Arabian Journal of Chemistry (2014) 7, 553–596

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

REVIEW

1st Heterocyclic Update

Synthetic and biological studies of pyrazolines and related heterocyclic compounds

Mohamad Yusuf *, Payal Jain

Department of Chemistry, Punjabi University, Patiala 147002, Punjab, India

Received 5 May 2011; accepted 10 September 2011
Available online 1 October 2011

KEYWORDS

Pyrazole;
Bispyrazoline;
Chalcones;
Bischalcone;
Cyclocondensation

Abstract This review provides a comprehensive survey relating to the synthesis and biological applications of pyrazolines and related heterocycles in the last five years (2007–2011). These compounds are usually prepared from the cyclization of chalcones with hydrazine and its derivatives under the alcoholic conditions. The major incentive behind the synthesis of these compounds was the immense biological activities associated to these heterocyclic derivatives. The aim of this review is to find out different methods for the synthesis of pyrazoline derivatives.

Contents

1. Introduction

The development of a clean procedure for the preparation of heterocyclic compounds is a major challenge in modern heterocyclic chemistry in view of the environmental, practical and economic issues. Pyrazolines are an important class of heterocyclic compounds containing two nitrogen atoms in the five membered ring. The substituted 2-pyrazolines have found application as activators for polymerization (Bauer and Piatert, 1981), dyes for wool, nylon (Evans and Waters,

* Corresponding author. Tel.: +91 175 2287607; fax: +91 175 2283073.
E-mail address: yusuf_sah04@yahoo.co.in (M. Yusuf).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2011.09.013

1978), as electro photographic conductors (Murayama and Mater, 1981) and as wavelength shifters in liquid and polymer scintillation (Poduzhailo et al., 1979). Pyrazoline derivatives are the electron rich nitrogen heterocycles which play an important role in the diverse biological activities. These heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Considerable attention has been focused on the pyrazolines and substituted pyrazolines due to their interesting biological activities. These compounds have been found to possess anti-fungal (Korgaokar et al., 1996), anti-depressant, anticonvulsant (Palaska et al., 2001; Rajendra et al., 2005; Ozdemir et al., 2007; Ruhogluo et al., 2005), anti-inflammatory (Udupi et al., 1998), anti-bacterial (Nauduri and Reddy, 1998) and anti-tumor (Taylor and Patel, 1992) properties. The pyrazole moiety is found in blockbuster drugs such as celecobix (Penning et al., 1997), sildenafil (Terrett et al., 1996) and rimonabant (Seltzmann et al., 1995). Recently a very important review has been published upon the studies of pyrazoline compounds (Kumar et al., 2009).

2. Discussion

1,3,5-Triaryl-2-pyrazolines **3** (Li et al., 2007) have been prepared through the reaction of chalcones and phenyl hydrazine hydrochloride (Scheme 1) in the presence of sodium acetate-acetic acid aqueous solution under ultrasound irradiation.

3,4,5-Metalated pyrazoles **6** and **7** were synthesized (Gonzalez-Nogal et al., 2007) by 1,3-dipolar cycloadditions of silyl, disilyl, and silylstannylacetylenes with N-phenylsydnone or trimethylsilyldiazomethane (Scheme 2).

The heterocyclics 5-(-4-(Substituted)phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-2-toluidinomethane thione **12** and 5-(substituted) phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1*H*-1-pyrazolyl-2-methoxyanilino methane thione **13** were obtained (Ali et al., 2007) by the reaction between hydrazine hydrate and chalcones **10** followed by condensation with the appropriate aryl isothiocyanate (Scheme 3).

Synthesis of 5-substituted-3-dimethoxyphosphono-pyrazoles **16** and **17** and 2-pyrazolines **20** and **21** has been accomplished (Conti et al., 2007) through 1,3-dipolar cycloaddition of a suitable nitrile imine to monosubstituted alkynes **15** and alkenes **19** as shown in Scheme 4.

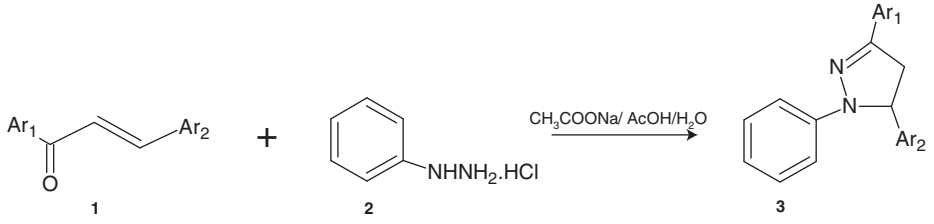
An interesting method ha been reported by Alexander V. Shevtson et al. (2007) for the synthesis of 1-mono- and 1,2-diacylpyrazolidines **23** as well as 1-arylsulfonyl-2-pyrazolines **24** which is described in Scheme 5.

The compounds 1-(2,4-dinitrophenyl)-3-(3-nitrophenyl)-5-(4-substituted phenyl)-2-pyrazolin-4-ones **30** have been prepared by the oxidation of 1-(2,4-dinitrophenyl)-3-(3-nitrophenyl)-5-(4-substitutedphenyl)-4-bromo-2-pyrazolines **29** with dimethylsulfoxide (Mishra et al., 2007). The later has been released via the reactions sequence which is depicted in Scheme 6.

An efficient method (Joshi et al., 2008) has been reported regarding the synthesis of 5-substituted-2-thiol-1,3,4-oxadiazoles **32** according to the protocol as shown in Scheme 7.

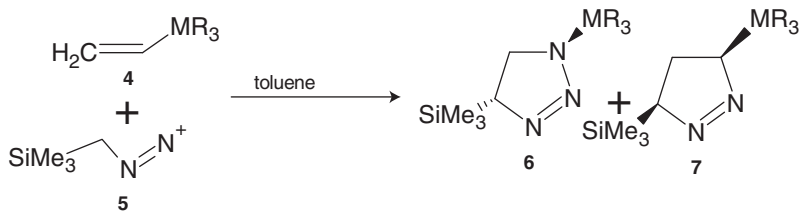
Braulio Insuasty et al. Insuasty et al. (2008) have synthesized new bis-3,5-diphenylpyrazolines **36** from the cyclization of bischalcones **35** with hydrazine hydrate in acetic acid medium. The later was prepared by the Claisen–Schmidt reaction of bis-acetophenone **35** with suitable aromatic aldehydes (Scheme 8).

Some biologically significant bis-heterocycles (Jayashankra and Lokanatha, 2008) bearing pyrazoline moieties **40** have been synthesized starting from pyrazolyl aldehyde **37** through the reaction sequence as described in Scheme 9.



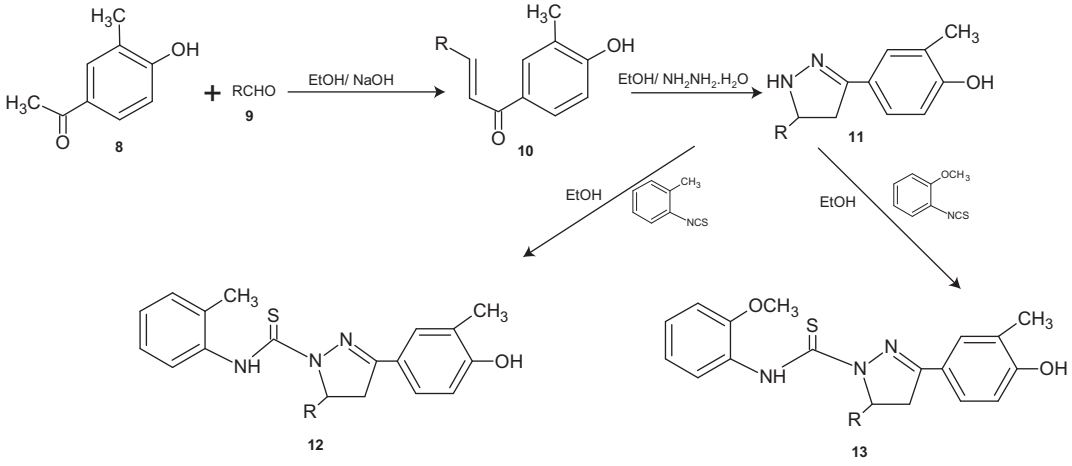
a) $Ar_1=C_6H_5$, Ar_2=4-$CH_3OC_6H_4$ b) $Ar_1=C_6H_5$, 4-$CH_3C_6H_4$ c) $Ar_1=C_6H_5$, $Ar_2=C_6H_5$ d) $Ar_1=C_6H_5$, Ar_2=4-ClC_6H_4, e) $Ar_1=C_6H_5$, Ar_2=3-ClC_6H_4, f) $Ar_1=C_6H_5$, Ar_2=2-ClC_6H_4, g) $Ar_1=C_6H_5$, Ar_2=3-BrC_6H_4, h) $Ar_1=C_6H_5$, Ar_2=4-$O_2NC_6H_4$, i) Ar_1=4-ClC_6H_4, $Ar_2=C_6H_5$, j)Ar_1=3-$O_2NC_6H_4$, $Ar_2=C_6H_5$,

Scheme 1

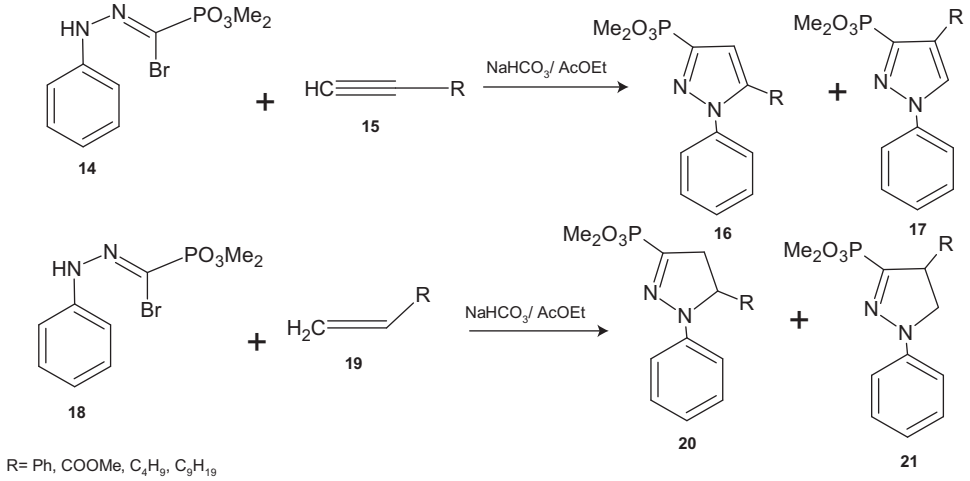


6a; $MR_3 = SiMe_3$; 6b; MR_3= $SiMe_2Ph$; 6c; MR_3= $SiPh_2Bu^t$; 6d; MR_3= $SnBu_3$

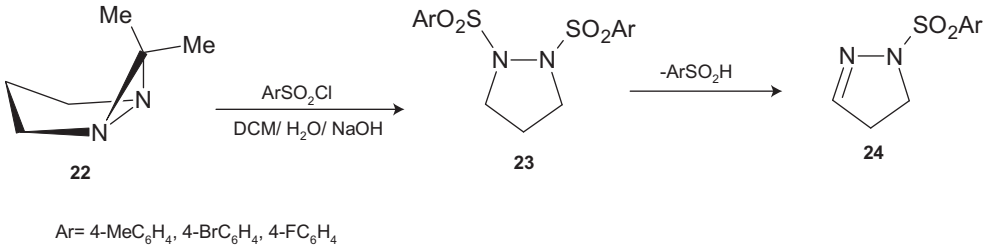
Scheme 2



Scheme 3



Scheme 4



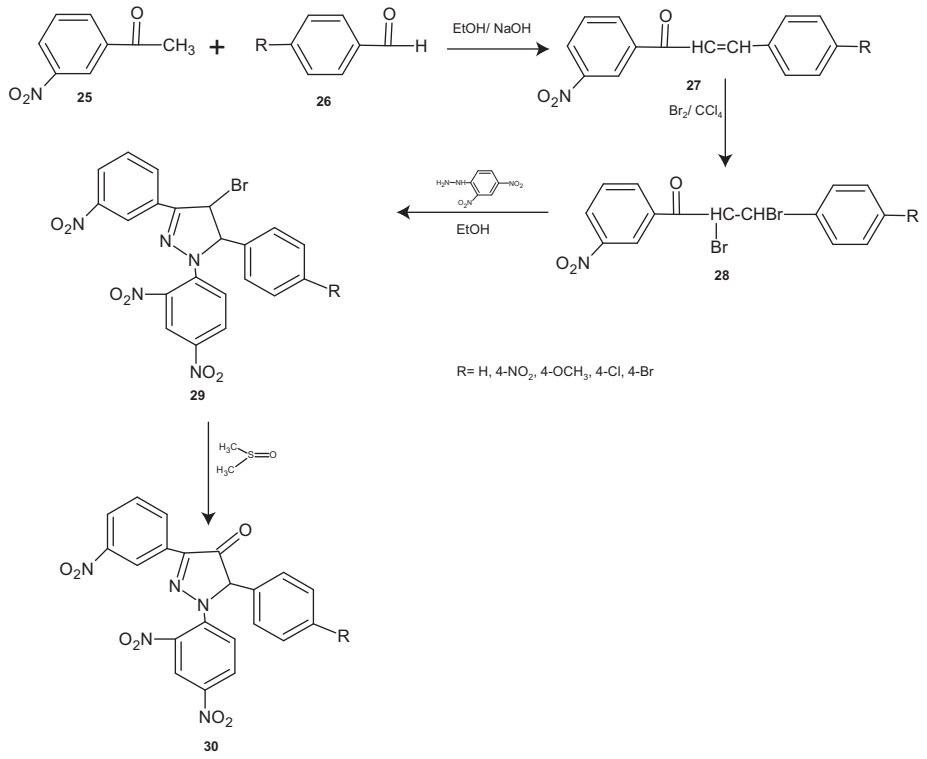
Scheme 5

3,5-Diaryl carbothioamide pyrazolines **44–46** designed as mycobactin analogs (mycobacterial siderophore) were reported to be potent antitubercular agents under iron limiting condition (Jayaprakash et al., 2008). These compounds were obtained via the usual protocol as given in Scheme 10.

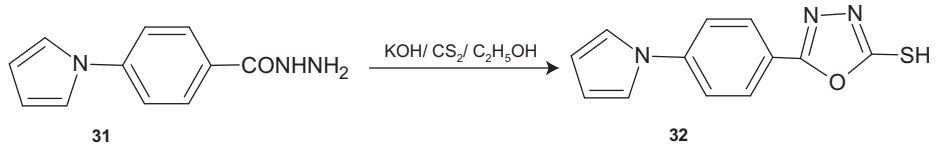
1,3,5-Trisubstituted pyrazolines **47** have been oxidized to the corresponding pyrazoles **48** in high yield with tris(4-bromophenyl)aminium (TBPA) hexachloroantimonate in chloroform at room temperature (Gang et al., 2008) (Scheme 11).

A number of 1,3-diaryl-5-(cyano-,aminocarbonyl-andethoxycarbonyl-)-2-pyrazoline, pyrrolo[3,4-c]pyrazole-4,6-dione and 1,3,4,5-tetraaryl-2-pyrazoline derivatives **52** were prepared (Abunada et al., 2008) by the reaction of nitrilimine with different dipolarophilic reagents (Scheme 12).

Recently the Michael accepters (Padmavathi et al., 2008), 1-arylsulfonyl-2-styrylsulfonylethenes **53** have been used as synthons to develop bis-pyrroles **55**, pyrrolyl pyrazolines **56** and pyrrolyl isoxazolines **57** by 1,3-dipolar cycloaddition of



Scheme 6



Scheme 7

tosylmethyl isocyanide, nitrile imines and nitrile oxides (Scheme 13).

A facile, $InCl_3$ and/or DABCO mediated synthesis (Krishna et al., 2008) of 3,5-disubstituted pyrazolines **61** and pyrazoles **63** and **66** has been achieved by 1,3-dipolar cycloaddition of ethyl diazoacetate (EDA) with various activated olefins **60** under solvent-free conditions at ambient temperature (Schemes 14 and 15).

A series of pyrazoline derivatives **69** were designed and prepared (Zhao et al., 2008) by introducing methoxyacrylate pharmacophore into the scaffold of 1-acetyl-3,5-diarylpyrazoline **68** according to the method which is shown in Scheme 16.

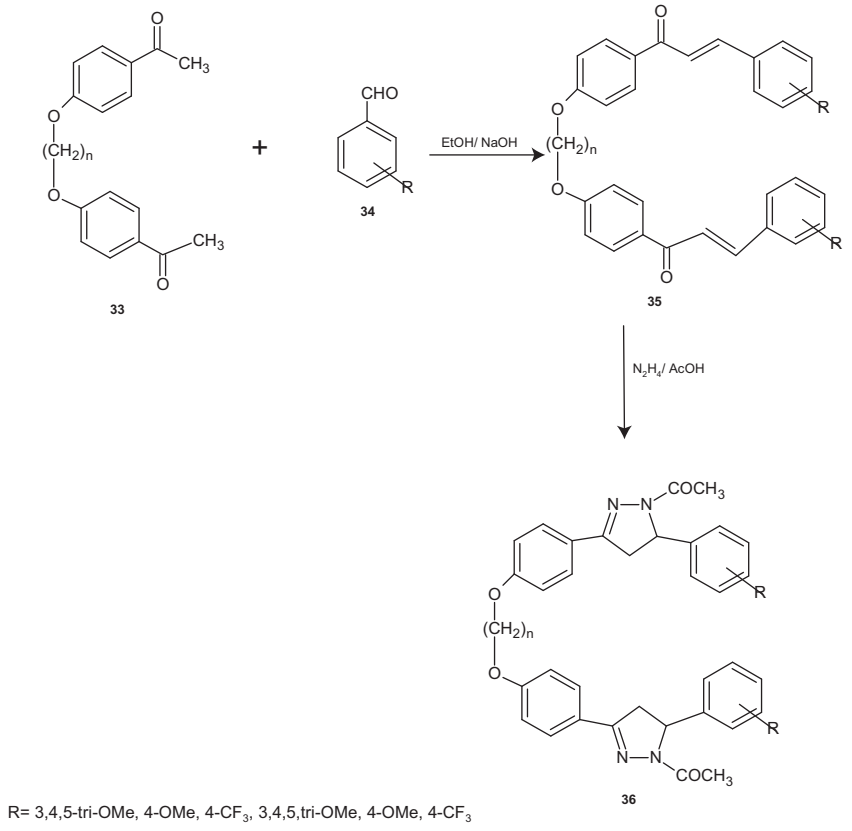
The synthesis of aryl-substituted pyrazolines **73** has been developed by Matthias Beller and co-workers (Alex et al., 2008) in which phenylhydrazine reacts with 3-butynol **71** in the presence of a catalytic amount of zinc triflate to give pyrazoline derivatives through the involvement of hydrazone **72** (Scheme 17).

A series of 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide hydrazone derivatives **75** were synthesized by Bao-Xiang Zhao et al. Xia et al. (2008) (Scheme 18) and the effects of all the compounds on A549 cell growth have also been investigated. The results showed that all compounds had almost inhibitory effects on the growth of A549 cells. The study on structure activity relationships and prediction of lipophilicities of compounds showed that compounds with Log *P* values in the range of 4.12–6.80 had inhibitory effects on the growth of A549 cell and the hydrazones derived from salicylaldehyde had much more inhibitory effects.

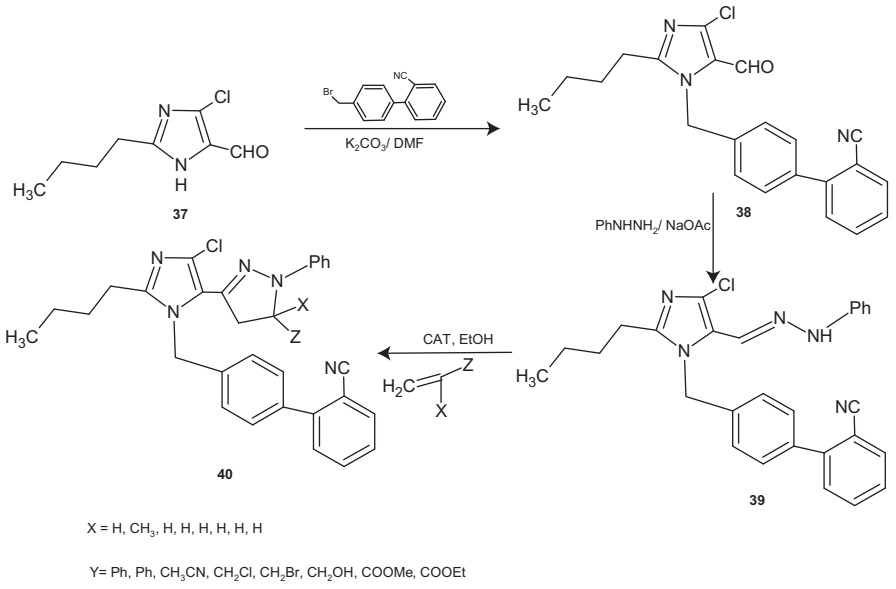
The analgesic and anti-inflammatory properties of novel 3/4-substituted-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-carboxyamidepyrazoles **77** (where 3/4-substituent are H/H, Me/H, Et/H, Pr/H, i-Pr/H, Bu/H, t-Bu/H, Ph/H, 4-Br-Ph/H and H/Me) were determined (Sauzem et al., 2008) and these compounds were synthesized in the exploration of the bioisosteric replacement of benzene present in salicylamide with a 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole scaffold (Scheme 19).

A series of N1-propanoyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives **81** were synthesized (Chimenti et al., 2008) from the usual reaction of chalcone **80** with hydrazine hydrate (Scheme 20).

The cyclocondensation reaction (Almeida da Silva et al., 2008) of 4-methoxy-1,1,1-trifluoro[chloro]-4-(substituted)-alk-3-en-2-ones **82** and isoniazid (INH) led to the formation of 3-substituted 5-hydroxy-5-trifluoro[chloro]methyl-1*H*-1-isonicotinoyl-4,5-dihydropyrazole **83** (Scheme 21).



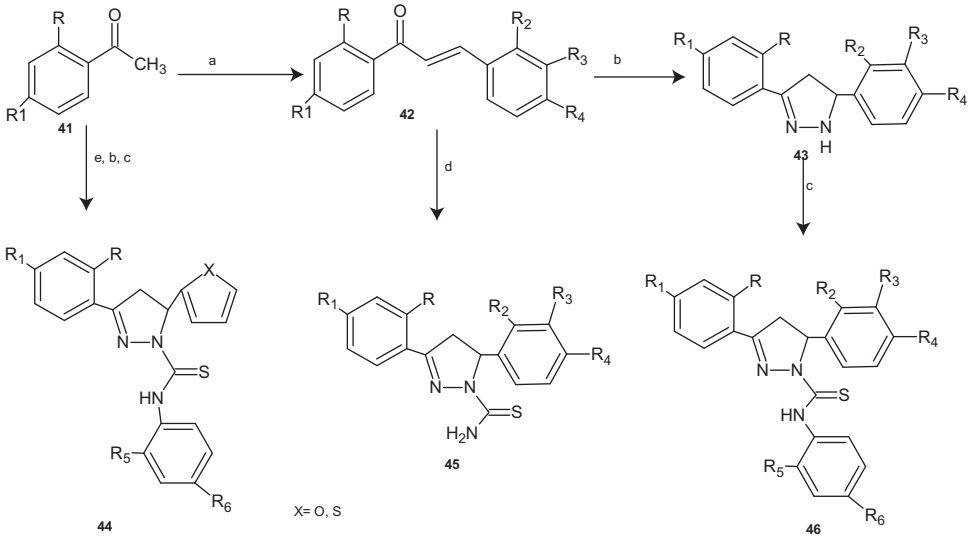
Scheme 8



Scheme 9

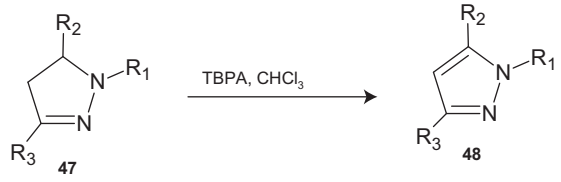
One pot and regioselective synthesis (Bonacorso et al., 2009) of a novel series of 3-aryl(heteroaryl)-5-triflouromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazolyl-carbohydrazides **86** and bis-(3-aryl-5-triflouromethyl-5-hydroxy-4,5-dihydro-1H-pyrazol-1-yl)methanones **87** have been reported from the reactions of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-triflouro-3-en-2-ones **85** under the reaction conditions which are shown in Scheme 22.

Eva Frank et al. (2009) have investigated a highly diastereoselective Lewis acid induced intramolecular 1,3-dipolar cycloadditions of alkenyl phenylhydrazones **90** (containing various substituents on the aromatic ring) under

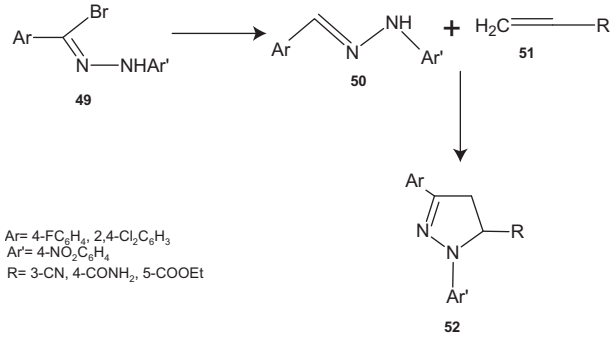


a) i: R_2, R_3, R_4-C_6H_2-CHO, aq. NaOH ii) HCl; b) NH_2NH_2/ H_2O, EtOH c) R_5, R_6-C_6H_3-NCS, EtOH d) $NH_2NHC(S)NH_2$, NaOH, MeOH, HCl e) thiophene-2-carboxaldehyde or furfuraldehyde

Scheme 10



Scheme 11



Scheme 12

fairly mild conditions to furnish andros-5-ene-fused arylpyrazolines **93** in good to excellent yields (Scheme 23).

The compounds **100** and **101** have been prepared from the cyclization of chalcone **99** with hydrazine hydrate and guanidine respectively (Solankee et al., 2009). The compounds **99** were released from the condensation of ketone **98** with suitable substituted aromatic/heterocyclic aldehydes under alkaline conditions. The compound **98** was obtained via two step reaction starting from **96** as shown in Scheme 24.

The cyclization reaction (Zsoldos-Mady et al., 2009) of 1-phenyl-3-ferrocenyl-2-propen-1-one **102** with substituted hydrazines led to the formation of pyrazolines **103–107**. The nature of substitutent on the hydrazine moiety had profound effect upon the products distribution in these reaction. The reaction with methylhydrazine could provide two regioisomeric pairs of pyrazolines **104**, **105** and **107** and pyrazoles **103** and **106** (Scheme 25).

