REVIEW ARTICLE

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Synthesis of biologically active chromene, coumarin, azole, azine and thiophene derivatives from 1,3-diketone

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Abstract: In the present review, we discuss new and diverse methods for synthesizing chromene, coumarin, pyrimidine, pyridine, pyrazole, thiazole and thiophene derivatives from 1,3-diketones, according to Knoevenagel condensation, Michael addition, Hantzsch reaction, and Gewald's reaction. Various catalysts and reagents were used to complete the cyclization processes. Most of the produced compounds showed remarkable activity against different types of cancer cell lines and toward Gram-negative and Gram-positive bacteria. Furthermore, anti-quorum sensing, in vitro COX-1 and COX-2 enzymatic inhibition assays were evaluated.

Keywords: 1,3-Diketone; chromene; pyridine; thiophene; anti-tumor.

1. Introduction

Compounds, containing chromene-2-one nucleus (2H-1-benzopyran-2-one), compose a significant class of heterocycles, which were used in the domain of synthetic organic chemistry and natural products.[1,2] In the market, some alkaloids containing chromene-2-one derivatives like lamellarin D **2** and ningalin B **1** are known to display immunomodulatory activity, cytotoxicity, and HIV-1 integrase inhibition.[3-5] All chromene-2-one derivatives summarized in (Figure 1) have pronounced biological significance. 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (warfarin **10**) (Figure 2) was known to reduce secondary malignant growths of intestinal cancers to a large extent[6] and also used as an adjunct to the surgical treatment of malignant carcinomas.[7] In addition, 7,8-dihydroxy-2H-chromen-2-one (daphnetin **11**) (Figure 2) was used to prevent epidermal growth factor receptor (EGFR), tyrosine kinase, protein kinase C and serine/threonine-specific protein kinase in vitro.[8] The attention as a contribution to develop novel methods for the synthesis of functionalized pyridocoumarins (5H-

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chromeno[4,3-b]pyridin-5-one derivatives) have been mobilized by the expansive range of their biological importance.[9] For example, compounds **13a,b-15a** have anticancer activities,[10] compound **15b** shows anti-inflammatory[11] and compound **16** has antibacterial activity.[12] Some inhibitors were known, like compound **13a**, to inhibit topoisomerases I, whereas compound **13b** for topoisomerases II and compound **14** has aromatase activity. In addition, the given structural motif is available in various alkaloids. The presently known natural chromeno pyridines involve compounds **17a-c** (phochrodines A-C), isolated from mangrove endophytic fungus Phomopsis sp.,[13a] compounds **18a,b** (ganocalicines A and B), isolated from Ganoderma calidophilum and exhibited antiallergic activity, compound **18c** (ganocochlearine G), isolated from Ganoderma cochlear,[13b] and compound **19** (cochlearine A),[13c] which acts as an inhibitor of T-type calcium channels (Figure 3).[13d-f]

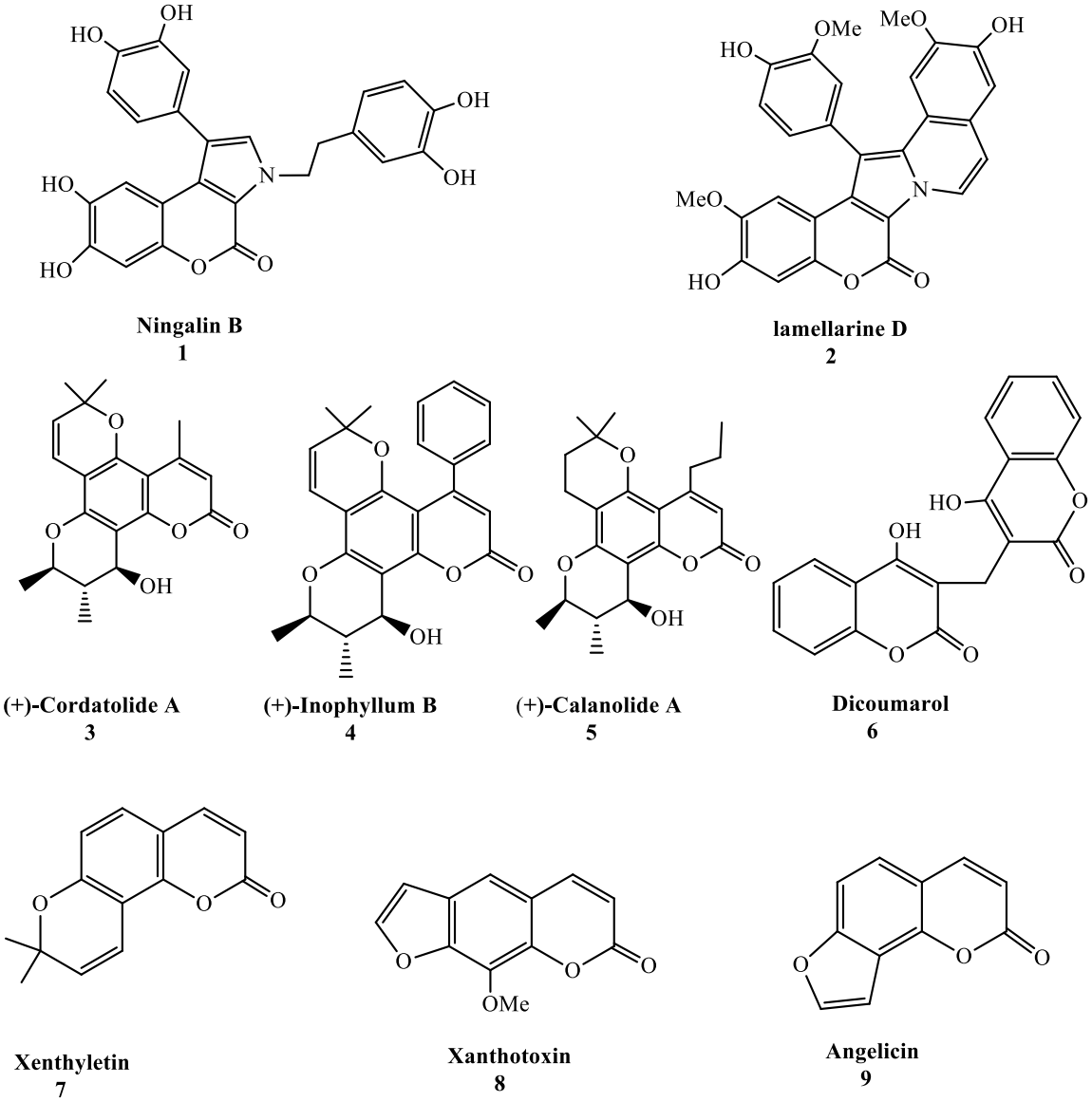
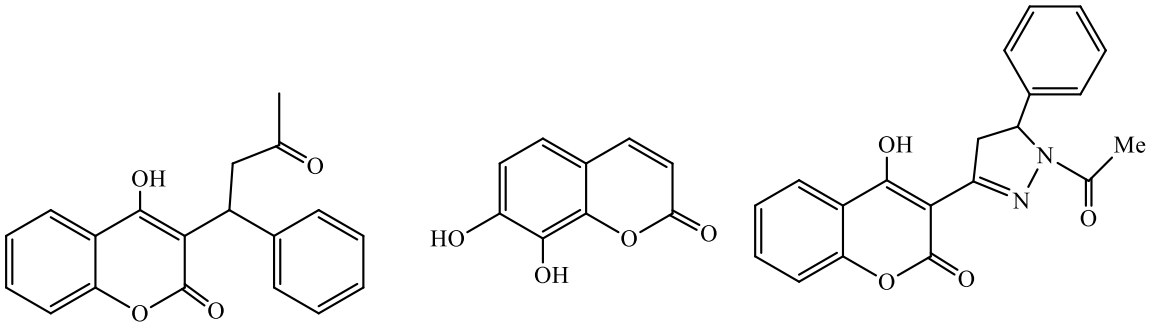
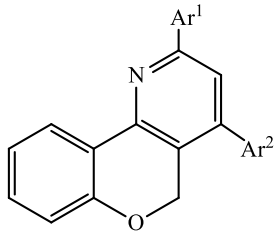


Figure 1. Biologically active and commercially important chromene-2-one derivatives

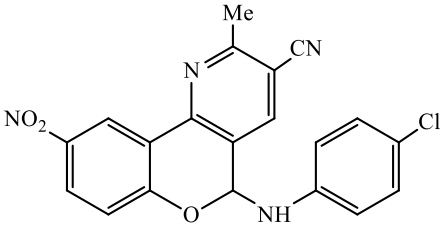


Warfarin **10** | Daphnetin **11** | Dihydropyrazole-subtituted benzopyran-2-one **12**

Figure 2. Anticancer and kinase inhibitors



13a, $Ar^1 = Ar^2$ = 2-furyl
13b, Ar^1 = 3- HOC_6H_4, Ar^2 = 4-HOC_6H_4



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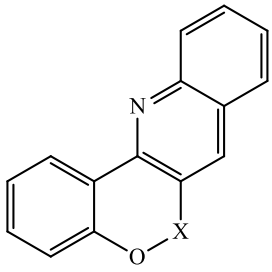
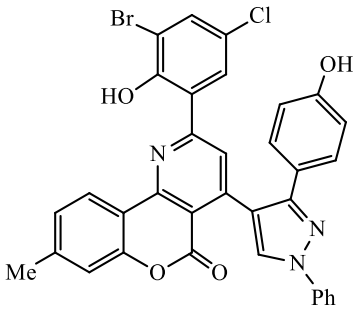


15a, X = C=O
b, X = $C(CH_2)_5$



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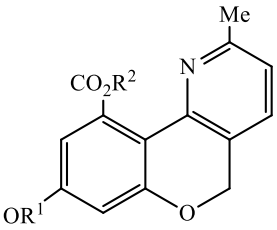
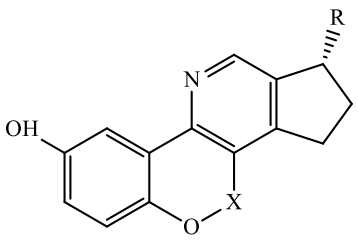
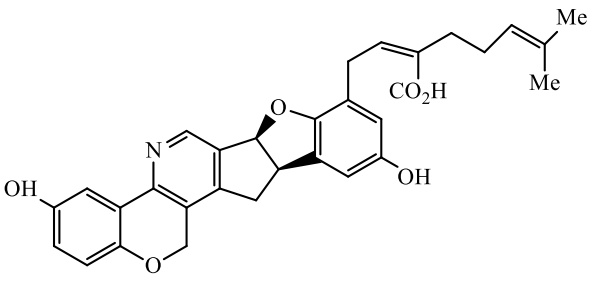


Phochrodine A (**17a**, $R^1 = R^2 =$ H)
Phochrodine B (**17b**, R^1 = H, R^2 = Me)
Phochrodine C (**17c**, R^1 = Me, R^2 = H)



Ganocalicine A **(18a,** X= CH_2, R = OMe)
Ganocalicine B **(18b,** X= CH_2, R = H)
Ganocochlearine G **(18c**, X= C=O, R = OH)



Cochlearine A (**19**)

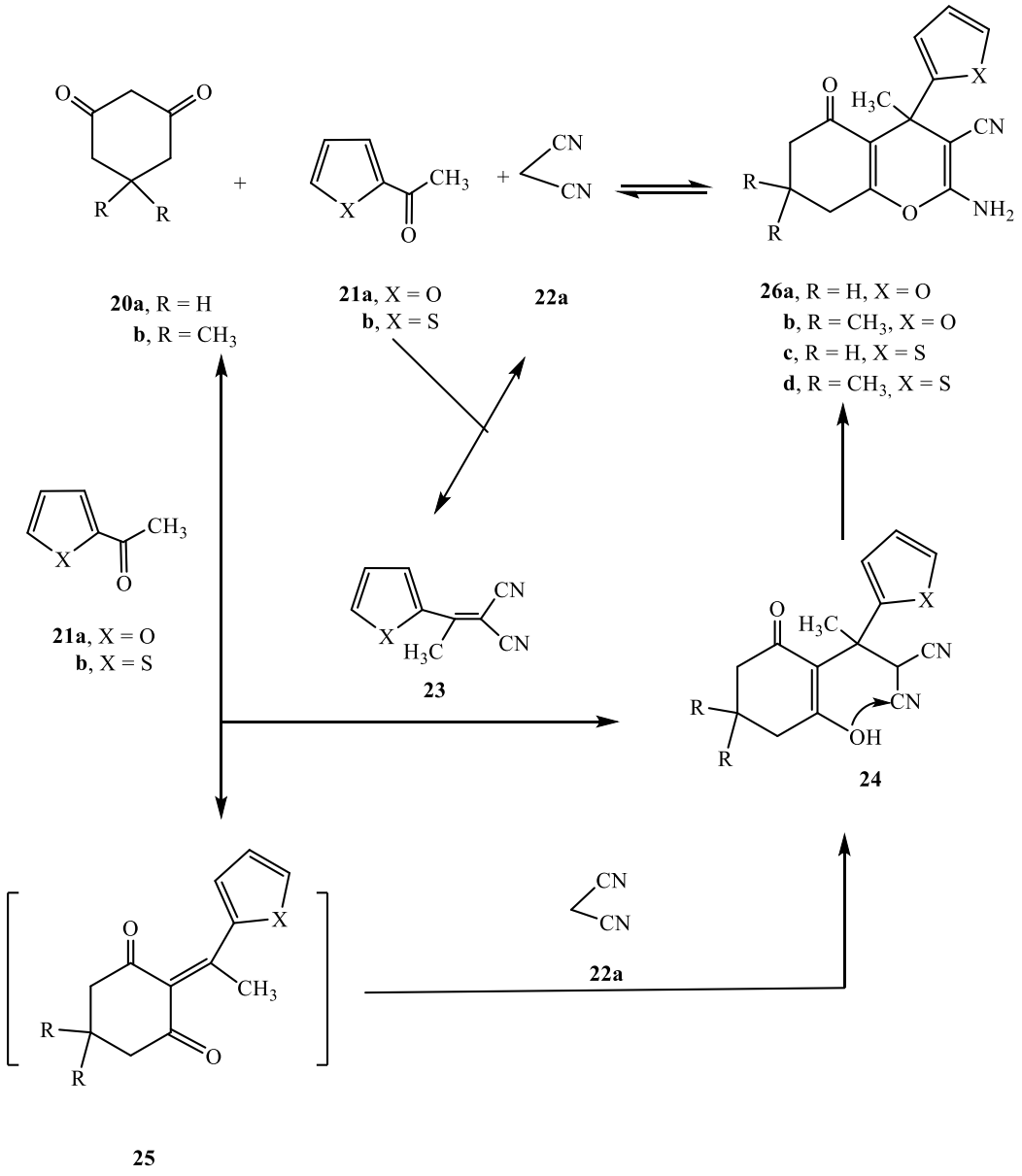
Figure 3. Synthetic and natural chromeno[4,3-b]pyridine derivatives

In this review, we demonstrated various methods for the synthesis of heterocyclic compounds using β--diketones. The produced compounds include six-membered rings like chromene and coumarin derivatives and five-membered rings like pyrazole, thiazole and thiophene derivatives. In addition, various catalysts were used as Fe_3O_4@GO-N-(pyridin4-amine) nanofilm, supported ionic liquid catalyst as heterogeneous catalyst (SILC), 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-(N,N-dimethylamino)pyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a heterogeneous Al-MCM-41-LDH@APTES (ALAM), Cinchonine, Ni(II)-Schiff base/SBA-15 as an environmentally benign catalyst, a new deep eutectic solvent (DES), saccharose, low transition temperature mixture (LTTM), Waste orange peel derived carbon (OPC) powder incorporated with sulfonic acid (OPC-SO_3H), all catalysts were used individually to produce derivatives of chromen, coumarin, pyridine, pyrimidine, pyrazole, thiazole, thiophene as we will notice by following this review. Moreover, a section for the biological importance of such compounds was added.

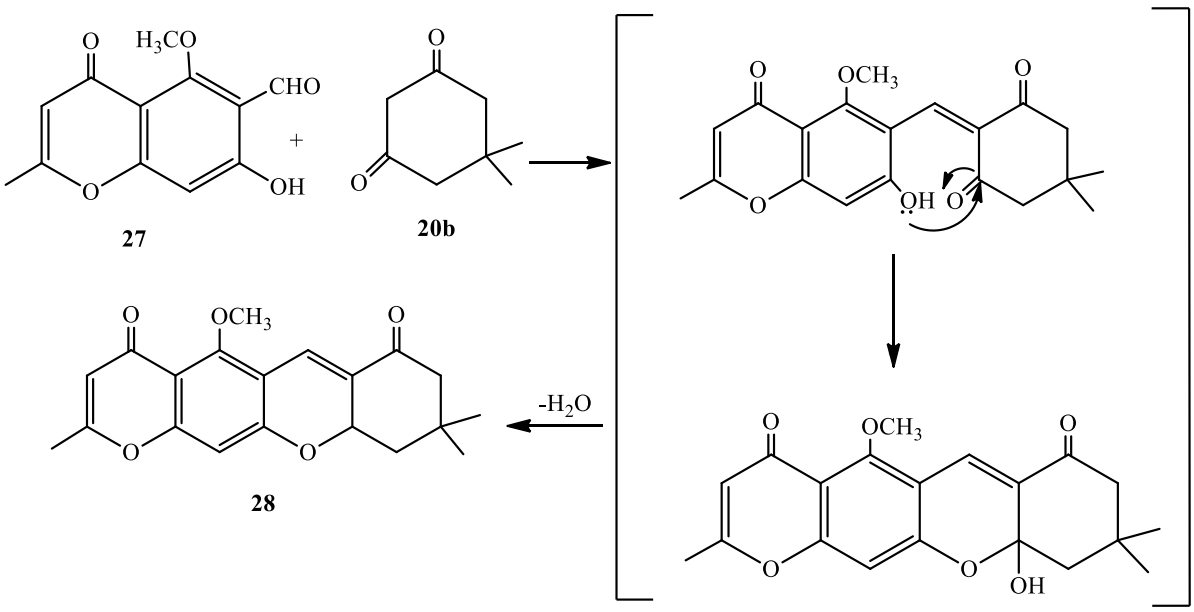
2. Synthesis of Biologically Active Chromene Derivatives from 1,3-Diketone

One-pot three-component cyclocondensation process was described by the reaction between, cyclohexa-1,3-dione (**20a**)/dimedone (**20b**), 2-acetylfuran (**21a**)/2-acetylthiophene (**21b**) and malononitrile (**22a**) in refluxing ethanol and sodium ethoxide as a catalyst to give the tetrahydrochromene derivatives **26a–d**, respectively (Scheme 1). Authors suggested two routes for the synthesis of chromene derivatives **26a–d**, the first route included condensation of 2-acetylfuran (**21a**) or 2-acetylthiophene (**21b**) with malononitrile (**22a**) to furnish the aralkylidene malononitrile derivative **23**, which underwent a Michael-addition of the active methylene of (**20a**) or (**20b**) to afford the acyclic intermediates **24a–d**, which were cyclized to give **26a–d**, respectively. On the other hand, the second route included condensation of any of the ketones (**21a**) or **(21b**) with either of the active methylene of (**20a,b**) to furnish the arylidenes **25a–d**, which underwent a Michael-addition of the active methylene of malononitrile (**22a**) to the activated double bond to produce the intermediate acyclic adducts **24a–d**, cyclization of which produced **26a–d**, respectively (Scheme 1). The authors confirmed these proposed mechanisms, and indicated that both routes led to the formation of tetrahydrochromene derivatives **26a–d**, respectively.[14]

Treatment of 7-hydroxy-5-methoxy-2-methyl-4-oxo-4H-chromene-6-carbaldehyde **27** with 5,5-dimethylcyclohexane-1,3-dione (**20b**) yielded the condensation product 5-methoxy-2,9,9-trimethyl-8,9,10,10a-tetrahydropyrano[3,2-b]xanthene-4,7-dione **28**. Formation of compound **28** was assumed to proceed through the *in situ* intramolecular cyclization of the non isolable intermediate *via* nucleophilic addition of the hydroxyl group to the carbonyl group, which was followed by elimination of water, (Scheme 2). Compound **28** was selected for the evaluation of its in vitro growth inhibitory activities against breast MCF7 and colon HCT cancer cells in comparison to the known anticancer drugs of vinblastine (IC_{50} = 2.97 µg/mL) and doxorubicin (IC_{50} = 3.7 µg/mL). Compound **28** showed approximately similar potency (IC_{50} = 3.1 µg/mL, IC_{50} = 4.2 µg/mL) against MCF7 and HCT respectively.[15]

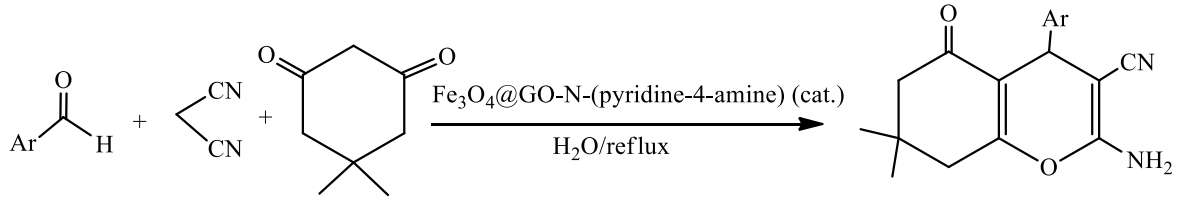


Scheme 1. Synthesis of chromene derivatives **26a-d**



Scheme 2. Synthesis of xanthene-4,7-dione derivative **28**

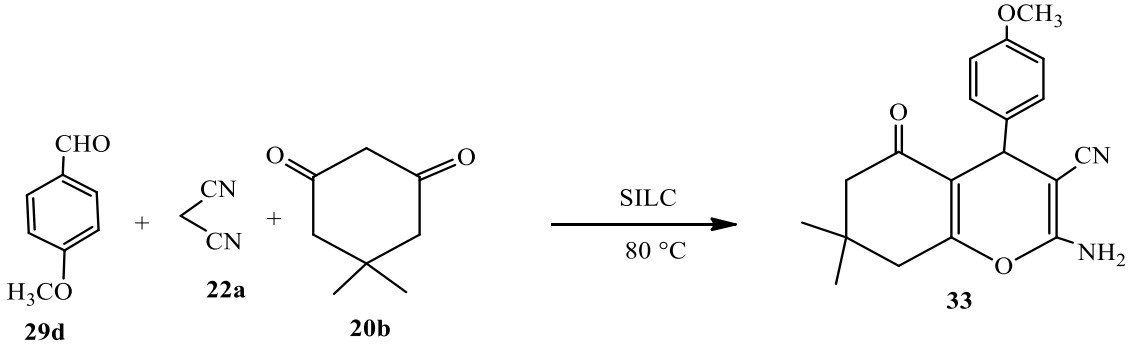
The multi-component reaction between either of the aldehydes (**29a-c**), malononitrile (**22a**) and dimedone (**20b**) in the presence of Fe_3O_4-supported N-pyridin-4-amine-functionalized graphene oxide as an efficient and recyclable heterogeneous magnetic nanocatalyst gave 4H-chromenes **30a-c** (Scheme 3).[16]



29a, Ar = C_6H_5 **22a** **20b** **30a-c**
b, Ar = 4-FC_6H_4
c, Ar = 4-MeC_6H_4

Scheme 3. Synthesis of 4H-chromenes **30a-d** under catalysis by Fe_3O_4@GO-N-(pyridin4- amine) nanofilms

Similarly, the reaction of *p*-methoxybenzaldehyde (**29d**), malononitrile (**22a**) and dimedone (**20b**) in the presence of a catalytic amount of supported ionic liquid catalyst as heterogeneous catalyst produced 4H-chromene **33** (Scheme 4).



29d **22a** **20b** **33**

Scheme 4. Synthesis of 2-amino-4H-chromene **33** using SILC

Dimedone (**20b**) was activated by a catalytic amount of SILC in step 1. The arylidene malononitrile derivative **33** was formed by Knoevenagel condensation between *p*-methoxy benzaldehyde (**29d**) and malononitrile (**22a**) in step 2. Then, Michael addition between activated dimedone (**20b**) and arylidene malononitrile to produce the intermediate **32**, followed by nucleophilic attack of hydroxyl group to cyano group to form chromene **33**. This suggested mechanism for the synthesis of chromene **33** was summarized in (Figure 4).[17]

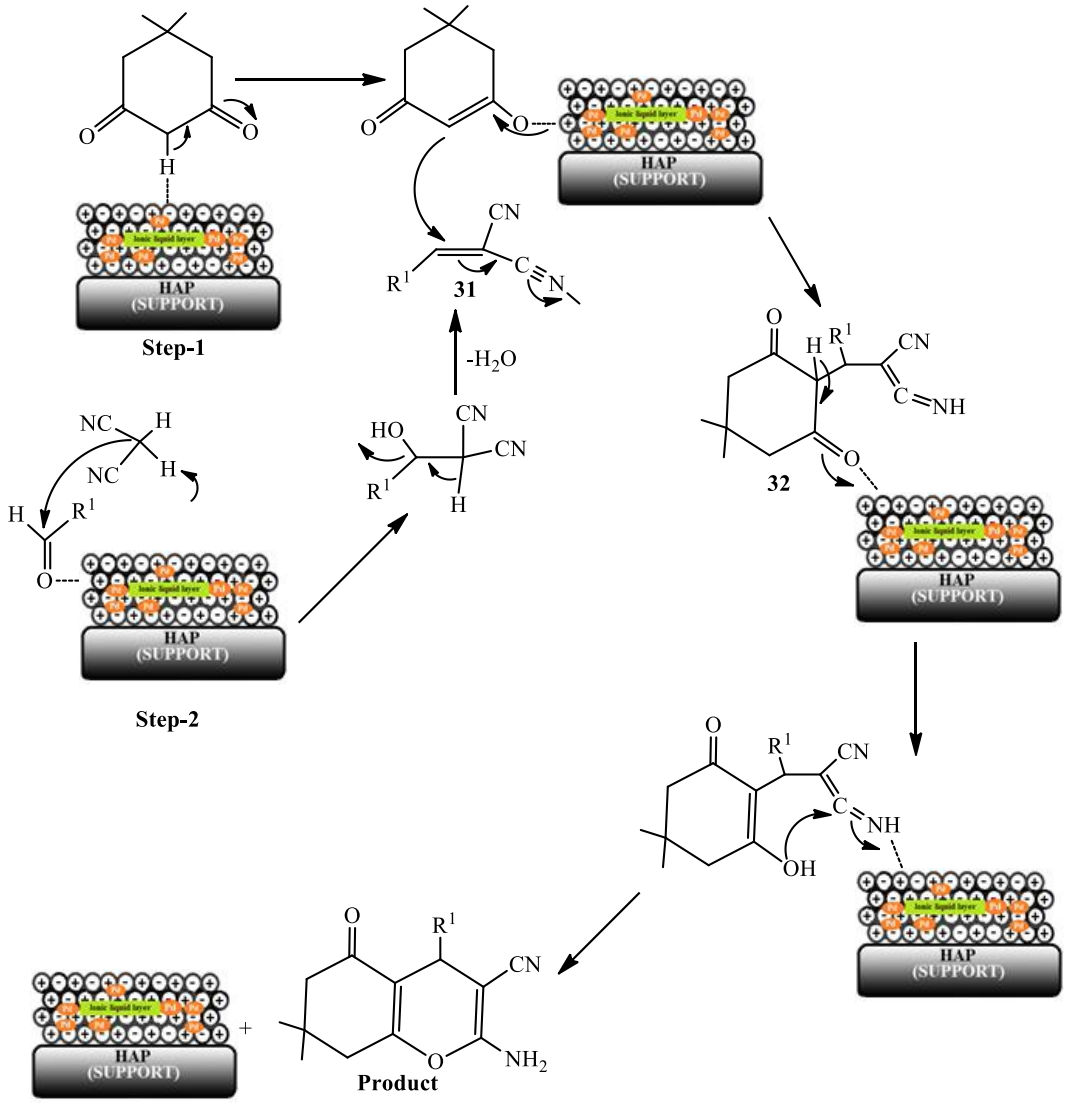
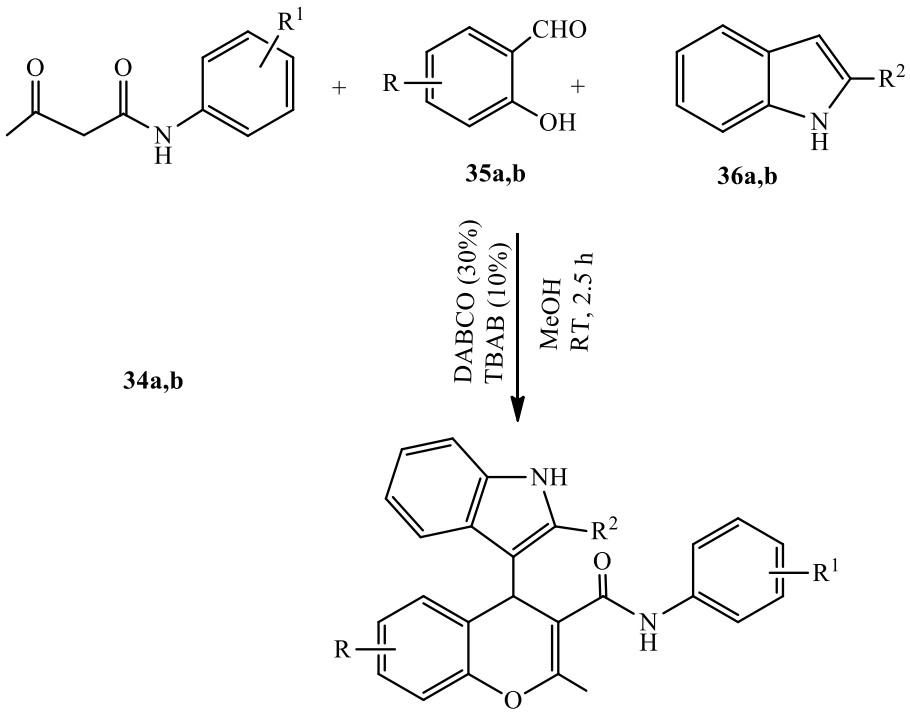


Figure 4. Plausible mechanism for the synthesis of chromene **33**

The reaction between 3-oxo-N-phenylbutanamide **34**, 2-hydroxy benzaldehyde (**35a**), and indole **36** in the presence of different catalysts afforded 4H-chromene-3-carboxamides **37a-p** (Scheme 5).



