Cyclic 1,3-Diones and their Derivatives–As Versatile Reactive Intermediates in the Syntheses of Condensed Fused Ring Heterocyles

Batchu Chandra Sekhar*

Process R&D, Glenmark Research Center, Navi-Mumbai, 400709, India

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Dedicated to Dr. M. R. Sarma on the occasion of his 65th birthday

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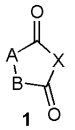
Contents

This review article deals with approaches to the synthesis of a wide range of mono and polycyclic heterocycles utilizing cyclic 1,3-diketones and their derivatives (**1**).

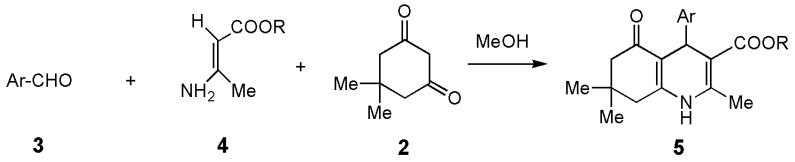


1

Introduction.

The present work covers the literature following earlier reviews [1,2] and through volume 137 of Chemical Abstracts, although parts of volume 138 received at the time of writing have also been scanned. The main objective of this survey is to provide a comprehensive account of the synthetic utility of cyclic 1,3-diones in building various heterocycles and to highlight their potential in developing better chemotherapeutic agents. These heterocycles have drawn attention for the following reasons: (1) Their preparations demand development of new synthetic approaches of general utility. (2) The investigation of the corresponding reaction mechanisms, addresses significant chemical problems. The present review is divided into sections 1-10 based on the nature of heterocycles formed, or employed or the type of reaction used.

Scheme 1



3 **4** **2** **5**

Ar	R	Ar	R
3,4,5-$(OMe)_3C_6H_2$	Me	3-$NO_2C_6H_4$	Et
3,4,5-$(OMe)_3C_6H_2$	Et	3-$NO_2C_6H_4$	*i*-Pr
3,4,5-$(OMe)_3C_6H_2$	*i*-Pr	2-NO_2-5-ClC_6H_3	Me
2-NO_2-C_6H_4	Et	NC_6H_4	Me
2-NO_2-C_6H_4	*i*-Pr	2,3-$Cl_2C_6H_3$	Me

1. Quinolines, Isoquinolines, Pyrazoloquinolines.

1.1 Quinolinecarboxylates.

Aryldihydropyridines have recently been found to be highly effective calcium antagonists [3]. Sainani and coworkers [4] reported the formation of alkyl-4-aryl-1,4,5,6,7,8-hexahydro-5-oxo-2,7,7-trimethylquinoline-1-carboxylates (**5**) by a Hantzsch synthesis involving the condensation of cyclic 1,3-diones with an aromatic aldehyde and an alkyl β-aminocrotonate (Scheme 1).

1.2 Octahydroquinoline-2,5-diones.

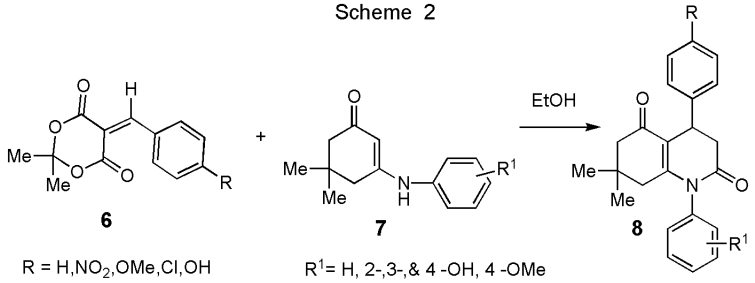
Strozher and Lieldriedis [5] have reported the synthesis of 1,4-diaryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-diones (**8**) from dioxanediones (**6**). Thus condensation of arylaminecyclohexenononones (**7**) with **6** in EtOH gave 54-86% of **8** (Scheme 2).

base afforded isoquinoline **12** *via* the intermediacy of dinitrile **11**. Hydrazinolysis of **10** yielded pyrazole **13**. Refluxing an ethanolic solution of benzil monohydrazone (**14**) and dimedone (**2**) in the presence of base afforded cinnoline (**15**) (Scheme 3).

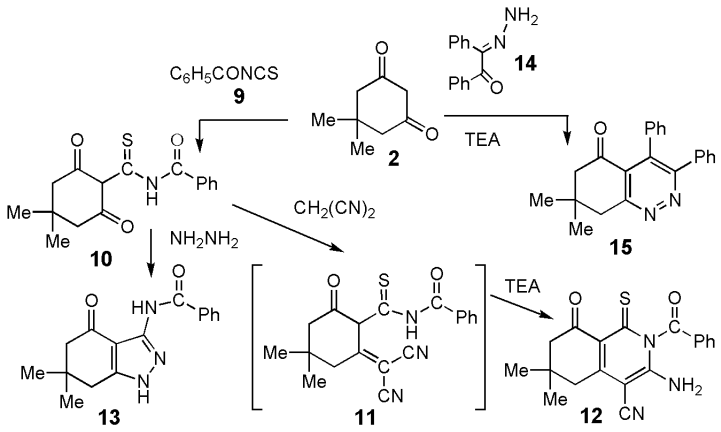
1.4 Annelated 3,4-Dihydroquinolines.

The annelation of 3,4-dihydroisoquinolines with 2-heteroaryl cyclohexane-1,3-diones was reported by Gulyakevich [8]. A cyclocondensation reaction of 2-chloroacetyl-1,3-cyclohexanedione with $RNAcSNH_2$ (R=H,Ph) in acetone gave 4-substituted 2-aminothiazoles (**16**). Heteroarylcyclohexanenedione (**16**) and (**17**) reacted with 3,4-dihydroisoquinolines (**18**) to give pentacyclic compounds (**19**) and (**20**) in 60% and 80% yield respectively (Scheme 4).

Scheme 2



Scheme 3



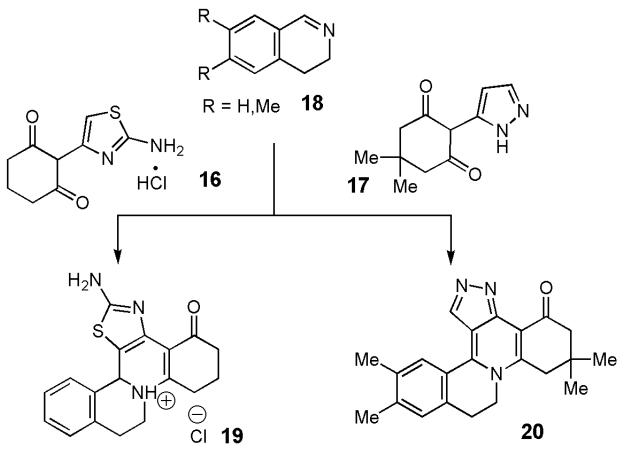
1.3 Isoquinolines, Pyrazoles.

Condensed heterocyclic systems of potential biological activity [6] by the heteroannulation of cyclic β-diketones and cyclic enaminones were reported by Assy [7]. Treatment of dimedone (**2**) with benzoyl isothiocyanate (**9**) gave thioamide (**10**). Cyclocondensation of **10** with malononitrile in the presence of

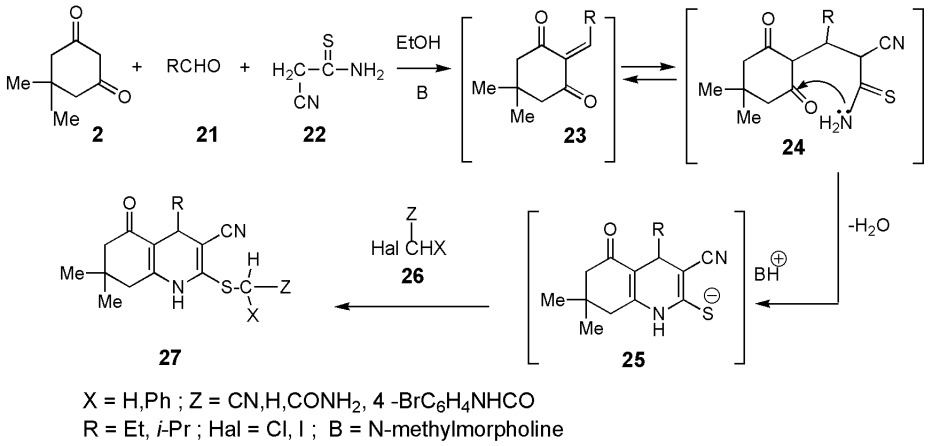
1.5 Hexahydroquinolines.

Functionally substituted, 3-cyanopyridine-2-(1*H*)-thiones are of considerable interest from the viewpoint of new biologically active compounds with a broad spectrum of action [9]. In this respect, derivatives of quinolinethiones have been much less studied, undoubtedly because of the relatively smaller number of convenient

Scheme 4



Scheme 5



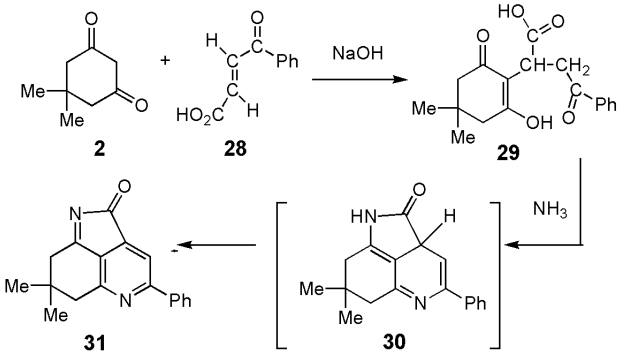
X = H,Ph ; Z = CN,H,$CONH_2$, 4 -BrC_6H_4NHCO
R = Et, *i*-Pr ; Hal = Cl, I ; B = N-methylmorpholine

methods for obtaining them. Dyorchenko and co-workers [10] reported a method based on reaction of arylmethylenecyanothioacetamides with dimedone. The authors found that the reaction of dimedone, aliphatic aldehydes and cyanothioacetamides in the presence of base, leads to a convenient synthesis of functionally substituted hexahydroquinolinethiones. Equimolar amounts of **2**, an aliphatic aldehyde (**21**) and cyanothioacetamide (**22**) in the presence of *N*-methylmorpholine at 20 °C in ethanol gave the corresponding Knoevenagel condensation product **23** to which, under the reaction conditions, CH-acidic **22** add in a Michael reaction. The adducts isolated **24** then undergo cyclocondensation to salts **25**. Subsequent S-alkylation by alkyl halides **26** yields sulfides **27** (Scheme 5).

1.6 Pyrroloquinolines.

Some naturally occurring alkaloids isolated from marine sponge, *e.g.*, batzellines, damirones, and makaluramines

Scheme 6



possess the pyrrolo[4,3,2-*de*]quinoline system as a key structural fragment [11]. Duboritskii and co-workers [12] reported the synthesis of 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline, which is the most structurally related and promising for the synthesis of analogs of the above natu-

rally occurring alkaloids. 5,5-Dimethyl-1,3-cyclohexanedione (**2**) and *trans* β-benzoylacrylic acid (**28**), on Michael condensation gave 58% of the β-keto acid **29** which was aminated in an autoclave at 150-160 °C in a solution of ammonia in methanol for 5 h. The amination resulted in closure of both pyrrole and pyridine rings and formation of 7,7-dimethyl-4-phenyl-1,2,6,7,8,8a-hexahydropyrrolo-[4,3,2-*d e*]quinoline-2-one (**31**) in 70% yield *via* an unstable air oxidation intermediate (**30**) (Scheme 6).

1.7 Pyrazoloisoquinolines.

Hennig and Alva [13] reported the synthesis of pyrazolo [3,4-*c*]isoquinolines (**35**). Pyrazoles (**32**), cyclic (**33**) and open-chain (**34**) 1,3-dicarbonyl compounds undergo addition, cyclization reactions in ethanol to give pyrazolo[3,4-*c*]isoquinolines (**35**) (Scheme7).

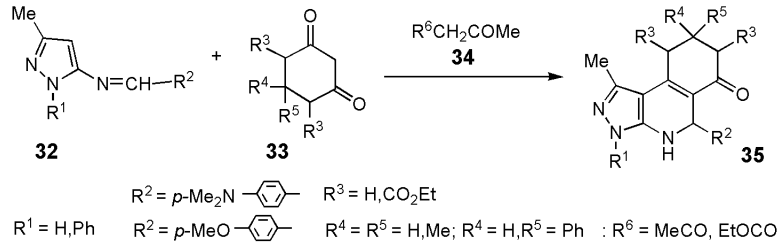
1.8 Tetrahydroquinolines.

Acridinediones namely floxacrine and deoxyfloxacrines showed very potent antimicrobial activity in experimental animal models [14]. Venugopal [15a] reported a few structural modifications of these acridine derivatives as potent antimalarials in animal studies. Treatment of 3-(4-chlorophenyl)maleic anhydride (**35**) with Me_3SiN_3 in chloroform gave the oxazinediones **36** and **37** in 23% and 12% yields respectively. Condensation of **36** or **37** with **38** in the presence of NaH gave quinoline **39** or **40**. The formation of these products could be envisaged by an initial attack of the carbanion of **38** on oxazinedione **37** followed by a sequence of intermediates similar to those in the reported [15b] reaction of isatoic anhydride with, cyclohexanediones (Scheme 8).

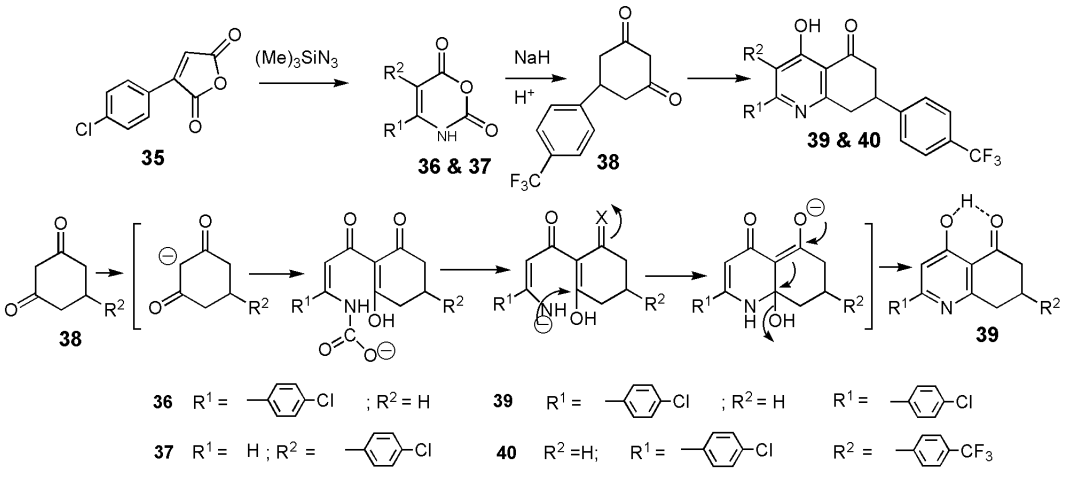
1.9 Isoquinoline Derivatives.

The acid chloride-imine reaction is very widely in use for the preparation of β-lactams. Akhrem and coworkers [16] developed a useful preparative method for the synthesis of 2-(2-acyltetrahydroisoquinolin-1-yl)-1,3-dicarbonyl compounds by the reaction of 3,4-dihydroisoquinolines with enolacylates of 1,3-dicarbonyl compounds. The reaction of dihydroquinolines (**42**) with equimolar amounts of carboxylic acid chlorides and dimedones (**2**), or cyclohexane-1,3-dione (**41**) in a chloroform solution, in the presence of pyridine, gave the 2-(2-acetyltetrahydroisoquinolin-1-yl)-1,3-dicarbonyl compounds (**44**) in 55-85% yield. The for-

Scheme 7

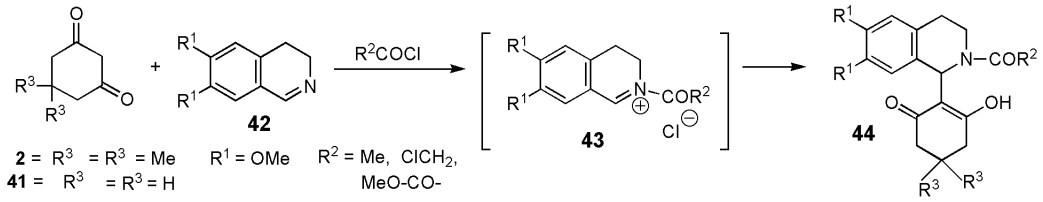


Scheme 8



mation of an intermediate *N*-acylammonium salt (**43**) is presumed to be the key step in the probable mechanism (Scheme 9).

Scheme 9



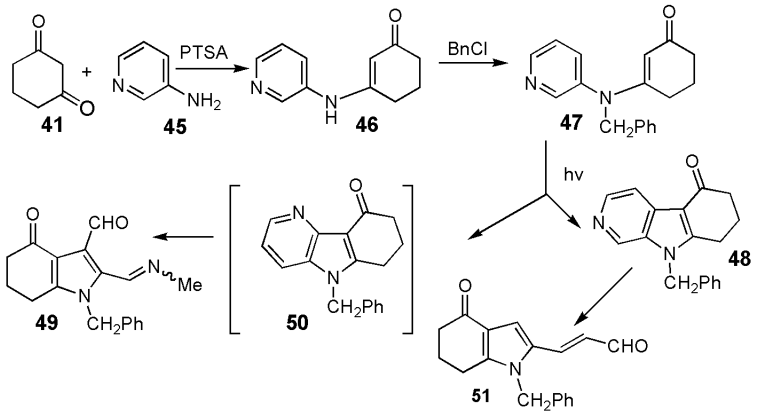
2. Carbazoles, Acridines, Annelated Indoles.

2.1 Azacarbazoles.

Interest in carbazole alkaloids has increased considerably because of the potential pharmacological activity [17] of new types of substances including pyrido[*b*]carbazoles, *e.g.*, ellipticin [18]. However, carbazoles are part of the framework of many complex alkaloids isolated from plants, which are difficult to prepare. Blache and co-workers [19] reported the synthesis of azacarbazoles.

Recently a new approach to this framework by using a photocyclisation arylenaminones as the key step has been described [20]. Condensation of 3-aminopyridine (**45**) with 1,3-cyclohexanedione (**41**) at low concentration gave the enamino ketone **46**. Transformation of the sec-enaminone **46** to terti- enaminone **47** was carried out using benzyl chloride and NaH. Photocyclization of **47** was conducted in deoxygenated benzene at 22 °C with a medium pressure mercury UV lamp (400 W) and gave a mixture of compounds **48**, **49** and **51** in 60%, 10% and 5% yield respectively. These results show that **47** cyclises to either of the available positions of the pyridine ring preferably to the C-4 position to give **48**, rather than C-2 to give **50**. Compounds **49** and **51** were photoreactive products formed from C-N cleavage of azacarbazoles (**48**) and (**50**) respectively (Scheme 10).

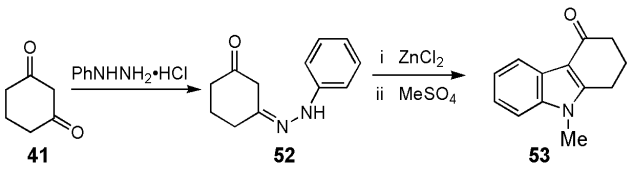
Scheme 10



2.2 Carbazoles.

The carbazole skeleton constitutes a principal pharmacophore moiety in the antiemetic drug ondansetron. Kuang and co-workers [21] reported the synthesis of 1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one in 3 steps *via* Fischer indole cyclisation starting from 1,3-cyclohexanedione. Thus treatment of **41** with phenylhydrazine

Scheme 11

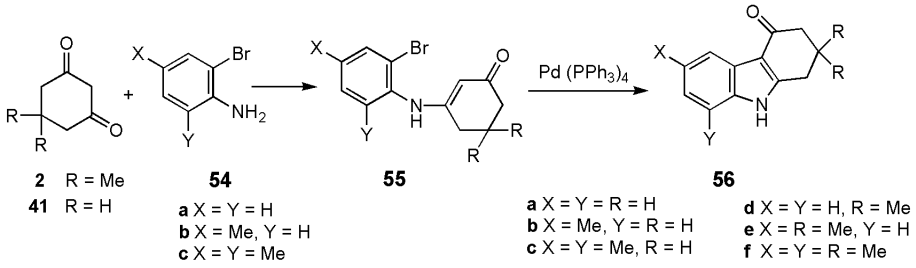


hydrochloride, followed by cyclization with zinc chloride and methylation with Me_2SO_4 gave the title compound (**53**) *via* the corresponding intermediate phenylhydrazone (**52**) (Scheme 11).

2.3 Substituted Carbazoles.

In the catalytic arylation of olefins *via* aryl-palladium σ-complexes, olefins employed are generally simple and most reactions are intermolecular [22]. The character of enaminones differs significantly from those of both enamines and ketones with respect to physical and chemical behavior. As the enaminone system is tridentate (sites a, b and c) towards electrophiles and bidentate (sites d and e) towards nucleophiles, diverse reactions are possible which are interesting and sometimes complicated. Despite the abundant literature [23] on alkylation and acylation at these reaction sites, there are few reports of arylation, although such processes are potentially useful. Minwang and co-workers [24] reported a method of intramolecular cyclization of bromoenaminones (**55**) catalysed with an arylpalladium intermediate to prepare tetrahydrocarbazoles (**56**). Thus condensation of 2-bromo-4,6-dimethylaniline **54c** with cyclohexane-1,3-dione (**41**) or dimedone (**2**) gave bromoenaminone (**55c**) or (**55f**) respectively. When bromoenaminones (**55a-f**) were treated with tetrakis[triphenylphosphine] palladium, in hexamethylphosphoric triamide in the presence of sodium bicarbonate, the corresponding tetrahydrocarbazoles (**56**) were obtained in moderate yields. The reaction proceeds by intramolecular cyclization of **55** involving aryl palladium complexes (Scheme 12).

Scheme 12



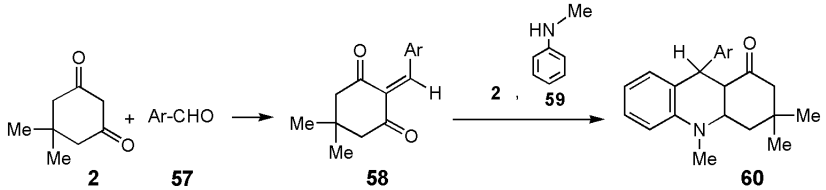
2.3. 9,10-Dihydroacridine.

Acridine-1,8-diones are interesting in view of the similarity in the properties with those of 1,4-dihydropyridines. They have been used as electron donors and electron acceptors. 9,10-Dihydroacridine derivatives are found to possess antitumor activity and are useful in the treatment of urinary incontinence [25]. Ahluwalia and co-workers [26] reported a one-pot synthesis of new acridine derivatives by an extension of the Hantzsch reaction. Condensation of *N*-methylaniline (**59**) with a substituted benzaldehyde (**57**) and dimedone (**2**) afforded the linear condensation products 9-aryl-1,2,3,4-tetrahydro-3,3,10-trimethyl-9*H*,10*H*-acridine-1-ones (**60**) in high yields. The reaction can be postulated as the Knoevenagel condensation of aldehyde and dimedone followed by Michael addition of *N*-methylaniline to the formed arylidinedimedone intermediates (**58**) and ring closure to afford the corresponding acridine derivatives (**60**) (Scheme 13).

2.4 Dihydropyridines.

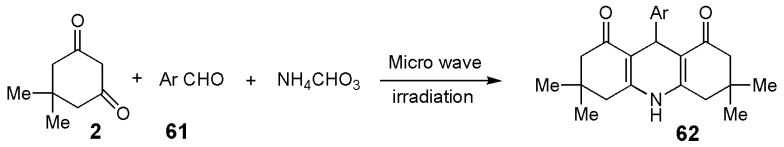
Organic reactions under dry conditions and microwave organic chemistry have been topics of continuing interest in heterocyclic chemistry. Zaisheng and Shujian [27a] reported the preparation of dihydropyridines (1,4-DHP'S), which are well known as calcium channel modulators [27b], by utilizing both microwave irradiation and dry reaction conditions [27c]. The reaction of dimedone, an aromatic aldehyde (**61**) and ammonium bicarbonate, under microwave irradiation, without energy transfer medium, gave acridines (**62**) in high yield (Scheme 14).

Scheme 13



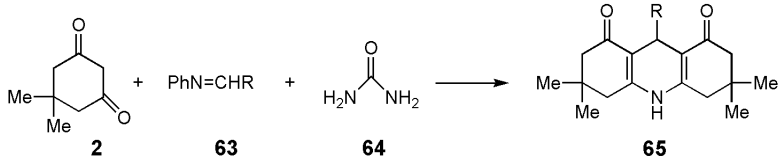
Ar = 2-$NO_2C_6H_4$, 4-$OMeC_6H_4$, C_6H_5, 4-ClC_6H_4, 3,4-$(MeO)_2C_6H_4$, 4-MeC_6H_4

Scheme 14



Ar = C_6H_5, 3-$NO_2C_6H_4$, 4-Cl C_6H_4, 2-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(OCH_2O)_2C_6H_3$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

Scheme 15



R = Ph, *p*-$Me_2NC_6H_4$, *p*-$NO_2C_6H_4$

2.5 Acridine-1,8-diones.

Acridine-1,8-diones have been shown to have very high lasing efficiencies and are also interesting in view of the similarity in the properties of with those of 1,4-dihydropyridines. They have been used as electron donors and electron acceptors. Bakibae and co-workers [28], reported a method for the synthesis of arylsubstituted acridine-1,8-diones by the reaction of 1,3-dicarbonyl compounds with azomethines. Cyclocondensation of dimedone (**2**) with PhN=CHR (**63**) and urea (**64**), in DMSO at 120 ºC, gave 49-80% hydroacridines (**65**) (Scheme 15).

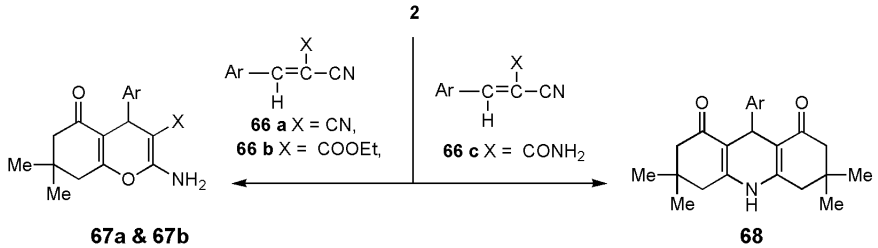
2.6 1,4- Benzopyrans and Dihydropyridines.

Polyfunctionalised 4*H*-benzo[*b*]pyrans are the structural units of a number of natural products and are used as versatile synthons [29] because of the inherent reactivity of α-cyanocinnamonitrile (**66a**) and β-cyano-β-carbethoxystyrene (**66b**) respectively with **2** in the presence of ammonium acetate, under microwave irradiation, without solvent. In contrast arylidine cyanoacetamide (**66c**) reacted with **2** under similar conditions giving acridine derivatives (**68**). The reactions were completed in 4-8 min with 76-96 % yield (Scheme 16).

2.7 Annelated Indoles.

The best-known $5HT_3$ antagonist is ondansetron, which is on the market as an antiemetic to prevent drug induced vomiting and in clinical trials to evaluate its potential use in anxiety, drug abuse and age associated memory impairment. On the basis of the structure of ondansetron, Wijngaarden and co-workers [31] reported a series of 1,7-annelated indole derivatives as very potent

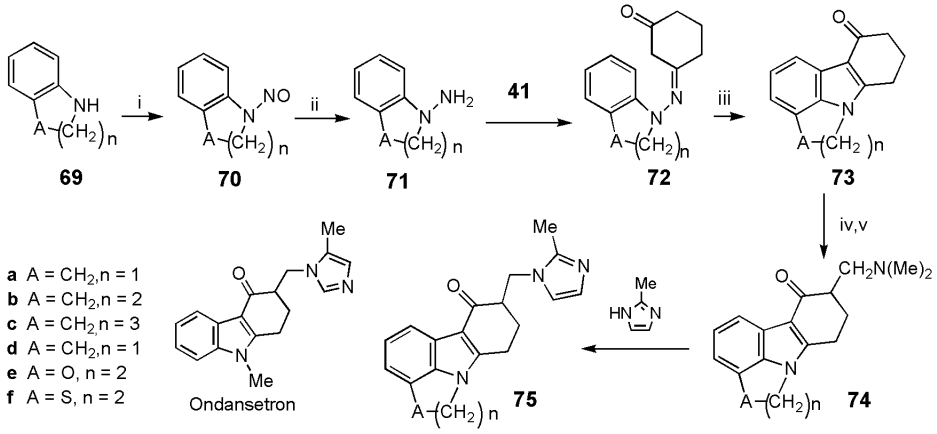
Scheme 16



Ar = C_6H_5, 2-Furyl, 2-ClC_6H_4, 4-ClC_6H_4,3-$NO_2C_6H_4$ 4-BrC_6H_4, 2-BrC_6H_4, 4-OHC_6H_4

the pyran ring. Tu and coworkers [30] reported the preparation of ethyl 2-amino-5-oxo-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-4*H*-benzo[b]pyran-3-carboxylate (**67a**) and corresponding carbonitrile (**67b**) by the reaction of 5-HT_3 antagonists [32]. Nitrosation of bicyclic heterocycles (**69**), followed by reduction with $LiAlH_4$ afforded the hydrazine derivatives (**71**) in high yield. The corresponding indoles (**73**) were prepared by means of the

Scheme 17

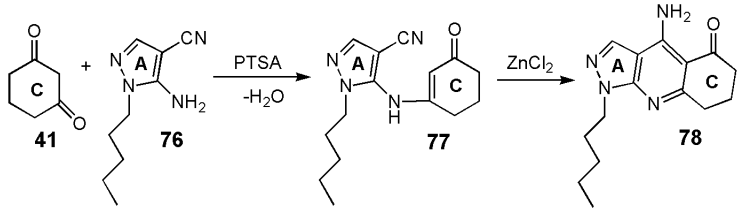


Fischer indole synthesis using 1,3-cyclohexanedione (**41**). The intermediate hydrazones (**72**) were isolated and converted into annelated indole derivatives (**73**) by boiling in acetic acid and conc. HCl for 1 h. A Mannich reaction of **73** with dimethylamine hydrochloride and paraformaldehyde in acetic acid gave the Mannich base intermediates (**74**). The replacement of the dimethylamino group by 2-methylimidazole, in water, at 100 ºC, for 2 h, yielded the annelated ondansetron derivatives (**75**), which were evaluated for affinity with 5-HT_3 receptor (Scheme 17).

