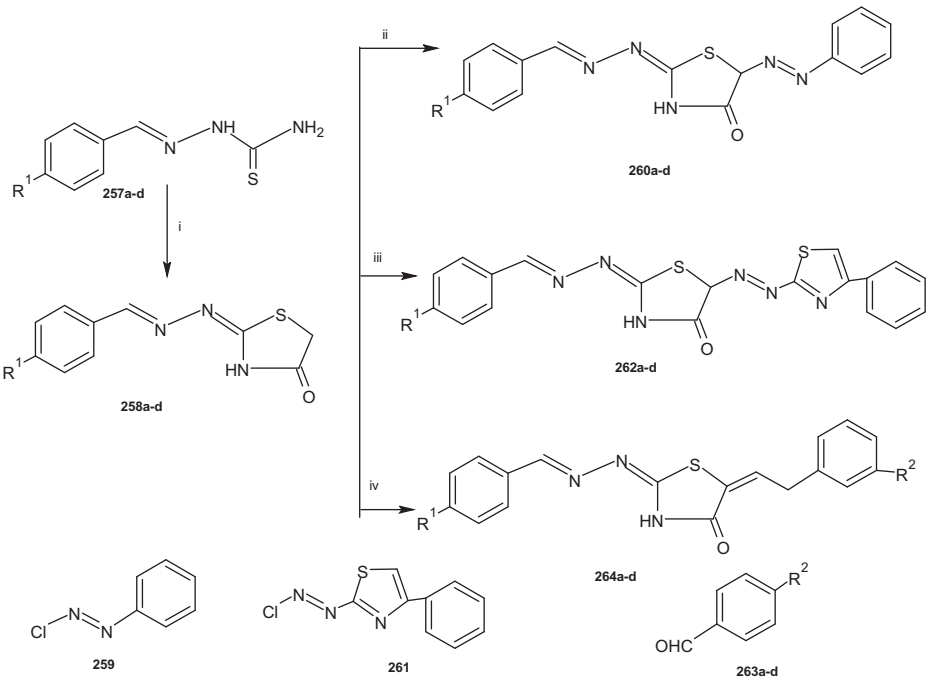
Kabilan and co-workers have investigated the synthesis of some novel 2,4-[diaryl-3-azabicyclo[3.3.1]nonan-9-yl]-5-spiro-4-acetyl-2-(acetylamino)-Δ-1,3,4-thiadiazolines (Rani et al., 2010) derivatives **285a–h**. These compounds were obtained by the cyclization of 2,4-[diaryl-3-azabicyclo[3.3.1]nonan-9-one thiosemicarbazones **284a–h** under acetic anhydride medium (Scheme 57).

The macrocyclic compounds containing heterocyclic subunits have attracted the attention of synthetic chemists as these molecules can act as ligand in the asymmetric catalysis (Cho et al., 2010) and as a host molecule for the incorporation of metal ions. Nam Sook Cho and et al