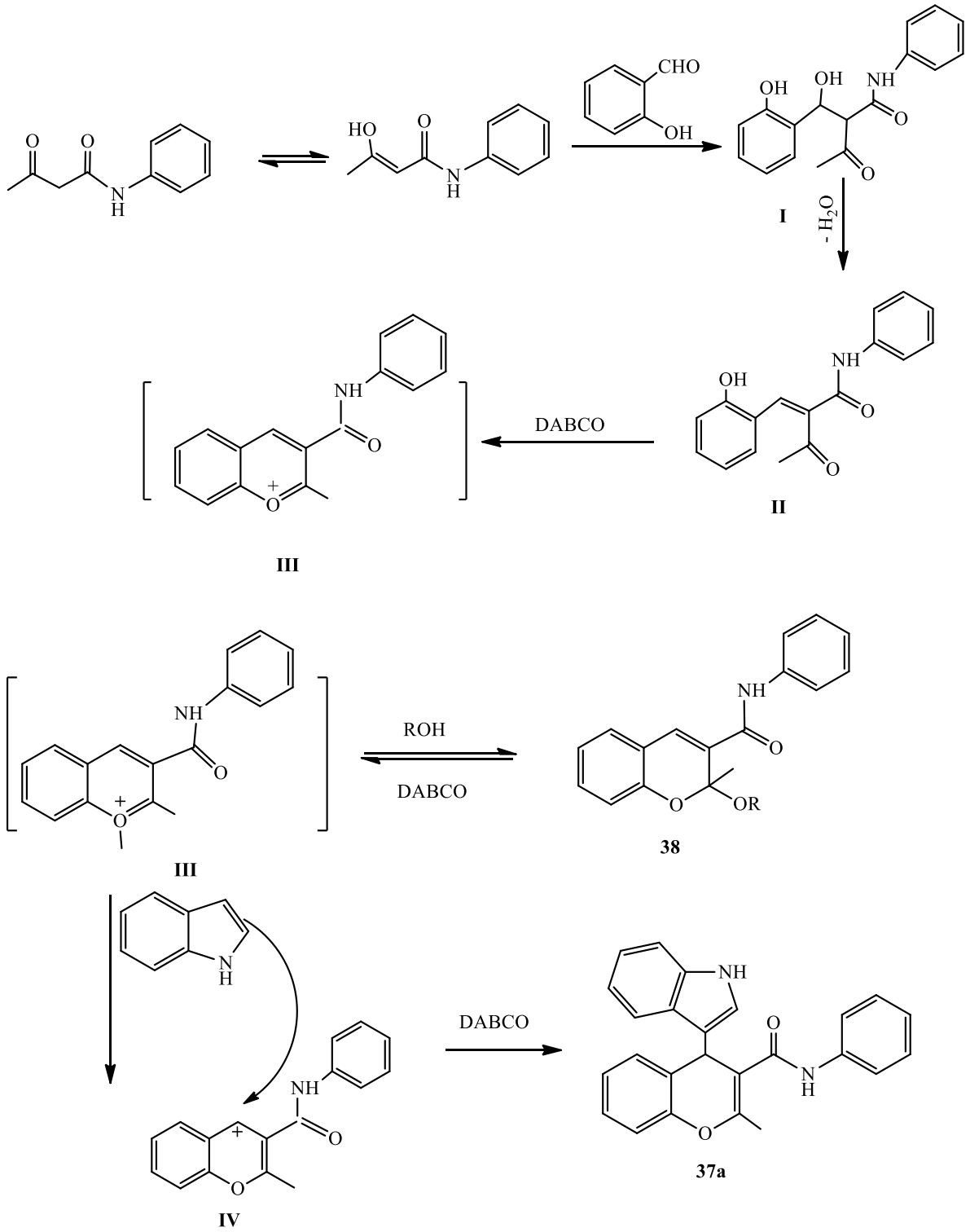
37a, R = H, R^1 = H, R^2 = H
b, R = H, R^1 = H, R_2 = 2-CH_3
c, R = H, R^1 = 2-CH_3, R^2 = H
d, R = H, R^1 = 2-CH_3, R^2 = 2-CH_3
e, R = H, R^1 = 4-CH_3, R^2 = H
f, R = H, R^1 = 4-CH_3, R^2 = 2-CH_3

37g, R = H, R^1 = 4-Cl, R^2 = H
h, R = H, R^1 = 4-Cl, R^2 = 2-CH_3
i, R = 3-OCH_3, R^1 = H, R^2 = H
j, R= 3-OCH_3, R^1 = H, R^2 = 2-CH_3
k, R = 3-OCH_3, R^1 = 2-CH_3, R^2 = H
l, R =3-OCH_3, R^1 = 2-CH_3, R^2 = 2-CH_3

37m, R = 3-OCH_3, R^1 = 4-CH_3, R^2 = H
n, R = 3-OCH_3, R^1 = 4-CH_3, R^2 = 2-CH_3
o, R = 3-OCH_3, R^1 = 4-Cl, R^2 = H
p, R = 3-OCH_3, R^1 = 4-Cl, R^2 = 2-CH_3

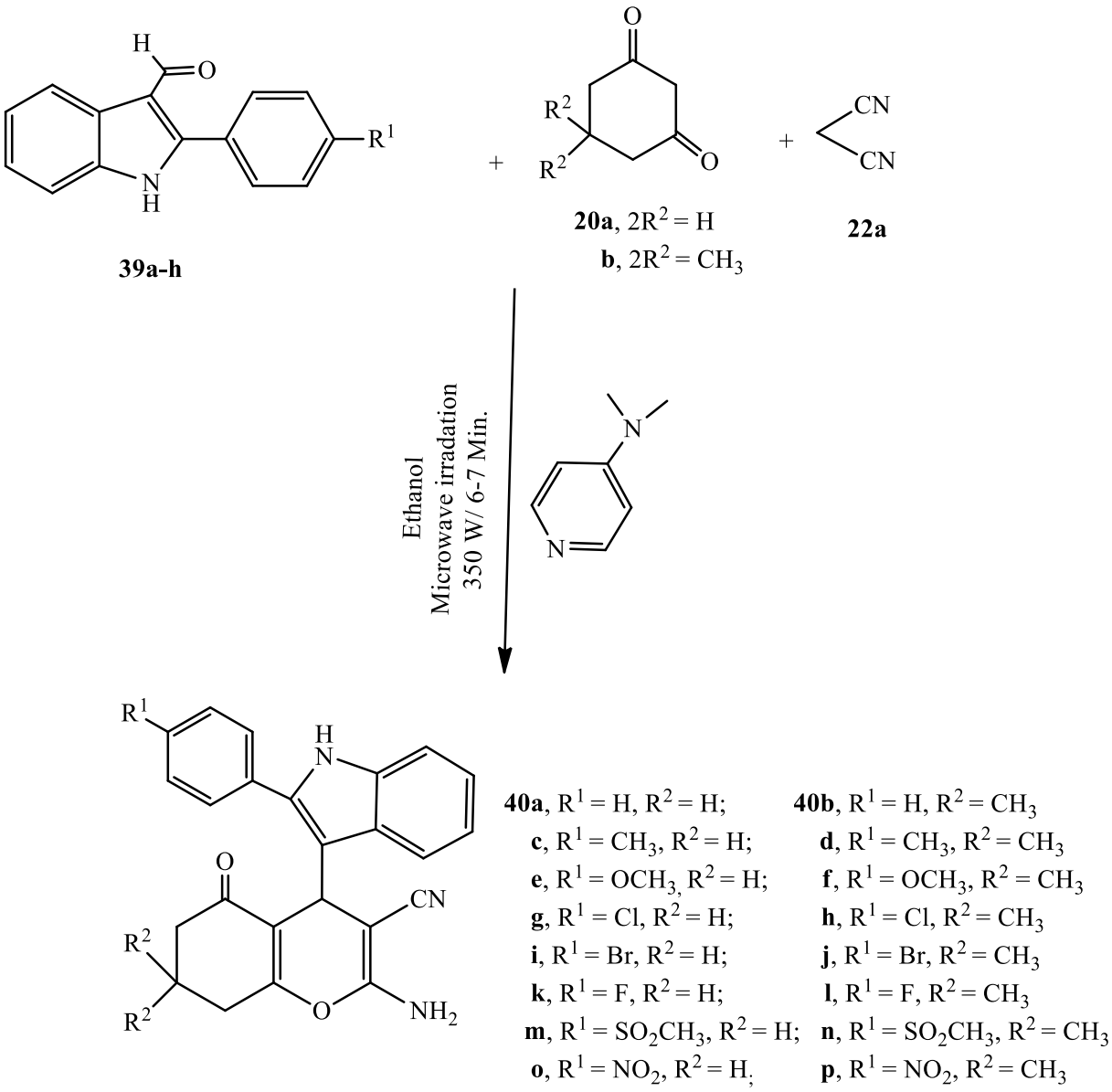
Scheme 5. Synthesis of indolyl-4H-chromene-3-carboxamides **37a-p**

Indolyl-4H-chromene-3-carboxamides **37a** was afforded *via* the multi-component reactions between acetoacetanilide, salicylaldehyde, and indole in the presence of methanol as a protic solvent, which played a significant role in the rearrangement and cyclization processes. In the first step compound **I** was formed according to Knoevenagel condensation between salicylaldehyde, acetoacetanilide, which was followed by formation of compound **38** *via* a benzopyrylium cation intermediate. In addition, the indole reacted with compound **38** in the presence of DABCO to give compound **37** through the elimination of the methoxy group (Scheme 6). An antioxidant evaluation for all the synthesized compounds **37a-p** was conducted by using DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity. The IC_{50} values of the newly synthesized compounds **37a–p** was compared with ascorbic acid as an available antioxidant. The results showed that compounds **37c**, **37d**, **37k**, **37l** and **37p** displayed good activity. Moreover, all of the synthesized compounds **37a-p** were subjected for in vitro antibacterial activity against different Gram-negative and Gram-positive bacterial strains. The results displayed that compound **37p** exhibited excellent activity against all the bacterial strains. In addition, compounds **37k** and **37l** showed good activity against *Micrococcus luteus* and *Staphylococcus aureus*, while compounds **37c** and **37d** displayed moderate inhibitory against *S. aureus* in comparison with ampicillin.[18]



Scheme 6. Plausible mechanism for the synthesis of indolyl-4H-chromene-3-carboxamides **37a**

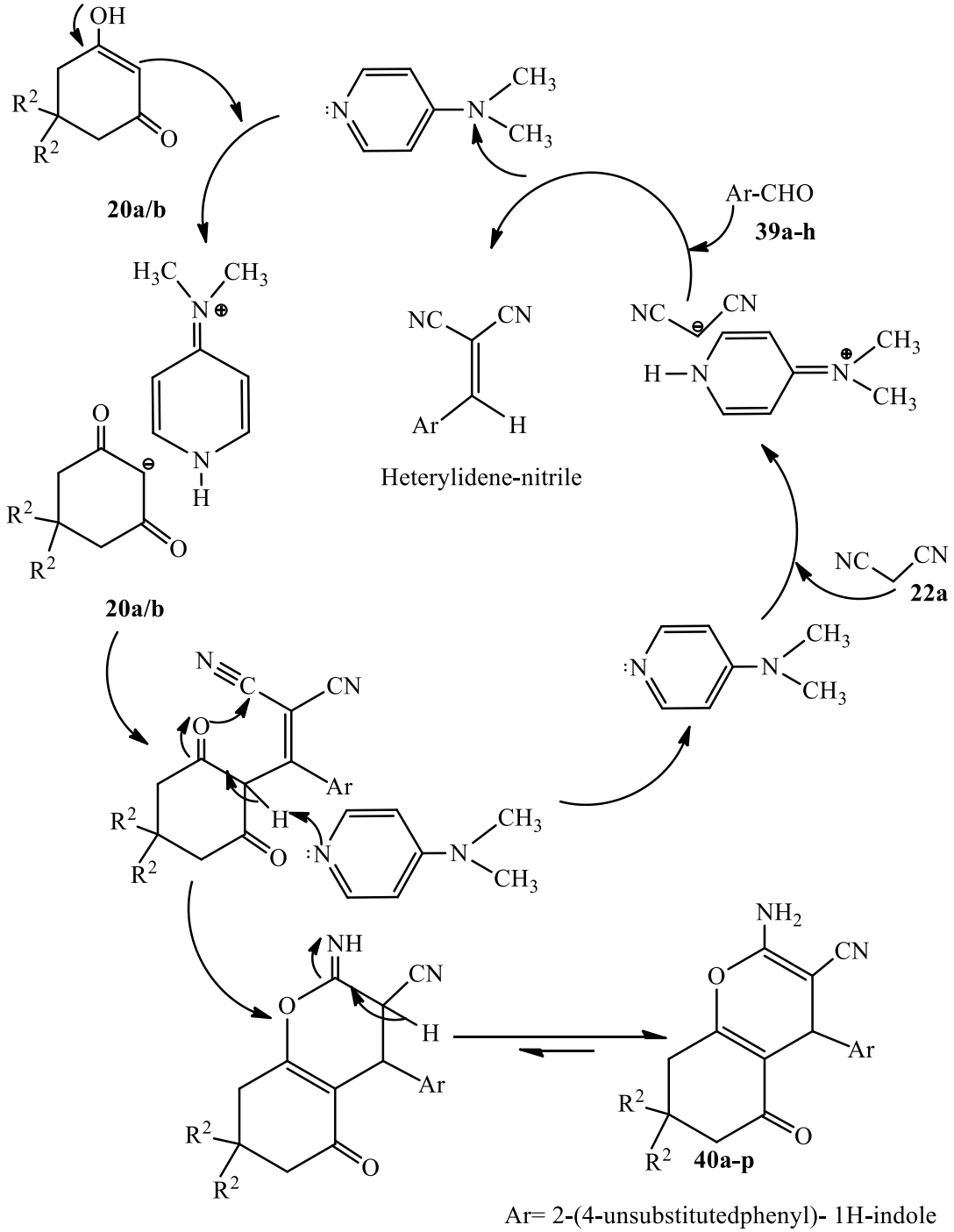
One-pot three-component cyclocondensation reaction between cyclohexanedione/dimedone (**20a**/**20b**), malononitrile (**22a**) and 2-phenyl-1H-indole-3-carbaldehyde **39a–h** under microwave irradiation and in the presence of DMAP as a catalyst afforded 4H-chromene derivatives **40a-p** (Scheme 7).[19]



Scheme 7. Synthesis of 4H-chromene derivatives **40a-p**

According to the suggested mechanism in the literature,[20] heterylidenenitrile was produced from Knoevenagel condensation between malononitrile (**22a**) and 2-phenyl-1H-indole-3-carbaldehyde **39a-h** in the presence of DMAP as a base, which was followed by Michael addition of (**20a**/**20b**) to heterylidenenitrile. Then a nucleophilic attack of the hydroxyl group to cyano yielded 4H-chromene derivatives **40a-p** (Scheme 8). The synthesized compounds **40a-p** were screened for their antibacterial efficacy towards antifungal (*Candida albicans* and *Aspergillus fumigatus*) as well as towards Gram-positive bacteria (*Streptococcus pneumoniae*, *Bacillus subtilis*, *Clostridium tetani*) and Gram-negative bacteria (*Salmonella typhi*, *Escherichia coli*, and *Vibrio cholerae*) at different concentrations as a primary screening. Further tests at different dilute concentrations for the compounds were displayed the highest efficacy in the primary screening. The minimum inhibitory concentration (MIC) was evaluated for each compound, and griseofulvin was used as a reference antifungal drug, while norfloxacin and ampicillin were used as reference antibacterial drugs. The results indicated that most of the compounds exhibited good antifungal and antibacterial activities when compared with reference drugs. Compounds **40d**, **40p** and **40n** showed high efficacy towards *C. albicans* when compared with griseofulvin. Compounds **40e**, **40h**, **40i**, and **40n** showed high antimicrobial activity towards *E. coli* and towards most of the used strains. While compound **40l** showed a high efficacy towards *B. subtilis*, compounds **40e**, **40m** and **40n**

displayed activity towards *C. tetani* when compared with ampicillin.. These results were obtained according to the second dilution indicated in the reference.[19]

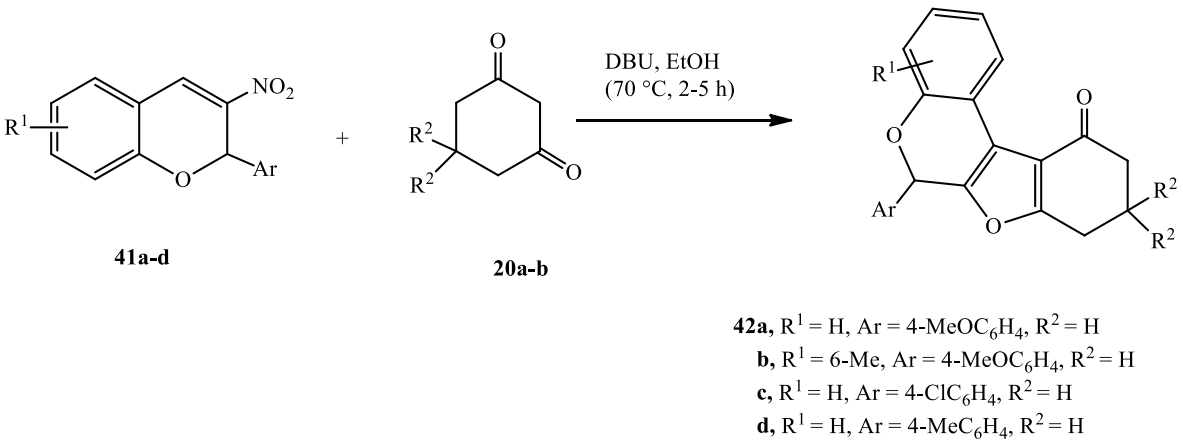


Scheme 8. Plausible mechanism for synthesis of 4H-chromene derivatives **40a-p**

Compounds **40b**, **40g** ,**40i** ,**40j** and **40k** towards *B. subtilis* as well as compounds **40b**, **40i**, **40l** and **40p** towards *C. tetani* displayed higher activities than ampicillin. Compounds **40d**, **40h** and **40o** exhibited similar activity toward ampicillin and compounds **40e** and **40m** showed equipotent activity towards *C. tetani* when compared with ciprofloxacin. In addition, compounds **40d**, **40e**,**40h**, **40n**, and **40o** exhibited equal results towards *B. subtilis* when compared to ampicillin. Moreover, compounds **40l**, **40i** displayed

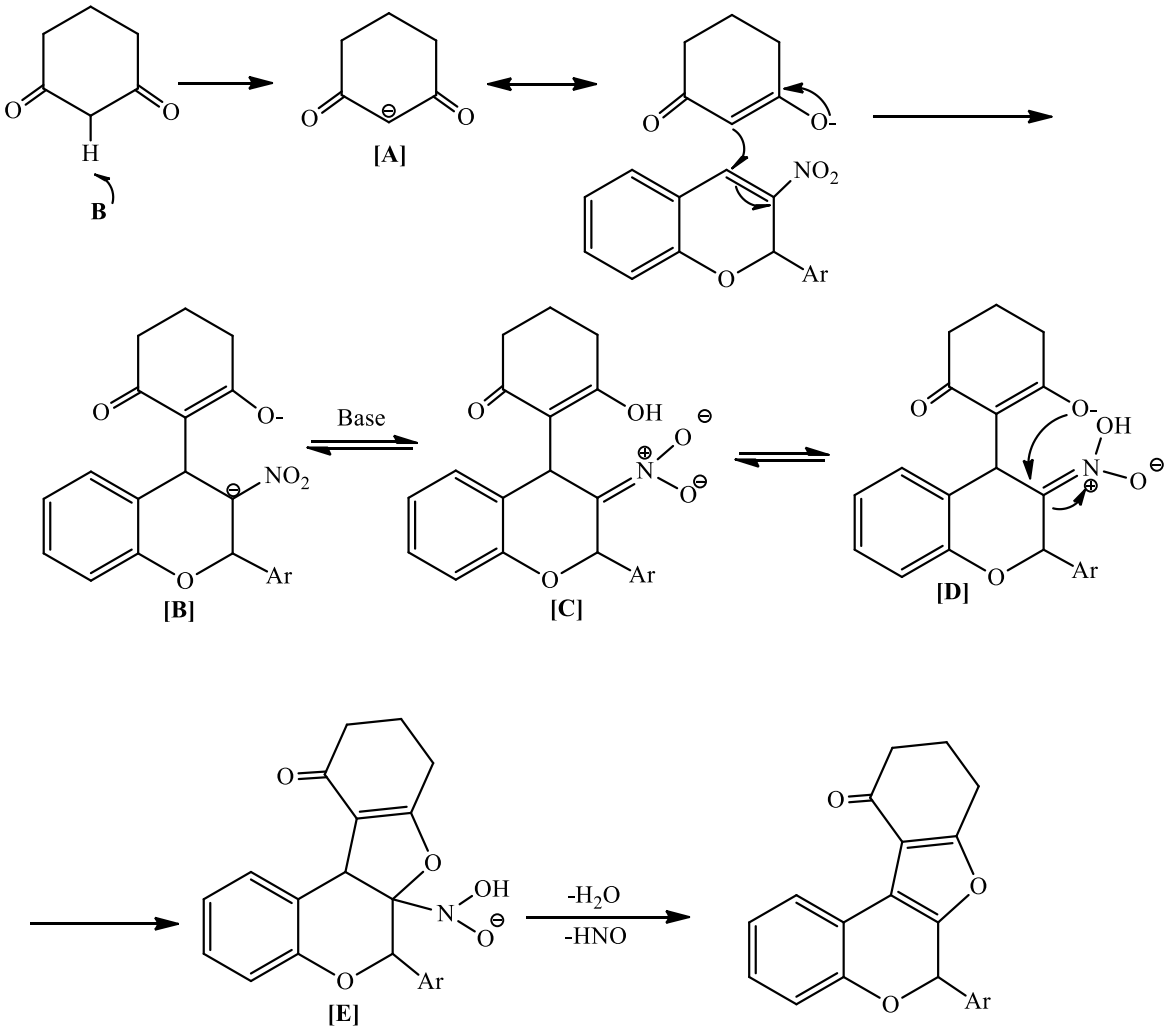
similar efficacy towards *S. pneumonia* when compared with norfloxacin and ampicillin, respectively. It was of great value to mention that compound **40m** and compounds **40g**, **40h** exhibited comparable efficacy towards *S. typhi* and *V. cholerae*, respectively, when compared with ampicillin. Finally, compounds **40d**, **40e**, **40f**, **40i** and **40e**, **40g**, **40m**, **40n** showed similar efficacy towards *C. albicans* and *E. coli* when compared with griseofulvin and ampicillin, respectively, whereas compounds **40e**, **40g**, **40m** and **40n** were found to be equally active compared to ampicillin towards *E. coli*. Compounds **40d**, **40e**, **40f** and **40i** were found to possess equipotent efficacy with griseofulvin towards *C. albicans*

3-Nitro-2-aryl-2H-chromenes **41**, possessing electron-withdrawing or electron-donating substituents on the phenyl moiety were reacted with 5,5-dimethyl-1,3-cyclohexanediones (**20b**) or 1,3-cyclohexanediones (**20a**) to produce benzofurochromenone derivatives **42a-d**, (Scheme 9).[21]



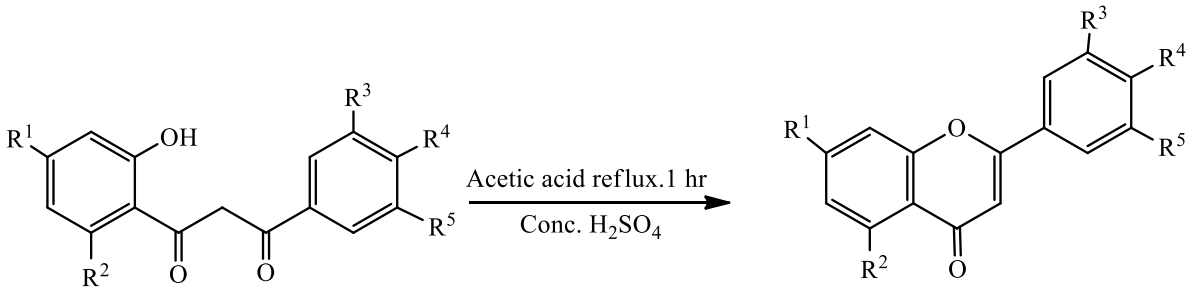
Scheme 9. Synthesis of benzofurochromenone derivatives **42a-d**

A possible mechanism for the synthesis of benzofurochromenone derivatives **42a-d** was based on authors' previous works and the literature reports (Scheme 10).[22-27] Initially, the intermediate carbanion [A] is formed in the presence of DBU as a base, acting on active methylene of 1,3-cyclohexanedione. Next, the intermediate [B] occurs through a Michael addition of 2-aryl-3-nitro-2H-chromene to enol [A], then, the intermediate enol [C] forms by the keto-enol tautomerism of the intermediate [B]. The intermediate enol anion [D] is produced with a proton shift, which is followed by an intramolecular cyclization to form the intermediate [E]. The chromenone derivatives **42a-d** were produced by elimination of water and HNO.[21]