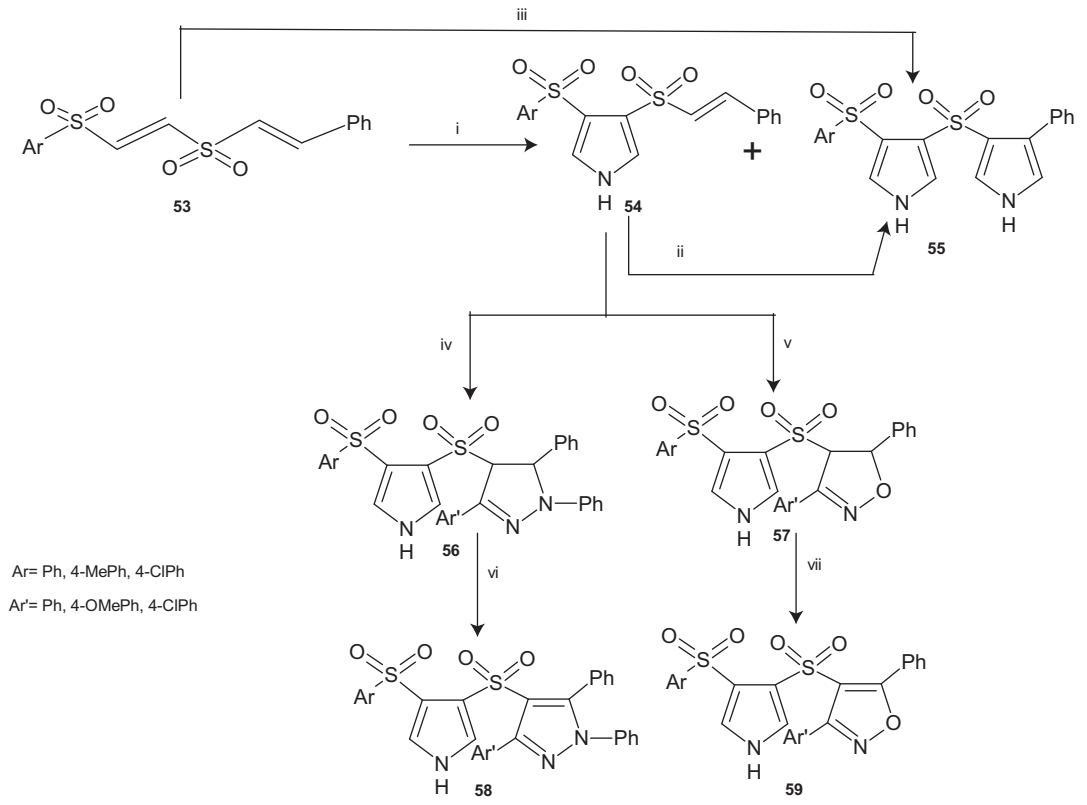
The compound 1,2 pyrazolines **113** have been prepared (Gowramma et al., 2009) because of the interesting pharmacological properties associated to these substrates (Scheme 26). The synthesized compounds were screened for their anti-cancerous activity. It was found that 1-(bis-*N*,*N*-(chloroethyl)-amino acetyl) 3,5-disubstituted-1,2-pyrazoline showed anticancer activity.

A variety of bis(3-aryl-4,5-dihydro-1*H*-pyrazole-1-thiocarboxamides) **115** and bis(3-aryl-4,5-dihydro-1*H*-pyrazole-1-carboxamides) **116** were prepared (Barsoum and Girgis, 2009) via the reaction of bis(2-propen-1-ones) **114** with thiosemicarbazide/KOH and semicarbazide/AcOH respectively (Scheme 27).

Novel series of 1-(2,4-dimethoxy-phenyl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl) propenone **119** had been prepared (Bandgar et al., 2009) by the Claisen–Schmidt condensation of 1-(2,4-dimethoxy-phenyl)ethanone **117** and substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehydes **118** (Scheme 28). The later compounds were obtained by the Vilsmeir–Haack reaction of acetophenone phenylhydrazones.

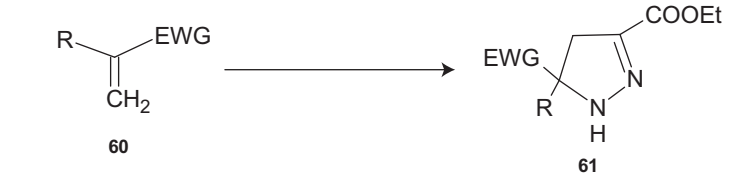
1-Aryl-4,4-dichlorobut-3-en-1-ones **123** were efficiently synthesized (Guirado et al., 2009) by the treatment of acetophenones with anhydrous chloral, followed by dehydration and reductive dechlorination (Scheme 29). The compounds **122** reacted with hydrazine hydrate and methylhydrazine to give **127** and **128** respectively in high to quantitative yields.

Mohamed Abdel-Aziz et al. (Shoman et al., 2009) have reported the synthesis of 3,5-diaryl-2-pyrazoline derivatives **132** which were obtained via the reaction of various chalcones **131** with hydrazine hydrate in ethanol. The



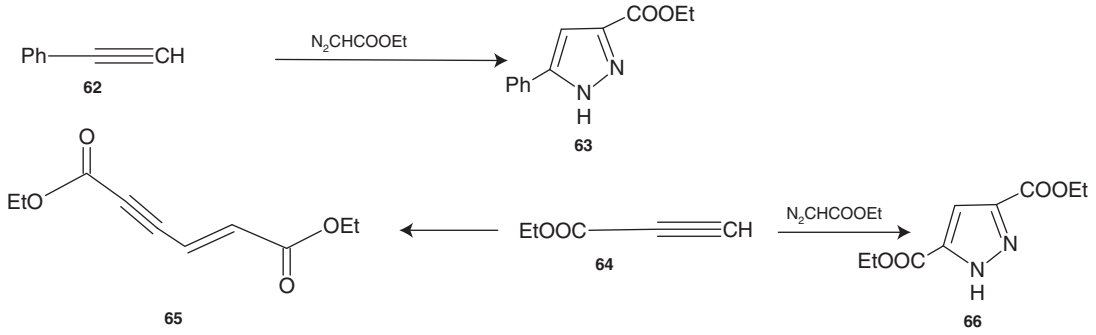
i) 2TosMIC/ NaH/ Et2O+DMSO ii) TosMIC/ NaH/ Et_2O+DMSO iii) 4TosMIC/ NaH/ Et_2O+DMSO iv) Ar'-CH=NNHPh/ chloramine-T.$3H_2O$/ MeOH v) Ar'-CH=NOH/ chloramine-T.$3H_2O$/ MeOH vi) chloranil/ xylene

Scheme 13

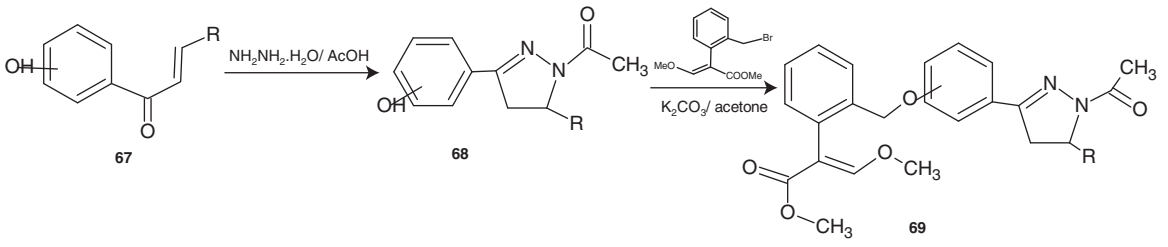


R= H, CH(R')OH; R'= H, alkyl, aryl; EWG = COOEt, CN etc.

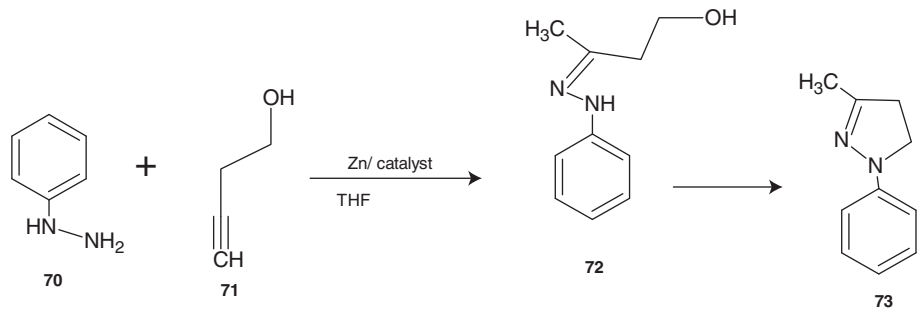
Scheme 14



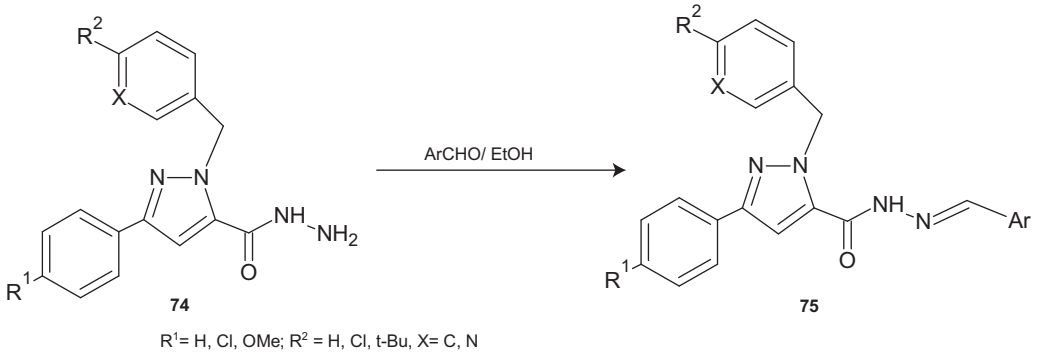
Scheme 15



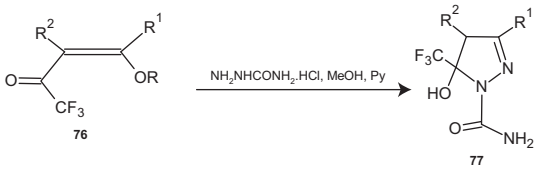
Scheme 16



Scheme 17



Scheme 18



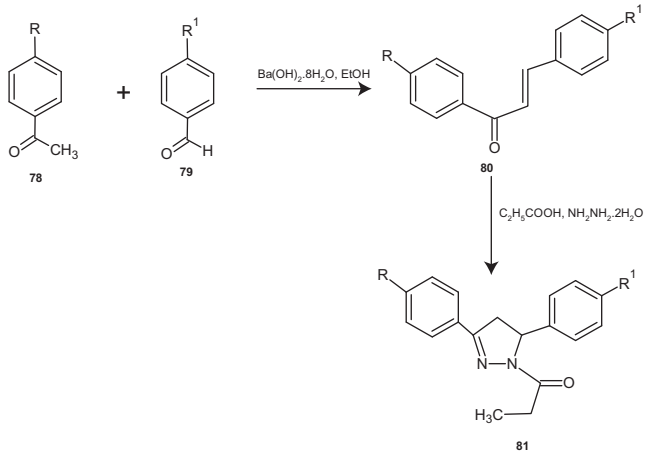
Scheme 19

compounds **132** were further converted to various N-substituted derivatives **133–138** according to the reaction conditions and protocol as given in Scheme 30.

Effective syntheses of endo- and exocyclic α,β-unsaturated ketones as C═C dipolarophiles (Mernyak et al., 2009) were carried out in the estrone series. 1,3-dipolar cycloadditions of unsaturated ketones of estrone 3-methyl and 3-benzyl ether with nitrilimines stereoselectively furnished two regioisomers of new condensed pyrazolines **140** and **141** in a ratio of 2:1 (Scheme 31).

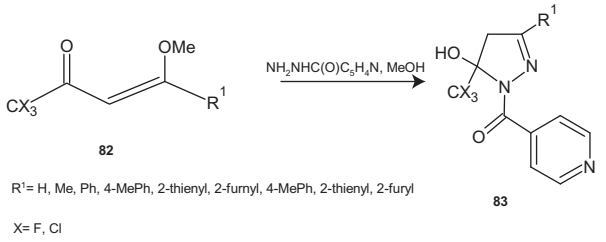
The reaction (Khode et al., 2009) of various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones **147** with phenylhydrazine in the presence of pyridine led to the synthesis of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines **148** (Scheme 32).

1-[(Benzoxazole/benzimidazole-2-yl)thioacetyl]pyrazoline derivatives **154** were obtained (Kaplancikli et al., 2009) by reacting 3,5-diaryl-1-(2-chloroacetyl)pyrazolines **153** with 2-marcaptobenzoxazole/benzimidazole. The later compounds were released starting from benzaldehydes **149** and **150** according to the reactions sequence which are depicted in Scheme 33.



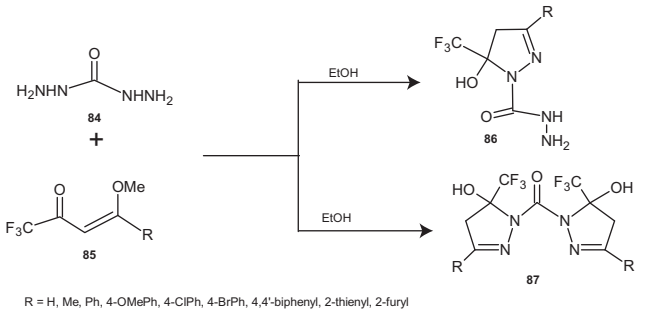
78 79 80 81

Scheme 20



82 83

Scheme 21



84 85 86 87

Scheme 22

Recently, N^1-acetyl-5-aryl-3-(substituted styryl)pyrazolines **158** have been prepared (Pathak et al., 2009) from the cyclocondensation of 1,5-substituted diphenyl-1,4-pentadien-3-ones **157** with hydrazine hydrate and a cyclizing agent such as acetic acid in ethanol (Scheme 34).

Tricyclic fused pyrazolines **160** have been synthesized (Scheme 35) from the reaction of 3-arylidenechromanones/thiochromones **159** with (4-carboxyphenyl)hydrazine in hot anhydrous pyridine solution (Levai and Jeko, 2009).

The oxidation of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **161** to the corresponding pyrazoles **162** has been achieved by utilizing tetrabromine-1,3,5,7-tetrazatricyclo[3.3.1.1]decane complex, Br_4-TATCD, in glacial acetic acid under microwave irradiation and conventional thermal condition (Scheme 36) at room temperature with excellent yields (Azarifar and Khosravi, 2009).

The reaction (Singh et al., 2009) of dibenzalacetone **165** with hydrazine hydrate and formic acid yielded a novel 2-pyrazoline 166 (Scheme 37).

The reaction of cholest-5-en-7-one **167** with thiosemicarbazide in sodium ethoxide (Scheme 38) afforded 2′-thiocarbamoyl-cholest [5,7-cd] pyrazoline **168**, [X = H] 2′-thiocarbamoyl-3β-acetoxycholest [X = OAc] pyrazoline **168**, and 2′-thiocarbamoyl-3β-chloro cholest pyrazoline [X = Cl] **168** respectively (Shamsuzzaman Khan and Alam, 2009).

The synthesis of pyrazolines **170** was carried out to study the effect of bromine on the biological activity (Kumar et al., 2009). These compounds were brominated by using bromine in acetic acid (Scheme 39). All synthesized compounds were tested for antimicrobial activity against gram positive and gram negative bacteria. It was found that most of the compounds were found active against all bacteria except *Escherichia coli*.

The substituted carboxylic acid hydrazides **171** reacted with ethenetetracarbonitril in dimethyl formamide (Scheme 40) with the formation of diacylhydrazines **172** and 5-amino-1-substiuted pyrazole-3,3,4-tricarbonitriles **173** (Abdel-Aziz et al., 2009).

A new series of 1*H*-3-(4′-substituted phenyl)-5-(6″-methoxy napthaline)-2-pyrazolines **179** and 1*H*-3-(4′-substituted phenyl)-5-(6″-methoxy napthaline)-2-isoxazolines **178** have been synthesized (Jadhav et al., 2009) from the reaction of 1-(4′-substituted phenyl)-3-(6″-methoxynapthaline)-2-propene-1-one **177** with hydrazine hydrate and hydroxylamine hydrochloride respectively (Scheme 41).

The enaminonitrile **181** was used as the key intermediate for the synthesis of polyfunctionally substituted heterocycles pyrazoles **184** (Scheme 42) incorporating benzothiazole **183** moiety via its reactions with some N-nucleophiles (Bondock et al., 2009).

Recently Sheena Shashikanth et al Rai et al. (2009) have reported the synthesis of a series of novel 2-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1*H*-pyrazol-4-yl]-5-(substituted-phenyl)-[1,3,4]oxadiazoles **189** from cyclization of substituted benzoic acid N-[1-(5-chloro-2-methoxy-phenyl)-5-methyl-1*H*-pyrazole-4-carbonyl]-hydrazide **188** with phosphorousoxychloride (Scheme 43).

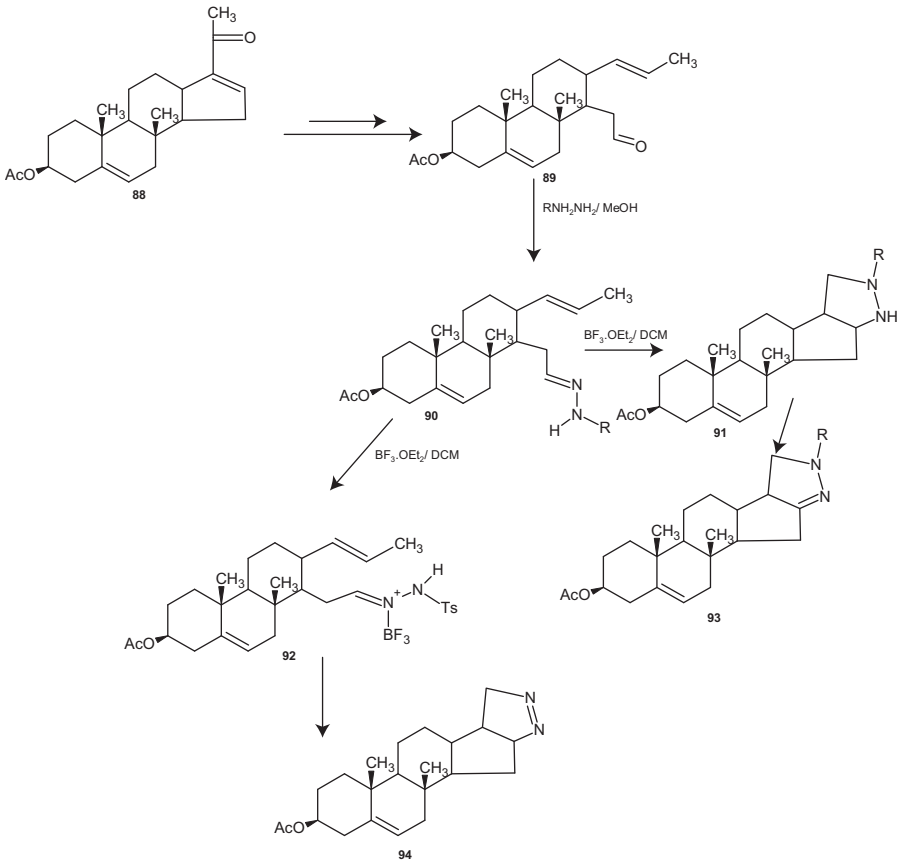
A new class of heterocycles, substituted pyrazoles **193**, isoxazoles **192**, pyrimidines **194**, thioxopyrimidines **195** were released from the Michael adducts **190**, 2-(1,2-diaroylethyl) malononitrile and 2-(1,2-diarylsulfonylethyl) malononitrile (Padmaja et al., 2009) which subsequently underwent cyclocondensation with the appropriate nucleophiles to produce the final compounds (Scheme 44).

The compounds 1-(4-methylcoumarinyl-7-oxyacetyl)-3,5-dimethyl-4(arylazo)pyrazoles **198** and 1-(4-methylcoumarinyl-7-oxyacetyl)-3-methyl-4-(substituted phenyl) hydrazono-2-pyrazolin-5-ones **199** were prepared (Manojkumar et al., 2009) according to the protocol which is described in Scheme 45.

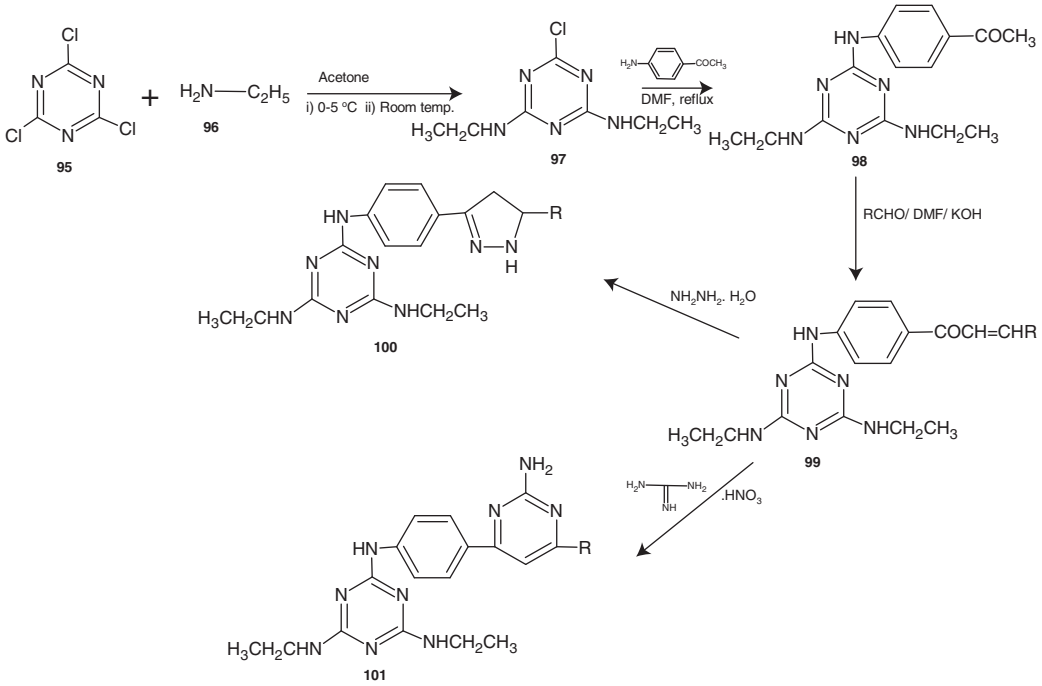
The thiocarbamoyl derivative **200** was reacted with hydrazine hydrate (Fadda et al., 2009) to afford the pyrazole derivatives **201** (Scheme 46).

A new series of chalcones **205** were synthesized (Revanasiddappa et al., 2010) from the condensation of simple aldehydes with substituted acetophenones under alkaline medium (Scheme 47). The cyclization reaction of chalcones with **206** in the presence of glacial acetic acid provided **207**.

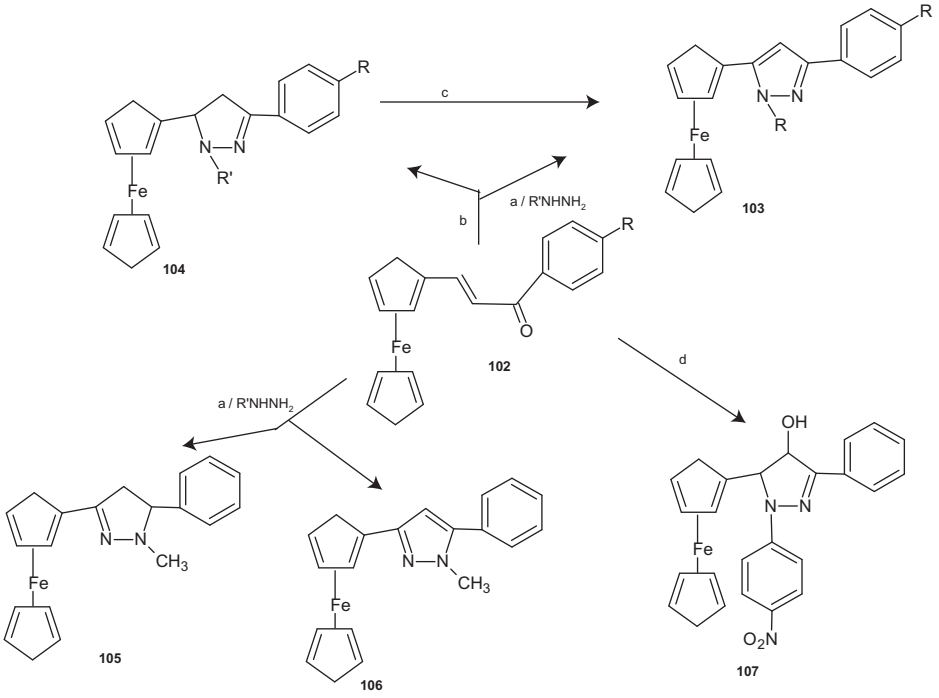
α-Pyranochalcones **208** and pyrazoline derivatives **210** and **214** were prepared (Warane et al., 2010) to discover chemically



Scheme 23



Scheme 24

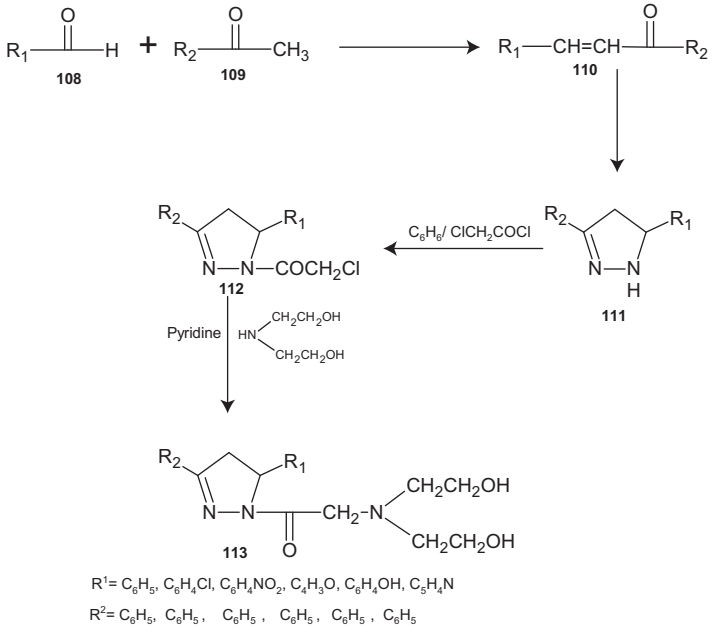


R= H, H, H, H, H, p-OH, p-OAc, p-OAc, p-OAc

R'= H, Ac, Ph, p-NO_2Ph, Me, Ph, Ph, Py, p-NO_2Ph

Reaction conditions A) Hydrazinolysis with RNHNH2: EtOH, RT; AcOH, reflux; AcOH-EtOH-H2O, reflux; MeOH, 40°C; toluene, reflux B) Acetylation with Ac_2O in pyridine at 0°C; C) Dehydroaromatization of pyrazolines to pyrazoles with Cu(NO3)2.3H2O under sonication, DCM for; b) NBS, CCl_4, reflux: c) DDQ, DCM, RT; toluene, reflux, partial oxidation during th reaction D) 11: by product

Scheme 25



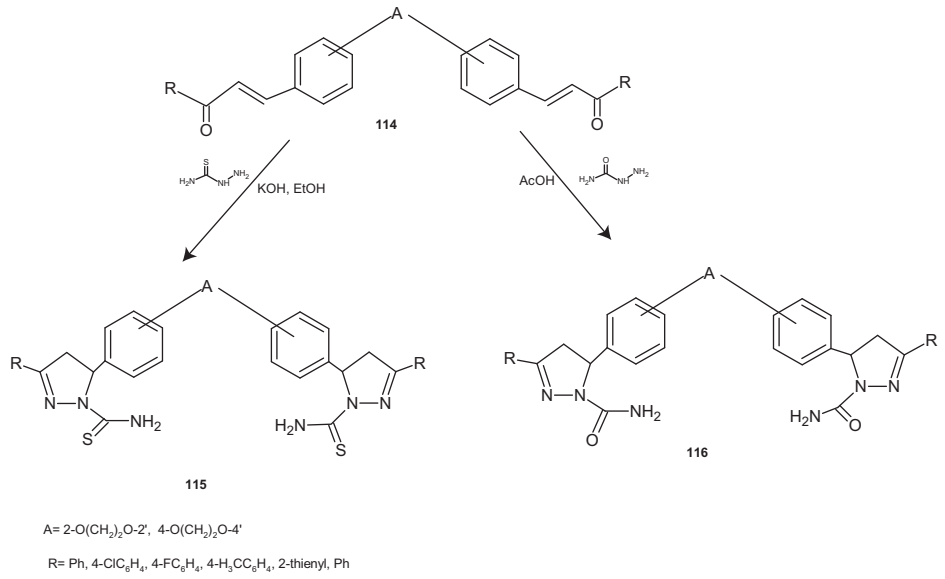
R^1= C_6H_5, C_6H_4Cl, $C_6H_4NO_2$, C_4H_3O, C_6H_4OH, C_5H_4N

R^2= C_6H_5, C_6H_5, C_6H_5, C_6H_5, C_6H_5, C_6H_5

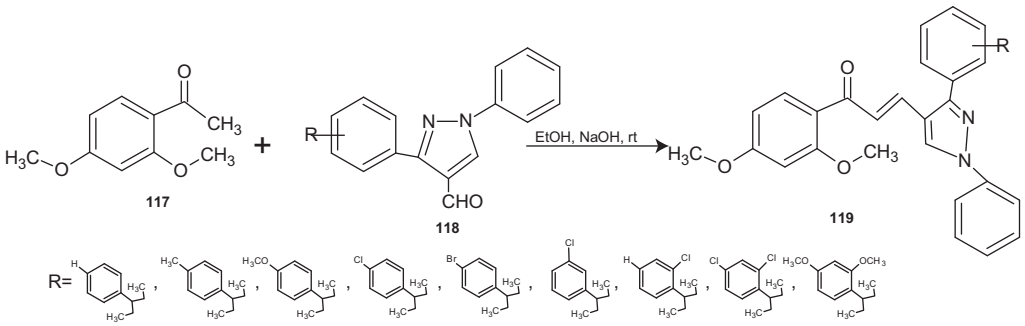
Scheme 26

diverse anti malarial leads (Schemes 48 and 49). This is the first instance wherein chromeno-pyrazolines have been found to be active antimalarial agents.