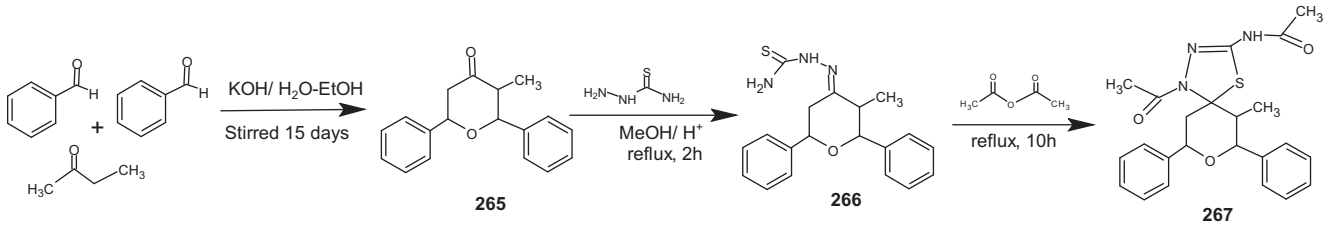


Scheme 50

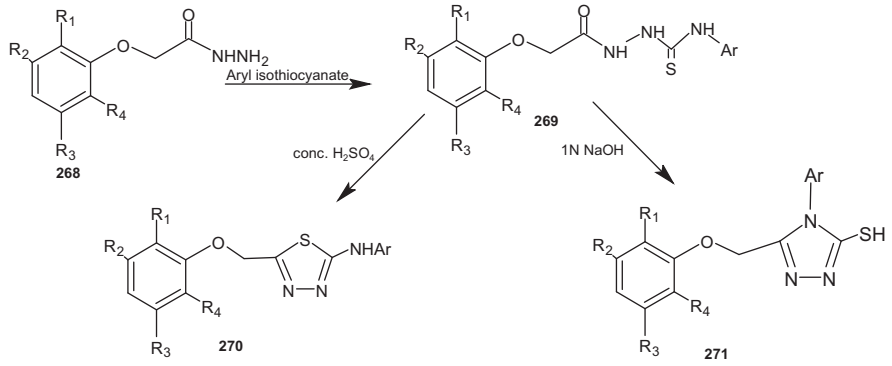
have developed the synthesis of novel macrocycles **289a–f** containing 2-imino-5-mercapto-3*H*-1,3,4-thiadiazoline unit linked at 3 and 5 positions through the ethyl, butyl and *m*-xylene moiety (Scheme 58). The X-ray diffraction studies could become helpful to ascertain the structure of these compounds.