Scheme 10. Suggested mechanism for the synthesis of benzofurochromenone derivatives **42a-d**

The chromene derivatives **44a-n** were synthesized from (o-hydroxydibenzoylmethane **43a-n**[28,29] in the presence of acetic acid and conc. H_2SO_4 under a reflux condition for 1 h (Scheme 11). They were purified using silica column chromatography employing ethyl acetate:hexane mixture (4:6) as a solvent.[30] A method of Matsuura et al[31] was used to determine advanced glycation end-products formation inhibitory efficacy **(**AGEs**),** where all the newly synthesized compounds **44a-n** were subjected to in vitro AGEs formation inhibitory efficacy. The results indicated that the synthesized compounds exhibited important AGEs formation inhibitory efficacy. Compound **44l** showed a better efficacy than the reference aminoguanidine. Compounds **44n**, **44k**, **44j**, **44m** and **44i** also showed pronounced inhibitory efficacy, while the compounds **44h**, **44f**, **44b, 44d**, **44a**, **44c**, **44g**, and **44e** showed lower antiglycation efficacy than aminoguanidine.[30] On the other hand, modified Ellman's method (Ellman et al. 1961)[32] was used to evaluate the acetylcholinesterase (AChE) inhibitory efficacy of all the synthesized compounds, which were tested in vitro, employing a rat brain homogenate, while donepezil was used as a standard drug. The results showed that compounds **44m**, **44b**, and **44j** exhibited higher inhibitory efficacy than donepezil. Compounds **44n**, **44g**, **44h**, and **44i** also exhibited important AChE inhibitory efficacy. The synthesized compounds **44k-n** with (-OH) group displayed a good AChE efficacy.[30]



o-Hydroxydibenzoylmethane

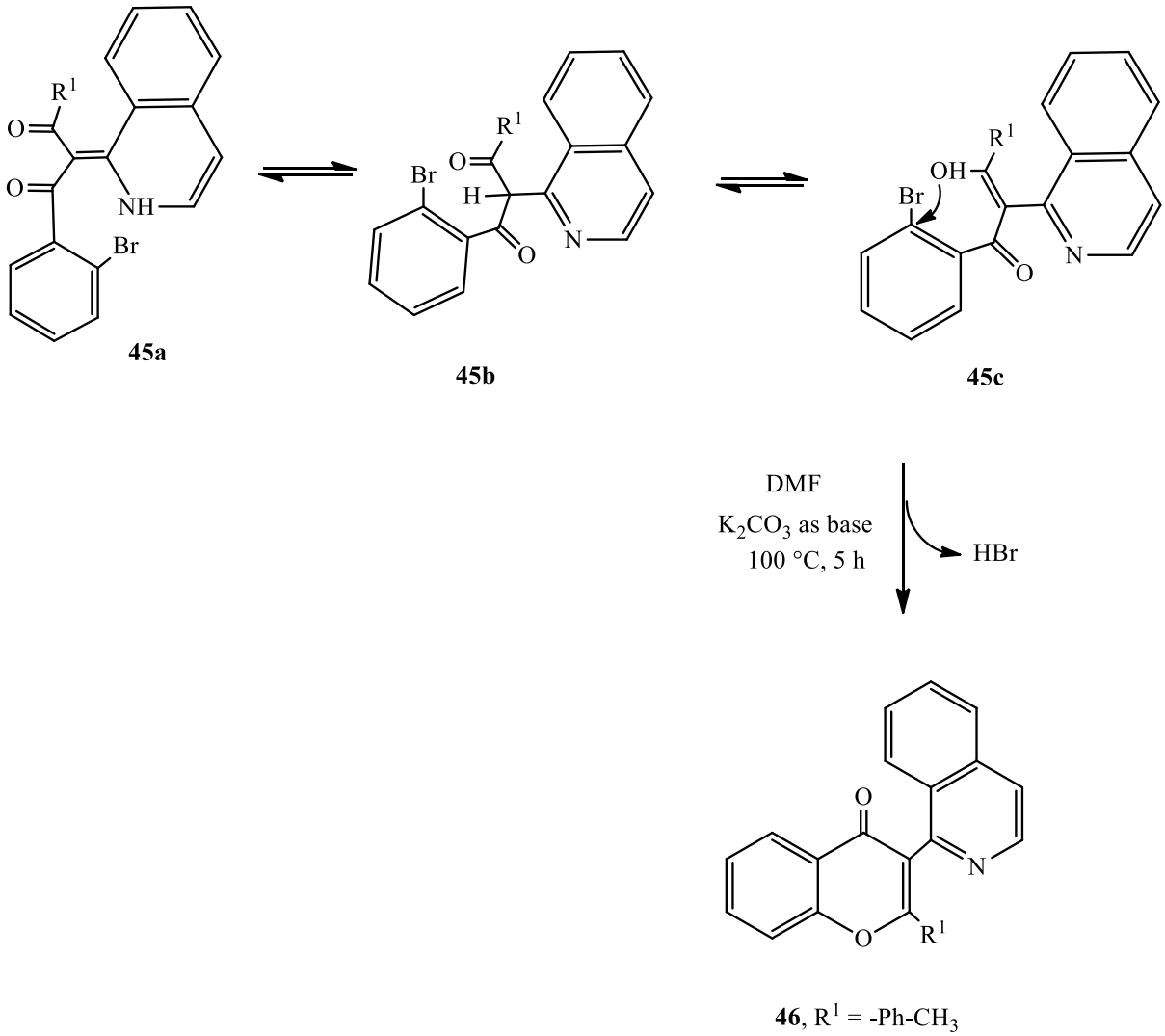
43a-n

Flavones

44a, $R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$
b, $R^1 = H$, $R^2 = H$, $R^3 = NO_2$, $R^4 = H$, $R^5 = H$
c, $R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = NO_2$, $R^5 = H$
d, $R^1 = H$, $R^2 = H$, $R^3 = Cl$, $R^4 = H$, $R^5 = H$
e, $R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = Cl$, $R^5 = H$
f, $R^1 = H$, $R^2 = H$, $R^3 = F$, $R^4 = H$, $R^5 = H$
g, $R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = F$, $R^5 = H$
h, $R^1 = H$, $R^2 = H$, $R^3 = H$, $R^4 = OCH_3$, $R^5 = H$
i, $R^1 = H$, $R^2 = H$, $R^3 = OCH_3$, $R^4 = OCH_3$, $R^5 = OCH_3$
j, $R^1 = H$, $R^2 = H$, $R^3 = NO_2$, $R^4 = H$, $R^5 = NO_2$
k, $R^1 = OH$, $R^2 = H$, $R^3 = H$, $R^4 = H$, $R^5 = H$
l, $R^1 = OH$, $R^2 = OH$, $R^3 = H$, $R^4 = H$, $R^5 = H$
m, $R^1 = OH$, $R^2 = H$, $R^3 = H$, $R^4 = F$, $R^5 = H$
n, $R^1 = OH$, $R^2 = H$, $R^3 = H$, $R^4 = OCH_3$, $R^5 = H$

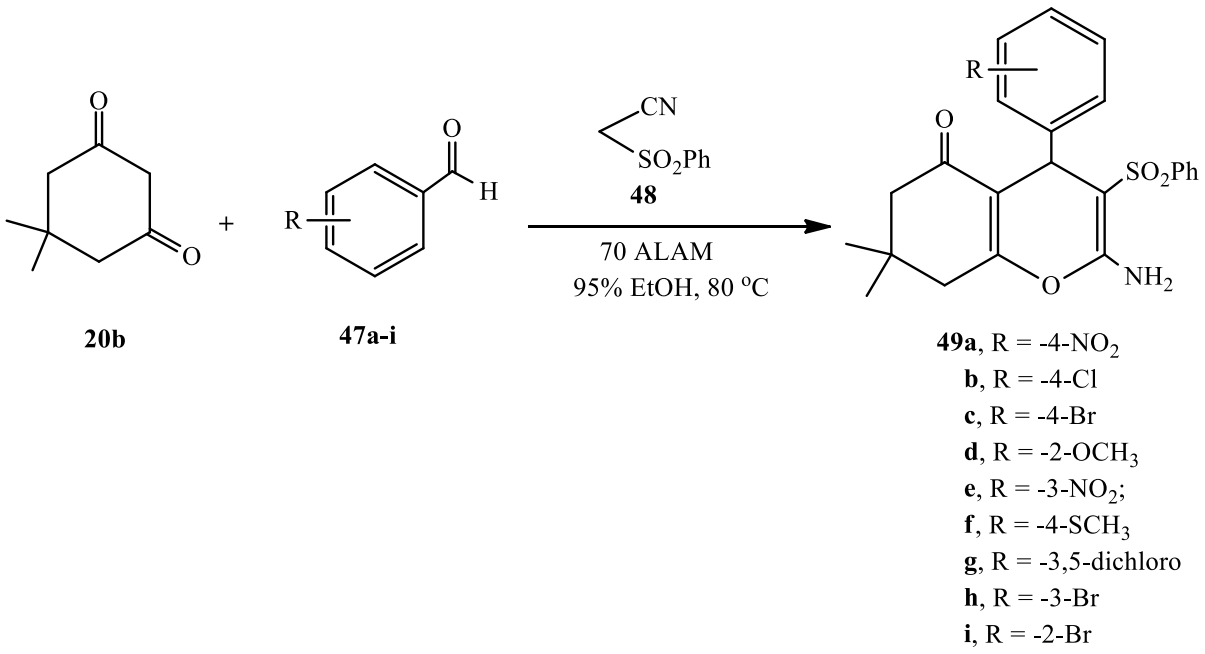
Scheme 11. Synthesis of 2-phenyl-4H-chromen-4-one derivatives **44a-n**

Treating of the tautomer **45a**, **45b**, or **45c** using K_2CO_3 as a base under standard conditions, the corresponding product **46** was obtained in 94% yield (Scheme 12).[33]



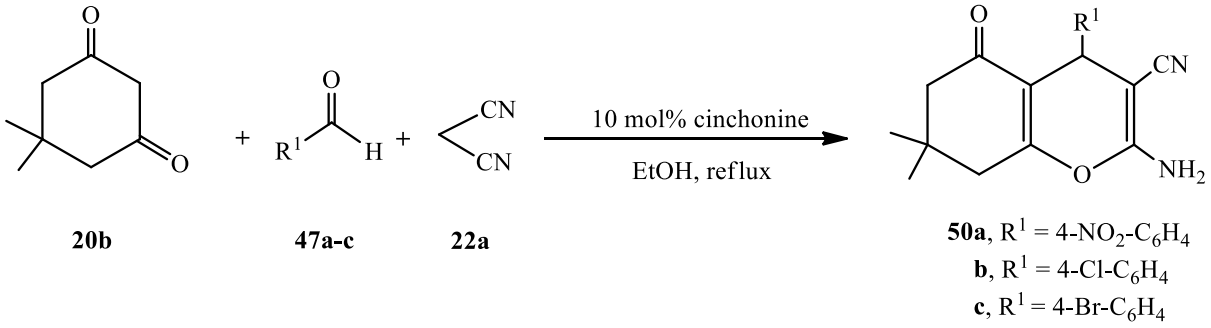
Scheme 12. Synthesis of 3-((iso)quinolin-1-yl)-4H-chromen-4-ones **46**

Treatment of dimedone (**20b**) with the aldehydes (**47a-i**) and (phenylsulfonyl)acetonitrile (**48**) in the presence of ALAM catalyst in ethanol afforded 2-amino-4H-chromene derivatives **49a-i** (Scheme 13). The reaction took place according to Knoevenagel condensation between (phenylsulfonyl)acetonitrile **48** and aryl aldehyde, which was followed by Michael addition to dimedone (**20b**), then, nucleophilic attack and, lastly, cyclization to give the target chromenes.[34]



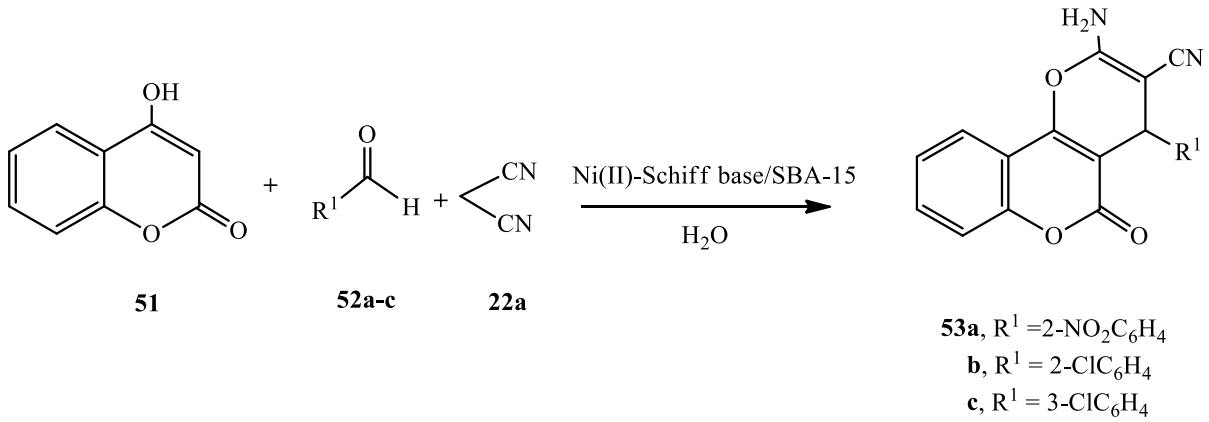
Scheme 13. Synthesis of chromene derivatives **49a-i**

Tetrahydro-4H-chromenes **50a-c** were produced *via* a one-pot domino Knoevenagel–Michael cyclocondensation reaction of activated C–H acids dimedone (**20b**), aromatic aldehydes (**47a-c**), and malononitrile (**22a**) as an active methylene compound in ethanol in the presence of cinchonine as a catalyst under reflux conditions (Scheme 14).[35]



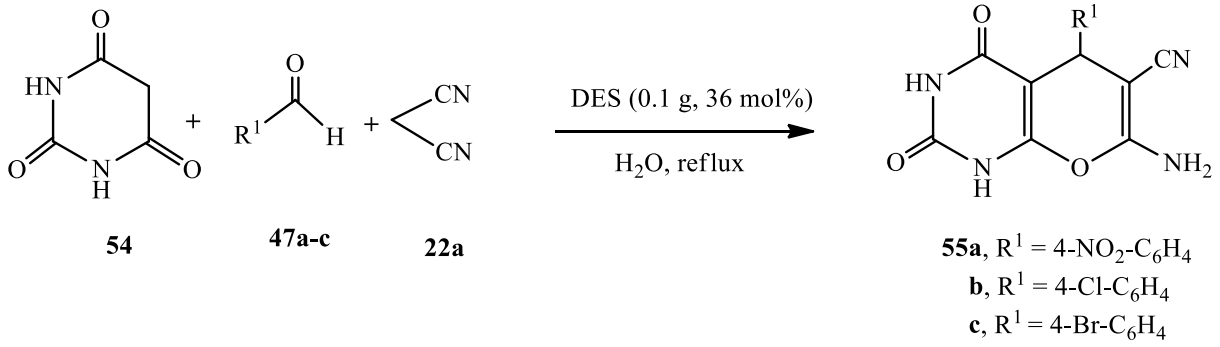
Scheme 14. Synthesis of tetrahydro-4H-chromene derivatives **50a-c**

One-pot three-component cyclocondensation process was described with the reaction between 4-hydroxycoumarin **51**, malononitrile (**22a**) and various aldehydes (**52a-c**) in aqueous media for the synthesis of 3,4-dihydropyrano[3,2-c]chromene derivatives **53a-c** in the presence of Ni(II)-Schiff base/SBA-15 as an environmentally benign catalyst (Scheme 15).[36]



Scheme 15. One-pot synthesis of 3,4-dihydropyrano[c]chromene derivatives **53a-c**

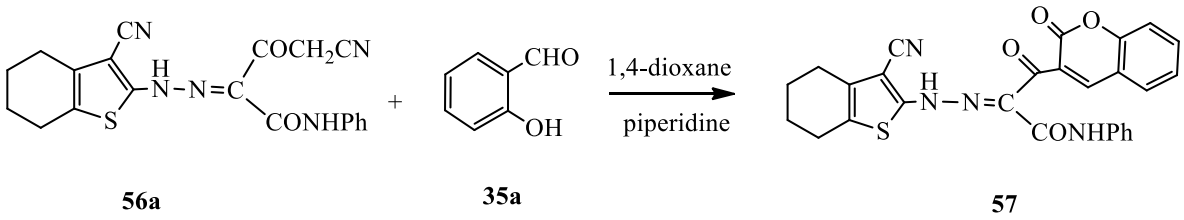
Biglari et al. described an efficient one-pot method for the synthesis of pyrano[2,3-d]pyrimidinone derivatives **55a-c** through a three-component reaction between enolizable C–H activated acidic compound (**54**), aldehydes (**47a-c**) and malononitrile (**22a**) using a new deep eutectic solvent (DES), made of choline chloride, urea and thiourea as a green catalyst (Scheme 16).[37]



Scheme 16. Synthesis of pyrano[2,3-d]pyrimidinone derivatives **55a-c**

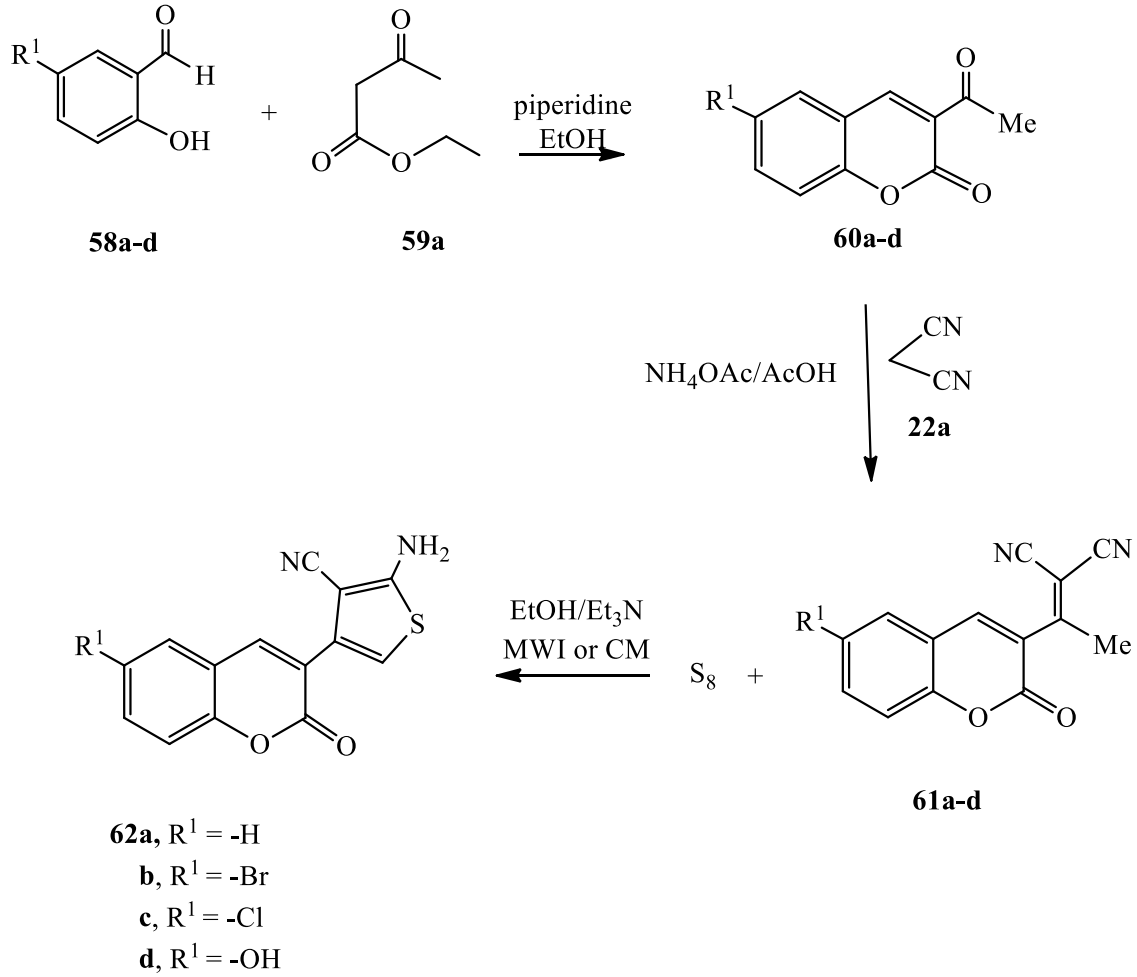
3. Synthesis of Biologically Active Coumarin Derivatives from 1,3-Diketone

The coumarin derivative **57** was synthesized through the reaction between the thiophene derivative **56a** and salicylaldehyde (**35a**) in 1,4-dioxane and piperidine (Scheme 17). Compound **57** showed a high inhibitory effect against different cancer cell lines, namely, breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460), central nervous system cancer (SF-268), and the normal fibroblast cells (WI 38) after a continuous exposure for 48 h and such activities were higher than the reference doxorubicin.[38]



Scheme 17. Synthesis of coumarin derivative **57**

Synthesis of 4-thienylcoumarin derivatives **62a-d**, using two protocols MWI and CM, in a stepwise was reported. Thus, treatment of ethyl acetoacetate (**59a**) with various substituted salicylaldehyde (**58a-d**) in ethanol and in the presence of piperidine afforded corresponding 3-acetylcoumarins **60a-d**. In addition, compounds **60a-d** were reacted with malononitrile (**22a**) to produce corresponding ethylidenemalononitrile derivatives **61a-d**. The latter compounds were reacted with elemental sulfur S_8 to produce the 4-thienylcoumarin derivatives **62a-d** (Scheme 18).

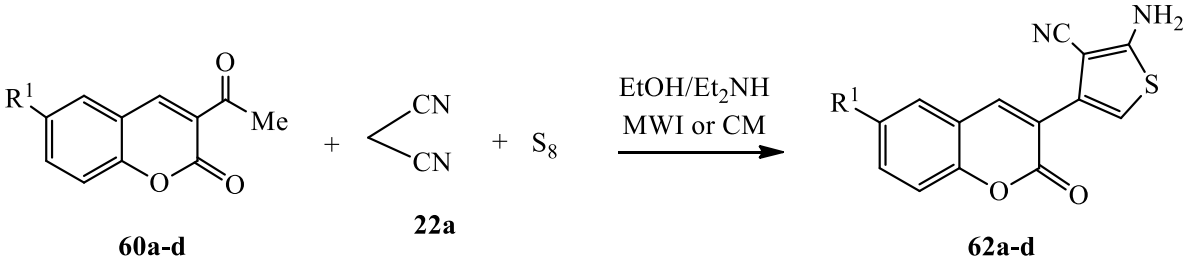


58a-d **59a** **60a-d** **22a** **61a-d**

62a, R^1 = -H
b, R^1 = -Br
c, R^1 = -Cl
d, R^1 = -OH

Scheme 18. Synthesis of coumarin-thiophene derivatives **62a-d**

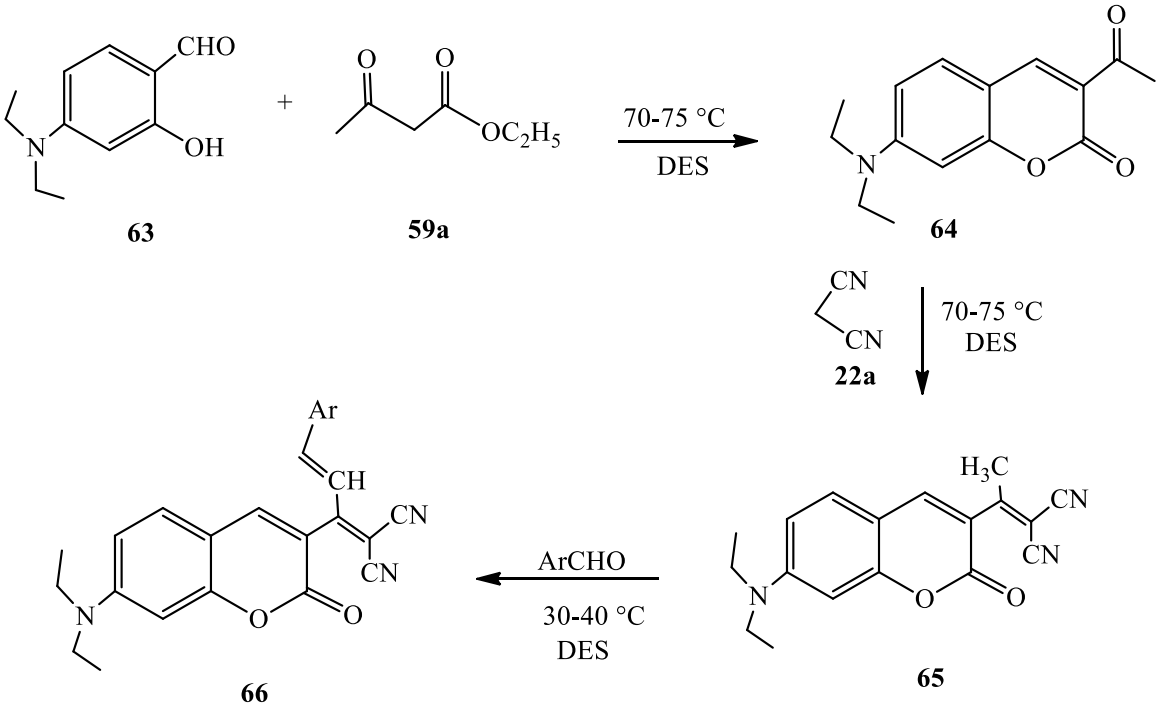
4-Thienylcoumarin derivatives **62a-d** were prepared in a one-pot three-component reaction in ethanol and in the presence of diethylamine for the CM and MWI in 80-85% and 82-90% yields, respectively. Moreover, the reaction durations for the CM and MWI were 14-20 min and 3-5 min, respectively (Scheme 19).[39]



60a-d **22a** **62a-d**

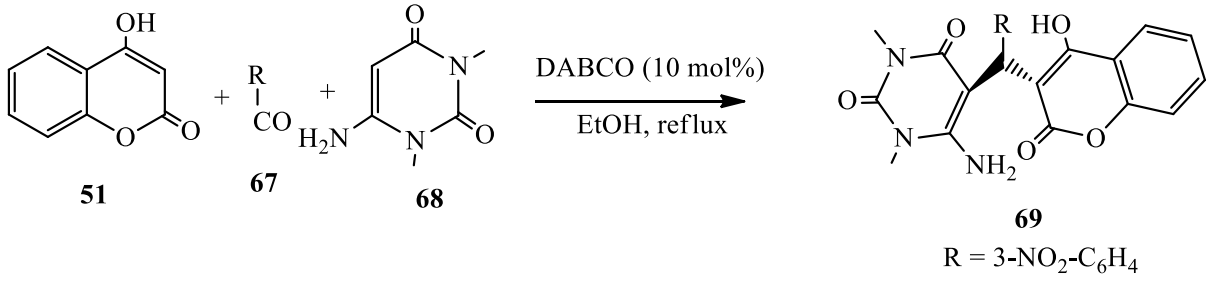
Scheme 19. Synthesis of coumarin-thiophene derivatives **62a-d**