2.9 Triazaphenalenes.

Triazaphenalene ring systems are potential new pharmacophores. Tshilunda and co-workers [35] reported the synthesis of the 2,3,7-triazaphenalene ring system by annulation of 5-oxo-tetrahydroquinolines. Tetrahydroquinolines could formally be obtained *via* "3+2+N" cyclisation. Michael addition of **41** onto enone **79**, gives intermediate **80** respectively, which cyclises into dihydropyridine **81** with ammonium acetate. Oxidation of **81** with *t*-BuOCl gives the pyridine **82** treatment of which

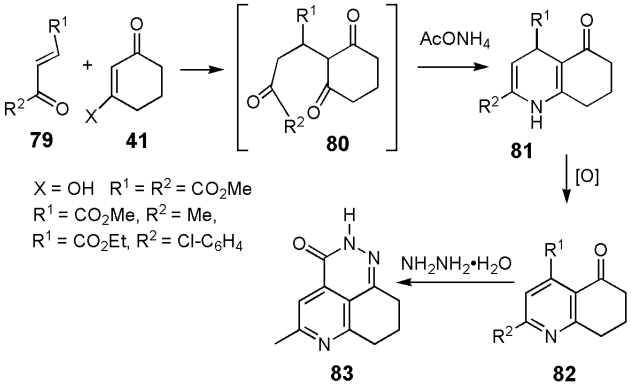
Scheme 18



2.8 Pyrazolopyridines.

Pyrazolopyridines are evaluated as possible anxiolytic agents [33]. Campbell and co-workers [34] reported a general synthesis for linearly fused tricyclic pyrazoloaminopyridines by a convergent coupling approach to assemble the fused pyridine **78** by the reaction of *o*-aminonitrile (A ring) **76** with cyclic 1,3- diones (C ring) to form linearly fused tricyclicpyridine systems **78**. Thus 1,3–cyclohexanedione (**41**) upon heating with 5-amino-4-cyano-1-pentylpyrazole (**76**) and *p*-TsOH in toluene, with azeotropic removal of water through the enaminone **77**, directly afforded the fused aminopyridine derivatives **78**, at room temperature in DMF in 3-4 h (Scheme 18).

Scheme 19

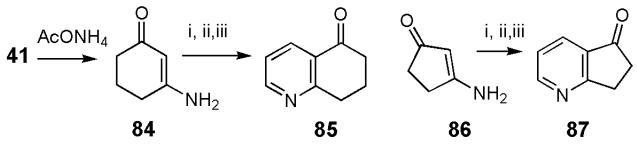


with hydrazine smoothly generates the novel 2,4,5,6-tetrahydro-2,3,7-triazaphenalene (**83**) ring system in high yield (Scheme 19).

2.10 Dihydroquinolines and Dihydropyridines.

7,8-Dihydroquinoline-5-ones are intermediates in organic synthesis and medicinal chemistry. Generally these are prepared [36] from unstable propionaldehyde and a corresponding enaminone. Huang and co-workers [37] reported the preparation of tetrahydroquinoline **85** from cyclic 1,3-diketones and ammonium acetate. Thus 1,3-cyclohexanedione (**41**) on reaction with ammonium acetate, under toluene azeotropic removal of water, gave the intermediate 3-amino-cyclohex-2-enone (**84**) in high yield. 7,8-Dihydroquinoline-5(6*H*)-one (**85**) is formed by the reaction of **84** with 1,1,3,3- tetraethoxypropane under xylene azeotropic removal of water. 6,7-Dihydro-5*H*-1-pyridin-5-one (**87**) was prepared in the same fashion from cyclopentane-1,3-dione (**86**) (Scheme 20).

Scheme 20



2.11 Spiropyran-4-yl-indolidine Derivatives.

The activity of phenoxon and 2*H*-aryl-4-hydroxy-3-methylmercapto-2- pyranone as anti-HIV agents has stimulated interest in the chemistry of 4*H*-pyrans [38]. The synthesis of compounds having both indolidene and 4*H*-pyran rings seemed to have value. F. Al-Omran and co-workers [39] reported the synthesis of 2-amino-3-substituted-4*H* pyrans *via* addition of active methylene carbonyl compounds to ylidine malononitriles in ethanolic piperidine. The reaction of 2-oxo-2,3-dihydroindole derivatives **88** with 1,3-cyclohexanedione (**41**) in AcOH and in presence of AcONa, the 2-aminospiropyranindolidinone **89** (Scheme 21).

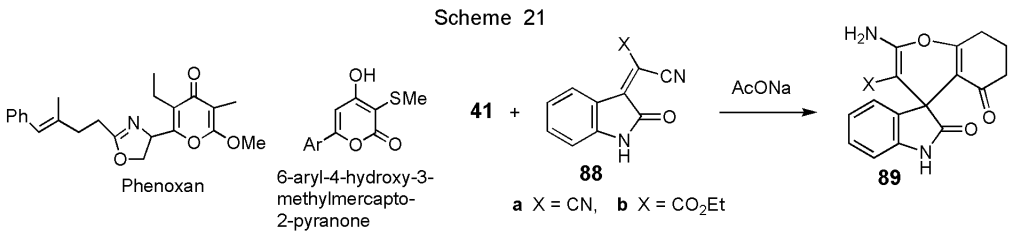
2.12 Hexahydroquinolines.

The design and synthesis of 1,4-dihydropyridines has attracted much attention in the last thirty years due to the calcium antagonist effect they display [40]. Suarez and coworkers [41] recently reported the synthesis of 1,4-dihydropyridines fused to one or two carbo- and heterocyclic rings and studied exhaustively, their calcium antagonist modulator activity. 1,4,5,6,7,8-hexahydroquinolines bearing an amino and a cyano group at C-2 and C-3 respectively **93** were synthesized from dimedone (**2**), an arylidene malononitrile (**90**) and excess of ammonium acetate, in acetic acid as solvent. Formation of the hexahydroquinoline system (**93**) takes places through a Hantzsch-like reaction by conjugate addition of the enamine intermediate **92** obtained from dimedone (**2**) and ammonium acetate, to the arylidene-malononitrile derivative **90**, followed by imino (**91**)-enamino (**92**) tautomerism and subsequent cyclization (Scheme 22).

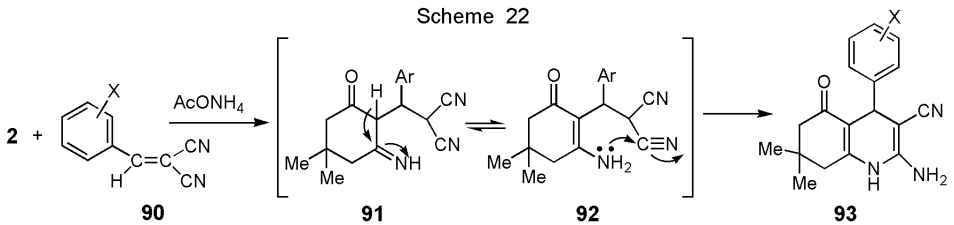
2.13 Cinnolines.

Nalidixic acid [42], cinoxacin [43] and pyrido[2,3-*b*]quinoxalines [44] have attracted attention as antibacterial agents. Yoshihisa and co-workers [45] reported the synthesis of quinoline analogues. The reaction of 3-(1-alkyl-

Scheme 21



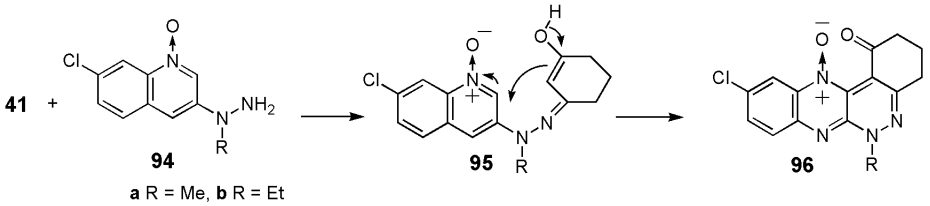
Scheme 22



90a X = H, **b** X = 2-Cl, **c** x = 2-Me, **d** X = 4-OH, **e** X = 4-OMe, **f** X = 4-N(Me)$_2$, **g** X = 4-NO$_2$
h X = 3-NO$_2$, **i** X = 2,4-Cl$_2$, **j** X = 2,4 (MeO)$_2$

hydrazino)-7-chloroquinoline-1-oxide (**94**) with 1,3-cyclohexanedione (**41**) gave the corresponding 6-alkyl-10-chloro-1-oxo-1,2,3,4,6,12-hexahydroquinoxalino-[2,3-*c*]cinnolines (**96**) *via* a hydrazone intermediate (**95**) (Scheme 23).

Scheme 23



2.14 Tetrahydroindol-4-ones.

5-Aminolevulininic acid (5-ALA) undergoes a number of important reactions and is the precursor of the haem pigment. Brown and Butler [46] reported the reactions of 5-ALA (**98**) with 5-methylcyclohexane-1,3-dione and cyclohexane 1,3-dione (**97& 41**) under acidic conditions to give 3- (2'-carboxy-3-hydroxy-4,5,6,7-tetrahydroindol-4-one (**102**). The mechanism demands that one hydrogen at the 2-position of the cyclohexane moiety of intermediate **99** is sufficiently acidic for imine to enamine (**100**) tautomerism. Cyclisation of **100** indicates that the steric constraints imposed by the cyclic nature of the diketone do not prevent formation of the heterocyclic ring **102** *via* **101** (Scheme 24).

3 Pyrazoles, Benzimidazoles, Indenopyridines.

3.1 Pyrazoloquinolizines.

Boiling pyrazolylcyclohexanediones (**103**) with dihydroisoquinolines (**104**) in EtOH affords a simple, one-step [47] prepartion of dibenzo[*af*]pyrazolo [*h*]quinolizines **105** & **106** in 69% and 68% yield, respectively involving annelation of cyclic Schiff bases (**104**) (Scheme 25).

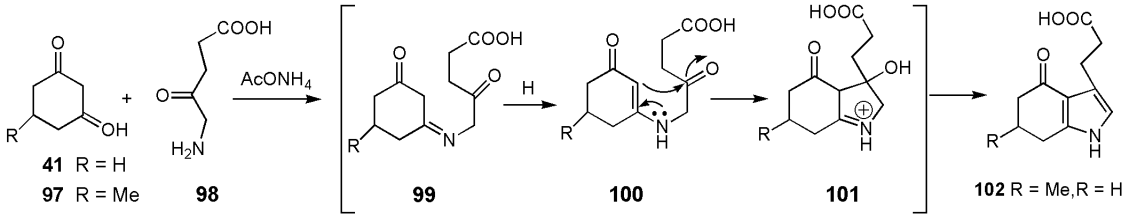
3.2 A quinazolin-5-one Derivative.

Methylenecyclohexanedione on reaction with F_2BOBu gave difluoroboron chelates of diaminomethylenediketones (**107**) which, on reaction [48] with NH_3, gave the 4-amino-5,6,7,8-tetrahydroquinazolin-5-one derivative (**108**) (Scheme 26).

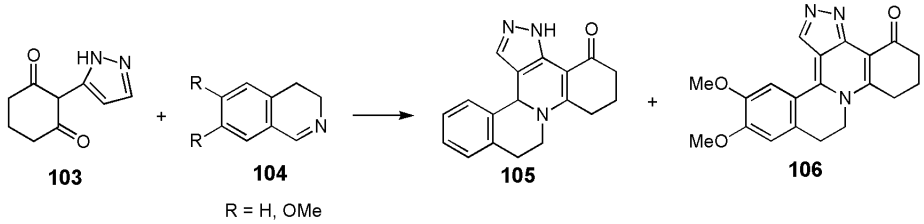
3.3 Pyrazole, Pyrimidine Derivatives.

N,N-Dimethylformamide acetals react with cylic-1,3-diketones (**41**, **86** and **109**) to produce enaminoketones [49a] (**111**), which can subsequently yield a vast array of

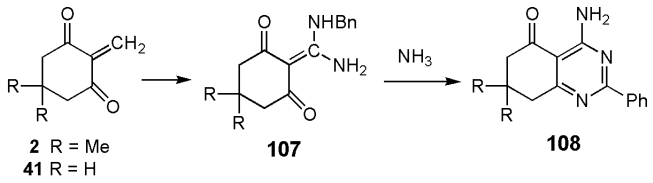
Scheme 24



Scheme 25

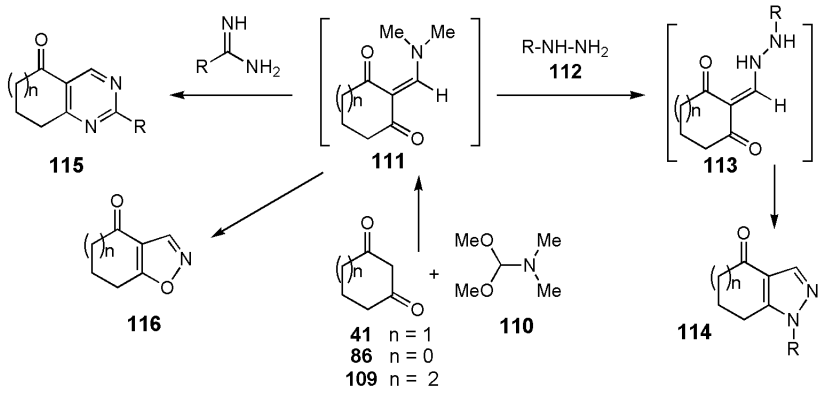


Scheme 26



heterocyclic compounds. Reactions of enaminoketones with appropriate bidentate nucleophiles give pyrazoles [49b], pyrimidines [49c], isooxazoles [49d], pyrroles [49e], pyridones [49f] and pyrimidines [49g]. Valentina and Mathew [49h] reported the synthesis of compounds **114**, from the corresponding enaminoketone (**111**) by treatment with substituted hydrazines (**112**). The reaction is a tandem addition-elimination/cyclodehydration, which takes place *via* a Michael addition of the terminal amino group of hydrazines (**112**), with elimination of Me_2NH to form the acyclic intermediates (**113**), followed by intramolecular cyclodehydration to pyrazole derivatives (**114**). The synthesis of compound **114** was carried out by microwave irradiation of an equimolar mixture of enaminoketone **111** and 2,4-dimethylphenylhydrazine in presence of aqueous AcOH. Similarly enaminoketones react with amidines or hydroxylamine to give pyrimidines, (**115**), or isooxazoles (**116**) respectively (Scheme 27).

Scheme 27

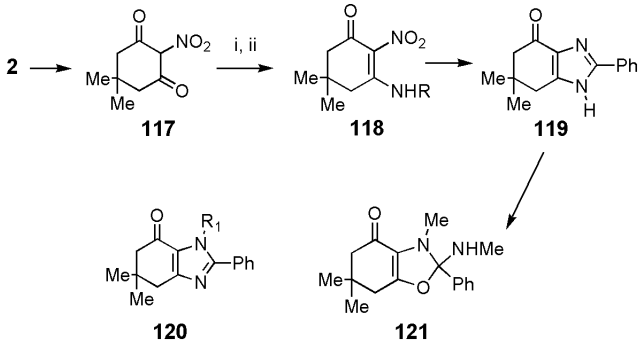


R = 2,4-Me_2 C_6H_3, Ph, 2,4-F_2-C_6H_3, 3,5-Me_2-C_6H_3, 2-Pyridyl, Cyclohexyl, *t*-Bu, H

3.4 Hydrogenated Benzimidazoles.

2-Nitro cyclic1,3-diketones are of great synthetic potential in organic chemistry. They are reactive compounds in which the C-C bond between the carbonyl group and the nitro group carrying carbon atom is easily cleaved by nucleophilic reagents. Krichevskii and co-workers [50] reported the synthesis of hydrogenated benzimidazole derivatives using 2-nitrodimedone (**117**). Treatment of (**117**) with $HC(OEt)_3$ and then with RNH_2 gave an aminocyclohexenone (**118**), cyclisation of **118** gave benzimidazolone (**119**), which was converted to **120** and benzoxazolone **121** (Scheme 28).

Scheme 28



R = hydroxyalkyl, benzyl, carboxyalkyl, i $HC(OEt)_3$ ii RNH_2
R_1 = Me, CH_2-CH_2-NEt_2

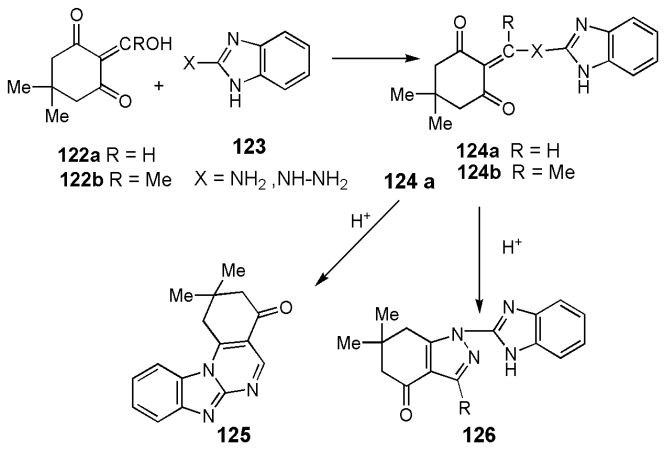
3.5 Benzimidazoles.

2-Aminobenzimidazoles have recently been recognized as useful building blocks for the synthesis of a wide variety of substituted benzimidazoles due to the polyfunctionality of the cyclic guanidine residue. Strakov and co-workers [51] reported that the reaction of 2-formyldimedone (**122a**) with 2-aminobenzimidazole (**123**) gave condensed product **124**. When acid was present, the product was 3-benzimidazoquinazolinone (**125**). Similarly, 2-acetyldimedone (**122b**) reacted with 2-hydrazinobenzimidazole (**123**) to give **124b**. In the presence of acid, cyclisation took place to give a benzimidazolylindazolone (**126**) (Scheme 29).

3.6 Tetrahydroindazoles.

The derivatives of hydrogenated indazoles, related pyrazolophenazines, and their derivatives are known to be bioactive compounds [52], which have applications

Scheme 29



as agrochemicals [53] and pharmaceuticals [54]. There is an increasing interest in the development of new procedures for the synthesis of pyrazoles and their derivatives. Strakov and co-workers [55] reported the synthesis of 1-(4-substituted aryl)-4-oxo-4,5,6,7-tetrahydroindazoles and a number of their derivatives. 2-Formyldimedone (**122a**), on reaction with 4-bromo, 4-fluoro and 4-trifluoromethylphenylhydrazines (**127**), yielded the corresponding 2-aryl hydrazinomethylenedimedones (**128**). Refluxing of **128** in methanol in the presence of hydrochloric acid led to 4-oxo-4,5,6,7-tetrahydroindazoles (**129**), oxidation of which with H_2SeO_3 gave 4,5-dioxo-4,5,6,7-tetrahydroindazoles (**130**). The reactions of α-diketones **130** with aromatic aldehydes and ammonium acetate in glacial acetic acid under reflux conditions gave 2,6-diaryl-4,4-dimethyl-4,5-dihydro-1*H*(*3H*)-indazolo[4,5-*d*]imidazoles (**131**) (Scheme 30).

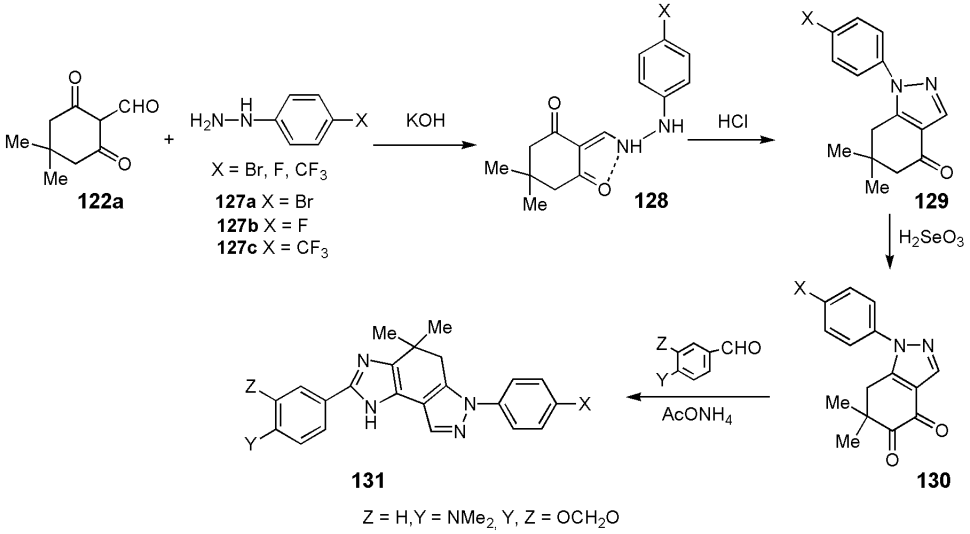
3.7 Indenopyridines/Indenothienopyridines.

Indenopyridines exhibit potent antispermatogenic activity and are useful inhibitors of spermatogenesis [56] in animals whereas indenopyrimidines show fungicidal activity [57]. Geies and El-Dean [58] reported the synthesis of condensed polyazaheterocycles containing a pyridine, pyrimidine ring fused with other heterocycles, mainly a thiophene ring, using activated nitriles. When indan-1,3-dione (**132a**) or 1-phenylimidoindan-3-one (**132b**) was reacted with an arylidenecyanothioacetamide (**133**) in ethanol in the presence of a catalytic amount of piperidine, a 4-aryl-3-cyano-5-oxo-(phenylimino)-indeno[1,2-*b*]pyridin-2[1*H*]thiones (**134**) was obtained. Refluxing of compounds **134** with halides in ethanol and in presence of the NaOAc, gave the corresponding *S*-alkylated derivatives (**135**), which underwent cyclisation into indenothienopyridine derivatives (**136**) when heated in ethanolic NaOEt (Scheme 31).

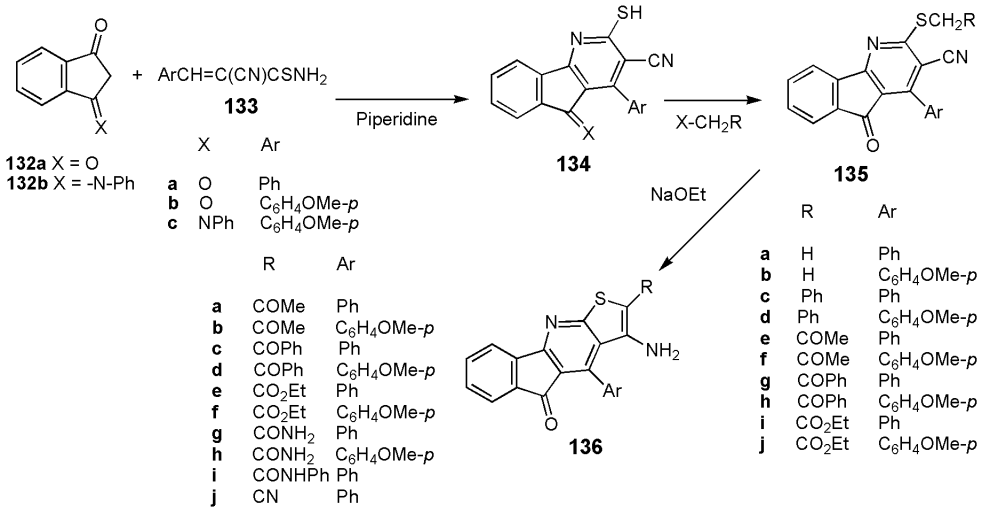
3.8 Hexahydrobenzophenanthridin-4-ones.

The reaction of cyclic 1,3-diketones with aromatic aldimines has been successfully employed for the synthesis of benzophenanthridine derivatives. Kozlov and Koroleva [59], reported the synthesis of 5-aryl-2-methyl-1,2,3,4,5,6-hexahydrobenzo[*a*]phenanthridin-4-one (**138**) in good yield by condensation of 5- methyl-1,3-cyclohexanedione (**97**) with an arylmethylene-2-napthylamine (**137**) (Scheme 32).

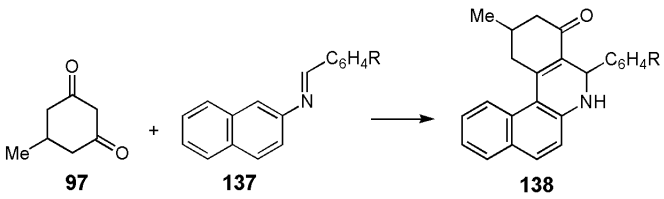
Scheme 30



Scheme 31

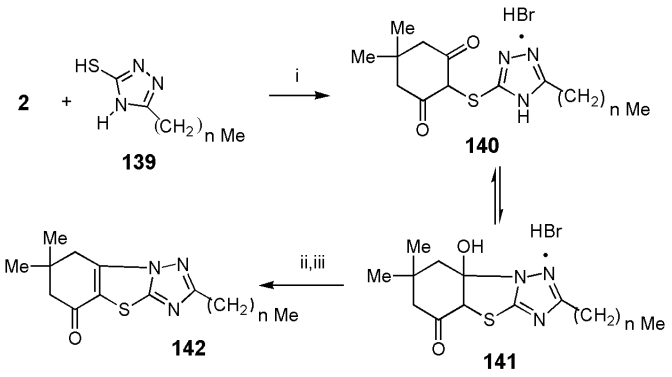


Scheme 32



presence of *N*-bromosuccinimide and a catalytic quantity of benzoyl peroxide produces 2-alkyl-5a-hydroxy-6,6-dimethyl-8-oxo-5,5a,6,7,8,8a-hexahydro-5-triazolo[3,2-*b*]benzothiazolines (**141**) in good yields. Dehydration of **141** by heating with PPA in anhydrous ethanol afforded the respective 2-alkyl-6,6-dimethyl-8-oxo-4,5,6,7-tetrahydro-*S*-triazolo[3,2-*b*]benzothiazoles (**142**) in excellent yields (Scheme 33).

Scheme 33



a n = 4 ; **b** n = 6 ; **c** n = 8 ; **d** n = 10 ; **e** n = 12 ; **f** n = 14

i NBS, ii Na_2CO_3, iii PPA

3.9 Triazolobenzothiazoles.

Derivatives of 3-mercaptotriazole were reported to be potent antagonists of angiotensin II. Ahmed and Khazi [60] reported that condensation of dimedone (**2**) with 3-alkyl-5-mercapto-1,2,4-triazoles (**139**) in benzene in

4. Pyrimidines, Pyranopyrimidines.

4.1 Pyrimidine Derivatives.

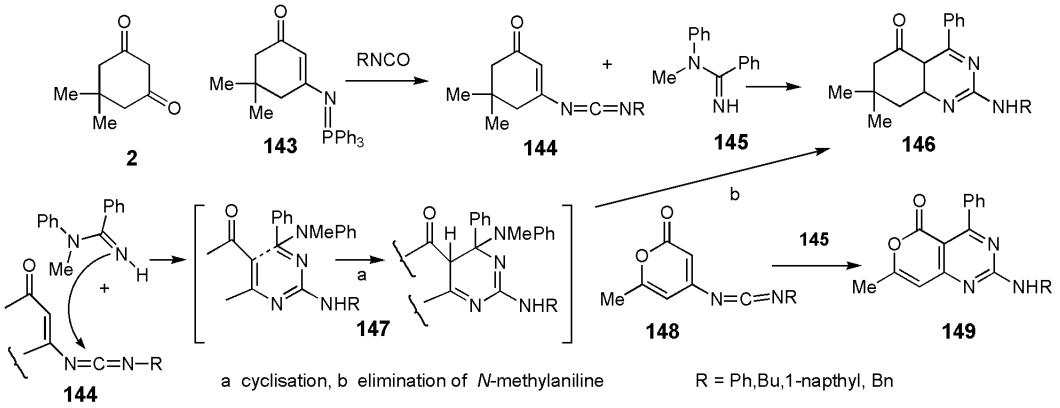
Conjugated carbodiimides were recognized as useful synthetic tools for heterocyclic systems. Their intermole-

cular cycloaddition as well as intramolecular cyclization provided nitrogen heterocycles such as pyridine and 1,3-diazepines. However, the pyrimidine ring formation *via* conjugated carbodiimides has limited attention as only a few examples were reported. Isomura and Yamasaki [61] reported the preparation of fused pyrimidine derivatives by the treatment of conjugated carbodiimides with an amidine by Tandem aza-Wittig electrocyclization reaction. *N*-(5,5-Dimethyl-3-oxo-1-cyclohexenyl)-*N*'-substituted carbodiimides (**144**) generated *in situ* by the aza- Witting reaction of iminophosphorane **143** with the corresponding R-NCO in dioxane, were allowed to react with *N*-methyl-*N*'-phenylbenzamidine (**145**) giving 2-(substituted amino) quinazoline systems as main products **146**. Nucleophilc attack of the imine nitrogen atom in amidine **145** to the carbon atom in carbodiimide **144** takes place giving guanidines **147**. The 6 π- electrocyclic ring closure of **147** gives dihydropyrimidine, which is aromatized to pyrimidine **146** with the elimination of *N*-methylaniline. Similarly, the reaction of *N*-[6-methyl-2-oxo-4-(2ω)-pyranyl]-*N*'-substituted carbodiimides (**148**) with amidine **145** afforded also pyrimidine derivatives **149** in moderate yield (Scheme 34).

