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Synthesis of biologically active heterocyclic compounds from *β*-diketones

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Abstract: This review focuses on the design, synthesis, and biological evaluation of novel heterocyclic compounds derived from *β*-diketones and cyanomethylene reagents through multicomponent and green synthetic methodologies. The study encompasses a wide range of heterocyclic scaffolds, including xanthene, chromene, chromenone, coumarin, acridine, quinoline, thiazole, thiophene, and spiro-heterocycles containing nitrogen, oxygen, and sulfur. A variety of catalysts were employed such as DBSA, *P*-TSA, $NbCl_5$, and nano-magnetic composites like $CuFe_2O_4$/chitosan to optimize reaction conditions for eco-friendly and high-yielding transformations. The developed synthetic strategies included one-pot, microwave-assisted, and solvent-free techniques, resulting in efficient routes to complex molecular architectures. The biological activity of the synthesized compounds was extensively screened, with several candidates exhibiting promising antimicrobial, antifungal, anticancer, and kinase-inhibitory properties. Structure-activity relationship (SAR) studies indicated that specific heteroatom substitutions enhanced biological potency, particularly in xanthene and chromenoquinoline derivatives. This work contributes to advancing heterocyclic chemistry by introducing new reaction pathways, novel molecular frameworks, and bioactive agents with potential pharmaceutical applications.

Keywords: Camphor; pyrazole; camphor dimethyl DL-tartrate; thiazole; biological activity.

1. Introduction

1,3-Diketones are indeed versatile intermediates in organic synthesis due to the presence of two carbonyl groups separated by a methylene ($-CH_2-$) group, often referred to as an "active methylene" group. These functional groups make them highly reactive, allowing them to participate in various chemical transformations, including condensation reactions, cyclizations, and nucleophilic additions.[1-7] Their ability to form enolates, combined with the active methylene group, enables them to act as key starting materials for the synthesis of diverse heterocyclic compounds such as 4*H*-chromenones, 2*H*-xanthenones, coumarins, acridinediones, b-enaminones, 1,4-dihydropyridine, and polyphenolic [8–13] as shown in Figure 1 and 2. These heterocyclic frameworks are often found in

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pharmaceuticals and agrochemicals due to their wide range of biological activities, including herbicidal, pesticidal [14, 15], antibacterial [16], and anticancer effects. [17, 18]

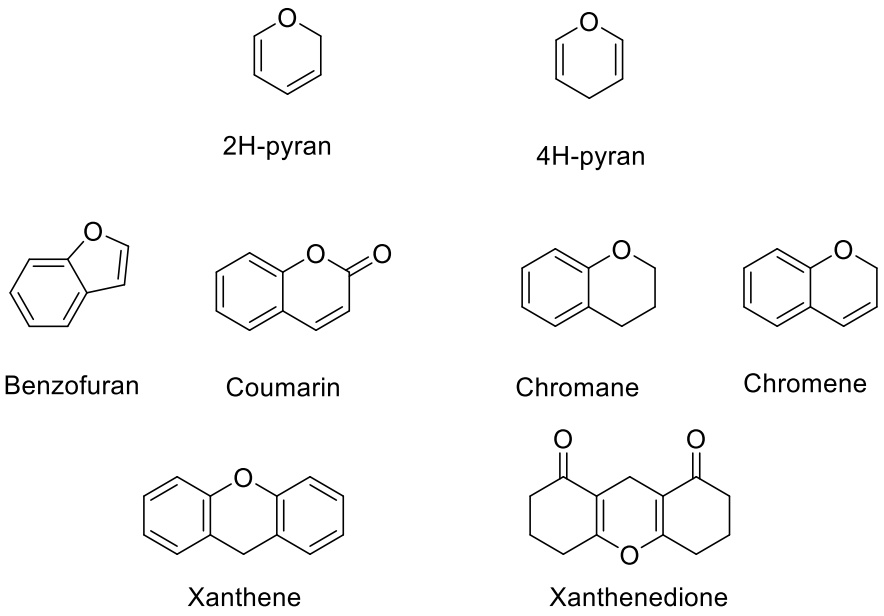


Figure 1. Examples of O-heterocycles

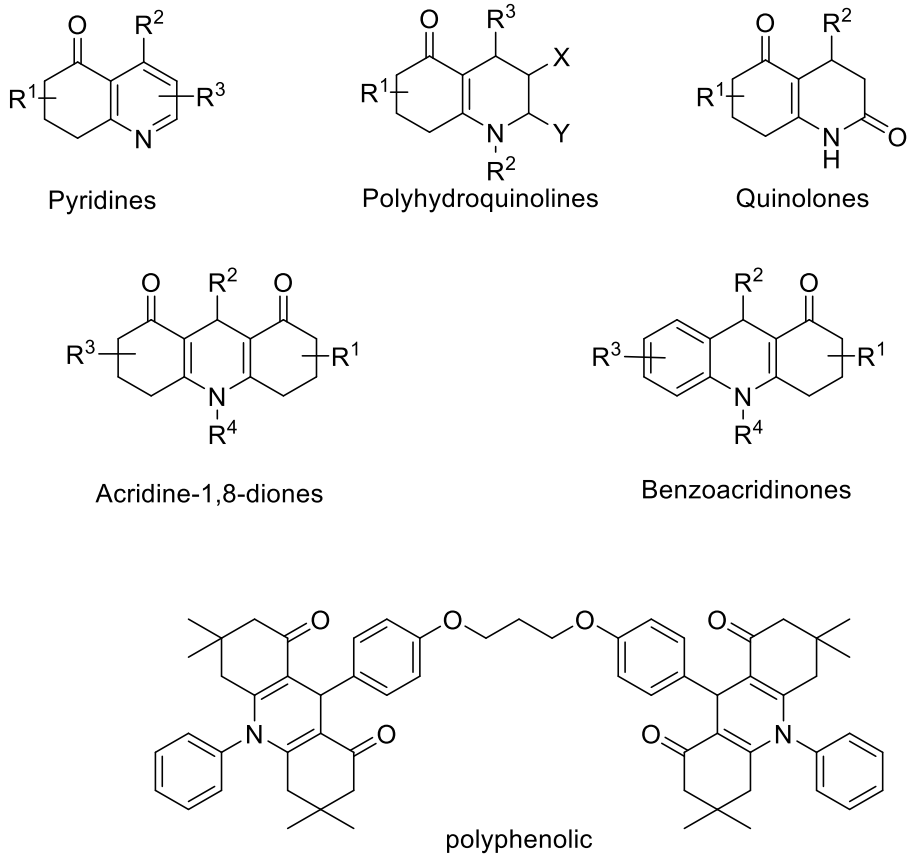
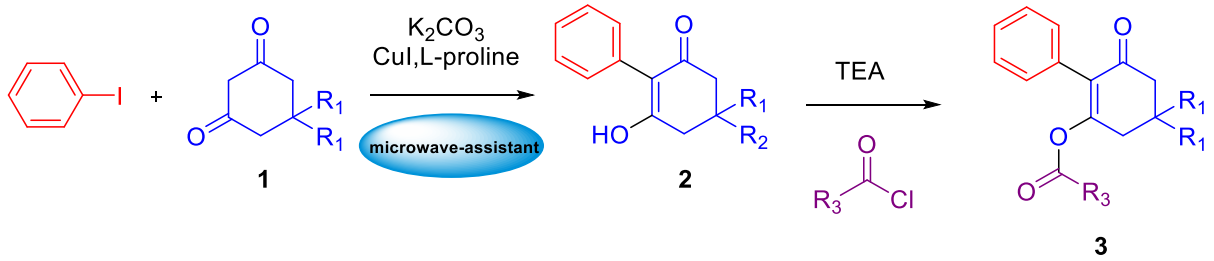


Figure 2. Examples of *N*-heterocycles

2. Some Reactions of β-diketones

Under optimal microwave irradiation conditions, a series of 3-hydroxy-2-phenylcyclohex-2-en-1-one derivatives **2** were synthesized from substituted 1,3-cyclohexanedione **1** and iodobenzene in DMSO. Initially, Lproline and CuI were used as the catalyst in a coupling process in CH_2Cl_2 to create the intermediate **2**, with yields ranging from 25.6 % to 43.8 %.
These encouraging results suggest that the synthesis of 3-hydroxy-2-phenylcyclohex-2-en-1-one via a coupling reaction is indeed viable. The synthetic pathway is illustrated in Scheme 1.

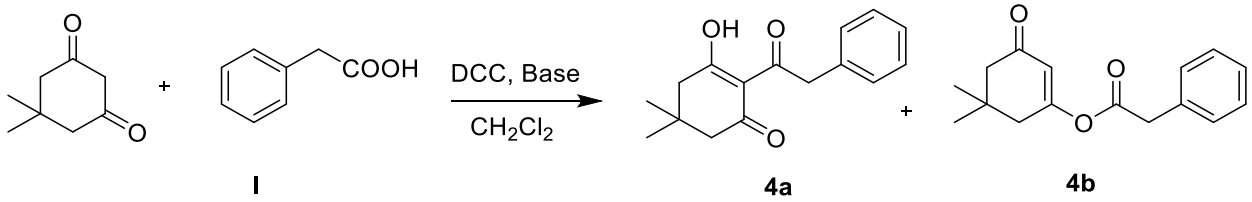
The author subsequently explored the impacts of microwave power, reaction time, bases, and solvents on the coupling reaction. It was determined that microwave power plays a critical role in this reaction, with a threshold of 200 W being essential for the reaction to proceed. Furthermore, an increase in microwave power consistently enhanced the reaction yields, peaking at 800 W. Optimal yields were attained by varying the reaction time between 5 and 40 minutes. Additionally, the bases utilized in the study included Et_3N, NaOH, and anhydrous K_2CO_3, with anhydrous K_2CO_3 being identified as the most effective acid-binding agent for this coupling reaction. [19]



Scheme 1. Route for the synthesis of compound **3**

To enhance reaction yields, the author investigated the influence of various solvents on the outcomes. The experimental findings demonstrated that DMSO yielded higher results compared to CH_2Cl_2, THF, and 1,4-dioxane, attributed to the efficacy of polar aprotic solvents in facilitating this coupling reaction. The optimal conditions identified were: 800 W power, a reaction duration of 40 minutes, and DMSO as the solvent. [19,20]

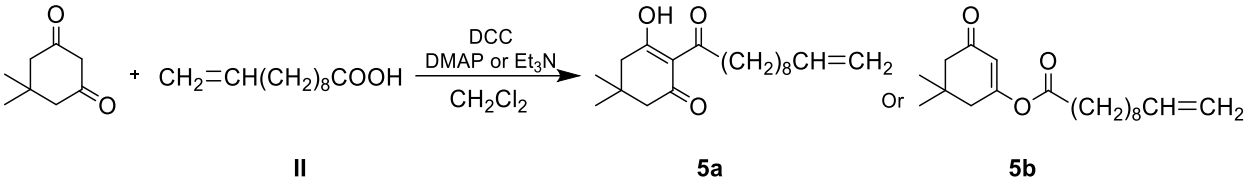
One-pot C-acylation of different cyclic 1,3-diketones is achieved by using phenylacetic acid **I**, derivatives of which have already been used [21]. DCC is utilized as a coupling agent and has been used to C-acylate diketones (Scheme 2). [20-22]



Scheme 2. Acylation of dimedone with phenylacetic acid (I)

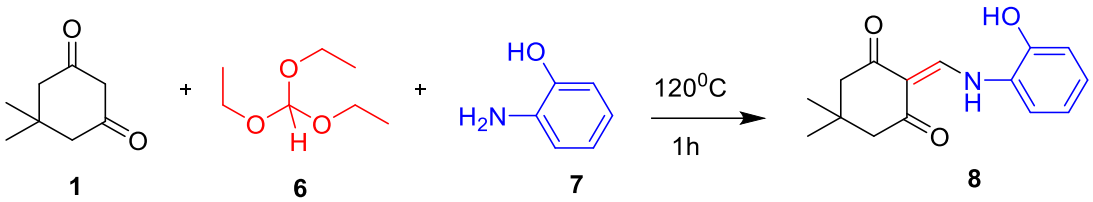
Studying the acylation's chemoselectivity was inspired by the formation of product mixtures using sterically hindered bases. A previously proposed (scheme 3) states that the reaction may take place in two stages. The enol ester is generated initially, and then DMAP is used to do the Fries rearrangement (Scheme 3). [23]

Biologically active heterocyclic compounds



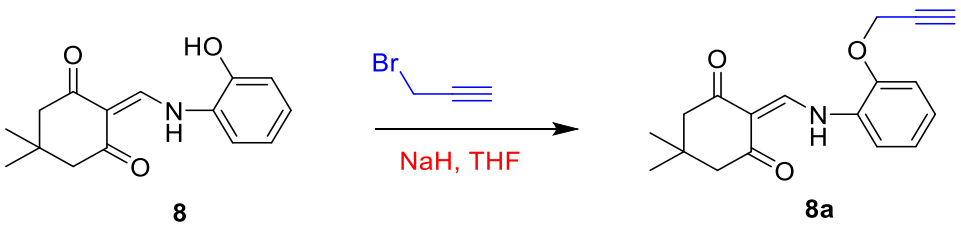
Scheme 3. Direct formation of different products with different bases as catalysts

In this reaction, dimedone **1** is refluxed at 120°C in triethylorthoformate **6** with *O*-hydroxy aniline **7**. The reaction conditions suggest that a condensation or cyclization reaction occurs between these components, resulting in the formation of the intended dimedone derivative **8** (Scheme 4).



Scheme 4. Synthesis of 2-(((2-hydroxyphenyl)amino)methylene)-5,5-dimethylcyclohexane-1,3-dione **8**

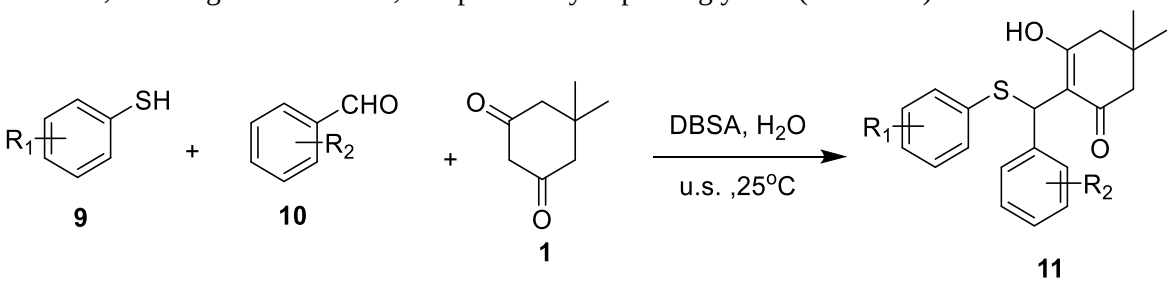
Subsequently, compound **8** underwent propargyl bromide treatment in THF solvent with sodium hydride serving as a base, yielding the dimedone derivative **8a** at room temperature (Scheme 5).



Scheme 5. Synthesis of 2-(((2-hydroxyphenyl)amino)methylene)-dimedone propargyl ether

The antibacterial potential of a library of dimedone derivatives **8a** was developed, produced, and tested against a small number of fungi strains, bacteria, and Gram-positive and Gram-negative bacteria. These findings indicate that an innovative path for the development of antibacterial drugs is provided by dimedone derivatives. [24]

The one-pot three-component synthesis involving thiophenol **9**, aromatic aldehydes **10**, and dimedone **1** under the catalytic action of dodecylbenzenesulfonic acid (DBSA) in water, coupled with ultrasound irradiation at 25°C, presents an efficient route to produce thioether derivatives **11**. The use of ultrasound in this reaction likely accelerates the process by enhancing the interaction between the reactants, reducing reaction times, and potentially improving yields (Scheme 6). [25]

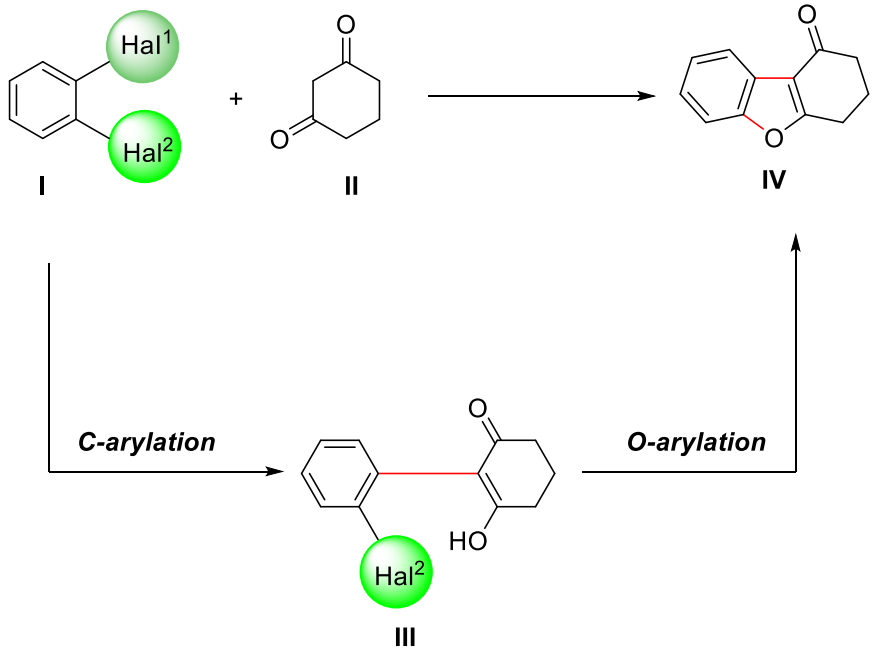


Scheme 6. One-pot three-component synthesis of compound **11**

3. Synthesis of Biologically Active Heterocyclic Compounds from Cyanomethylene Reagents and *β*-diketones.

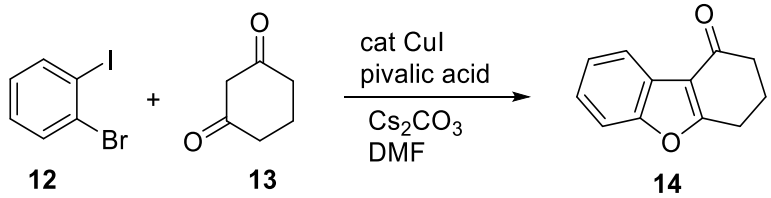
3.1. Synthesis of Benzofuran, Coumarin, Chromane, Chromene, Xanthene, Xanthenedione, Bisoctahydroxanthene and dioxabicyclo[3.3.1]nonanes Derivatives

The synthesis of dibenzo-[*b*,*d*]furan through a domino intermolecular *C*-arylation/intramolecular *O*-arylation involves a multistep process starting with 1,2-dihalobenzene and 1,3-cyclohexanedione as the key reactants. The reaction follows a cascade mechanism, where the coupling of these reactants proceeds through two key steps: an initial *C*-arylation followed by an intramolecular *O*-arylation, leading to the formation of the dibenzofuran core (Scheme 7).