Treatment of ethyl acetoacetate (**59a**) with 4-(diethylamino)-2-hydroxybenzaldehyde (**63**) in deep eutectic solvent (DES) (ChCl:urea),[40] afforded the chromene derivative **64**. Furthermore, compound **64** was reacted with malononitrile (**22a**) to give chromene derivative **65**, and the latter compound was reacted with different aromatic aldehydes to furnish the chromene derivative **66** (Scheme 20).[41]



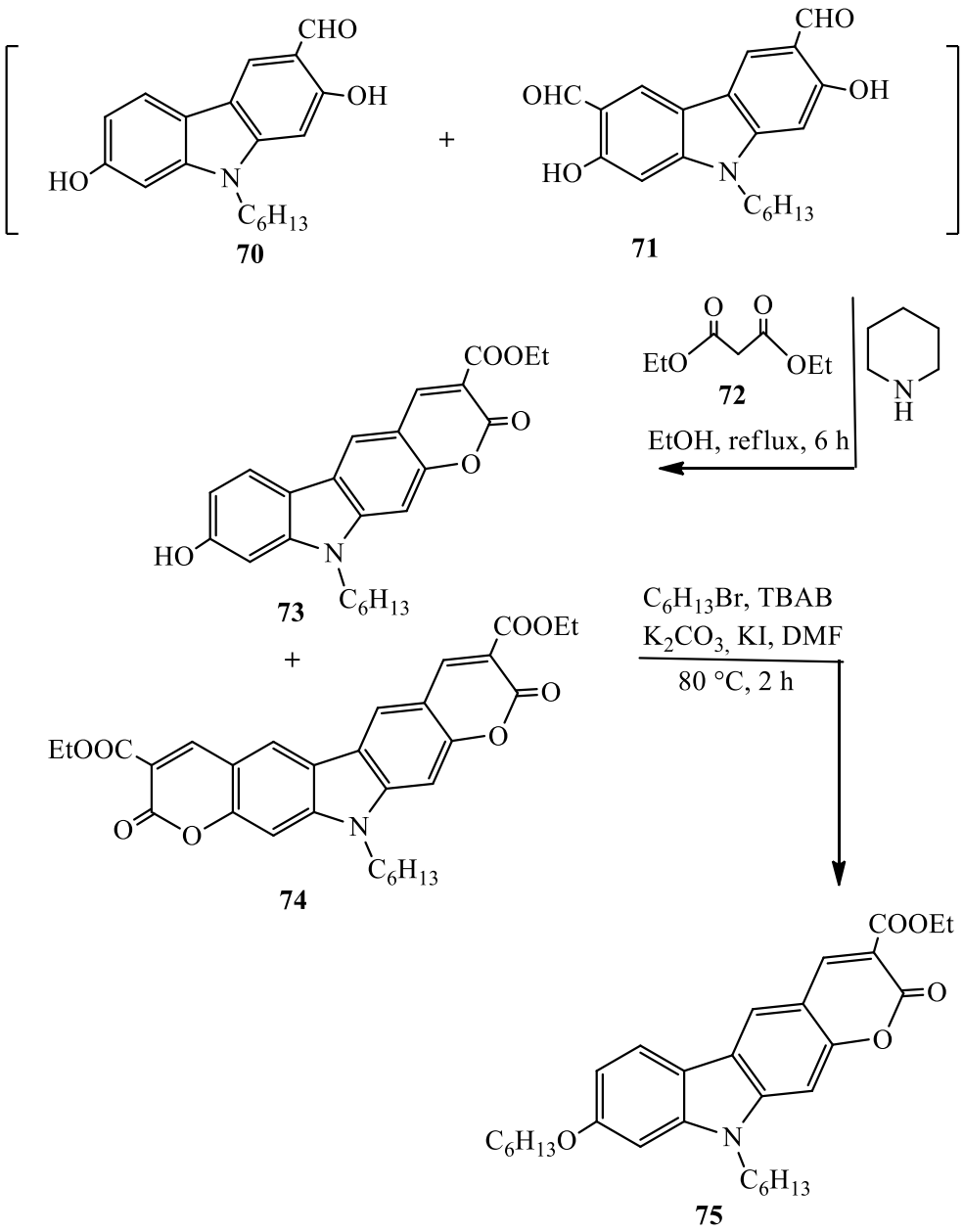
Scheme 20. One pot synthesis of fluorescent colorant **66** in deep eutectic solvents

Treatment of 4-hydroxycoumarin **51** with 3-nitrobenzaldehyde (**67**) and 6-amino-1,3-dimethyluracil (**68**) in the presence of DABCO in ethanol under reflux gave the coumarin derivative **69** in an excellent yield (Scheme 21).[42]



Scheme 21. Synthesis of coumarin derivative **69**

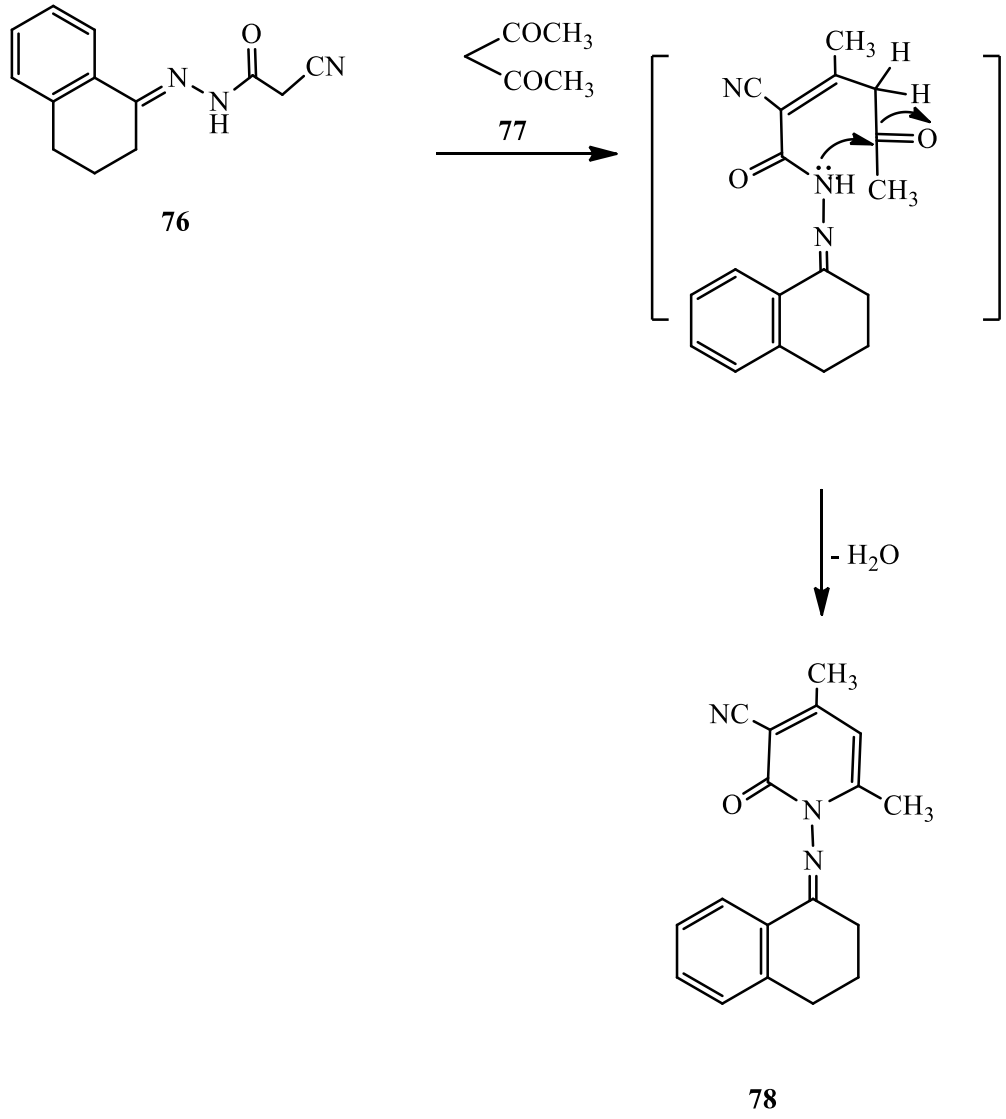
According to Li et al. the intermediates **70** and **71** were reacted, without separation, with diethyl-malonate (**72**) in ethanol and piperidine under reflux for 6 h to give the coumarins **73** and **74**, which were separated by column chromatography. Compound **74** was reacted with 1-bromohexane in the presence of anhydrous potassium carbonate, potassium iodide and tetrabutylammonium bromide (TBAB) in dimethylformamide (DMF) to produce coumarin **75** (Scheme 22).[43]



Scheme 22. Synthesis of coumarin derivative **75**

4. Synthesis of Biologically Active Pyridine Derivatives from 1,3-Diketone

The reaction of 2-cyano-N'-(3,4-dihydronaphthalen-1(2H)-ylidene)acetohydrazide **76** with acetylacetone (**77**) afforded the 2-pyridone derivative **78** (Scheme 23).[44]

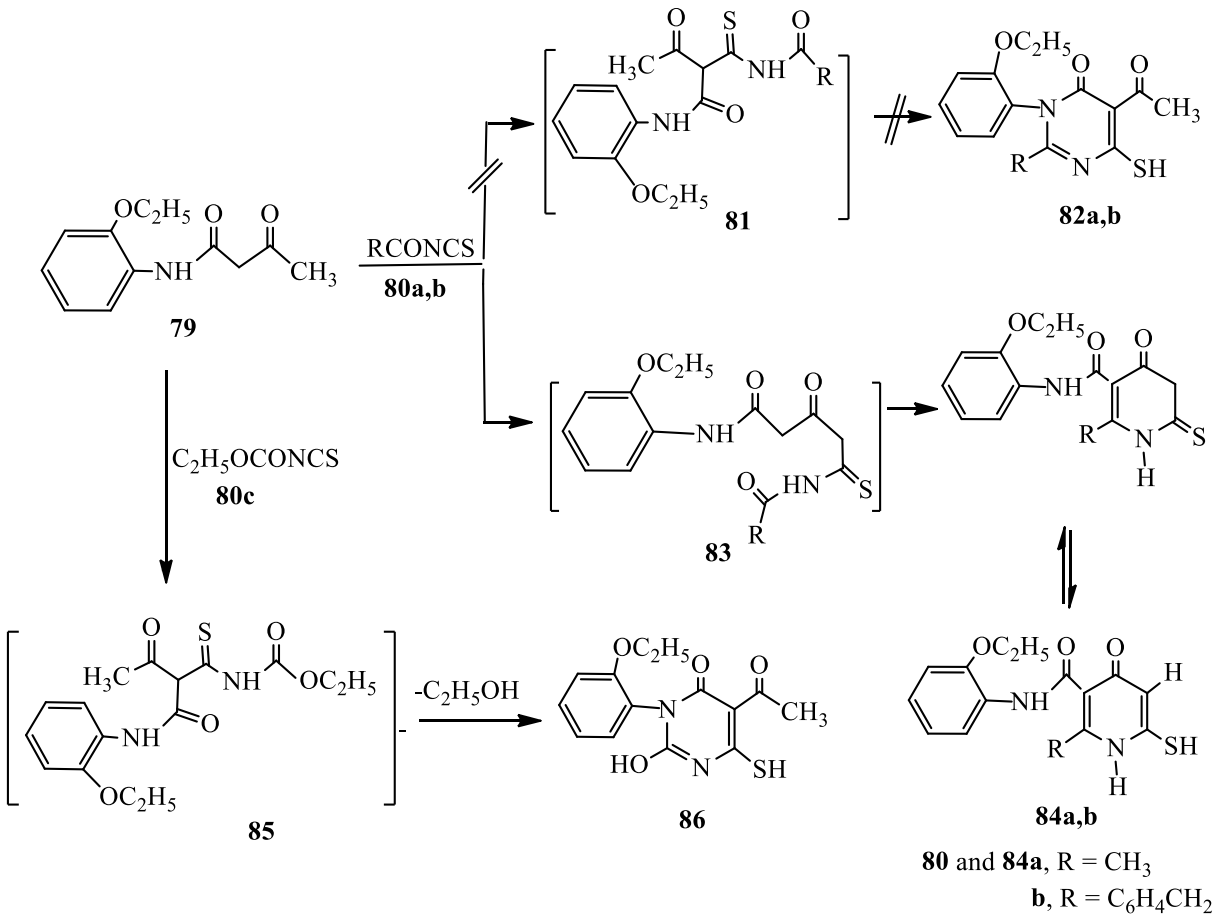


76

78

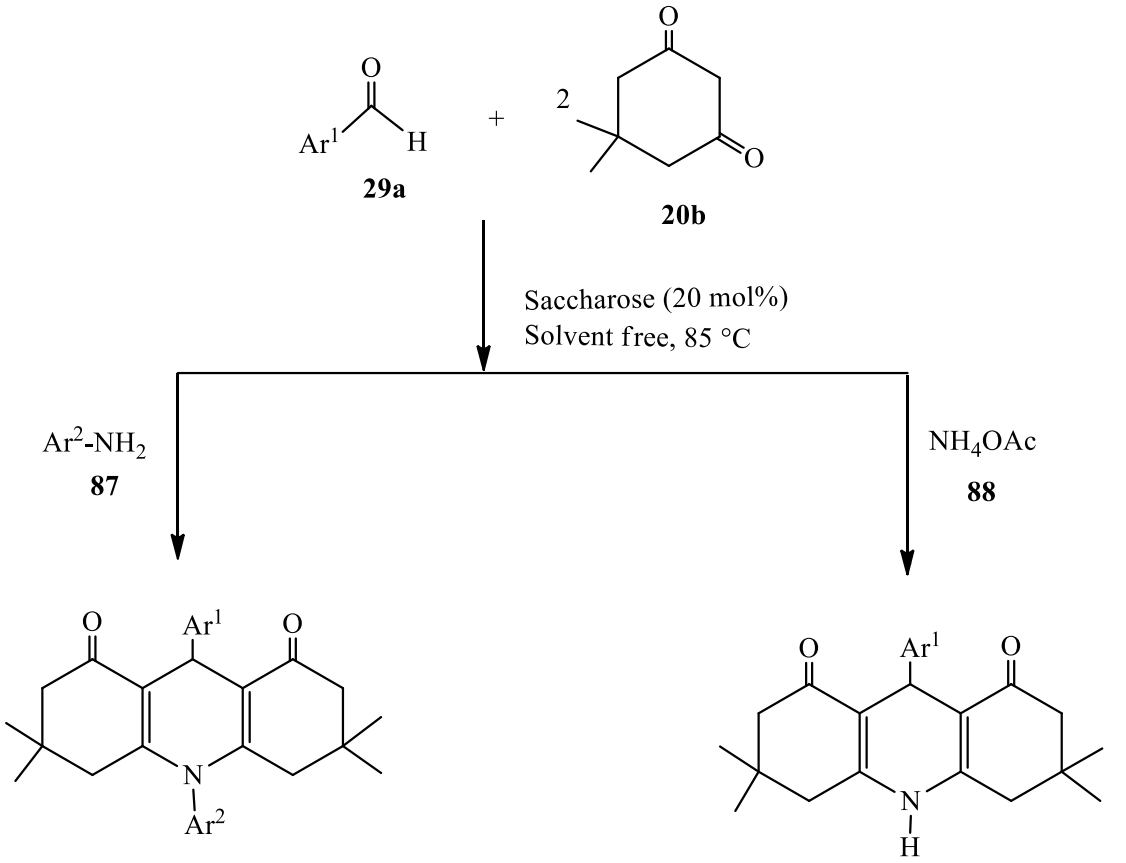
Scheme 23. Synthesis of 2-pyridone derivative **78**

β-Oxoanilide **79** was synthesized according to Bigi et al.[45] which involved the reacted with acetyl isothiocyanate (**80a**) in dry acetone to afford the unexpected pyridine derivative **84a**, rather than the expected pyrimidine derivative **82a**. On the other hand, ethoxycarbonyl isothiocyanate (**80c**) was reacted with β-oxoanilide **79** under the same reaction conditions to afford the expected pyrimidinethiol derivative **86** through the intermediate **85** (Scheme 24).[46]



Scheme 24. Synthesis of pyridine **84a,b** and pyrimidinethiol **86**

The reaction between dimedone (**20b**), various aryl aldehydes, and ammonium acetate or aryl amines in the presence of (20 mol%) of saccharose at 85 °C gave substituted 1,8-dioxodecahydroacridine in high yields (Scheme 25).

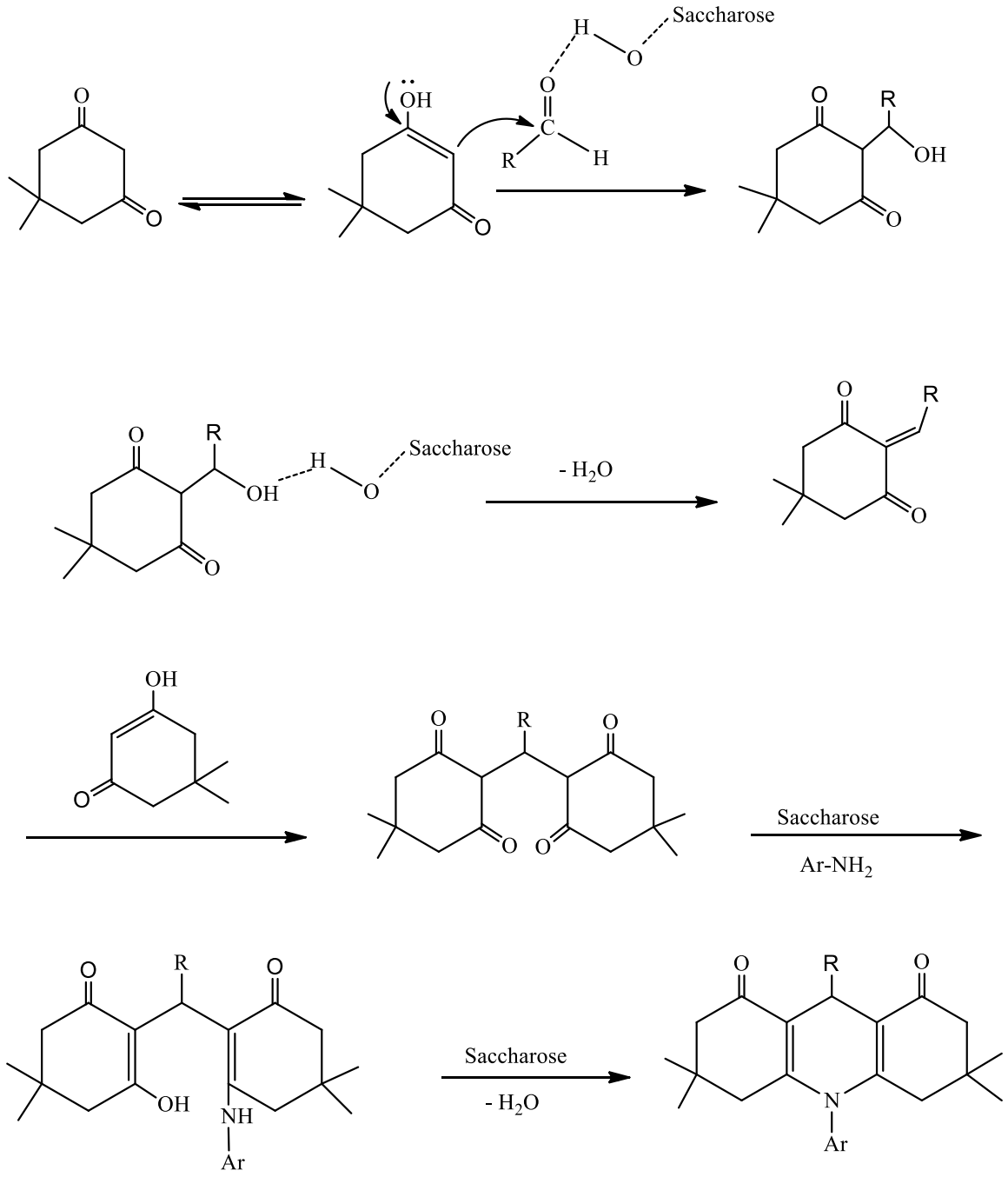


89a, Ar^1 = Ph, Ar^2 = Ph
b, Ar^1 = 4-ClC_6H_4, Ar^2 = Ph
c, Ar^1 = 4-ClC_6H_4, Ar^2 = 4-$MeOC_6H_4$
d, Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$
e, Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-$MeOC_6H_4$
f, Ar^1 = Ph, Ar^2 = 4-MeC_6H_4
g, Ar^1 = 4-ClC_6H_4, Ar^2 = 4-MeC_6H_4
h, Ar^1 = 3-$O_2NC_6H_4$, Ar^2 = 4-MeC_6H_4
i, Ar^1 = 4-OHC_6H_4, Ar^2 = 4-MeC_6H_4
j, Ar^1 = 4-ClC_6H_4, Ar^2 = 4-ClC_6H_4
k, Ar^1 = 4-ClC_6H_4, Ar^2 = 4-$O_2NC_6H_4$

90a, Ar^1 = Ph
b, Ar^1 = 4-$O_2NC_6H_4$
c, Ar^1 = 2,3-$(MeO)_2C_6H_3$
d, Ar^1 = 3-$O_2NC_6H_4$
e, Ar^1 = 4-$MeOC_6H_4$
f, Ar^1 = 4-HOC_6H_4
g, Ar^1 = $CH_3(CH_2)_5$

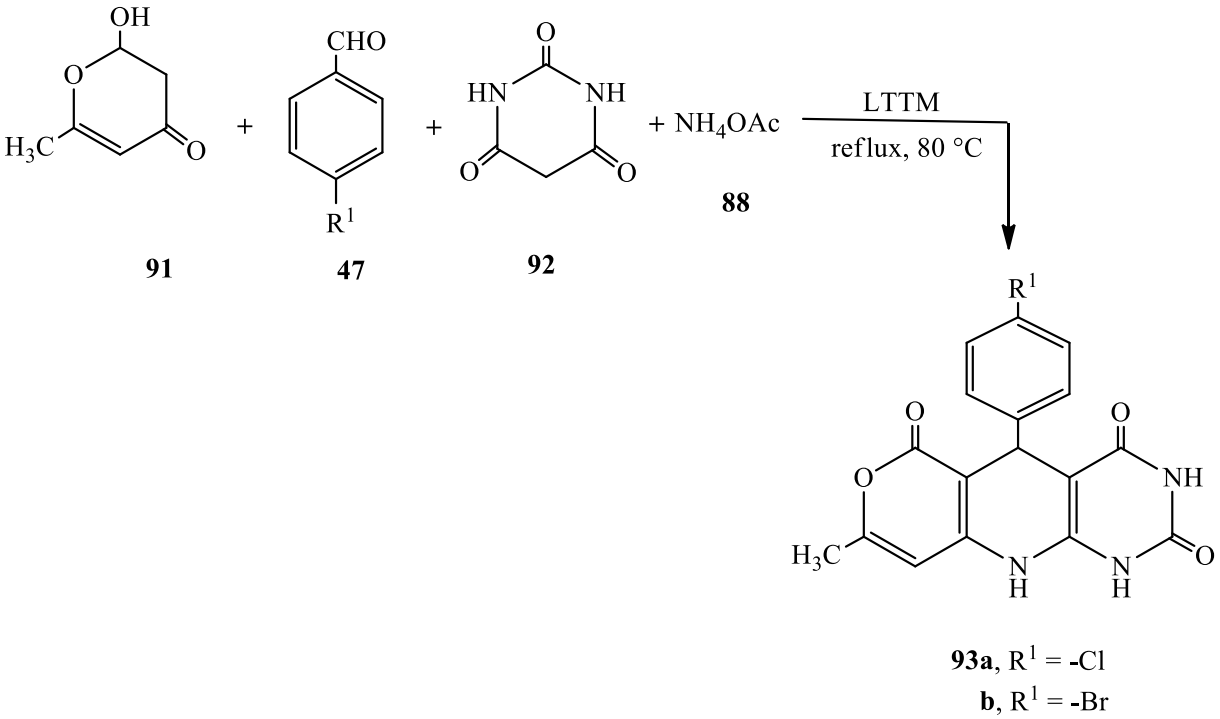
Scheme 25. Synthesis of 1,8-dioxodecahydroacridine derivatives **89a-k** and **90a-g**

According to Maghsoodlou et al. the carbonyl group of the aldehyde (**29a**) and dimedone (**20b**) were activated by saccharose, which catalyzes the reaction and makes them sensitive to nucleophilic attack (Scheme 26).[47]



Scheme 26. Proposed mechanism for the synthesis of 1,8-dioxodecahydroacridine derivatives

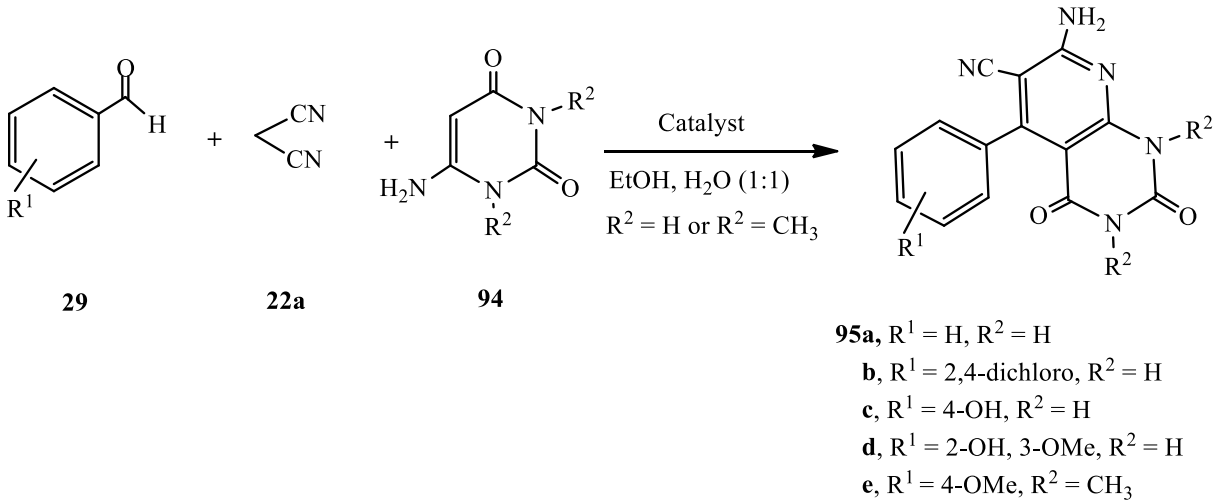
The reaction of 4-hydroxy 6-methyl 2-pyrone (**91**) with the aromatic aldehyde (**47**), barbituric acid (**92**), and ammonium acetate **88** in a low transition temperature mixture (LTTM) (glycerol:proline: 1:1) as a green solvent gave diverse substituted pyrido-pyrimidines **93a-b** (Scheme 27).[48]



93a, R^1 = -Cl
b, R^1 = -Br

Scheme 27. Synthesis of substituted pyrido-pyrimidine **93a-b**

Pyrido[2,3-d]pyrimidines **95a-e** were developed in the presence of Mn-ZIF-8@$ZnTiO_3$ as a heterogeneous recyclable nano-catalyst, in water and EtOH (Scheme 28).[49]