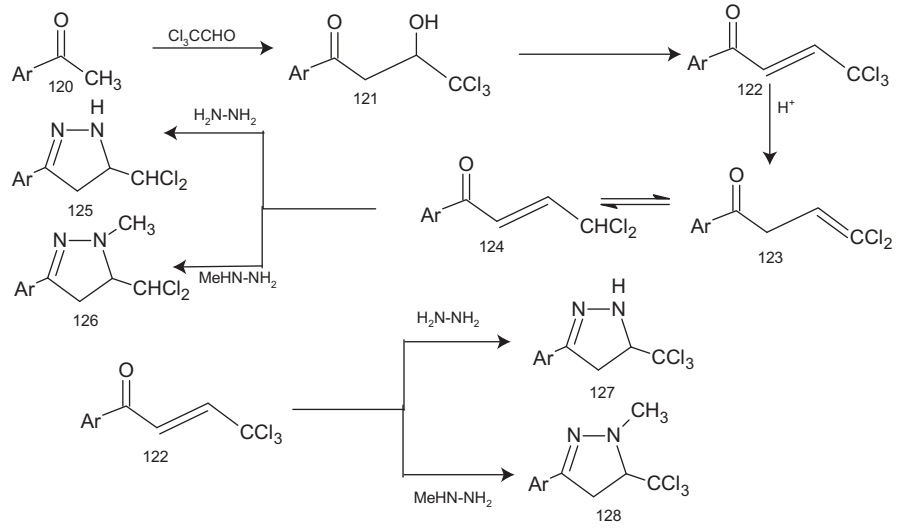
3,5-Diaryl pyrazolines analogs **217** were synthesized (Karuppasamy et al., 2010) from the reaction of **215** with hydrazine hydrate and evaluated for their monoamine



Scheme 27

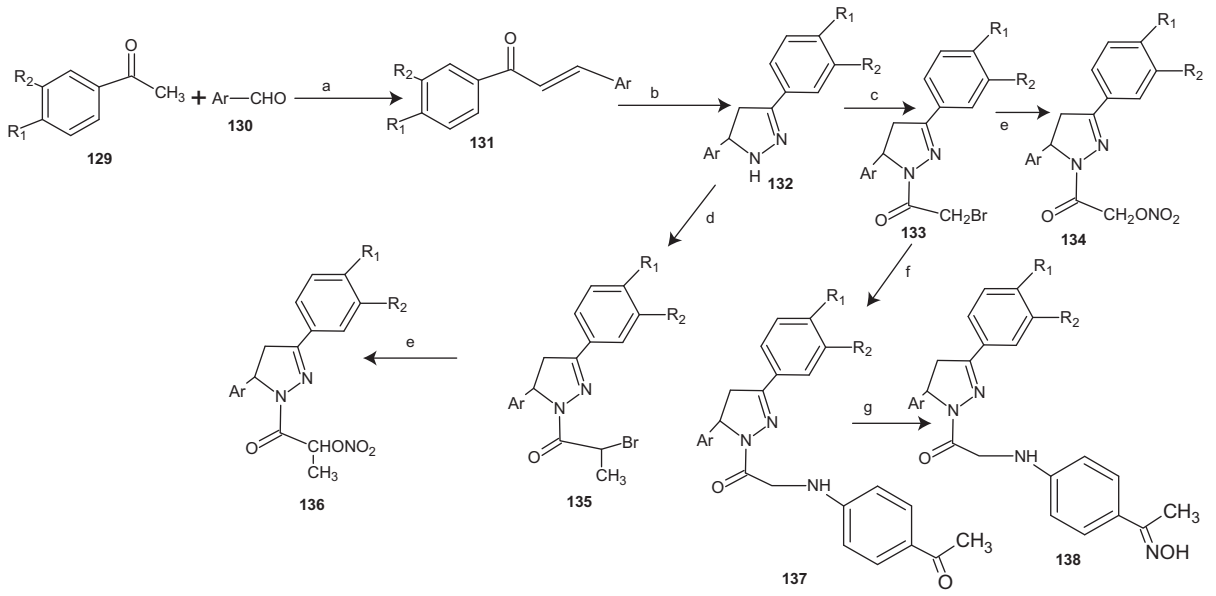


Scheme 28



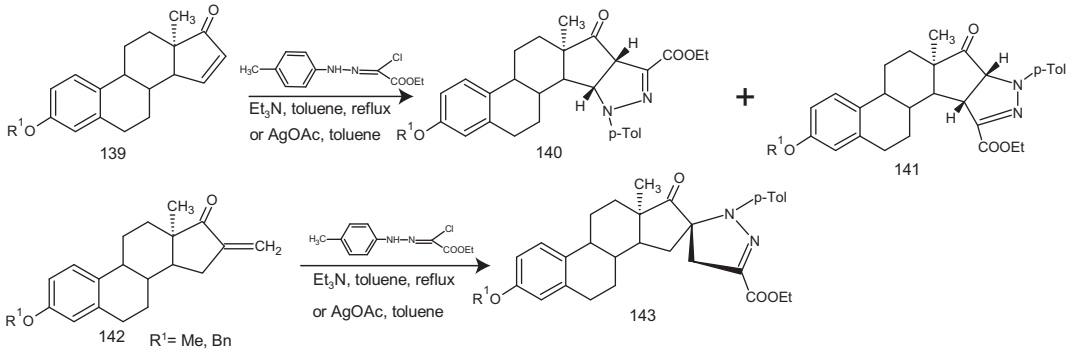
Ar= C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 4-$NO_2C_6H_4$, 4-Ph-C_6H_4, 2-$C_{10}H_7$, 2,4-$(CH_3)_2C_6H_3$

Scheme 29

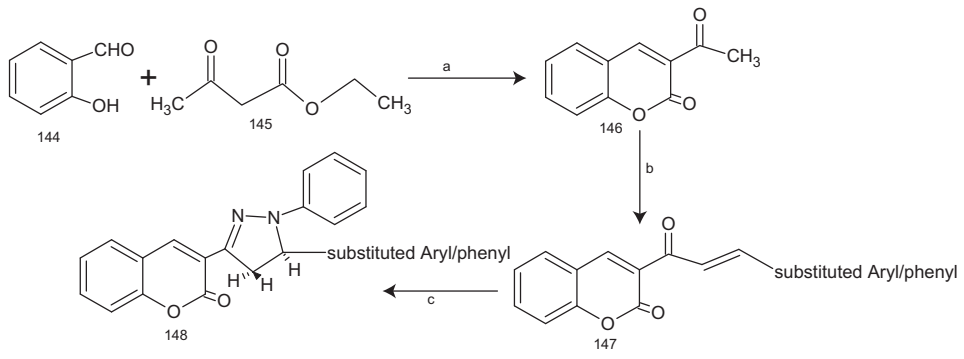


a)NaOH,EtOH; b)$NH_2NH_2.H_2O$, EtOH; c) $BrCH_2COBr$, K_2CO_3; d) $CH_3CH(Br)COOH$, ClCOOEt, Et_3N; e) $AgNO_3$, CH_3CN, f) p-NH_2 Acetophenone, K_2CO_3, acetone g) NH_2OH. HCl, EtOH

Scheme 30



Scheme 31

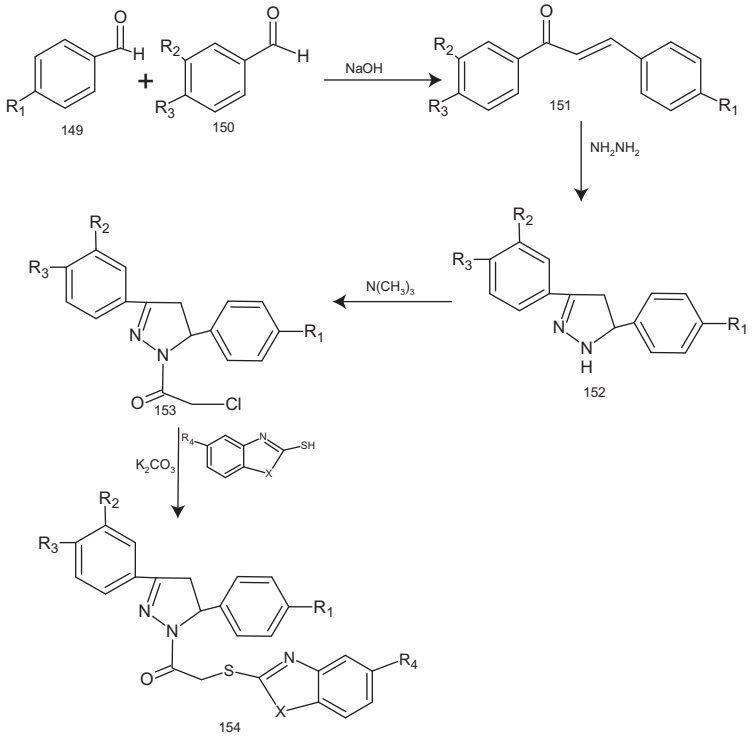


Reaction conditions: a) Piperidine, stir, rt, 20 min. b) Ar-CHO, piperidine/butanol c) hydrazine derivative, pyridine, reflux

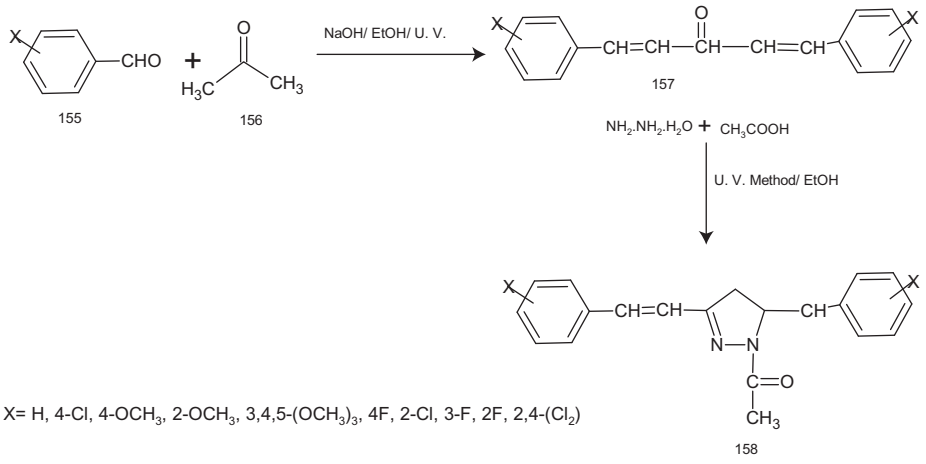
Scheme 32

oxidase (MAO) inhibitory activity (Scheme 50). These compounds were found reversible and selective toward MAO-A with selective index in the magnitude of 10^3–10^5.

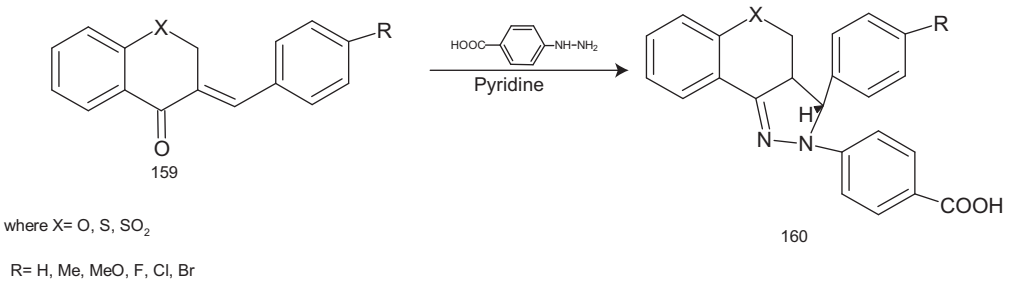
New pyrazolines derivatives **223** and **224** have been synthesized (Hussain and Sharma, 2010) according to the protocol as given in Scheme 51. In order to introduce



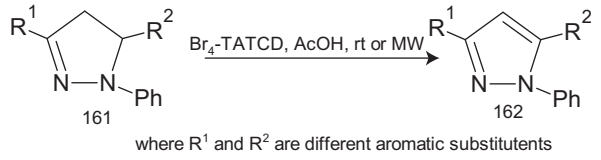
Scheme 33



Scheme 34



Scheme 35



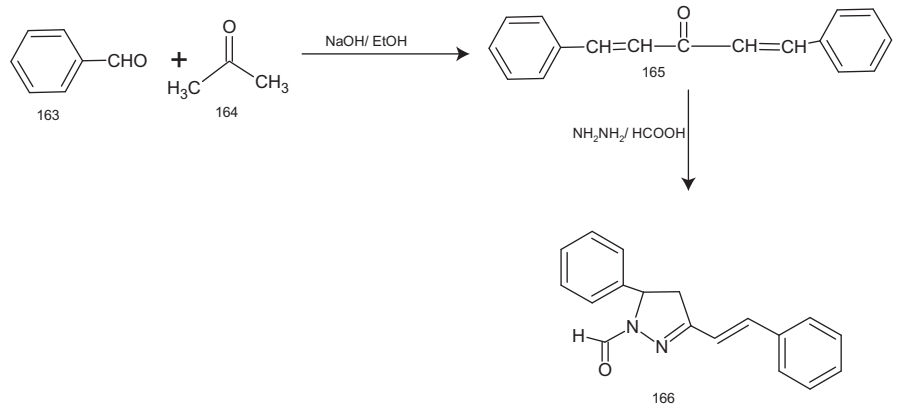
Scheme 36

methyl group at C-16 instead of C-13, dehydocestus lactone was allowed to react with an ethereal solution of diazoethane.

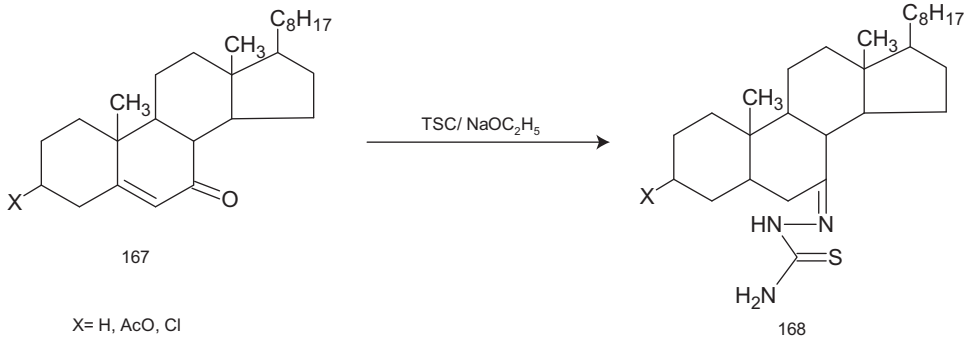
The synthesis (Sahoo et al., 2010) of novel 3,5-diaryl pyrazolines **226–230** have been investigated in order to study their monoamine oxidase (MAO) inhibitory property (Scheme 52). All the molecules were found to be reversible and selective inhibitor for either one of the isoform (MAO-A or MAO-B).

A series of 1,3,5-trisubstituted pyrazolines **234** were synthesized (Scheme 53) and evaluated for in vitro antimalarial efficacy against chloroquine sensitive (MRC-02) as well as chloroquine resistant (RKL9) strains of Plasmodium falciparum (Achraya et al., 2010). Some of the compounds showed better antimalarial activity than chloroquine against resistant strain of P. falciparum and were also found active in in vivo experiment.

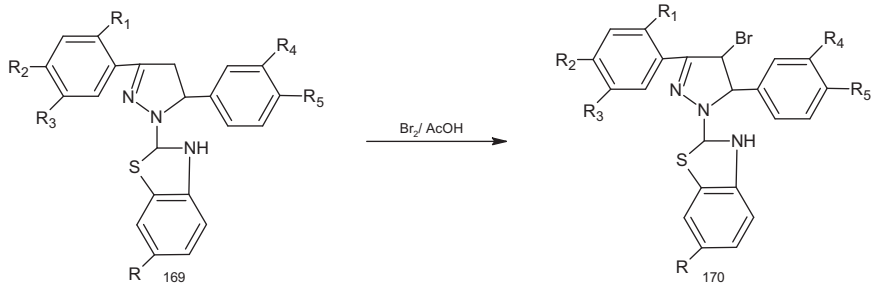
The reaction of pregnenolone **235** with substituted benzaldehydes resulted in the formation (Banday et al., 2010) of



Scheme 37

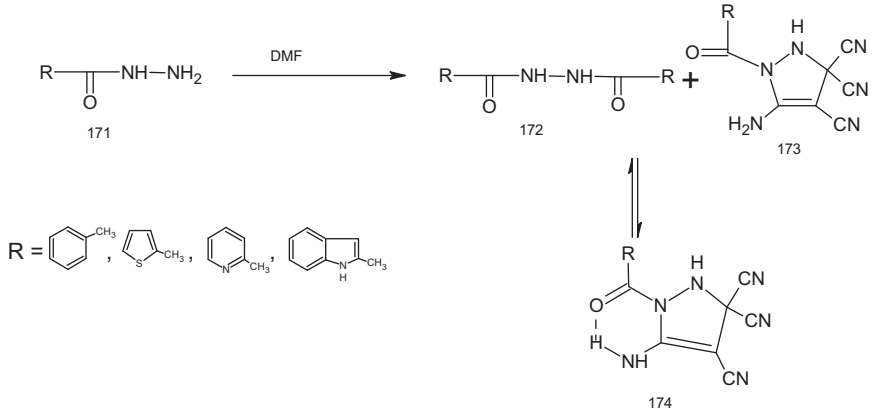


Scheme 38

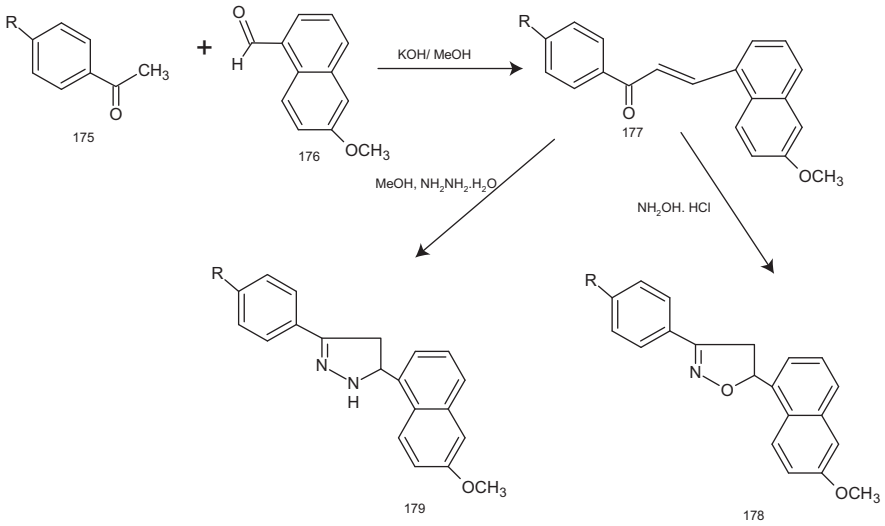


R= CH_3, R_1=R_2=R_3=R_4=R_5=H; R=OCH_3, R_1=OH, R_2=R_3=R_4=H, R_5=Cl; R=OCH_3, R1=H, R_2=Cl, R_3=R_4=H, R_5=Cl; R=CH_3, R_1=H, R_2=CH_3, R_3=H, R_4= R_5=OCH_3; R=OCH_3, R_1=OH, R_2=R_3=R_4=H = R_5

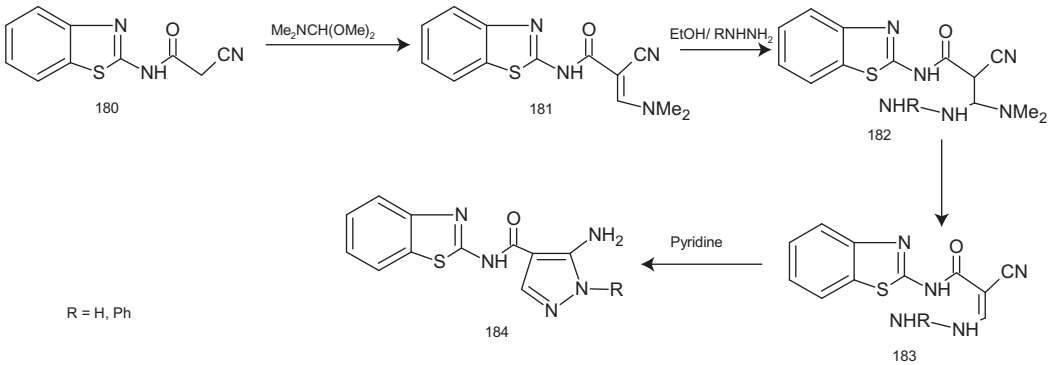
Scheme 39



Scheme 40



Scheme 41



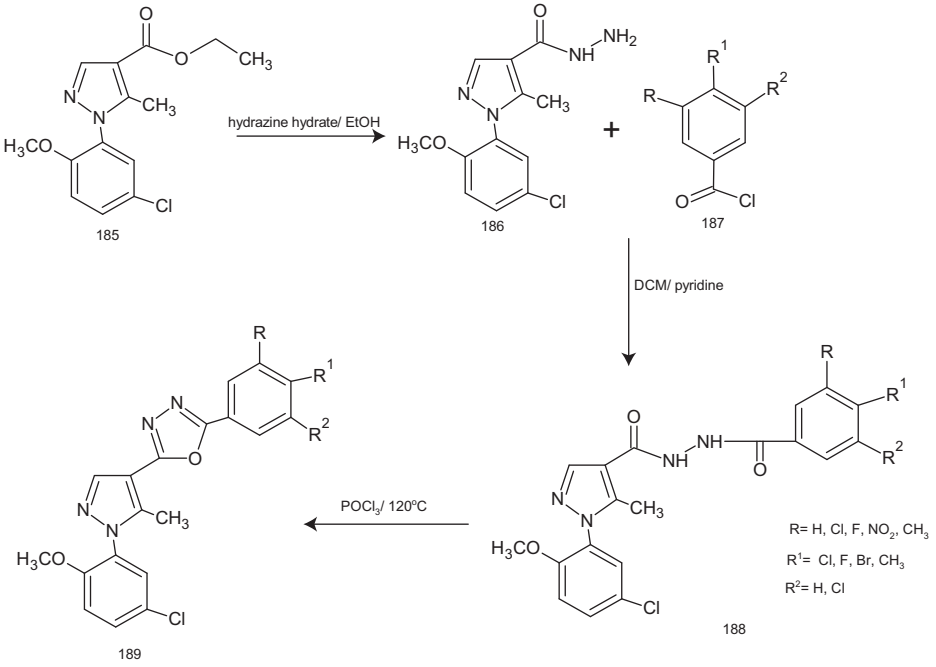
Scheme 42

the corresponding benzylidine derivatives **236** and finally the reaction of the later with hydrazine hydrate provided pyrazoline **237** as the final product (Scheme 54).

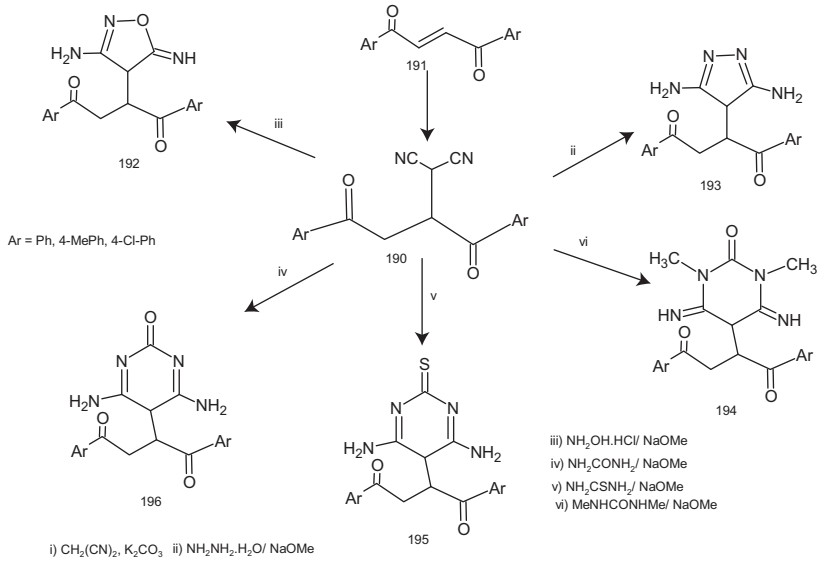
Novel pyrazolines **242** and **245** were synthesized (Chen et al., 2010) from the cyclization of chalcone **240** and **243** with hydrazines **241** and **244** respectively according to the protocol as given in the Scheme 55.

Chalcones **248** were prepared from substituted acetophenones and substituted benzaldehydes (Scheme 56) and condensed with hydrazine hydrate (Venkataraman et al., 2010) in methanol to yield the corresponding pyrazolines **249**.

Some new pyrazoline derivatives **254** were synthesized (Ramesh and Sumuna, 2010) by reacting chalcones **252** of



Scheme 43



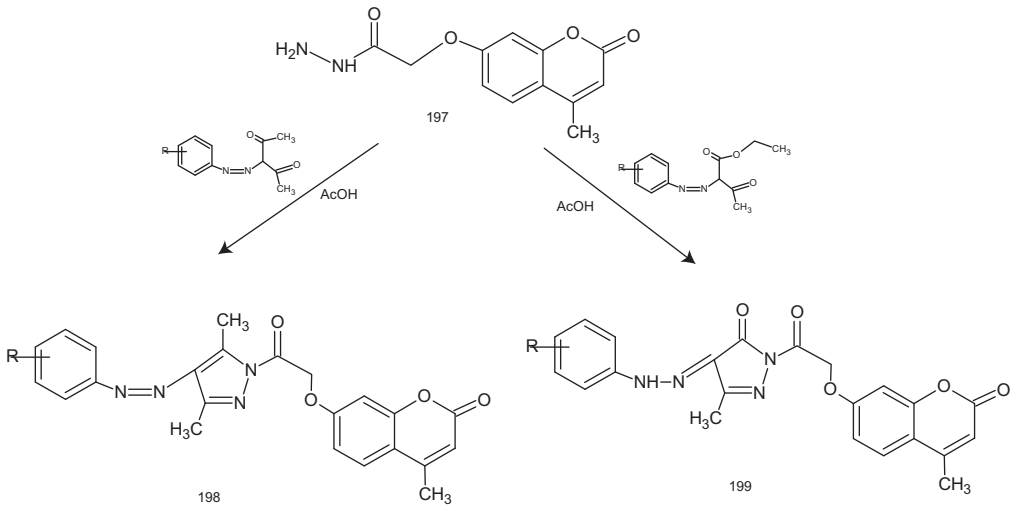
Scheme 44

2-acetyl thiophene **250** with phenyl hydrazine hydrochloride in the presence of alcohol and pyridine (Scheme 57).