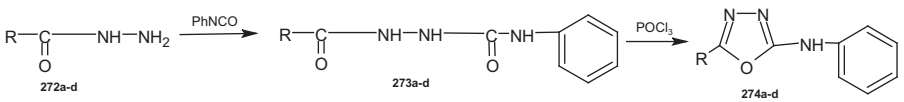
Scheme 51



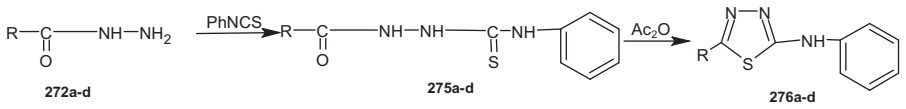
Scheme 52



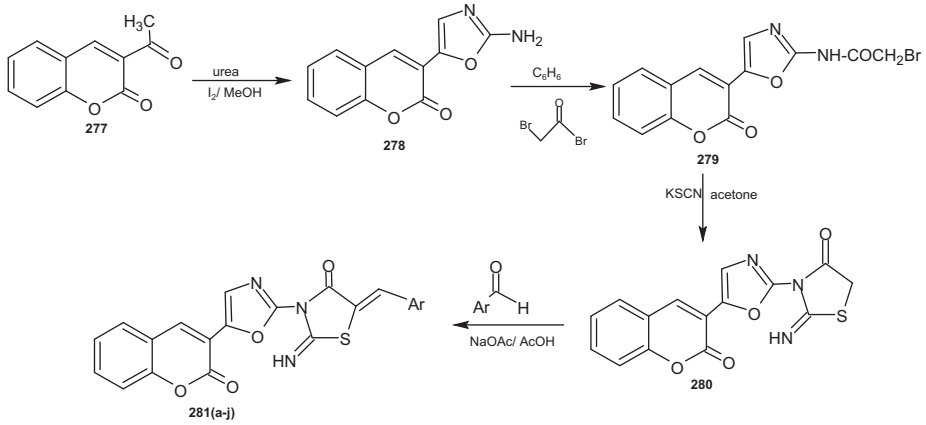
Scheme 53



Scheme 54

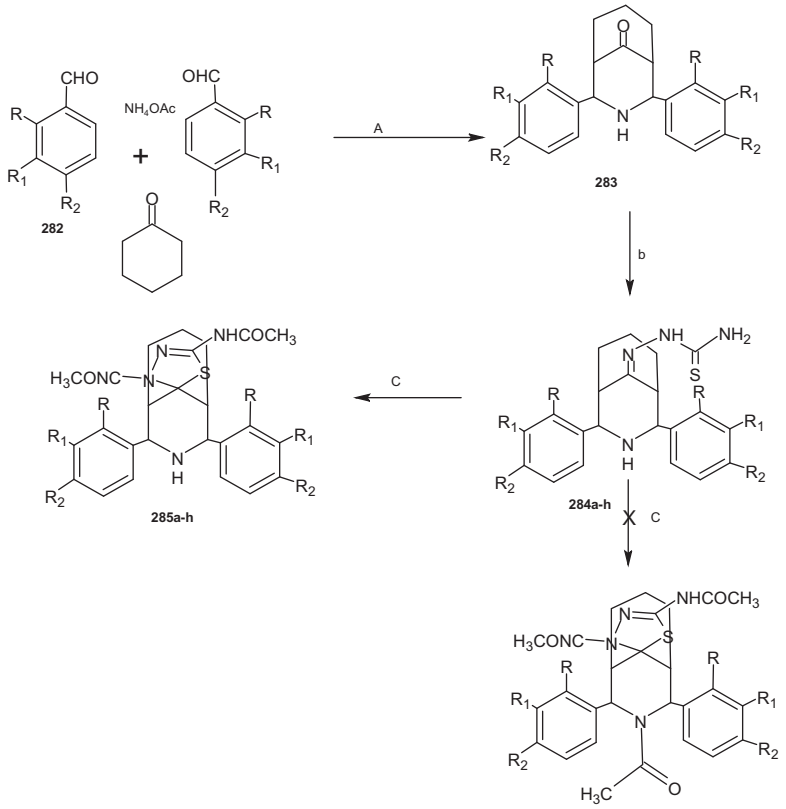


Scheme 55



(a) 4-methylphenyl; b)4-chlorophenyl; c) 4-nitrophenyl; d)3-nitrophenyl; e)4-hydroxyphenyl; f) 2,6 difluorophenyl; g)4-dimethylaminophenyl; h)4-hydroxy-3-methoxyphenyl; i) 2-furyl; J) pipernyl

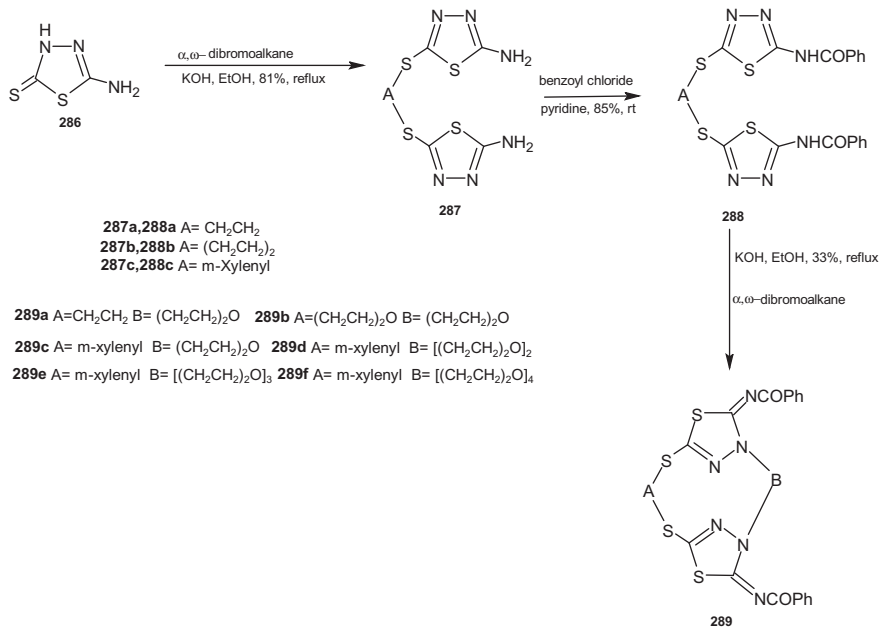
Scheme 56



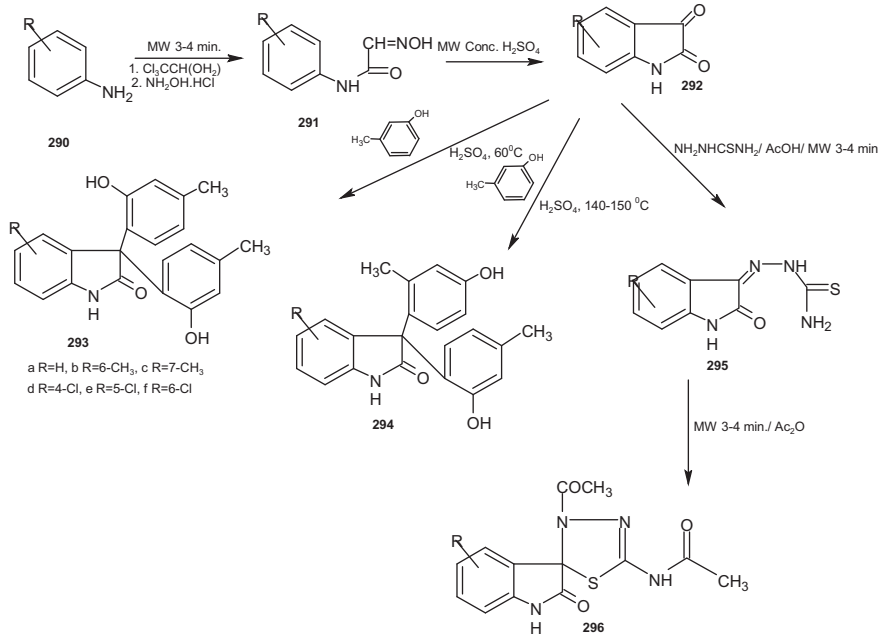
Conditions: A)EtOH, warm B) thiosemicarbazide, H^+ and C) acetic anhydride