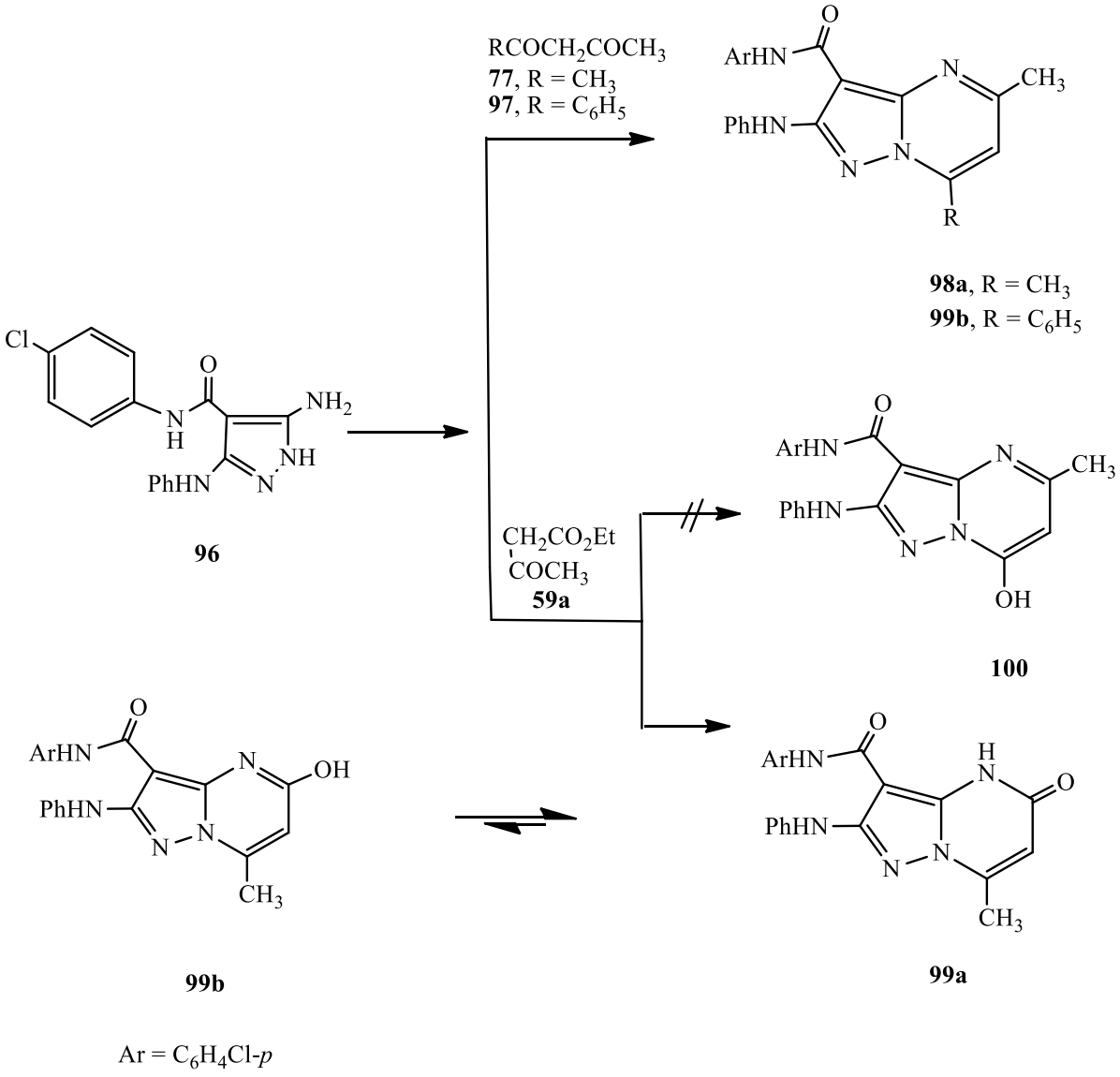


95a, R^1 = H, R^2 = H
b, R^1 = 2,4-dichloro, R^2 = H
c, R^1 = 4-OH, R^2 = H
d, R^1 = 2-OH, 3-OMe, R^2 = H
e, R^1 = 4-OMe, R^2 = CH_3

Scheme 28. Synthesis of pyrido[2,3-d]pyrimidines **95a-e**

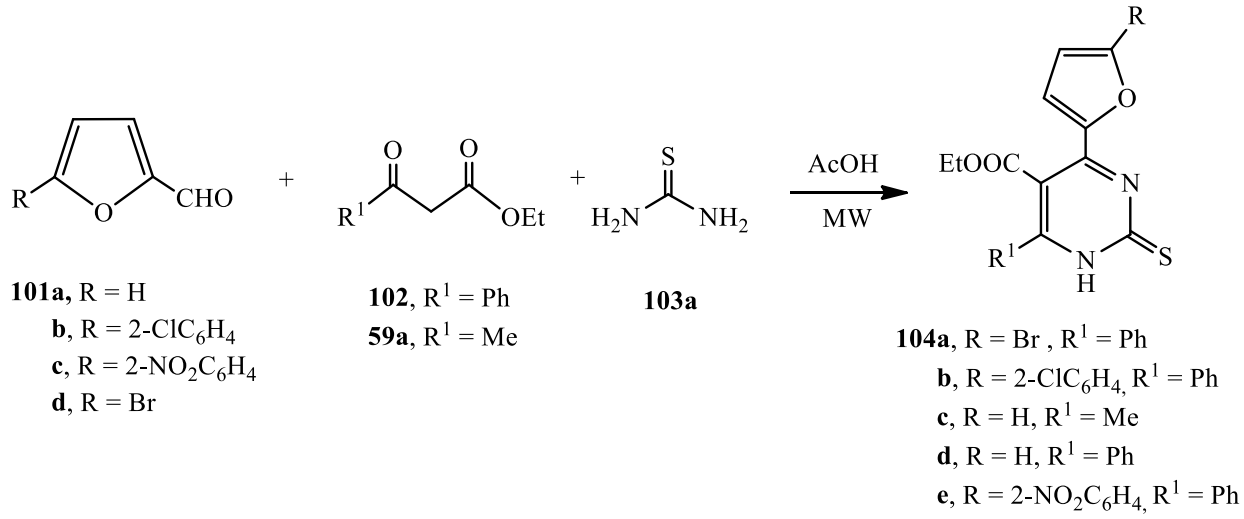
5. Synthesis of Biologically Active Pyrimidine Derivatives from 1,3-Diketone

Condensation of compound **96** with symmetrical and unsymmetrical diketones in acetic acid under reflux conditions furnished the pyrazolopyrimidine derivatives **98a,b**. On the other hand, the reaction of aminopyrazole **96** with ethyl acetoacetate (**59a**) in acetic acid afforded two possible isomeric products **99** and **100**. The structure of compound **100** was excluded on the basis of spectral data and analogy with previous work.[50] Compound **99** was found mainly in the keto form due to the presence of the carbonyl amide group for which there is a possibility of conjugation to form the enol form (Scheme 29).[51,52]



Scheme 29. Synthesis of pyrazolopyrimidine **98a,b** and **99**

Pyrimidine-2-thiones **104a–e** (Scheme 30) were prepared in a one pot reaction of (**101a–d**), ethyl acetoacetate (**59a**) or ethyl 2,4-dioxo-4-phenylbutanoate (**102**) and thiourea (**103a**) according to Bignelli reaction under assisted microwave irradiation technique.[53]



101a, R = H
b, R = 2-ClC_6H_4
c, R = 2-$NO_2C_6H_4$
d, R = Br

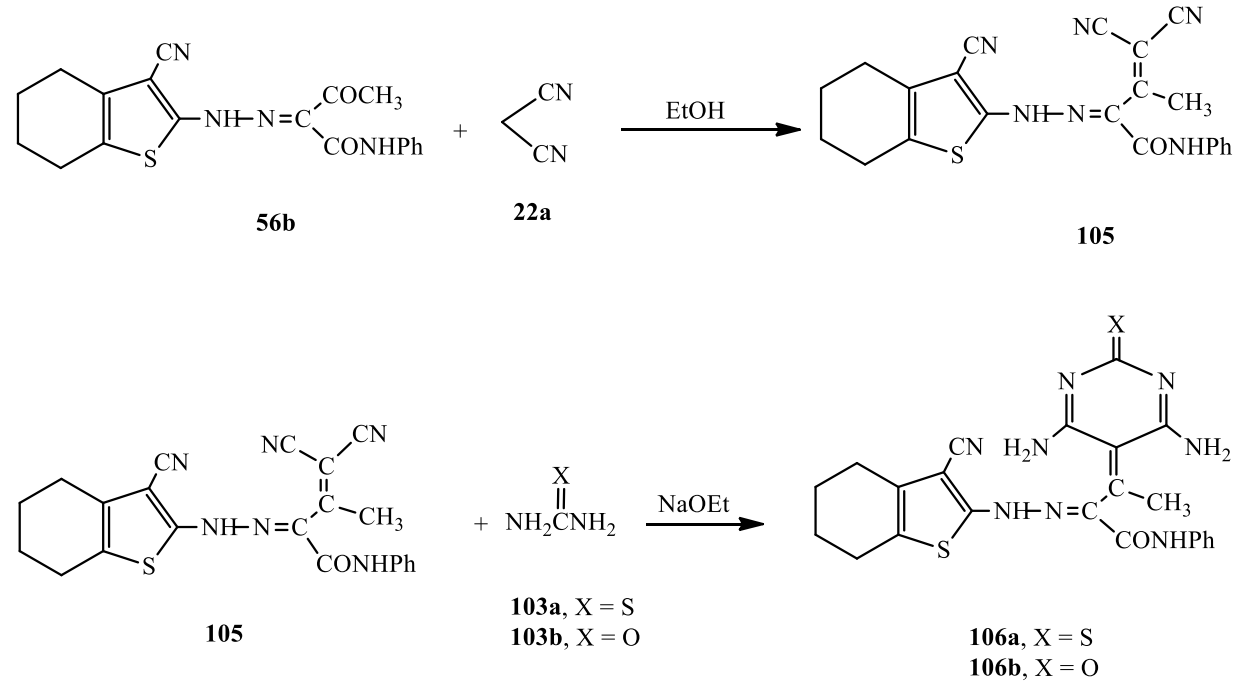
102, R^1 = Ph
59a, R^1 = Me

103a

104a, R = Br , R^1 = Ph
b, R = 2-ClC_6H_4, R^1 = Ph
c, R = H, R^1 = Me
d, R = H, R^1 = Ph
e, R = 2-$NO_2C_6H_4$, R^1 = Ph

Scheme 30. Synthesis of pyrimidine-2-thiones **104a-e**

The reaction of compound **56b** with malononitrile (**22a**) in ethanol gave the acyclic structure **105**. The reaction of **105** with either thiourea (**103a**) or urea (**103b**) in sodium ethoxide solution gave the pyrimidine derivatives **106a** and **106b** respectively (Scheme 31). Compound **106a** displayed high inhibition towards breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268), which was less than the reference doxorubicin.[38]

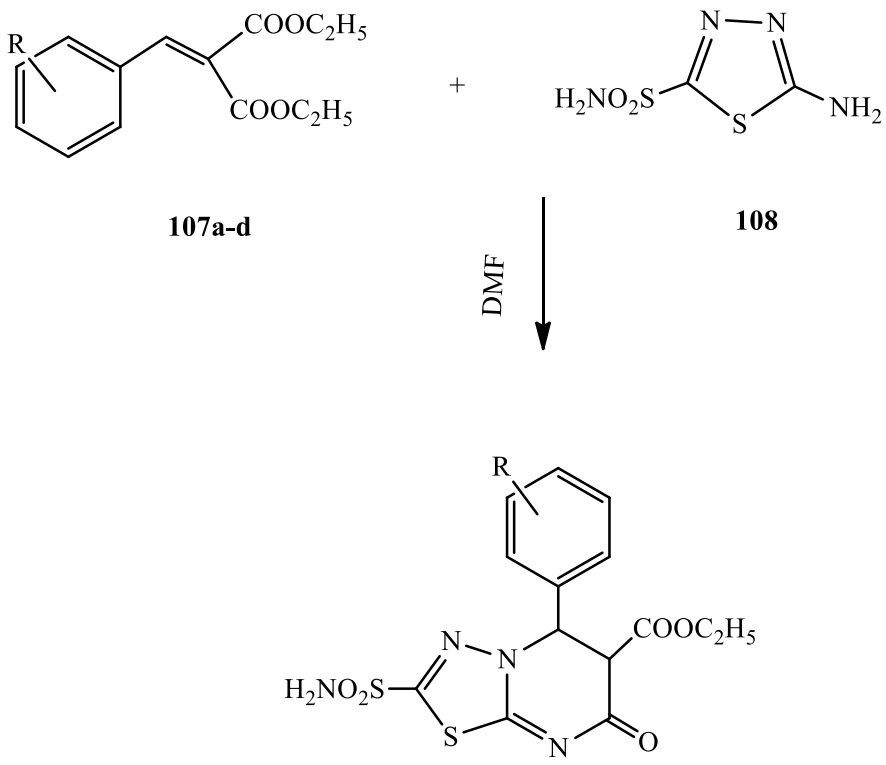


103a, X = S
103b, X = O

106a, X = S
106b, X = O

Scheme 31. Synthesis of the pyrimidine derivatives **106a,b**

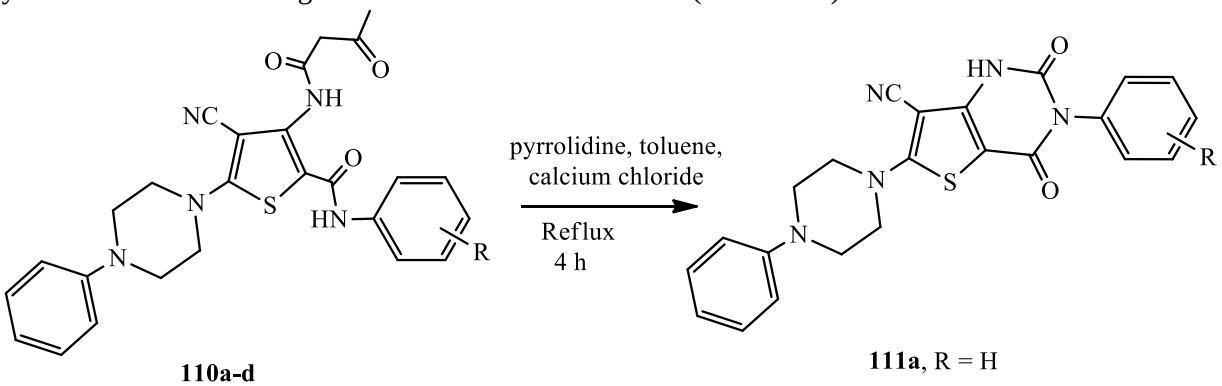
Cyclocondensation reaction between the benzylidene derivatives of diethyl-malonate **107a-d**,[54] and amine **108**, which was afforded by acid hydrolysis of 2-acetamido-1,3,4-thiadiazole-5-sulfonamide,[55] gave thiadiazolo-pyrimidine **109a-d** (Scheme 32).[56] Compound **109d** was screened for its in vitro growth inhibition efficacy towards nine cancer subpanels; namely, non-small cell lung, leukemia, CNS, colon, ovarian, melanoma, prostate, breast and renal cancer cells.[57-60] The growth inhibition (GI%) of the individual cell lines was evaluated and reported. Compound **109d** displayed broad spectrum anticancer efficacy towards various cancer subpanels with selective efficacy towards non-small lung cancer (HOP-92), leukemia (HL-60(TB)), renal cancer (A498) and melanoma (LOX IMVI) cell lines.[56]



109a, R = 4-Br
b, R = 4-Cl
c, R = 3,4-$(OCH_3)_2$
d, R = 4-$N(CH_3)_2$

Scheme 32. Synthesis of thiadiazolo-pyrimidine **109a-d**

β-keto amides **110a-d** were cyclized to thienopyrimidine-2,4-diones **111a-d** through heating with pyrrolidine in toluene using calcium chloride as a desiccant (Scheme 33).[61]

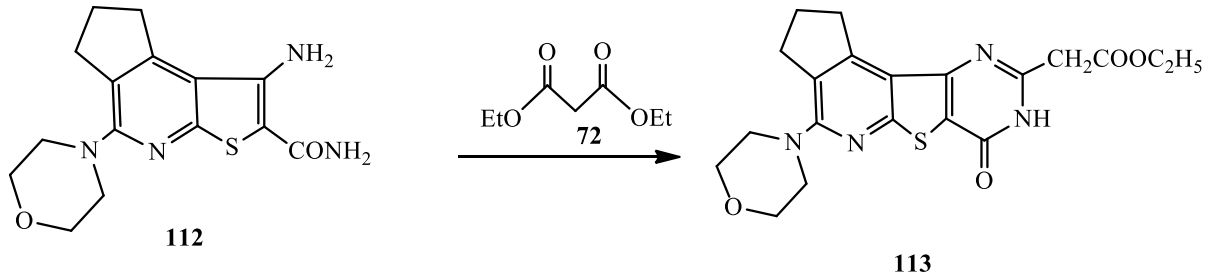


110a-d

111a, R = H
b, R = 4-Cl
c, R = 4-C_2H_5
d, R = 3-NO_2

Scheme 33. Synthesis of thienopyrimidine-2,4-diones **111a-d**

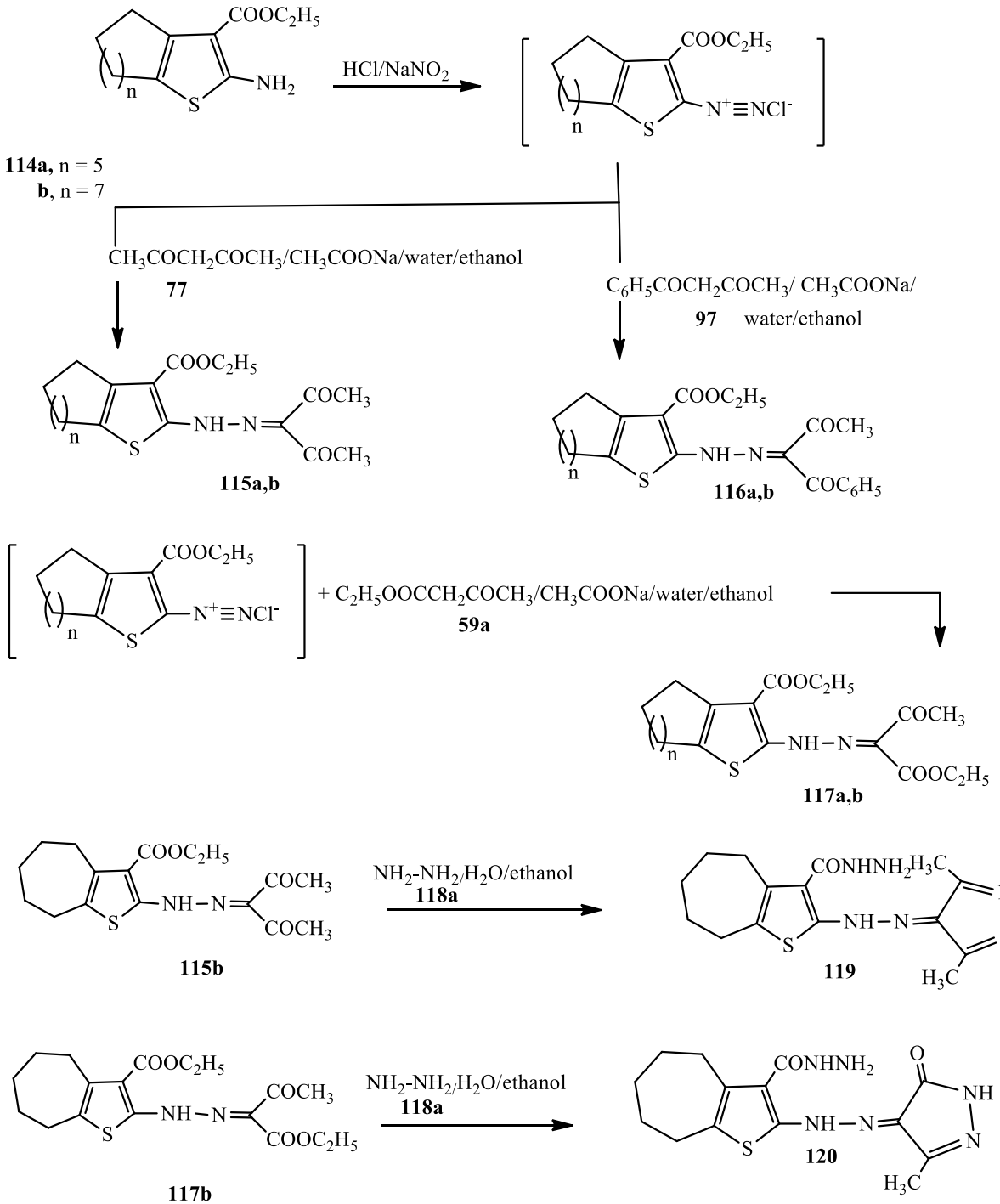
Cyclocondensation of compound **112** with diethyl-malonate (**72**) under solvent-free conditions furnished ethyl pyrimidinyl acetate **113** (Scheme 34).[62]



Scheme 34. Synthesis of pyrimidine derivative **113**

6. Synthesis of Biologically Active Pyrazole Derivatives from 1,3-diketone

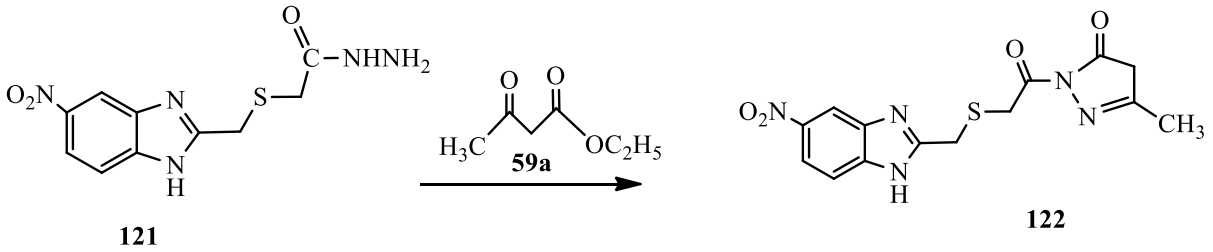
The hydrazone derivatives **115a,b-117a,b** were synthesized *via* diazotization of amines **114a,b**, followed by coupling with different active methylene compounds. Treatment of hydrazine hydrate (**118a**) with hydrazones **115b**,**117b** in ethanol afforded the hydrazonopyrazole derivatives **119-120** (Scheme 35).[63] In vitro antitumor screening of **115-120** was performed towards (HT-29), (MCF-7) and (HepG2) cancer cell lines using MTT assay,[64-66] and utilizing 5-fluorouracil as a standard agent. The results (IC_{50}, µM) showed that **117b** and **119** had the highest efficacy on all tested cell lines. Compounds **115a** and **117a** displayed promising activity against all the tested cell lines. Moreover, **116a** was indicated to have notable efficiency towards MCF-7 cell line.[63]



Scheme 35. Synthesis of pyrazole derivatives **119** and **120**

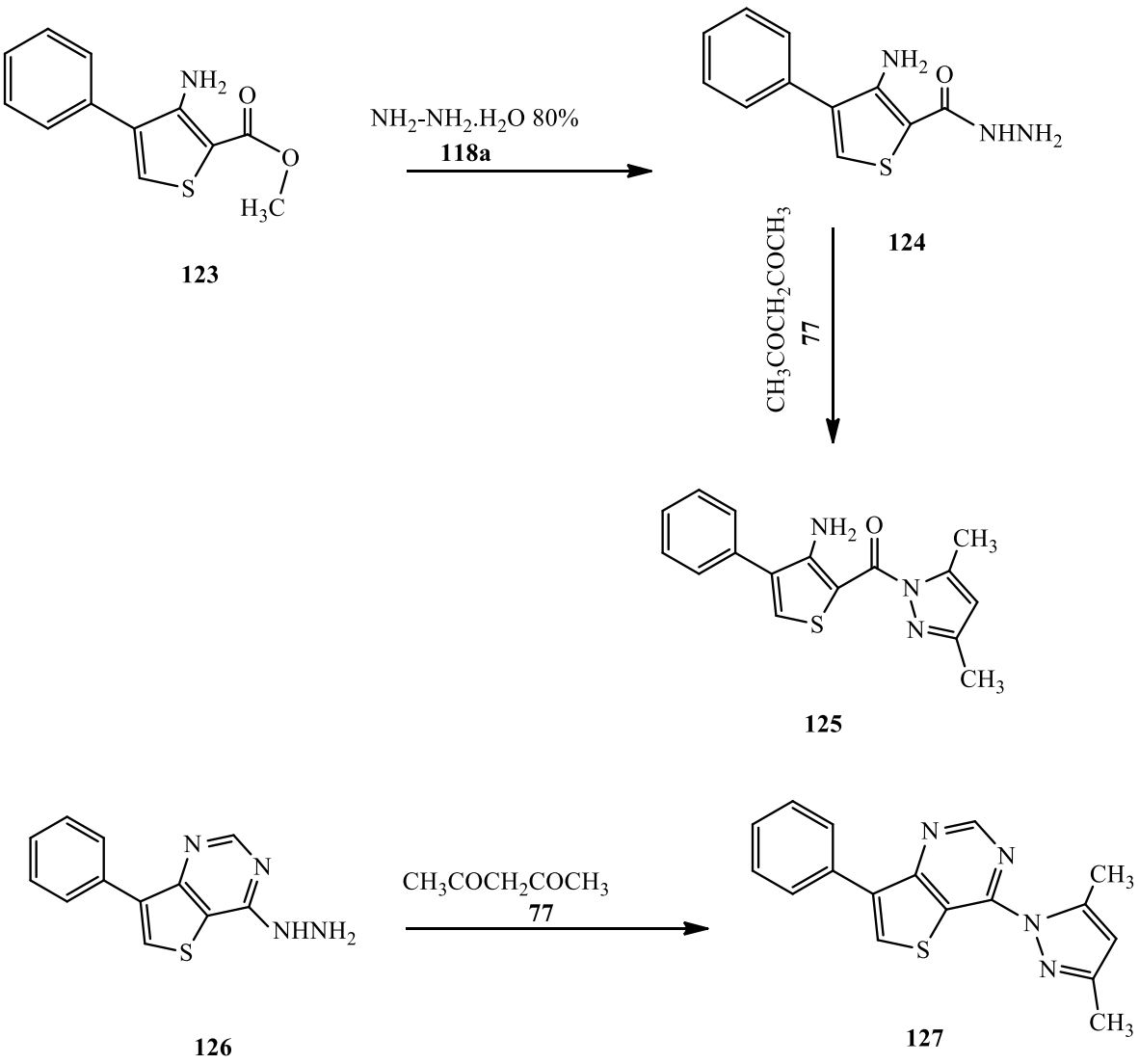
The pyrazolone derivative **122** was obtained *via* heating of acetohydrazide **121** with ethyl acetoacetate (**59a**) in ethanol and in the presence of K_2CO_3 (Scheme 36). Compound **122** was screened for its in vitro antimicrobial activity against *E. coli* (Gram-negative bacteria), *B. cereus*, *S. aureus* (Gram-positive bacteria), and *A. fumigatus*, *C. albicans* (pathogenic fungi),[67] ampicillin and fluconazole were used as a reference antibacterial and antifungal, respectively.[68-72] The minimum inhibitory concentration ((MIC) was specified for the pyrazolone derivative **122** and the results exhibited that compound **122** had various activities against Gram- positive bacteria and fungi more than the Gram-negative bacteria.[67] In addition, compound **122** was evaluated for its anti-quorum sensing activity against *C. violaceum*,[68,69,73] and catechin was used as a positive control. Quorum-sensing (QS) system liberated acyl homoserine lactones (acyl

HSLs) to regulate the formation of violacein (violet pigment), which is responsible for quorum-sensing communication between bacteria.[74,75] Then, the inhibition of quorum-sensing activity in *C. violaceum* prevented the liberation of violacein. Thus, the quorum-sensing inhibition (mm) was calculated from the total radius of both growth and pigment inhibition (r_2), which was subtracted from the radius of bacterial growth inhibition (r_1), given as follows: QS inhibition (mm) = (r_2-r_1). The results revealed that compound **122** had no anti-QS efficacy.[67]