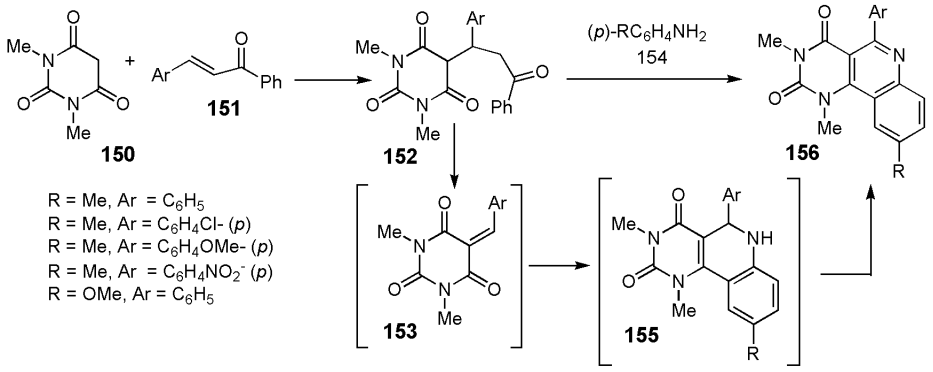
4.2 Annelated Pyrimidines.

With the development of clinically useful pyrimidine-based anticancer {(5-fluorouracil) [62]} and antiviral drugs (AZT, BVDU), appears interest in the synthetic manipulation of uracils. Zorob and Abou-elzahad [63] reported the reactivities of barbituric acid and their derivatives as centres of heteroannulation. 5-Benzoylethyl barbituric acid derivatives (**152**) were reported as precursors for the synthesis of pyrimidine fused heterocycles. The base catalysed addition of 1,3-dimethylbarbituric acid (**150**) to appropriate α,β-unsaturated ketones **151** afforded the Michael adducts **152**. The reaction of cyclic 1,3-diketones **152** by treatment with aniline derivatives (**154**) in xylene in presence of catalytic amount of PTS gave pyrimido-

Scheme 34



Scheme 35

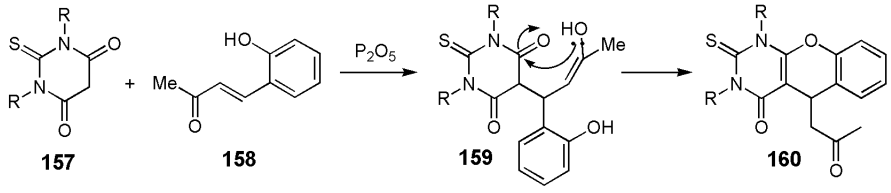


quinolines derivatives **156**. The probable mechanism for production of the pyrimidoquinolines **156** is believed to be through the formation of ylidine derivatives **153** *via* elimination of acetophenone molecule from the diketones **152** with subsequent addition of the aniline derivatives **154** to the formed ylidines **153** followed by cyclisation to dihydropyrimido[5,4-*c*]quinoline intermediates (**155**). This subsequently underwent oxidation in presence of ylidine derivatives **153** (Scheme 35).

4.3 Pyranopyrimidinethiones.

Pyranopyrimidine systems are associated with diverse physiological activity and a number of methods were developed for their synthesis. Ahluwalia and Kumar [64] reported synthesis of pyrano[2,3-*d*]pyrimidinones by the condensation of thiobarbituric acid **157** with *o*-hydroxy benzylidineacetones (**158**) under basic as well as acidic condition. The reaction of 1,3-bis(4-methylphenyl)-2-thiobarbituric acid (**157**) with *o*-hydroxybenzylideneacetone (**158**) was reported in pyridine at reflux temperature to give **160**. In this case, the reaction proceeds *via* Michael addition to give **159** and its phenolic OH is involved in the formation of benzopyran ring **160** (Scheme 36).

Scheme 36



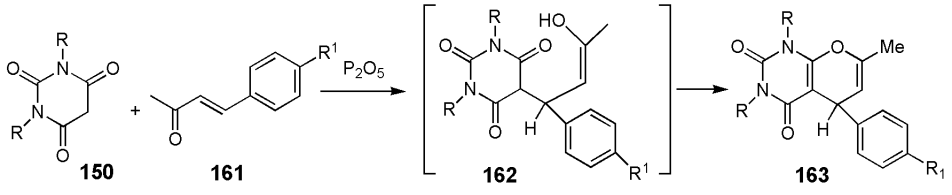
4.4 Pyranopyrimidinediones.

A variety of routes for the synthesis of pyranopyrimidine systems have been described, the majority of them were multi step and the yields are low. Ahluwalia and Aggarwal [65] reported an efficient method for the synthesis of these derivatives. The condensation of barbituric acids **150** with benzylideneacetones **161** in presence of acetic acid and phosphorous pentoxide at 120 °C, furnished the pyrano[2,3-*d*]pyrimidinediones **163** in 79-90% yield. The reaction is expected to proceed through the formation of the intermediate **162**, which underwent cyclocondensation to form the pyran ring (Scheme 37).

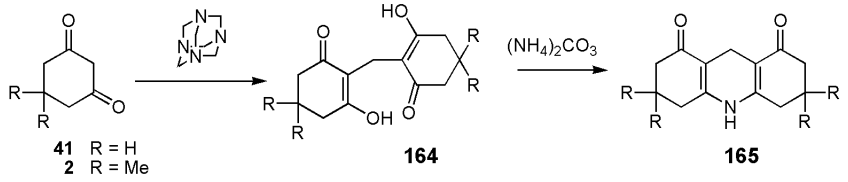
4.5 Tricyclic 1,4-Dihydropyridine Derivatives.

Since the observation of laser action from organic compounds, many classes of dyes have been demonstrated to give laser action. Several new compounds have been synthesized and investigated in order to get high laser efficiency, wide tenability and photostability. Toyoshima and Nomura [66] reported the synthesis of tricyclic 1,4-dihydropyridine derivatives from cylic β-diketones. The reaction of cyclic 1,3-diketones (**2** and **41**) and hexamine in aqueous methanol gave methylene bis–cyclic 1,3-diketones **164**. The tricyclic dihydropyridines derivatives **165** were obtained by treatment of **164** with conc. ammonia solution and ammonium carbonate in an autoclave (Scheme 38).

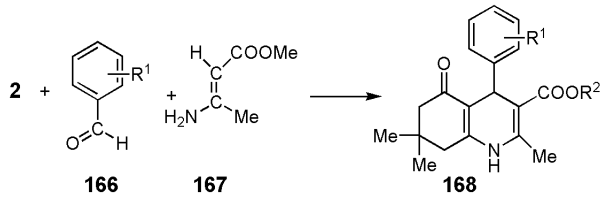
Scheme 37



Scheme 38



Scheme 39



4.64 Arylquinolinederivative.

Various aryl dihydropyridines like nifedipine and SKF24260 have been found to be highly effective Ca antagonist [67]. Ahluwalia and Goyal [68] reported a one step synthetic route for the 4-aryldihydropyridines. Dimedone (**2**), corresponding 4-aromaticbenzaldehyde (**166**) and β-aminocrotonate **167** were reacted in methanol afforded 4-aryl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5- oxoquinoline-3-carboxylates (**168**) (Scheme 39).

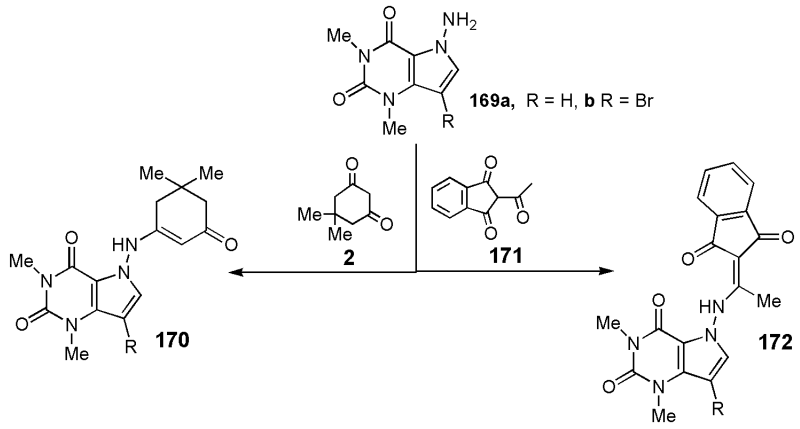
4.7 Pyrrolopyrimidines.

dazino[2,3-*d*]indoles. Pozharskii and Tsupak [69] have investigated similar reactions with 5-amino-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4-(1*H*,3*H*)-diones (**169**). Heating **169** with an excess of **2** without solvent at 140-200 °C produces the corresponding enaminoketones **170**. Similarly 2-acetylindane-1,3-dione (**171**) gave the corresponding enamino ketone (**172**) (Scheme 40).

4.8 Pteridines.

Tetrahydrobiopterin and tetrahydrofolic acid are cofactors in enzymatic redox and transfer processes in many different organisms. In addition, neopterin and oncopterin are good monitors for immune activity and are employed as indicators in the diagnosis of cancer and HIV infection [70]. Almost all biologically active pteridines have substituents on the C_6 position, regioselective synthesis of 6-substituted pteridines is a very important subject in the chemistry of pteridine. Shizuaki and Masato [71] reported 6-alkylatedpteridines, 6-triflouromethanesulfonyloxypteridines. Reaction of sodium enolate of 1,3-cyclohexanedione (**4 1**), dimedone (**2**) with 1,3 dimethyl-6-trifluoromethanesulfonyloxylumazine (**173**), yielded enol forms **174** together with furan derivatives **175** respectively. The

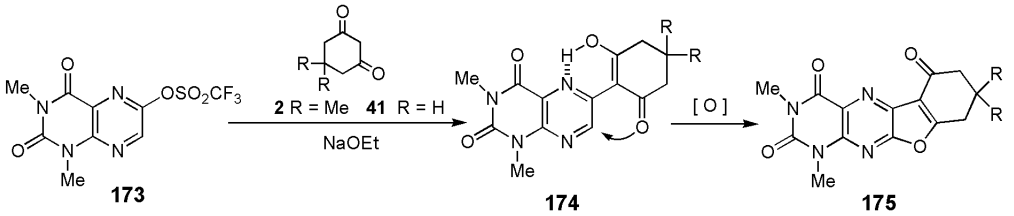
Scheme 40



N-Aminoindoles are useful starting materials for preparation of various types of novel heterocyclic compounds. Cyclic 1,3-diones react with *N*-aminoindoles to form enaminoketones that can then be converted to pyri-

C_7=N bond of pteridines are readily accessible to the attack of oxygen nucleophile and in **174**, the ketocarbonyl group existed in the same plane of the pteridine ring because of intramolecular attack of the oxygen atom on C_7 easily

Scheme 41

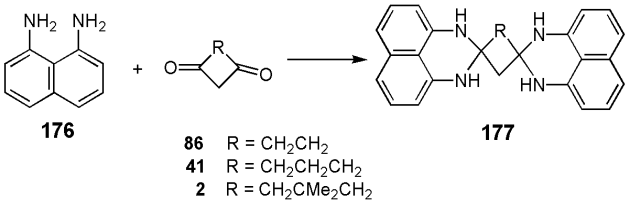


occurred to give the tetracyclicdihydropteridine derivative. Air oxidation of the intermediate afforded the furan derivatives **175** with fully conjugated pteridine ring (Scheme 41).

4.9 Dihydropyrimidines.

The synthesis of pyrimidine based heterocyclic systems by reaction of 1,8-diaminonapthalene and cyclic 1,3-diketones, is important in view of their application as dye intermediates and coloring agents for polymers [72]. Yavari and Mostafari [73] reported one step synthesis of bis (dihydropyrimidine-2-spiro) cycloalkanes (**177**) using cylic1,3-diketones **86, 41, 2** by direct heating with 1,8-diaminonapthalene (**176**) in methanol (Scheme 42).

Scheme 42

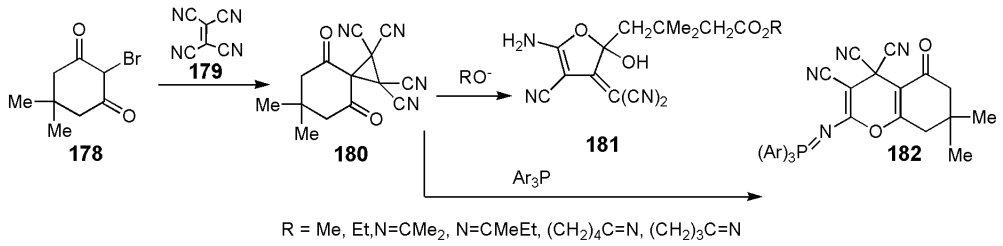


5. Benzofuran, Pyran, Xanthonediones.

5.1 Dihydrofuran and tetrahydrochromenes.

Kayukova and Lukin [74] reported reaction of 2-bromo-5,5-dimethyl–1,3-cyclohexanedione (**178**) with tetracyanoethylene (**179**) to furnish 6,6-dimethyl 4,5-dioxospiro[2,5] octane-1,2,2-tetracarbonitrile (**180**), which on reaction with alcohols and ketoximes furnished dihydrofurans **181**. Tetracarbonitrile **180** with triarylphosphines formed Chromonones **182** (Scheme 43).

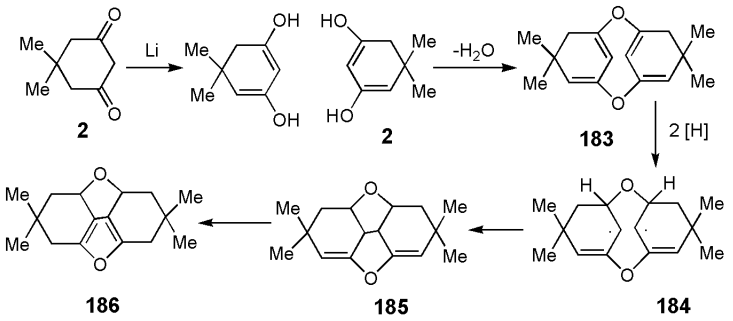
Scheme 43



5.2 Octahydrobenzofurobenzofurans.

The action of Lithium and ethylene diamine on a host

Scheme 44

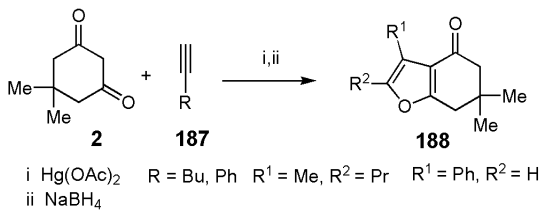


of compounds bearing various functional groups is the subject of investigation by many researchers. Pradhan and Ghosh [75] repoported the synthesis of 3,3,7,7-tetramethyl-1a,2,3,4,6,7,8,8a-octahydrobenzofuro[4,3,2-*bcd*]benzofuran (**186**) in one step by treating dimedone (**2**) with lithium metal in ethylenediamine. Dimedone (**2**) undergoes dehydration furnishing diether **183**. The diether being conjugated, the nascent hydrogen formed by lithium/ethylenediamine, attacked the electronically more dense carbon atoms bearing the oxygen atom, in **183** *i.e.*, the 1,1 position and produces two free radical sites in **184**, which results in C-C bond formation giving an intermediate **185**, which on isomerisation furnished **186** (Scheme 44).

5.3 Bicyclic Furans.

Chobanyan and Badanyan [76] reported derivatives of furans **188** from monosubstituted alkynes (**187**) and dimedone (**2**) by cyclisation in presence of $Hg(OAc)_2$ in dimethyl sulfoxide at 75 °C (Scheme 45).

Scheme 45



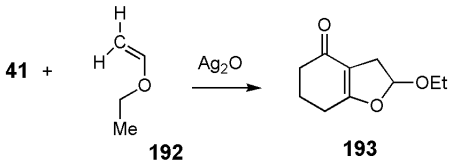
5.4 2-Nitrohexahydrobenzofurans.

1-Bromo-1-nitroalkanes are useful intermediates in organic synthesis, as they are good acceptors in the Michael addition of cyclic 1,3-diketones. Trukhm and Tebby [77] reported the preparation of 1-bromo-2-(*p*-chlorophenyl)-1-nitroethene (**189**) by bromination of *p*-chloro-ω-nitrostyrene, which reacted with 1,3-cylohexanediones (**2&41**) to give nitrotetrahydrobenzofuranones (**191**) *via* the intermediate (**190**) (Scheme 46).

5.5 Hexahydrobenzofuranone.

The oxidative addition of carbon-centered radicals to alkenes, mediated by metal salts (Mn^{III}, Ce^{IV}, Co^{II}) has received considerable attention in the last decade in organic synthesis for construction of carbon-carbon bonds. Utilization of high-valent metal salts in oxidative addition reactions have been particularly effective. Lee and Kim [78] reported, Silver (I) oxide / celite as an efficient and useful reagent for the oxidative addition of 1,3-dicarbonyl compounds to olefins, which furnished the synthesis of dihydrofuran in moderate yield. Silver (I) metal promoted oxidative additions are generally heterogeneous in nature and occurs under essentially mild neutral conditions. Two equivalents of silver (I) oxide/celite were used and the reactions were carried out by refluxing a solution of 1,3-cyclohexanedione (**41**), with ethyl vinyl ether (5 eq) (**192**), gave the desired dihydrofurans (**193**) in good yield (Scheme 47).

Scheme 47



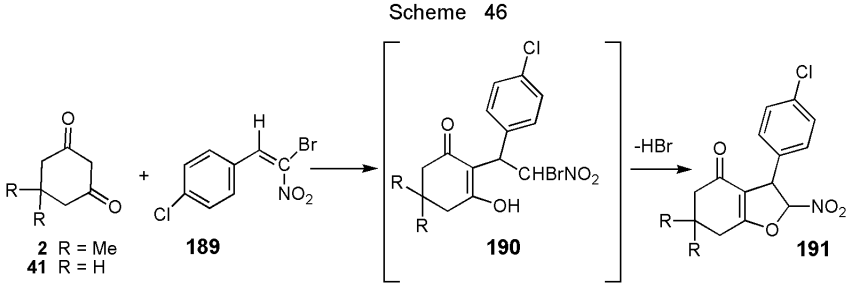
5.6 Oxohydrochromone.

Markova and Korobochkina [79] reported heterocyclisation of corresponding 2-(3-oxopropyl-1,3-cyclohexanedione) derivative (**194**) by heating in the presence of sulphuric acid and acetic acid mixture, resulting in the formation of oxohydrochromones (**195**) (Scheme 48).

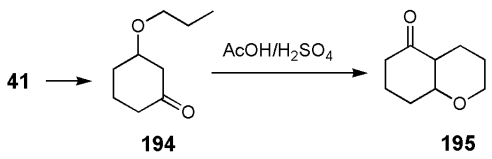
5.7 Xanthones and γ-Lactones.

In the literature, a considerable number of reports indicate the exclusive formation of *C*-alkylation prod-

Scheme 46

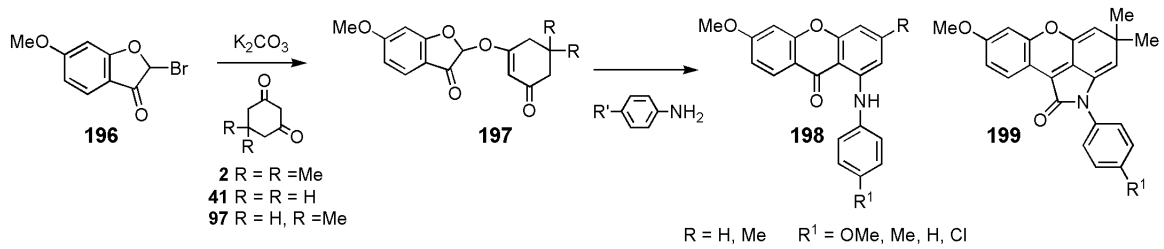


Scheme 48



case of *O*-alkylated derivative **197** (R = H) wherein **198** was isolated in 30% yield. Thus when **197** (R = H, Me) was condensed with *p*-anisidine in glacial acetic acid at its reflux temparature, instead of the expected γ-lactam derivative the product was found to be xanthone derivatives **198** (Scheme 49).

Scheme 49

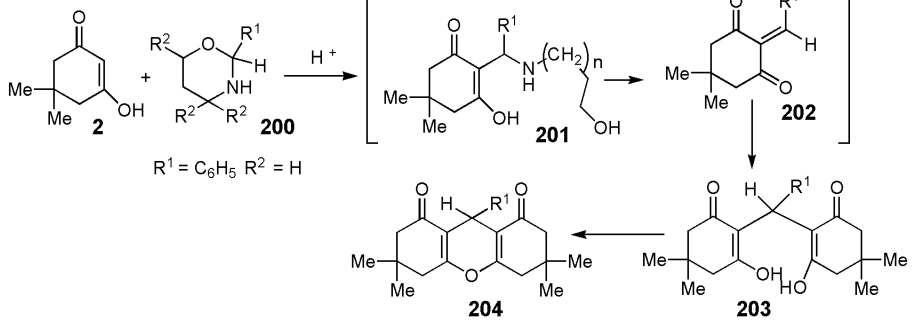


ucts during the reaction of α-bromoketones with cyclic1,3-diones. 1,4-Dicarbonyl compounds are most reactive and versatile substrates for the general synthesis of pyrroles, which could be formed from α-bromoketones by *C*-alkylation of cyclic 1,3-diones. The cyclization as well as condensation of 1,4-dicarbonyl systems with ammonia or primary amines has been well investigated and synthetically exploited in the field of pyrroles, whereas reports on similar studies involving *O*-alkylation are lacking. Ramadas and Sekhar [80] reported a transformation encountered in an attempted condensation of the *O*-alkylated product derived from 2-bromo-6-methoxy-benzofuran-3-one (**196**) and cylic 1,3-diones (**2**, **41** and **97**). The condensation of *O*-alkylated product with *p*-substituted anilines gave interesting results from the mechanistic and synthetic point of view. The *O*-alkylated derivative (**197**) was condensed with *p*-anisidine in glacial acetic acid at reflux temparature gave γ-lactum heterocycles **199** with cross conjugation. The presence of a gem dimethyl group in the pyran ring alters the course of the reaction as evidenced in the

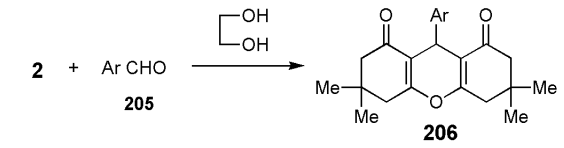
5.8 Xanthonediones and 4*H*-Benzopyrans.

Polyfunctionalised 4*H*-benzopyrans and xanthonediones constitute a structural unit of a number of natural products because of the inherent reactivity of the builtin pyran ring. Singh and Singh [81] reported the synthesis of fused pyran derivatives through carbon transfer reactions of 1,3-oxazines with carbon nucleophiles. 5,5-Dimethyl-1,3-cyclohexanedione (**2**), a mono carbon nucleophile with enhanced enolic character, was reacted with 2-phenyloxazinane (**200**) in refluxing acetonitrile:acetic acid (10:1) to furnish 2,2'-(phenylmethylene)bis[5'5-dimethyl-1-hydroxycyclohex-1-en-3-one] (**203**). Cyclodehydration of **203** in acetic acid gave octahydroxanthenes **204**. This reaction represents an overall transfer of C-2 unit of **200** at the level of aldehyde group oxidation in between two molecules of dimedone and could be visualized to proceed through initial intermediates **201** and **202**, followed by formation of **203** and cyclodehydration (Scheme 50).

Scheme 50



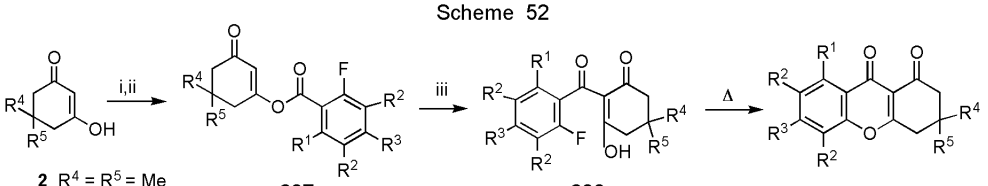
Scheme 51



Ar = C_6H_5, 4-MeC_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-OHC_6H_4, 3,4-$OCH_2OC_6H_3$, 4-$MeOC_6H_4$

and **97**) with 2-flourobenzoyl chlorides in presence of 1,8–diazabicyclo[5,4-*a*]undec-7-one (DBU) proceeded smoothly in acetonitrile at -10 °C to give the corresponding enol esters **207**. The Fries rearrangement of **207** with $AlCl_3$ in dichloromethane gave the cyclised product **209**, since the elimination of hydrogen fluoride in **208** occurred relatively smoothly under the reaction conditions (Scheme 52).

Scheme 52



2 $R^4 = R^5 = Me$
41 $R^4 = R^5 = H$
97 $R^4 = Me$ $R^5 = H$

I ArCOCl ii DBU iii $AlCl_3$

a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
b $R^1 = R^2 = R^3 = R^4 = H; R^5 = Me$
c $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = H$
d $R^1 = F$, $R^2 = R^3 = R^4 = R^5 = H$
e $R^1 = R^2 = H$, $R^3 = F$, $R^4 = R^5 = H$
f $R^1 = R^2 = R^3 = F$, $R^4 = R^5 = H$

5.9 Hexahydroxanthenes.

Condensation reaction of aromatic aldehydes with active methylene carbonyl compounds is one of the most important synthetic routes for formation of substituted alkenes. Bases or Lewis acids generally catalyze the reactions. Shujiang and Jiangfen [82] reported the preparation of hexahydroxanthenes **206** by treatment of aromatic aldehyde **205** with 5,5-dimethyl-1,3-cyclohexanedione (**2**) in ethylene glycol as solvent without catalyst. Knoevenagel condensation, Michael reaction, cyclodehydration have occurred simultaneously resulting in the formation of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-2,3,4,5,6,7-hexahydroxanthenes (**206**) in excellent yields (Scheme 51).

5.10 Xanthonediones.

A number of natural products contain the reduced xanthone unit, 3,4,4a, 9-tetrahydroxanthone moiety, which also features in the lactone ergochrisin, the beticolin toxins and antibiotic xanthoquinodin.A1 [83]. Gabbutt and co-workers [84] reported an efficient two-step procedure for the synthesis of tetrahydroxanthene-1,9-diones (**209**). A simple procedure for the preparation of 2-acylcyclohexane-1,3-diones has been described, which is based on the Fries rearrangement of enol esters derived from acylation of cyclohexane-1,3-diones (**2**, **44** and **97**). Chromones have been prepared by an intramolecular nucleophilic displacement of fluoride from ethyl 2-(2-fluorobenzoyl)-2-acylacetate and a combination of these two protocols was considered to offer a varied entry to the xanthone. Reaction cyclohexane-1,3-diones (**2**, **41**

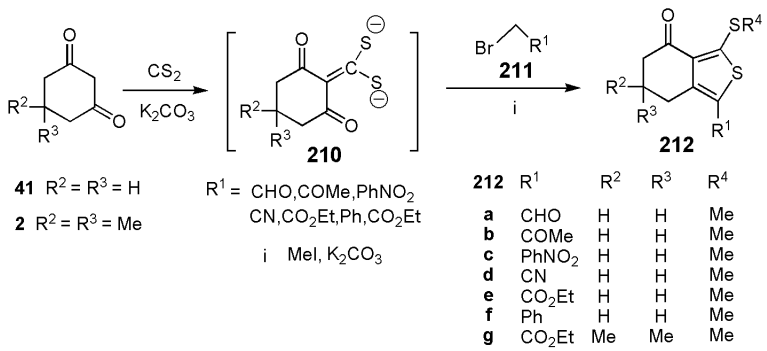
5.11 1,3 Disubstituted Thiophenes.

The chemistry of thieno[*c*]cycloalkanones as precursors of potential antifungal and antibacterial heterocyclic compounds has attracted the attention of heterocyclic chemist. Mono, di, and polyalkyl- as well as chloro and dichloro derivatives have been described, generally by cyclization of the corresponding ω-thiophenealkanoic acids. Prim and Kirsch [85] reported differently 1,3-disubstituted thiophene ring systems from 1,3-cyclohexanediones with carbon disulfide as the sulfur source. Condensation of 1,3-cyclohexanediones (**41**) with carbon disulfide in presence of potassium carbonate in DMF gave the dithioketene anion **210** as an intermediate. Successive quenching of the anion with active methylene halides **211** and methyl iodide leads to the formation of the 1,3-disubstituted-thiophene derivatives **212**. Generally the cyclisation step takes place spontaneously during the reaction (Scheme 53).