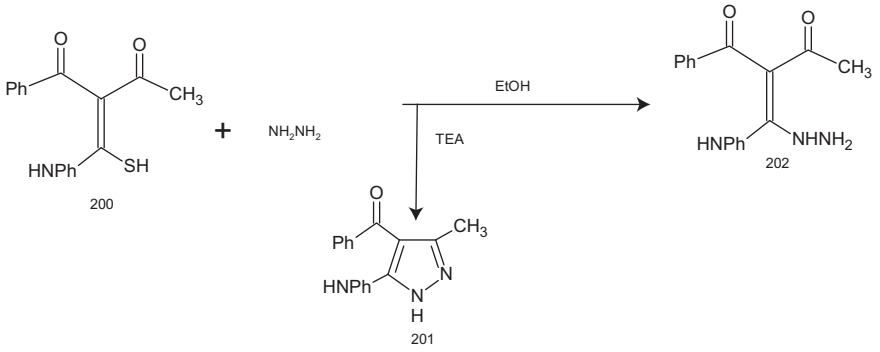
An efficient method has been established for the synthesis (Kasabe and Kasabe, 2010) of new pyrazoline derivatives **260** which were obtained from the reaction of chalcone **259** with thiosemicarbazide under alkaline alcoholic condition. The intermediate **259** was released from the reaction sequence as shown in Scheme 58.

The synthesis (Gembus et al., 2010) of biologically important 3,4-substituted pyrazolines **263** has been achieved by an organocatalyzed aza-Michael/transimination domino reaction between hydrazones and enones **262** making use of a mixture of heterogeneous resin-bound acid/base reagents (Scheme 59).

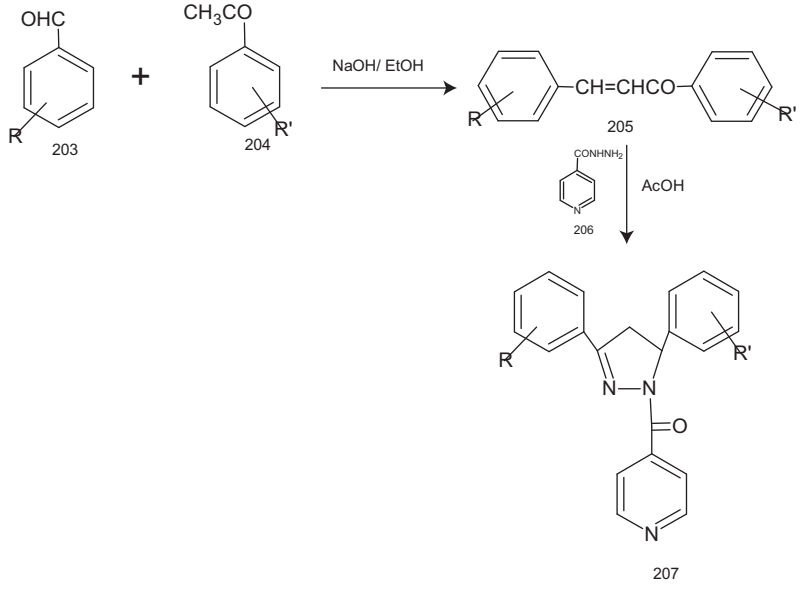
A series of new succinyl spacer bis-(3,5-substituted 2-pyrazolines and 1*H*-pyrazoles) and the non-symmetrical 2-pyrazolines derivatives had been synthesized (Bonacorso et al., 2010). The succinyl substituted bispyrazoles **266** were obtained from the cyclocondensation reactions of 4-substituted 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones **264** (where the 4-substituents are H, Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$,



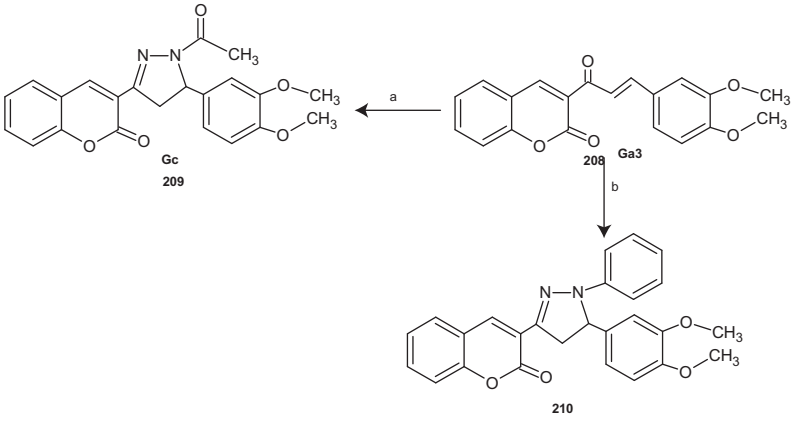
Scheme 45



Scheme 46

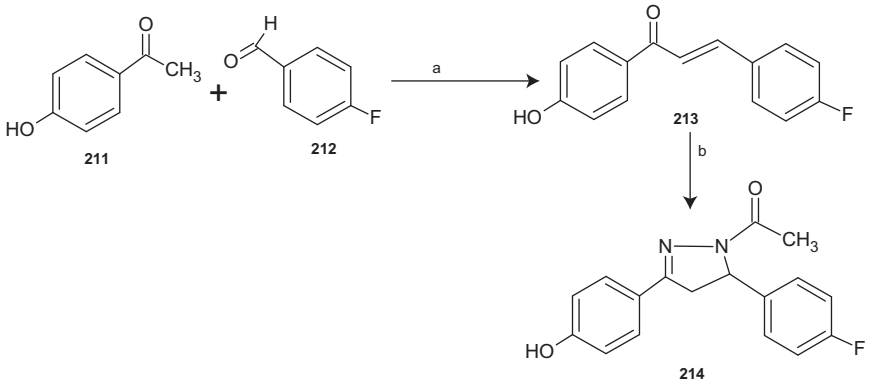


Scheme 47



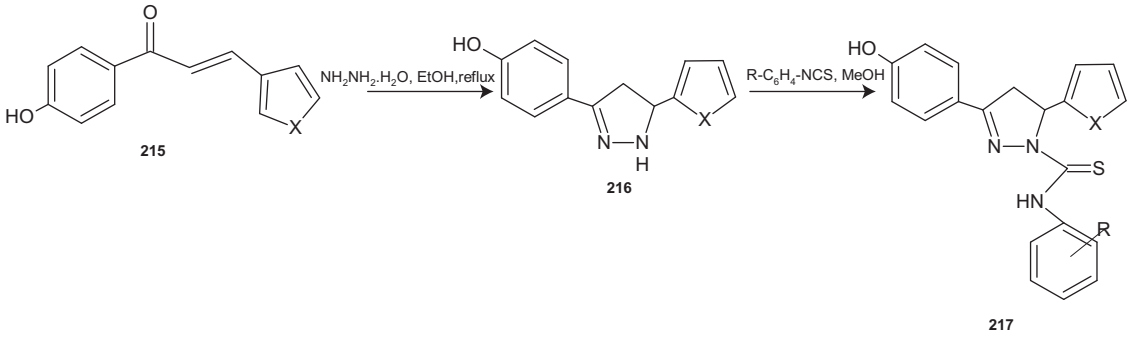
Reagents and conditions a) $NH_2NH_2.H_2O$, AcOH; b) MeOH, $PhNHNH_2$, AcOH

Scheme 48



Reagents and Conditions a) NaOH/ MeOH, rt b) $NH_2NH_2.H_2O$/ AcOH

Scheme 49

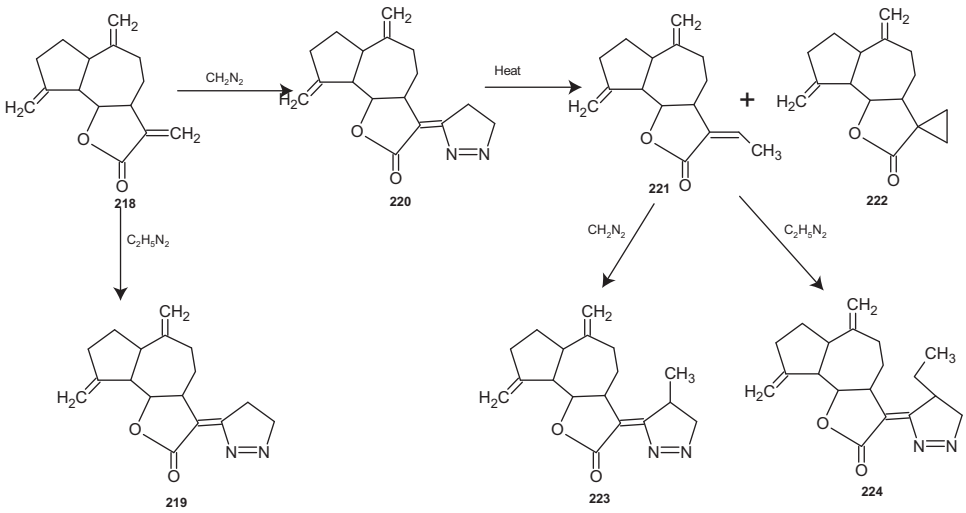


Scheme 50

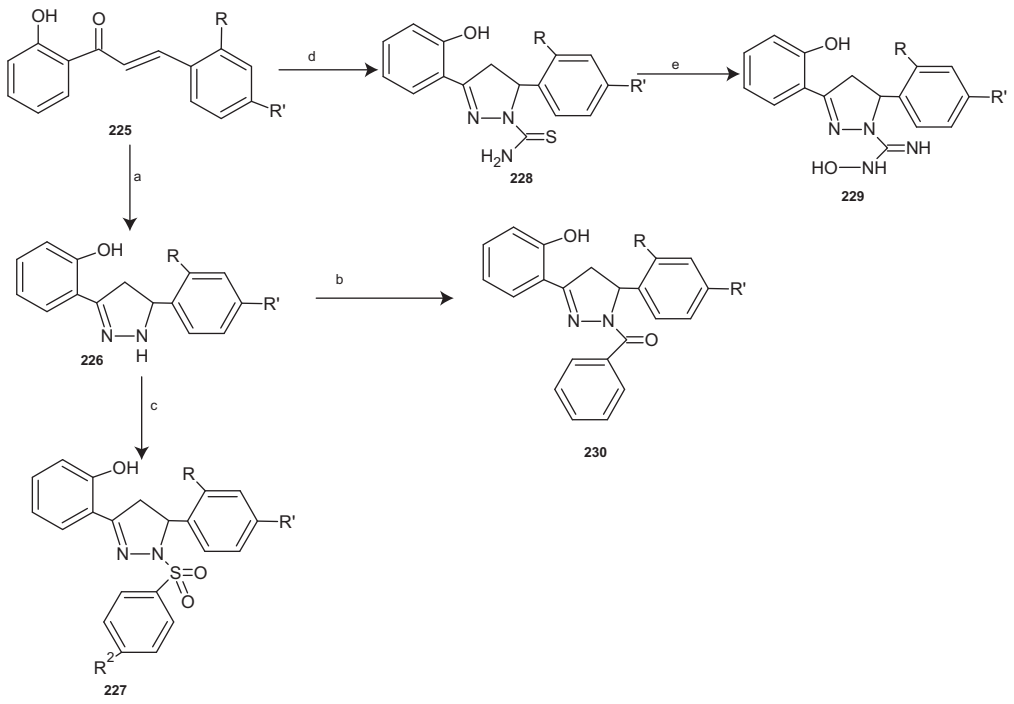
1-naphthyl and 2-furyl) with succinic acid dihydrazide in ethanol as solvent under the controlled reaction conditions (Scheme 60).

The complexes of 2-(8-quinolinol-5-yl)-amino methyl-3(4-methyl phenyl)-5-(phenyl)-pyrazoline **272** with Cu(II), Mn(II) and Zn(II) have been synthesized (Patel et al., 2010) according to the method which is described in Scheme 61.

Recently, B. Vibhute et al. Mokle et al. (2010) have prepared a series of 2-pyrazolines **274** from the cyclization reaction of α,β-unsaturated ketone **273** with hydrazine



Scheme 51



R=OH, H; R^1= H, OH; R^2= CH_3

a) $NH_2NH_2.H_2O$, EtOH; b) PhCOCl, pyridine, reflux, c) R^2-$C_6H_4SO_2Cl$, THF d) thiosemicarbazide, EtOH e) CH_3I/ NH_2OH

Scheme 52

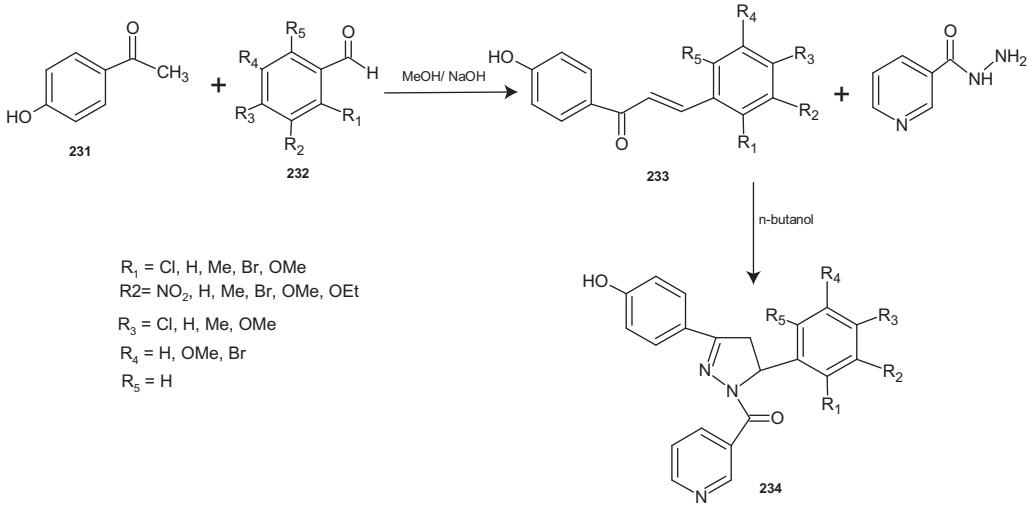
hydrate/phenyl hydrazine using triethanolamine as the solvent (Scheme 62).

New pyrazolines **278** were synthesized starting from the condensation of substituted aldehydes with substituted acetophenones in the presence of alkali to yield chalcones **277**. The resulted chalcones were further reacted with phenyl hydrazine hydrochloride in ethanol and pyridine (Das et al., 2010) to provide **278** as the final products (Scheme 63).

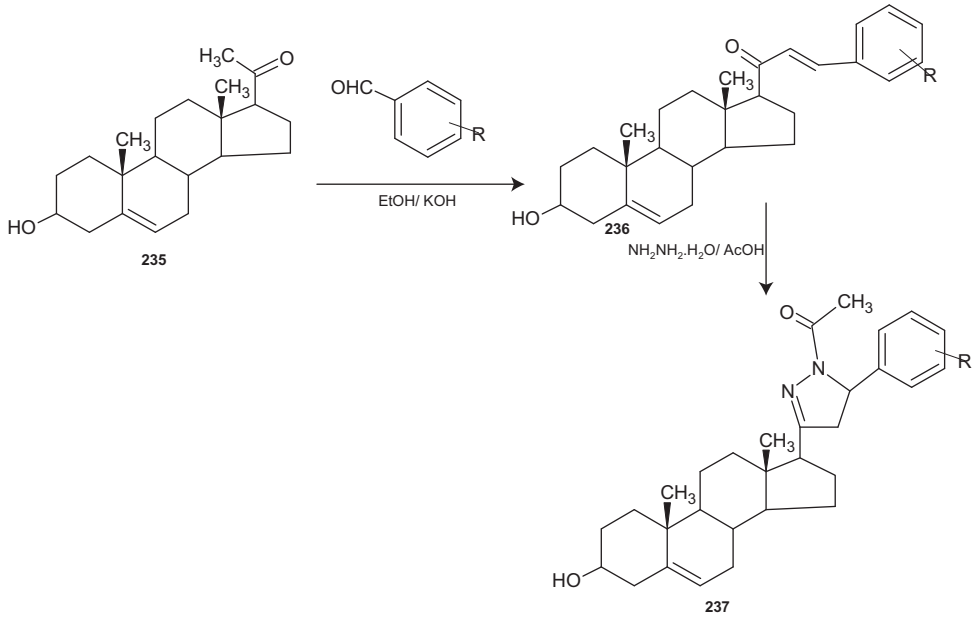
New pyrazolines have been obtained from the condensation of chalcones of 4^1-piperazine acetophenone with phenyl hydrazine hydrochloride (Rahaman et al., 2010).

The aldol condensation reaction (Nassar, 2010) between 3-indolaldehyde **279** and 4-methoxyacetophenone **280** afforded chalcone derivatives **281** which were further reacted with the cyclizing agents such as hydrazine hydrate and phenyl hydrazine to yield pyrazolines **282** and **281** (Scheme 64).

The heterocyclic compounds **286** have been synthesized (Gupta et al., 2010) starting from the Claisen–Schmidt reaction of aryl methyl ketones **284** and 4-chlorobenzaldehyde **285** to give **286**. The reaction of chalcone with phenylhydrazine in glacial acetic acid using ultrasonic irradiation led to the formation of 1,3,5-triphenyl-pyrazolines **287** (Scheme 65).



Scheme 53



Scheme 54

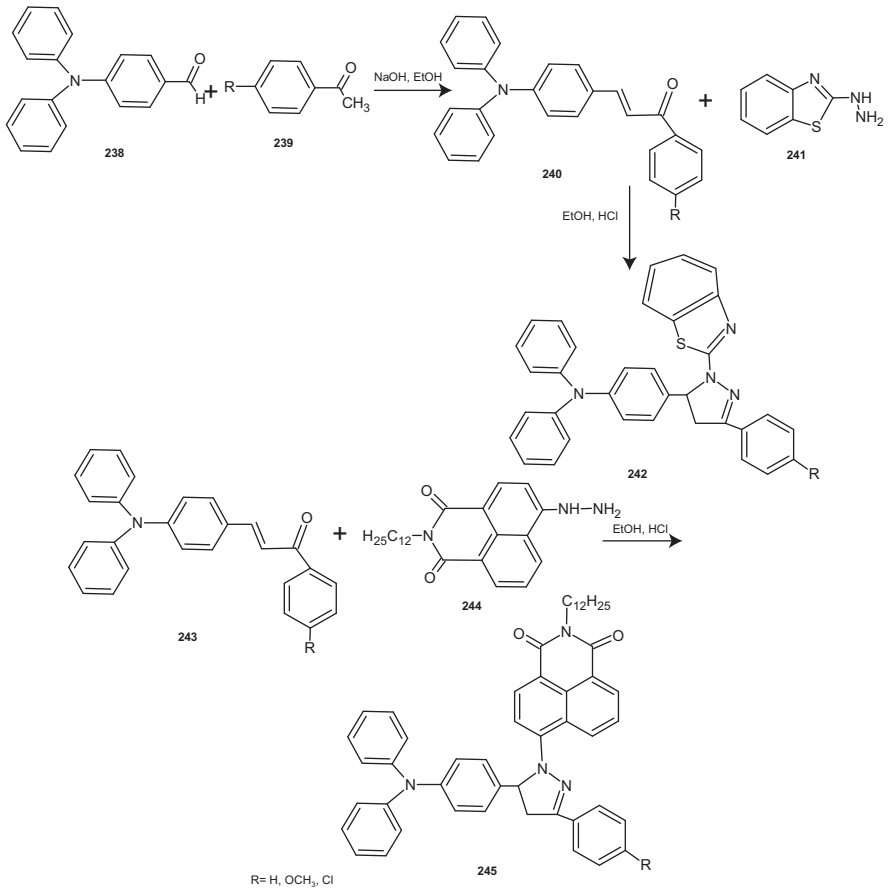
An efficient and simple procedure has been developed (Azarifar et al., 2010) for the oxidation of 1,3,5-trisubstituted 4,5-dihydro-1*H*-pyrazoles **289** and isoxazoles **289** to their corresponding aromatic derivatives which was promoted by bis-bromine-1,4-diazabicyclo[2.2.2]octane complex (DABCO-Br_2) in acetic acid at room temperature (Scheme 66).

1-Benzimidazolyl-3-aryl-prop-2-ene-1-ones **291** have been transformed into N1-substituted pyrazoline derivatives (Rajora et al., 2010) by reacting with phenyl hydrazine, hydrazine hydrate in the presence of formic acid under solvent free microwave induced protocol to give **292** and **293** respectively while the reaction of **291** with thiosemicarbazide under anhyd. K_2CO_3 could provide **294** (Scheme 67).

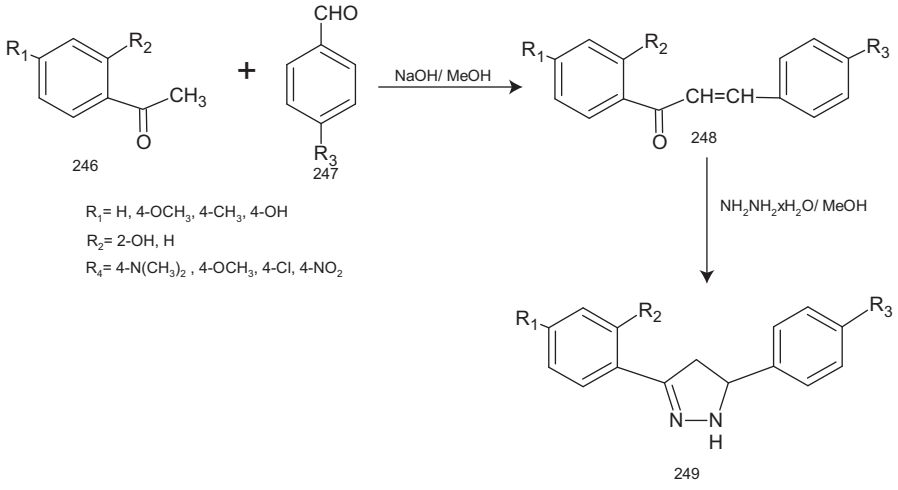
The chalcones **297** and **300** were released (Babu et al., 2007) starting from 2-acetyl benzofuran **295** and further condensed with different aromatic acid hydrazides to give the corresponding pyrazolines **298** and **301** (Scheme 68).

Pawan K. Sharma and co-workers (Sharma et al., 2010) have reported the synthesis of new pyrazolylpyrazolines **306**. These compounds were obtained by the reaction of appropriate chalcones **304** with 4-hydrazinobenzenesulfonamide hydrochloride in alcoholic medium (Scheme 69).

The pyrazoline compounds **309** and their 1-acetylated derivatives (Congiu et al., 2010), bearing a 3,4,5-trimethoxyphenyl moiety combined with a variety of substituted phenyl rings were obtained according to the reaction sequence as shown Scheme 70 and these compounds were also evaluated for antitumor activity. The results of the in vitro assay against a non-small cell lung carcinoma cell line (NCI-H460) showed several compounds to be endowed with cytotoxicity



Scheme 55

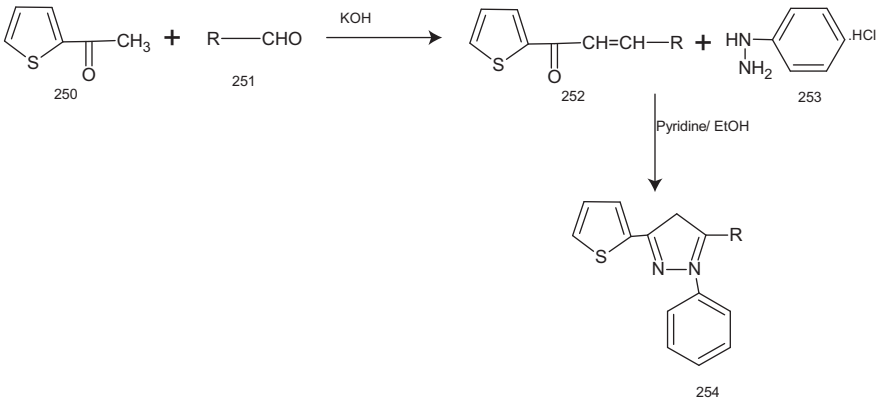


Scheme 56

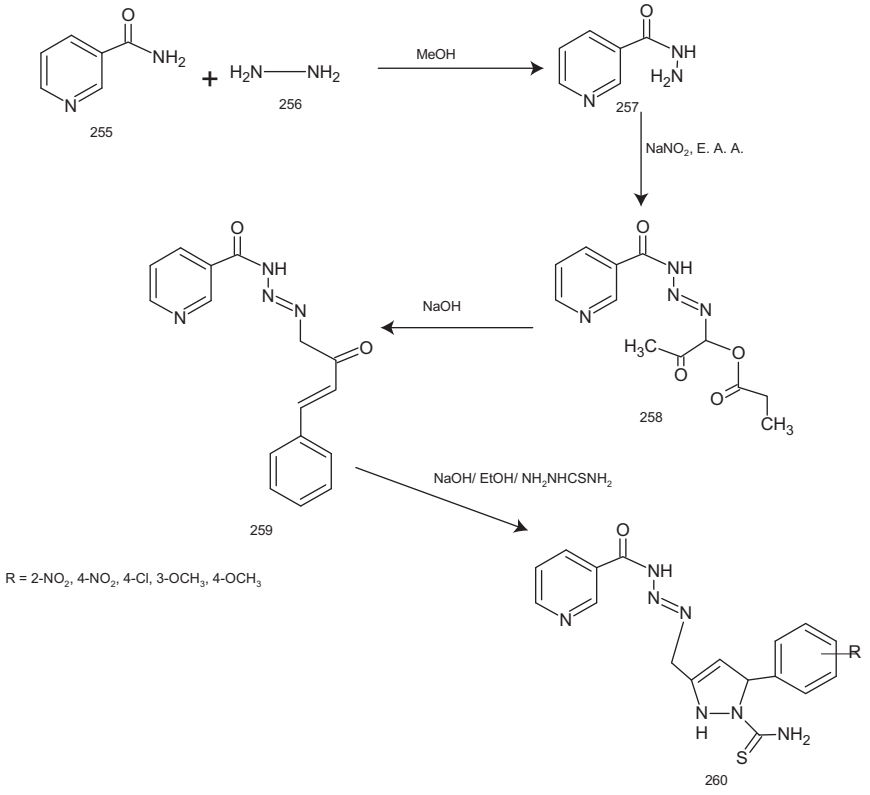
in micromolar to submicromolar range, depending on the substitution pattern and position of aryl rings on 4,5-dihydropyrazole core. Potent and selective activity was also observed in the NCI 60 human cancer cell line panel.

An efficient preparation of compounds **314** has been reported with the objective of discovering the novel (Scheme 71) and potent anti-inflammatory agent (Chandra et al., 2010). The compound 1-(2′,4′-Chloroacridine-9′-yl)-3-(5′-pyridine-4-yl)-(1,3,4-oxadiazol-2-ylthiomethyl)-pyrazole-5-one **314** showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg p.o.

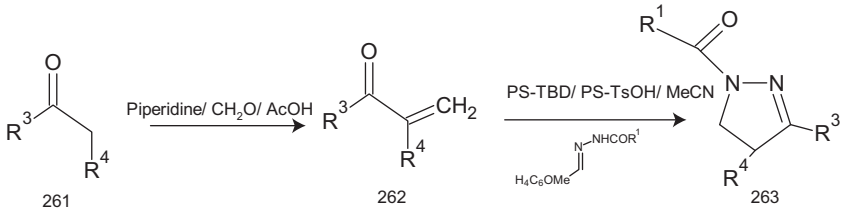
A series of 1-acetyl/propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-pyrazolines **318** were synthesized (Girisha et al., 2010) in one step by condensing suitably substituted propenones **317** with hydrazine in the presence of acetic/propionic acid (Scheme 72).