Scheme 57

The significant biological properties (Hossain et al., 2010) (like anti-oxidant, anti-microbial and anti-cancer) associated to the Isatins has promoted the synthesis and biological evaluation of the new heterocyclic compounds **293a–c**, **294d–**



Scheme 58



Scheme 59

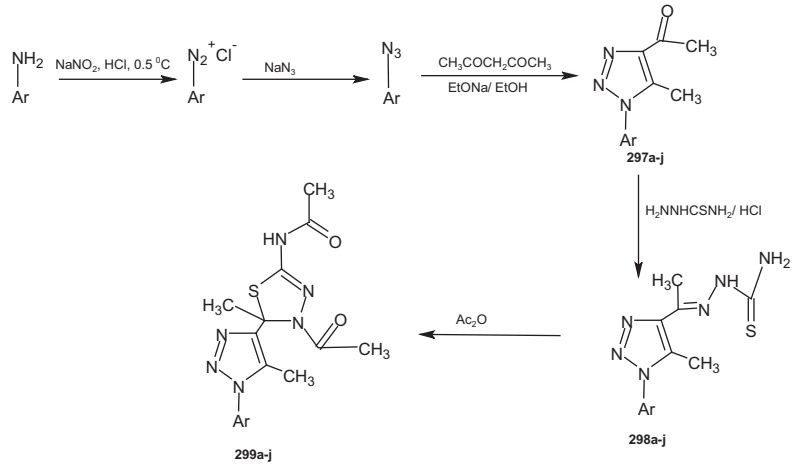
f and **296g–j**. These compounds were obtained by the synthetic routes as shown in Scheme 59.

Heng-Shan Dong et al. have synthesized *N*-[4-acetyl-4,5dihydro-5-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)-5-methyl-1,3,4-thiadiazol-2-yl]acetamide (Wang et al., 2010) derivatives **299a–j** according to the protocol as described in Scheme 60.

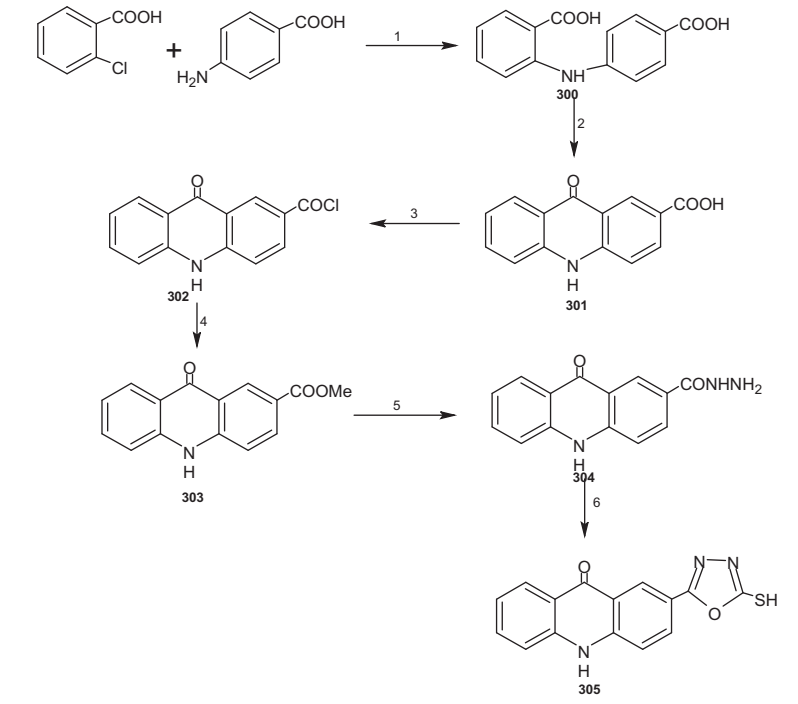
Recently, new acridone based 1,3,4-oxadiazoles (Salimon et al., 2010) **305** have been obtained starting from the reaction of 2-chlorobenzoic acid with 4-aminobenzoic acid (Scheme 61). These compounds are also associated with the significant anti-bacterial and anti-fungal activities.