5.12 Coumarin and Condensed 2*H*-Pyran-2-ones.

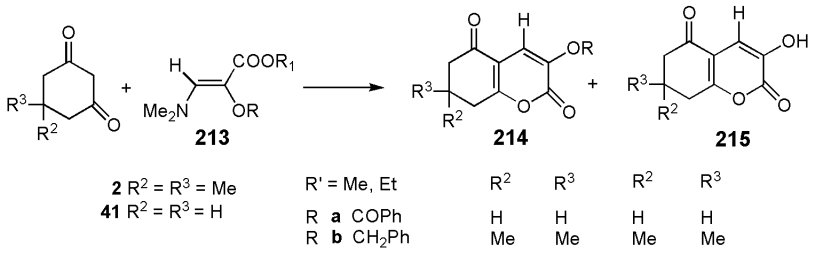
Fused 2*H*-pyran-2-one is an important biologically active compound as this ring system is found in numerous plant metabolites [86]. Rapid progress in the field of 2*H*-pyran-2-ones and condensed systems in recent years appeared due to the introduction of several drug receptor binding models leading to the formation of novel inhibitors of various enzymes such as HIV protease. Smodis and Stanovink [87] reported the synthesis of fused pyran-2-ones with a hydroxy or substituted hydroxy group attached at position 3 in the newly formed bicyclic compound from substituted 3-

Scheme 53



amino-2-hydroxypropenoates (**213**). Cyclohexane-1,3-dione (**41**) and dimedone (**2**) react with **213** to form 3-benzoyloxy-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**214**) and its 3-benzyloxy derivative (**215**) in 26% and 45% yield respectively (Scheme 54).

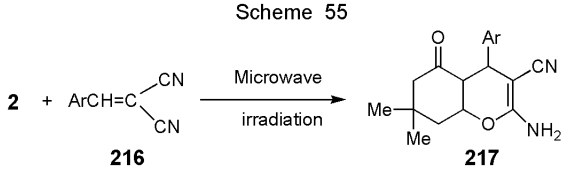
Scheme 54



5.13 Benzopyrans.

Microwave irradiation and its application in organic synthesis have been reviewed recently. Rate enhancement in many reactions has been reported in recent years. Shuajiang and co-workers [88] reported new synthetic methods for substituted 4*H*-benzo[*b*]pyrans by taking advantage of both microwave irradiation and dry reaction condition. 2-Amino-5,6,7,8-tetrahydro-5-oxo-4-aryl-7,7-dimethyl-4*H*-benzo[*b*]-pyran-3-carbonitriles (**217**) were prepared in a single step reaction of benzylidenemalononitriles (**216**) and dimedone (**2**) under microwave irradiation condition without using a catalyst and solvent. The reactions were completed within 2-4 minutes with 89-96% yield (Scheme 55).

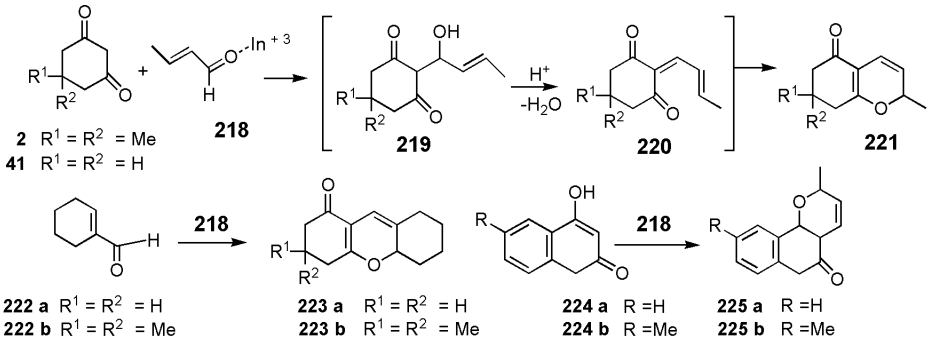
Scheme 55



5.14 Pyranocoumarins.

2*H*-Pyrans are distributed in nature as a key unit of natural products [89]. They have a variety of interesting biological activities and potential medical applications [90]. Lee and co-workers [91] reported general and efficient approach for the synthesis of 2*H*-pyrans. The indium (III) chloride-catalyzed reaction of cyclic 1,3-diones to α,β-unsaturated aldehydes has also been examined by the authors. A convenient and efficient one pot synthesis of 2*H*-pyrans by a tandem Knoevenagel-electrocyclic reaction was also achived. Reaction of 5,5-dimethyl-1,3-cyclohexanedione and 1,3-cyclohexanedione (**2** and **41**) with crotonaldehyde (**218**) in acetonitrile, indium (III) chloride afforded 2*H*-pyran **221** in 70% yield. Although the exact mechanism of the reaction is still not clear, it is best described as dimedone (**2**) first attacks aldehyde **218** to yield the alcohol **219**, which is dehydrated on heating in acidic condition to give **220**. The intermediate **220** then underwent electrocylic reaction giving rise to cyclic adduct **221**. Interestingly, in the case of 1-cyclohexene-1-carboxaldehyde, the expected pyrans **223a** and **223b** were also produced in 74 and 64 % yield. The reaction of 4-hydroxycoumarins (**224a** and **224b**) with crotonaldehydes afforded the biologically

Scheme 56

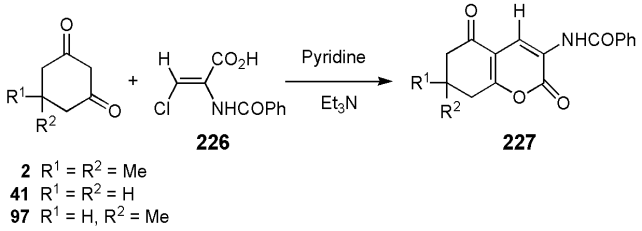


interesting pyranocoumarins **225a** and **225b** in good yield (Scheme 56).

5.15 Tetrahydrobenzopyran-2,5-diones.

Music and Golobie [92] reported the use of 2-benzoylamino-3- chloropropenoic acid (**226**) in the synthesis of 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones (**227**). Reaction of cyclic 1,3-diones (**2**, **41** and **97**) with 2-benzoylamino-3-chloropropenoic acid (**226**) in pyridine in the presence of triethylamine gave 3-benzoylamino-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,5-diones (**227**) (Scheme 57).

Scheme 57



6. Heterocycles formed by Cycloaddition Reactions.

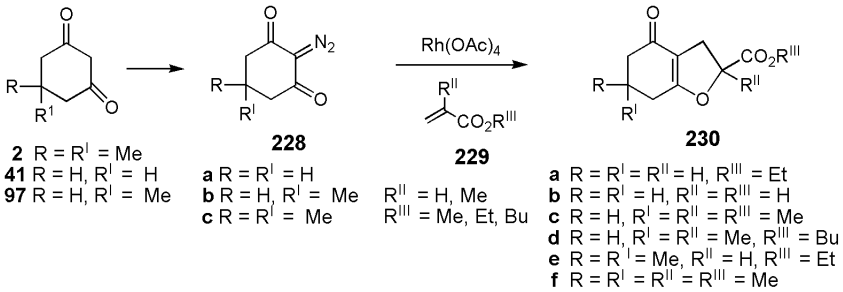
6.1 Tetrhydrobenzofuranones.

The rhodium–catalyzed decomposition of diazocarbonyl compounds has become an important method in the synthesis of heterocyclic frameworks such as furans or pyrazloes [93]. Lee [94] reported the rhodium catalysed cycloaddition of cylic-2-diazo-1,3-dicarbonyl compounds (**228**) with α,β-unsaturated esters (**229**), afforded the dihydrofuran **230**. α,β-Unsaturated esters were used as the substrate and solvent and rhodium acetate is used as catalyst. The formation of dihydrofurans likely proceeds *via* 1,3-dipolar cycloaddition of metal carbenoid to α,β-unsaturated esters; the exact mechanism of the reaction is still not clear (Scheme 58).

6.2 Fused Dihydrofuran, Oxazole, Oxothiole Derivatives.

The decomposition of diazo compounds in the presence of transition metal catalysts appeared to have remarkable potential in organic synthesis. These aforementioned catalysts mediate the formation of metallo carbenoids *in situ* and transfer the carbene moiety to a suitable acceptor providing a wide range of synthetic transformations such as cyclopropanation, C-H, C-X insertion and ylide formation.

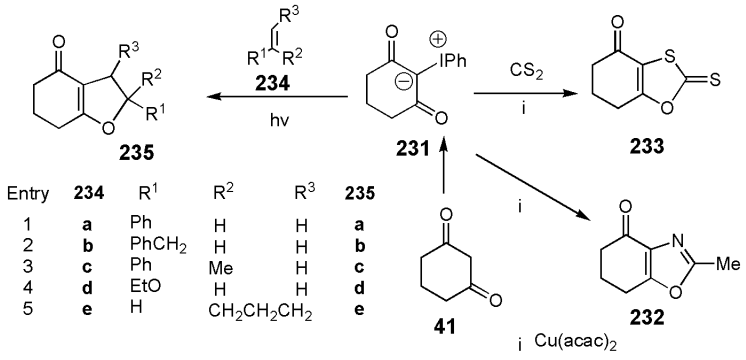
Scheme 58



The diazo compounds are potentially explosive, toxic and carcinogenic. Asouti and Hadjiarapoglou [95] reported the reaction of 1,3-cyclohexanedione (**41**) and diacetoxyiodobenzene under classical Schank's conditions [96] gave the iodonium ylide **231** in 83% yield. This ylide upon heating in acetonitrile in presence of catalytic amounts of

$Cu(acac)_2$, oxazole **232** was formed in 70% yield. By employing carbon disulphide, oxathiole **233** was isolated in 57% yield. The photochemical irradiation of a suspension of **231** (400 W medium pressure mercury lamp) and the alkene **234** (excess) in appropriate solvents for 30-240 min gave excellent yields of dihydrofurans **235**. It is believed that an electrophilic carbene might have been involved in this photochemical decomposition of the iodonium ylide (Scheme 59).

Scheme 59

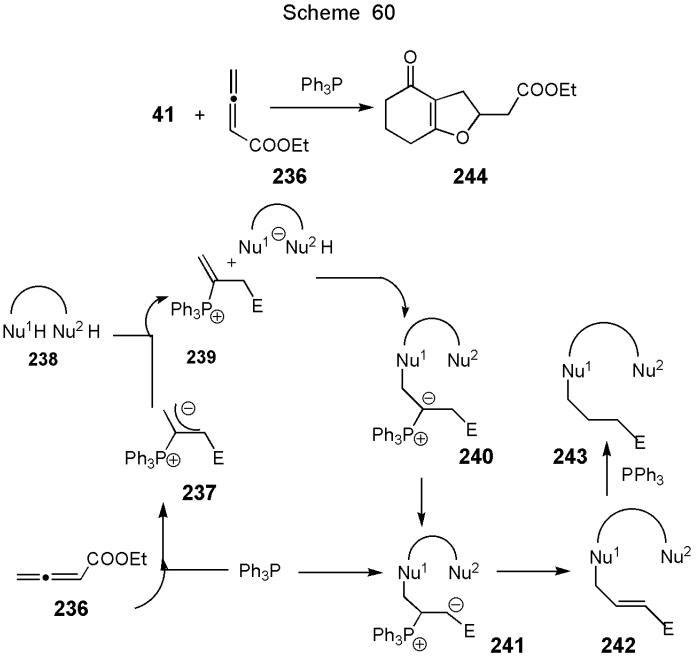


Entry	234	R^1	R^2	R^3	235
1	**a**	Ph	H	H	**a**
2	**b**	$PhCH_2$	H	H	**b**
3	**c**	Ph	Me	H	**c**
4	**d**	EtO	H	H	**d**
5	**e**	H	$CH_2CH_2CH_2$		**e**

6.3 Fused Dihydrofuran Derivatives.

Among the well-documented synthetic methods, tandem reactions are always chosen to construct heterocycles with high efficiency. Tandem nucleophilic addition can be achieved by adding a bifunctional nucleophile to electron deficient multiple bonds, (a bifunctional electrophile, *e.g.*, an allene or an alkyne) and intramolecular trapping of the intermediary monofunctional nucleophile with the appropriately located electrophilic center formed from the preceding addition reaction. Reaction of cyclohexane-1,3-dione (**41**) (a carbonucleophile as well as oxygen nucleophile) with ethyl 2,3-butadienoate (electron deficient allene) (**236**), catalyzed by triphenylphosphine in toluene at 110 °C gave the cyclised product **244** indicating that tandem nucleophilic additions were favored by stronger electron-withdrawing groups. The reaction was triggered by nucleophilic addition of a triphenylphosphine to the electron-deficient multiple bond in allene **236**. Then the zwitterionic intermediate **237** deprotonated the pronucleophile

Scheme 60



238, which facilitated the umpolung addition. Proton transfer and elimination of the triphenylphosphine from the resulting zwitterionic intermediates **240**, **241** gave the corresponding umpolung adduct (γ- or α- adduct). Finally the umpolung adduct effected the intramolecular conjugate addition reaction in the presence of triphenyl phosphine (Scheme 60) [97].

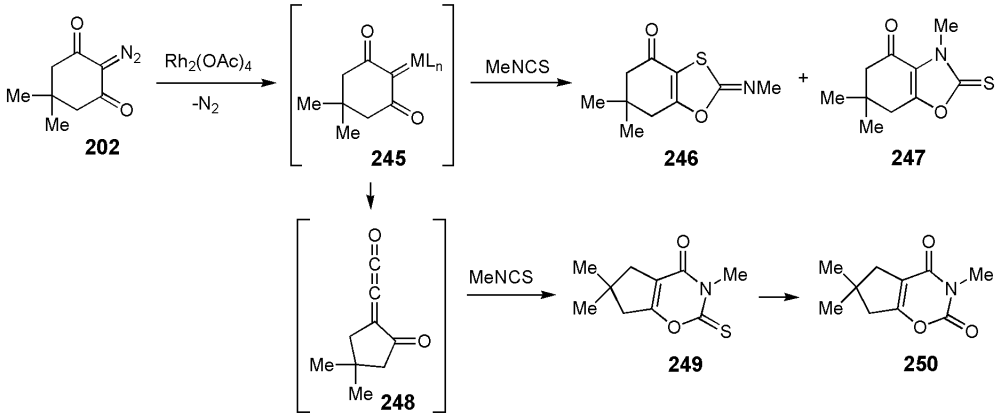
6.4 Oxazinediones and Thiones.

Rhodium (II) acetate has been utilized as an excellent catalyst for the mild decomposition of α-diazocarbonyl compounds to generate the corresponding ketocarbenoids to avoid the Wolff rearrangement in the various reaction systems [98]. Nakano and Ibata [99] reported that the rhodium (II) acetate, catalyzed reaction of α-diazocarbonyl compounds (**202**) in the presence of isothiocyanates gave 2-thioxo-2*H*-1,3-oxazin-4(3*H*)-one (**249**) and 2*H*-1,3-oxazine-2,4(3*H*)-dione (**250**) in 0.9 and 5.1 % yields respectively together with 2-methylimino-1,3-oxathiole (**246**) (45%) and oxazole-2(3*H*)-thiones (**247**) (2.2%). These results are explained by the intermediacy of rhodium carbenoid **245**, which gives **246** and **247** through ylide intermediates by the attack of isothiocyanates followed by intramolecular 1,5 cyclisation affording **249** and oxazinedione **250** *via* the Wolff rearrangement through acyl ketene **248** (Scheme 61).

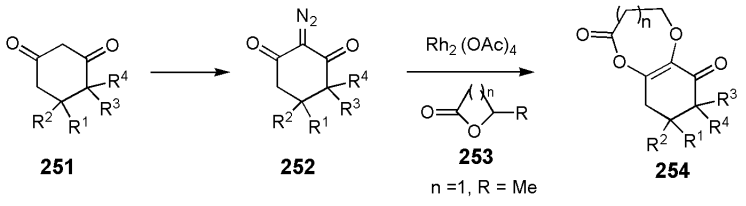
6. 5 Benzodioxepinones.

Metal catalysed conversion of lactones to dioxepinones involves the insertion of a metal species into the O-C bond of the lactone ring. Rhodium acetate and copper acetyl acetonate catalyse the reaction, their use being characterized by an induction period, which is significantly reduced if a diazocompound is included in the reaction mixture. A reaction did take place, however, when a β-lactones **253** and cyclic-2-diazo-1,3-dicarbonyl compounds **252** were reacted in presence of rhodium acetate affording the product unexpectedly namely the dioxepinones **254** [100]. The formation of benzodioxepinones can be understood in terms of nucleophilic attack by the lactones on an electrophilic carbenoid (Scheme 62).

Scheme 61



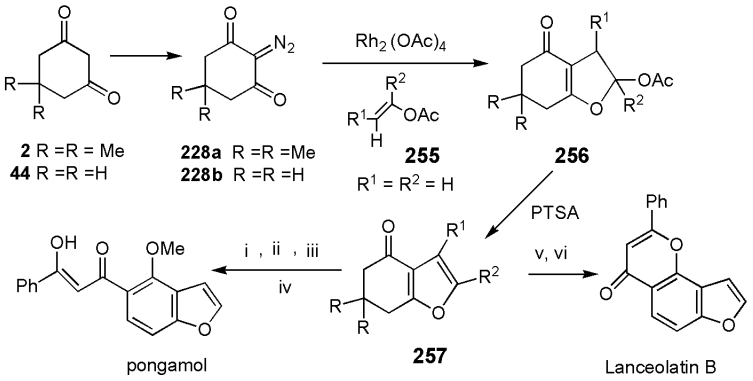
Scheme 62



251 & 252a $R^1 = R^2 = R^3 = R^4 = H$
252 & 252b $R^1 = R^3 = R^4 = H$, $R^2 = Me$
251 & 252c $R^1 = R^2 = Me$, $R^3 = R^4 = H$
251 & 252d $R^1 = R^3 = R^4 = H$, $R^2 = Ph$
251 & 252e $R^1 = R^2 = R^3 = H$, $R^4 = Me$
251 & 252f $R^1 = R^2 = H$, $R^3 = R^4 = Me$

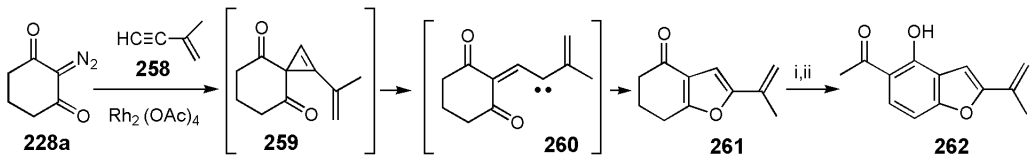
254a n =1 R=Me, $R^1 = R^2 = R^3 = R^4 = H$
254b n = 1, R = R^2 = Me, $R^1 = R^3 = R^4 = H$
254c n = 1 ,R = $R^1 = R^2$ = Me, $R^3 = R^4 = H$
254d n = 1, R = Me, $R^1 = R^3 = R^4 = H$, R^2 =Ph
254e n = 1, R = R^4 = Me, $R^1 = R^2 = R^3 = H$
254f n = 1, R = $R^3 = R^4$ = Me, $R^1 = R^2$ =H

Scheme 63



i NaH, $(MeO)_2CO$, ii DDQ, iii K_2CO_3, MeI iv $NaNH_2$, PhCOMe, v NaH, DMSO, vi PhCHO, piperidine.

Scheme 64



i NaH, 18- Crown-6 ii DDQ

6.6 Fused Dihydrofuran.

The formal 1,3-dipolar cycloaddition of dicarbonyl compounds with alkynes or with heteroatom substituted olefin, followed by elimination has been used for preparation of 3-acylfurans. Pirrung and Lee [101] developed an efficient method for obtaining benzofuran derivatives, which forms the key step in the construction of the natural products pongamol and lanceolatin B. The reaction of 2-diazao-1,3-dicarbonyl compounds (**228a** and **228b**) with vinyl acetate **255** with 10 fold excess of rhodium acetate in fluorobenzene gave the intermediate acetate **256**. Treatment of **256** with benzene solution of *p*-toluenesulfonic acid at its reflux temperature for 1 h afforded the furans **257** in overall good yields (Scheme 63).

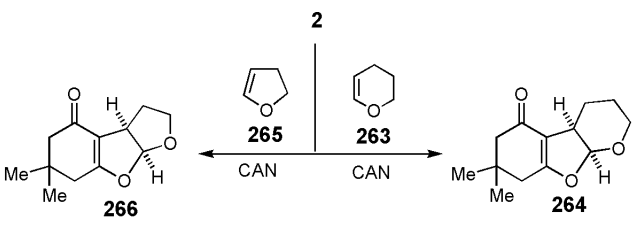
6.7 Isopropenylfuran.

Rhodium-mediated dipolar cycloaddition of cyclic diazoketones to aromatic heterocycles is a fast synthetic entry into complex poly heterocylic systems [102]. Pirrung and co-workers [103] reported the reaction of diazocyclohexane-1,3-dione (**228a**) with electron deficient and electron rich acetylenes. Previous reaction has been utilized in a straightforward synthesis of isoeuparin, a natural product of biogenetic mixed polyketide/isoprenoid. The cycloaddition of **228a** to isoprenylacetylene (**258**) occurs through the cyclopropyl **259** and carbenoid intermediates **260** in excellent yields to generate the isopropenyl furan **261** as substructures found in a wide range of terpenoids. The acetylation of the ketone, enolate **261** and aromatization with DDQ gave isoeuparin **262** (Scheme 64).

6.8 Fused Acetals.

The synthesis of fused acetals has attracted considerable attention to organic chemists in recent years, because the furofuran moiety is an important sub unit in a wide range of biologically active natural products [104]. Fused acetal derivatives can be effectively synthesised [105] by ceric ammonium nitrate (CAN) catalysed by cycloaddition of β-diketones or β-diketoesters to cyclic enol ethers in good yields. Thus treatment of **2** with cylic enol ether **263**, **265** in the presence of 1.2 equivalent of CAN and excess $NaHCO_3$ in acetonitrile at 0 °C for 2 h afforded fused acetals **264**, **266** in good yields (Scheme 65).

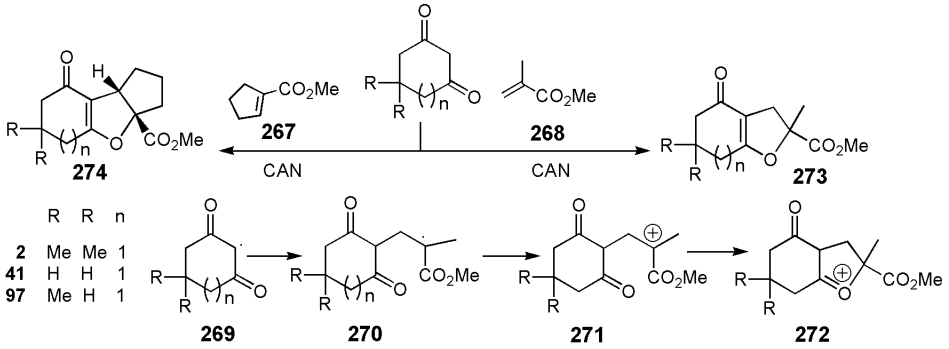
Scheme 65



6.9 Tricyclic, Bicyclic Fused Furans.

Recently ceric ammonium nitrate mediated oxidative cycloaddition of 1,3-diketones to alkenes, vinyl acetate, enolsilyl ethers, and enol ethers has been studied extensively. Lee and Kim [106] reported CAN-mediated cycloaddition of cylic and acylic 1,3-dicarbonyl compounds to a variety of conjugated compounds. Reaction of **2**, **41** and **97** with five fold excess of methyl methacrylate (**268**) in the presence of 2.2-equivalent of CAN and excess amount of $NaHCO_3$ in acetonitrile gave the corresponding fused dihydrofurans **273** in 50-66% yield. The oxidative cycloaddition of **2**, **41** and **97** with cyclic α,β-unsaturated esters (**267**) gave the tricyclic adducts **274**. The exact mechanism of oxidative cycloaddition reaction to cyclic ketones is not clear. The probable mechanism involves oxidation of cyclic 1,3-dione by CAN (IV) to generate the α-oxoalkyl radical **269**, which then attacks the methylmethacrylate (**268**) to give another carbon radical **270**. This radical **270** now undergoes fast oxidation by CAN (IV) to a carbocation **271**. Cyclization of **271** furnishes intermediate **272**, which finally undergoes elimination process to give the dihydrofuran **273** (Scheme 66).

Scheme 66



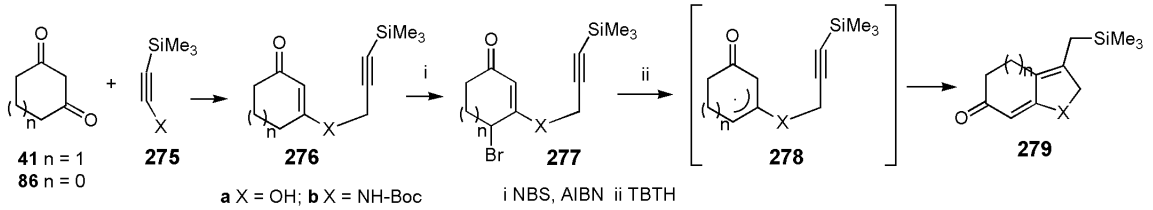
6.10 Bicyclic Furans, Pyrroles.

Radical reactions have emerged as one of the most useful synthetic methodologies in the formation of carbon-carbon bonds [107a]. Sha and Tseng [107b] reported intramolecular cyclization reactions of allylic enone radicals generated from 4-bromocycloalkanones. Cyclic-1,3-diones **41** and **86** were condensed with 3-trimethylsilylprop-2-yn-1-ol (**275a**) to afford vinylogous- esters **276a**. Condensation of 3-trimethylsilylpropynylamine (**275b**) with the corresponding cycloalkane-1,3-diones followed by reaction with di-*t e rt*-butyl dicarbonate and 4-dimethylaminopyridine (DMAP) yielded *tert*-butoxycarbonyl-vinylogous amides **276b**. Bromination of **276a** and **276b** with *N*-bromosuccinimide and 2,2'-azo-bis-isobutyrylnitrile (AIBN) in refluxing CCl_4 gave the corresponding 4-bromocompounds **277a** and **277b**. Radical cyclizations were carried out using tri-*n*-butyltin hydride to give bicyclic enones. Trimethylsilylbromovinylogous esters **277a** and vinylogous-amides **277b** cyclised at the γ-carbon in good yields to produce bicylicenoness **279** (Scheme 67).

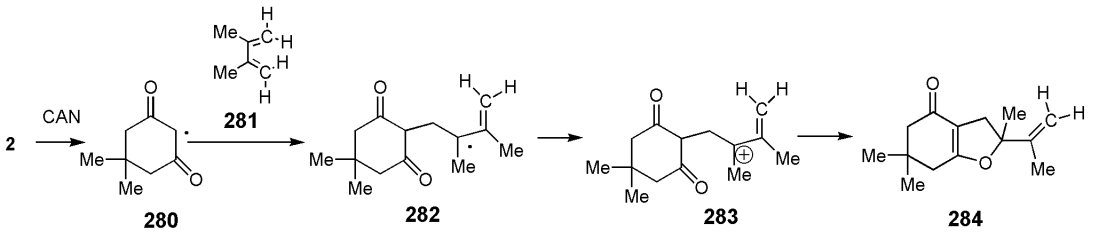
6.11 2-Isoprenyl Hexahydrobenzofuranones.

The generation of carbon-centered radicals and also their addition to a variety of substrates mediated by one electron oxidants such as Mn(III), Co(III) and Ce(IV) reagents have recently stimulated the attention of several research groups [108]. Nair and Balagopal [109] reported that CAN mediated oxidative addition of 1,3-dicarbonyl compounds to dienes offers an easy pathway towards the synthesis of dihydrofuran. The first step involves the CAN

Scheme 67



Scheme 68



mediated generation of the radical **280** from **2**, which is immediately trapped by the diene **281** giving the intermediate radical **282**. Subsequently radical **282** is oxidized by the second equivalent of CAN to the cation **283**. The latter then underwent cyclisation to afford the dihydrofuran derivative **284** (Scheme 68).

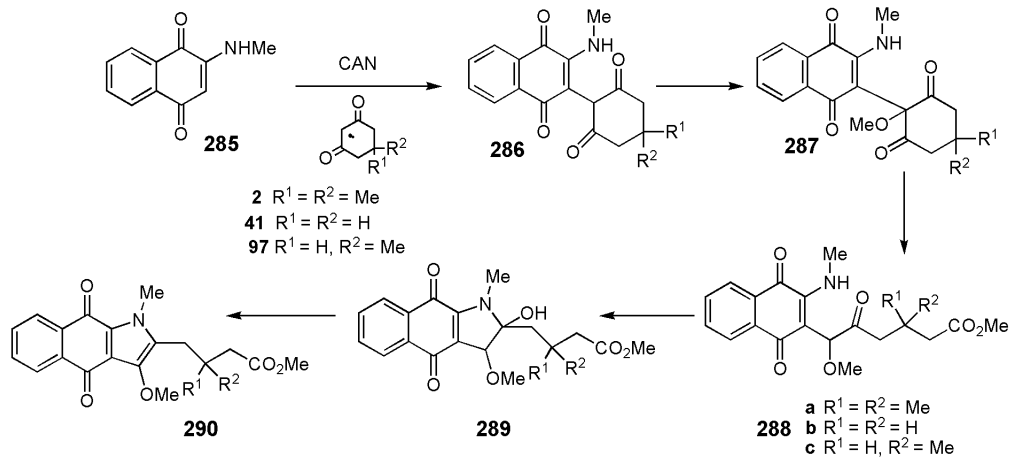
6.12 Indole Derivatives.

by oxidation to produce **286**, which undergoes further oxidation to afford **287**. Quinones **287** undergo retro Claisen to give **288** followed by addition and dehydration resulting in **289** to produce indoles **290** (Scheme 69).