Scheme 57

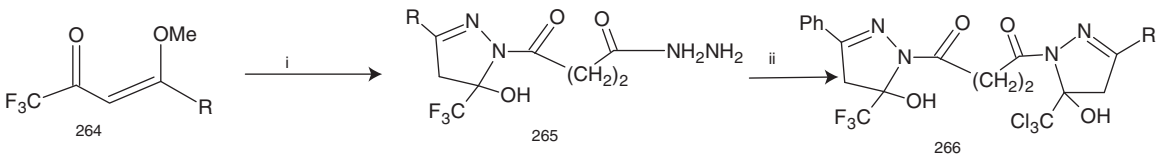


Scheme 58



Scheme 59

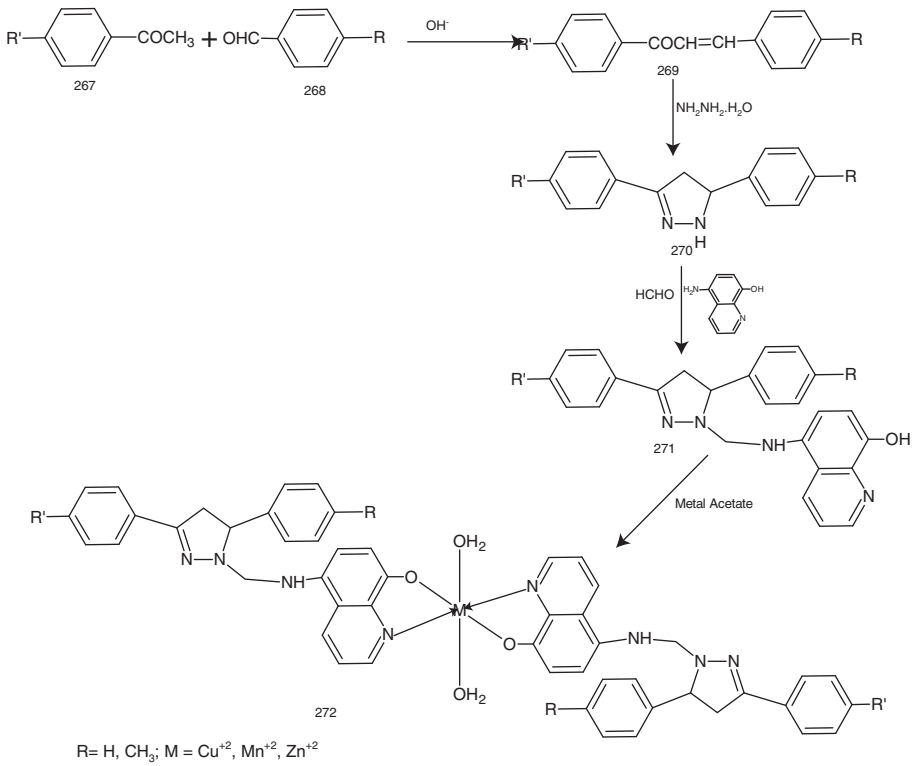
The reaction of 2-cyano-N-(9,10-dioxo-9,10-dihydro-anthracen-2-yl)-acetamide **320** with phenyl isothiocyanate/ dimethylsulphate afforded (Gouda et al., 2010) the corresponding ketene N,S-acetal **322** which upon treatment



R = Me, Ph, 4-OMePh, 4-NO_2Ph

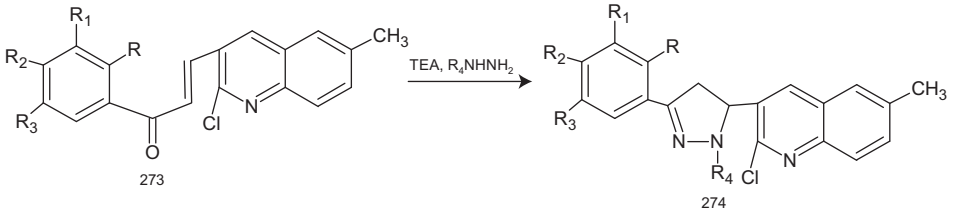
i= $(NH_2NHCOCH_2)_2$, EtOH ii) $CCl_3C(OMe)R$, EtOH

Scheme 60



R= H, CH_3; M = Cu^{+2}, Mn^{+2}, Zn^{+2}

Scheme 61



R = OH, H R_1 = I R_3= I, Cl; R_4= H

R_2= H, OH

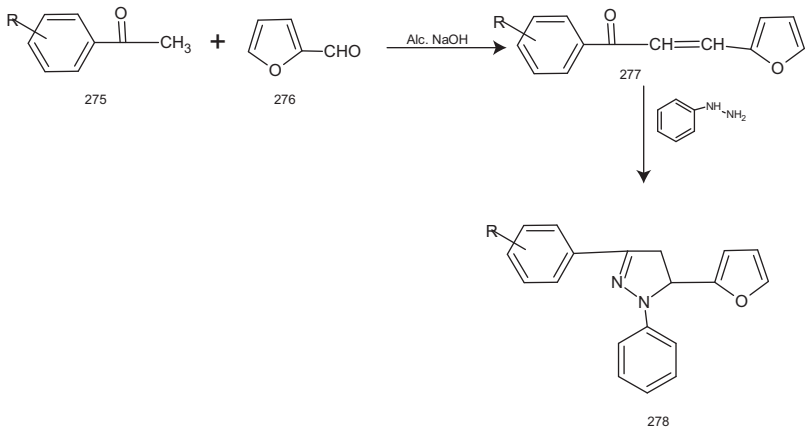
Scheme 62

with hydrazine hydrate and 4-aminoantipyrine resulted in the formation of pyrazole derivatives **323** and **324** respectively (Scheme 73).

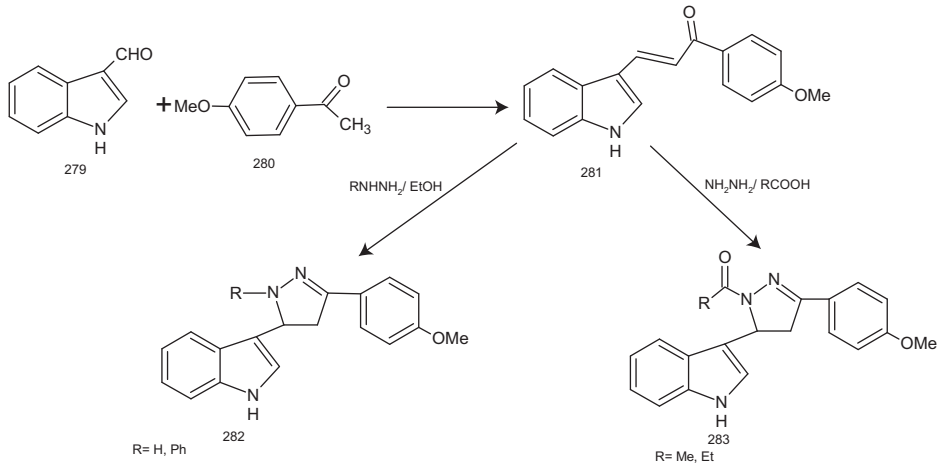
The treatment (Abu-Surrah et al., 2010) of 5-hydrazino-1,3-dimethyl-4-nitro-1*H*-pyrazole **325** with substituted benzaldehydes **326** in methanol gave new substituted Schiff base ligands **327** (Scheme 74).

Recently, synthesis and pharmacological evaluation of a new class of human carbonic anhydrase (hCA) inhibitors, 1,5-diarylpyrrole-3-carboxamides **331** have been reported (Gluszok et al., 2010) and these derivatives were prepared by a solid-phase strategy involving a PS(HOBt) resin (Scheme 75).

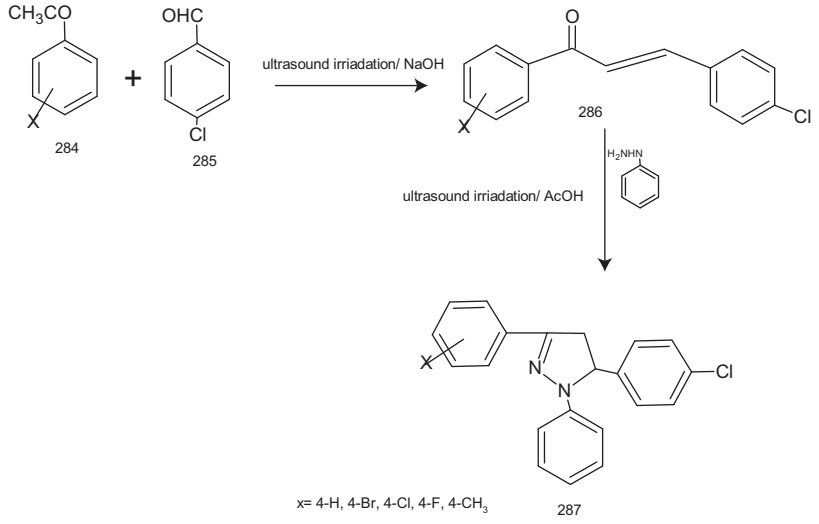
A series of novel 5-aryl-1-arylthiazolyl-3-ferrocenyl-pyrazoline derivatives **335** have been synthesized (Liu et al., 2010) by



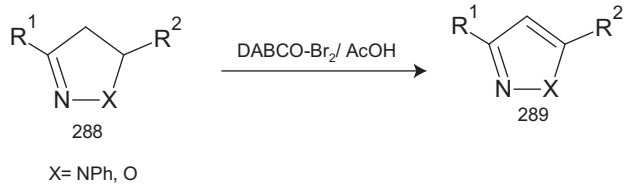
Scheme 63



Scheme 64



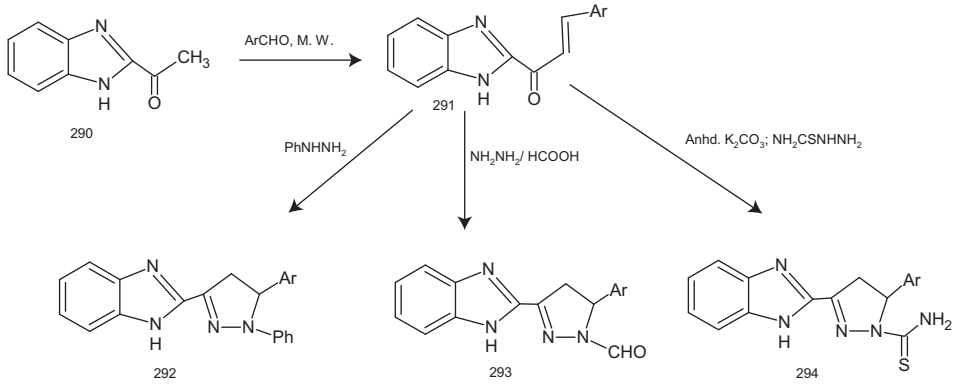
Scheme 65



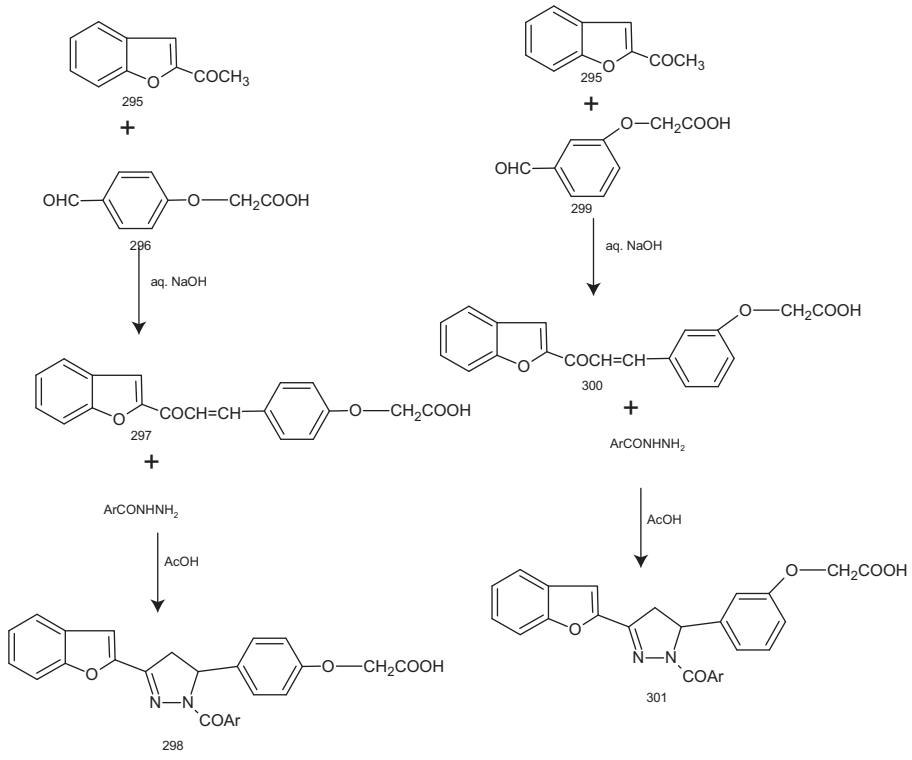
Scheme 66

the reaction of ferrocenyl chalcone **383** and thiosemicarbazide followed by the reaction with 2-bromo-1-arylethanone in 48–90% yields (Scheme 76).

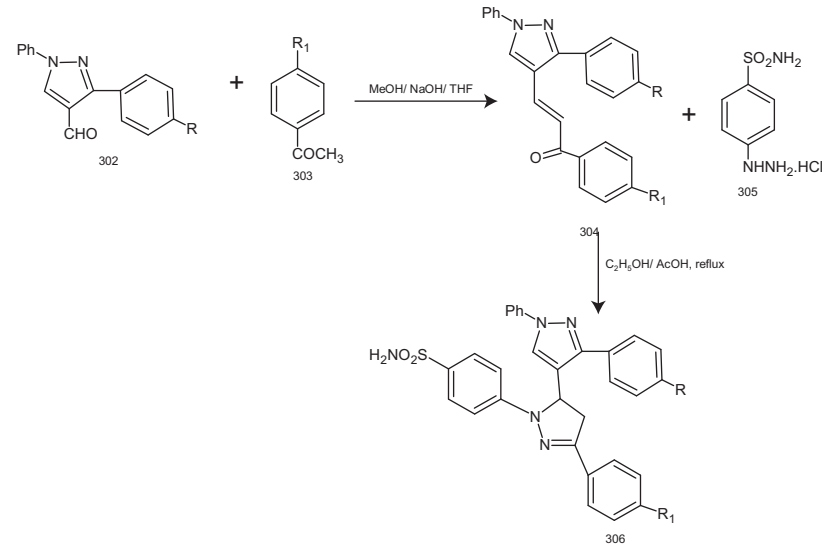
To find structural requirements for more active antiamoebic agents than metronidazole, the synthesis and comparative QSAR modeling was done on a variety of 1-N-substituted thiocarbamoyl-3-phenyl-2-pyrazolines **335a** (Adhikari et al., 2010). The best model was obtained by using PLS technique with R2A and R2CV value of 88.50% and 82.90%, respectively. Amoebicidal activity may increase when Wang–Ford charges at atom numbers 6 and 12 have large positive values. Number of six-membered ring and sum of Kier–Hall electrotopological states may also increase the amoebicidal activity when these have large positive values. Increasing value of rotatable bond fraction, approximate surface area and mean atomic polarizability scaled on carbon atom may be detrimental for antiamoebic activity. Decrease in values of electrostatic potential charges at atom numbers 1 and 12 may be conducive for activity and the electrophilic attacks may be favorable at these positions.



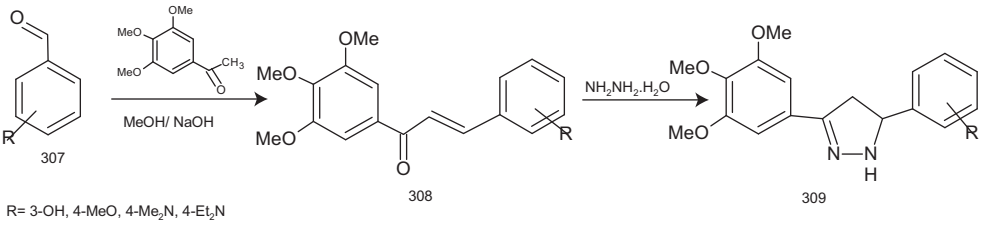
Scheme 67



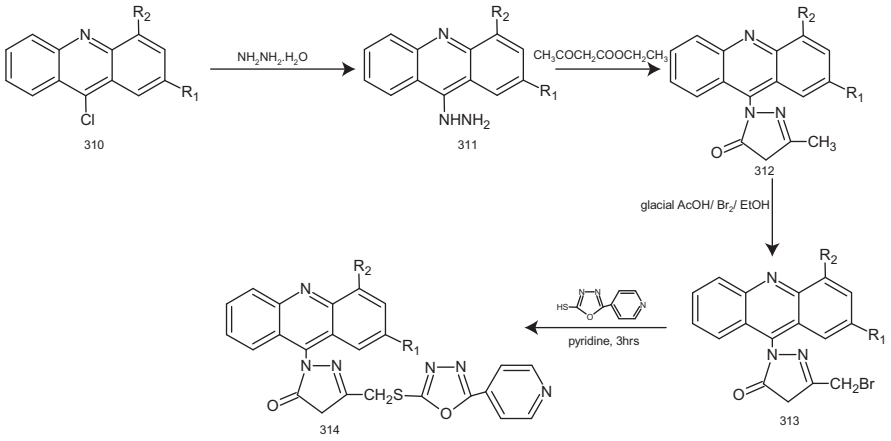
Scheme 68



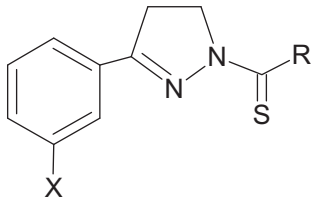
Scheme 69



Scheme 70



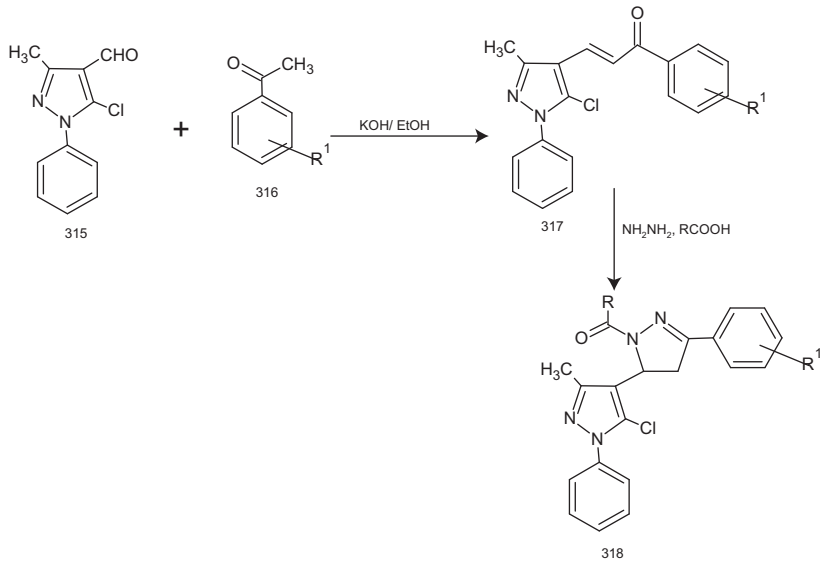
Scheme 71



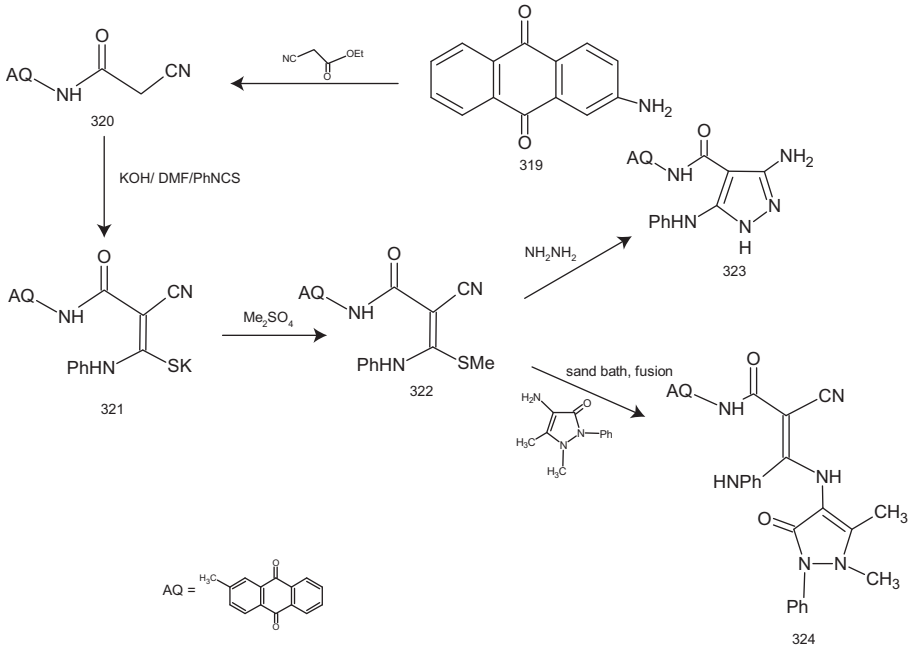
335a

The reaction of **336** with primary amine leads to the formation of pyrrole (Xue et al., 2010) while similar treatment of **336** with secondary amine provides **337** and **338** (Scheme 77).

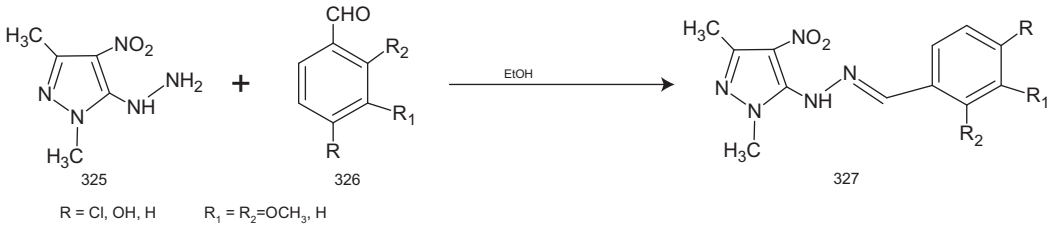
A convenient synthesis (Krishna and Prapurna, 2010) of pyrazolines **341** is reported via DABCO mediated reaction of



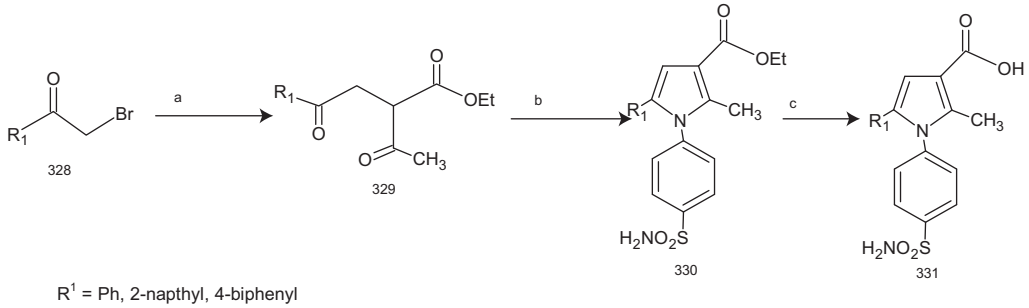
Scheme 72



Scheme 73



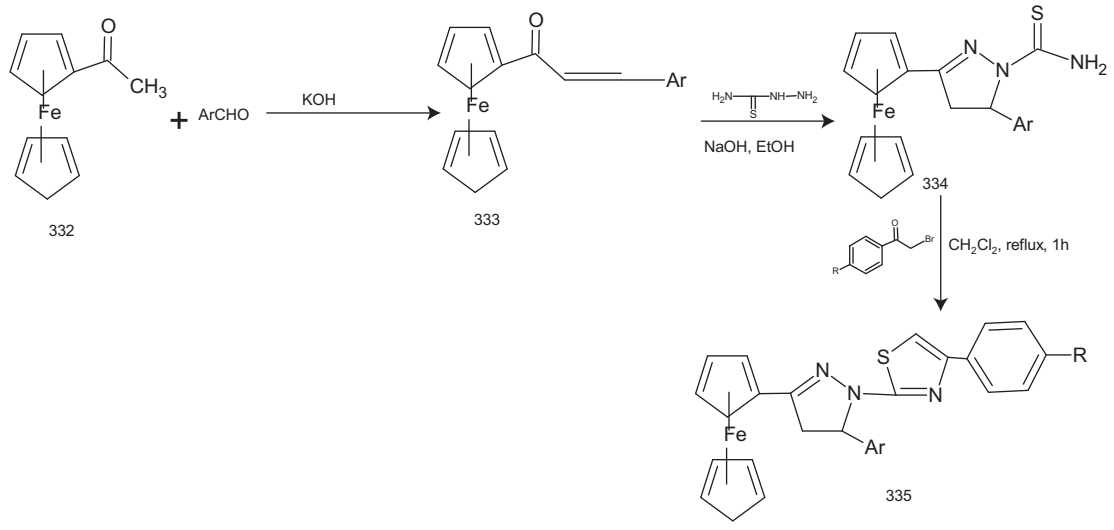
Scheme 74



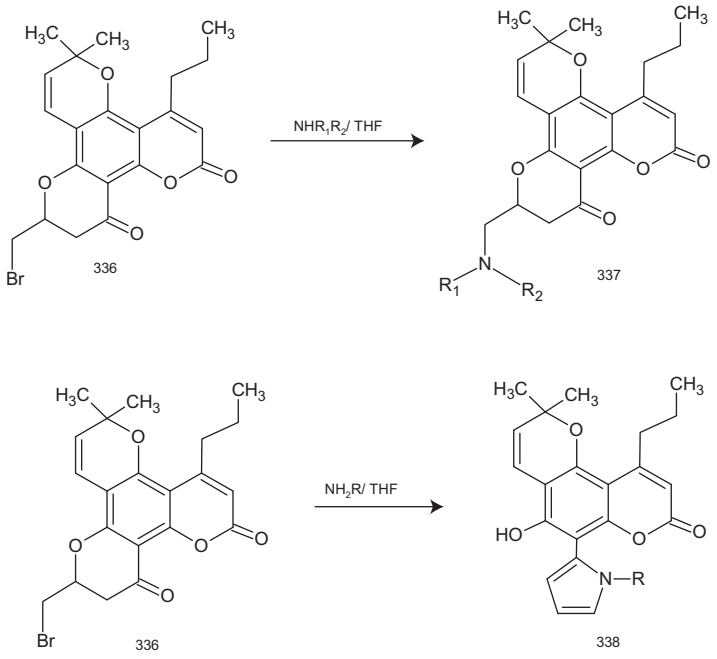
R^1 = Ph, 2-napthyl, 4-biphenyl

a = i) NaH, ethyl acetoacetate, THF ii) bromo ethyl ketone b) 4-amino benzenesulfonamide, p-toluenesulfonic acid, EtOH, c) NaOH, EtOH