Scheme 7. Proposed route for the Cu-catalyzed synthesis of 3,4-Dihydrodibenzo[*b*,***d***]furan-1(2H)-ones

In order to synthesis dibenzo-[*b*,*d*]furan **14**, the reaction between 1-bromo-2-iodobenzene **12** and 1,3-cyclohexanedione **13** at 130 °C in the presence of DMF as a solvent, using Cs_2CO_3 as a base and pivalic acid for the synthesis dibenzo-[*b*,*d*]furan **14** (Scheme 8).[26]

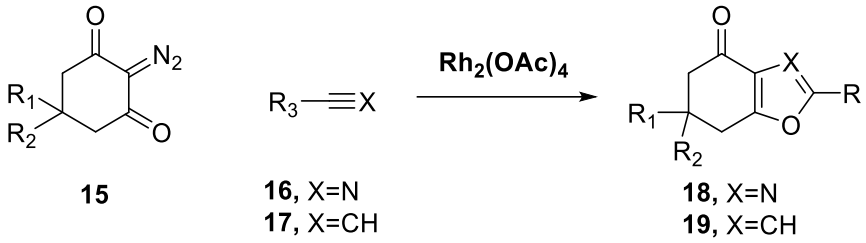


Scheme 8. Synthesis of furans derivative **14**

Research on the reactions of cyclic 2-diazo-1,3-diketones with transition metals has shown that nitriles and arylacetylenes can effectively afford oxazoles and furans via intramolecular 1,5-dipolar electrocyclization, ring opening, and Rh-catalyzed C≡X insertion. [27]

An efficient method was developed for the synthesis of benzo[*d*]oxazolones and benzofuranones, affording good to high yields under mild conditions through $Rh_2(OAc)_4$-catalyzed C≡X insertion followed by 1,5-dipolar electrocyclization (Scheme 9). In preliminary experiments,

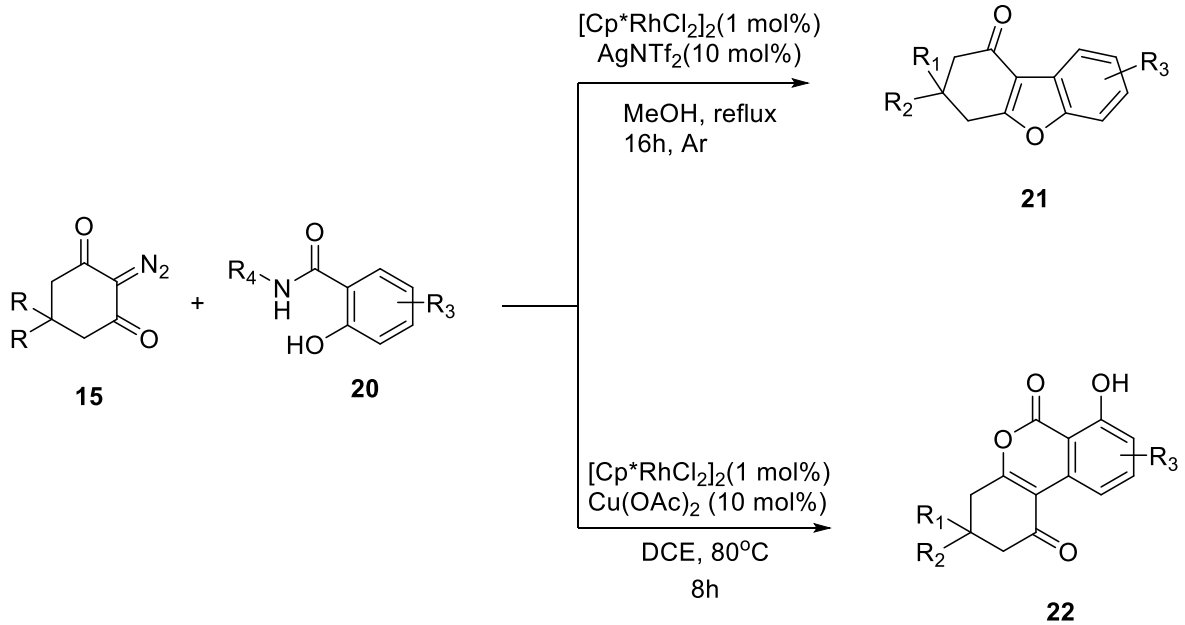
acetonitrile **16** and 2-diazocyclohexane-1,3-dione **15** were employed as model substrates, leading to the formation of benzo[*d*]oxazolones **18** and benzofuranones **19.**[28]



Scheme 9. Synthesis of oxazoles or furans via $Rh_2(OAc)_4$-catalyzed reaction of cyclic 2-diazo-1,3-diketones with nitriles and arylacetylenes

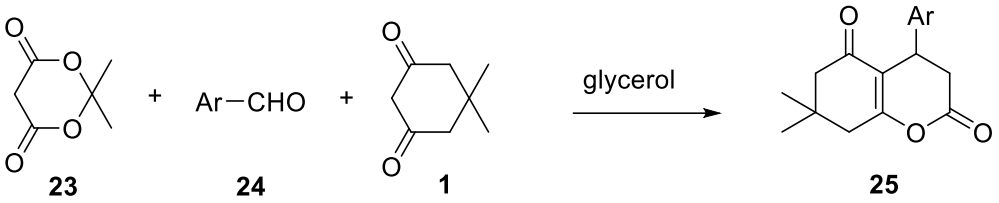
Results of Rh(III)-catalyzed C-C/C-O bond formation reactions between salicylamides and cyclic2-diazo-1,3-ketones have been reported recently. These reactions provide the synthesis of isocoumarins and tetrahydrobenzo[*b,d*]furans (Scheme 10).

The first reaction that was selected as a model reaction for improving the reaction conditions was the reaction between 2-diazo-5,5-dimethylcyclohexane-1,3-dione **15** and 2-hydroxy-*N*-methylbenzamide **20** in MeOH at reflux for 16 hours under an argon atmosphere. A preliminary attempt using $[Cp^*RhCl_2]_2$ (1.0 mol%) and $AgNTf_2$ (5 mol%) produced dibenzo[*b,d*]furan product **21** in 54%. $Cu(OAc)_2$ was then added to the second cyclic 2-dizao-1,3-diketones and evaluated a variety of isocoumarin derivatives **22** with good to high yields (60–86%). [29]



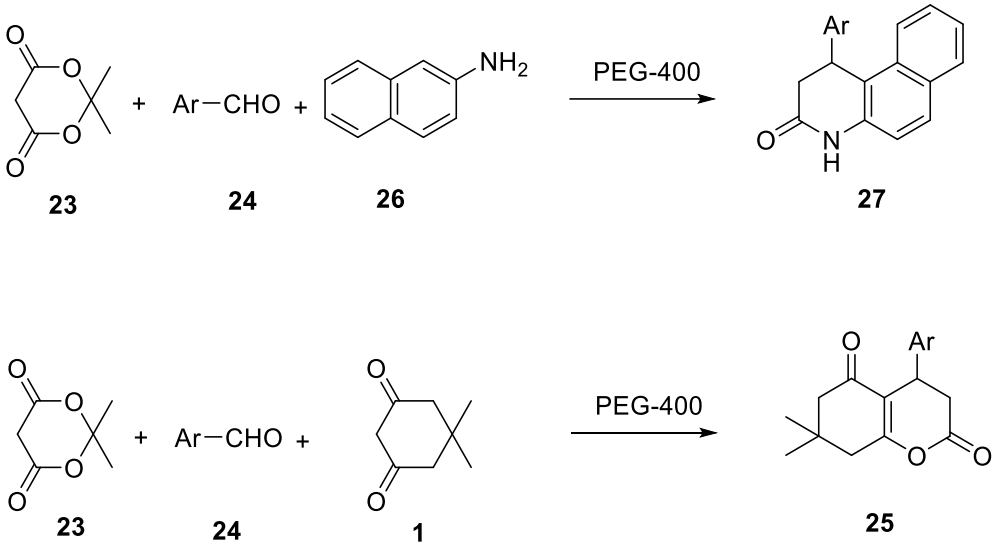
Scheme 10. Controllable chemoselectivity of C–C or C–N cleavage for the formation of tetrahydro-benzo[*b,d*]furans **21** and isocoumarins **22**.

A simple efficient technique for synthesizing several types of coumarin derivatives using Meldrum's acid **23**, benzaldehyde **24**, and dimedone **1** in glycerol media as one pot multicomponent reaction. High yields of hexahydrocoumarin derivatives **25** were observed (Scheme 11).[30]



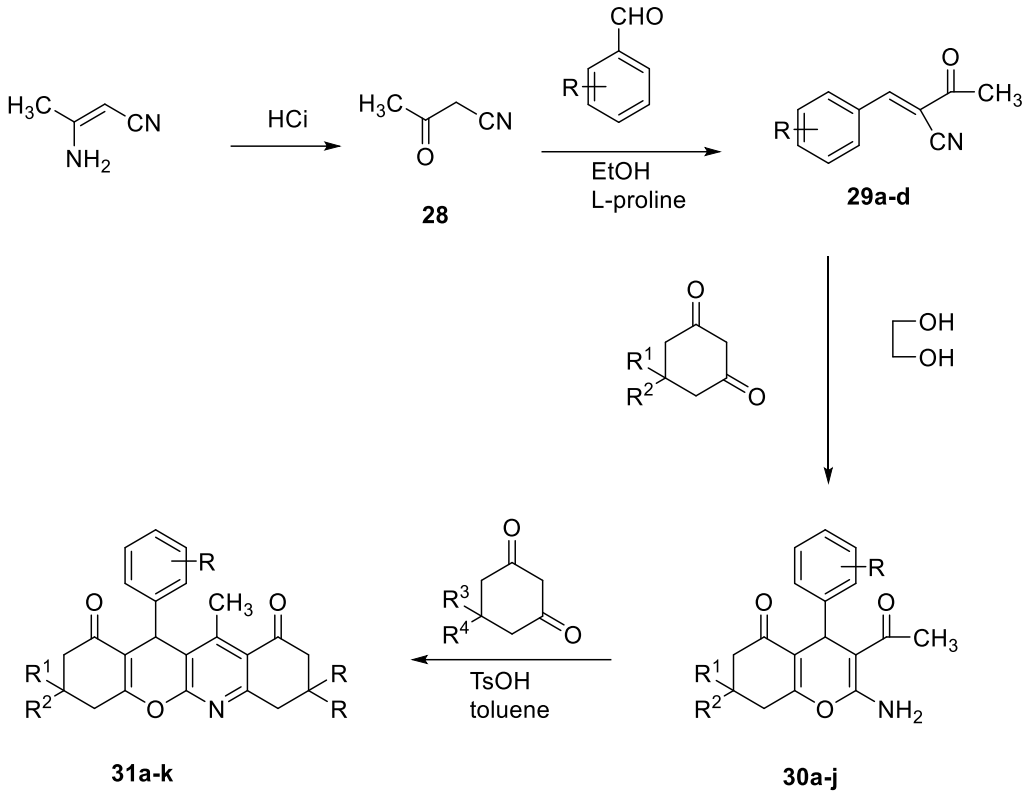
Scheme 11. One-pot synthesis of coumarin derivatives **25**.

By using the same method for the synthesis of a series of quinoline derivatives and coumarin derivatives by one-pot MCR of Meldrum's acid **23** with benzaldehyde **24** and naphthalene-2-amine **26** or dimedone **1** in PEG-400. Quinolin-3(4*H*)-one derivatives **27** or coumarin **25** were obtained in high yields (Scheme 12).[31]



Scheme 12. One-pot synthesis of benzoquinoline derivatives **27** and coumarin derivatives **25**

According to the Knoevenagel condensation between aldehydes and oxobutanenitrile **28** [32], which was produced by acid hydrolysis of *β*-aminocrotononitrile [33,34], the arylidene-3-oxobutanenitrile derivatives **29** used in this investigation were readily synthesized. 3-Acetyl-2-amino-4*H*-chromen-5(6*H*)-one derivatives **30** were created by reacting 5,5-dimethyl-1,3-cyclohexanedione with 2-arylidene-3-oxobutanenitrile **29** in ethylene glycol. By employing *p*-toluenesulfonic acid (PTSA) as a catalyst in toluene, compounds **30** and 5-substituted-1,3-cyclohexanedione undergo a Friedländer reaction to yield derivatives **31** of quinoline-1,10(2H)-dione (Scheme 13).

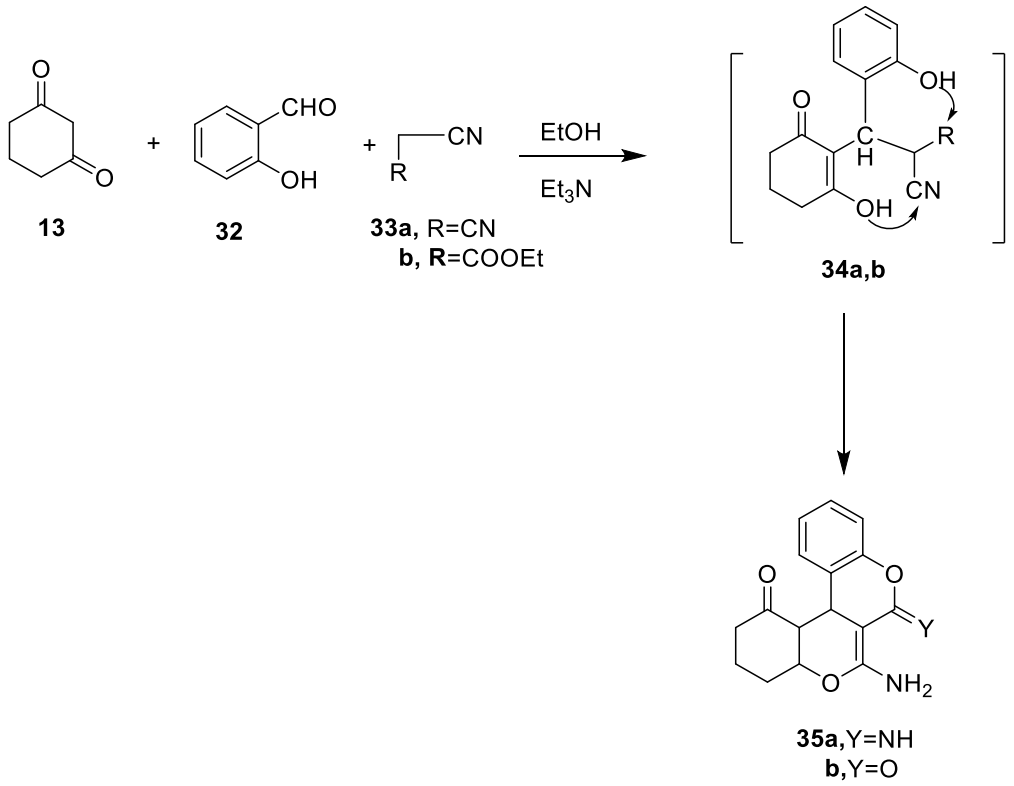


Scheme 13. synthesis of derivatives **31** of quinoline-1,10(2*H*)-dione

It was discovered that compound **31**'s reactivity would significantly increase when the amount of *P*-TSA is gradually increased, and that the reaction temperature should be maintained between 70 and 80 ^{o}C.[35]

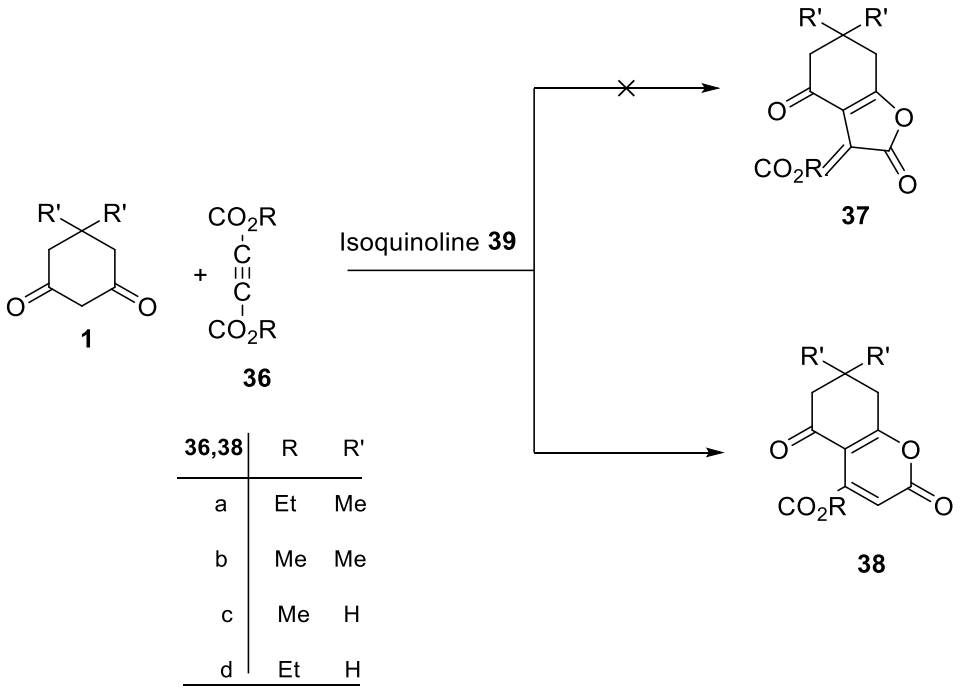
The chromeno[3,4-*c*]chromen-1-one derivatives **35a,b** were produced by the synthesis of a series of fused pyran derivatives using cyclohexan-1,3-dione **13**, which reacted with salicylaldehyde **32** and either malononitrile **33a** or ethyl cyanoacetate **33b** in ethanol with a catalytic quantity of triethylamine as shown in scheme 14. This reaction resulted from the intermediate synthesis of **34a,b,** which was followed by Michael's addition. It's worth noting that cyclohexan-1,3-dione's multi-component reaction with substituted aldehydes but not salicylaldehyde has already been documented in water with KHP acting as a catalyst at 50 ^{o}C. [36,37]

The compounds with the highest cytotoxicity of the synthesized compounds were chromeno[3,4-*c*]chromen-1-one derivatives **35a,b** that compound **35b (Y=O)** is more cytotoxic than compound **35a** (Y = NH), this is attributed to the presence of the oxygen atom as a substituent (scheme 14).[37]



Scheme 14. Synthesis of compounds **35a,b**

On the other hand, the reaction of diethylacetylenedicarboxylate (DEAD) **36** with dimedone **1** in the presence of isoquinoline **39** in dichloromethane afforded chromene-4-carboxylate **38** in 95% yield (Scheme 15).[38]



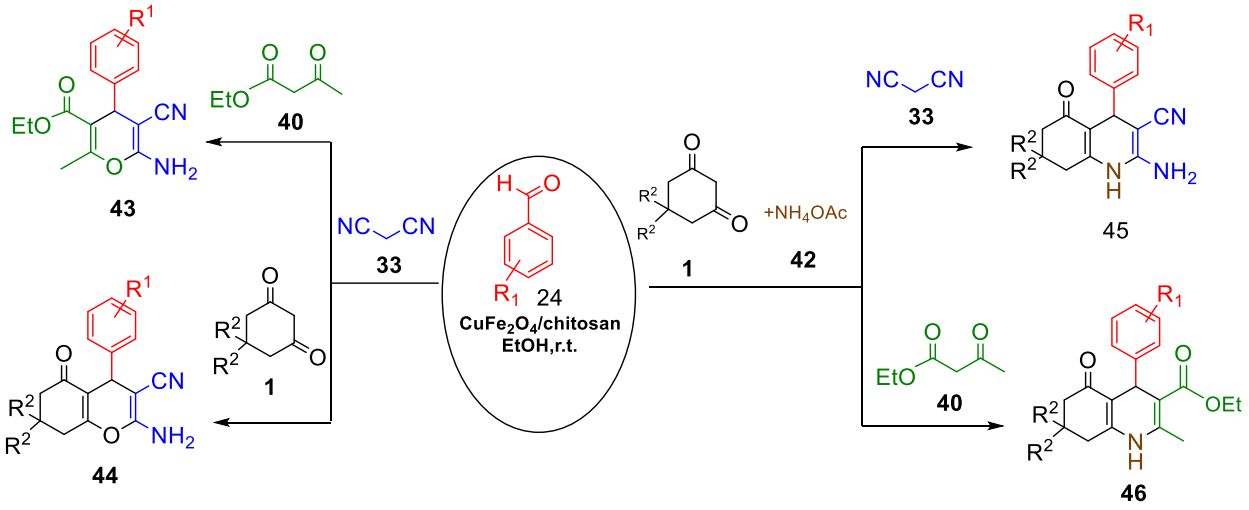
36,38	R	R'
a	Et	Me
b	Me	Me
c	Me	H
d	Et	H

Scheme 15. Reaction between acetylenedicarboxylates and dimedone or 1,3-cyclohexandione in the presence of isoquinoline **39**.

Biologically active heterocyclic compounds

Researchers are actively studying heterocyclic compounds today to improve a green and efficient synthesis method for the synthesis of some nitrogen- and oxygen-containing heterocycles using a magnetic nanocomposite, $CuFe_2O_4$/chitosan, as a recyclable and environmentally friendly catalyst.