6.13 Pyridines and Bridged Bipyridines.

The rapidly growing importance of the research areas supramolecular chemistry and domino reactions has

Scheme 69

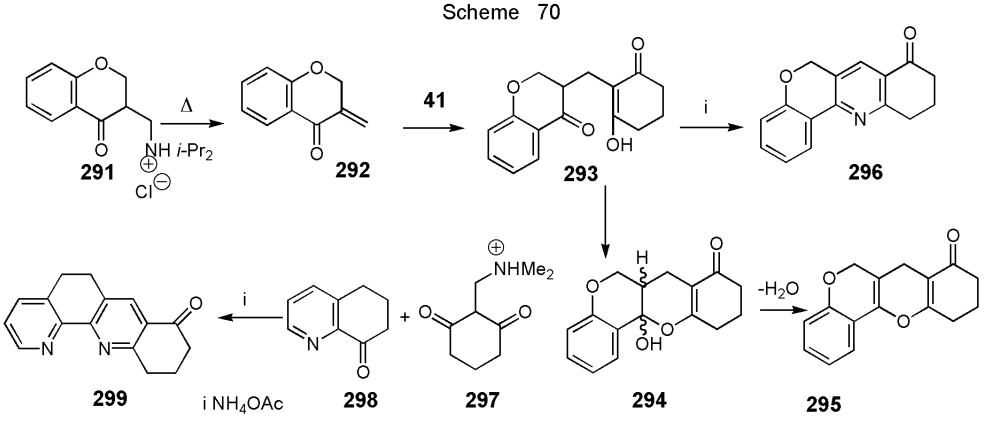


Free radical reactions have become increasingly important in organic synthesis in the last two decades [110]. Compounds containing the quinone group represent an important class of biologically active molecules that are widespread in nature [111]. The oxidative addition of electrophilic carbon- centered radicals to alkenes mediated by ceric ammonium nitrate (CAN) has been used most efficiently in the construction of carbon-carbon bonds. Wu and Chuang [112] reported a method for the synthesis of benzo[*f*]indole-4,9-dione by the oxidative free radical reaction between 2-amino-1,4-napthaquinone and 1,3-cyclohexanediones mediated by ceric (IV) salts. The reaction of 2-(methylamino)-1,4-napthaquinone (**285**) with 1,3-cyclohexanediones (**2**, **41** and **97**) and ceric ammonium nitrate in methanol at room temperature gave indole **290**. Oxidation of **2**, **41** and **97** by CAN produced a radical, which undergoes intermolecular addition to the quinone **285**, followed

been documented in an increasing number of publications during the last few years [113]. Pyridine or bipyridine building blocks play an important role in supramolecular chemistry. Keuper and Risch [114] reported the synthesis of polycyclic pyridines, bipyridines by varied efficient domino reactions, which find application in supramolecular chemistry. The reaction of di-isopropyl-(4-oxo-chroman-3-ylmethyl) ammonium chloride (**291**) (resulting from the aminomethylation of 4-chromanone) and **41** led to the formation of two crystalline products **295** and **296**. Thermally induced amine elimination of **291**, should form the α,β-unsaturated ketone **292**, from the intermediate diketone **293**, which on reaction with ammonium acetate undergoes corresponding Hantzsch cyclisation to give pyridine derivative **296**. In the other case the intermediate **294** having a hemiacetal structure, eliminate water leading to the formation of the hetero-

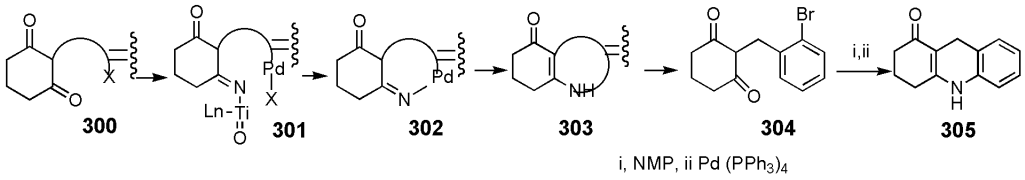
cylic compound **295**. Similarly the bipyridine **299** was reported from the aminomethylated 1,3-cyclohexanedione (**297**). The bipyridine **299** is formed by the conversion of Mannich base **297** and 6,7-dihydro-5*H*-quinoline-8-one (**298**) (Scheme70).

Scheme 70



6.14 Octahydrocarbazole.

Scheme 71

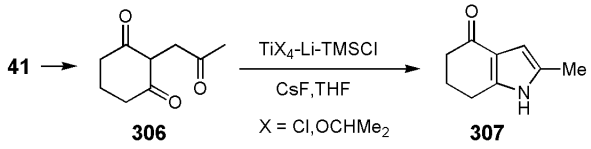


The fixation of molecular nitrogen has attracted the attention of many research groups. The nitrogenation method by use of titanium-nitrogen complex in organic synthesis as a nitrogen incorporation reagent [115] has lead to a new C-N-C bond formation and the construction of heterocycles by use of this reaction was reported by Mori and Uozumi [116]. Ketones and vinyl halides couple to give divinylamines in the presence of the titanium isocyanate complex [3THF.Mg_2Cl_2O.TiNCO], with a palladium catalyst, *via* transmetallation of titanium imine complex with arylpalladium bromide **301**. Thus the cylization of bromophenylcylohexanedione (**304**) with titanium isocyanate complex in *N*-methyl-2-pyrrolidine in presence of $Pd(Ph_3P)_4$ gave 87% of 4-oxo-1,2,3,4,5,6,7,8-octahydrocarbazole (**305**) (Scheme 71).

6.15 Indole Derivatives.

There have been quite large numbers of reports concerning molecular nitrogen fixations by various transition metals [117]. It is well known that reduction of atmospheric nitrogen to ammonia is catalysed by nitrogenase and thus fixation of atmospheric nitrogen in the laboratory remains quite challenging. Mori and Hori [118] reported the first example of fixation of atmospheric nitrogen by TiX_4-Li-TMSCl and the synthesis of heterocycle using atmospheric nitrogen as the nitrogen source. A solution of $TiCl_4$, TMSCl and Li in THF was hydrolysed under nitrogen for 24 h and then treated with cyclohexanedione derivatives **306**, to produce indole derivatives **307** in 80% yield (Scheme 72).

Scheme 72



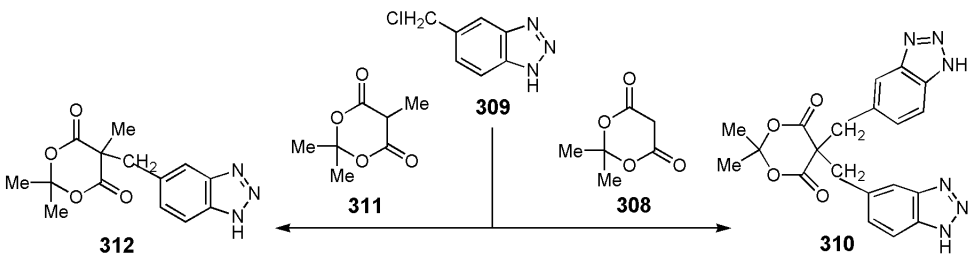
7. Meldrum's Acid Derivatives.

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) is a valuble and versatile synthetic reagent [119] in its own right for the following reasons. Firstly the acidity of Meldrum's acid is comparable to that of acetic acid and its stable enolate

anion is susceptible to the attack of various electrophiles even under nearly neutral conditions. Secondly, Meldrum's acid is capable of nucleophilic attack at the carbonyl groups, which results in ring cleavage. Among the reactions of Meldrum's acid derivatives, the following sections have been frequently used for organic synthesis.

dimethyl-1,3-dioxane-4,6-dione (**310**) in 37% yield. Similarly 5-chloromethylbenzotriazole (**309**) reacted with 2,2,5-trimethyl-1,3-dioxane-4,6-dione (**311**) in DMSO to give 5-(benzotriazol-5-ylmethyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**312**) in 32% yield (Scheme 73).

Scheme 73



7.1. Alkylation Reactions.

7.2. Ring Opening Reactions

7.3. Pyrolysis

Alkylation Reactions

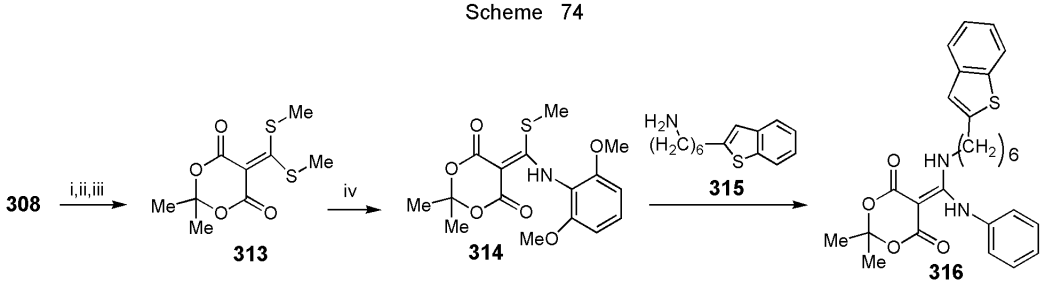
7.1.1 Benzotriazole-Mediated Meldrum's Acid Derivatives.

Syntheses and reactions of numerous 5-alkyl, alkenyl and aryl substituted Meldrums's acids were reported by Katritzky and Ji [120]. Two Meldrum's acid derivatives 5,5-di-(benzotriazol-5-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**310**), and 5-(benzotriazol-5-ylmethyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (**312**) have been reported from benzotriazole and sodium enolate of Meldrum's acid. The alkylation of Meldrum's acid usually gives symmetrical dialkyl products.

7.1.2 Diaminomethylenedioxanedione Derivatives.

Diaminomethylenedioxanedione derivatives are known to display inhibition of Acyl-Coenzyme A and Cholesterol Acyltransferase (ACAT). Compounds of this type are responsible in reducing cholesterol adsorption and its effect on athreosclerosis. The compounds of this category are prepared by Fobare and Strike [121] by reaction of Meldrum's acid (**308**) converting them to the corresponding 5-bis-(methylthio) methylene derivative with carbon disulfide and methyl iodide in DMSO in presence of base such as triethylamine. The condensation of 5-bis-(methylthio) derivative **313** with 2,4-dimethoxyaniline, in *t*-butanol at reflux temperature for 24 h gave the amine **314** in 80% yield. Condensation of 2-(1-hexylamino)benzo-[*b*]thiophene (**315**) and **314** in presence of $HgSO_4$ in acetonitrile gave **316** (Scheme 74).

Scheme 74

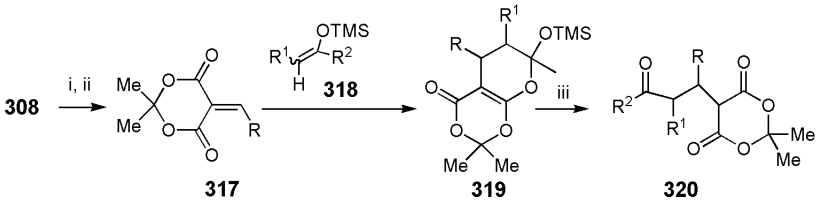


5-Chloromethylbenzotriazole (**309**), when reacted with sodium enolate of Meldrum's acid in DMSO medium at 100 °C, gave 5,5-di-(benzotriazole-5-ylmethyl)-2,2-

7.1.3 Alkylidene Meldrum's Acids.

Michael reaction of silyl enol ethers is one of the most important tools for C-C bond formation. Michael reaction

Scheme 75



R=Me,Et,Ph R^1= H, Me R^2= Ph $R^1 = R^2$ = cyclhexyl, cyclopentyl

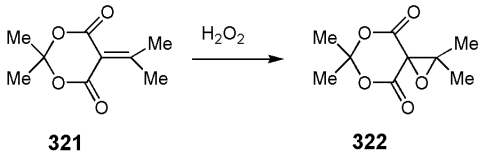
i RCHO, NaOMe, ii CH_2Cl_2 iii HCl

in neutral condition is still in development eventhough Lewis-acid promoted Michael addition of silyl enol ethers to α,β-unsaturated orthoesters was developed by Mizukami and Kihara [122]. Alkylidene Meldrum's acid is known to be a strong electrophile and is expected to be a good Michael acceptor. Silyl enol ethers are more nucleophilic and more easily available. The reaction of silyl enol ethers **318** with **317** gives hetero Diels-Alder adducts **319** and hydrolysis of these products gave Michael adducts **320** diastereoselectively in high yield (Scheme 75).

7.1.4 Methylene Meldrum's Acid.

Epoxidation of α,β-unsaturated carbonyl compounds is one very important and useful method in organic synthesis. Several tri and tetra substituted, electron deficient carbons have been converted to epoxides by reaction with H_2O_2 in

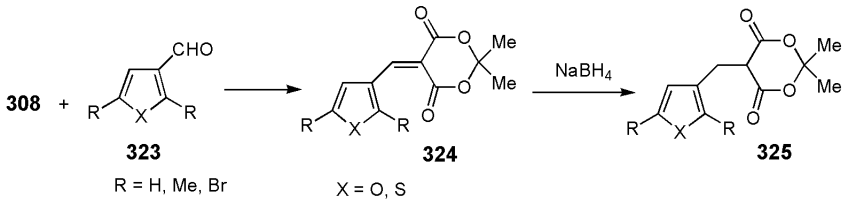
Scheme 76



7.1.5 Furfurlydinedioxanediones.

2,2-Dimethyl-5-(3-R-furfurlydine)–1,3-dioxane-4,6-diones are prepared by Krapivin and Valter [124] from 3-furancarboxaldehyde (**323**) and Meldrum's acid (**308**). Selective hydrogenation of the exocylic double bond in **324** was accomplished with $NaBH_4$ to give **325** (Scheme 77).

Scheme 77

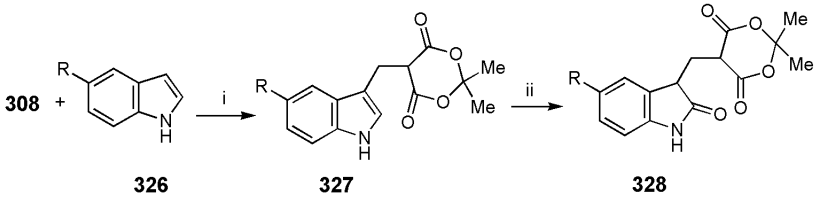


the absence of any catalysts though required pH controls. Methylene Meldrum's acids are well known as organic Lewis acids, and therefore, these compounds are very reactive electrophiles and can easily be attacked by nucleophiles, hence they are expected to be epoxidised under milder conditions by H_2O_2 in the absence of any catalyst and any base. Tsuno and Sugiyama [123] reported the facile epoxidation of methylene Meldrum's acid (**321**) with H_2O_2 in acetonitrile medium at room temparature without any catalyst or any base affording the compounds containing an oxirane ring (**322**) as good crystalline product (Scheme 76).

7.1.6 Oxindolyl Derivatives.

Aldose inhibitors are known [125] to be responsible for diabetic complications such as retinopathy, neuropathy, and nephropathy. Structurally diverse aldose reductase inhibitors such as 5-[(5-flouroindol-3yl)methyl]-2,2,dimethyl-1,3-dioxane-4,6-dione, are reported by Rajeswara and Labroo [126]. Treatment of indoles **326** with Meldrum's acid (**308**) and formaldehyde in acetonitrile medium gave indolyl derivatives (**327**) in 80-96% yield. The indolyl derivatives **327**, reacted with 1 equivalent of NBS in *t*-butanol/water mixture gave the corre-

Scheme 78



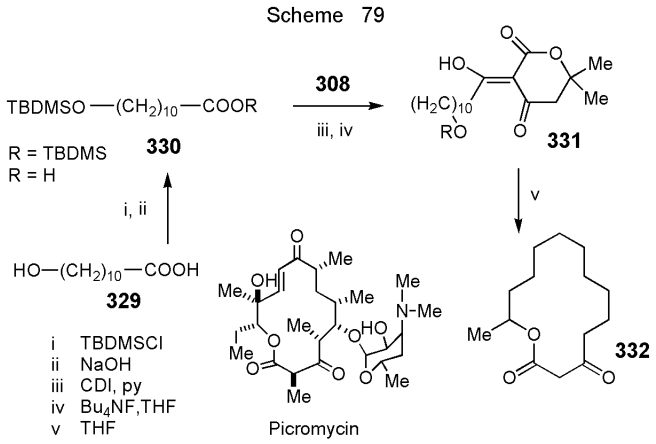
sponding oxindolyl derivatives **328** in 62-67 % yield (Scheme 78).

Ring Opening Reactions.

7.2.1 Lactones.

β-Ketolactones have been found in a number of macrocylic natural products Picromycin [127a], Narbomycin [127b] and Kromycin [127c] are 14-membered β-keto lactone antibiotics that have attracted interest as synthetic targets. Lermer and Neeland [127d] reported a general method for the synthesis of β-keto lactones using Meldrum's acid derivatives. 11-Hydroxy undecanoic acid (**329**) reacted with *tert*-butyldimethylchlorosilane in DMF to obtain silylester **330**. The condensation of Meldrum's with undecanoic acid **329** gave, acyl Meldrum's acid derivative **331**, which on thermolysis in refluxing THF gave 3-oxo-13-tridecanolide (**332**) (Scheme 79).

Scheme 79



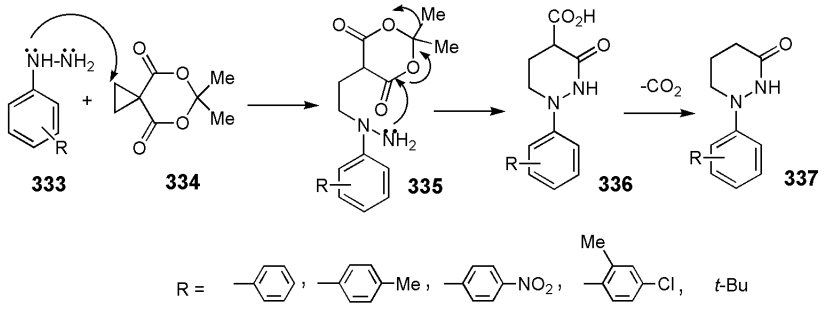
7.2.2 Pyridazine-3-one.

Hwang and Park [128] have reported pyridazine-3-one **337** by simple and easily available cyclopropane dicarboxylate **334** in refluxing acetonitrile to afford the corresponding 1-phenylsubstituted-1,4,5,6-tetrahydropyridazine-3-(2*H*)–ones (**337**). The formation of these compounds mechanistically takes place *via* nitrogen-carbon bond formation (**335**) followed by cyclisation and decarboxylation to afford the cyclic intermediates **336**. The reaction between hydrazine derivatives **333** and **334** involves the electrophilic attack by the substituted nitrogen atom of hydrazine **335** towards electrophile **334** resulting in **337** in 3 steps (Scheme 80).

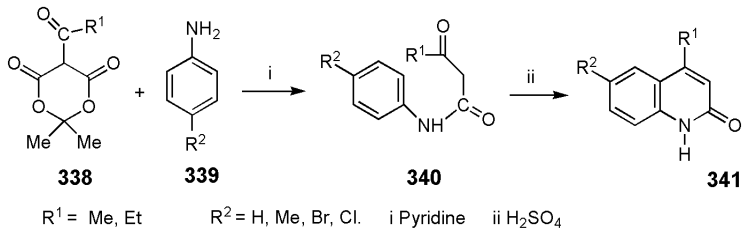
7.2.3 Alkyl-2-quinolinones.

Huang and Wu [129] by microwave irradiation of 5-acylisopropylidenemalonate (**338**) (R^1= Me, Et) with 4-substituted anilines (**339**) in CH_2Cl_2 and pyridine prepared the amide **340**. Cyclization of **340** with conc. sulphuric acid yielded 4-alkyl-2-quinolinones **341** (Scheme 81).

Scheme 80



Scheme 81



7.2.4 γ-Pyrones.

Substituted γ-pyrones are versatile intermediates in organic synthesis. These can be used as polyketide synthons useful in the preparation of spiroketal containing natural products [130] as well as cycloaddition substrates for the construction of complex polycyclic system. Zawacki and Crimmins [131] reported an efficient general synthesis of unsymmetrical substituted γ-pyrones as important synthetic building blocks out of acylated Meldrum's acid and vinyl ethers. Meldrum's acid was readily acylated with various acyl chlorides in presence of pyridine in DCM medium to give acyl Meldrum's acid **342**. The acylated Meldrum's acid **342** when refluxed in benzene with *n*-butylvinyl ether led to the formation of pyrandione **343**. This product is believed to be formed in a sequential order inwhich the vinyl ether adds to the acylated Meldrum's acid with assistance of the oxygen to give an oxonium species. Acetone is then lost prior decarboxylation after which the intermediate undergoes ring closure to the pyrandione **343**, which can be readily transformed to the γ-pyrone **344** by treatment with *p*-TSA in 4:1 THF:H_2O mixture (Scheme 82).

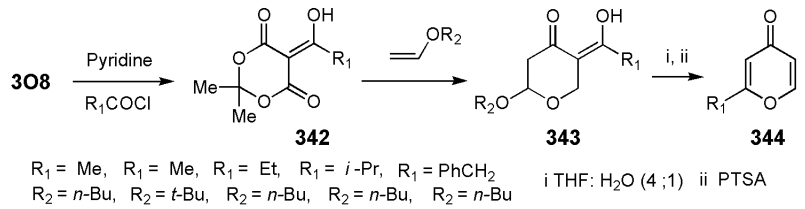
7.2.5 Octahydroquinolines.

1,4-Dihydropyridines are well known compounds in view of their pharmacological profiles as calcium channel modulators [132]. The related analogues of the 1,4-DHP containing two fused rings have been less studied. Verdecia and Morin [133] reported the synthesis of 1,4-DHP related structures having different heterocyclic moieties fused to the pyridine ring. The synthesis of 4-aryl-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinolines (**346**). This has been further studied by refluxing equimolar amounts of Meldrum's acid (**308**), dimedone (**2**) and the corresponding aromatic aldehyde **345** with an excess of ammonium acetate in acetic acid. Formation of the octahydroquinolines **346** takes place through a Hantzsch-like mechanism *via* conjugate addition of the enamine intermediate, followed by imine-enamino tautomerism and subsequent 6-exo-trig cyclization [134]. The subsequent loss of acetone and carbon dioxide yields (**346**) (Scheme 83).

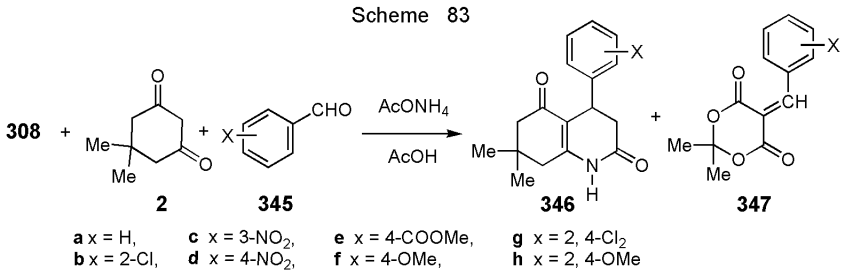
7.2.6 5-Substituted 3-Isooxazoles.

The 3-isooxazolol moieties are a constituent of a number of biologically active compounds. 5-Methyl-3-isoxazolol (Tachigaraen) and the phosphorothioate

Scheme 82

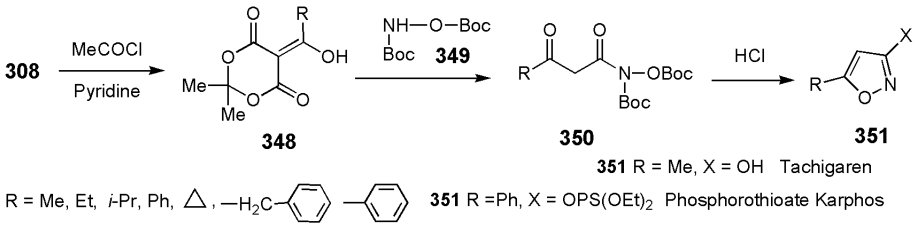


Scheme 83



Karphos are examples of biologically active 3-isooxazolols, which are used as soil fungicides and a broad-spectrum insecticide respectively [135]. Incorporation of the 3-isooxazolol moiety into compounds with potential biological activity normally requires cyclisation of β-ketoester with hydroxylamine, which sometime leads to the undesired byproduct. Sorensen and Falch [136] reported an efficient synthetic route to 5-substituted-3-isoxazolols starting from acyl Meldrum's acid. Meldrum's acid (**308**) can be acylated with carboxylic acid chlorides to give acyl derivatives **348**. The aminolysis of acyl Meldrum's acid with *N*,*O*-diBoc-protected hydroxylamine (**349**) in toluene at 65 °C furnished β-ketohydroxamic acid derivatives **350**. The cyclisation of the β-ketohydroxamic acid in methanolic HCl gave 5-substituted 3-isooxazolols **351** in 92% yield (Scheme 84).

Scheme 84



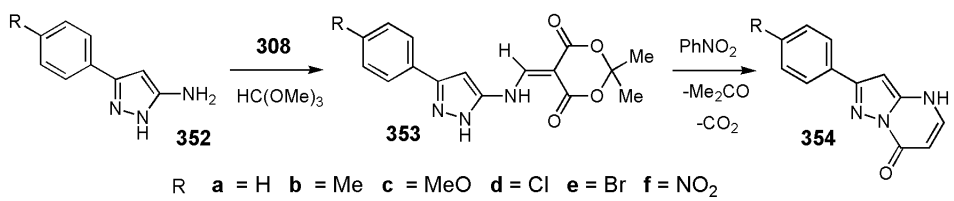
7.2.7 Pyrazolopyrimidines.

Considerable interest has been focused on derivatives of pyrazolo[1,5-*a*]pyrimidine during the last twenty years, due to their physiological and biological activities [137]. Quiroga and Hormaza [138] described procedures for the synthesis of aromatic derivatives of pyrazolo[1,5-*a*]-pyrimidine from methoxymethylene derivatives of Meldrum's acid and 5-amino-3-arylpyrazoles **352**. A solution of Meldrum's acid and methyl orthoformate was refluxed with 5-amino-3-arylpyrazole (**352**) for 10-15 min to give corresponding 5-pyrazolylaminomethylene derivatives of Meldrum's acid (**353**). The cyclisation of **353** was carried out in nitrobenzene refluxing for 30 min to give pyrazolo[1,5-*a*]pyrimidine-3-ones (**354**) in 40-50% yield (Scheme 85).

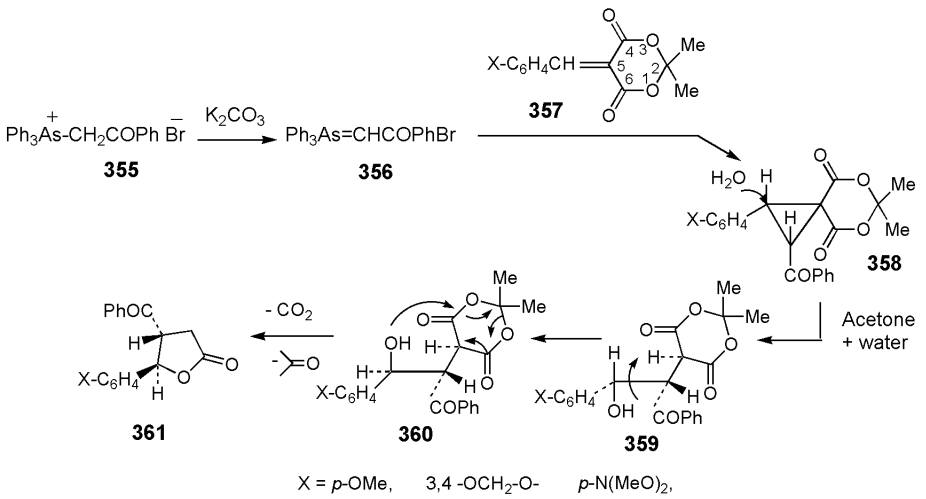
7.2.8. Butyrolactones.

γ-Butyrolactone is an important compound present in a large number of natural products and pharmaceutical molecules [139]. There is a close relationship between the configuration of substituted butyrolactone groups and bioactivity of pharmaceuticals. Cao and Ding [140] reported an efficient and highly stereoselective syntheses of γ-butyrolactones, which are important target molecules in synthetic organic chemistry. Benzoylmethyltriphenylarsonium bromide (**355**) reacted with 2,2-dimethyl-1,3-dioxa-5-substituted-benzylidene-4,6-dione (**357**) in the presence of K_2CO_3 and a trace amount of water at room temparature to furnish β,γ-*trans*-β-benzoyl-γ-aryl-γ-butyrolactones (**361**) in good yields. Firstly the arsonane **356** derived from arsonium bromide **355** reacts with olefin **357** to form the *cis*-cyclopropane derivatives **358**, which are then attacked by a molecule of water at C_1 from the less hindered side of the cyclopropane ring to yield the intermediates **359**. β,γ-trans-γ-butyrolactone **361** is formed through the attack of the hydroxy group on the ester group to break the Meldrum's acid with the elimination of a molecule of acetone and a molecule of carbon dioxide (Scheme 86).