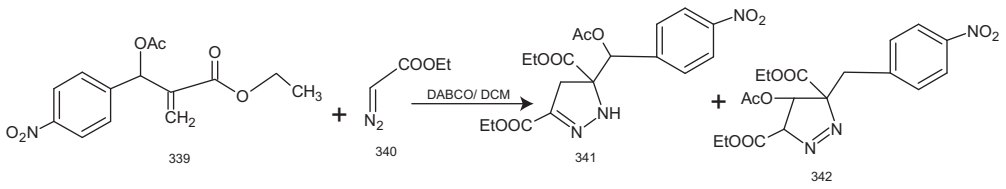
Scheme 75



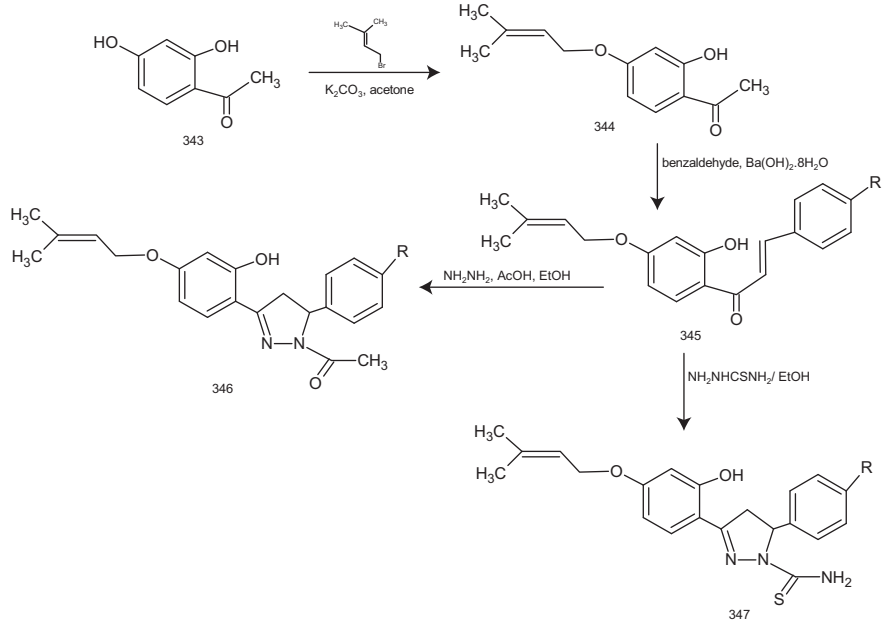
Scheme 76



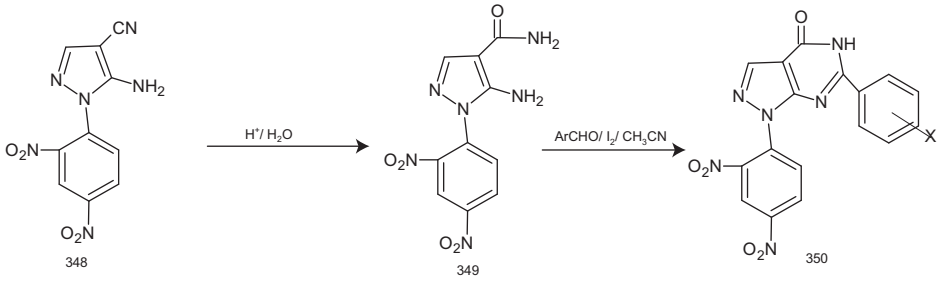
Scheme 77



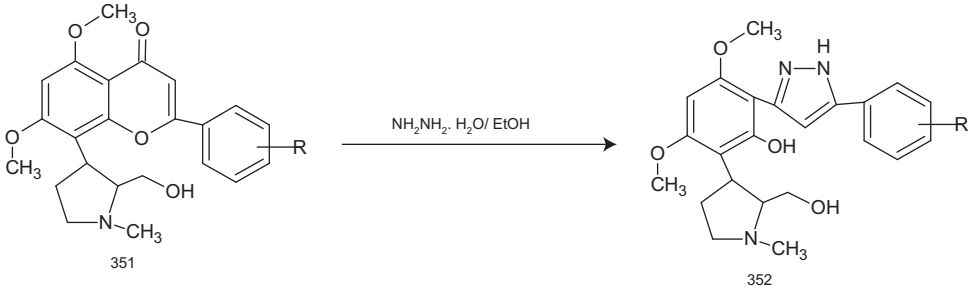
Scheme 78



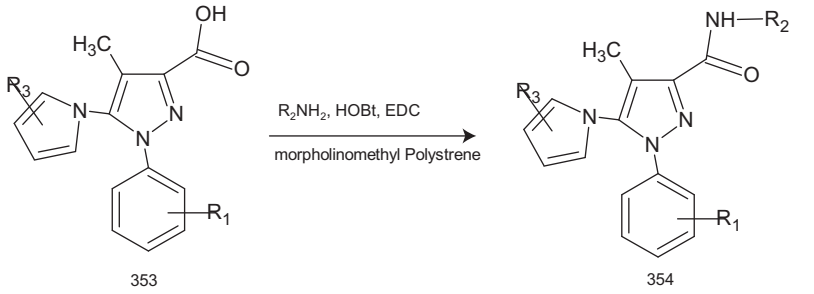
Scheme 79



Scheme 80

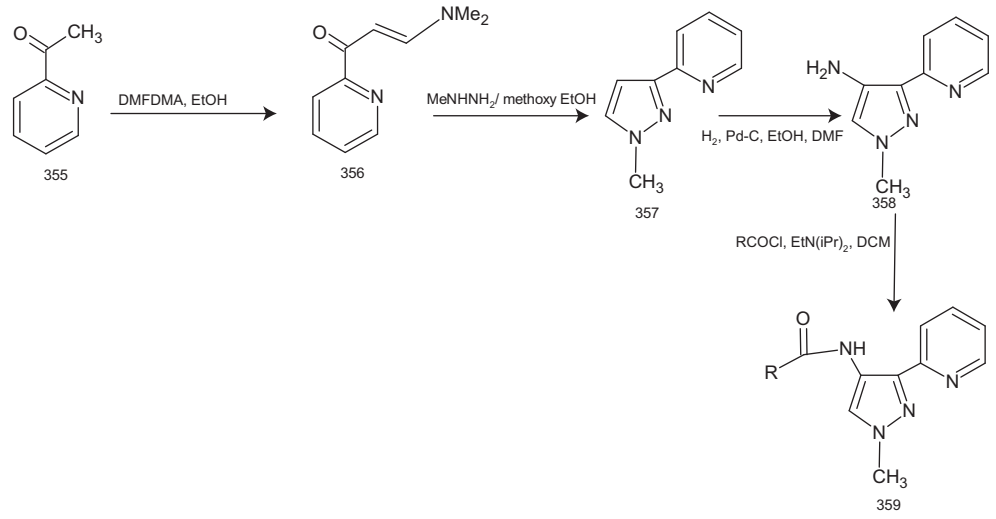


Scheme 81



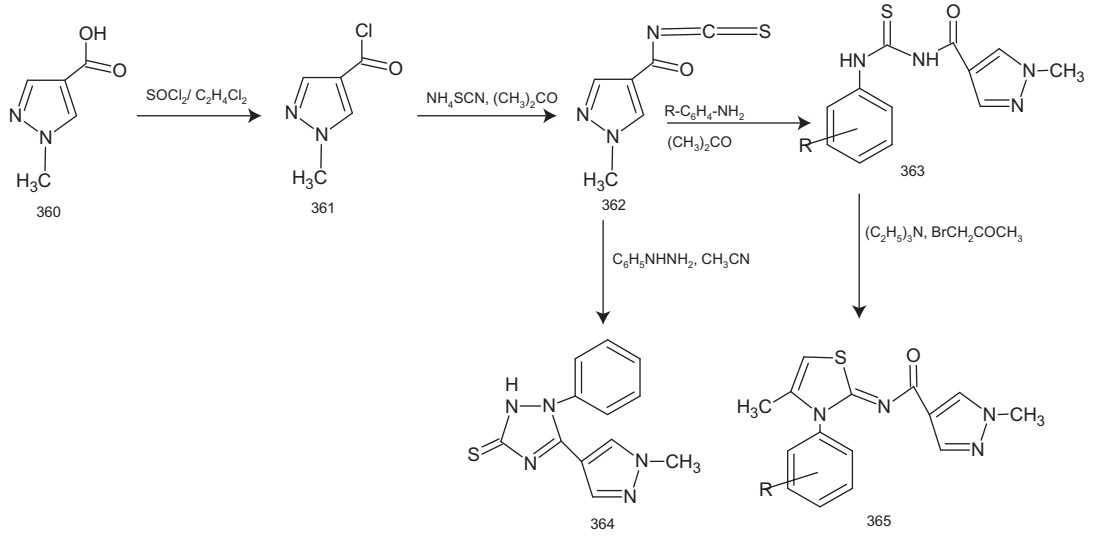
353 354

Scheme 82



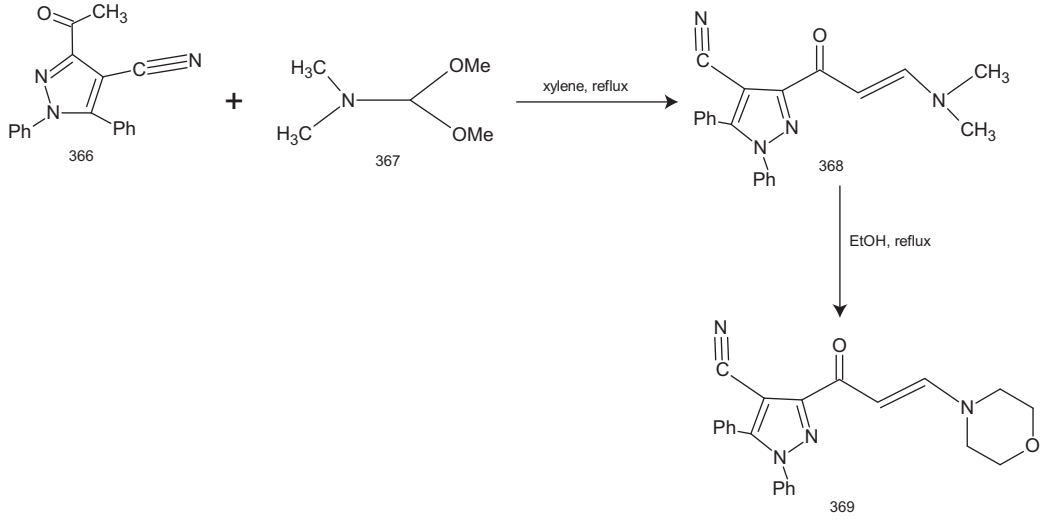
355 356 357 358 359

Scheme 83

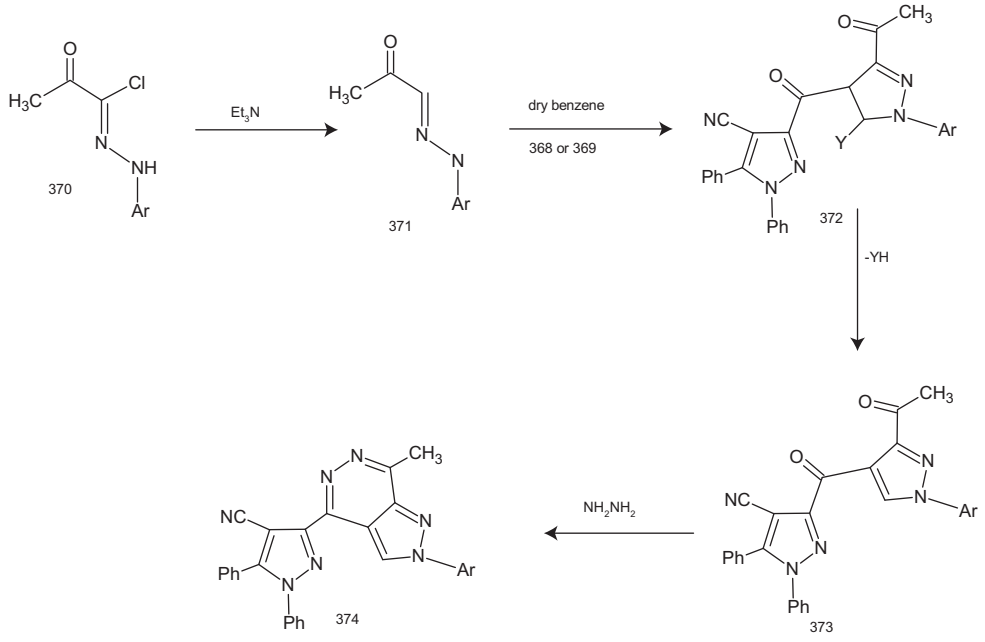


360 361 362 363 364 365

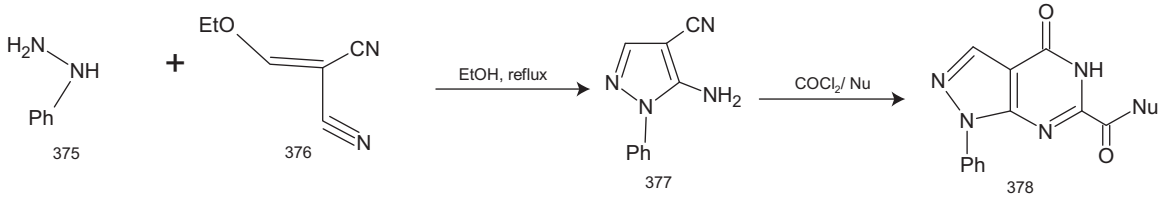
Scheme 84



Scheme 85



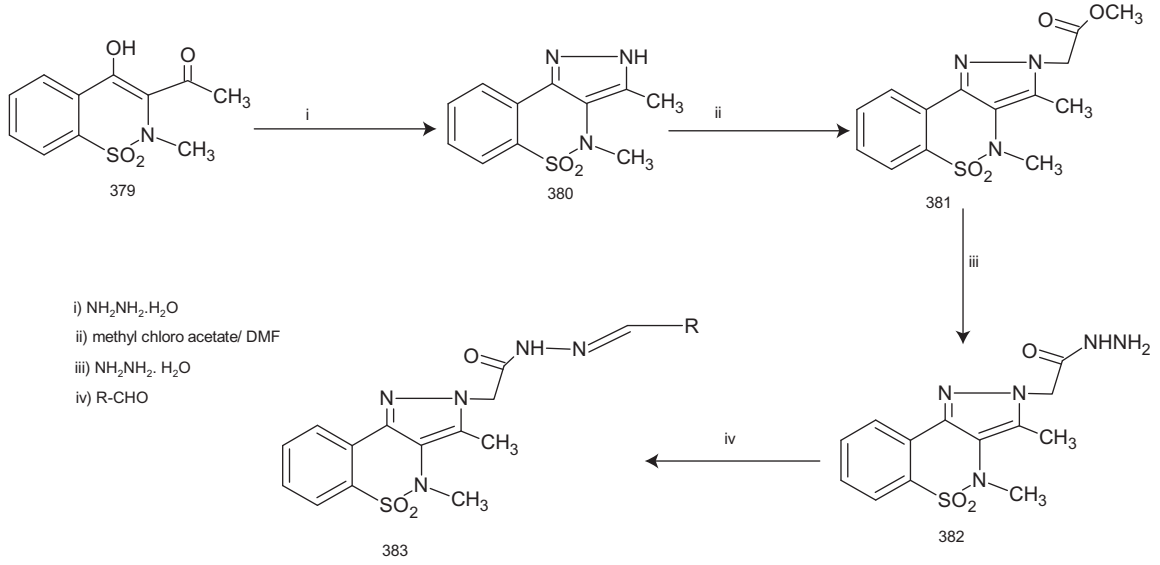
Scheme 86



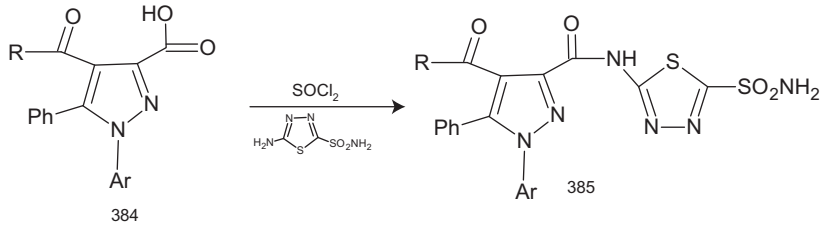
Scheme 87

ethyl diazoacetate (EDA) with Baylis–Hillman acetates (Scheme 78). Here the products were obtained in good to excellent yields (70–95%).

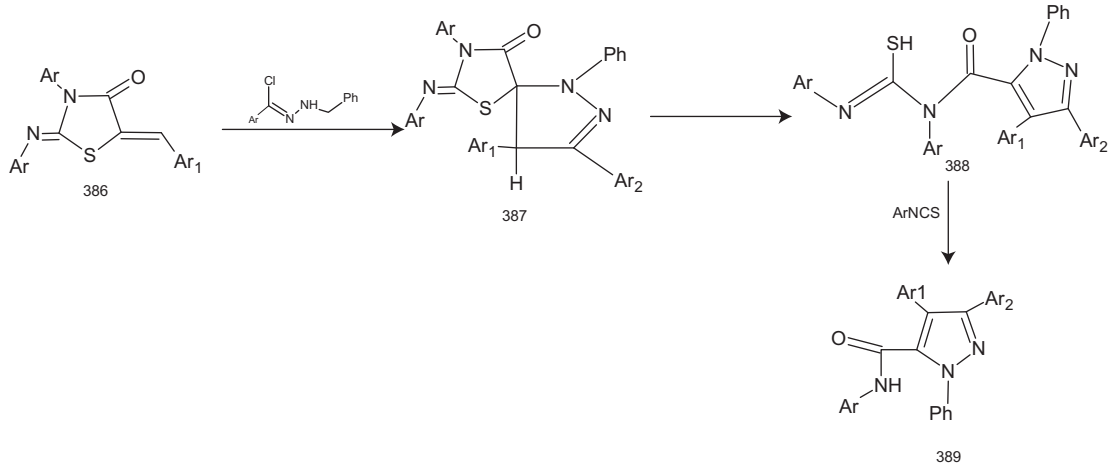
A series of N-substituted-3-[(2′hydroxy-4′prenyloxy)-phenyl]-5-phenyl-4,5-dihydro-(1*H*)-pyrazolines **346** and **347** were synthesized (Scheme 79) and tested on human monoamine oxi-



Scheme 88



Scheme 89

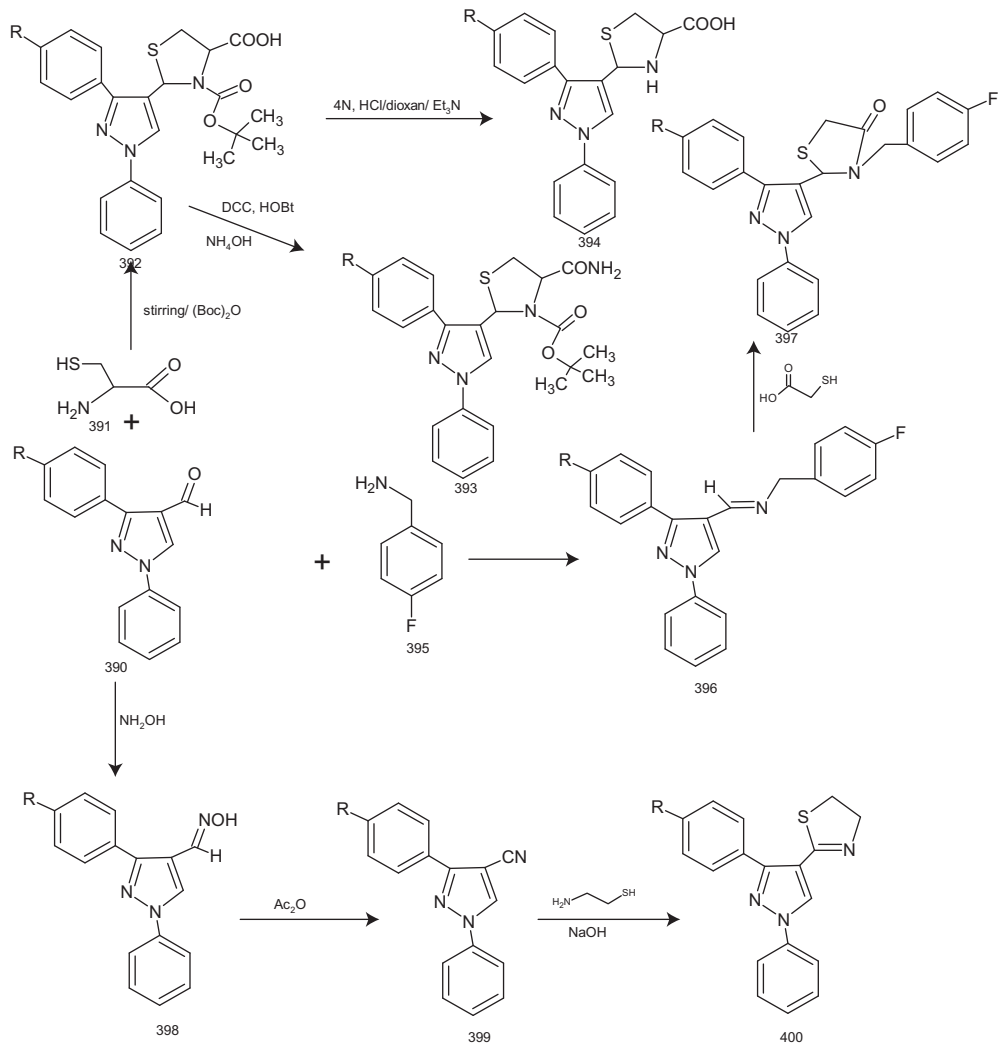


Scheme 90

dase-A and -B isoforms (Fioravanti et al., 2010). The structure activity relationships and molecular modeling showed that some substituents, such as benzyloxy or chlorine, improve the best interaction with active site of hMAO-B.

Iodocyclization of 5-amino-1-(2,4-dinitrophenyl)-1*H*-4-pyrazolcarboxamides **349** with aromatic aldehydes **350** gave a new series of pyrazolo[3,4-d]pyrimidine derivatives **350** in a single step (Bakavoli et al., 2010) and their antibacterial activity was found to be comparable to Streptomycin which was used as a reference drug (Scheme 80).

Bandgar et al. (2010) have described the synthesis of a combinatorial library of 3,5-diaryl-pyrazole derivatives **352**



Scheme 91

using 8-(2-(hydroxymethyl)-1-methylpyrrolidin-3-yl)-5,7-dimethoxy-2-phenyl-4*H*-chromen-4-one **351** and hydrazine hydrate in absolute ethanol under the refluxing conditions (Scheme 81).

Recently, a series of N-alkyl 1-aryl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-3-carboxamides **354** have been synthesized as new ligands of the human recombinant receptor hCB1 (Silvestri et al., 2010). n-alkyl carboxamides brought out different SARs from the branched subgroup (Scheme 82).

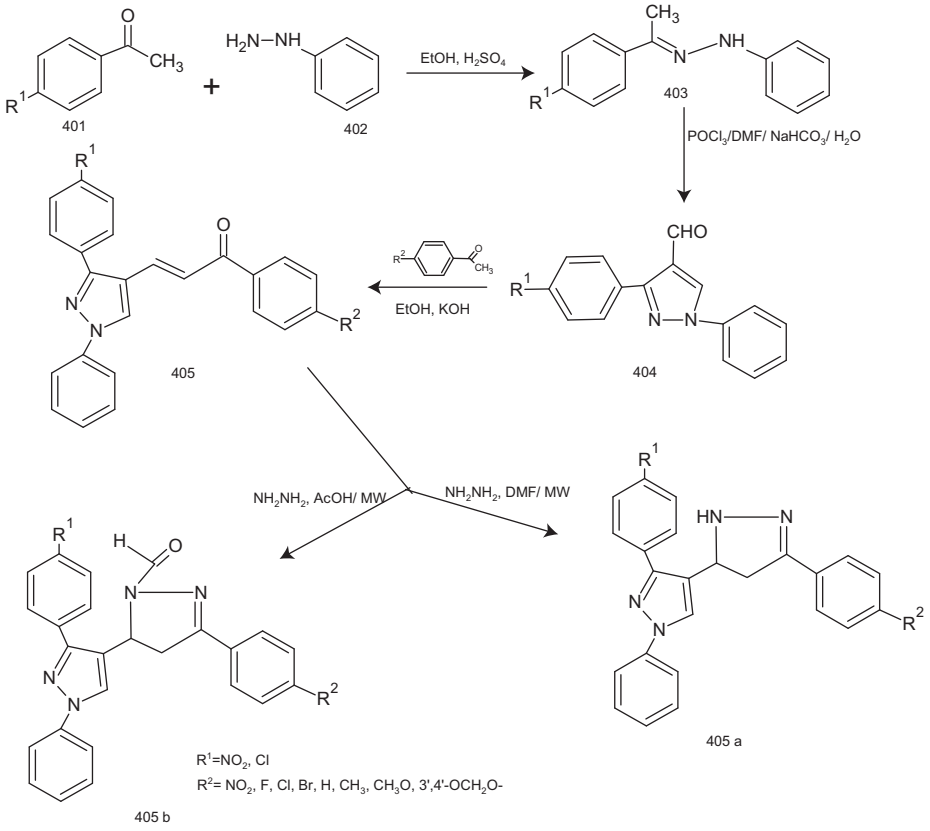
The novel 3,4-disubstituted pyrazoles **359** were prepared (Franchini et al., 2010) according to the reaction sequence as shown in Scheme 83.

The functionally substituted pyrazole compounds **364** and **365** have been prepared (Nitulescu et al., 2010) and evaluated in vitro for their antiproliferative effects on a panel of 60 cellular lines, according to the National Cancer Institute screening protocol (Scheme 84). Three of the 12 tested compounds showed moderate antitumor activity, one of them being chosen for the 5-dose assay and presented logGI50 values up to 5.75.

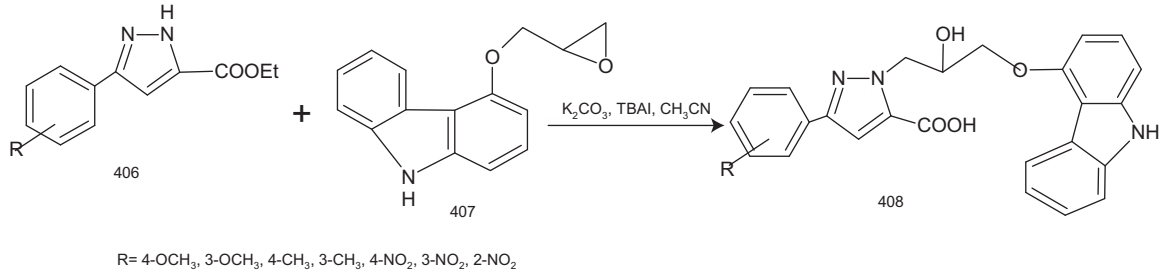
The new compound 3-[(E)-3-(dimethylamino)acryloyl]-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile **369** was prepared (Farag et al., 2010) via the reaction of 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carbonitrile **366** with dimethylformamid-dimethylacetal (DMF-DMA) (Scheme 85). The heterocyclic compound **374** has been obtained starting from **370** via various steps as shown in Scheme 86.

The novel dipyrazole ethandiamide compound of pyrazolo[3,4-d]pyrimidine 4(5*H*)-one **377** was synthesized (Youssef et al., 2010) and reacted with a number of nucleophiles to yield **378**. These compounds were tested in several in vitro and in vivo assays (Scheme 87). Two compounds were notable for their anti-inflammatory activity that was comparable to that of the clinically available cyclooxygenase-2 inhibitor celecoxib. Modeling studies by using the molecular operating environment module showed comparable docking scores for the two enantiomers docked in the active site of cyclooxygenase-2.

A series of potential anti-oxidant and anti-bacterial N′-arylmethylidene-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4*H*)-yl)acetohydrazides **383** were synthesized (Ahmad et al., 2010) in a facile way starting from commercially available saccharine. The various steps involved in these syntheses are shown in Scheme 88.



Scheme 92



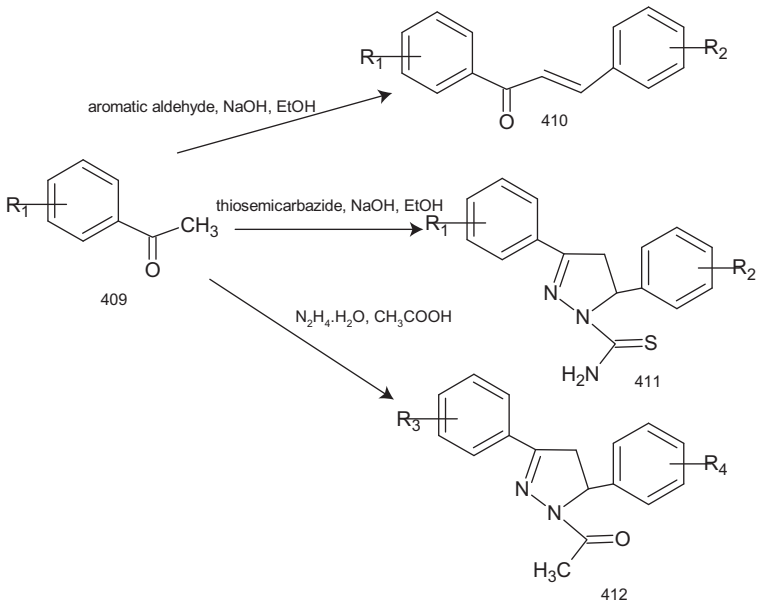
Scheme 93

Pyrazole carboxylic acid derivatives (Kasimogullari et al., 2010) of 5-amino-1,3,4-thiadiazole-2-sulfonamide (inhibitor 1) **385** were obtained from ethyl 3-(chlorocarbonyl)-1-(3-nitrophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate compound (Scheme 89).