A novel series of pyridyl substituted oxadiazole (Shirote and Bhatia, 2011) **309a–f** have been synthesized through the cyclization of carbonyl hydrazone under the excess of acetic anhydride and subsequent condensation with various aromatic amines (Scheme 62). These compounds were also screened for their goat pulmonary vein relaxant activity and compound PSMB9 was found to be the most active derivative exhibiting 83.33% relaxation.

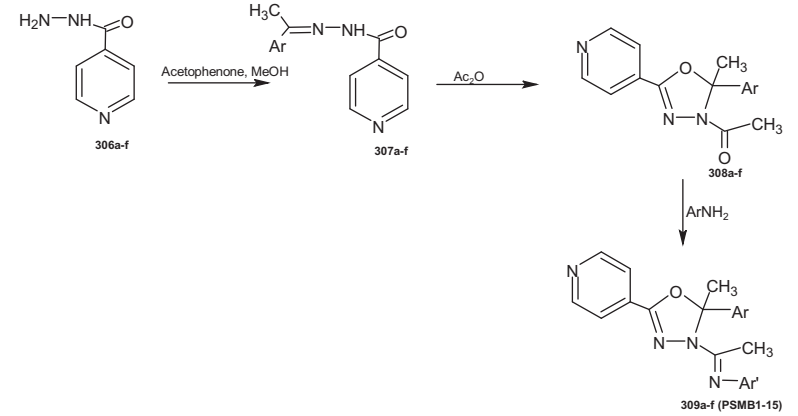
Recently, synthesis and anti-microbial analysis of some new 1,2,4-thiadiazolinediones (Alagawadi and Alegaon, 2011) **314a–g** and **318a–g** (Schemes 63 and 64) have been reported