Scheme 85



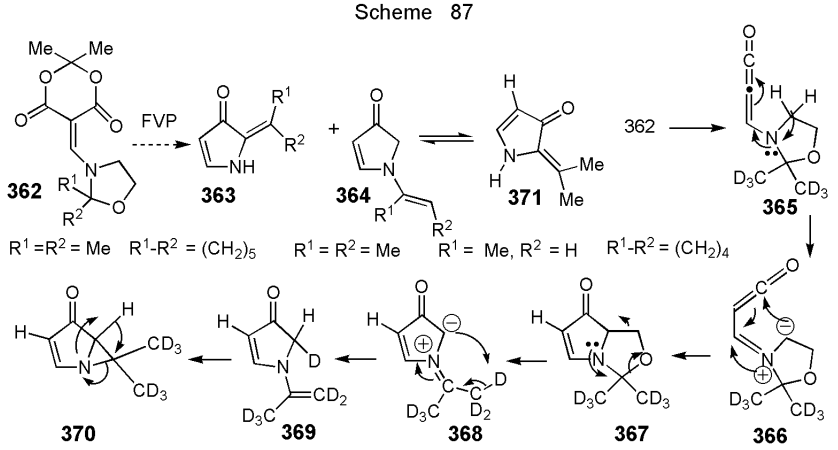
Scheme 86



Pyrolysis.

7.3.1 *N*-Alkenyl Pyrroles.

Scheme 87



N-Alkenyl-2-functionalised 3-hydroxypyrroles are essential for the synthesis of analogues of prodigiosin series of antibiotics [141]. Flash vacuum pyrolysis (FVP) of the oxazolidine derivatives **362** at 600 °C (10^{-3} Torr) by Hunter and McNab [142] gave two products **363** and **364** in 1:2.7 ratio (total yield 70%) by sequential collapse of two dipolar intermediates. In the stepwise mechanism, standard pyrrolone formation results in the bicylic intermediate **367** which can extrude CH_2O in a well precedented manner under the conditions of pyrolysis to afford the azomethine ylide intermediate **368**, which leads to the alkenylpyrrole **369** by intramolecular hydrogen transfer (Scheme 87).

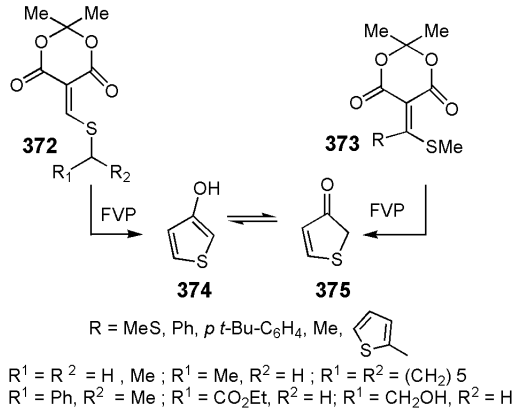
7.3.2 3-Hydroxythiophene.

3-Hydroxythiophene (**374**), because of its sensitive nature has not been explored and also not well studied. 3-Hydroxythiophene and a range of its 2-substituted 2,2-disubstituted and 5-substituted derivatives have been made by flash vaccum pyrolysis (FVP) of an appropriate alkylsulfanylmethylene derivative of Meldrum's acid **372**, **373** [143]. The above-referred compounds are readily obtained, either by reaction of methoxymethylene Meldrum's acid with alkylthiols in refluxing acetonitrile. The pyrolysis proceeds by a hydrogen- transfer cyclisation mechanism in which there is extensive loss of configuration at the chiral centre of the reaction site (Scheme 88).

7.3.3 Tetramic Acids.

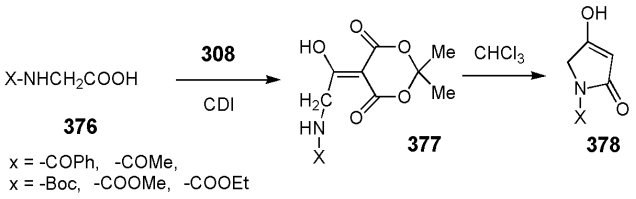
Meldrum's acid, an exceptionally acidic methylene compound, has been employed in a general and versatile synthesis of β-ketoesters. Hamilakis and Kontonassios

Scheme 88



reported a simple and convenient acylation of Meldrum's acid (**308**) with chiral *N*-protected amino acids **376** *via* the imidazolides of the *N*-protected glycines [141]. The acylation compounds **377** were readily converted into N-protected tetramic acids **378** when heated in chloroform or ethyl acetate or by thermal process (Scheme 89).

Scheme 89



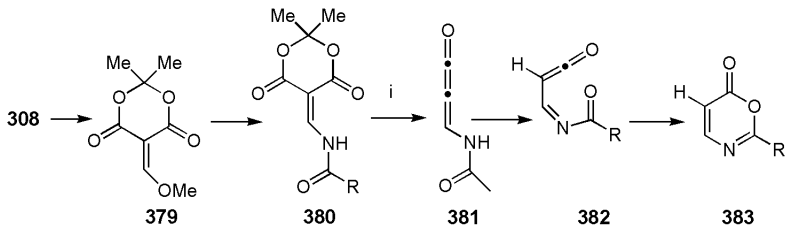
7.3.4 2-Substituted 1,3-Oxazine-6-ones.

In recent years transformation of Meldrum's acid derivatives into other heterocyclic ring systems using pyrolytic methodology is gaining importance because of the synthesis of a range of monocylic, bicylic and their aza analogues of heterocycles reported earlier [145a,b]. Methoxymethylene Meldrum's acid (**379**) is a very reactive electrophilic reagent for both nitrogen and carbon nucleophile. Primary, aromatic and heterocyclic amides react as N-nucleophiles with **379** to give amide derivatives **380** in acetonitrile in fairly good yields. Flash vacuum pyrolysis (FVP) of the Meldrum's acid derivatives **380** at 500-550 °C and 0.01 Torr yielded the 2-substituted 1,3-oxazine-6-ones (**383**) in 62-80% yield. The method is compatible with primary, secondary, and tertiary substitutents at the 2-position of **383** as well as aromatic and heterocycle substituents [145c]. Formation of the oxazine-6-ones **383** presumably involves the formation of methyleneketene intermediate **381**, with a hydrogen transfer leads to a conjugated ketene **382**, with the final step being the electrocyclization of an acylimino ketene intermediate **382** into the desired product **383** (Scheme 90).

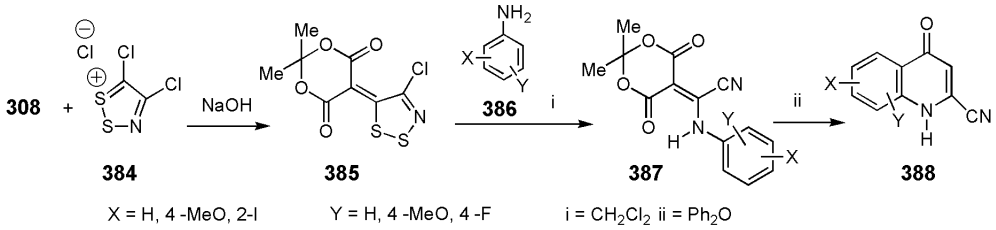
7.3.5 Cyanoquinolines.

In recent years flash vacuum pyrolysis of (aryl and alkylamine) methylene derivatives of Meldrum's acid have attracted much attention owing to its potential synthetic utility and much theoretical and mechanistic interest in the formation of products. Jeon and Kim [146] reported that 4,5-dichloro-5*H*-1,2,3-dithiazolium chloride (**384**) on

Scheme 90

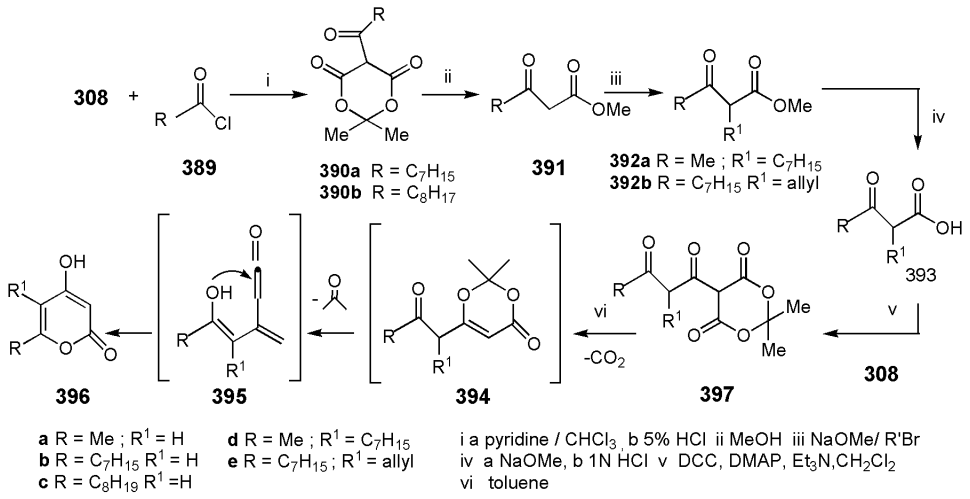


Scheme 91



reaction with Meldrum's acid (**308**) gave 5-(4-chloro-5*H*-1,2,3-dithiazol-5ylidine)-2,2-dimethyl-1,3-dioxane-4,6-dione (**385**). Further **385** was known to react with primary arylamine **386** affording 5-[(arylamino)(cyano)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones (**387**) in excellent yields. By heating in diphenyl ether compounds **387** are readily converted into 2-cyano-4-quinolinones **388** (Scheme 91).

Scheme 92



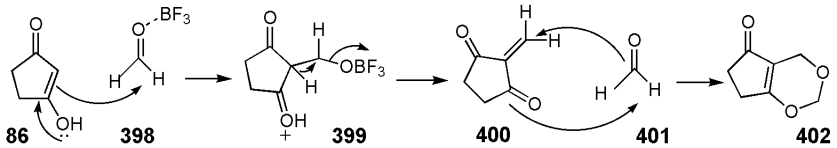
7.3.6 4-Hydroxypyrones.

Alkyl derivatives of 4-hydroxy-2-pyrones attracted considerable attention because of their broad chemical and biological properties. Synthesis of such, complex natural 2-pyrones as verrucosodin [147], citreoviridin [148], citromontanin [149] and many other such compounds cover an extensive area of chemical and biological methods of molecule transformation. Lokot and Pashkovsky [150] reported for the construction of 2-pyrones with various alkyl substituents by thermolysis of acetoacylated Meldrum's acid as a key step for the construction of the 2-pyrone-ring system. Meldrum's acid (**308**) on reaction with carboxylic acid chloride **389** gave acylated Meldrum's acid **391**. Alcoholysis of synthetic equivalent of a mixed diketone acylated Meldrum's acid **390** furnished β-dicarbonyl compounds **391**. The α-alkylsubstituents were introduced into acylic β-dicarbonyl compounds such as esters by classical reaction giving compounds (**392**). The methyl β-oxoesters **392** are saponified by alkali in almost quantitative yields to afford acids **393**. The condensation of Meldrum's acid with β-ketoacid **393** by the action of DCC in presence of triethylamine and DMAP resulted in good yield of the key compound **397**. The alkyl pyrones **396** were obtained in 46-91 % by refluxing the key precursors **397** in toluene for 5-15 h. This reaction proceeds through formation of α-oxoketene **395** as a key intermediate followed by its intramolecular addition to an enolic hydroxyl compound **394** is readily obtained by the reaction of Meldrum's acid with diketene (Scheme 92).

8. Dioxin, Dioxospirodiones.

8.1 Dihydrocyclopentadioxone.

Scheme 93



1,3-Dioxin derivatives derived from cyclic-1,3-diketones are valuable building blocks for the construction of natural and unnatural carbocyclic products [151]. Chen and Brook [152] reported the synthesis of 6,7-dihydrocyclopenta-1,3-dioxin-5-(4*H*)-one (**402**) starting with 1,3-cyclopentane-

dione (**86**), 1,3,5-trioxane and boron trifluoride.etherate. This reaction can also be generalized by employing a large excess of paraformaldehyde and 3 equivalents of boron trifluoride.etherate. The reaction can be accounted by Prins mechanism thus assuming the enol of the 1,3-diketone adds to the Boron trifluoride- aldehyde complex **398**. Incorporation of a second equivalent of aldehyde followed by cyclisation yields the dioxin (**402**) (Scheme 93).

8.2 Arylidene Spirodiones.

5-Alkylidene-1,3-dioxane-4,6-dione derivatives are very reactive electrophiles, which can act as an effective unsymmetrical dienophile activated by a cylic acylal group in the Diels Alder reaction. Xu and Ding [153] reported the condensation of 2,2-pentamethylene-1,3-dioxane-4,6-dione (**403**) with aromatic aldehydes **404** to afford arylidenespirodiones **405** in fairly good yields (Scheme 94). Chen and Jian [154] reported 1,5-bisaryl-8,15-dioxadispiro[5,2,5,2]hexadecane-3,7,16-trione (**408**), by reaction of dioxospiroundecanedione **407** with **406** in ethanol in presence of potassium hydroxide and polyethylene glycol (Scheme 95).

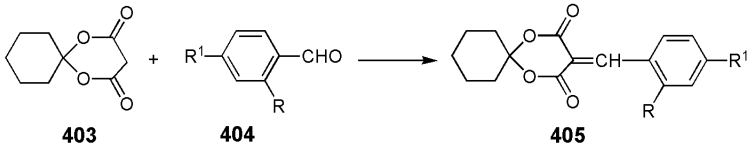
9 Thiazolidinediones.

Five membered cyclic imides containing a sulfide linkage are well defined as thiazolidinediones. Depending on the position of the carbonyl group in the ring they are described as 2,4-thiazolidinediones or 2,5-thiazolidinediones. In both cases the dioxo tautomer predominates. 2,5-Thiazolidinediones are used in peptide synthesis, whereas 2,4-thiazolidinedione derivatives represent an important class of heterocyclic compounds for which diverse pharmaceutical properties have been documented during the past decade [155].

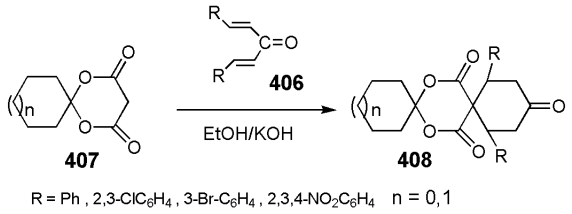
9.1 Flavonoid Thiazolidine Derivative.

Flavonoid derivatives are also known to have antibacterial activity [156]. It was envisaged that compounds containing a flavanoid possessing 2,4-thiazolidinedione moiety in the same molecule might show enhanced biological activity. Ayhan-Kilegil and Altanalar [157] reported the synthesis of some 2,4-thiazolidinediones having flavanoid moiety as a substituent in 5th position. The 3-substituted phenacyl-2,4-thiazolidinediones **411** were prepared by reacting with potassium 2,4-thiazolidinediones (**409**) and phenacylbromide derivatives **410** in hot methanol. Flavone-6-carboxaldehyde (**412**) was condensed to 3- (substitutedphenacyl)-thiazolidine-2,4-diones **411** in acetic acid/anhydrous sodium acetate mixture by Knoevenagel reaction. The Arylidine-thiazolidine-2,4 diones **413** were in *Z* configuration and showed meaningful activity against C.albicans and S.aurens (Scheme 96).

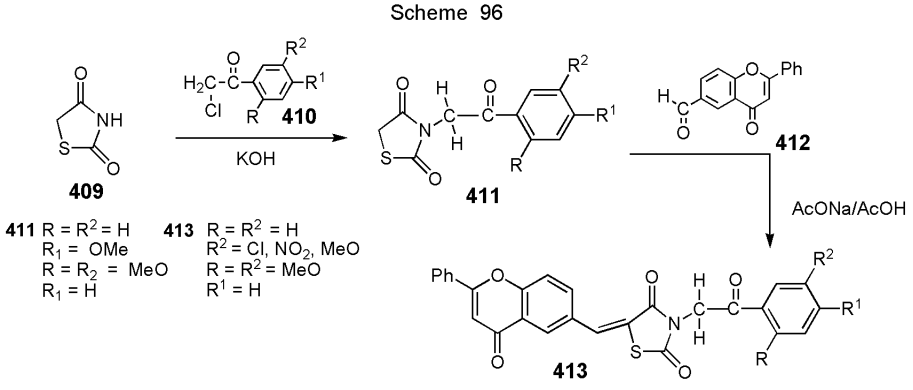
Scheme 94



Scheme 95



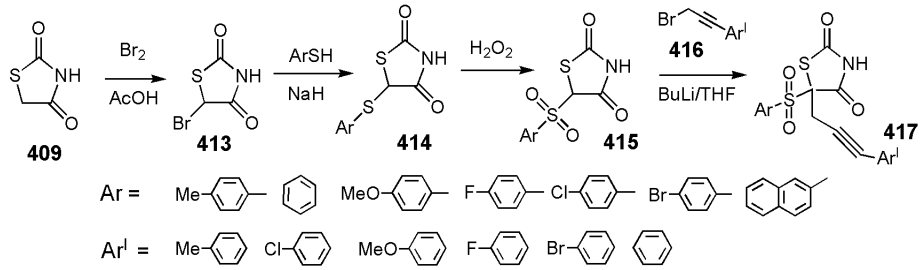
Scheme 96



9.2 Aryl-propynyl, Aryl Sulfonyl Thiazolidinediones.

Substituted thiazolidinedione derivatives represent a class of compounds employed for the control of non-insulin-dependent diabetes mellitus (NIDDM) through potentiation of peripheral insulin action. Novel 5-[3-aryl-prop-2-ynyl)-5-(arylsulfonyl)thiazolidine-2,4-diones, which are useful for lowering the blood glucose levels in hyperglycemic mammals are reported by Wrobel and Li [158]. The requisite 5-bromo-2,4-thiaolidinedione (**413**) was obtained by bromination of 2,4-thiazolidinedione (**409**) with bromine in acetic acid. A base mediated coupling of a thiol with 5-bromo-2,4-thiazolidinedione gave the thio intermediate **414** which was oxidised to the sulfone **415** using an excess of H_2O_2 in acetic acid. *C*-5 Alkylation of thiazolidindiones **415** with appropriate (3-arylprop-2-ynyl)-bromide (**416**) using NaH afforded the 5-[3-aryl-prop-2-ynyl]-5-(aryl-sulfonyl)-thiazolidine-2,4-diones (**417**) in good yields (Scheme 97).

Scheme 97



9.3 Chromene Thiazolidinediones.

Troglitazone has a very potent lipid peroxide-lowering activity and can improve the action of insulin. Troglitazone was first synthesized in 1982 in 8 steps from trimethylhydroquinone (TMHQ) and *p*-nitrophenol [159]. Recently Cossy and Mencin [160] reported the synthesis of troglitazone in five steps from bromoacetal (**418**) and TMHQ (**420**). Reaction of bromoacetal **418** with 4-hydroxybenzaldehyde **419** in presence of potassium carbonate and sodium iodide produced unsaturated ether **421** which react with TMHQ **420** in acid medium to give rise to a 2,2–disubstituted chromene that will be the precursor of troglitazone. Chromene **422** was acetylated using acetic anhydride in presence of catalytic amount of 4-dimethylaminopyridine to produce the acetylchromene **423**. The Knoevenagel condensation of **423** with **409** in toluene in presence of piperidine afforded thiazolidine **424** in 60 % yield. Hydrogenation of **424** using Pd-C in methanol followed by hydrolysis with a mixture of acetic acid and hydrochloric acid gave the **425** in 66 % yield (Scheme 98).

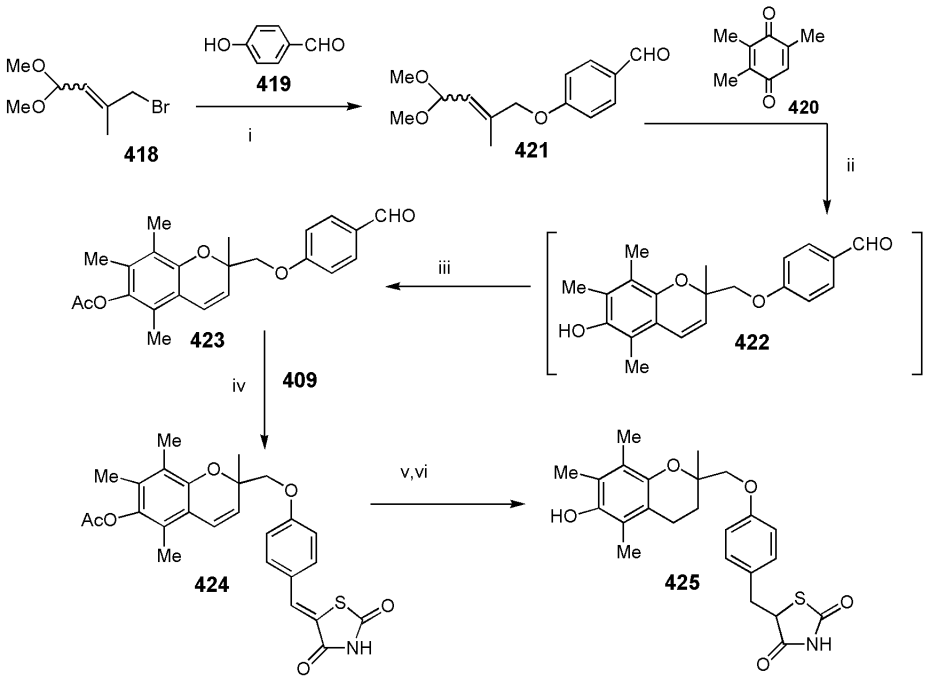
9.4 Napthylthiazolidinodiones.

Combination of two active pharmacophores into one molecule is one of the novel drug designing techniques used in drug discovery programme. Prabhakar and Madhusudhan [161] reported synthesis of such potential drugs with two active pharmacophores such as antidiabetic drugs of thiazolidine troglitazone and a methoxy napthyl moiety of nabumetone, which is under clinical investigation for the treatment of inflammatory disease. The reaction of nabumetone (**426**) with 2,4-thiazolidinediones (**409**) under the standard Knoevenagel reaction conditions led to the formation of the unsaturated mixtureof *E* and *Z* compounds of **427**. The mixture was hydrogenated with Pd-C catalyst to give a mixture of diastereoisomers **428**. The reaction of enol ketone **429**, with 2,4-thiazolidinedione (**408**) gave a mixture of *E* and *Z* compounds **430** and **431**. Similar reactions of 2,4-thiazolidinedione (**408**) with acetylnaroline (**437**), 4-(6-hydroxy-2-napthyl)-butan-2-one (**438**), 2-acetyl thiophene (**432**) and 2-acetyl furan (**435**) gave the corresponding unsaturated compounds **436**, **439**, **435**, **434** respectively (Scheme 99).

9.5 Chromanthiazolidinedione.

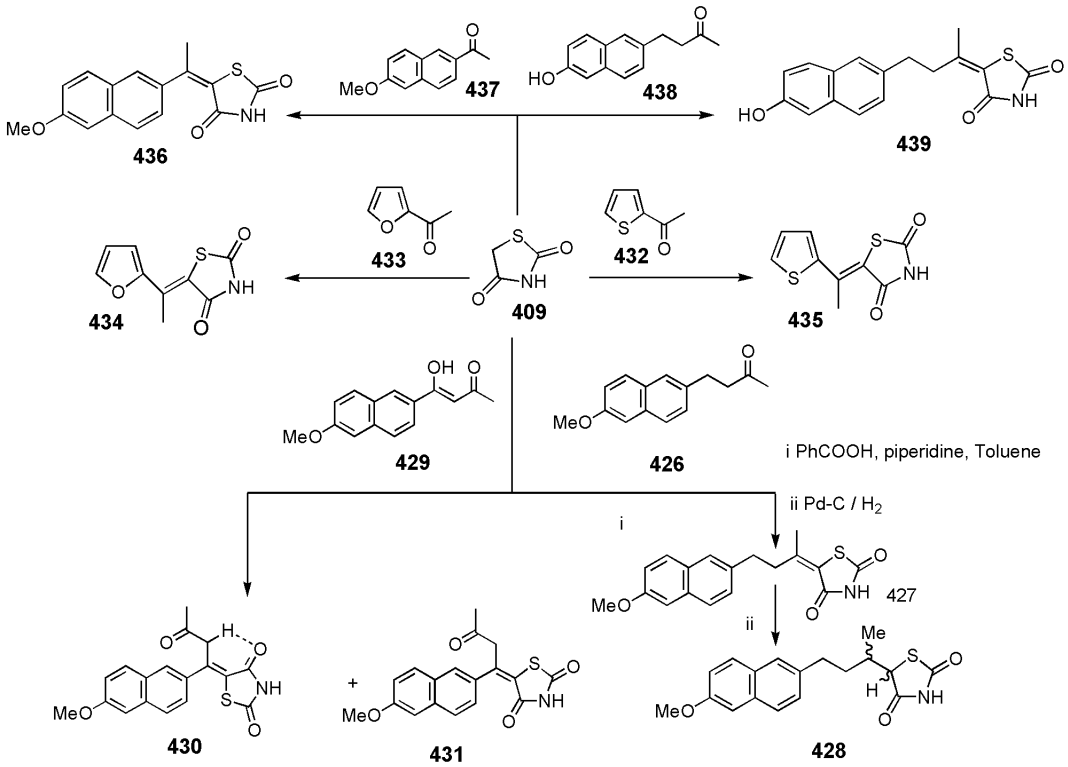
Troglitazone, that has a beneficial antioxidant property and it has been withdrawn from European market due to hepatic dysfunction and increase in lipoprotein. Reddy and Lohray [162] reported molecules that preserve the beneficial antioxidant property but they also found superior euglycemic and hypolipedemic activities compared to troglitazone. The introduction of –N-R group between Chroman ring and phenoxyethyl moiety might improve its plasma glucose and triglyceride lowering activity compared to troglitazone 2,5,7,8-

Scheme 98

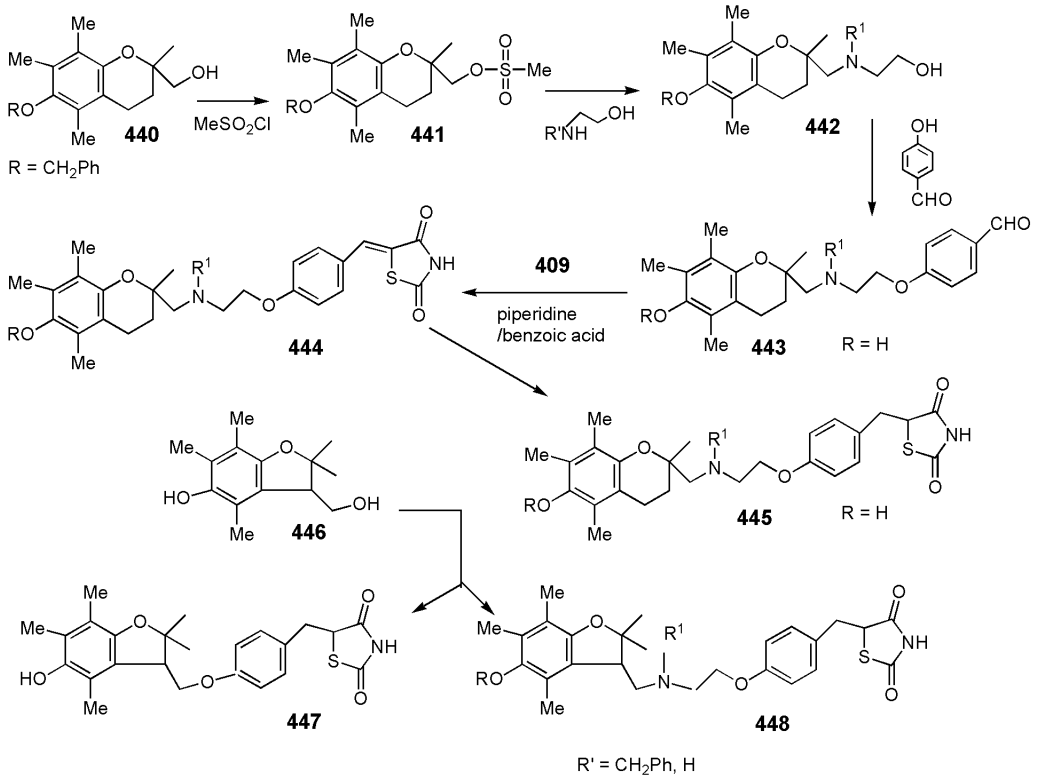


i K_2CO_3, NaI, acetone, ii *i*-$PrNH_2$, CH_2Cl_2, iii Ac_2O, DMAP, THF
iv piperidine, toluene, v H_2 / Pd-C, MeOH, vi H^+, H_2O

Scheme 99



Scheme 100

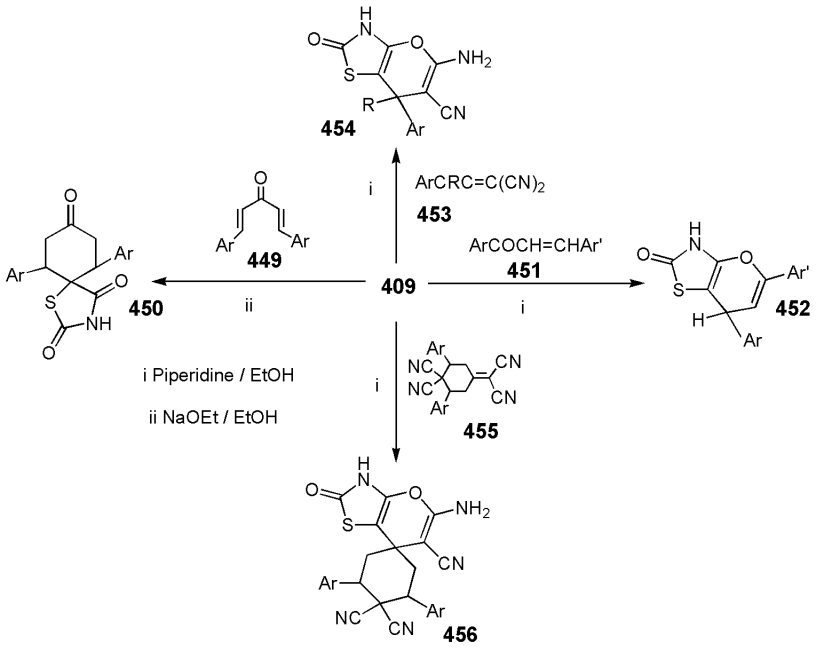


Tetramethyl-6-benzyloxychroman-2-methanol (**440**) was treated with methane sulfonyl chloride in pyridine at 0 °C gave 98% of mesylate derivative, which on further treatment with 2-(methylamino)ethanol afforded 95% yield of **442**. Reaction of **442** with $SOCl_2$ followed by *p*-hydroxy benzaldehyde afforded **443** in 97% yield. The aldehyde **443** was condensed with 2,4-thiazolidinedione (**409**) in presence of piperidine benzoate in toluene to furnish 98% of **444**. The later can be reduced to **445** using magnesium/methanol followed by treatment with a mixture of acetic acid and HCl. Similar synthetic strategy was adopted to obtain dihydrobenzofuran analogs **447** and **448** employing 2,3-dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran-3-methanol (**446**) (Scheme 100).