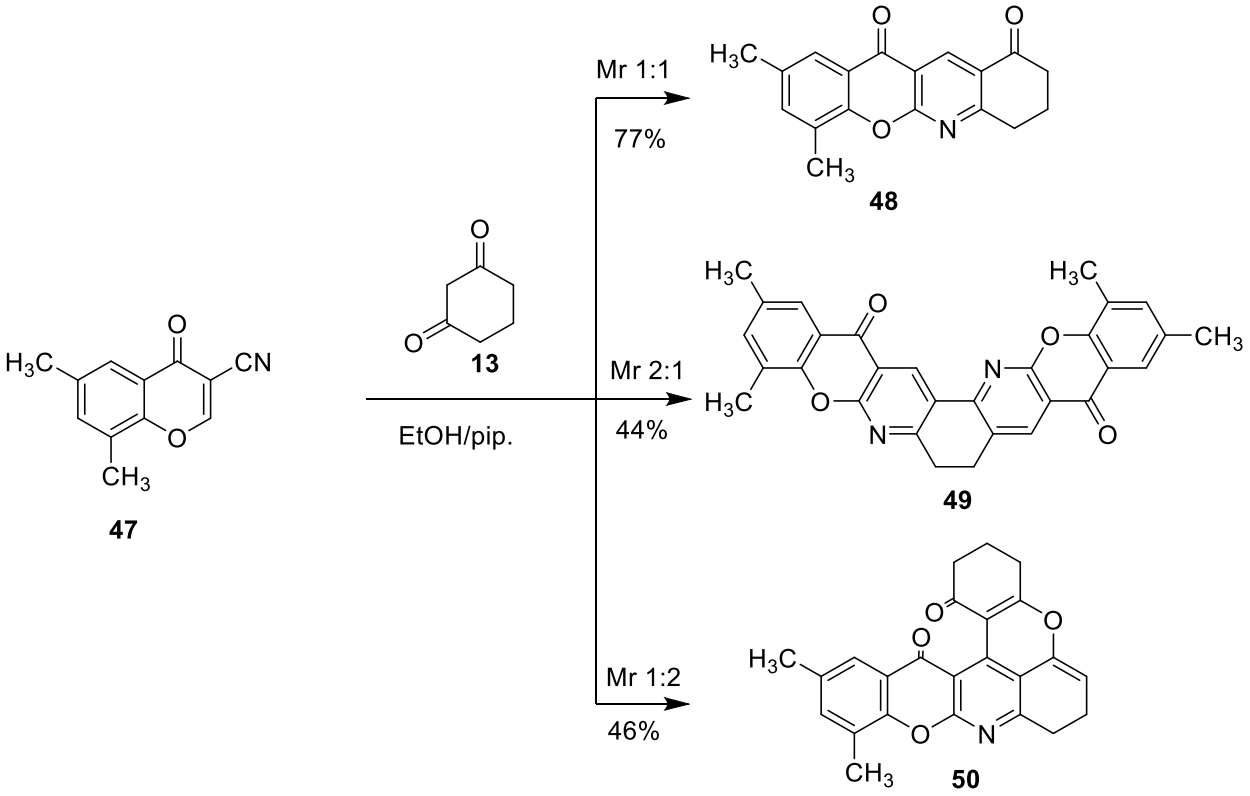
The authors claimed that this is the first time that $CuFe_2O_4$ combined with chitosan has been used as a catalyst in the synthesis of these heterocyclic classes. Two forms of polyhydroquinolines were examined: 2-amino-4*H*-chromens and 2-amino-4*H*-pyrans, four distinct N- and O-heterocycles. High to exceptional yields were obtained for the synthesis of 2-amino-4*H*-pyrans **43** by a one-pot, three-component reaction involving an aldehyde **24**, malononitrile **33**, and ethylacetoacetate **40**. Mild reaction conditions were used during the reaction with the efficient and reusable catalyst $CuFe_2O_4$/chitosan present.



Scheme 16. Synthesis of 2-amino-4*H*-pyrans, 2-amino-4*H*-chromens and polyhydroquinolines.

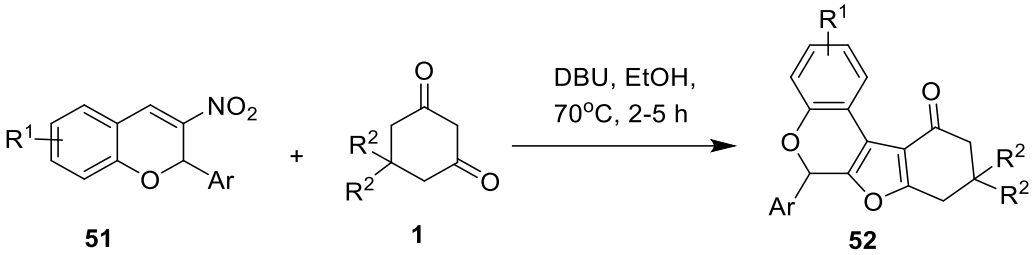
Under moderate conditions, another one-pot, the three-component reaction was performed utilizing $CuFe_2O_4$/chitosan in ethanol to produce 2-amino-4*H*-chromen derivatives **44**. The reaction involved three components: an aldehyde **24**, malononitrile **33**, and dimedone **1**. $CuFe_2O_4$/chitosan is used as the catalyst in ethanol at room temperature to carry out asymmetric Hantzsch condensation of an aldehyde **24**, malononitrile **33** or ethylacetoacetate **40**, cyclohexane-1,3-dione or dimedone **1**, and ammonium acetate **42** to obtain a range of polyhydroquinoline derivatives **45,46** (Scheme 16) .[39]

Furthermore, the interaction between carbonitrile **47** and 1,3-cyclohexanedione **13** was investigated at various molar ratios. (Mr. 1:1) of 1,3-cycloheaxnedione and carbonitrile **47** condensed to produce derivative **48** of chromenoquinoline. Derivative **49** of chromenophenanthroline was obtained by repeating the preceding process with a 2:1 molar ratio (carbonitrile: 1,3-cyclohexanedione) (Scheme 17). It's interesting to note that the unique angular heterocyclic system **50** was produced by the reaction of carbonitrile **47** with 1,3-cyclohexanedione in boiling ethanol containing piperidine at a 1:2 molar ratio (carbonitrile: 1,3-cyclohexanedione) (Scheme 17).[40]



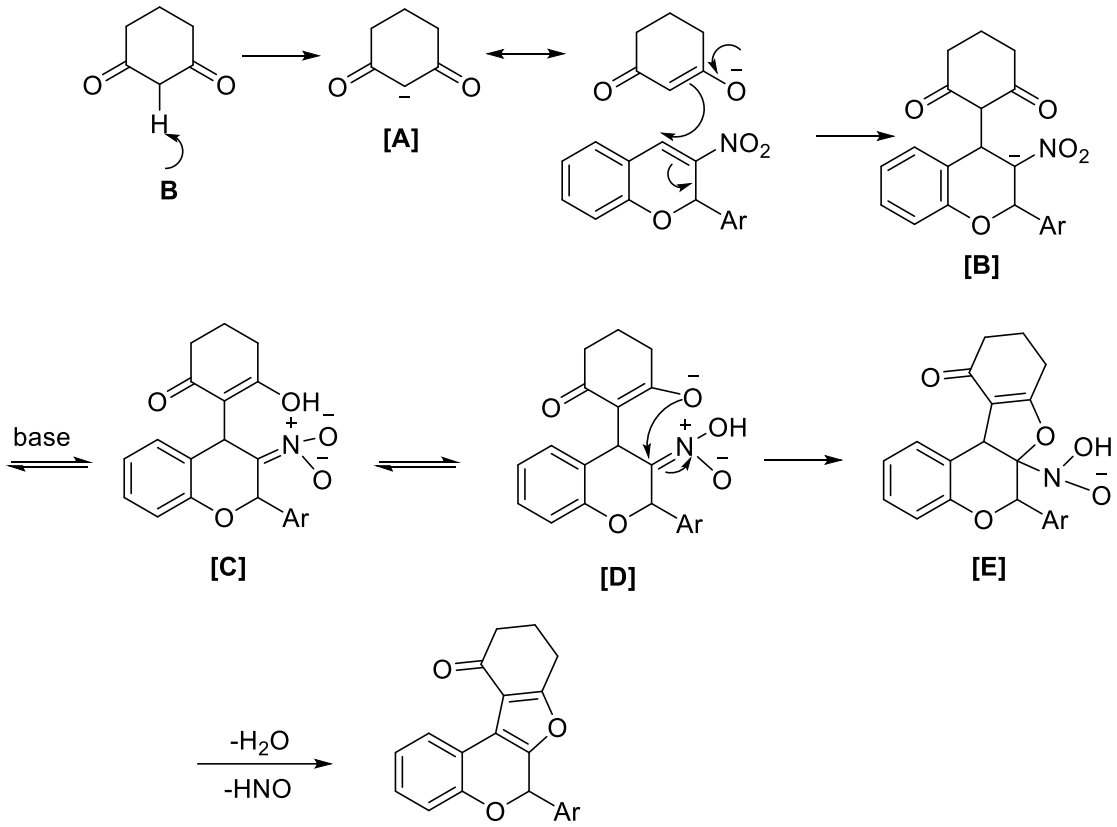
Scheme 17. Condensation of carbonitrile 1 with 1,3-cyclohexanedione.

The required chromenone (**52**) was formed via the reaction of chromene (**51**) and 1,3-cyclohexanedione derivative **1** as substrates in dry EtOH for 4 hours at 70 °C with DBU as a base (scheme 18).[41]



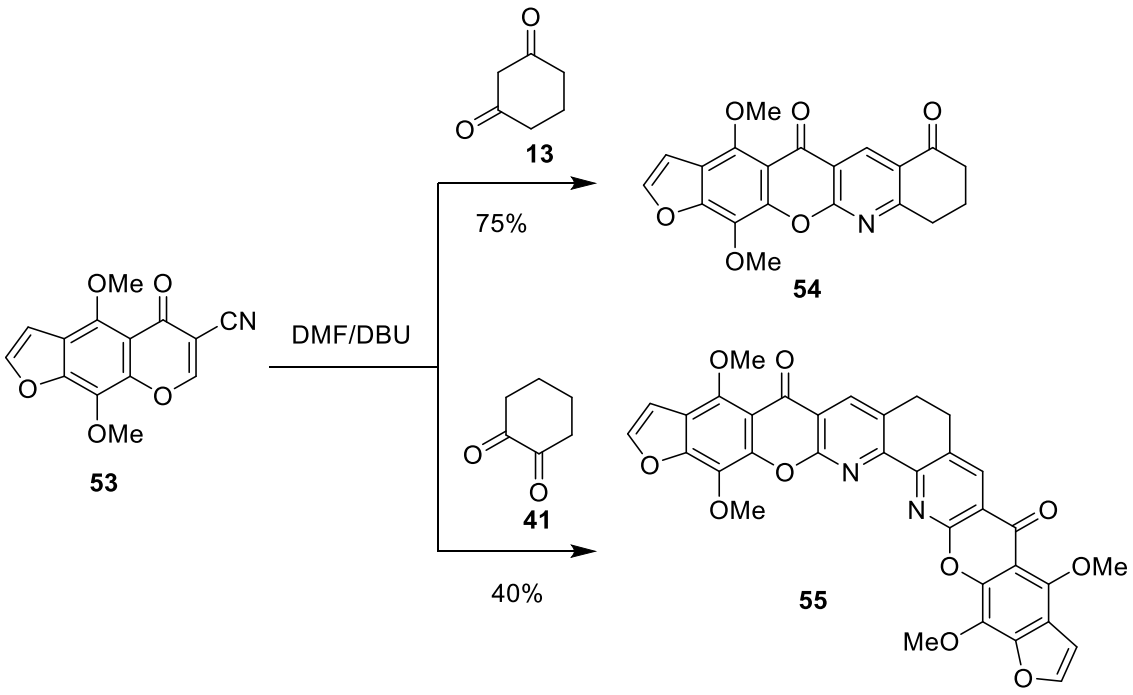
Scheme 18. Synthesis of 11H-benzofuro[2,3-*c*]chromenone derivatives **52**

The suggested mechanism DBU is first used as a base to react with an active methylene of 1,3-cyclohenanedione to produce an intermediate carbanion [A]. The Michael Adduct [B] was then produced by increasing the addition of enol [A] to the nitro-chromene with DBU. The intermediate [B] then undergoes keto-enol tautomerism to provide an intermediate enol [C], and additional proton shifting results in the formation of an intermediate enol anion [D]. The enol anion [D] undergoes sequential intramolecular cyclization to provide the intermediate benzofuro[2,3-*c*]chromenone [E]. After that, the final product is formed by removing water and HNO (scheme 19).[41,42]



Scheme 19. Tentative reaction mechanism

When boiling DMF containing diazabicycloundecene (DBU), the behavior of carbonitrile compound **53** was examined toward 1,3-cyclohexanedione **13**, yielding chromenoquinoline (**54**). Similarly, in the previous conditions, 1,2-cyclohexanedione **41** and carbonitrile **53** interacted in a 1:2 molar ratio to yield chromenophenanthroline (**55**) (Scheme 20).

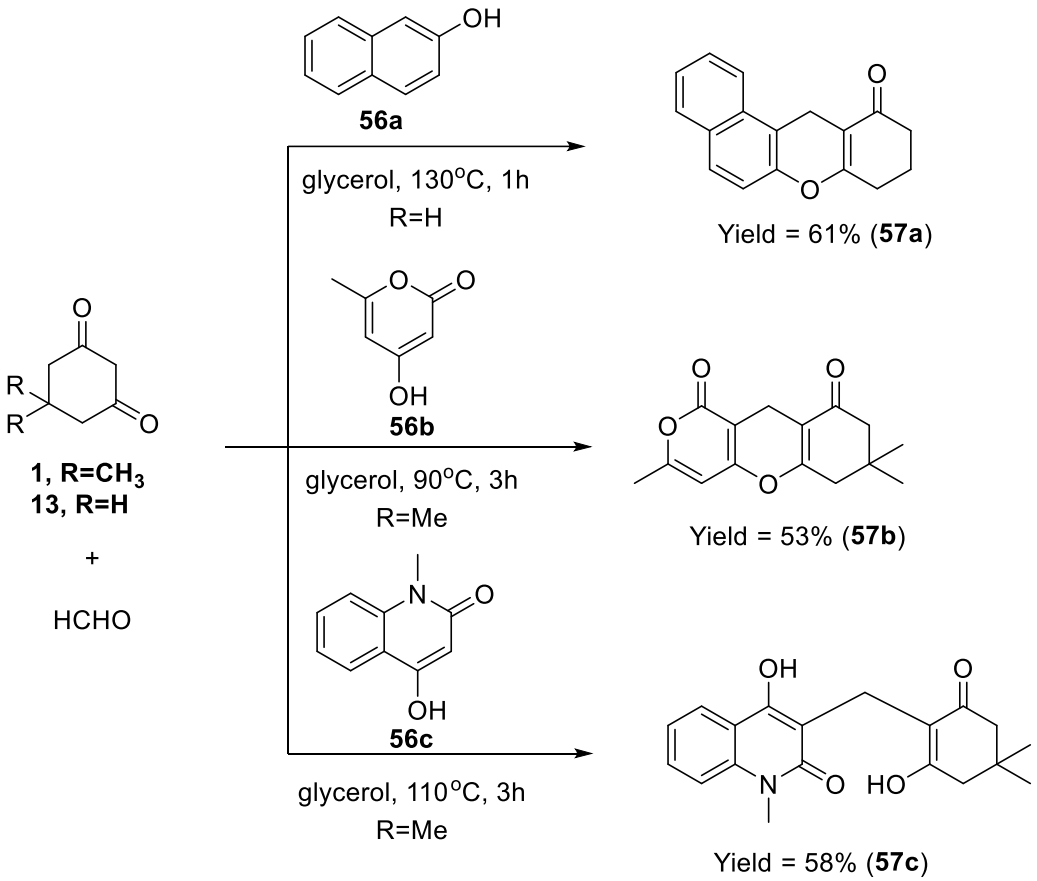


Scheme 20. Reaction of carbonitrile 1 with 1,3-cyclohexanedione and 1,2-cyclohexanedione

Compound **55** had significant antimicrobial activity against the investigated bacteria. This could be explained by the presence of benzofuran with various functional groups and annulated *bis*-(furochromeno)[1,10]phenanthroline. Compound **54** exhibited a significant level of activity towards Candida albicans, the yeast.[43]

Therefore, establish many new MCRs that offer an efficient and straightforward route to some valuable skeletons. In all cases, these MCRs involve a methylenation step of electron-rich carbons with formaldehyde, which generate active intermediates that are then trapped by the next nucleophiles.

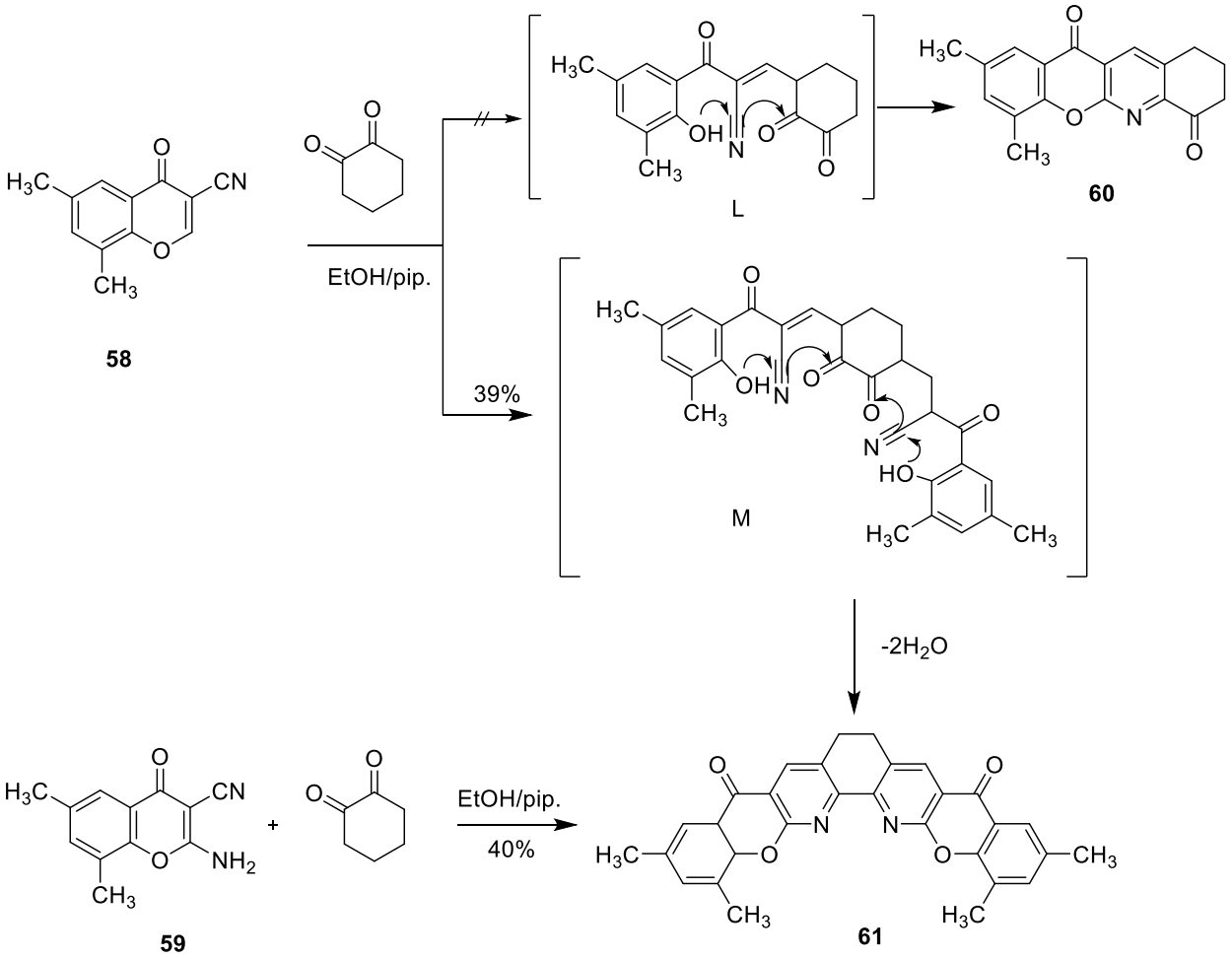
As shown in (Scheme 21), 2-naphthol **56a**, 4-hydroxy-6-methyl-2-pyrone (**56b**), and 4-hydroxy-1-methyl-2-quinolone (**56c**) were found to be able to react with formaldehyde and **1** or **13** in glycerol, affording three complex skeletons (**57a**, **57b**, and **57c**) in moderate to good yields.[44,45]



Scheme 21. Other three-component reactions of 1,3-cyclohexanediones and formaldehyde in glycerol.

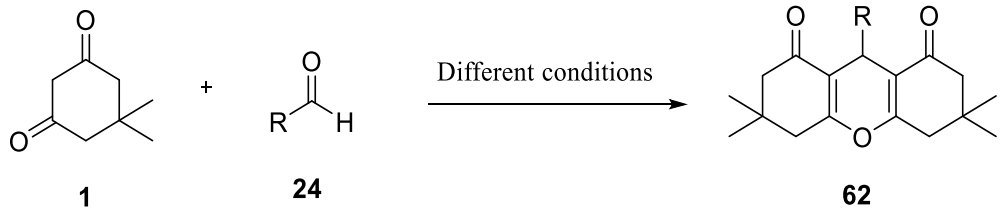
In boiling ethanol containing piperidine, carbonitrile **58** treated with 1,2-cyclohexanedione produced bis[1]chromeno[1,10]phenanthroline derivative **61**. Scheme 22 shows that the chromoquinoline derivative **60** (via intermediate L) was not included in this reaction.

The ring opening of two molecules of carbonitrile **58** with one molecule of 1,2-cyclohexanedione providing intermediate **M** may result in the formation of chromenophenanthroline **61**. Subsequent cycloaddition and cyclodehydration processes yield a heptacyclic fused system **61**. Similar reaction conditions were used to create the same product by reacting component **59** with 1,2-cyclohexanedione (Scheme 22).[46]



Scheme 22. Condensation of carbonitrile **58** and compound **59** with cyclohexane-1,2-dione.