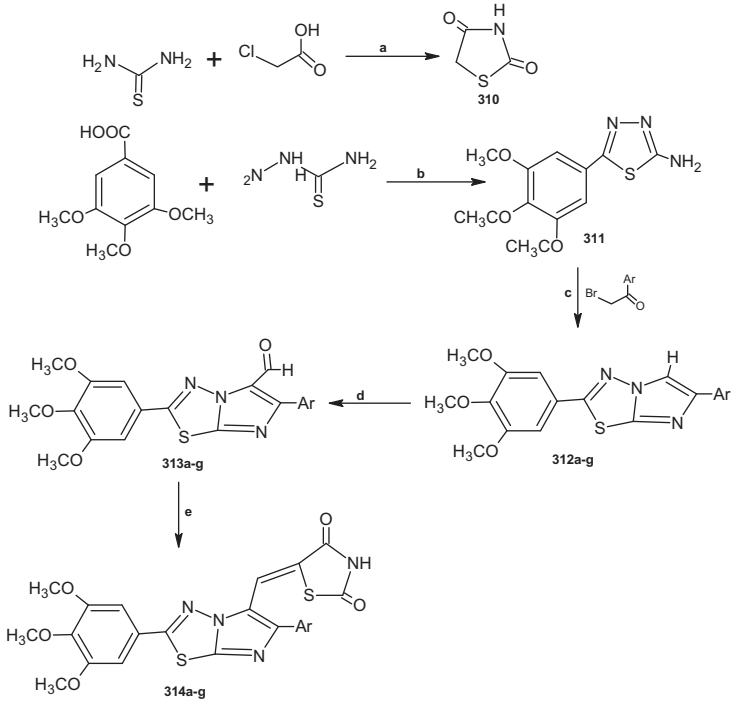
Scheme 60



Scheme 61

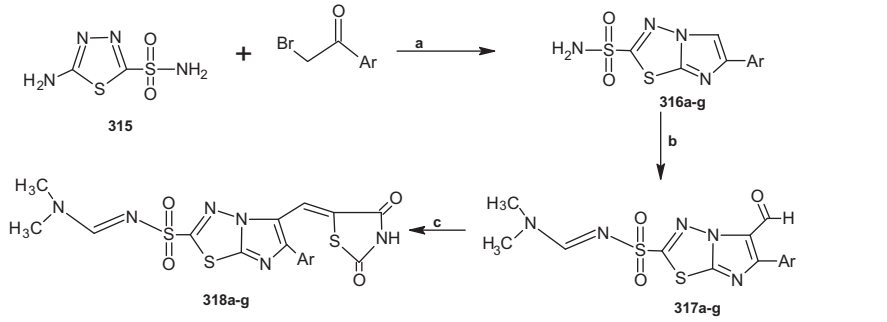


Scheme 62



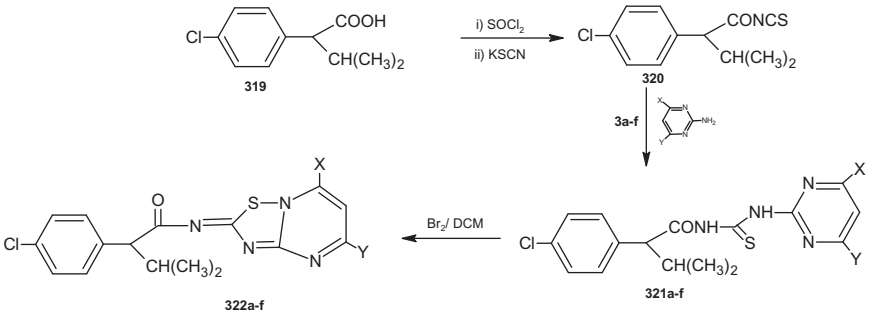
Reagents:a) HCl b) Phosphorusoxychloride, 5h, 80% c) dry EtOH, 10h, 80-85% d) Vilsmeiere-Haack reagent,8h,78-86% e)**1**,piperidine,acetic acid,toluene,10h

Scheme 63



Reagents: a) dry EtOH, 10h, 80-85%, b)Vilsmeiere-Haack Reagent, 8h, 78-86% c) **1**, piperidine, acetic acid, toluene 10h, 85-92%

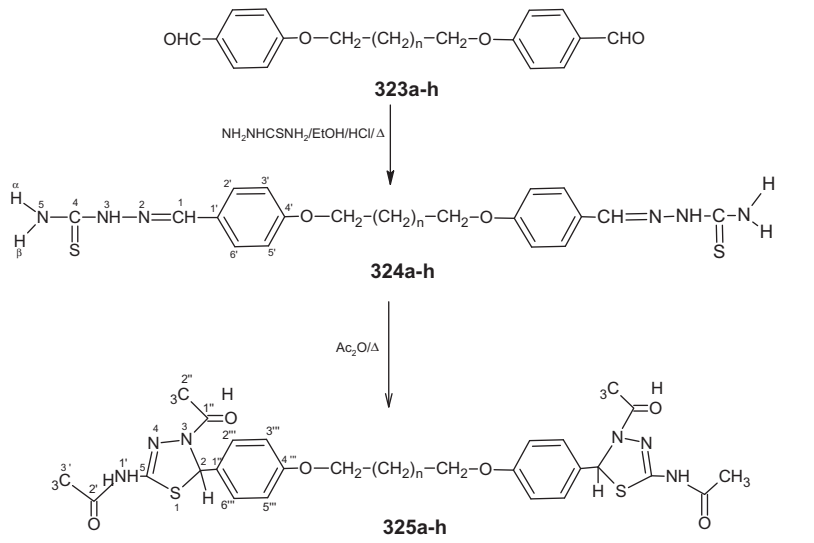
Scheme 64



Scheme 65

by Shankar G. Alegaon and co-workers. These heterocycles exhibited high to moderate biological behaviour against the tested bacteria and fungi strains.

Recently, synthesis of new heterocyclic compounds (Duan et al., 2010) **322a–f** has been carried out through the multi step reactions as shown in Scheme 65. The