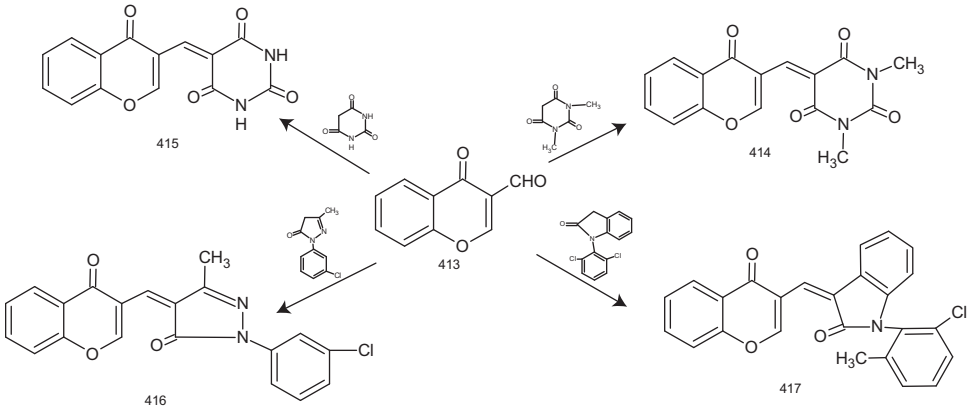
Regioselective 1,3-dipolar cycloaddition of nitrilimines with 5-arylidene-2-arylimino-4-thiazolidinones and with 2-(4-arylidene)thiazolo[3,2-a]benzimidazol-3(2*H*)-ones **386** afforded (Abdel-Aziz et al., 2010) the corresponding 1,3,4-triaryl-5-N-arylpyrazole-carboxamides **388** and pyrazolylbenzimidazoles **389** (Scheme 90).

Adam A. Bekhit et al. (2010) have reported the synthesis of a novel series of 4-thiazolylpyrazolyl derivatives **400** according to the reaction sequence as given in Scheme 91. All the newly synthesized compounds were examined for their anti-inflammatory activity using cotton pellet-induced granuloma and carrageenan-induced rat paw edema bioassays. Their inhibitory activities of cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2), ulcerogenic effect and acute toxicity were also determined.

The heterocyclic compounds (E)-1-aryl-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)prop-2-en-1-ones **405** (pyrazolic chalcones) were synthesized (Insuasty et al., 2010) from a Claisen–Schmidt reaction of 3-aryl-1-phenylpyrazol-4-carboxaldehydes **404** with several acetophenone derivatives. Subsequently, the microwave-assisted cyclocondensation reaction of chalcones **405** with hydrazine afforded the new racemic 3-aryl-4-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-1-phenyl-1*H*-pyrazoles **405 a** or their N-acetyl derivatives **405 b** when the reactions were carried out in DMF or acetic acid, respectively (Scheme 92).



Scheme 94



Scheme 95

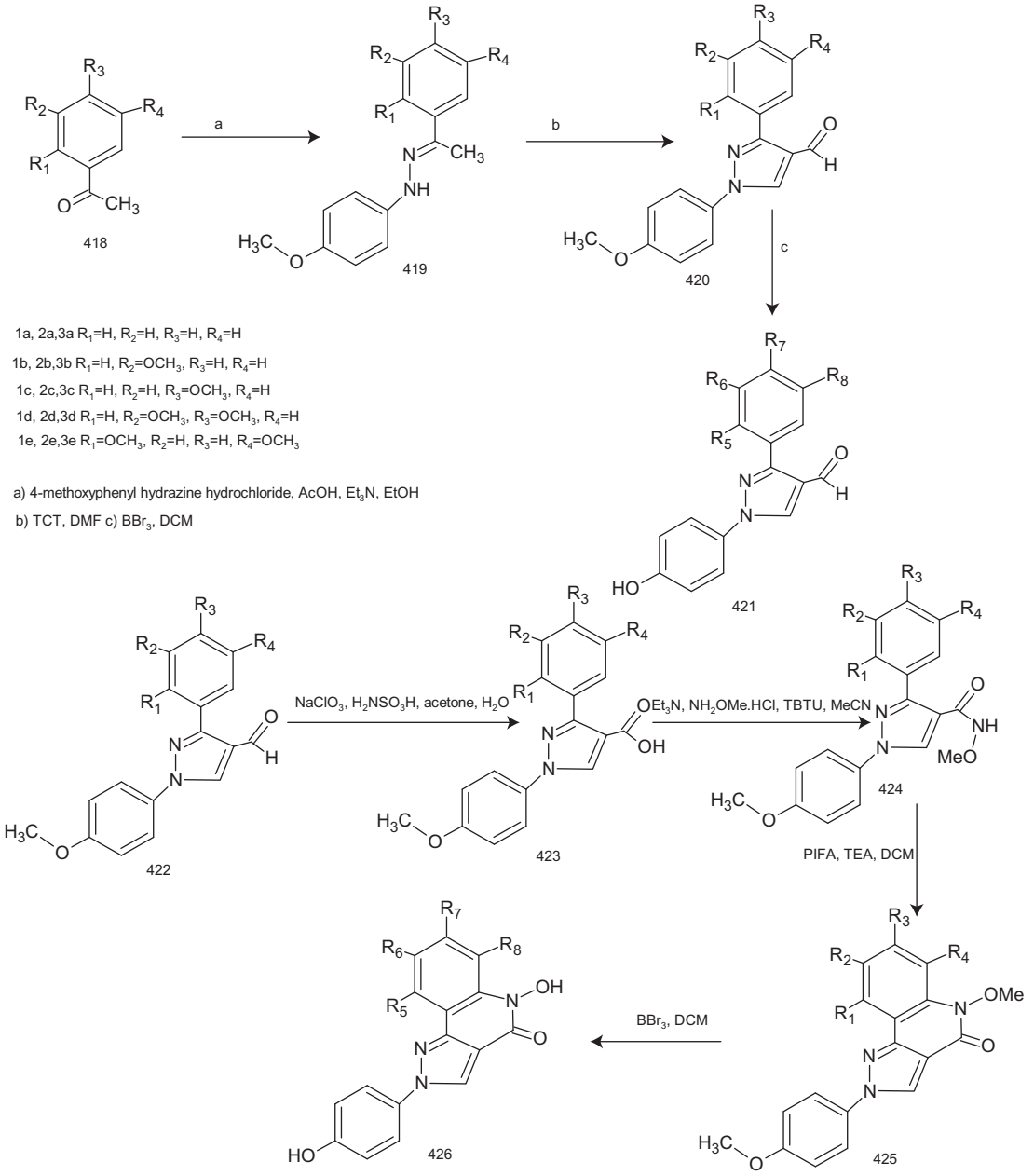
1-(3′-(9*H*-carbazol-4-yloxy)-2′-hydroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylic acid derivatives **408** have been prepared (Nagarapu et al., 2010) by the reaction of ethyl 3-aryl-1H-pyrazole-5-carboxylate **406** with 4-oxiranylmethoxy-9H-carbazole **407** in moderate to excellent yields (Scheme 93). The cytotoxicity of synthesized compounds was evaluated by a SRB (sulforhodamine B) assay against cancer cells such as SK-N-SH human neuroblastoma (NB), human A549 lung carcinoma, human breast cancer MCF-7 cell lines. The results showed that seven compounds can suppress SK-N-SH tumor cancer cell growth.

Two series of pyrazole derivatives **411** and **412** (Lv et al., 2010) designing for potential EGFR kinase inhibitors have been investigated (Scheme 94). Some of them exhibited significant EGFR inhibitory activity. The compound 3-(3,4-dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **411** (C5) displayed the most potent EGFR inhibitory activity with IC50 of 0.07 lM, which was comparable to the positive control erlotinib.

A number of biologically significant conjugates were synthesized by the combination of chromone-pyrimidine, chromone-indolinone, chromone-pyrazole, indole-pyrimidine, indole-indolinone and indole-pyrazole moieties (Singh et al., 2010) according to the method which is described in Scheme 95.

Recently, Serkos A. Haroutounian et al. (Christodoulou et al., 2010) have investigated the synthesis of a series of novel trisubstituted pyrazole derivatives **421** and these compounds have also been PIFA-mediated converted to molecules bearing the fused pyrazolo[4,3-c]quinoline ring. The various steps involved in these syntheses have been described in Schemes 96.

New 1-N-substituted-3,5-diphenyl-2-pyrazoline derivatives **430** have been synthesized (Scheme 97) and their cyclooxygenase (COX-1 and COX-2) inhibitory activities have also been evaluated (Fioravanti et al., 2010). The results of these biological assays showed that all the new derivatives are not endowed with improved anti-inflammatory activity against COX-1, but some of them showed a good activity against COX-2.



Scheme 96

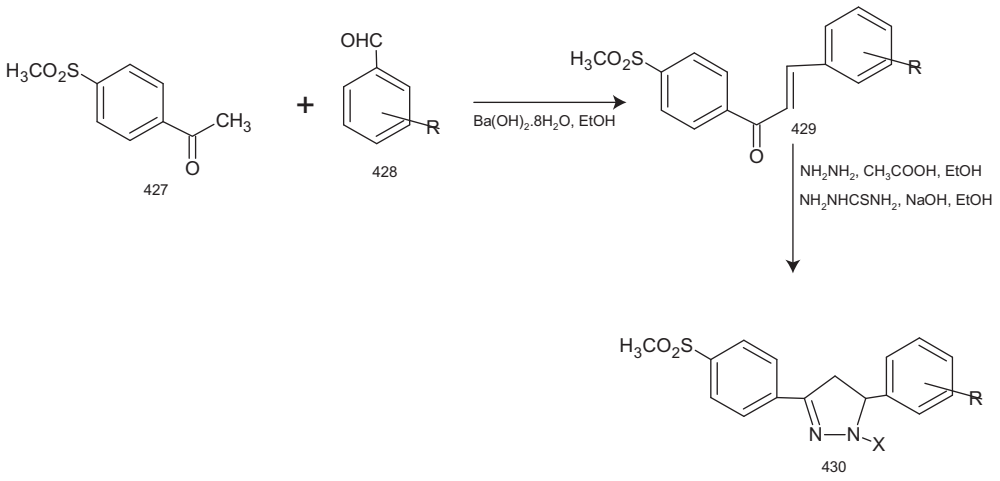
The compounds **439** have been released (Velankar et al., 2010) starting from benzyl nitrile **431** through the multistep reactions and their conditions have been depicted in Scheme 98. The synthesized compounds showed interleukin-2 inducible T-cell kinase (ITK) which is one of the five kinases that belong to the Tec kinase family and it plays an important role in T-cell and mast cell signaling. Various reports point to a role of ITK in the treatment of allergic asthma.

The synthesis of a series of pyrazoles **443** has been reported (Scheme 99) and these heterocyclics were also evaluated for their PDE4 inhibitory activity (Biagini et al., 2010). All the pyrazoles were found devoid of activity, whereas some of the pyrazolo[3,4-d]pyridazinones showed good activity as PDE4 inhibitors.

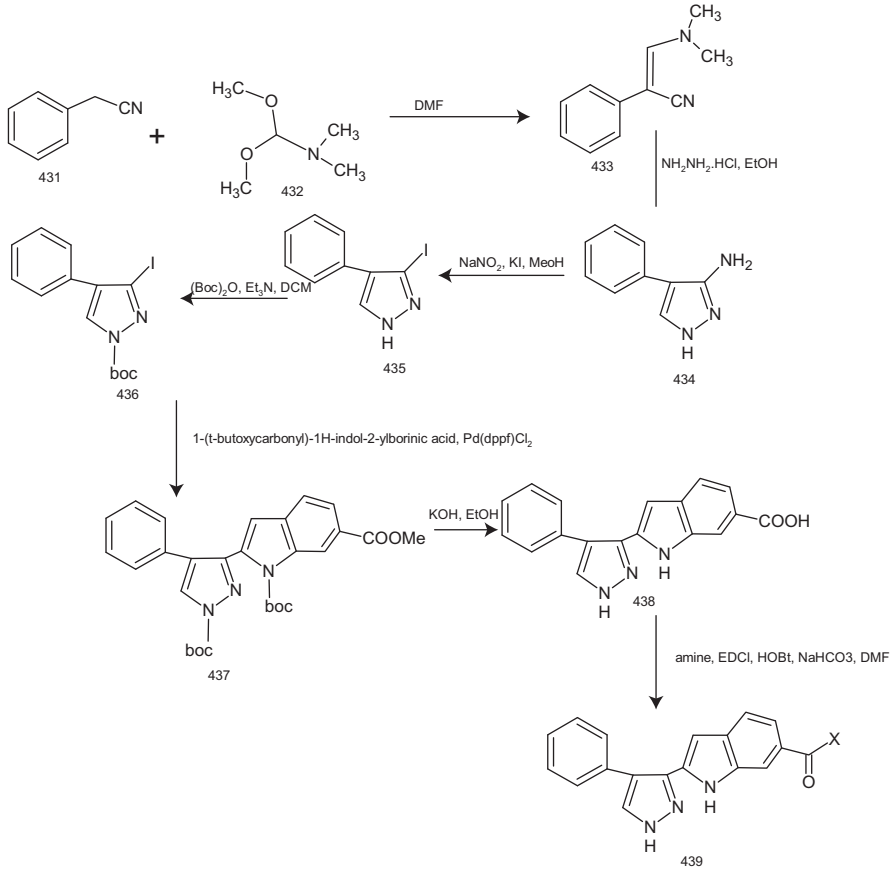
3,5-Diaryl-1*H*-pyrazoles **446** were prepared (Shaw et al., 2010) from the cyclization of 1,3-diketone **446** with hydrazine hydrochloride (Scheme 100). The major interest in the study was to obtain a molecular template which may act as growth-inhibitory agents.

The cyclization of chalcones **450** with 2-(quinolin-8-yloxy) acetohydrazide **451** under basic condition (Hayat et al., 2010) led to the formation of new pyrazoline derivatives **452** (Scheme 101).

In order to find a new class of antimicrobial agents (Bondock et al., 2010), a series of pyrazole **460** and **462** and other related products **458** containing benzothiazole moiety have been reported by Samir Bondock et al. according to the detailed protocol which is given in Scheme 102.



Scheme 97

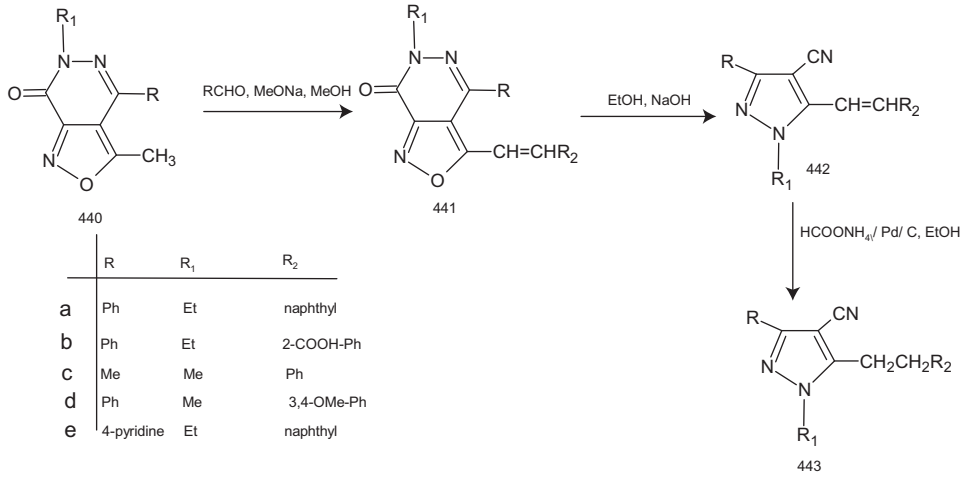


Scheme 98

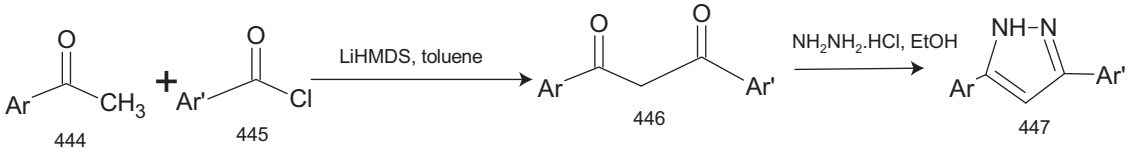
Novel 1,5-diaryl pyrazole derivatives **466** and **467** were synthesized (Ragavan et al., 2010) from the condensation of **464** with phenyl hydrazine in alcoholic medium (Scheme 103).

An effective and solvent free method for the synthesis (Kumar et al., 2011) of pyrazole-substituted chalcones **470** has been achieved by grinding pyrazole aldehydes **468** and acetophenones **469** in the presence of activated barium hydroxide (C-200). The products of these reactions have been obtained in high yield and within short span of time (Scheme 104).

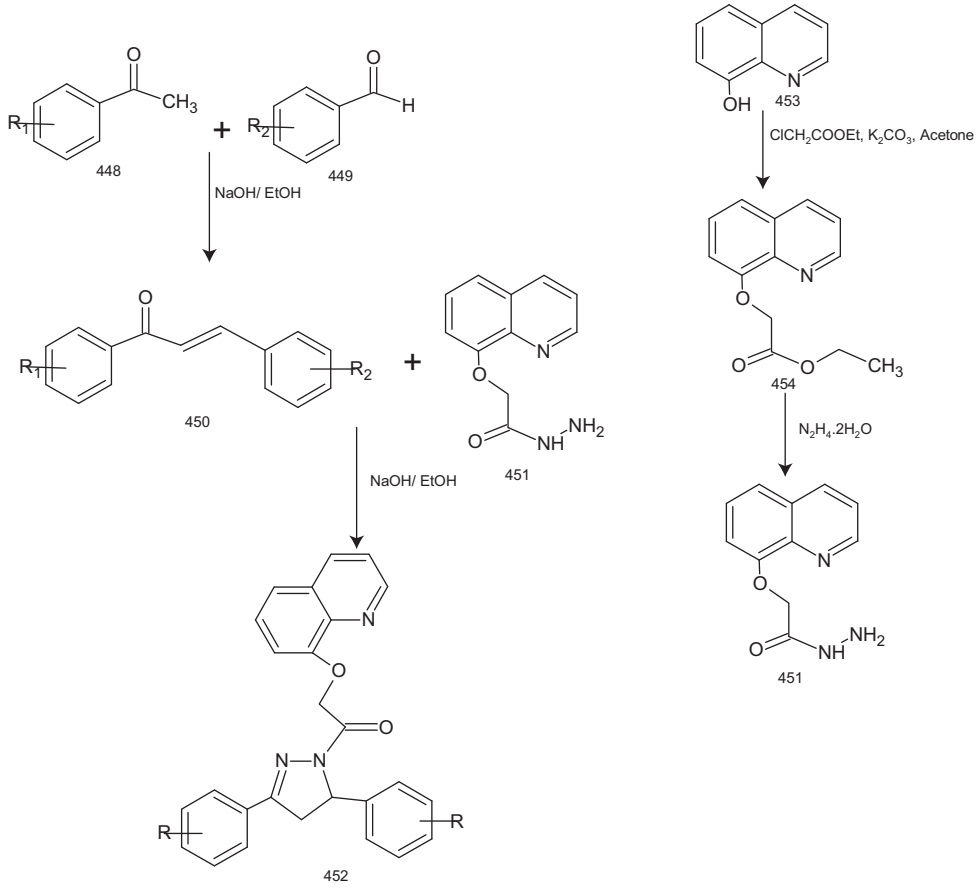
A series of new 1,3,5-trisubstituted-2-pyrazolines **473** were prepared (Srinath et al., 2011) by reacting chalcones **471** with phenylhydrazine hydrochloride **472** (Scheme 105).