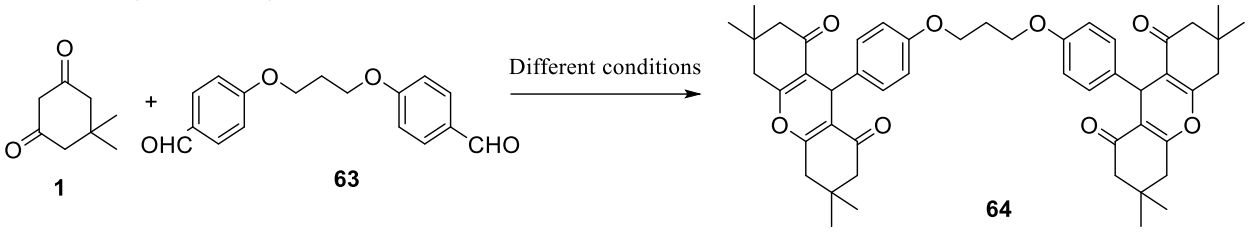
Several approaches have already been reported for synthesizing xanthenedione, and condensation between aldehydes and *β*-cyclic 1,3-dicarbonyl systems is one of the simplest methods to access symmetrical ones. There are various catalysts that have been utilized in this method for preparing these xanthenes, both homogeneous [47-49] and reusable heterogeneous nanocatalysts were also described. [50–51] The reactions are done both in solvents but also in solvent-free conditions.[58, 52–53] They have also been performed under conventional heating, microwave assistance [54–55], or ultrasound irradiation (Scheme 23). [56–61]



R= Aromatic and heteroaromatic moieties

Scheme 23. Reported methods for the synthesis of symmetric xanthenes.

The synthesis of xanthene derivative **64** was achieved by the reaction between four equivalents of dimemdone **1** and one equivalent of dibenzaldehyde derivative **63** as a model reaction under various conditions (Scheme 24). [64]

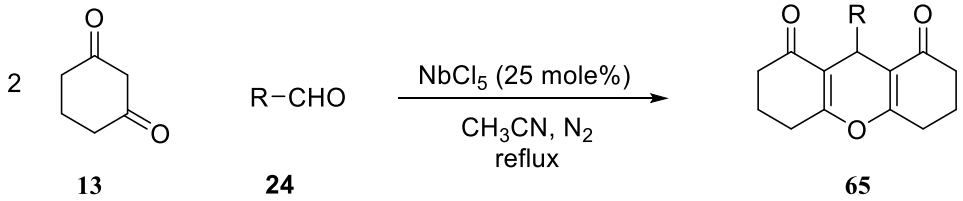


Scheme 24. Synthesis of bis(hexahydro-1*H*-xanthene-1,8(2*H*)-dione) **64**.

The organic acid catalyst *p*-TSA, which is inexpensive and easily accessible and has good catalytic properties, particularly as a proton donor, was used in both the absence and the presence of the reaction.[62-64]

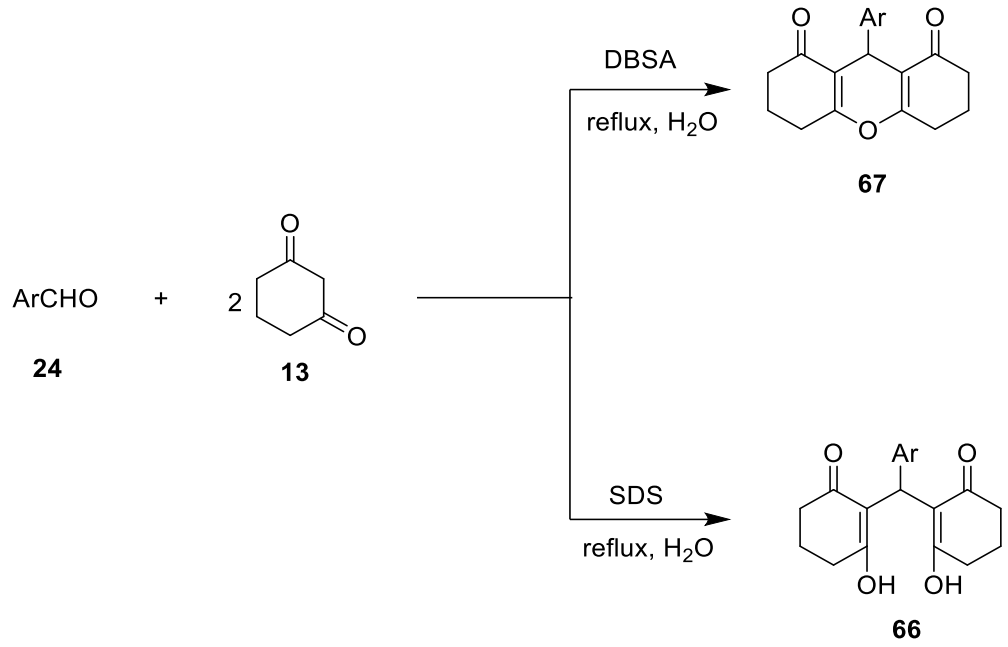
A new method for the preparation of xanthenedione derivatives **63** has been described, involving a one-pot reaction between aldehyde derivatives **24** and 1,3-cyclohexanedione **13** promoted by niobium pentachloride, as part of the ongoing investigation into the use of $NbCl_5$ as a promoter in organic reactions (Scheme 25)

Stronger Lewis acid niobium pentachloride is recently gaining attention as a reagent in organic synthesis; it can be used as an efficient catalyst in many kinds of organic reactions. [65,66]



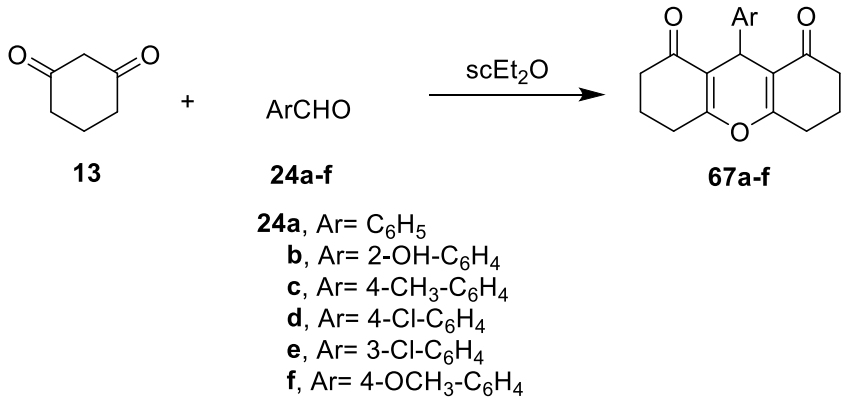
Scheme 25. Synthesis of xanthenedione derivatives.

In aqueous media, the corresponding hydroxanthene derivatives **67** and bis(3-hydroxy-2-cyclohexene-1-one) **66** were obtained in good yields via an ordinary general experimental procedure that involved heating a solution of an aromatic aldehyde **24** and cyclohexanedione **13** in water under reflux water in the presence of a catalytic amount of DBSA or SDS for the duration of time required to complete the reaction (Scheme 26).[67]



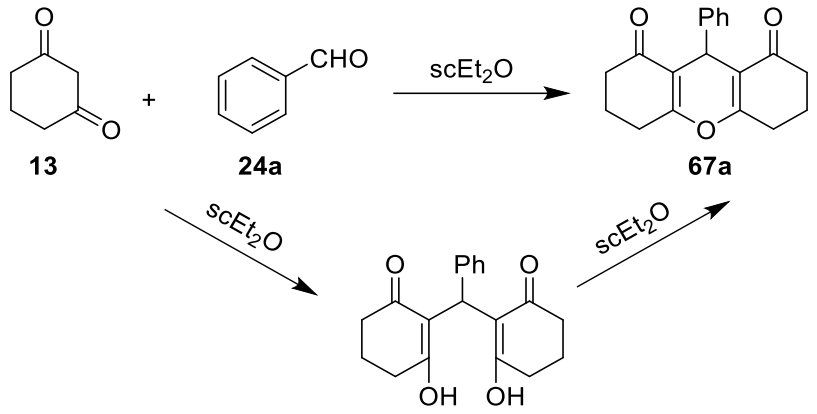
Scheme 26. Synthesis of 9-aryl-1,8-dioxooctahydroxanthene derivatives **67** and 2,2′-arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) **66** in water

Furthermore, 1,3-cyclohexadione (**13**) and arylaldehyde (**24**) successfully reacted in supercritical diethylether at 200 ºC for 60 min without needing a catalyst to produce the equivalent xanthenedione derivatives **67**. No byproducts were produced (Scheme 27). [68]



Scheme 27. Reaction of aldehydes with 1,3-cyclohexanedione in the presence of super-critical diethylether.

The reaction time between benzaldehyde **24a** and 1,3-cyclohexadione **13** in the presence of diethylether at 200 °C for 60 min was identified as the test reaction, and different reaction parameters were studied for the formation of corresponding xanthenedione **67a**. During this experiment, there is no observation of the open chain intermediate 2,2-(phenylmethylene)bis(3-hydroxycyclohex-2-en-1-one) by GC-MS (Scheme 28). [68]

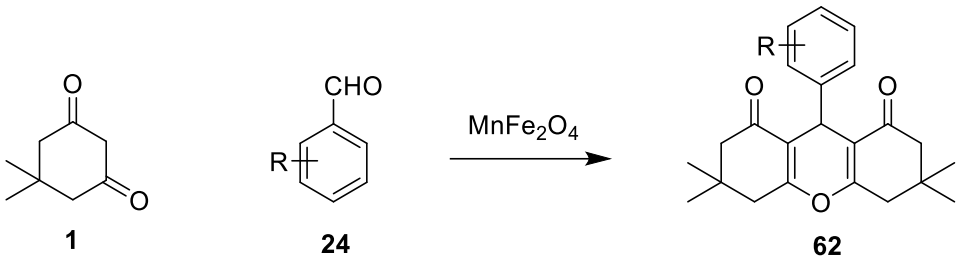


2'-2-(phenylmethylene)bis(3-hydroxycyclohex-2-en-1-one)

Scheme 28. Condensation and cyclisation reaction of 1,3-cyclohexadione **13** and benz-aldehyde **24a** in $scEt_2O$.

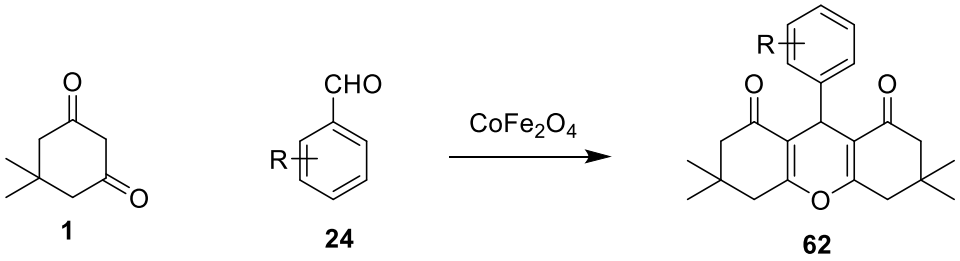
By utilizing dimedone and several aromatic aldehydes in the presence of nanosized manganese ferrite ($MnFe_2O_4$) at 110 °C in solvent-free conditions, dioxooctahydroxanthene derivatives were synthesized (Scheme 29).

The proposed mechanism is that $MnFe_2O_4$ first activates the carbonyl group of aldehydes, which then makes it easier for dimedone's enol form to be attacked by nucleophiles and produces the appropriate carbocation. Following this carbocation's reaction with the activated dimedone, an intermediate is produced. This intermediate is subsequently dehydrated to produce the finished product.[69]



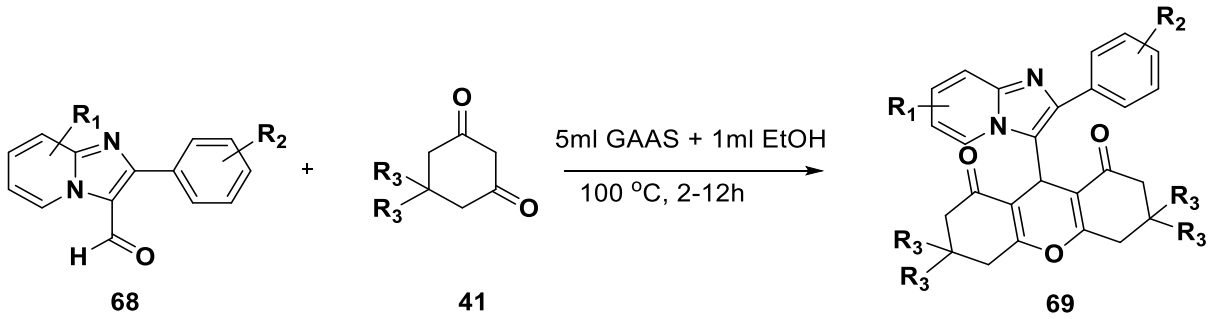
Scheme 29. Synthesis of 1,8-dioxooctahydroxanthene

The condensation of aldehydes with 4-hydroxycoumarin by using $CoFe_2O_4$ in water/ethanol (1:1) as a solvent with reflux produced the appropriate bis-(4-hydroxycoumarin) and different aldehydes. The Knoevenagel condensation of aromatic aldehydes with 4-hydroxycoumarin in the presence of $CoFe_2O_4$, which is then followed by Michele addition of the second 4-hydroxycoumarin, is the suggested mechanism for the synthesis of the xanthenedione derivates (Scheme 30). [69]



Scheme 30. Synthesis of 1,8-dioxooctahydroxanthenes in the presence of cobalt ferrite ($CoFe_2O_4$)

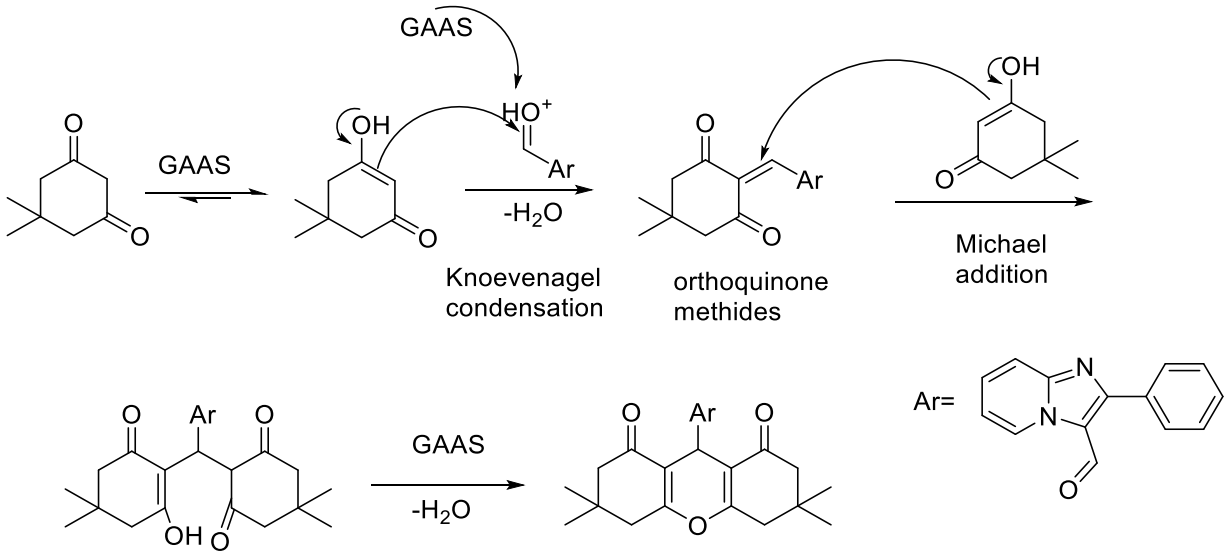
Imidazopyridine derivates **69** were achieved via the reaction of various substituted 2-phenylimidazo[1,2-*a*]pyridine-3-carbaldehyde **68** with various 1,3-cyclohexandione derivatives **41**. The gluconic acid aqueous solution acts as a catalyst and solvent, which has been developed via domino reactions (Scheme31).



68 41 69

Scheme 31. Synthesis of novel fused imidazopyridine bearing xanthenedione.

The mechanism of reaction involves Knoevenagel condensation, followed by Michael addition, along with cyclization and tautomerization steps (Scheme 32).[70]



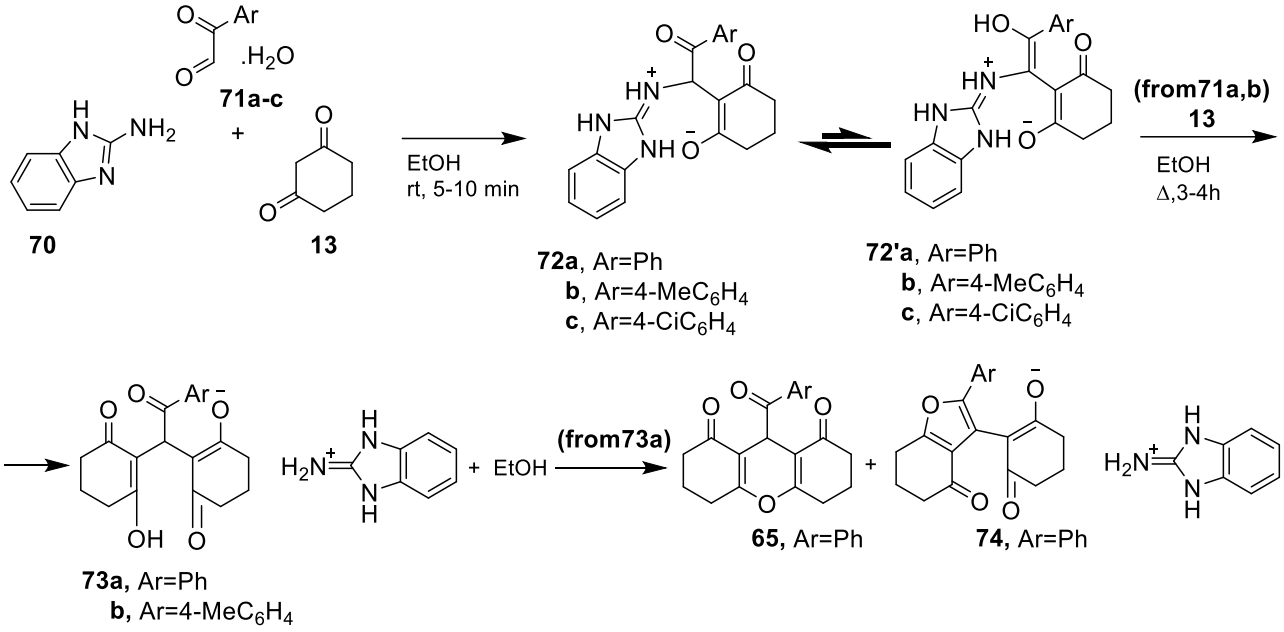
Scheme 32. Proposed reaction mechanism of imidazopyridine fused xanthenedione synthesis.

Experiment with various reaction parameters for the condensation of three-components aminobenzimidazole, cyclohexanedione, and arylglyoxal hydrates to determine the optimal conditions for regioselective isomeric compound formation. Aminobenzimidazole **70**, arylglyoxals **71a-c**, and 1,3-cyclohexanedione (**13**) were mixed together in equal amounts and briefly stirred in ethanol. The result was the formation of compounds **71a-c** as hardly soluble precipitates, with high yields (Scheme 33). [71]

No new compounds formed in the reaction mixture as a result of the extended refluxing of adducts **72a–c** in alcohols. subsequently, more than one equivalent of 1,3-diketone **13** was added to the reaction mixture, and a gradual dissolving of precipitates **72a–c** was detected.