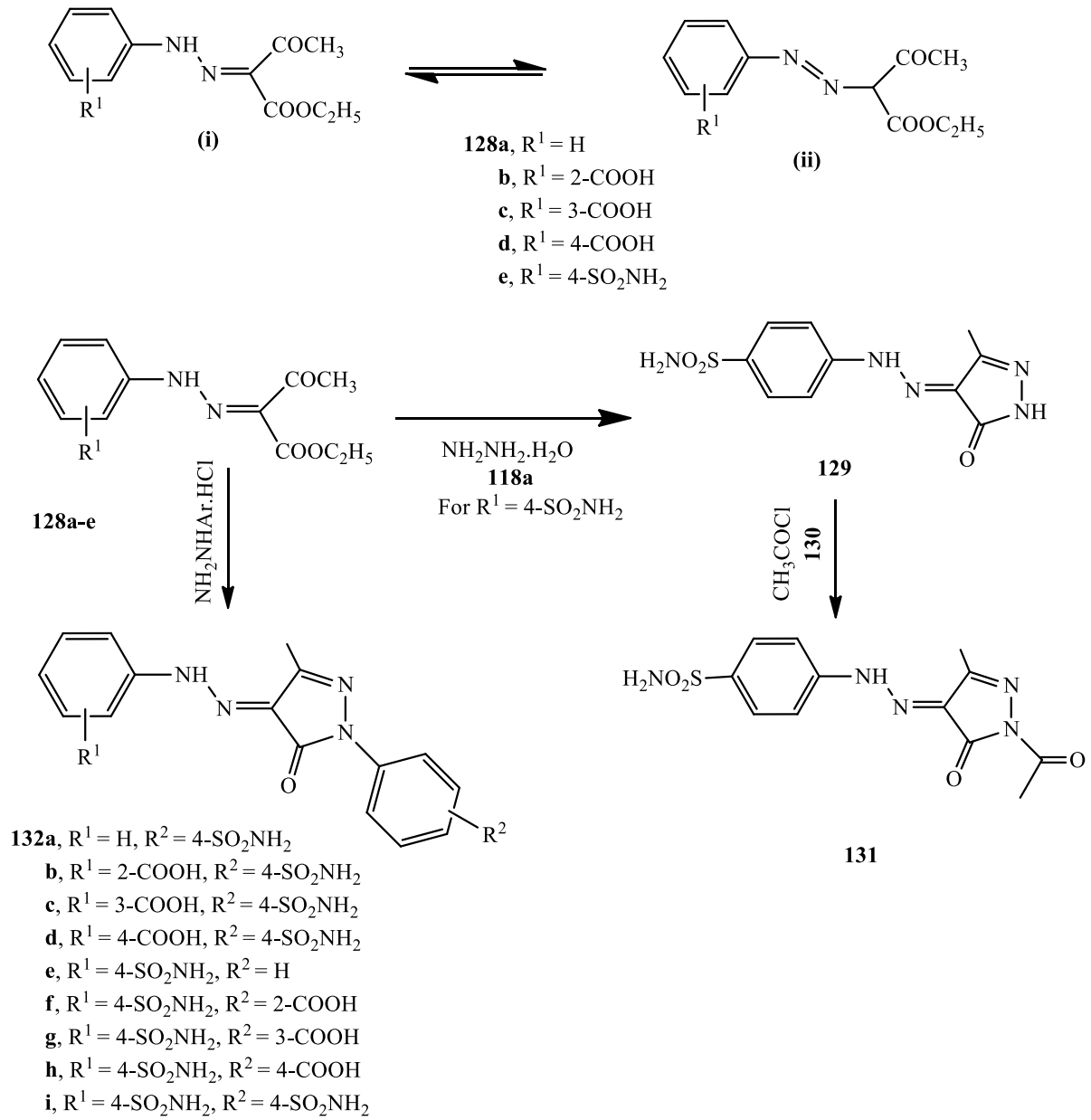
Scheme 36. Synthesis of pyrazolone derivative **122**

3-Amino-4-phenylthiophene-2-carbohydrazide **124** was synthesized from treatment of compound **123** with hydrazine hydrate (**118a**), which reacted with acetylacetone (**77**) in ethanol to afford the pyrazole derivative **125**. On the other hand, heating of compound **126** with acetylacetone (**77**) furnished pyrazolyl analogs **127** (Scheme 37). Cayman colorimetric COX (ovine) inhibitor screening assay kit was used to evaluate the in vitro inhibition of ovine cyclooxygenase1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes by the synthesized compounds **125** and **127** through measuring the peroxidase efficacy of both isoenzymes. The half maximal inhibitory concentration (IC_{50}, μM) for both isoenzymes and the COX-2 selectivity indices (SI) of the test compounds were evaluated. While celecoxib was used as a selective standard drug, indomethacin was used as a non-selective COX-2 inhibitors. The results indicated that compounds **125** and **127** showed less inhibition of COX-1 enzyme when compared to indomethacin. In a different manner, compounds **125** and **127** displayed variable inhibitory activities of COX-2 isoenzyme. Compound **125** showed moderate COX-2 selective inhibition, whereas compound **127** demonstrated less activity. Furthermore, compounds **125** and **127** exhibited higher selectivity indices against COX-2 than COX-1, when compared to the selectivity indices of celecoxib and indomethacin, respectively.[76]



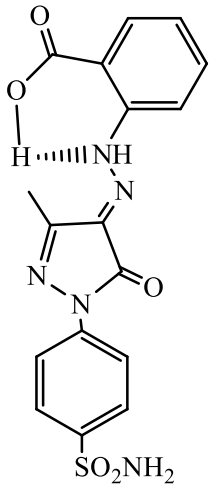
Scheme 37. Synthesis of 3,5-dimethyl pyrazole **125** and 1**27**

Cyclo-condensation reaction between hydrazine hydrate (**118a**) and 3-oxo-2-[(4-sulfamoylphenyl)hydrazono]butyric acid ethyl ester **128e** in ethanol furnished pyrazolone **129**, heating of which with acetyl chloride (**130**) produced the pyrazolone **131** in an excellent yield. Treatment of hydrazones **128a–e** with different substituted phenylhydrazine hydrochlorides in ethanol gave the pyrazolone derivatives **132a–i** in high yields. The reaction occurred through the addition of NH_2 hydrazine group, which is the more nucleophilic toward the reactive carbonyl group of acetyl chloride (CH_3COCl). It was followed by intra-molecular cyclization, which took place by nucleophilic substitution and loss of ethanol molecule (Scheme 38).[77]

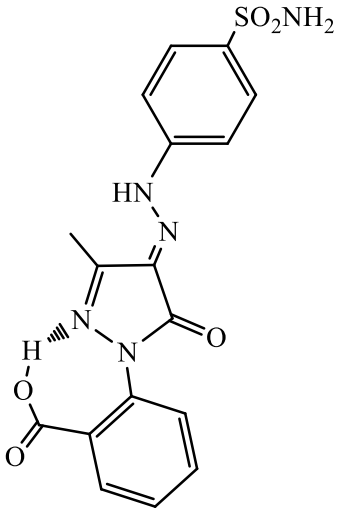


Scheme 38. Synthesis of pyrazolone **129**, **131** and **132a-i**

Carrageen induced rat foot paw edema model was used to evaluate the AI activity of all synthesized compounds, and celecoxib was used as a standard drug.[78,79] Compounds **129**, **131** and **132a–i** displayed a wide range of edema inhibition percentage (EIP) at 2 and 4 h after carrageenan injection. Compounds **132b** and **132f** showed the most AI activity at 2 and 4 h. This AI activity was due to the carboxyl group at position 2, which facilitated the intramolecular hydrogen bond formation and increased absorption and membrane permeability (Figure 5). The newly synthesized compounds **132a**, **132c**, **132d** and **132h** exhibited good AI activities in sequence of **132c** = **132h** > **132a** = **132d** after 2 h and **132d** > **132c** > **132h** > **132a** after 4 h. The five derivatives **129**, **131**, **132e**, **132g** and **132i** showed lower AI activity in the order of **129** = **132i** > **131** = **132e** > **132g** at 2 and 4 h. Furthermore, effective dose 50% (ED_{50}) for all the synthesized compounds was measured, and it was noticed that compound **132f** was the most active AI agent at two different time intervals relative to celecoxib, whereas compounds **132b**, **132c** and **132d** exhibited high AI activity. In addition, compounds **129**, **131**, **132a**, **132e**, **132g**, **132h** and **132i** showed moderate AI activity, and the compounds potency were in sequence of **132h** > **132a** > **132i** > **129** > **132g** > **131** > **132e**.[77]



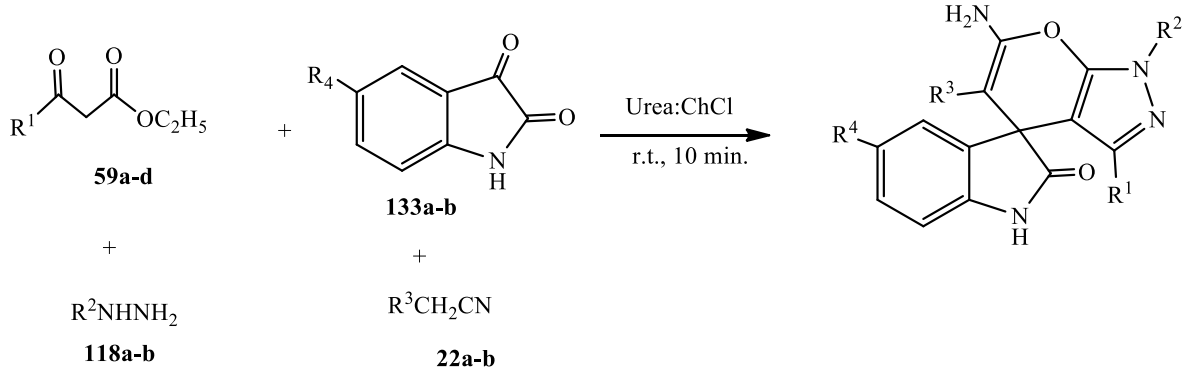
132b



132f

Figure 5. Intra-molecular hydrogen bonds in **132b** and **132f**

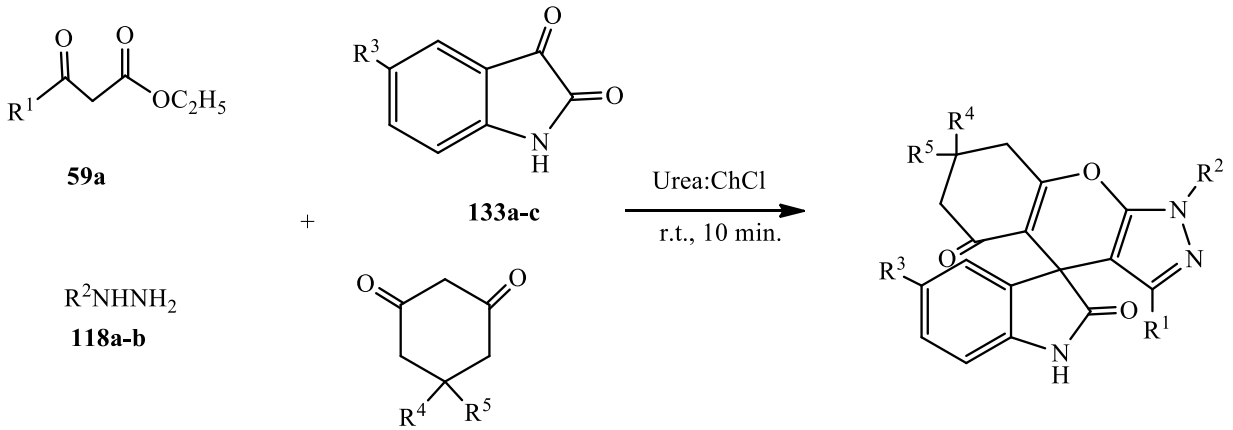
The reaction between 1,3-diketones (**59a-d**), isatins **133a-b**, phenylhydrazines (**118a-b**), and malononitrile **(22a**) or ethyl acetoacetate (**22b**) in deep eutectic solvent (*DESs*) at 25 °C gave the spiro-indoline-pyrano-pyrazole derivatives **134a-i**, (Scheme 39).



134a, $R^1 = CH_3$, R^2 = Ph, R^3 = CN, R^4 = H
b, $R^1 = (CH2)_2$-CH_3, R^2 = Ph, R^3 = CN, R^4 = H
c, R^1 = CH-$(CH3)_2$, R^2 = Ph, R^3 = CN, R^4 = H
d, $R^1 = CH_3$, R^2 = Ph, R^3 = CN, R^4 = Cl
e, R^1 = CH-$(CH3)_2$, R^2 = Ph, $R^3 = COOC_2H_5$, R^4 = H
f, $R^1 = (CH2)_2$-CH_3, R^2 = Ph, $R^3 = COOC_2H_5$, R^4 = H
g, $R^1 = CH_3$, R^2 = H, R^3 = CN, R^4 = H
h, R^1 = Ph, R^2 = H, $R^3 = COOC_2H_5$, R^4 = H
i, R^1 = Ph, R^2 = H, R^3 = CN, R^4 = H

Scheme 39. Synthesis of pyrazole derivatives **134a-i**

Similarly, the reaction between 1,3-diketones (**59a-d**), isatins (**133a-b**), phenylhydrazines (**118a-b**), and cyclohexane-1,3-dione (**20a**) or 5,5-dimethylcyclohexane-1,3-dione (**20b**) in deep eutectic solvent (DESs) at 25 °C gave the spiro-indoline-pyrano-pyrazole derivatives **134j-r**, (Scheme 40).[80]

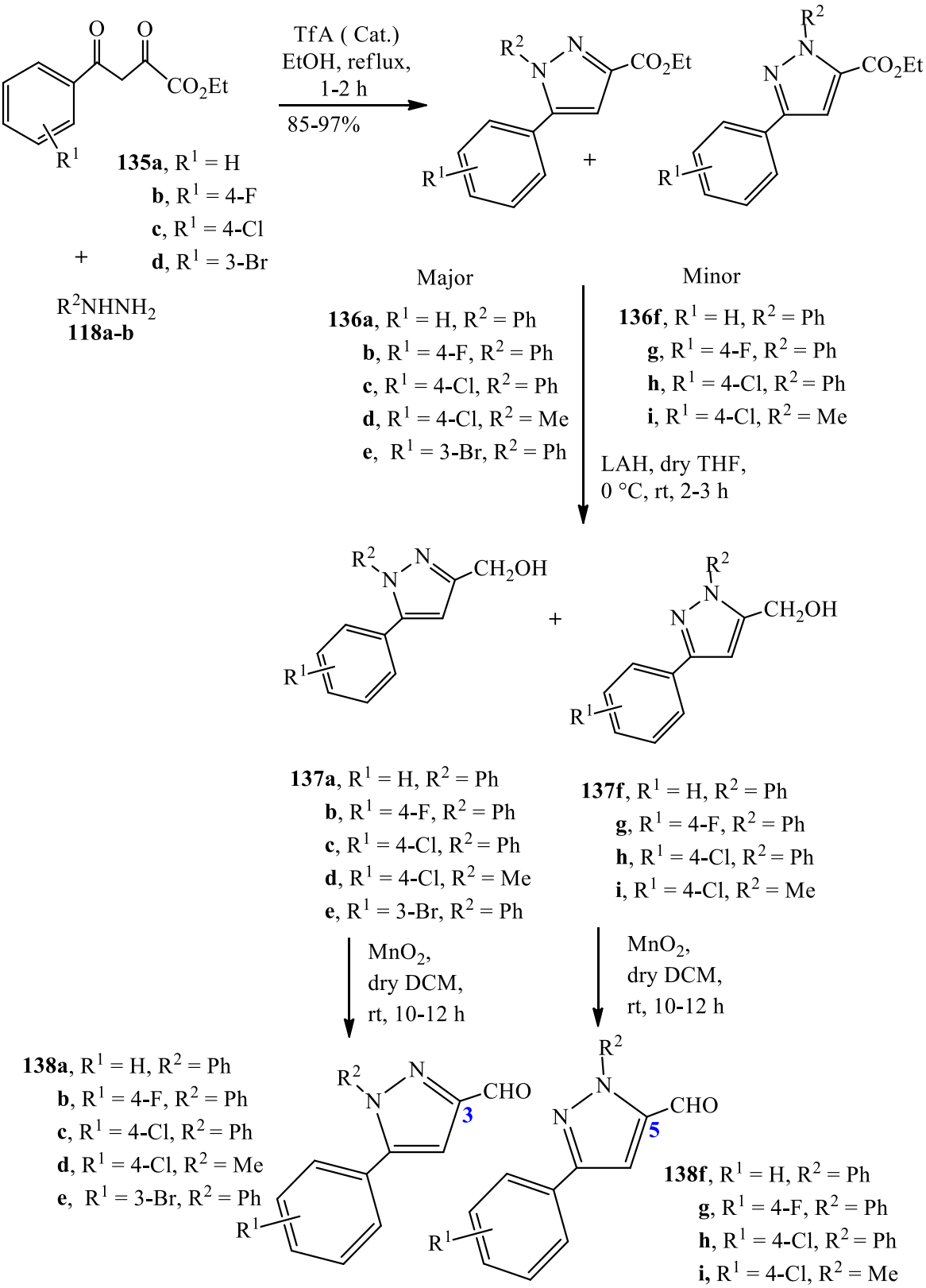


134j, $R^1 = CH_3$, R^2, $R^3 = H$, R^4, $R^5 = CH_3$
k, $R^1 = CH_3$, $R^2 = H$, $R^3 = Br$, R^4, $R^5 = CH_3$
l, $R^1 = CH_3$, $R^2 = H$, $R^3 = Cl$, R^4, $R^5 = CH_3$
m, $R^1 = CH_3$, R^2, R^3, R^4, $R^5 = H$
n, $R^1 = CH_3$, $R^2 = H$, $R^3 = Br$, R^4, $R^5 = H$
o, $R^1 = CH_3$, $R^2 = Ph$, $R^3 = H$, R^4, $R^5 = CH_3$
p, $R^1 = CH_3$, $R^2 = Ph$, $R^3 = Br$, R^4, $R^5 = CH_3$
q, $R^1 = CH_3$, $R^2 = Ph$, R^3, R^4, $R^5 = CH_3$
r, $R^1 = CH_3$, $R^2 = Ph$, $R^3 = Br$, R^4, $R^5 = H$

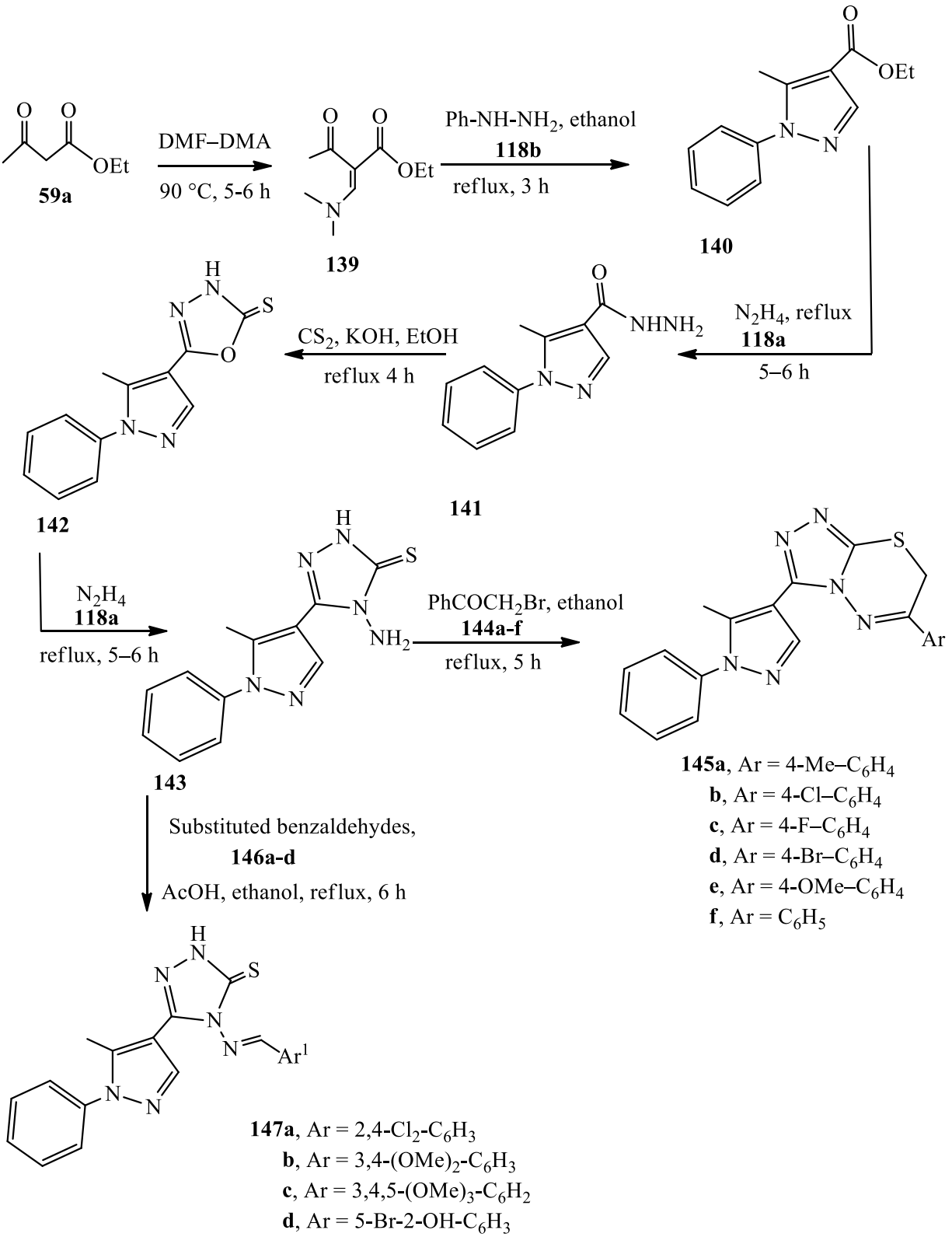
Scheme 40. Synthesis of pyrazole derivatives **134j-r**

Treatment of 1,3-diketoesters (**135a-d**) with hydrazines (**118a–b**) in ethanol in the presence of trifluoroacetic acid as a catalyst under the reflux conditions produced an inseparable mixture of pyrazole C-3(5) esters **136a–i**. Regarding the separation, these regioisomers, i.e. a mixture of pyrazole C-3(5) esters **136a–i**, were reduced with $LiAlH_4$ in dry THF to produce pyrazole alcohols **137a–i**, which were easier to separate by column chromatography. Furthermore, the pyrazole alcohols **137a–e** and **137f–i**, which were afforded as the major and minor products, respectively, were subjected to an oxidation process with MnO_2 to give the pyrazole carbaldehydes **138a–i (**Scheme 41).[81]

The pyrazole derivative **142** was synthesized through the reaction between N,N-dimethyl formamide-dimethyl acetal (DMF-DMA), ethyl acetoacetate (**59a**) and phenylhydrazine (**118b**), which was followed by the reaction with hydrazine hydrate (**118a**) and carbon disulfide.[82,83] Furthermore, the pyrazole derivative **142** was reacted with hydrazine hydrate (**118a**) to give the pyrazole derivative **143**. It was then reacted with phenacyl bromide derivatives **144a-f** to produce triazolothiadiazine derivatives **145a**–**f**. The pyrazole derivative **142** was reacted with benzaldehyde derivatives (**146a**–**d**) in ethanolic alcohol in the presence of acetic acid to afford the triazole-3-thione derivatives **147a**–**d** (Scheme 42). The newly synthesized compounds **145a**–**f** and **147a**–**d** showed good antibacterial activity against *Enterococcus faecalis*, *S. aureus*, *P. aeruginosa* and *E. coli*. Particularly, chloro, fluoro and dimethoxy substituted derivatives displayed good activity compared to the other derivatives.[84]

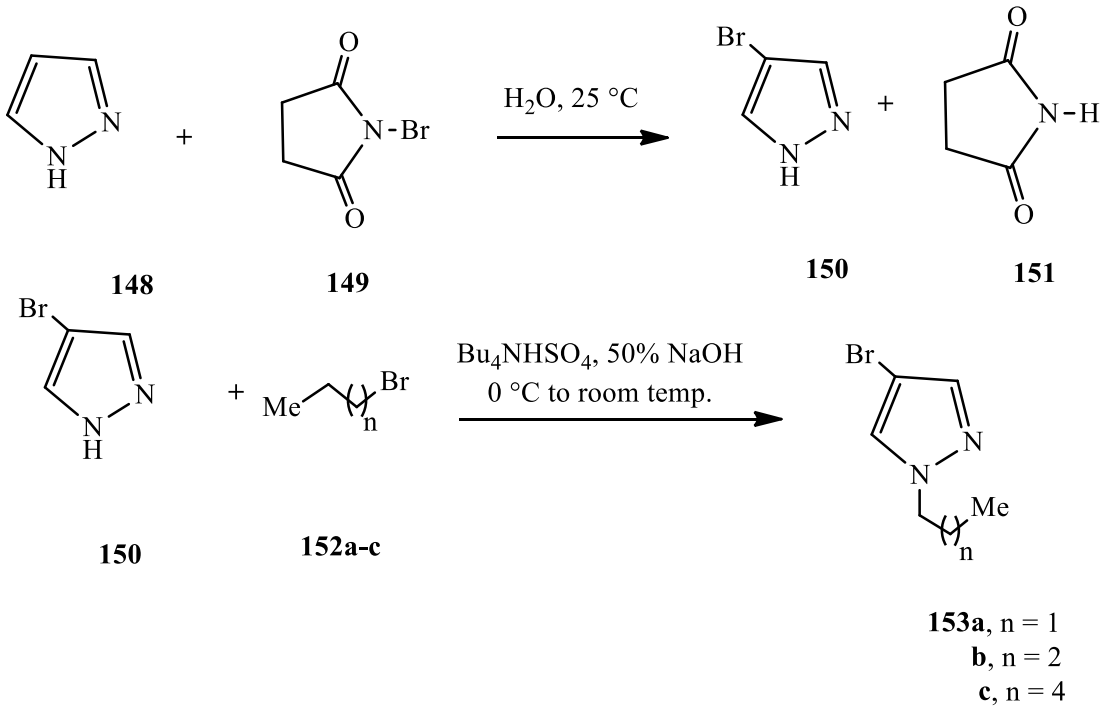


Scheme 41. Synthesis of diversely substituted pyrazole C-3(5) carbaldehydes **138a-i**