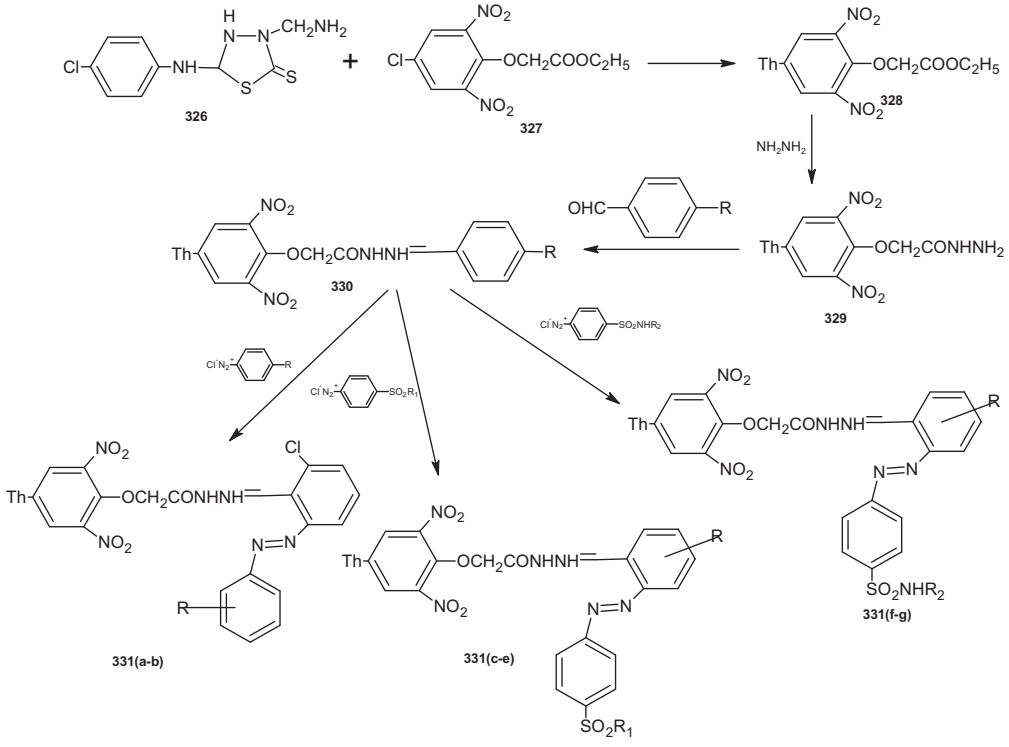


a(n=0), b(n=1), c(n=2), d(n=3), e(n=4), f(n=6), g(n=8), h(n=10)

Scheme 66

herbicidal activities of these compounds have also been examined against a variety of weeds. This study showed that most of the synthesized compounds had moderate inhibitory activities and selectivities against root and stalk of monocotyledon and dicotyledon plants. The chiral compounds showed improved herbicidal activities to some extent over their racemic counterparts against a variety of tested weeds.

The bisthiadiazolines (Yusuf and Jain, 2012) **325a–h** built around the alkyl chains of varying lengths have been synthesized in good yields by refluxing bisthiosemicarbazones **324a–h** in acetic anhydride. The reactions of bisaldehydes **323a–h** with thiosemicarbazide in alcoholic medium provided **324a–h**. The formation and stereochemical features of the bisthiadiazolines **325a–h** were found to be independent of the internal spacer length (Scheme 66).



330a: R=2-Cl, 330b: R=3-OCH_3, 4-OH; 331a-b:R=2-Cl, R_1=4-NO_2, 2-CH_3-4-NO_2; 331c-e: R= 2-Cl, R_1=OH, NH_2, guanidino; 331f-g: R=3-OCH_3, 4-OH, R_1=Pyrimidinyl, 4,6-dimethyl pyrimidinyl

Scheme 67

5-(4-Chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole (Sah et al., 2014) was refluxed with formaldehyde and ammonium chloride in ethanol to yield Mannich base 5-(4-chloro phenyl amino)-3-aminomethyl-2-mercapto-1,3,4-thiadiazole **326**. Esterification of later with 4-chloro-(2,6-dinitrophenoxy)-ethyl acetate **327** under anhydrous conditions gave the intermediate **328** which upon subsequent hydrazinolysis with hydrazine hydrate gave the corresponding hydrazide 3-amino methyl-5-(4-chloro phenyl amino)-2-mercapto-4′-(2′,6′-dinitro phenoxy)-acetyl hydrazide **329**. The hydrazide was converted into the Schiff bases **330a–b** by reacting with 2-chlorobenzaldehyde and 3-methoxy-4-hydroxy-benzaldehyde in presence of methanol containing 2–3 drops of acetic acid. The diazotization of **330a–b** with aromatic amines, sulfanilic acid and sulfur drugs gave the formazans **331a–g,** respectively (Scheme 67).

Acknowledgement

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