9.6 Pyranothiazoles and Spirothiazolidinediones.

Thiazolidinedione and its derivatives have drawn considerable interest as potential building blocks for the synthesis of many heterocyclic compounds especially in view of their pharmacological properties [163]. The active methylene group in 2,4-thiazolidinedione can undergo Knoevenagel condensation with araldehydes under the influence of mild bases like piperidine. Rao and Arun Kumar Gupta [164] reported the synthesis of spiro-heterocyclic and bi-heterocyclic compounds by utilizing active the α-methylene group in the 2,4-thiazolidinedione, employing various chalcones and α,β-unsaturated nitriles. 6,10-Diaryl-1-thia-3-azaspiro-[4,5]decane-2,4,8-triones (**450**) and its derivatives were synthesized by the double Michael addition of 2,4-thiazolidinedione (**409**) with 1,5-diaryl-1,4-pentadiene-3-one (**449**) in presence of strong base like sodium ethoxide in ethanol under reflux conditions. The same 2,4-thiazolidinedione (**409**) on reaction with ω-arylideneacetophenone **451** underwent Michael addition followed by cyclisation brought by piperidine in ethanol giving 5,7-diphenyl-6-oxo-6,7-dihydropyrano[3,2-*d*]-5,7-thiazole (**452**). α-Cyanoacrylonitrile (**453**) and 1,1-icyano-2,6-diaryl-4-(2,2-dicyano)-cyclohexanone (**455**) reacted readily with 2,4-thiazolidinedione **409** under the influence of piperidine yielding 2-amino-3-cyano-6-oxo-4-alkyl-6,7-dihydropyrano[3,2-*d*]-5,7-thiazoles (**454**) and 2- amino-3-cyano-6,7-dihydro-6-oxo-[6,6]spiro-1',1'-dicyano-2',6'-diarylpyrano[3,2-*d*]-4,7-thiazoles (**456**) (Scheme 101).

Scheme 101

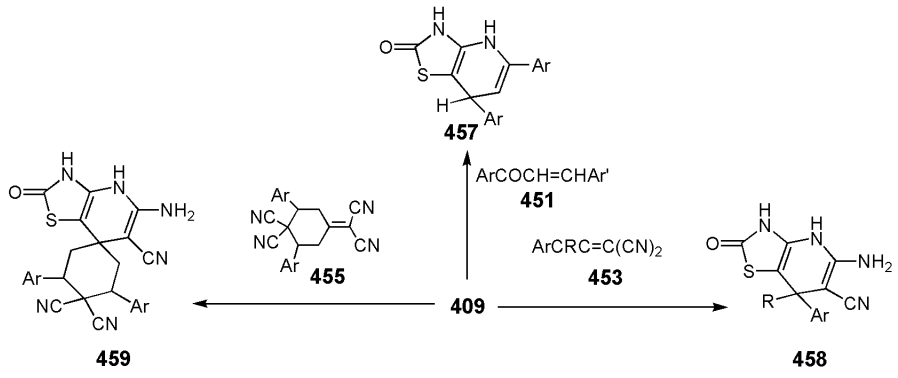


450,456 Ar = Ph, 4 -MeC_6H_4, 4 -$OMeC_6H_4$, 4 -ClC_6H_4 4 -BrC_6H_4, 3 -$NO_2C_6H_4$, 2,4-Cl_2-C_6H_3, 4 -$NO_2C_6H_4$, 2-ClC_6H_4
452 Ar = Ph, 4 -MeC_6H_4, 4 -OMe, 4-ClC_6H_4 Ar"=Ph, 4 -MeC_6H_4, 4 -OMe, 4-ClC_6H_4, 4 -ClC_6H_4, 3 -$NO_2C_6H_4$

9.7 1,4-Dihydropyridinethiazolidinediones.

1,4-Dihydropyridines are very interesting synthetic therapeutic and bioorganic compounds [165]. Rao and by cyclisation. 2,4-Thiazolidinedione (**409**) on reaction with ω-arylidieneacetophenone **451**, underwent Michael addition followed by cyclization in excess of ammonium

Scheme 102



Ar = Ph, 4 -MeC_6H_4, 4 -ClC_6H_4,4 -BrC_6H_4, 3 -$NO_2C_6H_4$, 2,4-Cl_2-C_6H_3, 4 -$NO_2C_6H_4$, 2-Cl-C_6H_4
Ar = Ph, 4 -MeC_6H_4, 4 -OMe, 4-ClC_6H_4 Ar"=Ph, 4 -MeC_6H_4, 4 -OMe, 4-ClC_6H_4, 4 -ClC_6H_4, 3 -$NO_2C_6H_4$

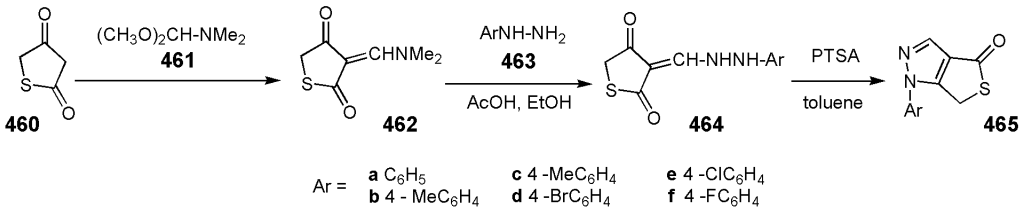
Gupta [166] reported the synthesis of fused spiro-1,4-dihydropyridines by utilizing the methylene group in the 2,4-thiazolidinedione with different types of α-β-unsaturated nitriles, carbonyls employing Michael addition followed acetate in ethanol affording 5,7-diaryl-2-oxo-1,3-thiazolo[4,5-*b*]-2,3,4,7-tetrahydropyridine (**457**). α-Cyanoacrylonitriles **453** and 1,1-dicyano-2,6-diaryl-4-(2,2-dicyano)-cyclohexanone (**455**) interacted readily with 2,4-

thiazolidinedione in a similar manner yielding 5-amino-2-oxo-7-aryl-2,3,4,7-tetrahydro[1,3]thiazolo[4,5-*b*]pyridine-6-yl-cyanide (**458**) and 5-amino-9,11-diaryl-2-oxo-4-aza-spiro-7-[5,5]-undeca-2,3,4,7-tetrahydro-1,3-thiazolo[4,5-*b*]pyridine-6,10,10-tricarbonitriles (**459**) (Scheme 102).

9.8 Thienopyrazoles.

Substituted pyrazolecarboxylates exhibited appreciable antiinflammatory, analgesic, antipyretic activities. Menozzi and Mosti [167] reported the synthesis of 1-aryl-1,6-dihydro-4*H*-thieno[3,4-*c*]pyrazol-4-ones (**465**) resulting from an unsymmetrical heterocylic synthon, namely 3-aminomethylenethiophene-2,4-(3*H*,5*H*)-dione (**462**) was

Scheme 103



ultimately obtained by reaction of thiophene-2,4-(3*H*,5*H*)-dione (thiotetronic acid) (**460**), employing excess of *N*,*N*-dimethylformamide dimethylacetal (**461**). Reaction of synthon **462** with arylhydrazines afforded the desired 1-aryl-1,6-dihydro-4*H*-thieno[3,4-*c*]pyrazol-4-ones (**465**) occurred in two steps, namely *via* the intermediates 3-[(2-arylhydrazino)methylene]thiophene-2,4(3*H*,5*H*)-diones (**464**). Finally cyclization of **464** in refluxing toluene containing a catalytic amount of PTSA gave the final product **465** in excellent yields (Scheme 103).

10 Miscellaneous Class of Heterocycles.

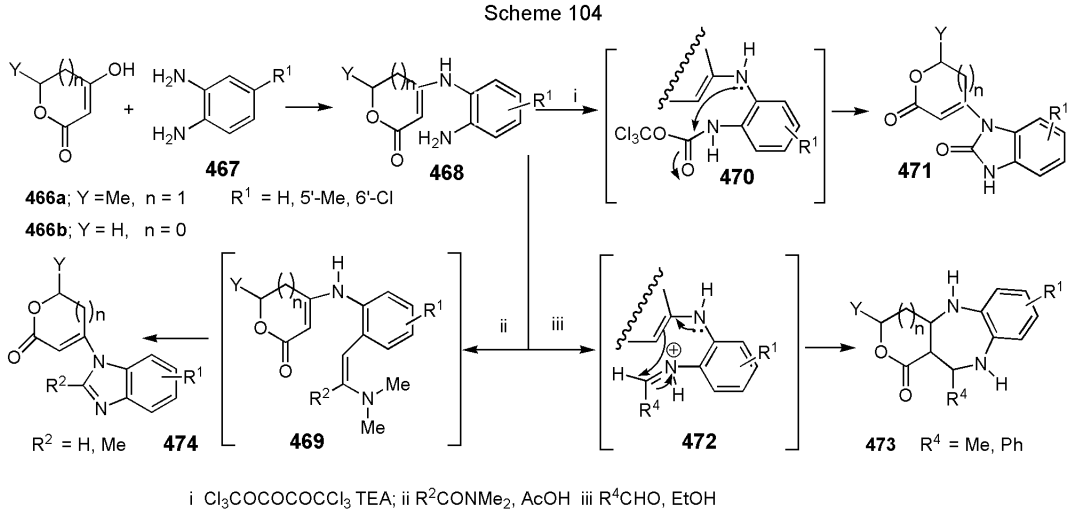
10.1 Benzodiazepines and Benzimidazolones.

Benzimidazoles have been shown to exhibit a large number of biological activities. Some of them like thiabendazole, mebendazole, or albendazole are widely used as antihelmentic drugs [168] due to their ability to bind selectively with great affinity with the β-subunit of helminth microtubule protein. Since pyrones and tetronic acid derivatives are wide spread in nature and exhibit a large number of interesting biological activities. It was assumed by Amari and Fodili [169] that it might be advantageous to combine with the above-mentioned structural moieties in the hope of preparing biologically relevant compounds. Interaction of 5,6-dihydro-4-hydroxy-6-methyl-2-pyrone (**466a**) or tetronic acid (**466b**) with *o*-phenylenediamine derivatives **467** in ethanol gave enaminones **468**. Reaction of **468** with triphosgene permits the access to benzimidazolones **471** bearing either a pyrone or a tetronic acid moiety. This reaction results from attack of the harder nucleophile nitrogen on the carbonyl group in the intermediate **468**, which is well known as the electrophilic center. The reaction of **468** with an aldehyde leads first to iminium salt **472**, since the reaction was carried out in acidic conditions. Cyclisation occurs through the soft nucleophile with the double bond reacting with the polarisable soft electrophilic carbon thereby leading to benzodiazepines **473**. The reaction of diamino compounds **468** with *N*,*N*'-dialkylacetamide dimethylacetal leads to unstable intermediate **469**, which ultimately underwent cyclisation to give **474** (Scheme 104).

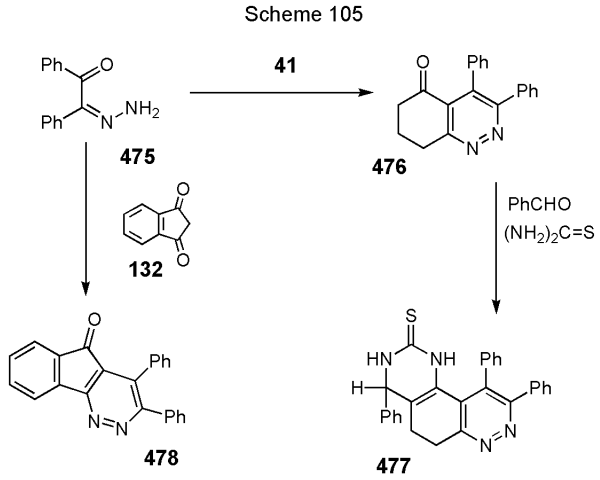
10.2 Pyridazine and Fused Pyridazine.

Several pyridazine derivatives were reported to have antibacterial, antitubercular and antifungal activities. Assy and Abd El-Ghani [170] described efficient approaches for the synthesis of fused pyridazine heterocyclic systems from benzilmonohydrazone. Benzilmonohydrazone (**475**) appeared to be a good starting material possesing a suitably located functionality for direct conversion into pyridazine ring utilizing activated keto methylene reagents. Condensation of **475** with 1,3-cyclohexanedione (**41**) in presence of triethylamine in ethanol gave tetrahydropthalazinone **476**. A mixture of **476**, benzaldehyde, thiourea and sodium ethoxide in ethanol on refluxing afforded pyrimidopthalazine **477**. Condensation of **475** with 1,3-indanedione (**132**) similarly gave indenopyridazine-5-one **478** (Scheme 105).

Scheme 104



Scheme 105



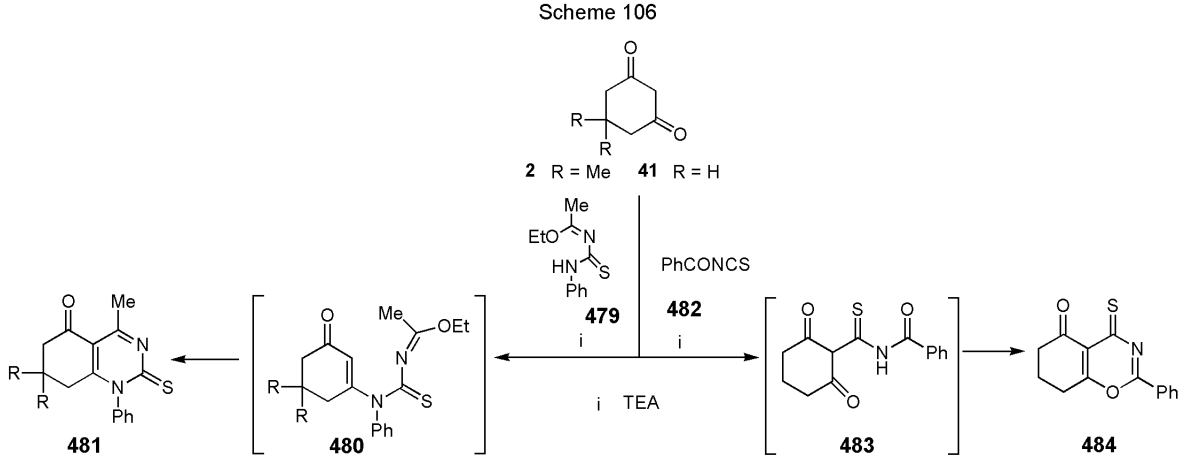
10.3 Quinazoline, Oxazine Derivatives.

Fused quinazoline and oxazine derivatives have been reported for biological activity. Assy and Amar [171] reported an efficient approach for the synthesis of above-mentioned heterocyclic derivatives from β-diketones by heteroannulation. Cyclocondensation of cyclic 1,3-diones (**2** and **41**) with iminoethers of type **479** in the presence of triethylamine gave the corresponding quinazoline **481** *via* the activated enaminone **480**. Thioamide **483** was obtained when 1,3-cyclohexanedione (**2** and **41**) reacted with benzoylisothiocyanate (**482**) in refluxing dioxane. Thioamide **483** in refluxing xylene in presence of triethylamine afforded oxazine **484** as the product of cyclodehydration (Scheme 106).

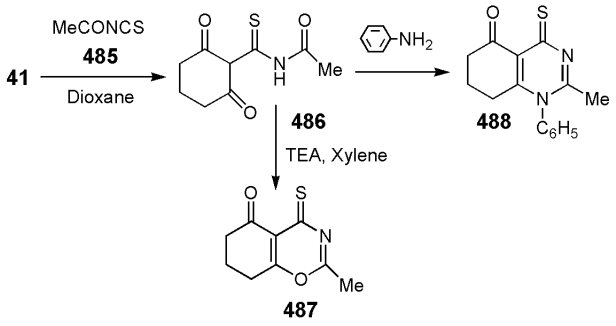
10. 4 Quinazolinones.

Acyl and aroyl isothiocyanates are versatile building units that have been mostly utilized extensively in organic synthesis of heterocycles utilizing aroyl isothiocyanates and simple reagents. Acetyl isothiocyante (**485**) reacted with 1,3-cyclohexanedione (**41**) in refluxing dioxane to afford thioamide **486**. Thioamide **487** under reflux condi-

Scheme 106



Scheme 107



tions in xylene containing triethylamine afforded oxazine **487** as the product of cyclodehydration. Thioamide **486** refluxed with aniline in ethanol medium for 1 h gave quinazolinone **488** in good yield [172] (Scheme 107).

dimedone (**2**) to form new derivatives of 4-imino-substituted 1,3-oxazines **491** *via* the intermediate *O*-alkylation products (**490**)(Scheme 108).

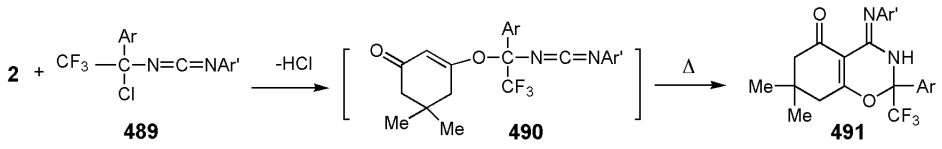
10. 6 Hexahydro-2*H*-1,3-benzoxazin.

1,3-Oxazines and their benzo analogs have been known to posses various pharmacological activites [175]. Safak and Simsek [176] reported 2,4-diaryl-1,3-benzoxazine derivatives **502** by condensing cyclohexane-1,3-dione (**41**) with aromatic aldehyde **499** and ammonium acetate (Scheme 109).

10.7 Longianone.

Longianone, isolated from the fungal strain xyloria longiana. It possesses an unusual 1,7-dioxaspiro[4,4]-non-2-

Scheme 108

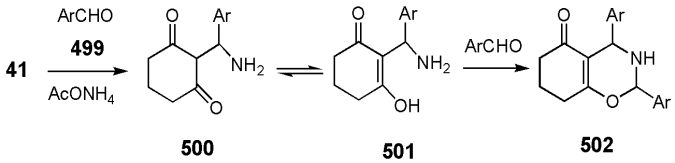


489, 490, 491 (a) Ar = C_6H_5 (b) Ar' = 4-MeC_6H_4

10.5 4-Imino-1,3-oxazines.

1-Chloroalkylcarbodiimides are polyfunctional electrophilic systems containing reaction sites at the α-carbon atom of the alkyl radical and also at the carbon atom of the heterocumulene group. In 1-chloroalkylisocyanates [173], the above-mentioned sites are almost in equal activity in contrast to the aforesaid sites in carbidiimides **489**. The α-carbon atom of an alkyl radical is more reactive due to the influence of the donor imino group. Cyclic 1,3-diones are ambidient nucleophiles characterized by keto-enol tautomerism. Vovk and Dorokhov [174] reported *C*-carbamoylation products by reaction of carbodiimides with β-diketones. 1-Chloroalkylcarbodimide **489** reacts with

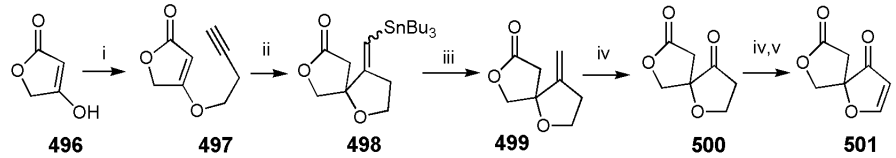
Scheme 109



Ar = Ph, 2-ClC_6H_4, 4 -ClC_6H_4, 2 -$OMeC_6H_4$, 2 -OHC_6H_4, 2 -$NO_2C_6H_4$,

ene-4,8-dione skeleton. Reflecting this unusual intermediate there has been considerable interest in the synthesis of these natural products. Steel [177] reported a highly concise synthesis of (±)- longianone, which has potential to provide advanced intermediates for the synthesis of other

Scheme 110



i but-3-ynol, *p*-TsOH, PhH, ii Bu_3SnH, AIBN, PhH
iii 1 *M* HCl, CH_2Cl_2 iv O_3,CH_2Cl_2 v PhSeCl, THF, H_2O

natural products. Condensation of but-3-ynol with tetronic acid (**496**) was obtained by refluxing in toluene containing a catalytic amount of *p*-toluenesulfonic acid. Slow addition of tri-*n*-butyltin hydride to a refluxing solution of this vinylogous ester **497** in benzene containing 2,2'-azobisisobutyronitrile afforded the desired spirocyclic stannone **498**. Protiodestannylation of spirocyclic stannane **498** with 1 *M* hydrochloric acid in dichloromethane gave alkene **499**. Subsequent ozonolysis of the resulting alkene **499** with a reductive work up using dimethyl sulfide proceeded smoothly to afford the desired bicylic ketone **500**, in good overall yield. The selenoketone was obtained in moderate yield by reaction of **500** with phenylselenyl chloride. The oxidation of selenoketone using ozone as the oxidant gave the desired enone **501** (Longianone) (Scheme 110).

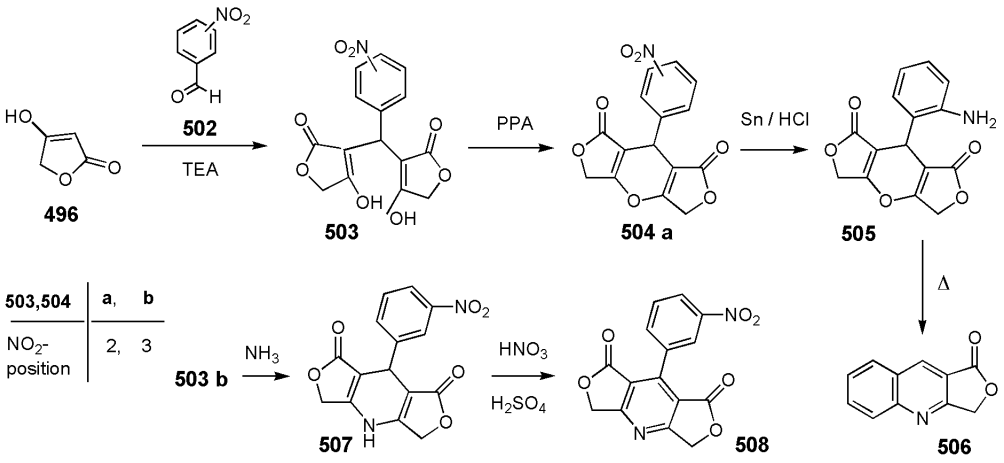
10.8 Bis annulated Dihydropyridines.

4-Aryl-2,6-dimethyl-4*H*-pyran-3,5-dicarboxylates, the sponding pyridine **508** (Scheme 111).

10.9 Benzothiphenes.

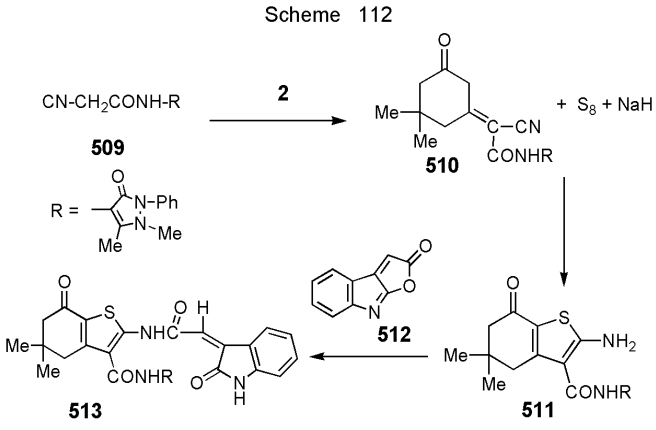
The synthesis of α,β-unsaturated esters, amides and nitriles *via* Wittig reaction using carbonyl compounds and further condensation reactions with compounds possessing an active methylene groups followed by structural modifications furnished diverse types of heterocycles of interest as potential drugs [179]. Condensation of dimedone (**2**) with cyanoacetamide **509** in alcohol using piperidine as catalyst gave the corresponding α,β-unsaturated nitriles **510**. Cyclisation of **510** with elemental sulfur in presence of morpholine gave the corresponding substituted 2-amino tetrahydrobenzo[*b*]thiophene (**511**) respectively. Acylation of **511** was carried out by reflux in alcohol to afford 2*H*-furo[2,3-*b*]indol-2-one (**512**) and corresponding α,β-unsaturated amide **513** (Scheme 112) [180].

Scheme 111

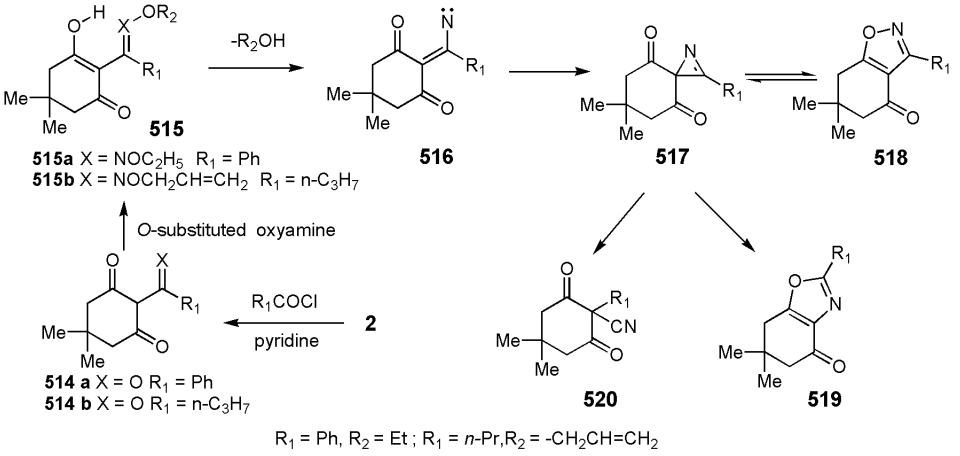


oxa analogs of 1,4-dihydropyridine (DHP) are known for their CNS activity. Bis (lactone)-annulated 4*H*-pyrans and 1,4-dihydropyridines from 3,3'-(nitrobenzylidene)-bistetronic acids were reported by the authors [178]. The bistetronic derivatives **503**, obtained by base catalysed reaction of the aldehyde **502** with excess tetronic acid (**496**). Cyclised **503** in polyphosphoric acid yielded the 4*H*-pyran **504**. The amino derivative **505** formed by reduction of the nitro group underwent easy splitting to afford the furoquinoline (**506**). The ammonium bistetronate **503** on heating undergoes ring closure leading to the bis annulated 1,4-dihydropyridine **507** which is dehydrogenated to the corre-

Scheme 112



Scheme 113



10. 10 Azirines.

In the thermal reactions of oximes, it is known that the common reaction is homolytic N-O bond fission, which leads to the formation of very reactive iminyl radical species. Reartes and Yranzo [181] described the flash vacuum pyrolysis (FVP) reactions of aromatic oximes, and nitriles together with the formation of benzoisoxazoles by an intramolecular addition of conjugated-stabilised iminoxyl radical. Cyclic 2-acyl-1,3-diones (**514**) were prepared from **2** and corresponding acid chloride. *O*-Substituted oxyamine was added to **514** to obtain the corresponding oximated derivatives **515**. Flash vacuum pyrolysis of 2-alkoxyiminated-alkyl (**515b**) and 2-alkoxyiminated-arylcyclohexane-1,3-diones derivative (**515a**) were carried out in gas phase using oxygen-free nitrogen as carrier gas. In flash vacuum pyrolysis of these compounds, azirines, oxazoles or nitriles are the reaction products depending on the exothermicities of the reaction as well as on ring substitution. The α-elimination of the alcohol in **515** affords a vinylnitrine **516**, which afforded azirnes **517**. The isoxazoles **518**, oxazoles **519** and nitriles **520** are formed from azirines **517** respectively under the above mentioned reaction conditions (Scheme 113).