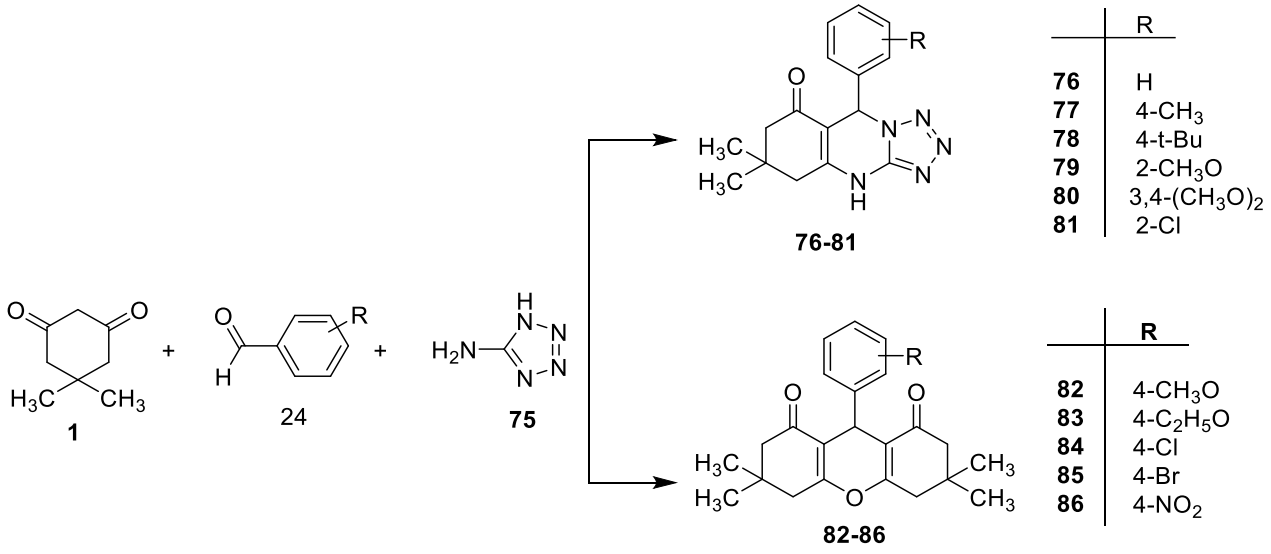
After such reaction mixtures were refluxed for a long time, salts **73a** and **b** were produced. Compounds **73a,b** were not successfully converted into condensation products with 2-aminobenzimidazole **70** by fusion without a solvent or by refluxing in acetic acid or DMF. In all cases,

xanthenedione **65** and salt **74** mixtures were produced (Scheme 33). Compound **65** is the more soluble of the two compounds, which were isolated from ethanol by recrystallization.



Scheme 33. condensation of three-components aminobenzimidazole, cyclohexanedione, and arylglyoxal hydrates

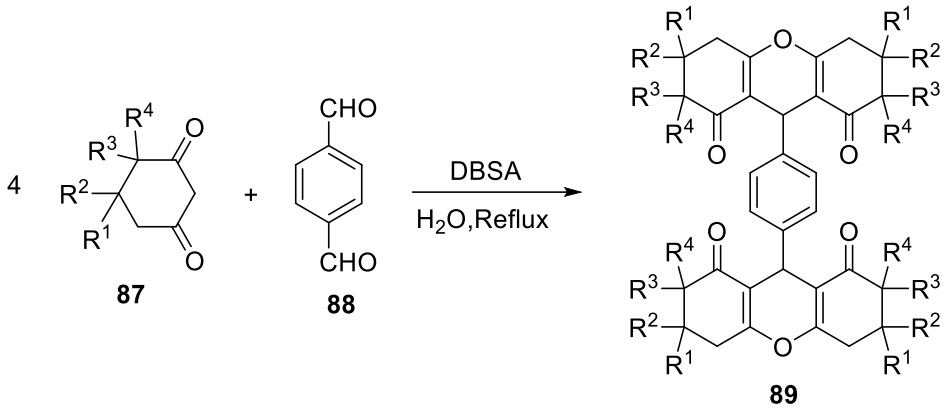
After that the reaction of dimedone **1** with a mixture of aminotetrazole compound **75** and substituted aromatic aldehyde **24** taken in an equimolar ratio without solvent and catalyst at a temperature of 160–170°C for 5–10 min afforded tetrazoloquinazolinones derivatives **76-81** or xanthen-diones derivative **82-86** (Scheme 34).[72]



Scheme 34. for synthesis tetrazoloquinazolinones derivatives **75-81** or xanthen-diones derivative **82-86**

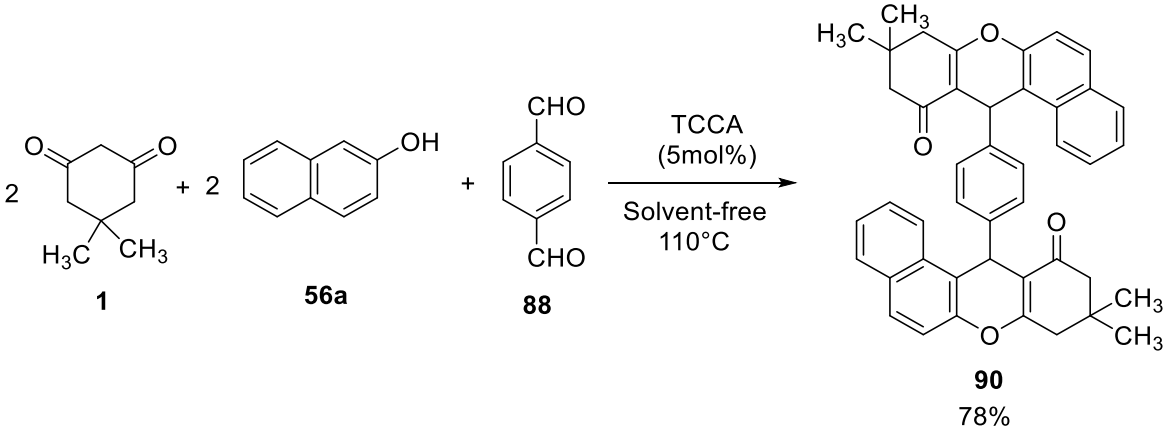
One-pot processes have been employed for the synthesis of bisoctahydroxanthene **89**. Octahydroxanthene-1,8-dione **89** is typically obtained by the condensation of dimedone derivative **87** with aldehydes **88** in the presence of *p*-dodecylbenzene sulfonic acid (DBSA), which is utilized as a Lewis acid catalyst (Scheme 35).

Synthesized compounds showed antimicrobial activity against S. aureus,B. cereus, C. albicans, and R. rubra, except P. aeroginosa and P. vulgaris. The present study provides new data on the relationships between xanthenes and their antimicrobial activities. [73]



Scheme 35. Synthesis of bisoctahydroxanthene derivatives **89**

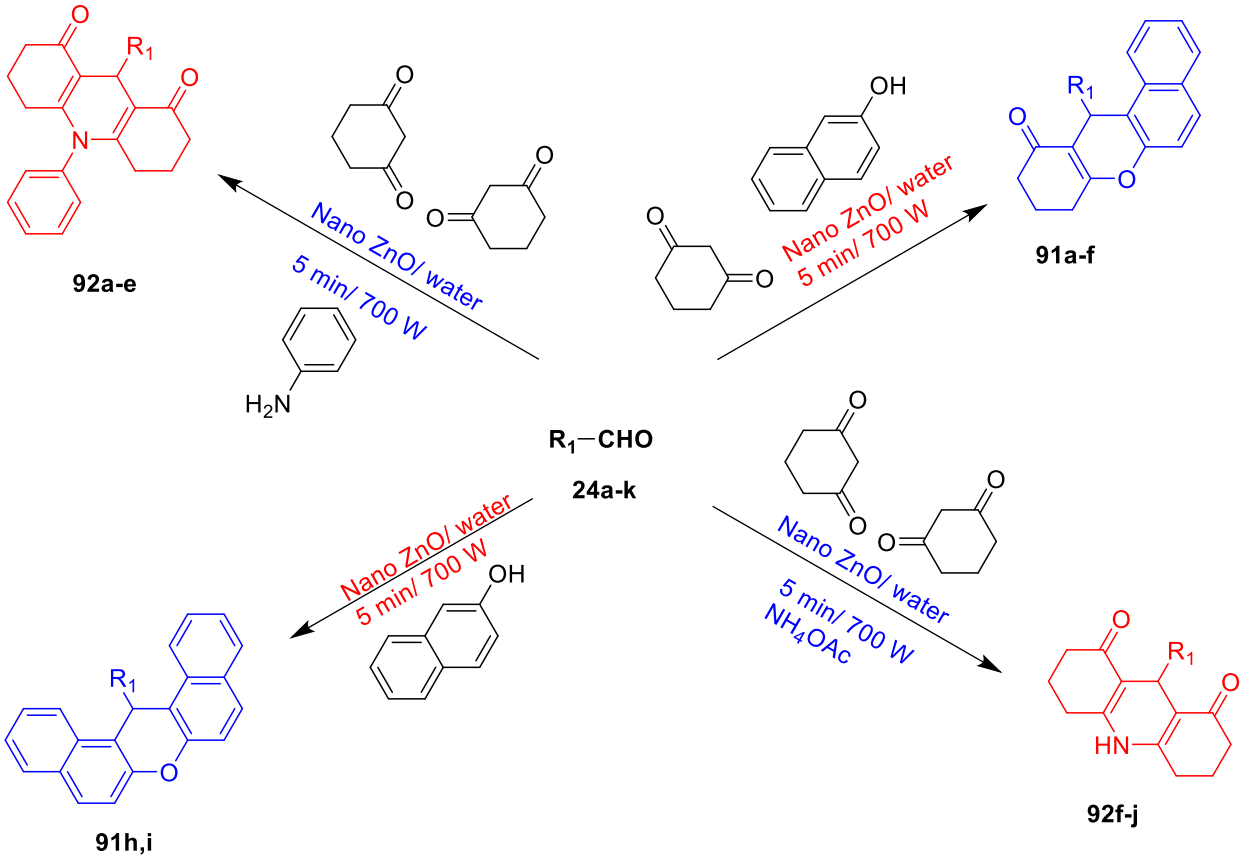
Ultimately, a one-pot effective synthetic technique was employed to synthesize a derivative of bis-12-aryl-tetrahydrobenzo[*a*]xanthene-11-ones **90** in a 2:1:1 molar ratio of β-naphthol **56a**, dimedone **1**, and terephthaldehyde **88**, utilizing 10 mol% of TCCA to produce compound **90** (Scheme 36). As anticipated, the reaction proceeded smoothly for 40 min at 110°C, yielding a 78% product in a solvent-free environment. [74]



Scheme 36. Reaction between terephthaldehyde with 5,5-dimethyl-1,3-cyclohexanedione and *β*-napthol in the presence of TCCA.

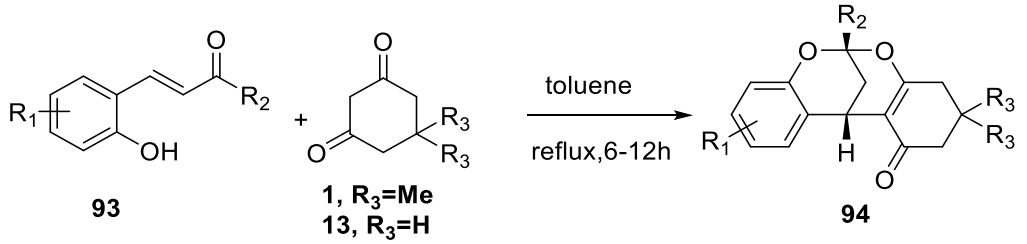
Next, the study demonstrates a one-pot synthesis of xanthenes and acridine derivatives using a nanocrystalline ZnO as a catalyst by MWI in a water medium. Xanthenone **91a** was prepared by microwave-irradiating a solution containing a mixture of Prydine-2-carboxaldehyde, cyclohexane-1,3-dione, and 2-napthol **56a** using ZnO Nps as catalyst at 700 watts. Similar steps were repeated for **91b-i**; however, the cyclohexane-1,3-dione was not used for the xanthenes, **91h**, or **91i** synthesis.

In the same way, the procedure of preparing acridinones **92** involves combining cyclohexane-1,3-dione, anilines, and ZnO Nps catalyst with water, which is then microwave-irradiated at 700 watts to produce **92a**. For xanthenes, **92g-l** formations, ammonium acetate **42** was used instead of anilines (Scheme 37). [75]



Scheme 37. General scheme for the synthesis of 2-substituted xanthenediones and acridindiones

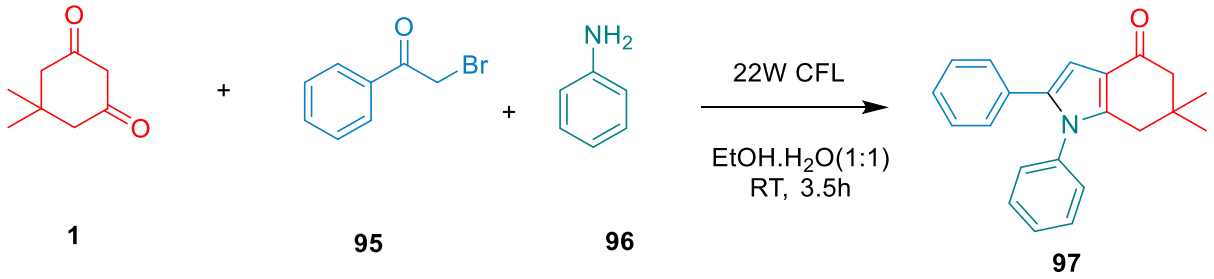
Finally, cyclohexanedione dervitive **1**, **13** was employed to react with 3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one **93** derivatives under standard reaction conditions, giving the corresponding products **94** in good yields (70−87%) as shown in (Scheme 38). [76]



Scheme 38. Synthesis of 1,3-Cyclohexanedione-Fused 2,8-Dioxabicyclo[3.3.1]nonanesa,b

3.2. Synthesis of Tetrahydroindoles, Tetrahydroindazolones, Pyrazole-Dimedone, Pyridine, Imidazoquinolines, Acridineone, Triazine, and Tetrazine Derivatives

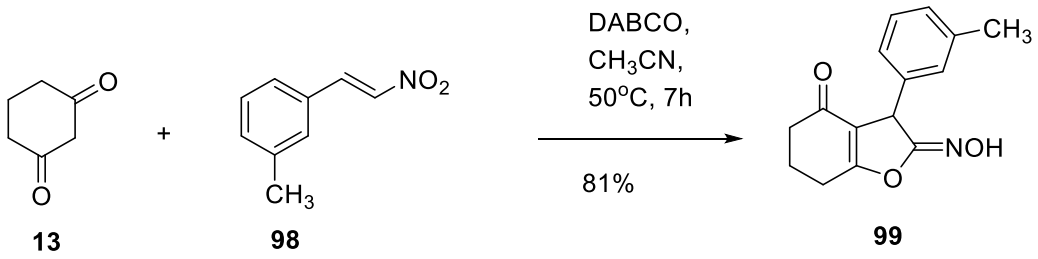
To synthesize compound **97**, the reaction of dimedone **1**, phenacyl bromide **95**, and aniline **96** was employed as a model system. The product was obtained after 3.5 hours of exposure to radiation using a 22 W CFL lamp in a 1:1 ethanol–water solution at room temperature (Scheme 39).[77]



Scheme 39. Synthesis of 4-oxo-tetrahydroindoles in ethanol–water

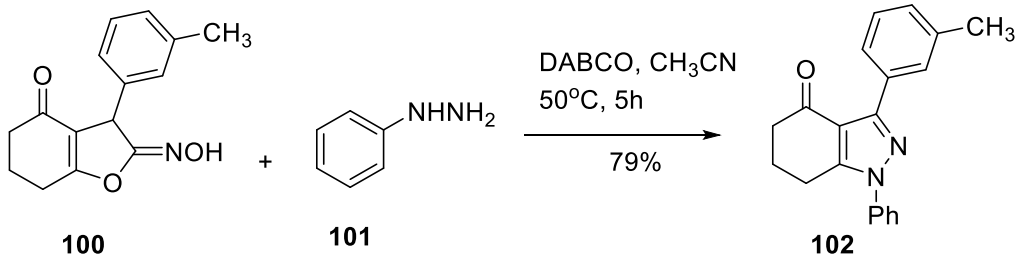
A simple three-component reaction involving *β*-nitrostyrenes, *β*-dicarbonyl compounds, and amines has been developed for the synthesis of *β*-enaminones [78]. According to the proposed mechanism, the *β*-dicarbonyl compound undergoes a Michael addition to the *β*-nitrostyrene to generate a furan oxime intermediate, which is subsequently attacked by a nucleophilic amine in a regioselective manner to afford the corresponding *β*-enaminones.

The author concluded that the most likely pathway involves a sequential Michael addition, intramolecular cyclization, and ring-opening reaction. Initially, intermediate **99** was formed via the reaction of 1,3-cyclohexanedione **13** with *β*-nitro-3-methylstyrene **98** under the optimized reaction conditions (Scheme 40).[78]



Scheme 40. Reaction of 1,3-cyclohexanedione **13** and *β*-nitro-3-methylstyrene (**99**)

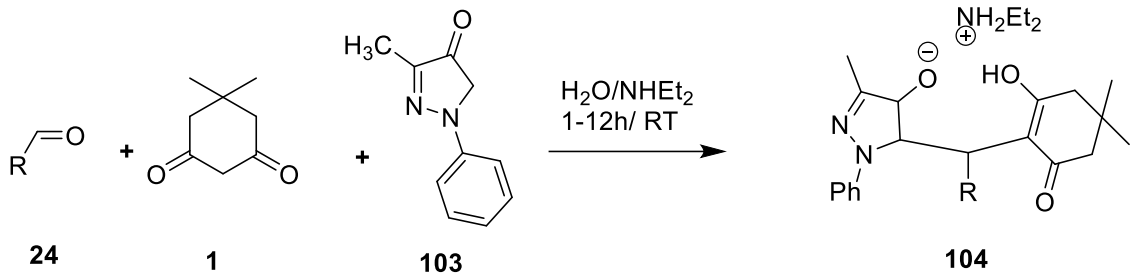
Next, the intermediate 2-(hydroxyimino)furanone **100** reacted favorably with phenylhydrazine **101b** under the same reaction conditions to produce the corresponding product **102** (Scheme 41).
One of these compounds, tetrahydroindazolone, has been shown low nanomolar antiproliferative activity against various cancer cell lines and to be a strong inhibitor of heat shock protein 90 (HSP90). [79]



Scheme 41. Reaction of 2-(hydroxyimino)furanone **100** and phenylhydrazine **101b**.

The one-pot Knoevenagel condensation Michael addition of different aldehydes **24**, dicarbonyl compound (dimedone) **1**, and phenyl-pyrazol-5-one derivative **103** mediated by aqueous $NHEt_2$ were used to generate the pyrazole dimedone derivatives **104** as described in (Scheme 42). The

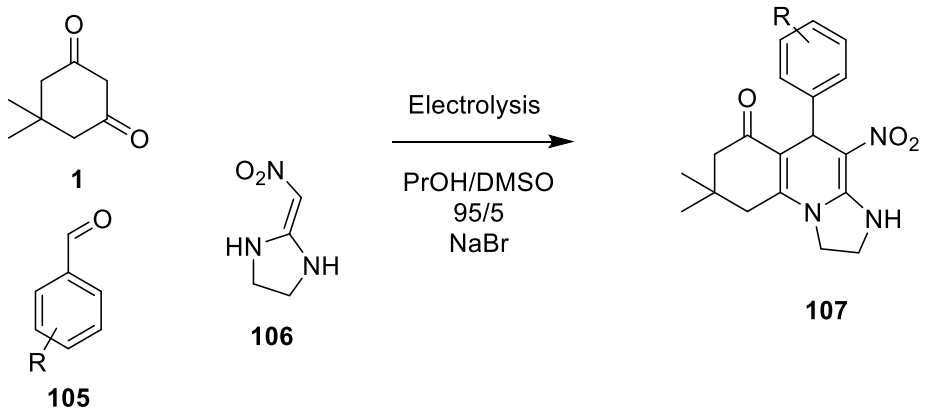
newly produced pyrazole-dimedone derivatives' antifungal efficacy was evaluated against the mold C. albicans (ATCC 2091).[80]



Scheme 42. Substrate scope of the cascade reaction: variation of pyrazole-dimedone adducts

A new environmentally friendly approach for the synthesis of Imidazoquinoline derivatives **107** has been developed, employing dimedone **1**, aldehydes **105**, and 2-(nitromethylene)imidazolidine **106** in an undivided cell with an alcoholic solvent, using NaBr as the electrolyte, as illustrated in (Scheme 43).