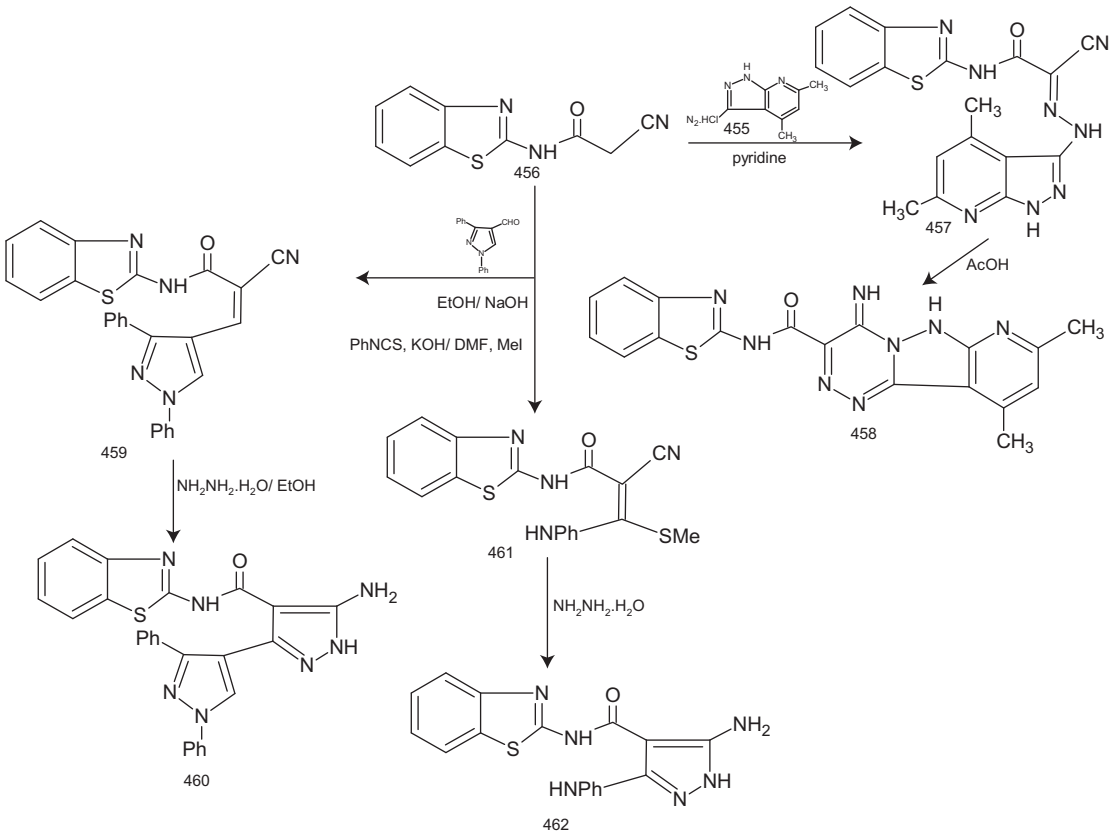
Scheme 99



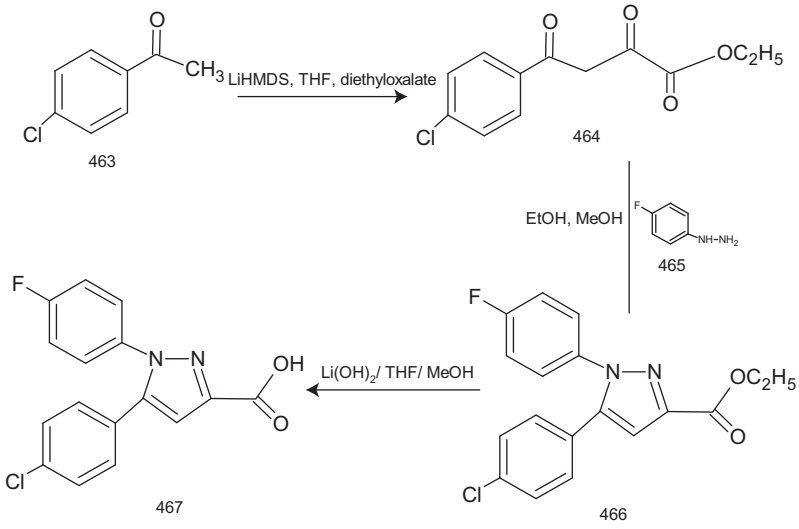
Scheme 100



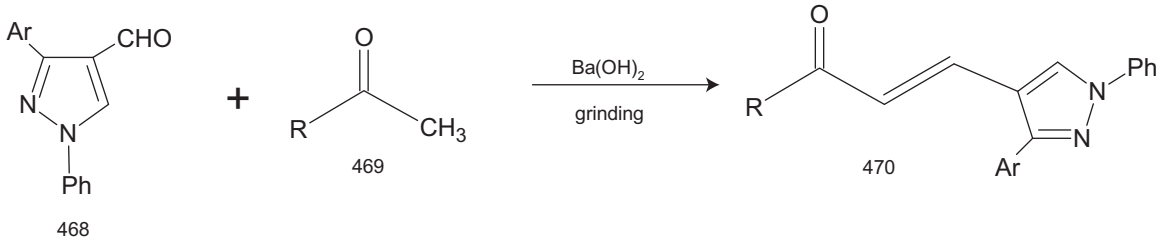
Scheme 101



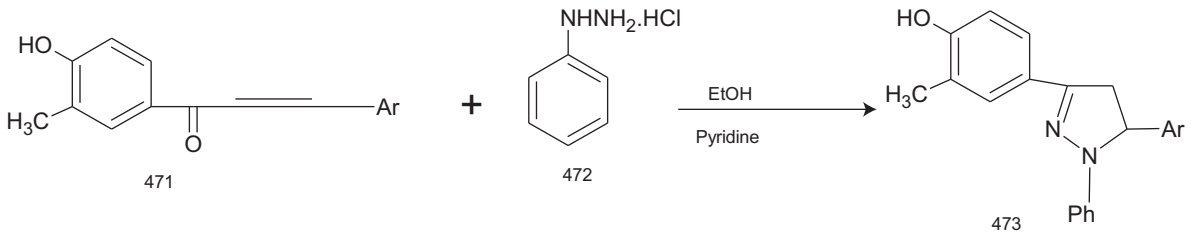
Scheme 102



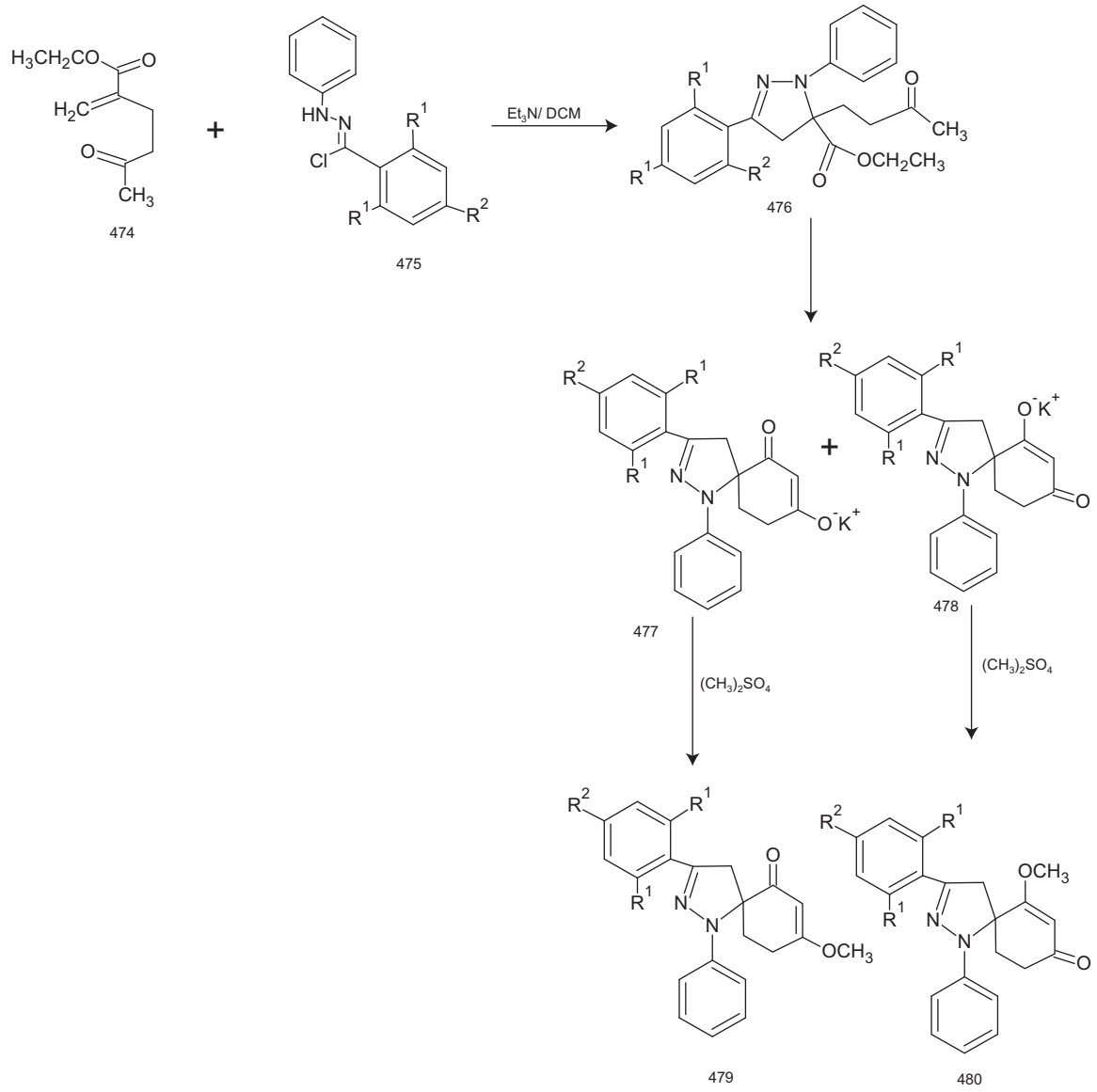
Scheme 103



Scheme 104



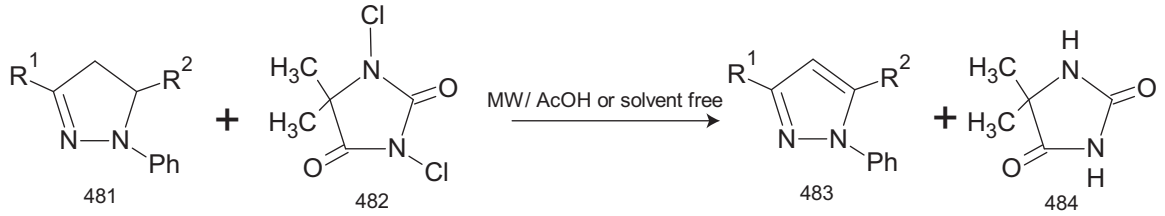
Scheme 105



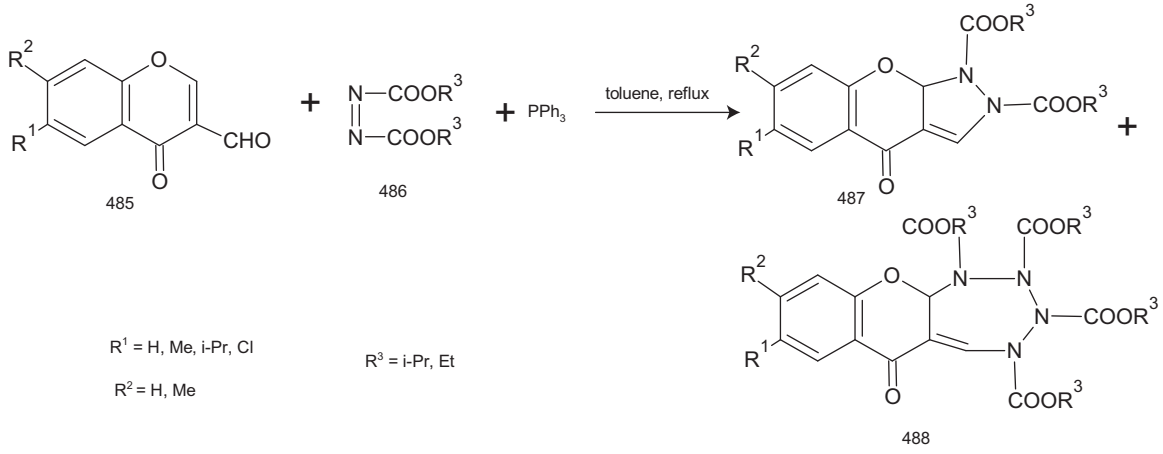
Scheme 106

Regioisomeric spiropyrazolines **479** and **480** were synthesized (Dadiboyena and Hamme, 2011) through a tandem intramolecular cyclization/methylation reaction of a functionalized 5,5-disubstituted pyrazoline in one reaction vessel (Scheme 106).

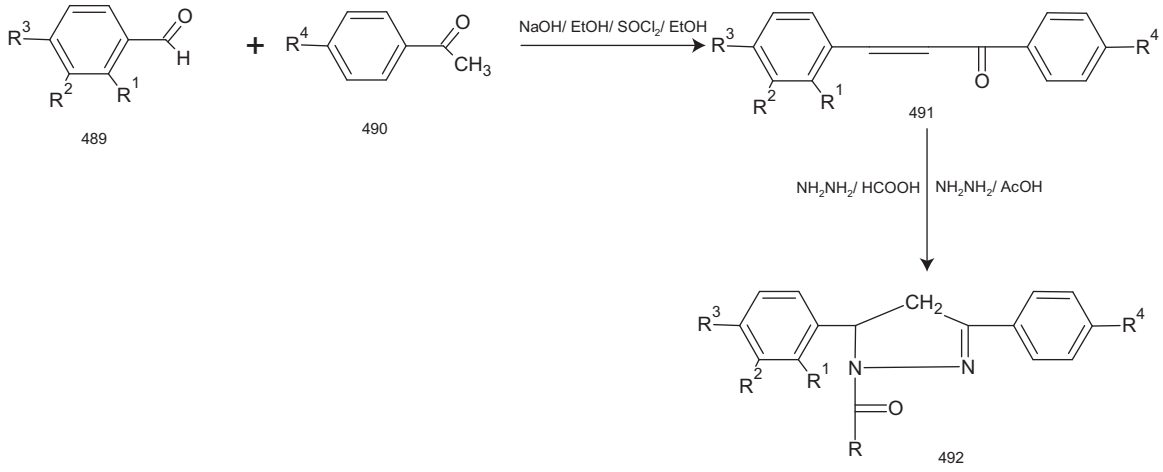
1,3,5-Trisubstituted pyrazolines **481** are rapidly and conveniently oxidized (Azarifar et al., 2011) to their corresponding pyrazoles **483** by 1,3-dichloro-5,5-dimethylhydantoin (DCH) in solution and solvent-free conditions under microwave irradiation (Scheme 107). The presence of silica gel as a



Scheme 107



Scheme 108



Scheme 109

supporting agent is shown to be effective in reducing the reaction times and increasing the yields.

The zwitterionic intermediates generated from dialkyl azodicarboxylates and triphenylphosphine displayed excellent reactivity (Papafilippou et al., 2011) toward 3-formylchromones to afford chromeno[2,3-c]pyrazolines **487** and chromeno[2,3-e]tetrazepines **488** (Scheme 108).

A series of 2-pyrazolines **492** have been synthesized (Panta et al., 2011) from α,β unsaturated ketones **491** and hydrazine hydrate with acetic/formic acid in ethanol/DMSO as shown in Scheme 109.

Acknowledgment

Authors are highly thankful to DST (SERC, Fast Track Scheme no. SR/FT/CS-041/2010), New Delhi for providing the financial support for this research work.

References

Abdel-Aziz, M., Abuo-Rahma, G.E.-D.A., Hassan, A.A., 2009. Eur. J. Med. Chem. 44, 3480.

Abdel-Aziz, H.A., El-Zahabi, H.S.A., Dawood, K.M., 2010. Eur. J. Med. Chem. 45, 2427.

Abunada, N.M., Hassaneen, H.M., Kandile, N.G., Miqdad, O.A., 2008. Molecules 13, 1011.
Abu-Surrah, A.S., Abu Safieh, K.A., Ahmad, I.M., Abdalla, M.Y., Ayoub, M.T., Qaroush, A.K., Abu-Mahtheieh, A.M., 2010. Eur. J. Med. Chem. 45, 471.
Achraya, B.N., Saraswat, D., Tiwari, M., Shrivastava, A.K., Ghorpade, R., Bapna, S., Kaushik, M.P., 2010. Eur. J. Med. Chem. 45, 430.
Adhikari, N., Maiti, M.K., Jha, T., 2010. Bioorg. Med. Chem. Lett. 20, 4021.
Ahmad, M., Siddiqui, H.L., Zia-ur-Rehman, M., Parvez, M., 2010. Eur. J. Med. Chem. 45, 698.
Alex, K., Tillack, A., Schwarz, N., Beller, M., 2008. Org. Lett. 10 (12), 2377.
Ali, M.A., Shaharyar, M., Siddiquig, A.A., 2007. Eur. J. Med. Chem. 42, 268.
Almeida da Silva, P.E., Ramos, D.F., Bonacorso, H.G., Iglesia, A.I., de la Oliveira, M.R., Coelho, T., Navarini, J., Morbidoni, H.R., Zanatta, N., Martins, M.A.P., 2008. Inter. J. Antimicrob. Agents 32, 139.
Azarifar, D., Khosravi, K., 2009. J Chin. Chem. Soc. 56, 43.
Azarifar, D., Khasravi, K., Veisi, R.-A., 2010. Arkivoc 9, 178.
Azarifar, D., Elahe Nadimi, E., Ghanbari, M.M., 2011. Chin. Chem. Lett. 22, 447.
Babu, V.H., Sridevi, C., Joseph, A., Srinivasan, K.K., 2007. Ind. J. Pharamaceut. Sci., 470.
Bakavoli, M., Bagherzadeh, G., Vaseghifar, M., Shiri, A., Pordel, M., Mashreghi, M., Pordeli, P., Araghi, M., 2010. Eur. J. Med. Chem. 45, 647.
Banday, A.H., Mir, B.P., Khazir, J., Suri, K.A., Kumar, H.M.S., 2010. Steroids doi:10.1016/j.steroids.2010.02.014.
Bandgar, B.P., Shrikant, S., Gawande, S.S., Bodade, R.G., Gawande, N.M., Khobragade, C.N., 2009. Bioorg. Med. Chem. 17, 8168.
Bandgar, B.P., Totre, J.V., Gawande, S.S., Khobragade, C.N., Warangkar, S.C., Kadam, P.D., 2010. Bioorg. Med. Chem. 18, 6149.
Barsoum, F.F., Girgis, A.S., 2009. Eur. J. Med. Chem. 44, 2172.
Bauer, H., Piatert, G., 1981. German Patent 1981, (DOS) 3039311, Chem. Abstract. 95, 63146.
Bekhit, A.A., Fahmy, H.T.Y., Rostoma, S.A.F., Bekhit, A.E.-D.A., 2010. Eur. J. Med. Chem. 45, 6027.
Biagini, P., Biancalani, C., Graziano, A., Cesari, N., Giovannoni, M.P., Cilibrizzi, A., Piaz, V.D., Vergelli, C., Crocetti, L., Delcanale, M., Armani, E., Rizzi, A., Puccini, P., Gallo, P.M., Spinabelli, D., Caruso, P., 2010. Bioorg. Med. Chem. 18, 3506.
Bonacorso, H.G., Cechinel, C.A., Deon, E.D., Sehnem, R.C., Luz, F.M., Martins, M.A.P., Zanatta, N., 2009. Arkivoc 2, 174.
Bonacorso, H.G., Cechinel, C.A., Pittaluga, E.P., Ferla, A., Porte, L.M.F., Martins, M.A.P., Zanatta, N., 2010. J. Braz. Chem. Soc. 21 (9), 1656.
Bondock, S., Fadaly, W., Metwally, M.A., 2009. Eur. J. Med. Chem. 44, 4813.
Bondock, S., Fadaly, W., Metwally, M.A., 2010. Eur. J. Med. Chem. 45, 3692.
Chandra, T., Garg, N., Lata, S., Saxena, K.K., Kumar, A., 2010. Eur. J. Med. Chem. 45, 1772.
Chen, G., Wang, H.-Y., Liu, Y., Xu, X.-P., Ji, S.-J., 2010. Dyes Pigments 85, 194.
Chimenti, F., Fioravanti, R., Bolasco, A., Manna, F., Chimenti, P., Secci, D., Rossi, F., Turini, P., Ortuso, F., Alcaro, S., Cardia, M.C., 2008. Eur. J. Med. Chem. 43, 2262.
Christodoulou, M.S., Liekens, S., Kasiotis, K.M., Haroutounian, S.A., 2010. Bioorg. Med. Chem. 18, 4338.
Congiu, C., Onnis, V., Vesci, L., Castorina, M., Pisano, C., 2010. Bioorg. Med. Chem. 18, 6238.
Conti, P., Pinto, A., Tamborini, L., Rizzo, V., Micheli, C.D., 2007. Tetrahedron 63, 5554.
Dadiboyena, S., Hamme, A.T., 2011. Tetrahedron Lett. 52, 2536.
Das, B.C., Bhowmik, D., Chiranjit, B., Mariappan, G., 2010. J. Pharm. Res. 3 (6), 1345.
Evans, N.A., Waters, P.J., 1978. J. Soc. Dyers Colour 94, 252.
Fadda, A.A., Abdel-Latif, E., El-Mekawy, R.E., 2009. Eur. J. Med. Chem. 44, 1250.
Farag, A.M., Ali, K.A.K., El-Debss, T.M.A., Mayhoub, A.S., Amr, A.G.E., Abdel-Hafez, A.N., Abdulla, M.M., 2010. Eur. J. Med. Chem. 45, 5887.
Fioravanti, R., Bolasco, A., Manna, F., Rossi, F., Orallo, F., Ortuso, F., Alcaro, S., Cirilli, R., 2010. Eur. J. Med. Chem. 45, 6135.
Fioravanti, R., Bolasco, A., Manna, F., Rossi, F., Orallo, F., Yanez, M., Vitali, A., Ortuso, F., Alcaro, S., 2010. Bioorg. Med. Chem. Lett. 20, 6479.
Franchini, M.C., Bonini, B.F., Camaggi, C.M., Gentili, D., Pession, A., Rani, M., Strocchi, E., 2010. Eur. J. Med. Chem. 45, 2024.
Frank, E., Mucsi, Z., Zupko, I., Rethy, B., Falkay, G., Schneider, G., Wolfling, J., 2009. J. Am. Chem. Soc. 131, 3894.
Gang, S., Wen, T.W., Jian, T.W., Long, M.W., 2008. Chin. Chem. Lett. 19, 1013.
Gembus, V., Bonnet, J.J., Janin, F., Bohn, P., Levacher, V., Briere, J.-F., 2010. Org. Biomol. Chem. 8, 3287.
Girisha, K.S., Kalluraya, B., Padmashree, V., 2010. Eur. J. Med. Chem. 45, 4640.
Gluszok, S., Frédérick, R., Foulon, C., Klupsch, F., Supuran, C.T., Vullo, D., Scozzafava, A., Goossens, J.-F., Masereel, B., Depreux, P., Goossens, L., 2010. Bioorg. Med. Chem. 18, 7392.
Gonzalez-Nogal, A.M., Calle, M., Cuadrado, P., Valero, R., 2007. Tetrahedron 63, 224.
Gouda, M.A., Berghot, M.A., Shoeib, A.I., Khalil, A.M., 2010. Eur. J. Med. Chem. 45, 1843.
Gowramma, B., Jubie, S., Kalirajan, R., Gomathy, S., Elango, K., 2009. Inter. J. Pharma. Tech. Res. 1 (2), 347.
Guirado, A., Martiz, B., Andreu, R., Bautista, D., 2009. Tetrahedron 65, 5958.
Gupta, R., Gupta, N., Jain, A., 2010. Ind. J. Med. 49B, 351.
Hayat, F., Salahuddin, A., Umar, S., Azam, A., 2010. Eur. J. Med. Chem. 45, 4669.
Hussain, S., Sharma, M., 2010. Acad. J. Plant Sci. 3 (1), 23.
Insuasty, B., Martinez, H., Quiroga, J., Abonia, R., Nogueras, M., Cobo, J., 2008. J. Heterocyclic Chem. 45, 1521.
Insuasty, B., Tigreros, A., Orozco, F., Quiroga, J., Abonia, R., Nogueras, M., Sanchez, A., Cobo, J., 2010. Bioorg. Med. Chem. 18, 4965.
Jadhav, S.B., Shastri, R.A., Gaikwad, K.V., Gaikwad, S.V., 2009. E.-J. Chem. 6 (S1), S-183.
Jayaprakash, V., Sinha, B.N., Ucar, G., Ercan, A., 2008. Bioorg. Med. Chem. Lett. 18, 6362.
Jayashankra, B., Lokanatha, R.K.M., 2008. E-J. Chem. 5 (2), 309.
Joshi, S.D., Vagdevi, H.M., Vaidya, V.P., Gadaginamath, G.S., 2008. Eur. J. Med. Chem. 43, 1989.
Kaplancikli, Z.A., Turan-Zitouni, G., Ozdemir, A., Can, O.D., 2009. Eur. J. Med. Chem. 44, 2606.
Karuppasamy, M., Mahapatra, M., Yabanoglu, S., Ucar, G., Sinha, B.N., Basu, A., Mishra, N., Sharon, A., Kulandaivelu, U., Jayaprakash, V., 2010. Bioorg. Med. Chem. 18, 1875.
Kasabe, A., Kasabe, P.J., 2010. Int. J. Pharm. Pharmaceut. Sci. 2 (2), 132.
Kasimogullari, R., Bülbül, M., Arslan, S.B., Gökçe, B., 2010. Eur. J. Med. Chem. 45, 4769.
Khode, S., Maddi, V., Aragade, P., Palkar, M., Ronad, P.K., Mamledesai, S., Thippeswary, A.H.M., Satyanarayana, D., 2009. Eur. J. Med. Chem. 44, 1682.
Korgaokar, S.S., Patil, P.H., Shah, M.J., Parekh, H.H., 1996. Ind. J. Pharm. Sci. 58, 222.
Krishna, P.R., Prapurna, Y.L., 2010. Tetrahedron Lett. 51, 6507.
Krishna, P.R., Sekhar, E.R., Mongin, F., 2008. Tetrahedron Lett. 49, 6768.
Kumar, S., Bawa, S., Drabu, S., Kumar, R., Gupta, H., 2009. Recent Patents on Anti- Infective Drug Discovery 4, 154.

Kumar, B., Pathak, V., Rani, S., Kant, R., Tewari, I.C., 2009. Int. J. Microbiol. Res. 1 (2), 20.
Kumar, P., Kumar, S., Husain, K., Kumar, A., 2011. Chin. Chem. Lett. 22, 37.
Levai, L., Jeko, J., 2009. Acta Chim. Slov. 56, 566.
Li, J.-T., Zhang, X.-H., Lin, Z.-P., 2007. Beilstein J. Chem. 3, 13.
Liu, W.-Y., Xie, Y.-S., Zhao, B.-X., Wang, B.-S., Lv, H.-S., Gong, Z.-L., Lian, S., Zheng, L.-W., 2010. J. Photochem. Photobiol. A: Chem. 214, 135.
Lv, P.C., Li, H.-Q., Sun, J., Zhou, Y., Zhu, H.-L., 2010. Bioorg. Med. Chem. 18, 4606.
Manojkumar, P., Ravi, T.K., Gopalakrishnan, S., 2009. Eur. J. Med. Chem. 44, 4690.
Mernyak, E., Kozma, E., Hetenyi, A., Mark, L., Schneider, G., Wolfing, J., 2009. Steroids 74, 520.
Mishra, S.K., Sahoo, S., Panda, P.K., Mishra, S.R., Mohanta, R.K., Ellaiah, P., Panda, C.S., 2007. Acta Poloniae Pharmaceut.-Drug Res. 64 (4), 359.
Mokle, S.S., Vibhute, A.Y., Khansole, S.V., Zangade, S.B., Vibhute, Y.B., 2010. Res. J. Pharm. Biol. Chem. Sci. 1 (3), 631.
Murayama, T., Mater, N., 1981. New Processess Electrochem. Technol. 1, 192.
Nagarapu, L., Gaikwad, H.K., Sarikonda, K., Mateti, J., Bantu, R., Raghu, P.S., Manda, K.M., Kalvendi, S.V., 2010. Eur. J. Med. Chem. 45, 4720.
Nassar, E., 2010. J. Am. Sci. 6 (8), 463.
Nauduri, D., Reddy, G.B., 1998. Chem. Pharm. Bull. (Tokyo) 46, 1254.
Nitulescu, G.M., Draghici, C., Missir, A.V., 2010. Eur. J. Med. Chem. 45, 4914.
Ozdemir, Z., Kandilici, H.B., Gumusel, B., Calis, U., Bilgin, A.A., 2007. Eur. J. Med. Chem. 42, 373.
Padmaja, A., Payani, T., Reddy, G.D., Padmavathi, V., 2009. Eur. J. Med. Chem. 44, 4557.
Padmavathi, V., Radhalakshmi, T., Mahesh, K., Mohan, A.V.N., 2008. Ind. J. Chem. 47B, 1707.
Palaska, E., Aytemir, M., Uzbay, I.T., Erol, D., 2001. Eur. J. Med. Chem. 36, 539.
Panta, G.J.N., Singha, P., Rawatb, B.S., Rawata, M.S.M., Joshi, G.C., 2011. Spectrochim. Acta A 78, 1075.
Papafilippou, A., Terzidis, M.A., Stephanidou-Stephanatou, J., Tsoleridis, C.A., 2011. Tetrahedron Lett. 52, 1306.
Patel, B.N., Patel, P.S., Patel, V.G., 2010. Der Pharm. Chem. 2 (1), 295.
Pathak, V.N., Joshi, R., Sharma, J., Gupta, N., Rao, V.M., 2009. Phosphorous Sulfur Silicon 184, 1854.
Penning, T.D., Talley, J.J., Bertenshaw, S.R., Carter, J.S., Collins, P.W., Docter, S., Graneto, M.J., Lee, L.F., Malecha, J.W., Miyashiro, J.M., Rogers, R.S., Rogier, D.J., Yu, S.S., Anderson, G.D., Burton, E.G., Cogburn, J.N., Gregory, S.A., Koboldt, C.M., Perkins, W.E., Seibert, K., Veenhuizen, A.W., Zhang, Y.Y., Isakson, P.C., 1997. J. Med. Chem. 40, 1347.
Poduzhailo, V.F., Pareyaslova, D.F., Shripkina, V.I., Verezubora, S.A., Andreeva, L.A., Zh. Prikl. Spektrosk. 1979 26, 357 Chem. Abstract 86 (1977), 162579.
Ragavan, R.V., Vijayakumar, V., Kumari, N.S., 2010. Eur. J. Med. Chem. 45, 1173.
Rahaman, S.A., Prasad, Y.R., Bhuvaneswari, K., Kumar, P., 2010. Int. J. Chem. Tech. Res. 2 (1), 16.
Rai, N.P., Narayanaswamy, V.K., Shashikanth, S., Arunachalam, P.N., 2009. Eur. J. Med. Chem. 44, 4522.
Rajendra, P.Y., Lakshmana, R.A., Prasoona, L., Murali, K., Ravi, K.P., 2005. Bioorg. Med. Chem. Lett. 15, 5030.
Rajora, J., Yadav, J., Kumar, R., Srivastava, Y.K., 2010. Ind. J. Chem. 49B, 989.
Ramesh, B., Sumuna, T., 2010. E-J. Chem. 7 (2), 514.
Revanasiddappa, B.C., Rao, R.N., Subrahmanyam, E.V.S., Satyanarayana, D., 2010. E-J. Chem. 7 (1), 295.
Ruhogluo, O., Ozdemir, Z., Calis, U., Gumusel, B., Bilgin, A.A., 2005. Arzneimittelforschung 55, 431.
Sahoo, A., Yabanoglu, S., Sinha, B.N., Ucar, G., Basu, A., Jayaprakash, V., 2010. Bioorg. Med. Chem. Lett. 20, 132.
Sauzem, P.D., Machado, P., Rubin, M.A., Sant'Anna, G.dS., Faber, H.B., de Souza, A.H., Mello, C.F., Beck, P., Burrow, R.A., Bonacorso, H.G., Marcos, A.P., Martins, N.Z., 2008. Eur. J. Med. Chem. 43, 1237.
Seltzmann, H.H., Carroll, F.I., Burgess, J.P., Wyrick, C.D., Burch, D.F., 1995. J. Chem.Soc., Chem. Commun., 1549.
Shamsuzzaman Khan, M.S., Alam, M., 2009. J. Chil. Chem. Soc. 4, 54.
Sharma, P.K., Kumar, S., Kumar, P., Kaushik, P., Kaushik, D., Dhingra, Y., Aneja, K.R., 2010. Eur. J. Med. Chem. 45, 2650.
Shaw, A.Y., Liau, H.-H., Lu, P.-J., Yang, C.-N., Lee, C.-H., Chen, J.-Y., Xu, Z., Flynn, G., 2010. Bioorg. Med. Chem. 18, 3270.
Shevtson, A.V., Kislukhin, A.A., Kuznetson, V.V., Petukhova, V.Y., Maslennikov, V.A., Borissova, A.O., Lyssenko, K.A., Makhova, N.N., 2007. Mandeleev Commun. 17, 119.
Shoman, M.E., Abdel-Aziz, M., Aly, O.M., Farag, H.H., Morsy, M.A., 2009. Eur. J. Med. Chem. 44, 3068.
Silvestri, R., Ligresti, A., Regina, G.L., Piscitelli, F., Gatti, V., Lavecchia, A., Brizzi, A., Pasquini, S., Allarà, M., Fantini, N., Carai, M.A.M., Bigogno, C., Rozio, M.G., Sinisi, R., Novellino, E., Colombo, G., Marzo, V.D., Dondio, G., Corelli, F., 2010. Eur. J. Med. Chem. 45, 5878.
Singh, P., Negi, J.S., Pant, G.J.N., Rawat, M.S.M., Budakoti, A., 2009. Molbank, M 614.
Singh, P., Kaur, M., Holzer, W., 2010. Eur. J. Med. Chem. 45, 4968.
Solankee, A., Lad, S., Solankee, S., Patel, G., 2009. Ind. J. Chem. 48B, 1442.
Srinath, N., Prasad, Y.R., Mukkanti, K., 2011. Int. J. Curr. Pharm. Res. 3 (1), 76.
Taylor, E.C., Patel, H.H., 1992. Tetrahedron 48, 8089.
Terrett, N.K., Bell, A.S., Brown, D., Ellis, P., 1996. Bioorg. Med. Chem. Lett. 6, 1819.
Udupi, R.H., Kushnoor, A.S., Bhat, A.R., 1998. Ind. J. Heterocycl. Chem. 8, 63.
Velankar, A.D., Quintini, G., Prabhu, A., Weber, A., Hunaeus, G., Voland, B., Wuest, M., Orjeda, C., Harel, D., Varghese, S., Gore, V., Patil, M., Gayke, D., Herdemann, M., Heit, I., Zaliani, A., 2010. Bioorg. Med. Chem. 18, 4547.
Venkataraman, S., Jain, S., Shah, K., Upmanyu, N., 2010. Acta Poloniae Pharm. Drug Res. 67 (4), 361.
Warane, G., Aher, R., Kawathekar, N., Ranjan, R., Kaushik, N.K., Sahal, D., 2010. Bioorg. Med. Chem. Doi: 10.1016/j.bmcl.2010.05.069.
Xia, Y., Fan, C.-D., Zhao, B.-X., Zhao, J., Shin, D.-S., Miao, J.-Y., 2008. Eur. J. Med. Chem. 43, 2347.
Xue, H., Ma, T., Wang, L., Liu, G., 2010. Chin. Chem. Lett. 21, 1291.
Youssef, A.M., Neeland, E.G., Villanueva, E.B., White, M.S., El-Ashmawy, I.M., Patrick, B., Klegeris, A., Abd-El-Aziz, A.S., 2010. Bioorg. Med. Chem. 18, 5685.
Zhao, P.-L., Wang, F., Zhang, M.-Z., Liu, Z.-M., Huang, W., Yang, G.F., 2008. J. Agric. Food Chem. 56, 10767.
Zsoldos-Mady, V., Ozohanics, O., Csampai, A., Kudar, Veronika, Frigyes, D., Sohar, P., 2009. J. Organomet. Chem. 694, 4185.