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REFERENCES AND NOTES

* Corresponding author E-mail: batchuchandrasekhar@hotmail.com

[1] A. Strakova, E. Gudriniece and I. D. Strakov, *Latv. Kim. Z.,* **4**, 387 (1994).
[2] E. Gudriniece and A. Strakov, *Latv. Kim. Z.,* **1**, 3 (1994).
[3] E. M. Sorkin, S. P. Clissold and R. N. Brogdon, *Drugs*, **30**,182 (1985).
[4] B. J. Sainani, C. A. Shah and P. V. Arya, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.,* **33B**, 526 (1994).
[5] F. M. Strozher and F. I. Lieldriedis, *Khim. Geterotsikl.* Soedin., **9**, 1227 (1993).
[6a] S. El-Bahaie, A. G. Assy and Y. A. Ibrahim, *Sulfur Lett.*, **8**, 199 (1988).
[6b] S. El-Bahaie, A. M. Kadry, M. G. Assy and Y. A. Ibrahim, *Pharmazie*, **43**, 537 (1988).
[6c] S. El-Bahaie and M. G. Assy, *Sulfur Lett.*, **9**, 193 (1989).
[6d] M. G. Assy, M. M. Hassanien and S. Abdel Rahman, *Pharmazie*, **45**, 792 (1990).
[7] M. G. Assy and F. M. Abd-Ell Motti, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.,* **35B**, 608 (1996).
[8] O. V. Gulyakevich and A. L. Mikhal'chuk, *Dokl. Akad. Nauk SSSR*, **345**, 776 (1995).
[9a] V. P. Litvinov, L. A. Rodinovskaya, Yu. A. Shanin, A. M. Shetsopalov and S. Sennig, *Sulfur Reports*, **13**, 1 (1992).
[9b] V. P. Litvinov, *Phosphorus, Sulfur and Silicon*, **74**, 139 (1993).
[10] V. D. Dyachenko, V. N. Nesterov, S. G. Krivokolysko and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.),* **33**, 684 (1997).
[11] M. Alvarez, M. Salas and J. A. Joule, *Heterocycles*, **32**, 759, (1991).
[12] S. V. Dubovitskii and V. A. Kaminskii, *Zh. Org. Khim.,* **33**, 1048 (1997).
[13] L. Hennig, M. Alva-Astudillo, R. Meusinger and G. Mann, *Monatsh. Chem.*, **124**, 893 (1993).
[14a] L. M. Werbel, U. S. Patent 4,291,034, (1981); *Chem. Abstr.*, **96**, 6611d (1982).
[14b] W. Raether and E. Finke, *Ann. Trop. Med. Parasitol.,* **76**, 507 (1982).
[14c] E. Winklemann and W. Raether, *Arzneim-Forsch Drug Res.*, **37**, 647 (1987).

[15a] B. Venugopal, C. P. Bapat, E. P. Desouza and N. J. Desouza, *Indian J. Chem., Sect. B,* **31B**, 35 (1992).

[15b] W. Duerckheimer, W. Raether and H. G. Seliger, German Patent. D S. 2,337,474, (1975); *Chem. Abstr.*, **83**, 9827w (1975).

[16] A. A. Akhrem, E. V. Borisov and Yu. G. Chernov, *Zh. Org. Khim.,* **31**, 1715 (1995).

[17] T. Naid, T. Kitahara, M. Kaneda and S. Nakamura, *J. Antibiot.*, **40**, 157 (1987).

[18] P. Potier, *Tetrhedron*, **42**, 2389 (1986).

[19] Y. Blache, O. Chavignon, M. E. Sinibaldi-Troin, A. Gueiffier, J. C. Teulade, Y. Troin and J. C. Gramain, *Heterocycles*, **38**, 1241 (1994).

[20] J. C. Gramain, H. P. Hussain and Y. Trein, *Tetrahedron Lett.*, **26**, 2323 (1985).

[21] Y. Kuang, S. Zhang and X. Sun, *Zhongguo Yiyao Gongye Zazhi,* **25**, 36 (1994).

[22] M. Mori, K. Chiba and Y. Ban, *Tetrahedron Lett.*, 1037 (1977).

[23] T. Nishio, C. Kajima and Y. J. Omate, *Synth. Org. Chem. Jpn.*, **34**, 526 (1976).

[24] H. M. Wang, H. L. Chou and L. C. Chen, *J. Chin. Chem. Soc.*, (Taipei), **42**, 593 (1995).

[25] C. J. Ohmmachi, Eur. Pat. Appl. EP, 539,153 (1992); *Chem. Abstr.*, **119**, 117144s (1993).

[26] V. K. Ahluwalia, R. Sahay and U. Das, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **35B**, 1211 (1996).

[27a] T. Shu-Jian, L. Zaisheng, S. Daquingt, Y. Changsheng, G. Yuan and G. Cheng, *Synth. Commun.*, **32**, 2181 (2002).

[27b] M. Vater, *Med. Res. Rev.*, **9**, 291 (1989).

[27c] K. Tanaka and F. Toda, *Chem. Rev.*, **100**, 1025 (2000).

[28] A. A. Bakibae, V. D. Filimonov and E. S. Nevzgodova, *Zh. Org. Khim.,* **27**, 1519 (1991).

[29] S. Hatakeyama, H. Numata and S. Takane, *J. Chem. Soc., Chem. Commun.,* 1202 (1988).

[30] S. J. Tu, C. B. Miao, Y. Gao, Y. J. Feng and J. C. Feng, *Chinese J. Chem.,* **20**, 703 (2002).

[31] I. Van.Wijngaarden, D. Hamminga, R. WanHes, P. J. Standaar, J. Tipker,
M. T. M. Tulp, F. Mol, B. Oliveir and A. De. Jonge, *J. Med. Chem.*, **36**, 3693 (1993).

[32] A. Dumnis, M. Sebben, and J. Bockaert, *Arch. Pharmacol.*, **34**, 403 (1989).

[33] T. M. Bare and A. F. Heald, U. S. Patent, 4,511,568 (1985); *Chem. Abstr.*, **100**, 121059t (1984).

[34] J. B. Campbell and J. W. Firor, *J. Org. Chem.*, **60**, 5243 (1995).

[35] T. Mulamba, G. R. ElBoukili, D. Seraphin, E. Noe, C. Charlet- Fagnere, J. Henin, J. Laronze, J. Sapi, and R. Barret, *Heterocycles*, **41**, 29 (1995).

[36] B. W. Caprathe, J. C. Jaen and L. D. Wise, *J. Med. Chem.*, **34**, 2736 (1991).

[37] Y. Huang and R. W. Hartmann, *Synth. Commun.*, **28**, 1197 (1998).

[38] J. N. V. Prasad, *J. Am. Chem. Soc.*, **116**, 6989 (1994).

[39] F. Al-Omran, I. El-Ghamry and M. H. Elnagdi, *Org. Prep. Proced. Int.*, **30**, 36 (1998).

[40] W. G. Mayler, Calcium. Antagonists, Academic Press, London, 1989.

[41] M. Suarez, Y. Verdecia, E. Ochoa, N. Martin, R. Martinez, M. Quinteiro, C. Seoanc, J. L. Soto, H. Novoa, N. Blaton, O. M. Peters and C. DeRanter, *J. Heterocyclic Chem.*, **37**, 735 (2000).

[42] G. Y. Leshor, E. J. Froelich and M. D. Gruett, *J. Med. Chem.*, **5**, 1063 (1962).

[43] J. Matsumoto, T. Miyamoto and A. Minamida, *J. Med. Chem.*, **27**, 282 (1984).

[44] M. Pesson, P. De Lajudie, M. Antoine and P. Girard, *C. R. Hebd. Seances. Acad. Sci.,* **282**, 861 (1976).

[45] Y. Kurasawa, K. Sakurai, S. Kaziwan, K. Harada, Y. Okamato and H. S. Kin, *J. Heterocyclic Chem.*, **37**, 1257 (2000).

[46] E. H. Brown and R. A. Butler, *J. Chem. Res. (S)*, **8**, 458 (1998).

[47] O. V. Gulyakesich and A. L. Mikhal'chuk, *Zh. Obshch. Khim.*, **65**, 166 (1995).

[48] V. A. Dorokhov and M. A. Present, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **8,** 1504 (1993).

[49a] K. M. Dawood, A. M. Kandeel and Z. E. Kandoel, *J. Chem. Res., Synop.*, 98 (1999); [b] R. Olivera, R. SanMartin and E. Dominguez, *J. Org. Chem.*, **65**, 7010 (2000); [c] O. Bruno, S.Schenone, A. Ranise, F. Bondavalli, W. Filippelli, G. Falcone, G. Motota and F. Mazzeo, *Farmaco*, **54**, 95 (1999); [d] R. Olivera, R. San Martin and E. Dominguez, *Synlett.*, 1028 (2000); [e] E. Cohnen and R. Dewald, *Synthesis*, 566 (1987); [f] P. Fossa, R. Boggia, E. Lopresti, L. Mosti, P. Dorigo and M. Floreaan, *Farmaco*, **52**, 523 (1997); [g] W. D. Jr. Jones, E. W. Huber and J. M. Grisar, *J. Heterocyclic Chem.,* **24**, 1221 (1987); [h] M. Valentina, H. Mathew, M. Long, C. P. Christine and W. M. Dean, *Synthesis,* **12**, 1669 (2002).

[50] S. Krichevskii, L. M. Alekseeva, O. S. Anisimova and V. G. Granik, *Khim. Farm. Zh.*, **29**, 50 (1995).

[51] A. Y. Strakov, M. V. Petrova, Yu Popelis, A. A. Krasnova, and I. A. Strakova, *Khim. Geterotsikl. Soedin.*, **2**, 247 (1996).

[52] S. A. Paulsen and R. J. Quinn, *J. Med. Chem.*, **39**, 4156 (1996).

[53] J. W. Luga, R. M. Patera, M. J. Plummer and D. A. Yuhas, *Pestic. Sci.*, **42**, 29 (1994).

[54] M. Ikeda, T. Maryama, Y. Nobuhava and S. O. Kobe, *Chem. Pharm. Bull.*, **44**, 1700 (1996).

[55] A. Y. Strakov, N. N. Tonkikh, M. V. Petrova and I. A. Strakova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **33**, 1443 (1997).

[56] C. E. Cook, Y. W. Lee and M. C. Wani, U. S. Patent, 5,319,084 (1993); *Chem. Abstr.*, **112**, 265250 (1995).

[57] N. Umeda, K. Saito and S. Hashimota, Japan Patent, 303,771 (1991); *Chem. Abstr.*, **119**, 203428u (1993).

[58] A. A. Geies and A. M. K. El-Dean, *Bull. Acad. Pol. Sci., Ser. Sci. Chem.*, **45**, 381 (1997).

[59] N. G. Kozlov, I. I. Petrusevich, K. N. Gusak and E. V. Koroleva, *Zh. Org. Khim.*, **36**, 858 (2000).

[60] I. Ahmed, M. Khazi, C. S. Mahajansetti and A. K. Gadad, *Indian J. Heterocycl. Chem.*, **9**, 127 (1999).

[61] Y. Isomura, S. Yamasaki, H. Okada and M. Noguchi, *Heterocycl. Commun.*, **1**, 421 (1995).

[62] C. Heidelberger and F. Arafield, *J. Cance. Res.,* **23**, 1226 (1963).

[63] H. H. Zoorob, M. M. Abou-ElZahad, M. Abdel Mogib and M. A. Ismail, *Tetrahedron*, **52**, 10147 (1996).

[64] V. K. Ahluwalia, R. Kumar and R. Aggarwal, *Org. Prep. Proced. Int.,* **24**, 675 (1992).

[65] V. K. Ahluwalia, R. Agrawal and R. Kumar, *Indian J. Chem., Sect. B,* **32B**, 963 (1993).

[66] Y. Toyoshima, M. Nomura, H. Kondoh and N. Abe, *Akita Daigaku Kyoi Kuga Kubu Kenkyu Kiyo, Shizen Kagaku,* **48**, 19 (1995).

[67] E. M. Sorkin, S. P. Clissold and R. N. Brogden, *Drugs*, **30**, 182 (1985).

[68] V. K. Ahluwalia and B. Goyal, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, **35B**, 1021 (1996).

[69] A. F. Pozharskii, Yu. N. Tkachenko and E. B. Tsupak, *Chem. Heterocyl. Compd. (Engl. Transl.),* **35**, 319 (1999).

[70] W. Pfleiderer, *J. Heterocyclic Chem.*, **42**, 483 (1992).

[71] M. Shizuaki, K. Masato, S. Takashi, M. Katsuhiko and S. Chihiro, *Heterocycles*, **50**, 117 (1999).

[72] K. Watanabe and H. Hareda, Japan KoKai 77,85,218 (1977); *Chem. Abstr.*, **88**, 8499g (1977).

[73] I. Yavari, H. Mostafari, D. Tahmassebi and R. Hekmatsshoar, *Monatsh. Chem.*, **128**, 675 (1997).

[74] O. V. Kayukova, P. M. Lukin, Ya. S. Kayukov, O. E. Nasakin and V. N. Nesterov and M. Yu. Antipu, *Chem. Heterocycl. Compd. (Engl.*

Transl.), **34**, 148 (1998).
[75] B. P. Pradhan and P. Ghosh, *Indian J. Chem., Sect. B,* **31B**, 762 (1992).
[76] Zh. A. Chobanyan, T. L. Badanyan, M. R. Tisakyan and Sh. O. Badanyan, *Zh. Org. Khim.*, **29**, 1067 (1993).
[77] E. V. Trukhm, J. Tebby, S. V. Makarenko and V. M. Berestovitakaya, *Zh. Org. Khim.*, **32**, 478 (1996).
[78] Y. R. Lee, B. So. Kim and J. Hee Lee, *Bull. Korean Chem. Soc.*, **17**, 585 (1996).
[79] L. I. Markova, N. G. Korobochkina and V. G. Kharchenko, Russian
Federation 2,044,732 (1995); *Chem. Abstr.,* **125**, 10618w (1996).
[80] S. R. Ramadas, B. C. Sekhar and D. V. Ramana, *Tetrahedron*, **56**, 5947 (2000).
[81] K. Singh, J. Singh and H. Singh, *Tetrahedron*, **52**, 14273 (1996).
[82] T. Shujiang, Z. Jiangfen, L. Zaisheng, D. Xu, S. Daquing and W. Suhul, *Synth. Commun.*, **32**, 3063 (2002).
[83] K. Matsuzaki, N. Tabata, H. Tomoda, Y. Iwai, H. Tanaka and S. Omura, *Tetrahedron Lett.*, **34**, 8251 (1993).
[84] C. A. Gabbutt, J. D. Hepworth, J. W. Michael Urqubart and L. M. Vazquegde, *J. Chem. Soc.,Perkin Trans. 1*, **12,** 1819 (1997).
[85] D. Prim and G. Kirsch, *Synth. Commun.*, **25**, 2449 (1995).
[86] G. Feuer, in Progress in Medicinal Chemistry, G. P. Ellis and G. B. West, ed., North Holland, Publishing Company, 1974, New York, NY, pp 85-158.
[87] J. Smodis and B. Stanovink, *Tetrahedron*, **54**, 9799 (1998).
[88] T. ShuaJiang, G. Yuan, G. Cheng, S. Daqing and L. Zaisheng, *Synth. Commun.,* **32**, 2137 (2002).
[89] T. Mckee, R. W. Fuller, C. D. Covington, H. Cardellina, R. J. Gulakowski, B. L. Krepps, J. B. McMohan and M. R. Boyd, *J. Nat. Prod.*, **59**, 754 (1996).
[90] E. Abd and A. Hisham, *Pharmazie*, **52**, 28 (1997).
[91] Y. R. Lee, D. H. Kim, J. J. Shim, S. K. Kim, J. H. Park, J. S. Cha and C. S. Lee, *Bull. Korean Chem. Soc.,* **23**, 998 (2002).
[92] I. Music, A. Golobie and B. Vercek, *Heterocycles*, **48**, 353 (1998).
[93] T. Ye and M. A. Mckervey, *Chem. Rev.*, **94**, 1091 (1994).
[94] Y. R. Lee, *Synth. Commun.*, **28**, 865 (1998).
[95] A. Asouti, L. P. Hadjiarapoglou and P. Lazaros, *Tetrahedron Lett.*, **39**, 9073 (1998).
[96] K. Schank and C. Lick, *Synthesis*, 892 (1983).
[97] L. Cheng and L. Xiyan, *Organic Letters,* **26**, 4677 (2002).
[98] A. Padwa and S. F. Hornbuckel, *Chem. Rev.*, **91**, 263 (1991).
[99] H. Nakano and T. Ibata, *Bull. Chem. Soc. Jpn.*, **66**, 238 (1993).
[100] P. D. Cunningham, N. W. A. Geraghty, P. J. McArdle and P. V. Murphy, *J. Chem. Soc., Perkin Trans. 1,* **1**, 1 (1997).
[101] M. C. Pirrung and Y. R. Lee, *Tetrahedron Lett.,* **35**, 6231 (1994).
[102] M. C. Pirrung, J. Zhang and A. T. McPhail, *J. Org. Chem.*, **56**, 6269 (1991).
[103] M. C. Pirrung, J. Zhang and A. T. Morehead, *Tetrahedron Lett.,* **35**, 6229 (1994).
[104] S. C. Bobzin and D. J. Faulkner, *J. Nat. Prod.*, **54**, 225 (1991).
[105] S. C. Roy and P. K. Mandal, *Tetrahedron*, **52**, 12495 (1996).
[106] Y. R. Lee, B. S. Kim and D. H. Kim, *Tetrahedron,* **56**, 8845 (2000).
[107a] D. P. Curan, in Comprehensive Organic Synthesis, Vol **4**, B. M. Trost and I. Fleming, ed., Pregmon Press, New York, NY, 1991, pp 715-831.
[107b] C. K. Sha, W. H. Tseng, K. T. Huang, K. M. Liu, H. Y. Lin and S. Y. Chu, *Chem. Commun.,* 239 (1997).
[108] J. Iqbal, B. Batia and N. K. Nayyar, *Chem. Rev.*, **94**, 519 (1994).
[109] V. Nair, L. Balagopal and J. Mathew, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.,* **39B**, 352 (2000).
[110] C. Olliver and P. Renand, *Chem. Rev.*, **101**, 3415 (2001).
[111] T. H. William and J. F. Blount, *J. Antibiot.*, **35**, 1627 (1982).
[112] C. Chung, T. Seng, Y- Lung Wu and C. Peng Chuang, *Tetrahedron*, **58**, 7625 (2002).
[113a] L. F. Tietze, *Chem. Rev.*, **96**, 115, (1996).
[113b] J. M. Lehn, Supramolecular Chemistry-Concepts and Perspectives, VCH, New York, NY,1995.
[114] R. Keuper and N. Risch, *Eur. J. Org. Chem.*, **11**, 2609 (1998).
[115] M. Y. Uzomi, N. Kawasaki, E. Mori, M. Mori and M. Shibasaki, *J. Am. Chem. Soc.*, **111**, 3725 (1989).
[116] M. Mori, Y. Uozumi and M. Shibasaki, *Heterocycles*, **33**, 819 (1992).
[117] M. Hidai and Y. Mizobe, *Chem. Rev.*, **95**, 1115 (1995).
[118] M. Mori, K. Hori, M. Akashi, M. Hori, Y. Sato and M. Nishida, *Angew. Chem.,Int. Ed. Engl.,* **37**, 636 (1998).
[119a] H. McNab, *Chem. Soc. Rev.*, **7**, 345 (1978).
[119b] B. C. Chen, *Heterocycles*, **32**, 529 (1991).
[120] A. R. Katritzky, F. B. Ji, W. Q. Fan and I. Delpralo, *Synth. Commun.*, **23**, 2019 (1993).
[121] W. F. Fobare and D. P. Strike, U. S. Patent 5,187,284 (1993); *Chem. Abstr.*, **119**, 8819v (1993).
[122] S. Mizukami, N-Kihara and T. Endo, *Tetrahedron Lett.*, **34**, 7437 (1993).
[123] T. Tsuno, K. Sugiyama and H. Ago, *Heterocycles*, **38**, 2631 (1994).
[124] G. D. Krapivin, N. I. Valter, V. E. Zavodnik, D. Vegh, L. Fishera and V. G. Kulnevich, *Khim. Geterotsikl. Soedin.*, **7**, 899 (1995).
[125] I. O. Donkor, Y. S. Abdel-Ghaney, P. F. Kadar and D. D. Miller, *Eur J. Med. Chem.*, **33**, 315 (1992).
[126] W. Rajeswara, R. B. Labroo and L. A. Cohon, *J. Org. Chem.*, **64**, 1369 (1999).
[127a] C. Tsai, J. J. Stezowski and R. E. Hughes, *J. Am. Chem. Soc.*, **93**, 7286 (1971).
[127b] V. Prelog, A. M. Gold, G. Talbot and Z. Zomojski, *Helv. Chim. Acta.*, **45**, 4 (1962).
[127c] R. K. Beckman, Jr and J. R.Pruitt, *J. Am. Chem. Soc.*, **111**, 8286 (1989).
[127d] L. Lermer, E. G. Neeland, J. Ounsworth, R. J. Sims, S. A. Tischler and L. Weiler, *Can. J. Chem.*, **70**, 1427 (1992).
[128] K. J. Hwang and K. H. Park, *Heterocycles*, **36**, 219 (1993).
[129] Z. Huang, L. Wu and X. Huang, *Huaxue Shiji,* **21**, 369 (1999).
[130] F. Perron and K. F. Albiazati, *Chem. Rev.*, **86**, 1617 (1989).
[131] F. J. Zawacki and M. T. Crimmins, *Tetrahedron Lett.*, **37**, 6499 (1996).
[132] N. Martin and C. Seoane, *Quim. Ind.*, **36**, 115 (1990).
[133] Y. Verdecia, O. Morin, N. Martin, M. Quinteria, M. Surz, E. Ochoa, H. Novoa, N. Blaton and O. M. Peters, *Tetrahedron*, **55**, 875 (1999).
[134] J. E. Baldwin and M. J. Lusch, *Tetrahedron*, **38**, 2939 (1982).
[135] K. Sato, S. Sugai and K. Tumita, *Agric. Biol. Chem.*, **50**, 1831 (1986).
[136] U. S. Sorensen, E. Falch and L. P. Krogsga, *J. Org. Chem.*, **65**, 1003 (2000).
[137] K. Senga, T. Norison and H. R. Wilson, *J. Med. Chem.*, **24**, 610 (1981).
[138] J. Quiroga, A. Hormaza, and B. Insuasty, *J. Heterocyclic Chem.*, **35**, 61 (1998).
[139] T. Hudlicky and T. C. Lovelace, *Synth. Commun.*, **20**, 1721 (1990).
[140] W. Cao, W. Ding, Y. Chen and M. Qiu, *Synth. Commun.*, **30**, 3793 (2000).
[141] N. N. Gerber, *Crit. Rev. Microbiol.*, **3**, 469 (1975).
[142] G. A. Hunter and H. McNab, *J. Chem. Soc., Chem. Commun.*, **9**, 794 (1993).
[143] G. A. Hunter and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1209 (1995).
[144] S. Hamilakis, D. Kontonassios and C. Sandris, *J. Heterocyclic Chem.*, **33**, 825 (1996).

[145a] H. McNab, *J. Org. Chem.*, **46**, 2809 (1981).
[145b] H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 653 (1987).
[145c] H. McNab and K. Withell, *Tetrahedron*, **52**, 3163 (1996).
[146] M. K. Jeon and K. Kim, *Tetrahedron Lett.*, **41**, 1943 (2000).
[147] K. Whang, R. J. Cooke, G. Okay and J. K. Cha, *J. Am. Chem. Soc.*, **112**, 8985 (1990).
[148] H. Suh and C. S. Wileox, *J. Am. Chem. Soc.*, **110**, 470 (1988).
[149] P. Patel and G. Patteden, *J. Chem. Soc., Perkin Trans. 1*, 1941 (1991).
[150] I. P. Lokot, F. S. Pashkovsky and F. A. Lakhrich, *Tetrahedron*, **55**, 4783 (1999).
[151] A. B. Smith III, in Strategies and Tactics in Organic Synthesis, Vol **1**, T. Lindberg, ed., Academic Press, New York, 1984, pp 224-254.
[152] K. Chen, S. Brook and A. B. Smith, *Org. Synth.*, **75**, 189 (1998).
[153] F. Xu and W. Ding, *Shanghai Keji Daxue Xuebao,* **14**, 96 (1991).
[154] H. Chen, X. Jian and Z. Lin, *Huaxi Yaaxue Zazhi,* **10**, 150 (1995).
[155a] I. M. Labouta, H. M. Salma and N. H. Eshba, *Eur. J. Med. Chem.*, **22**, 485 (1987).
[155b] A. J. S. Goes, M. C. A. Delima and S. L. Galdino, *Ann. Pharm. Franc.*, **49**, 92 (1991).
[155c] M. C. A. Lima, D. L. B. Costa and A. J. S. Goes, *Pharmazie*, **47**, 182 (1992).
[155d] B. C. Cantello, M. A. Cawthrone and G. P. Cottom, *J. Med. Chem.*, **37**, 3977 (1994).
[155e] J. G. Delima, M. Perrisin and J. Chantegrel, *Arzneim-Forsch/Drugs Res.*, **44**, 831 (1994).
[155f] D. H. Boschelli, D. T. Conner and P. J. Kuipers, *Bioorg. Med. Chem. Lett.*, **2**, 705 (1992).
[156] A. Mori, C. Nishino and N. Enoki, *Phytochemistry*, **26**, 2231 (1987).
[157] G. Ayhan-Kilegil and N. Altanalar, *Arzneim.-Forsch.*, **50**, 154 (2000).
[158] J. E. Wrobel, Z. Li and A. J. Dietrich, WO 95, 24, 400 (1995); *Chem. Abstr.*, **124**, 117303w (1996).
[159] Y. Aizawa, T. Kanai, T. Fujita, H. Hirokoshi and T. Yoshioka, *eterocycles*, **32**, 285 (1991).
[160] J. Cossy, C. Mencin, H. Rakotoavison, P. H. Kahn and J. R. Desmura, *Bioorg. Med. Chem. Lett.*, **9**, 3439 (1999).
[161] C. Prabhakar, G. Madhusudhan, K. Sahadev, C. M. Reddy, M. R. Sarma, G. Om Reddy, R. Chakrabarti, C. Seshagiri Rao, T. Dileep Kumar and R. Rajagopalan, *Bioorg. Med. Chem. Lett.*, **8**, 2725 (1998).
[162] K. A. Reddy, B. B. Lohray, B. Vidya, A. S. Reddy, P. HariKrishna, V. V. Rao, V. Saibaba, A. C. Bajji, B. M. Rajesh, K. V. Reddy, R. Chakrabarti and R. Rajagopalan, *Bioorg. Med. Chem. Lett.*, **8**, 999 (1998).
[163a] F. C. Brown, *Chem. Rev.*, **61**, 463 (1961); [b] S. P. Singh, S. S. Parmar and K. Raman, *Chem. Rev.*, **81**, 175 (1981).
[164] V. S. Rao, S. V. S. Arun Kumar Gupta, P. Giridhar, N. Jai Ganesh and B. S. Reddy, *Indian J. Heterocycl. Chem.*, **9,** 247 (2000).
[165] O. Almarasson and T. C. Braice, *J. Am. Chem. Soc.*, **115**, 2125 (1993).
[166] V. S. Rao, S. V. S. A. Gupta, P. Giridhar, N. J. Ganesh and B. S. Reddy, *Asian J. Chem.*, **12**, 286 (2000).
[167] G. Menozzi, L. Mosti, P. Shenone, M. D. Amico, A. Filippelli and F. Rossi, *Farmaco Ed. Sci*, **47**, 1495 (1992).
[168] P. Kohler, *Int. J. Parasitol.*, **31**, 336 (2001).
[169] M. Amari, M. Fodili and B. N. Kolli, *J. Heterocyclic Chem.*, **39**, 811 (2002).
[170] M. G. Assy and E. Abd El-Ghani, *Pol. J. Chem.*, **69**, 685 (1995).
[171] M. G. Assy and A. M. Amar, *Pol. J. Chem.*, **69**, 873 (1995).
[172] M. G. Assy, *Phosphorus, Sulfur Silicon Relat Element*, **108**, 15 (1996).
[173] V. I. Gorbatenko and L. I. Samorai, *Synthesis*, 2, 85 (1980)
[174] M. V. Vovk and V. I. Dorokhov, *Zh. Org. Khim.,* **33**, 96 (1997).
[175] M. Baumgard, R. Gericke, R. Bergmann and J. DePeyer, Ger. Offen. 3,840,011 (1990); *Chem. Abstr.*, **114**, 164251m (1991).
[176] C. Safak, R. Simsek, Y. Altas, K. Erol and S. Boydag, *Bull. Chim. Formaceutico-Ann.,* **8**, 482 (1996).
[177] P. G. Steel, *Chem. Comm.*, 2257 (1999).
[178] K. Gorlitzer, J. Trittmacher and U. Bartke, *Pharmazie*, **57**, 606 (2002).
[179a] M. A. M. Massoud, *Boll. Chim. Farmaceutico*, **138**, 223 (1999).
[179b] J. M. J. Tronchet and M. A. M. Massoud, *Heterocycles,* **29**, 419 (1989).
[180] M. A. M. Massoud, *Mans. J. Pharm. Sci.*, **15**, 99 (1999).
[181] N. R. Reartes, G. J. Yranzo and J. D. Perez, *J. Anal. Appl. Pyrolysis.,* **32**, 161 (1995).