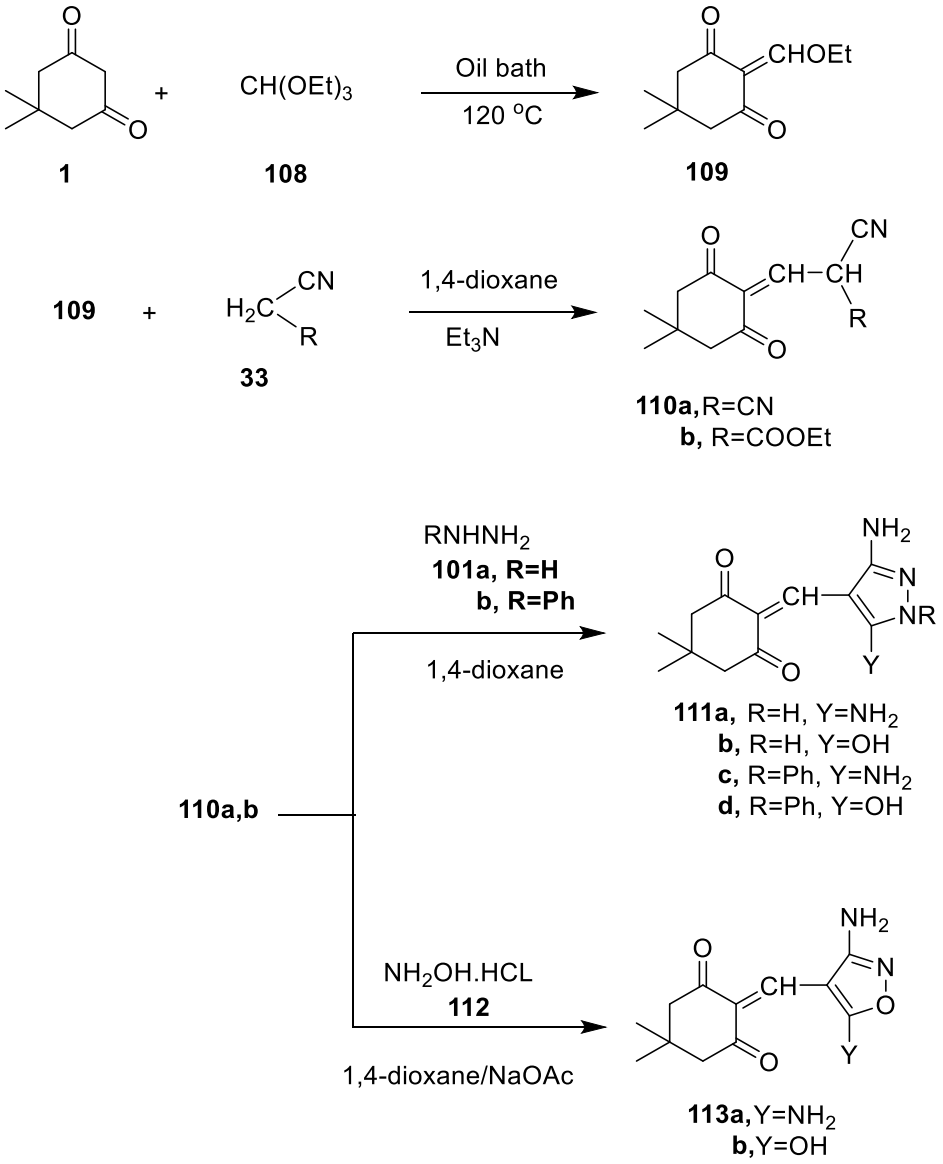
The research determined that the most effective conditions for minimizing synthesis time and achieving higher yield involved using a dry propanol/dimethylsulfoxide (95:5, PrOH/DMSO) mixture, a current density of 80 mA cm^{-2} (with I = 400 mA and an electrode surface of 5 cm^2), a magnesium anode, and operating at room temperature. [81]



Scheme 43. General schematic for the preparation of octahydroimidazo[1,2-*a*]quinolin-6-one derivatives

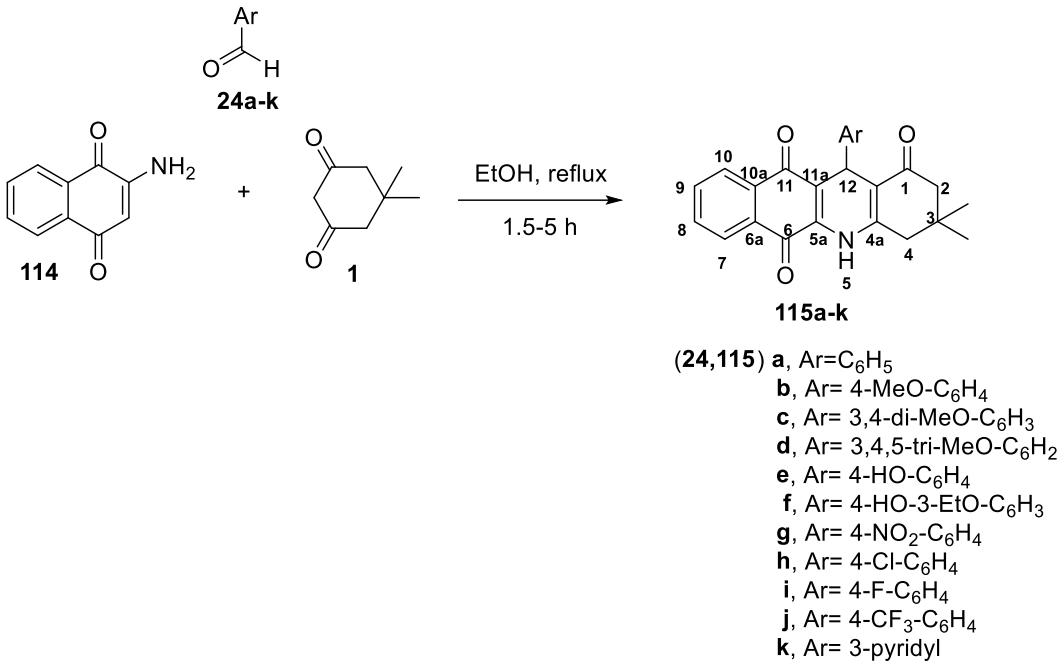
Heating the mixture of dimedone **1** and triethoxymethane **108** in an oil bath at 120 °C led to the formation of compound (**109**). Compound **109** reacted with ethyl cyanoacetate **33b** or malononitrile **33a** to yield alkylated products **111a** and **111b**, respectively. Compounds **111a** and **111b** have been utilized for synthesis of pyrazole derivatives by reacting with either phenylhydrazine **101b** or hydrazine hydrate **101a** to yield the corresponding pyrazole derivatives, **111a–d**. As an alternative, isoxazole derivatives **113a** and **113b** were produced by reacting components **110a** or **110b** with hydroxylamine hydrochloride **112** in 1,4-dioxane containing sodium acetate (Scheme 44).

The produced compounds exhibited strong cytotoxicities when screened against the six cancer cell lines.[82]

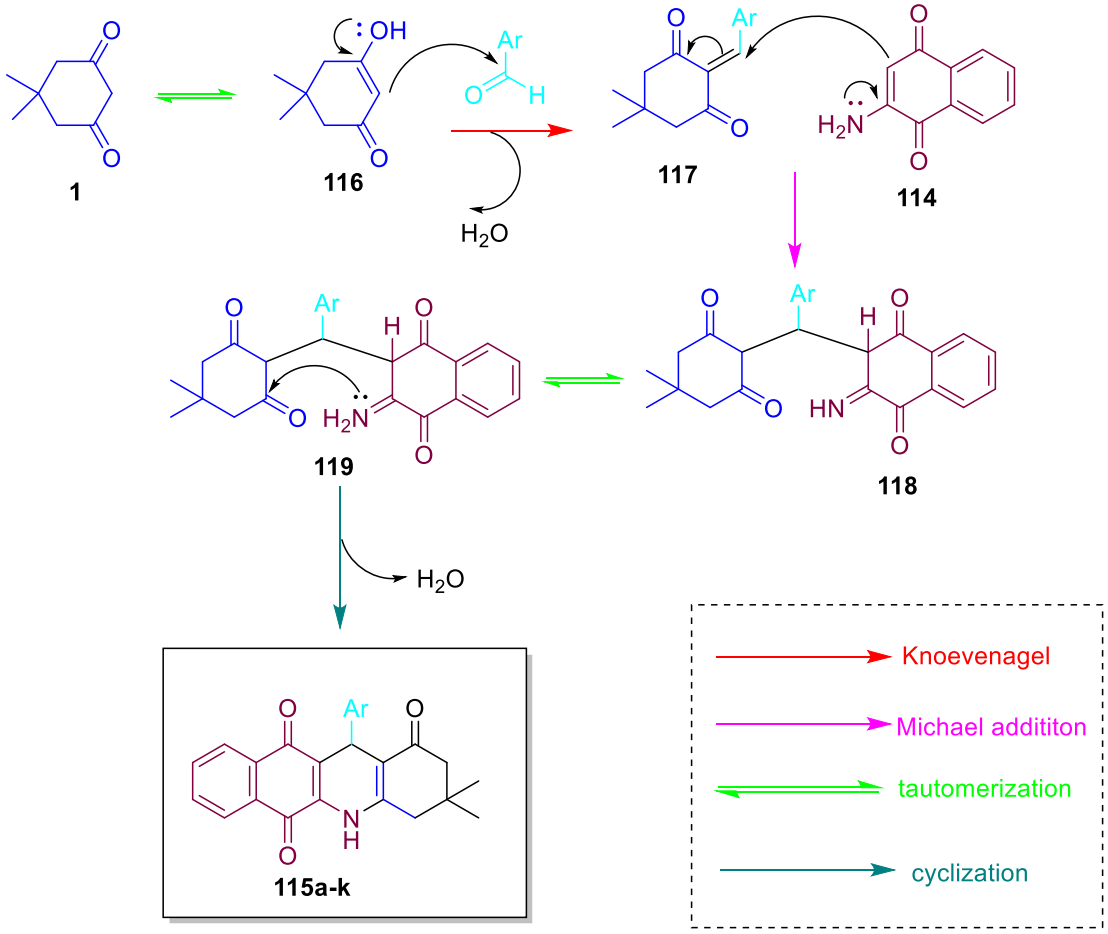


Scheme 44. Synthesis of compounds **110a, b**, **111a–d**, and **113a, b**

In (Scheme 45), the synthesis of a series of benzoacridinone derivatives **115a–k** was achieved via a one-pot, three-component reaction in ethanol (EtOH) as a green solvent under reflux conditions. The reaction involved an equimolar mixture of aromatic aldehydes **24a–k**, 2-amino-1,4-naphthoquinone **114**, and dimedone **1**.



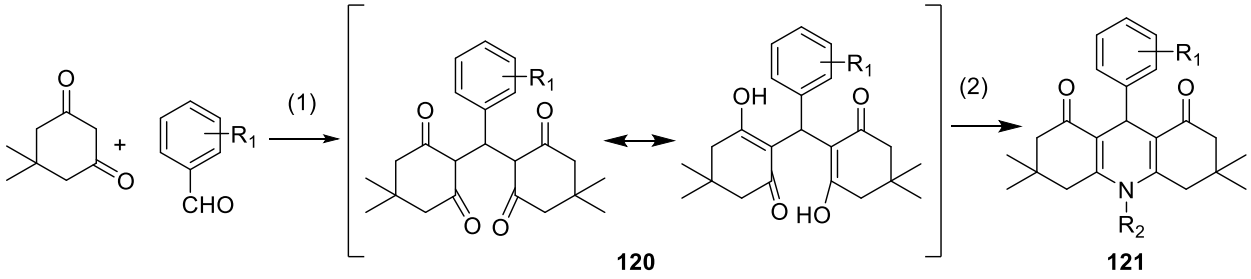
Scheme 45. Three-component synthesis of 12-substituted-3,3-dimethyl-3,4,5,12-tetrahydrobenzo[*b*]acridine-1,6,11(2*H*)-triones **115a–k**



Scheme 46. Possible mechanism for the synthesis of 12-substituted-3,3-dimethyl-tetrahydro-benzo[*b*]acridine-1,6,11(2*H*)-trione(**115a–k**)

A possible mechanism for the reaction is presented in (Scheme 46). Most likely, the reaction begins with the keto-enol tautomerization of dimedone **1**. The resulting enol **116** then reacts with the aldehydes **24** by the Knoevenagel condensation to produce the corresponding *α, β*-unsaturated dicarbonyl intermediates **119**. The intermediates **117** and 2-amino-1,4-naphthoquinone **114** undergo Michael addition, resulting in the Michael adducts **118**. After **118** tautomerizes to intermediate **119** containing a 1° amine group, intramolecular nucleophilic cyclization transforms **119** into the desired 1,4-naphthoquinone fused with 4-substituted 7,7-dimethyl-4,6,7,8-tetrahydroquinolin-5(1*H*)–one polyheterocyclic compounds **115a–k**.[83]

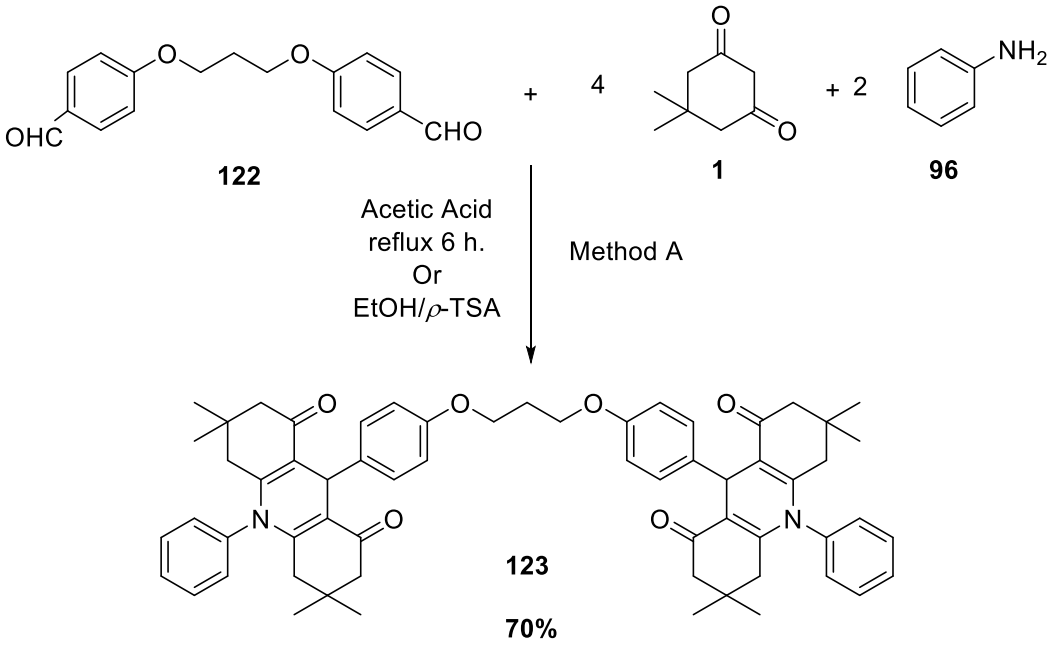
To syntheses a variety of derivatives **121** of arcidinediones by reacting component **120** with amines. Compound **121** was successfully synthesized by using dimedone and aldehydes using the Michael, Knoevenagel, and cyclization processes at room temperature with a very small quantity of L-proline acting as a catalyst this is shown in (Scheme 47). These substances had inhibitory effects on HepG2 cells. Furthermore, compared to the other compounds, compounds **122** had greater inhibitory action. It would be highly beneficial to the ongoing research on the biological functions of these chemicals. [84]



Scheme 47. synthesis of derivatives **121** of arcidinediones
(R1 = 2'-Cl; 4'-CH_3; R2 = -H; -C_6H_5; 4''-ClC_6H_5)
(1) methanol/ethanol mixture (1:1), L-proline, r.t., 1.5~4 h; (2) substituted ammonium, acetic acid, reflux, 24 h.

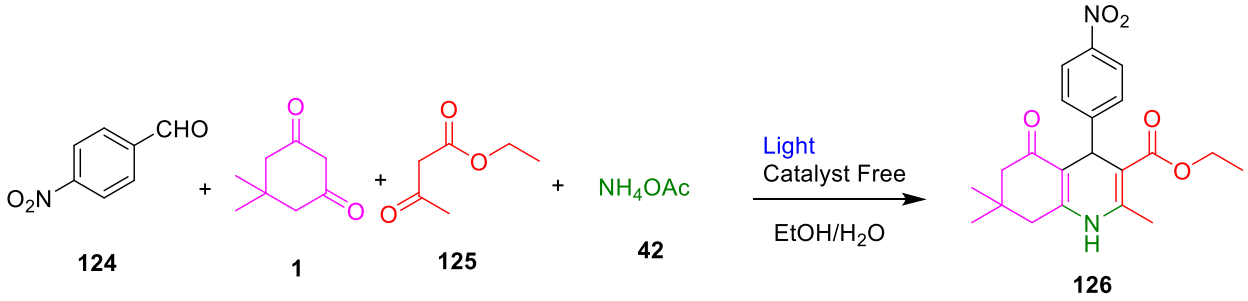
In order to produce the target Bis(heterocycles) **123** (Scheme 48), the multi-component reaction of dibenzaldehyde **122**, cyclohexanedione derivative **1**, and aniline **96** was investigated. The reaction was run both with and without *p*-TSA acting as an organic acid catalyst to determine the optimal experimental reaction conditions.

The best results were obtained when the reaction was carried out using acetic acid as both a catalyst and a solvent or when the reaction worked well in ethanol with 15% mol% of *p*-TSA present. It was discovered that a 5–7-hour reaction time produced a greater yield (Scheme 48). [85]



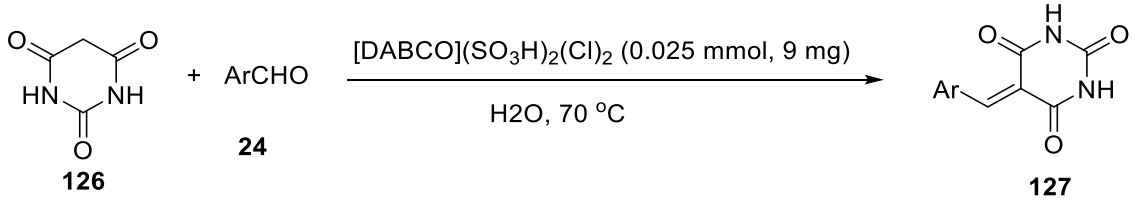
Scheme 48. Synthesis of bis(hexahydroacridine-1,8(2*H*,5*H*)-dione) **123**.