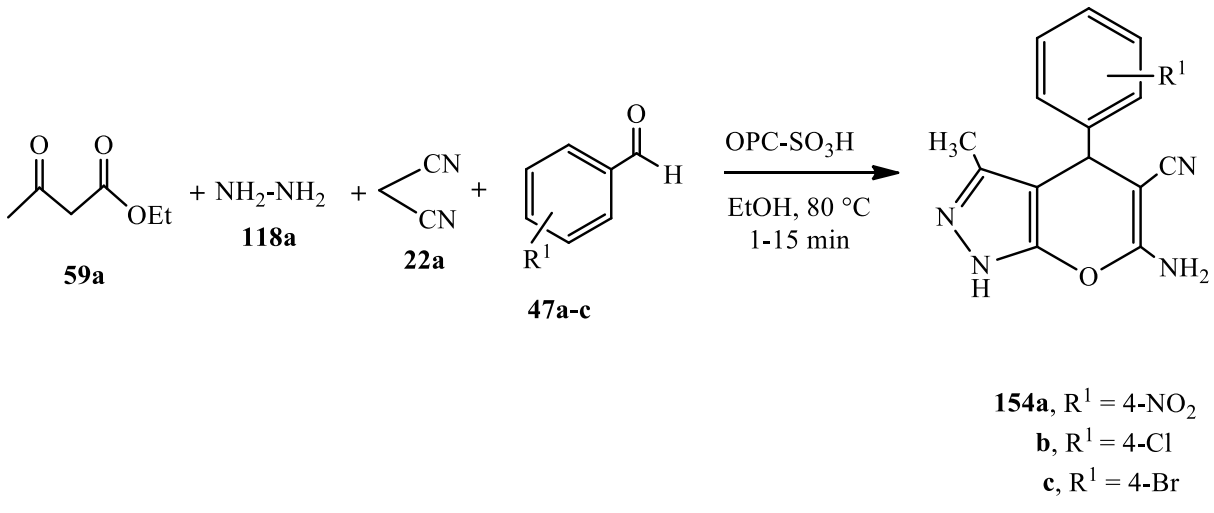
Scheme 42. Synthesis of pyrazole derivatives **145a-f** and **147a-d**

The reaction between pyrazole **148** and N-bromosuccinimide NBS (**149**) at room temperature in the presence of water afforded 4-bromopyrazole **150** and succinimide **151**. Treatment of 4-bromopyrazole **150** with alkyl bromides **152a**–**c** in the presence of tetrabutylammonium hydrogen sulfate (TBAHS) and sodium hydroxide gave the N-alkyl-4-bromopyrazole derivatives **153a-c** (Scheme 43).[85]



Scheme 43. Synthesis of N-alkyl-4-bromopyrazole derivatives **153a-c**

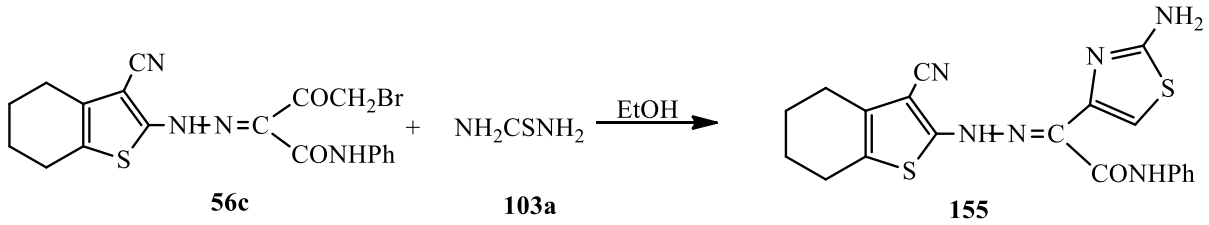
One-pot four-component reaction was described *via* the reaction between ethyl acetoacetate (**59a**), hydrazine hydrate (**118a**), malononitrile (**22a**) and various aldehydes (**47a-c**) in water as a solvent in the presence of OPC-SO_3H powder catalyst at room temperature for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives **154a-c** (Scheme 44).[86]



Scheme 44. Synthesis of dihydropyrano[2,3-c]pyrazole derivatives **154a-c**

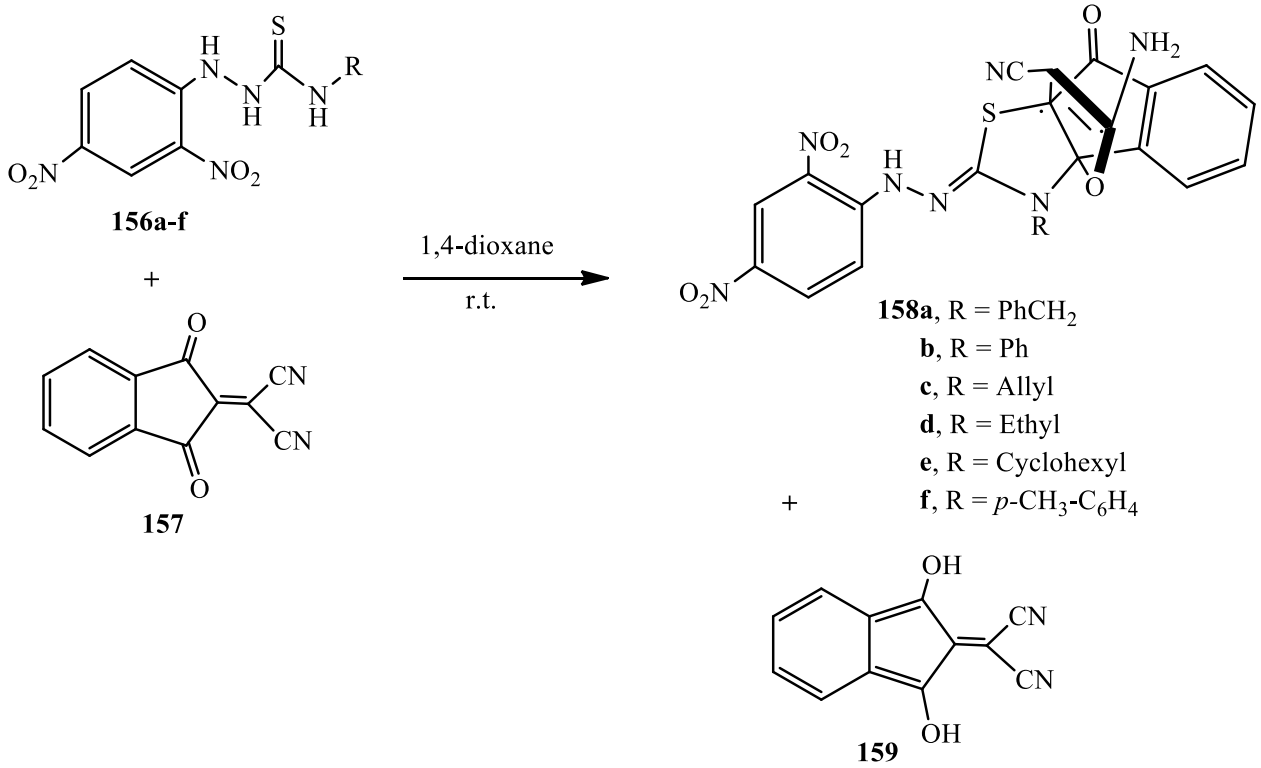
7. Synthesis of Biologically Active Thiazole Derivatives from 1,3-Diketone

The reaction of compound **56c** with thiourea (**103a**) in ethanol under the reflux conditions gave the thiazole derivative **155** (Scheme 45).[38]



Scheme 45. Synthesis of thiazole derivative **155**

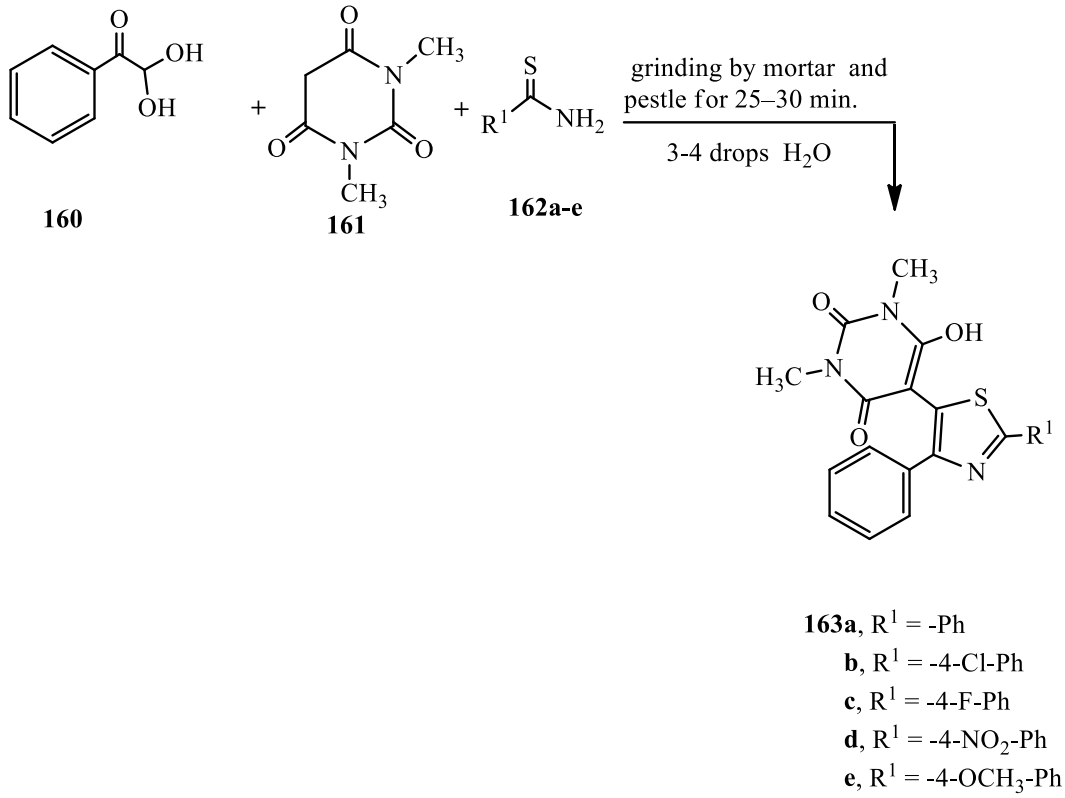
The furothiazolo[3.3.3]propellane derivatives **158a–f** were obtained in high purity and in good yields from mother liquor produced from the reaction between substituted-2-(2,4-dinitrophenyl) hydrazinecarbothioamides **156a–f** and dicyanomethylene-1,3-indanedione **157** in 1,4-dioxane, which were separated by PLC chromatography (Scheme 46).[87]



Scheme 46. Synthesis of furothiazolo[3.3.3]propellane derivatives **158a-f**

Multi-component reactions of phenylglyoxal monohydrate (**160**), 1,3-dimethylbarbituric acid (**161**) and thiobenzamide (**162a-e**) were conducted in the absence of any catalyst. Grinding and pasting for 25-

30 minutes in the presence of a few drops (3–4) of water at the time of grinding gave a very encouraging yields in a shorter reaction time (Scheme 47).[88]

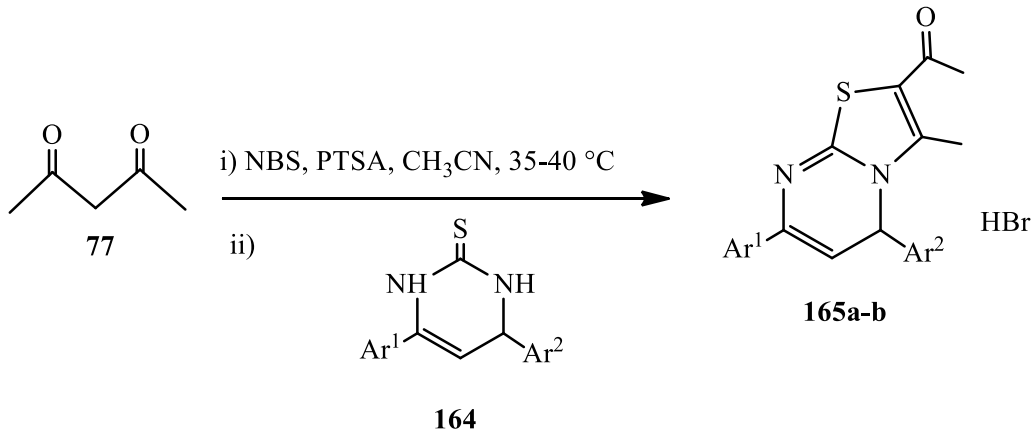


160 161 162a-e

163a, R^1 = -Ph
b, R^1 = -4-Cl-Ph
c, R^1 = -4-F-Ph
d, R^1 = -4-NO_2-Ph
e, R^1 = -4-OCH_3-Ph

Scheme 47. Synthesis of novel diphenyl-1,3-thiazole linked barbituric acid hybrids **163a-e**

Acetylacetone (**77**) was allowed to react with N-bromosuccinamide NBS (**149**) in acetonitrile in the presence of PTSA at 35-40 °C to afford the corresponding thiazolopyrimidine hydrobromide **165a-b** (Scheme 48).[89]

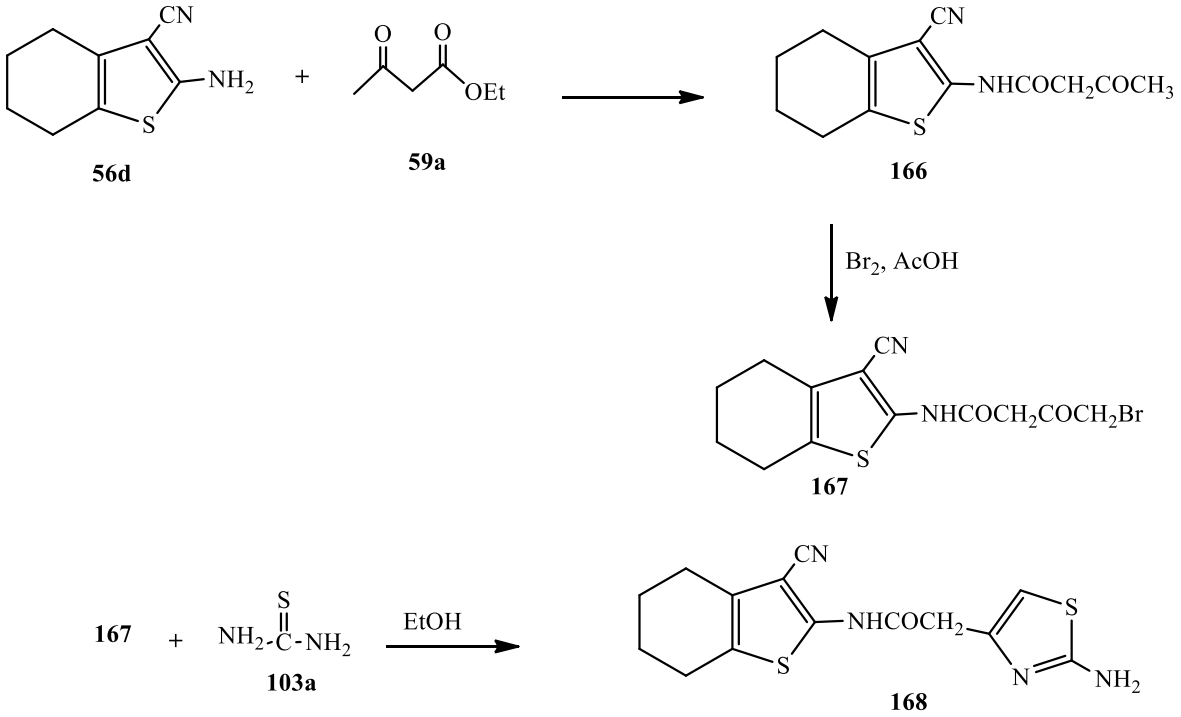


77 164 **165a-b**

Scheme 48. Synthesis of thiazolopyrimidine hydrobromide **165a-b**

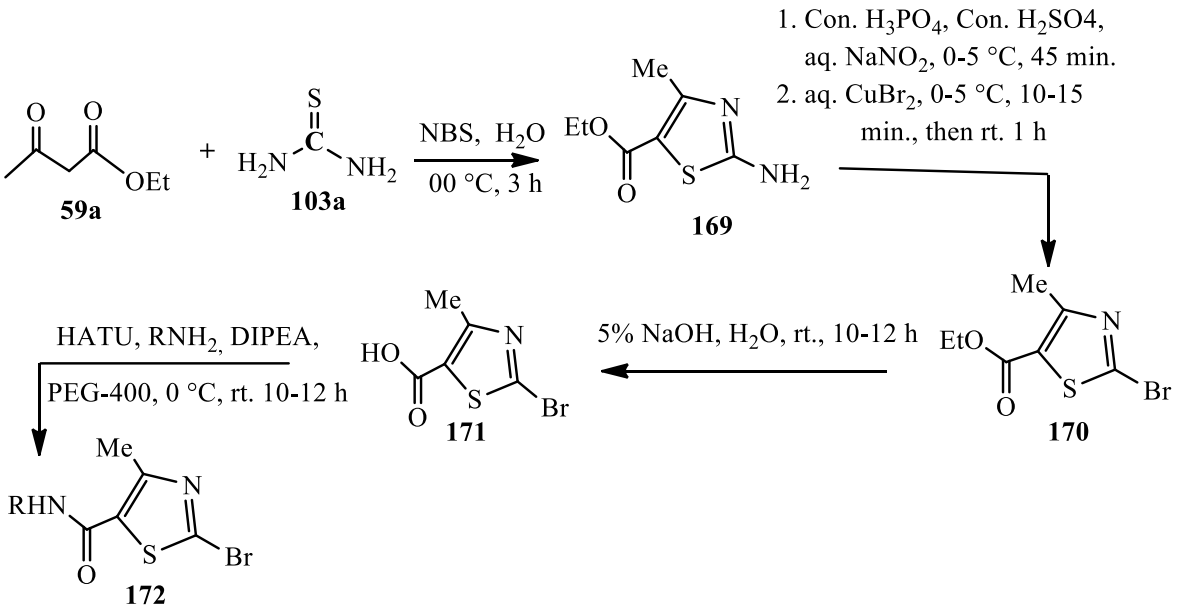
The reaction between thiophene derivative **56d** and ethyl acetoacetate (**59a**) in a dry condition in an oil bath gave the amide derivative **166**. Compound **166** reacted with bromine in acetic acid at 60 °C to give the α-bromo derivative **167**. Compound **167** reacted with thiourea (**103a**) in ethanol to afford the thiazole derivative **168** (Scheme 49). The effect of compound **168** was estimated on in vitro growth of three human tumor cell lines representing different tumor types, namely, CNS cancer (SF-268), non-small cell lung cancer (NCI-H460) and breast adenocarcinoma (MCF-7) after a continuous exposure for 48 h.

The results revealed that compound **168** showed the lowest inhibitory effect towards the entire three tumor cell lines.[90]



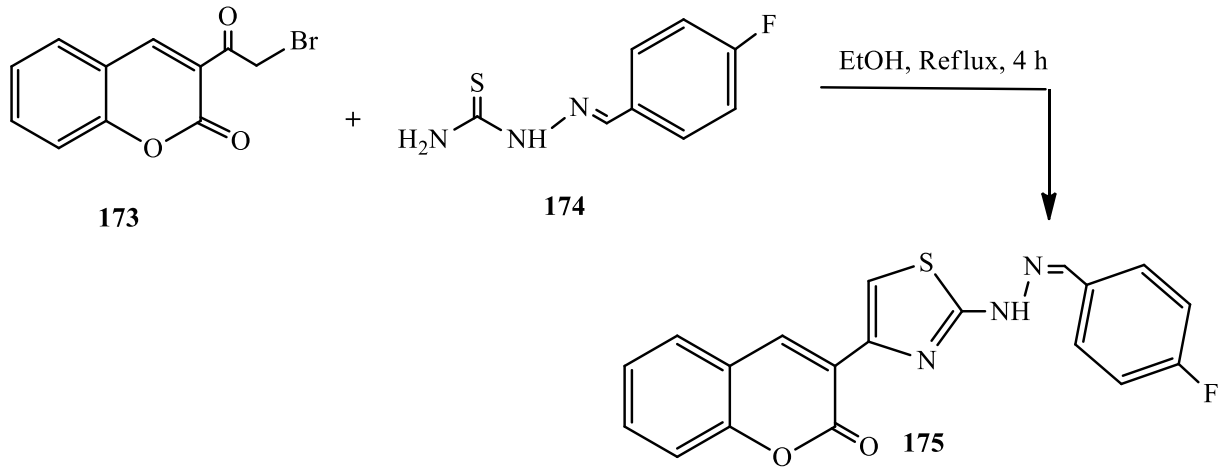
Scheme 49. Synthesis of thiazole derivative **168**

The thiazole derivative **169** was synthesized from the reaction between ethyl acetoacetate (**59a**) and thiourea (**103a**) in water in the presence of N-bromosuccinimide NBS. Compound **169** was reacted with copper bromide in con. H_3PO_4/Con. H_2SO_4 to produce 2-bromo thiazole **170**. The reaction between 2-bromo thiazole **170** with NaOH under a reflux condition produced **171**, which was followed by its reaction with polyethyleneglycol-400 (PEG-400) and DIPEA to give **172** (Scheme 50). The thiazole derivative **172** showed high antibacterial activity towards various bacteria strains.[91,92]



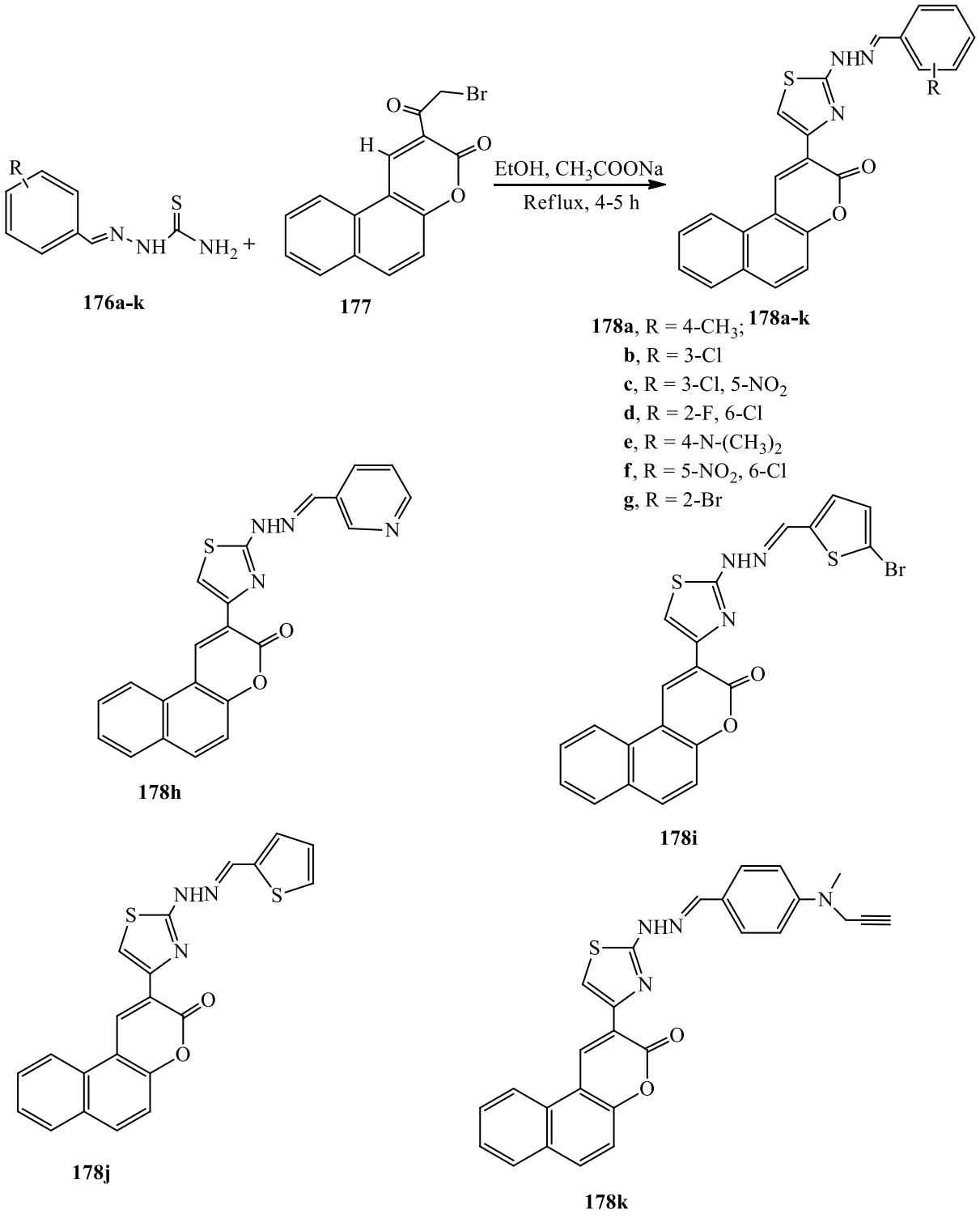
Scheme 50. Synthesis of thiazole derivative **172**

3-(2-Bromoacetyl)-2H-chromen-2-one **173** was reacted with 2-(4-fluorobenzylidene)hydrazine carbothioamide **174** in refluxing ethanol for 4 h to afford the corresponding thiazole derivative **175** (Scheme 51). Biological species start to adhere to the coating surface under various service conditions and this can eventually lead to damage of coatings. Biocide additives are commonly employed to prohibit or retard, the growth of bacteria or fungi on the coating surface. In paint manufacture, there are two types of biocide additives, one is used to prohibit organisms from depravation the paint during storage, and the second is used to prohibit algae and fungi from growing on the coated surface. Thiazoles are chemically stable being able to transmit anti-microbial activity properties when included into polymers. The blank and blended polyurethane varnish formulations were subjected to fungi Gram-positive bacteria and Gram-negative bacteria in order to determine their anti-microbial activities. The results showed that incorporation of thiazole derivative **175**, by physical means, into polyurethane coating in various levels resulted in an excellent anti-microbial activity, compared with a blank polyurethane. It was also noticed that the anti-microbial activity towards the microorganisms increased with the increase in the biocide additive level. Compound **175** showed high anti-microbial activity towards *B. subtilis* and S. *pneumoniae* (Gram-positive bacteria), moderate anti-microbial activity towards *E. coli* and *P. aeruginosa* (Gram-negative bacteria) and mild anti-microbial activity towards *G. candidum* and *A. fumigatus* (fungi). The anti-microbial activity of polyurethane coating was improved with the addition of thiazole derivatives. Thiazole and 1,3-thiazole are heterocyclic molecules found in many potent biologically active compounds. Thiazole ring exhibits remarkable activity towards bacteria due to its aromaticity and presence of (=N-C-S) group. Finally, 2-amino thiazole derivatives are reported to display important biological activity.[93]



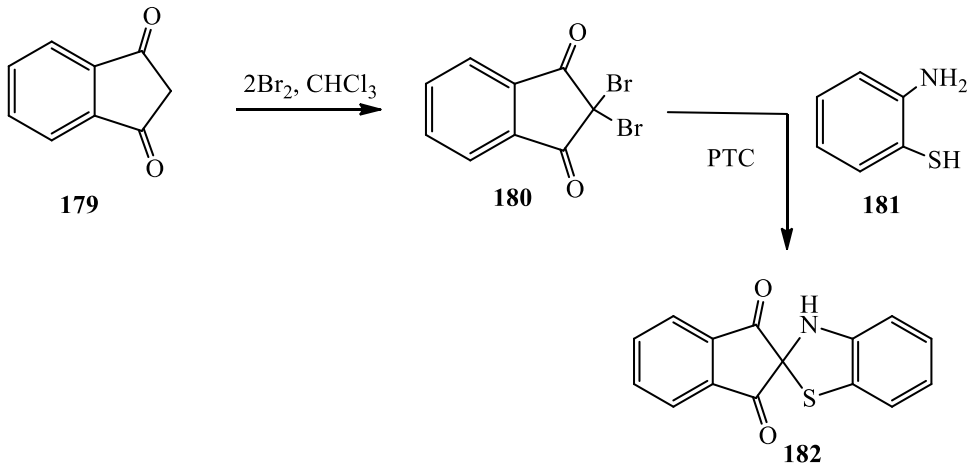
Scheme 51. Synthesis of thiazole derivative **175**