The reaction of 4-nitrobenzaldehyde **124**, dimedone **1**, ethyl acetoacetate **125** and ammonium acetate **42** in the presence of 18 W blue light in EtOH at 70 °C under air atmosphere, the intended product 1,4-dihydropyridine **126** was produced as shown as (Scheme 49).[86]



Scheme 49. synthesize 1,4-dihydropyridine

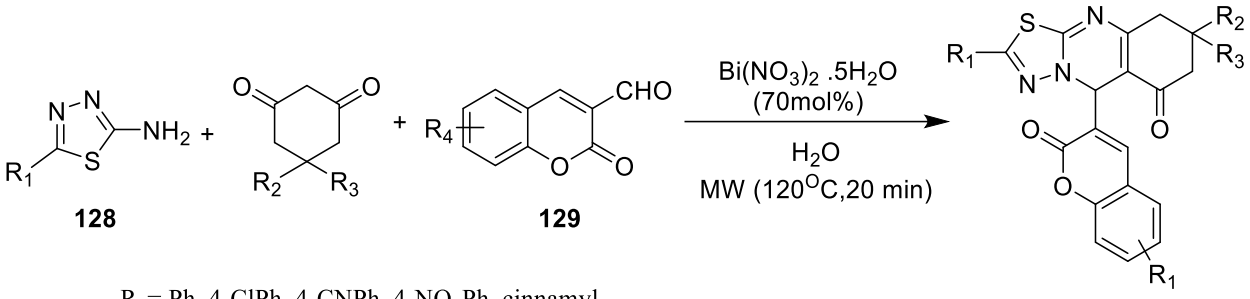
In order to the above-mentioned reactions, the condensation of the aldehyde **24**, barbituric acid **126**, and [DABCO](SO$_3$-H)$_2$Cl$_2$ in water was heated at 70 °C. After completion of the reaction to give a pure pyrimidine-2,4,6-trione compound **127** (Schemes 50). [87]



Scheme 50. [DABCO](SO$_3$H)$_2$Cl$_2$ catalyzed the synthesis of 5-arylmethylene pyrimidine-2,4,6- trione derivatives

A three-component condensation reaction of thiadiazol-2-amines **128** with 1,3-dicarbonyls derivative and chromene-3-carbaldehydes **129** in the presence of catalytic amounts of Bi(NO$_3$)$_2$.5H$_2$O

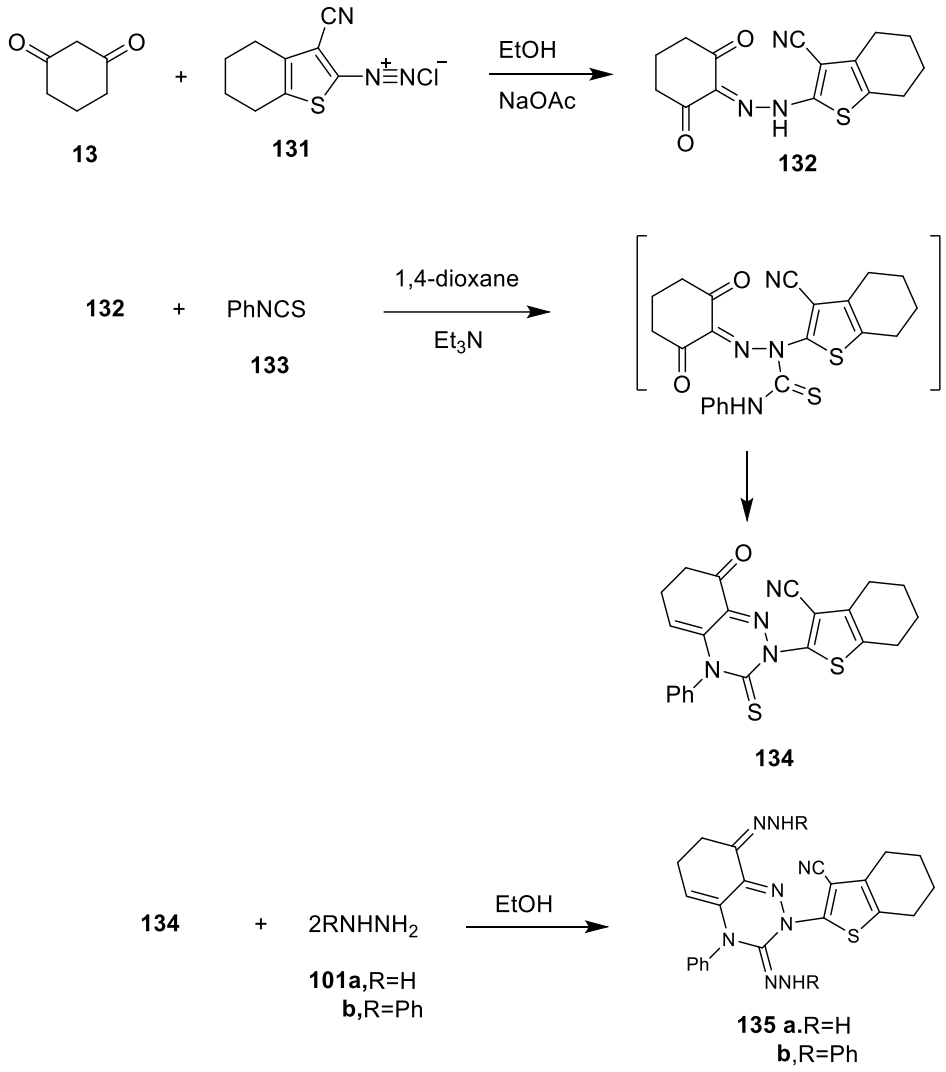
in water under microwave irradiation is the environmentally friendly method used to synthesize coumarin-linked thiadiazoloquinazolinones **130** (Scheme 51).[88]



R_1= Ph, 4-ClPh, 4-CNPh, 4-NO_2Ph, cinnamyl
R_2,R_3=H,Me
R_4=H, 7-F, 7-Cl

Scheme 51. synthesis of 8-alkyl 5-(2-oxo-2*H*-chromen-3-yl)-2-aryl-8,9-dihydro-5*H*-[1, 3,4]thiadiazolo[2, 3-*b*]quinazolin-6(7*H*)-ones.

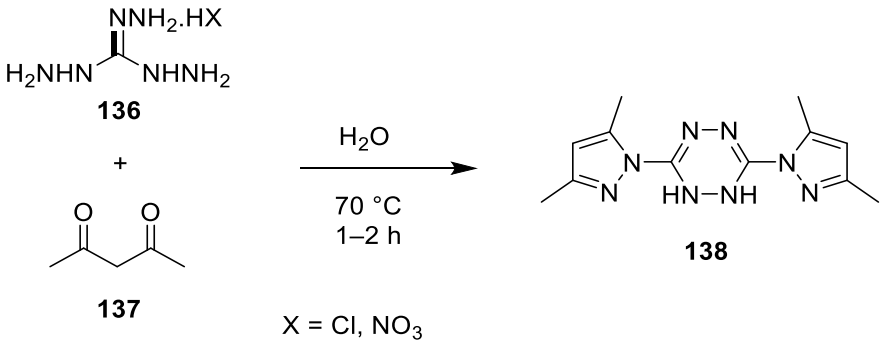
Triazine was achieved in three steps initially. The thiophene-carbonitrile **132** was obtained by reacting cyclohexanedione **13** with thiophene-diazonium chloride derivative **131** in ethanol with sodium acetate at 0–5 °C. The previous compound was vital for initiating the synthesis of 1,2,4-triazine. It reacted with phenylisothiocyanate **133** in ethanol with triethylamine, producing the triazine derivative **134**. Compound **134** underwent a reaction with two moles of hydrazine hydrate **101a** or phenylhydrazine **101b** to produce hydrazone derivatives **135a** and **135b**, respectively. (Scheme 52). [89]



Scheme 52. Synthesis of compounds **132,134** and **135a,b.**

The main advantages of the reported reaction are the simplicity of utilizing the starting materials, short reaction times, a one-pot process, solvent-free conditions, and good product yields.[90]

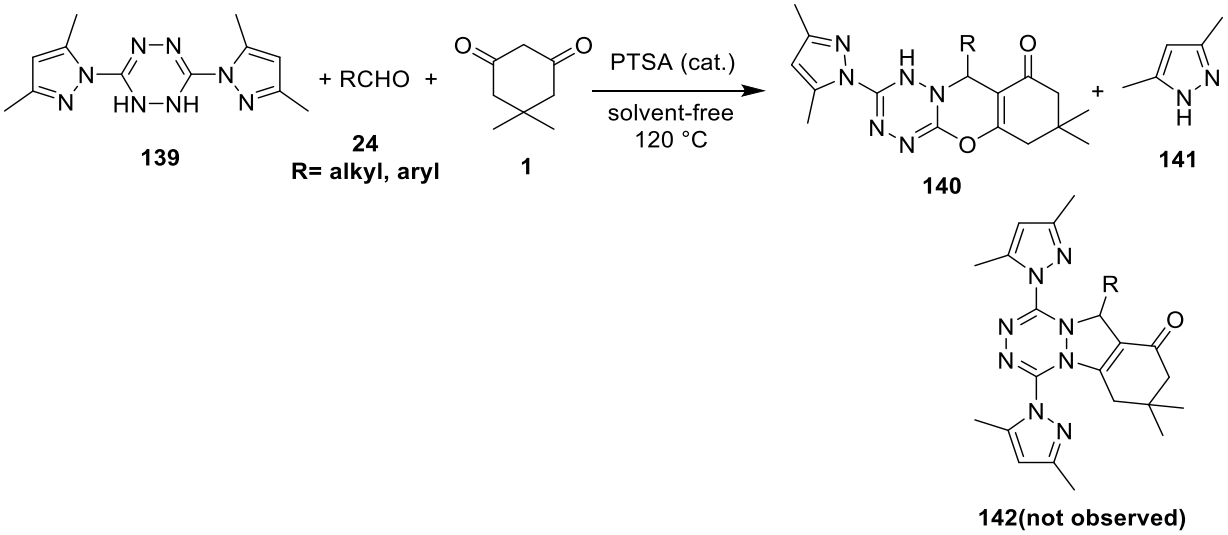
Thus, tetrazine **138** was initially used in MCR. This heterocycle is easily made by the condensation reaction of an acetylacetone **137** and a triaminoguanidinum salt **136** in water, as indicated in (Scheme 53).



Scheme 53. Synthesis of bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (DHBPTz)

In this scheme, tetraazinobenzoxazin-7-ones **140** have been synthesized via a unique one-pot reaction.

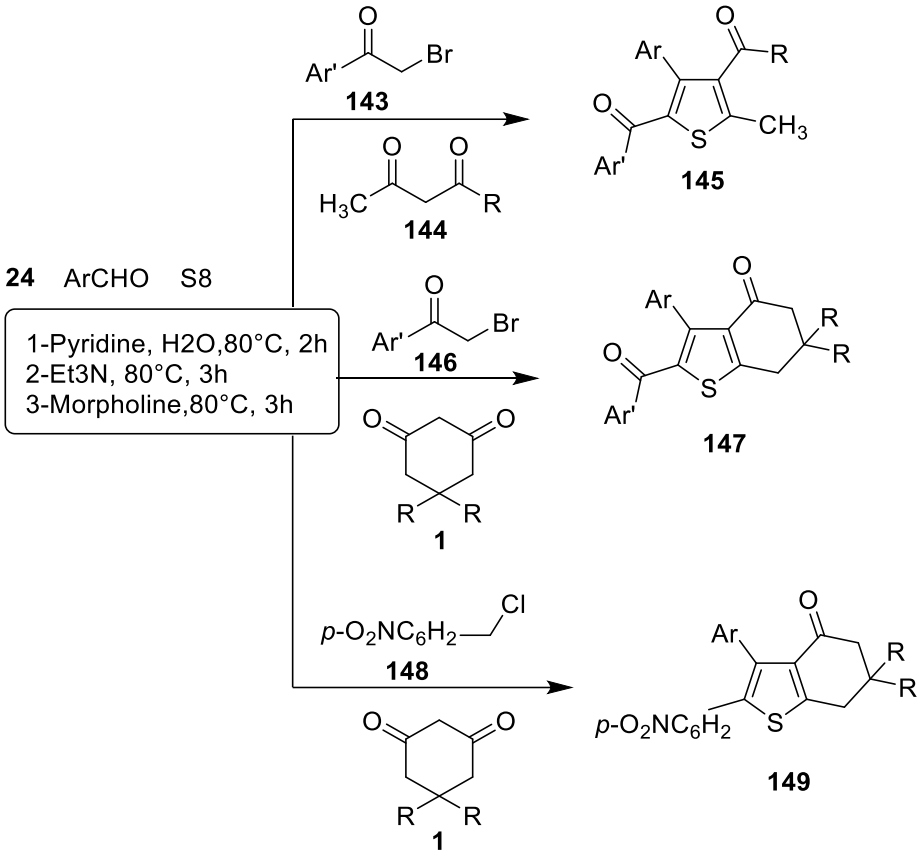
Consequently, under the reaction conditions shown in Scheme 54, a mixture of tetrazine **139** an aldehyde **24**, and dimedone **1**, which also included a catalytic amount of *p*-toluenesulfonic acid (*P*-TSA), was heated at 120 °C under solvent-free conditions, affording the corresponding tetraazinobenzoxazin-7-ones **140** in excellent yields (Scheme 54). [90]



Scheme 54. Three-component reaction between DHBPTz, aldehydes, and dimedone – synthesis of 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones **140**

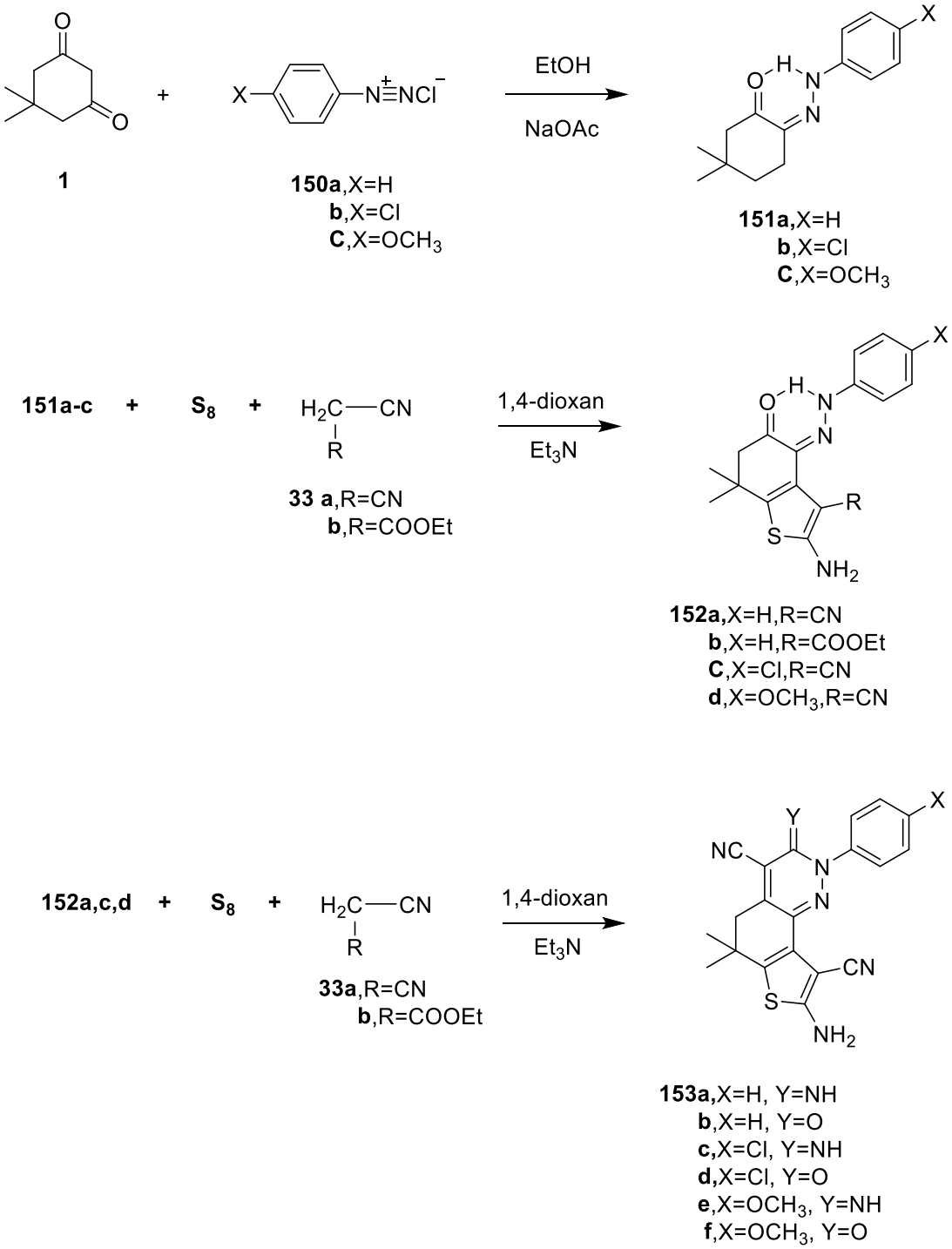
3.3. Synthesis of Thiophene, Thiophene-Fused, Thieno[2,3-B]Thiophene, New Thiazole, Thiazolidine-2-Thione Derivatives

A one-pot, four-component reaction with different aldehydes **24**, 1,3-dicarbonyl compounds (linear or cyclic), activated methylene halides, and elemental sulfur in water at 80 °C for three hours made a library of highly substituted thiophenes with good to excellent yields. As bases and catalysts for synthesizing intermediate and target molecules, pyridine, triethylamine, and morpholine play crucial and critical roles in this reaction (Scheme 55).[91]



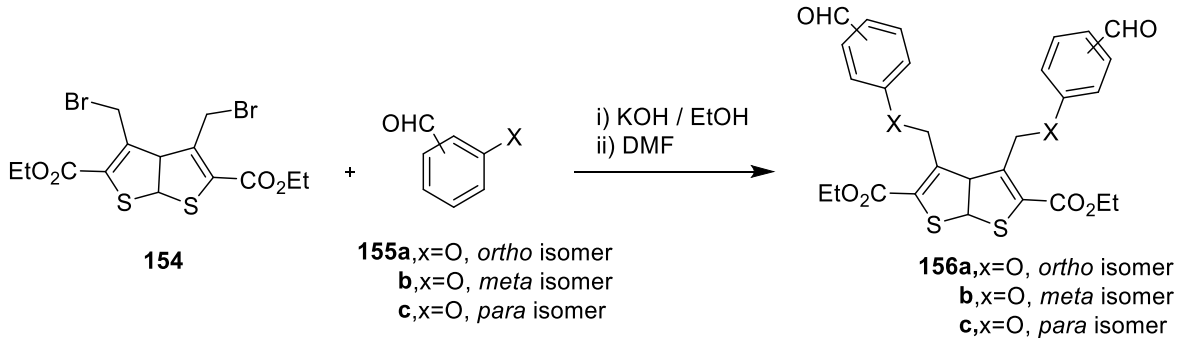
Scheme 55. Four-component syntheses of mono-and bicyclic thiophenes.

Dimedone **1** reacted with the aryldiazonium salts **150a–c** in sodium acetate-containing ethanol to produce the arylhydrazone derivatives **151a–c**, in that order. The arylhydrazone form of compounds **150a–c** appears due to intramolecular N–H–O=C– hydrogen bonding stabilizes this structure (Drew 1982). Subsequently, the derivatives fused with thiophene are prepared by using Gewald's thiophene synthesis. Firstly, Study the reaction of all arylhydrazo compounds **150a–c** with elemental sulfur and ethylcyanoacetate **33b** or malonitrile **33a** to get the corresponding thiophene derivatives **152a–f.** next focus on the method for producing cinnoline derivatives, which involves reacting either of the compounds **152a, c**, or e with either ethyl cyanoacetate **33b** or malononitrile **33a** to produce the corresponding cinnoline derivatives, **153a–f** (Scheme 56).[92]



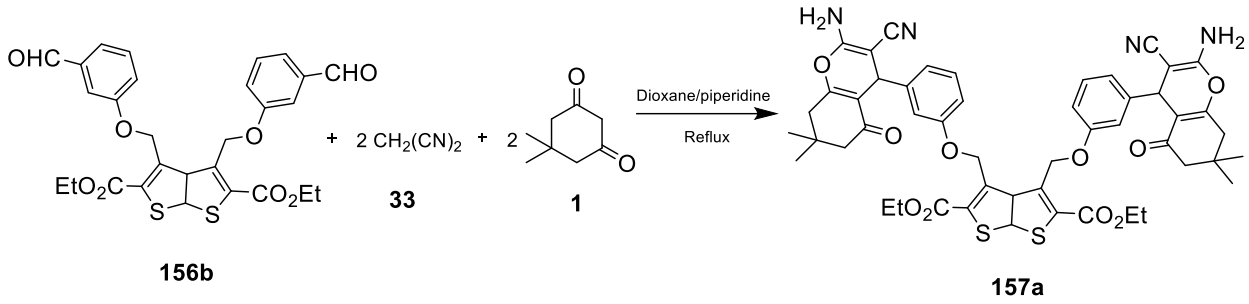
Scheme 56. Synthesis of compounds **151a–c, 152a–f,** and **153a–f**

The bis(aldehydes) **156a-c** were employed as starting materials for the synthesis of various new bis(heterocycles) connected to a thienothiophene core through a phenoxymethyl linker. To obtain the target compounds, diethyl 3,4-bis(bromomethyl)thieno[2,3-b]thiophene-2,5-dicarboxylate **154** was reacted with the potassium salts of salicylaldehyde **155a**, *m*-hydroxybenzaldehyde **155b**, and *p*-hydroxybenzaldehyde **155c** in DMF under reflux conditions (Scheme 57). [93–96]



Scheme 57. Synthesis of bis(aldehydes) **156a-c** incorporating thieno[2,3-b]thiophene derivatives

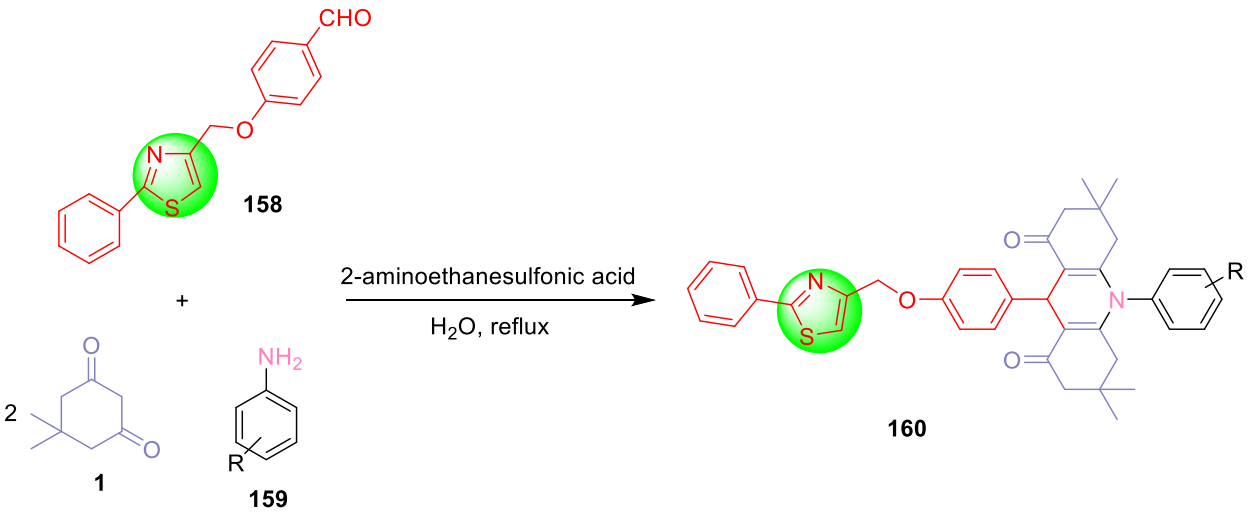
Subsequently, it was determined how reactive **156a-d** was to various active methylene compounds. Therefore, the formation of the bis-chromene-3-carbonitrile, which is connected to thieno[2,3-b]thiophene-2,5-dicarboxylate **157a** in good yield, was the result of a three component reaction of the bis(aldehyde) **156b** with both of malononitrile **33** and dimedone **1** in the presence of piperdine as a basic catalyst in dioxane at reflux (Scheme 58). [97]



Scheme 58. Synthesis of bis-chromene-3-carbonitrile **157a**

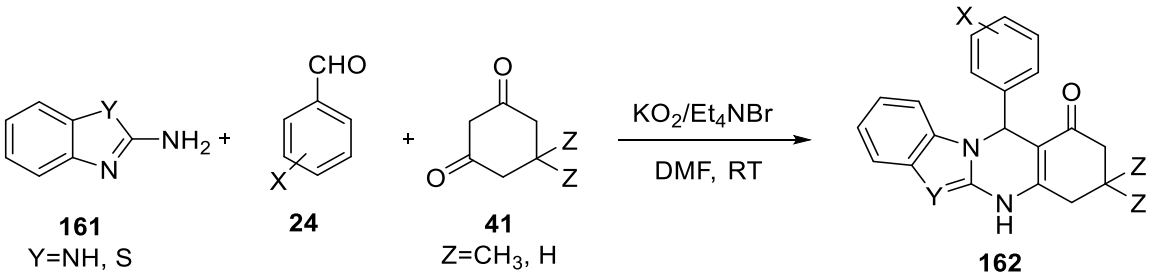
The corresponding thiazole derivative **160** was successfully formed by the reaction of several substituted amines (aromatic and heterocyclic) **159** with 4-[(2-phenylthiazol-4-yl)methoxy]-benzaldehyde **158** and dimedione **1** in an aqueous medium with 2-aminoethanesulfonic acid. The results clearly showed that the amines with functional groups that donate electrons and withdraw electrons at various locations reacted with **158** and **1** simplicity and produced the appropriate product in good to excellent yields (Scheme 59).[98]

Newly synthesized thiazole derivatives **160** were tested for the antimicrobial activity against four pathogenic bacteria and three fungi including, *Escherichiacoli*, *Pseudomonasaeruginosa*, *Staphylococcusaureus*, *Bacillussubtilis*, *Candidaalbicans*, *Aspergillusniger* and *Aspergillusflavus* in vitro using Ampicillin, Ciprofloxacin and Miconazole used as positive controls. The results exhibited significant antibacterial activity against *Staphylococcusaureus* and *Bacillussubtilis.*



Scheme 59. Synthesis of compounds **160**.

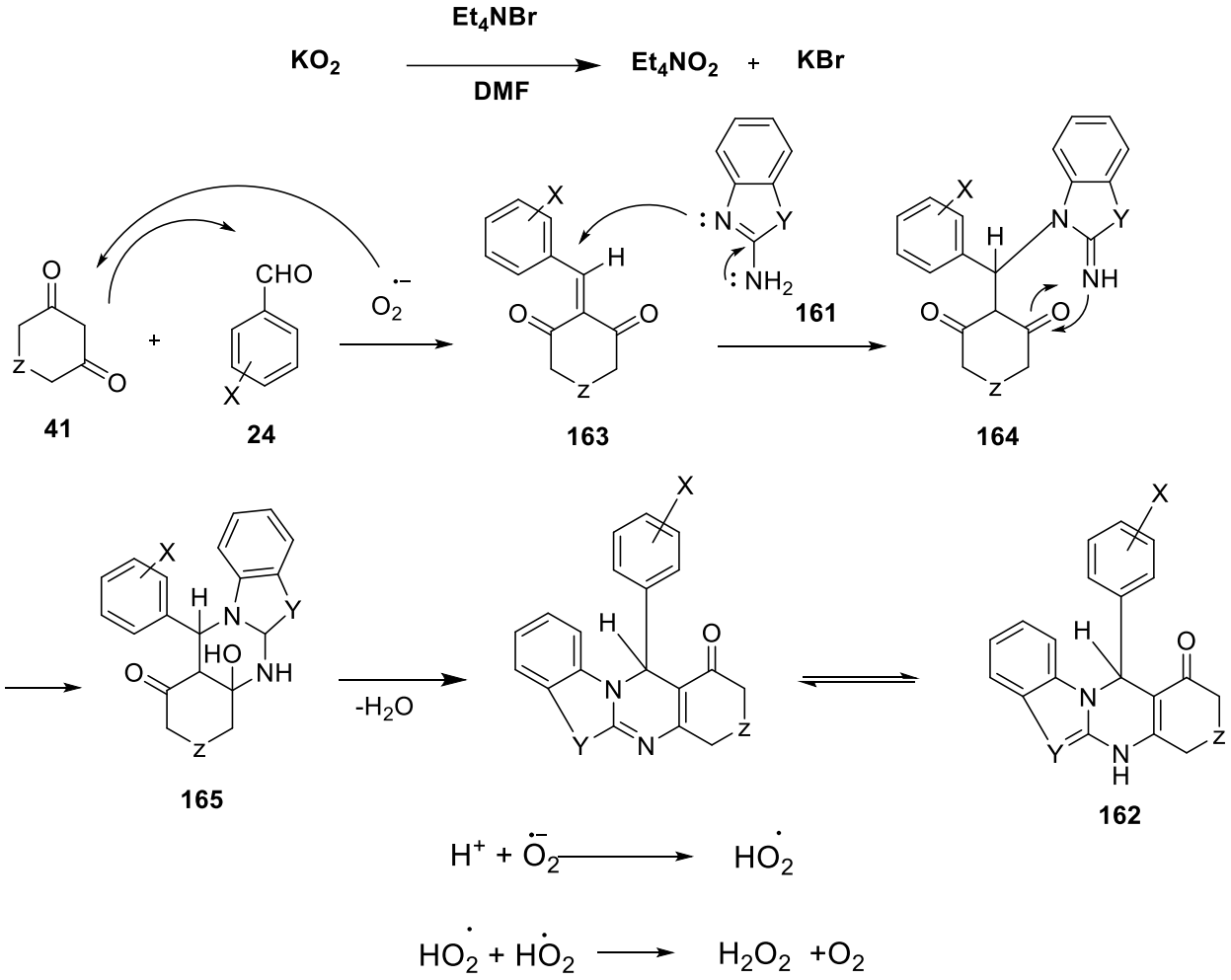
In (scheme 60), the one-pot three-component condensation reaction involving various aromaticaldehydes **24** and 1,3-diketones **41** with 2-aminobenzimidazole/2-aminobenzothiazole **161** using tetraethylammonium superoxide under non-aqueous conditions and DMF as a solvent produced benzomidazolo/benzothiazoloquinazolin-1-one ring systems **162**. The results of this study absolutely indicate that, in terms of both reaction time and product yield, DMF was the best solvent among all those examined.



Scheme 60. Synthesis of tetraheterocyclicBenzimidazolo/benzothiazolo quinazolin-1-one

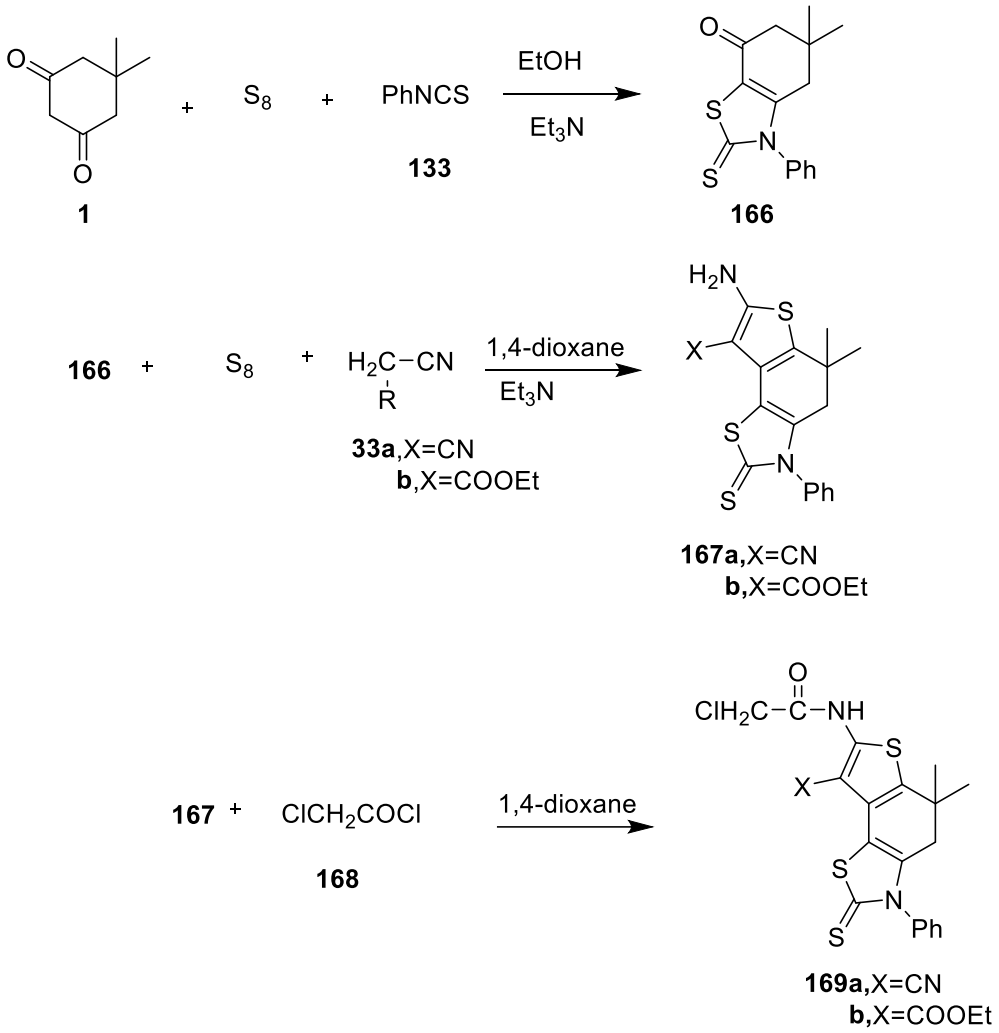
(Scheme 61) presents the proposed mechanism for the formation of the target compound **162**. The process begins when tetraethylammonium superoxide, generated in situ via a phase-transfer reaction between potassium superoxide and tetraethylammonium bromide, abstracts a proton from 1,3-diketone **41**. Subsequently, benzaldehyde **24** undergoes a Knoevenagel condensation, leading to the formation of olefin 3-benzylidene-2,4-hexanedione **163** via dehydration.

Compound **163** then reacts with 2-aminobenzimidazole or 2-aminobenzothiazole **161** through a Michael addition to form an intermediate of type **164** which undergoes further cyclization to yield the tetraheterocyclic benzimidazolo/benzothiazoloquinazolin-1-one ring system **165**. [99]



Scheme 61. Mechanism for the synthesis of tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-ones.

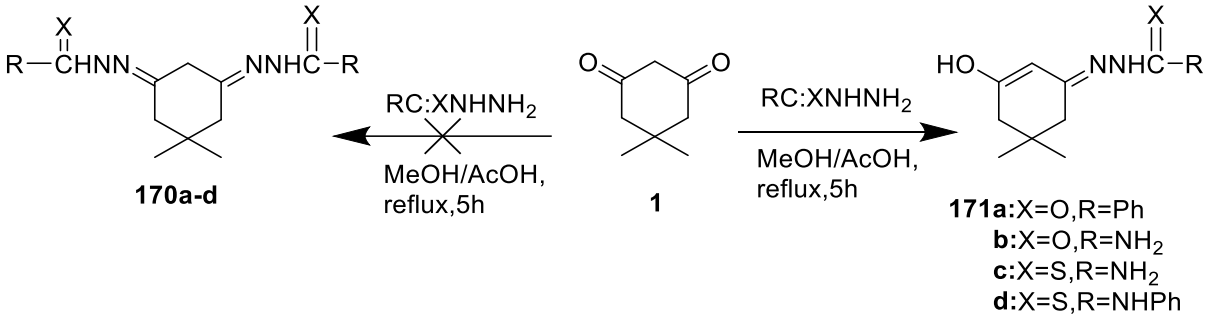
In 1,4-dioxan containing triethylamine, the dimedone **1** interacted with elemental sulfur and phenylisothiocyanate **133** to yield the thiazole derivative **166**. The thiazole derivatives **167a** and **167b** respectively, were therefore produced by compound **166** reacting with elemental sulfur and either malononitrile **33a** or ethyl cyanoacetate **33b**. The chloroacetamido derivatives **169a** and **169b** were produced when compound **167a** or compound **167b** reacted with chloroacetyl chloride **168**, respectively (Scheme 62).[100]



Scheme 62. Synthesis of compounds **166, 167a,b**, and **169a,b**

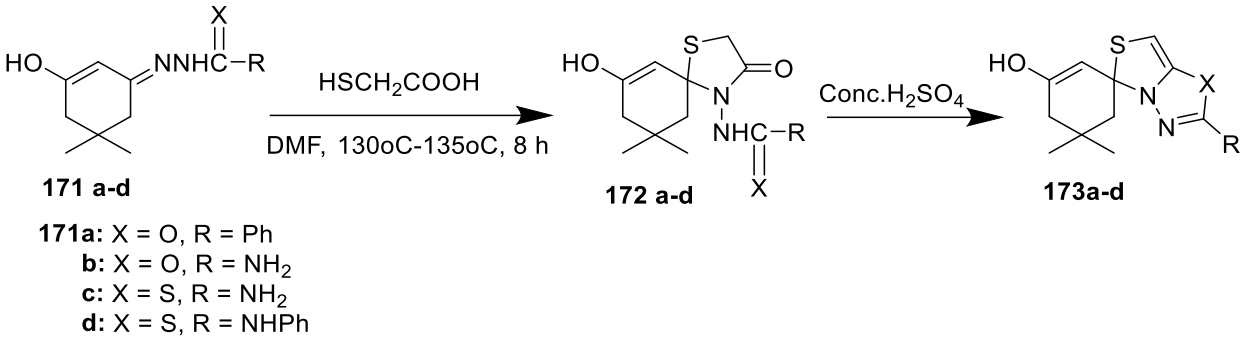
3.4. Synthesis of Spiro Heterocycles Containing Nitrogen, Oxygen, and Sulfur

By using dimedone **1**, benzoyl hydrazine, semicarbazide, thiosemicarbazide, and 4-phenyl thiosemicarbazide, an acid-catalyzed condensation was carried out to produce the corresponding hydrazone **171** (a: X=O, R=Ph), semicarbazone (b: X=O; R=NH_2), thiosemicarbazone (c: X=S; R=NH_2), and phenylthiosemicarbazone (d: X=S; R=NHPh). The formation of the monohydrazone and carbazone derivatives (**171a–d**) from dimedone rather than the bis-hydrazone and carbazone derivatives (**170a–d**) supports the conclusion that dimedone exists predominantly in its enol form under the reaction conditions (Scheme 63). [101-102]



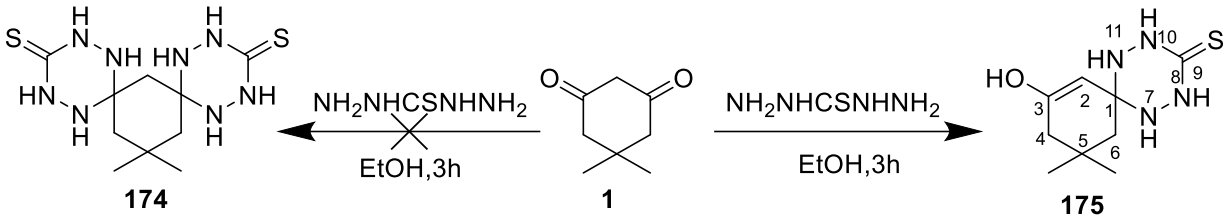
Scheme 63. Synthetic route for compounds **176a–d**.

The spiro thiazolidinone derivatives **172a–d** are obtained by refluxing an equimolar quantity of thioglycolic acid in methanol with the hydrazone, semicarbazone, andthiosemicarbazone derivatives of dimedone **171a–d** (Scheme 64). When cold concentrated sulfuric acid (H_2SO_4) is applied to the spiro heterocycles **172a–d**, dehydrative cyclization takes place, resulting in the formation of spiro oxadiazolo/thiazolo[3,2-*c*]thiazoline derivatives **173a–d** (Scheme 64).



Scheme 64. Synthetic route for compounds **173a–d.**

A similar kind of enolized mono spiro-s-tetrazine intermediate **175** was produced by condensation of dimedone **1** with thiocarbohydrazide (Scheme 65). [102]

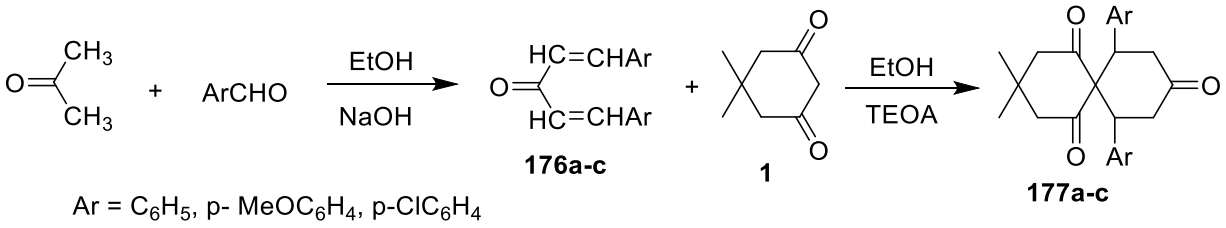


Scheme 65. Synthetic pathway for the preparation of spiro-s-tetrazine **175.**

The antibacterial activity of each synthesized compound was tested against two types of bacteria: gram positive S. aureus and gram-negative E. coli. While some of them show good to moderate activity, only a small number are shown to be extremely active against the same bacterium. [102]

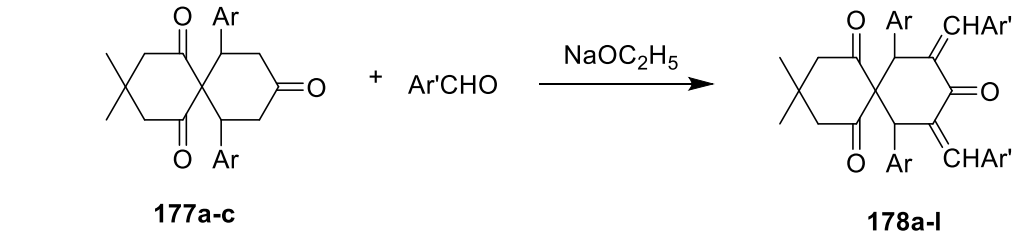
By condensing acetone and aryl aldehydes in ethanolic NaOH, the diarylideneacetones **176a–c** were produced. Following this, spiro compounds **177a–c** were produced via the Michael addition

reaction between diarylideneacetones **176a–c** and dimedone **1** in the presence of triethanolamine (TEOA) as shown in (Scheme 66).



Scheme 66. Synthesis of spiro compounds **177a–c.**

The spiro diarylidene derivatives **178a-l** were obtained by refluxing the spirans **177a–c** with various aryl aldehydes in the presence of EtONa at a 2:1 molar ratio (Scheme 67). [103]



Scheme 67. Synthesis of spiro diarylidene derivatives **178a–l**

4. Conclusion

In this review, a comprehensive and systematic investigation was conducted to explore the reactivity of *β*-diketones and cyanomethylene reagents in the synthesis of novel heterocyclic compounds. A wide range of one-pot, multi-component, and microwave-assisted reactions was developed to efficiently generate structurally diverse and biologically relevant heterocycles. These methods were optimized using various acid catalysts and environmentally friendly reaction media, aligning with the principles of green chemistry.

Several newly synthesized compounds have shown strong biological activity, especially in antimicrobial and anticancer assays. Some derivatives based on xanthene and chromenone exhibited notable inhibitory effects against cancer cell lines and pathogenic microbes. These findings indicate their potential as lead compounds for drug development.

Overall, this research provides valuable insights into synthetic methodologies for heterocyclic chemistry and identifies promising candidates for future pharmaceutical and medicinal applications. This work opens avenues for further exploration of functionalized heterocycles as therapeutic agents, particularly through mechanism-based optimization and advanced biological screening.

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