The reaction between thiosemicarbazones **176a-k** and 2-(2-bromoacetyl)-3H-benzo[f]chromen-3-one **177** in ethanol in the presence of sodium acetate afforded thiazole derivatives **178a-k** (Scheme 52). The newly synthesized compounds **178a–k** were subjected to in vitro growth inhibitory activity against breast cancer cells (MCF-7) and cervical carcinoma cells (HeLa) employing (MTT) assay, and cisplatin was used as a positive control, having 89% inhibition. The results indicated that compounds **178a–k** exhibited less inhibitory effect against breast cancer cell lines. On the other hand, the cytotoxicity of thiazole derivatives was evaluated towards cervical carcinoma cells (HeLa) employing MTT assay. The results exhibited that compound **178g** was the most active among all the compounds with 69.7% inhibition. In addition, compounds **178c**, **178f**, **178h** and **178k** had low inhibitory effect of 59.2%, 55.8%, 54.6% and 63.1%, respectively, against HeLa cervical carcinoma cells. The remaining thiazole derivatives exhibited the lowest inhibitory effect against HeLa cells.[94]

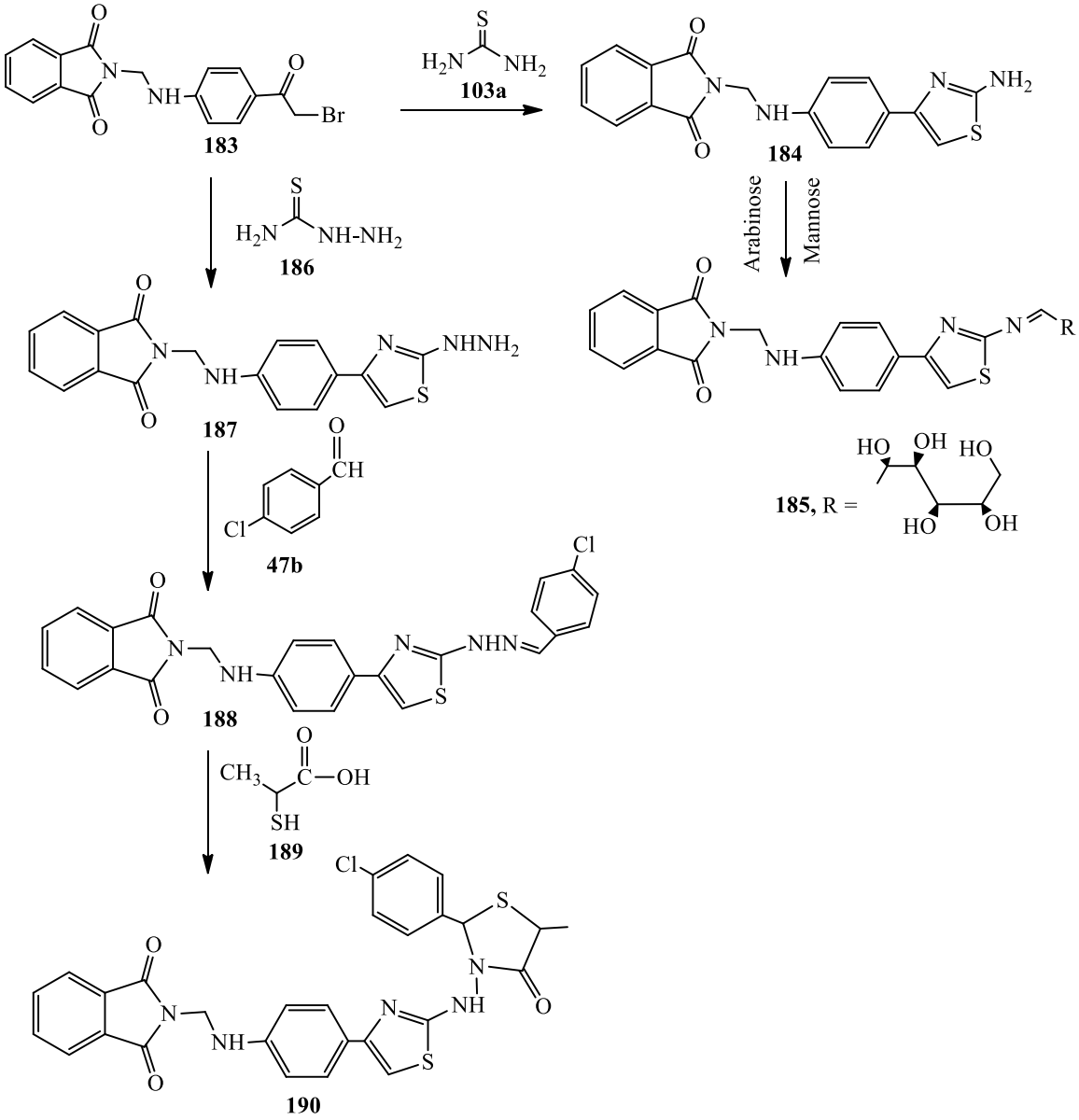


Scheme 52. Synthesis of thiazole derivatives **178a-k**

2,2-Dibromo-1,3-indandione[95] **180** was treated with *o*-aminothiophenol (**181**) under phase transfer catalysis conditions [1,4-dioxane/K_2CO_3/(TBAB)] to give the corresponding spiro indandione derivative **182** (Scheme 53).[96]



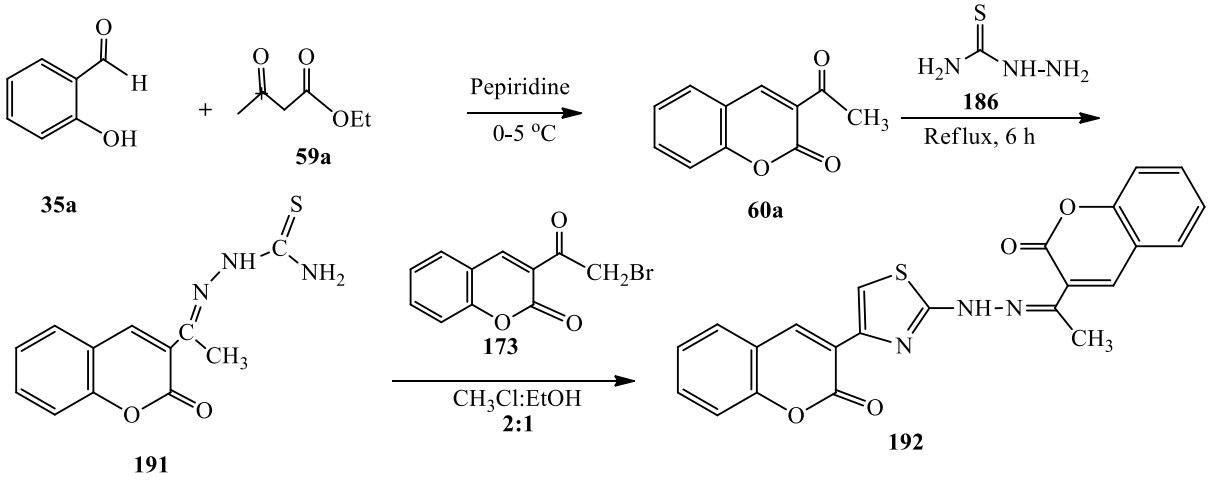
Scheme 53. Synthesis of spiro indandione derivative **182**



Scheme 54. Synthesis of thiazole derivatives **184**, **185**, **187**, **188**, **190**

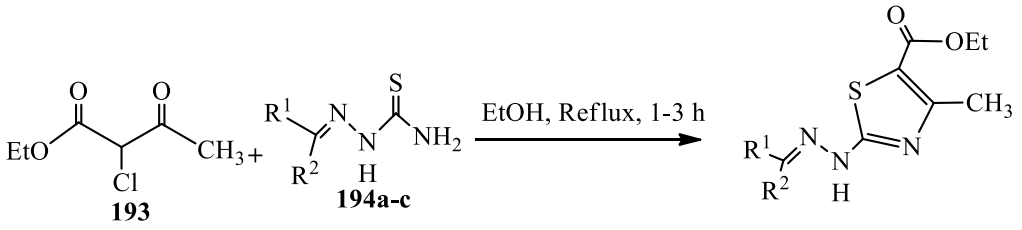
The 1,3-thiazole derivative **184** was furnished from the reaction between α-bromoketone **183** and thiourea (**103a**) in ethanol, according to Hantzsch thiazole synthesis. Compound **184** reacted with Arabinose/mannose in ethanolic alcohol in the presence of a base as a catalyst to afford **185**. Furthermore, condensation of α-bromoketone **183** with thiosemicarbazide (**186**) afforded hydrazino-thiazole derivative **187**. Heating of compound **187** with para-chlorobenzaldehyde (**47b**) produced **188**. Treatment of the Schiff's base **188** with thiolactic acid (**189**) gave the thiazolidinone derivative **190** (Scheme 54). The novel phthalimide compounds **184**, **185**, **187**, **188** and **190** were subjected to antimicrobial screening. The results indicated that the thiazole Schiff's base derivative **185** was moderately active as an antimicrobial agent (MIC = 25-200 μg/ml) among the tested phthalimide derivatives.[97]

3-Acetylcoumarin **60a** was prepared from the reaction between salicylaldehyde (**35a**) and ethyl acetoacetate (**59a**) according to Knoevenagel condensation. It was then reacted with semicarbazide (**168**) in glacial acetic acid to produce hydrazine thiosemicarbazide coumarin derivative **191**, which was subjected to cyclization process with 3-bromoacetylcoumarin **173** to synthesize the hydrazinylthiazolyl of coumarin derivative **192** (Scheme 55). The coumarin-thiazole derivative **192** was studied for its in vitro growth inhibitory activity against Human Periodontal Ligament Fibroblast (HPDLF) cells. The results revealed that **192** displayed less toxicity against HPDLF.[98]



Scheme 55. Synthesis of coumarin thiazole derivative **192**

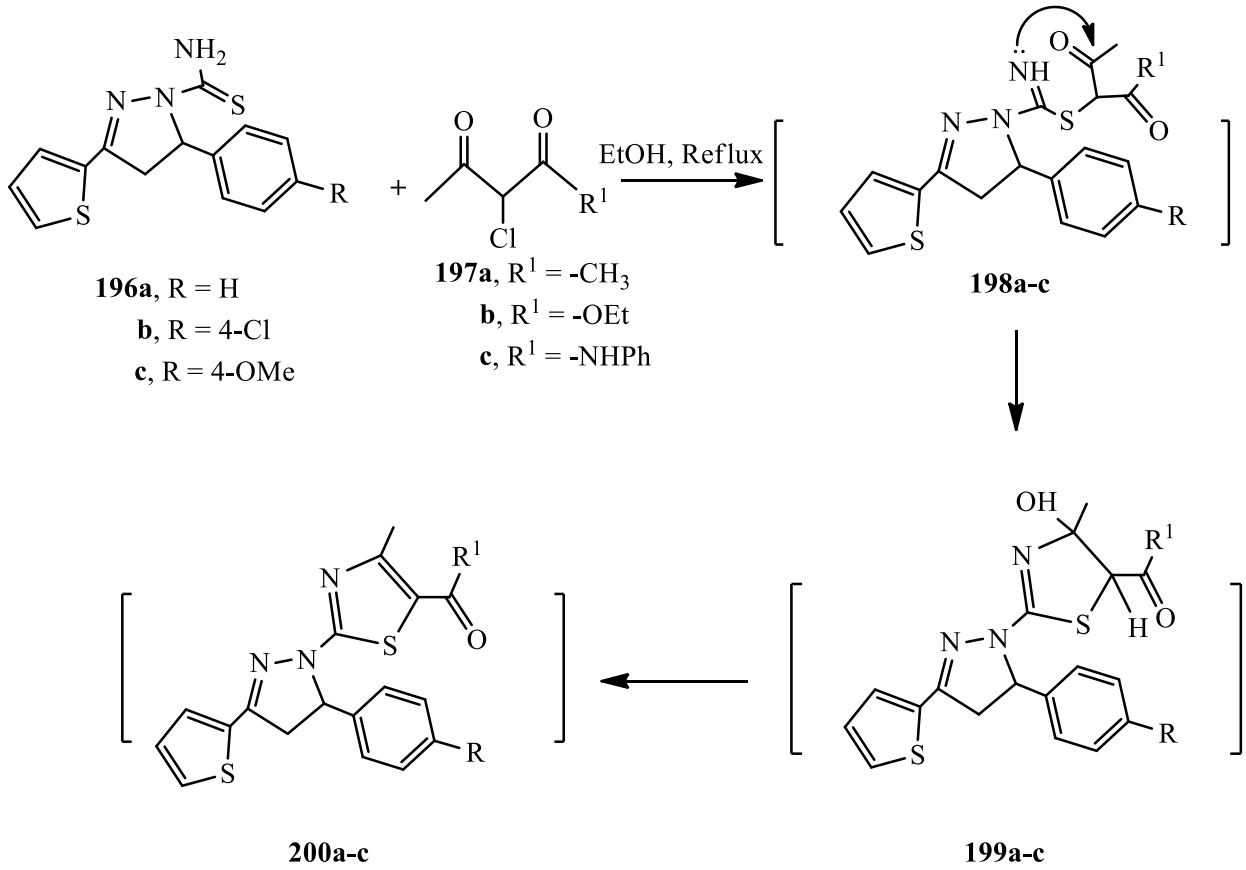
Heating of the aliphatic α-halo ketone (**193**) with thiosemicarbazones **194a-c** in ethanol afforded the 2-(2-hydrazinyl)thiazole derivatives **195a-c** (Scheme 56). The synthesized compounds **195b** and **195c** were screened for their in vitro growth inhibitory efficacy towards Mtb and $H_{37}Rv$ with minimum inhibitory concentration (MIC) values 25 μM and 12.5 μM sequentially. The results demonstrated that the compounds with structural properties of hydrogen bond donor or hydrogen bond acceptor at position two of the aromatic substituents stimulated the efficacy. The protein–ligand interaction studies displayed that the hydrogen bonding interactions of **195a** and **195c** with β-ketoacyl-ACP synthase (Kas A) protein of Mtb are similar to that of TLM.[99]



195a, R^1 = H , R^2 = -ph
b, R^1 = H, R^2 = -2-OH-Ph
c, R^1 = CH_3, R^2 = -2-pyridyl

Scheme 56. Synthesis of 2-(2-hydrazinyl)thiazole derivatives **195a-c**

The thiophenylpyrazolylthiazoles **200a-c** were synthesized from the reaction between thioamide derivative **196a,** R = H and chloroacetone derivatives **197a–c**, respectively (Scheme 57).[100] The suggested mechanism involves the formation of hydrazine, which was followed by addition of N–H to the carbonyl of the propenone moiety.[101] The synthesized compounds **200a-c** were tested for their in vitro antimicrobial activities towards *B. cereus*, *S. aureus* (Gram-positive bacteria), *P. aeruginosa*, *K. pneumonia* (Gram-negative bacteria) and *Syncephalastrum racemosum*, *C. albicans*, *A. fumigatus*, *A. flavus*, *Penicillium expansum* (pathogenic fungi). Compound **200b** displayed the highest activity towards *A. fumigatus* and *C. albicans*, compared with griseofulvin as a reference drug. Additionally, they exhibited moderate or low activities towards all the bacteria strains.[100]



196a, R = H
b, R = 4-Cl
c, R = 4-OMe

197a, R^1 = -CH_3
b, R^1 = -OEt
c, R^1 = -NHPh

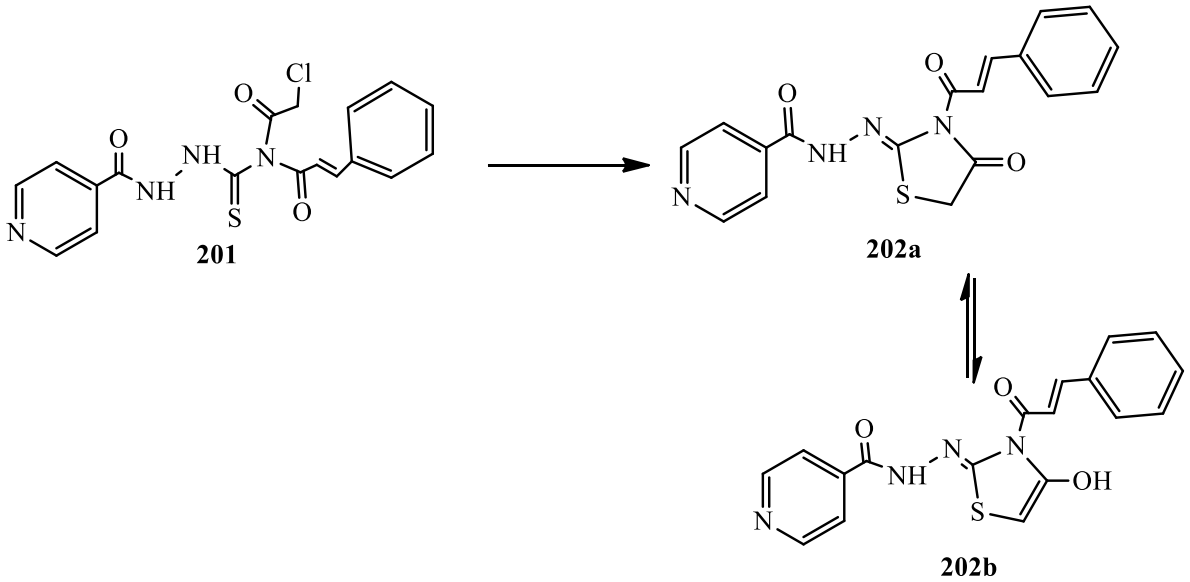
198a-c

199a-c

200a-c

Scheme 57. Synthesis of thiophenyl-pyrazolyl-thiazoles **200a-c**

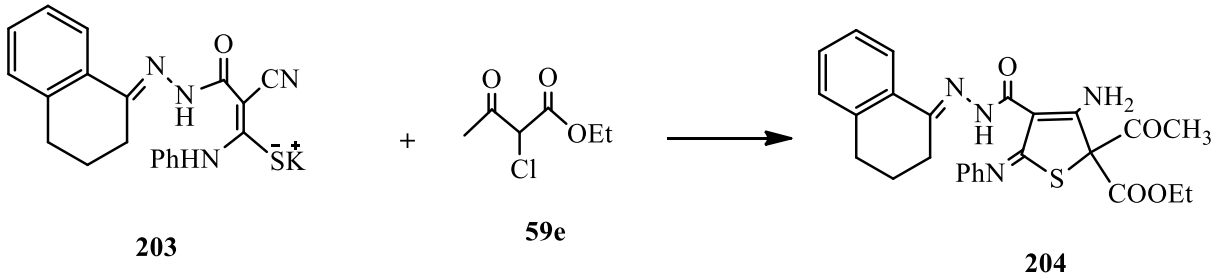
The thiazole derivative **202** was obtained *via* intramolecular cyclization of the intermediate **201** and loss of HCl (Scheme 58). The antimicrobial activity of compound **202** was evaluated against six microbial strains, namely, *S. aureus, B. subtilies, S.typhimurium, E. coli, A. falvus* and *C. albicans*. The newly synthesized compound **202** showed moderate activity against *S. aureus, S. typhimurium* and C. *albicans*. On the other hand, no activity was observed against the three other microbials.[102]



Scheme 58. Synthesis of N'-(3-cinnamoyl-4-hydroxythiazol-2(3H)-ylidene)isonicotinohydrazide **202**

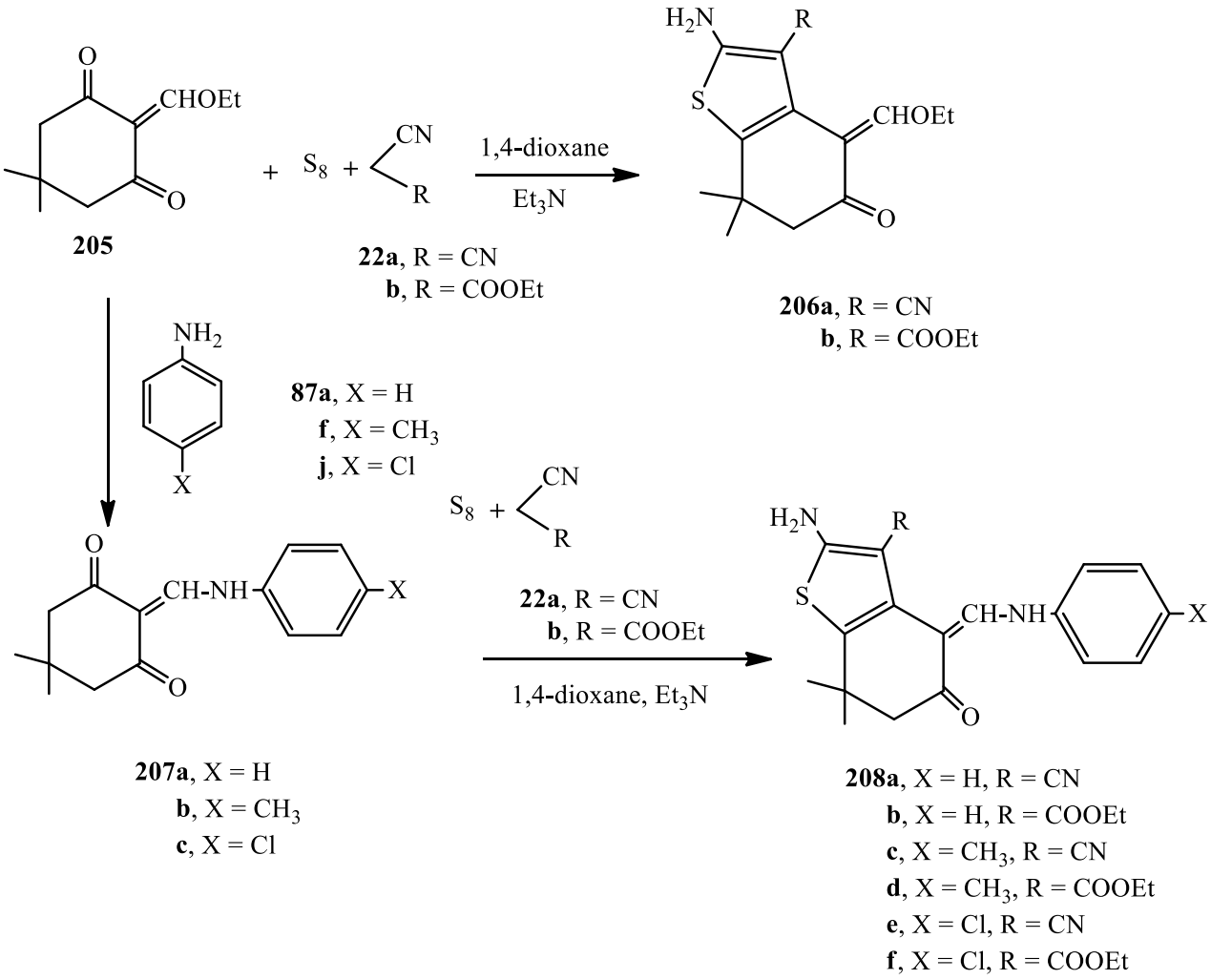
8. Synthesis of Biologically Active Thiophene Derivatives from 1,3-Diketone

Treatment of the non-isolable intermediate **203** with ethyl α-chloroacetoacetate (**59e**) produced a single product, which was characterized to be 2,5-dihydrothiophene derivative **204** (Scheme 59).[44]



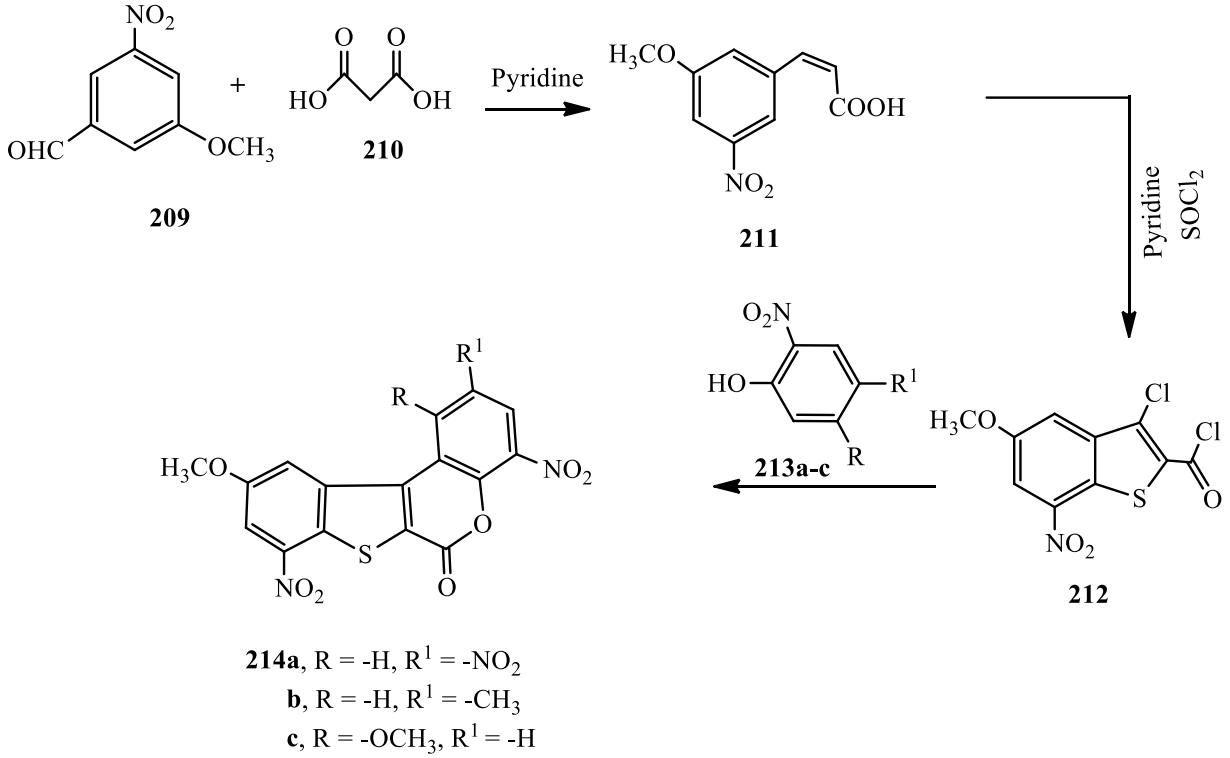
Scheme 59. Synthesis of 2,5-dihydrothiophene derivative **204**

The 6,7-dihydrobenzo[b]thiophene derivatives **206a** and **206b** were synthesized from the reaction of compound **205** with elemental sulfur and either malononitrile (**22a**) or ethyl cyanoacetate (**22b**) in 1,4-dioxane. On the other hand, the arylaminomethylene cyclohexane derivatives **207a-c** were afforded through the reaction between **205** and either aniline (**87a**), 4-methylaniline (**87f**), or 4-chloroaniline (**87j**). In addition, the arylaminomethylene-6,7-dihydrobenzo[b]thiophene derivatives **208a–f** were furnished with treatment of **207a**, **207b**, or **207c** with elemental sulfur and either malononitrile (**22a**) or ethyl cyanoacetate (**22b**) in 1,4-dioxane and triethylamine (Scheme 60). The synthesized compounds were evaluated against six tumor cell lines, namely, HT29 (human colon cancer), A549 (non-small cell lung cancer), U87MG (human glioblastoma), MKN-45 (human gastric cancer), H460 (human lung cancer), and SMMC-7721 (human liver cancer), employing (MTT) assay in vitro, where foretinib was used as a positive control. The results indicated that compounds **206b**, **208e**, and **208f** showed the most inhibitory effect towards the six tumor cell lines. They were subjected to further tests of five tyrosine kinases c-Kit, Flt-3, VEGFR-2, EGFR, and PDGFR and Pim-1 kinase. Compound **206b** displayed the highest inhibitions against the five tyrosine kinases and Pim-1 kinase.[103]



Scheme 60. Synthesis of thiophene derivatives **206a,b** and **208a-f**

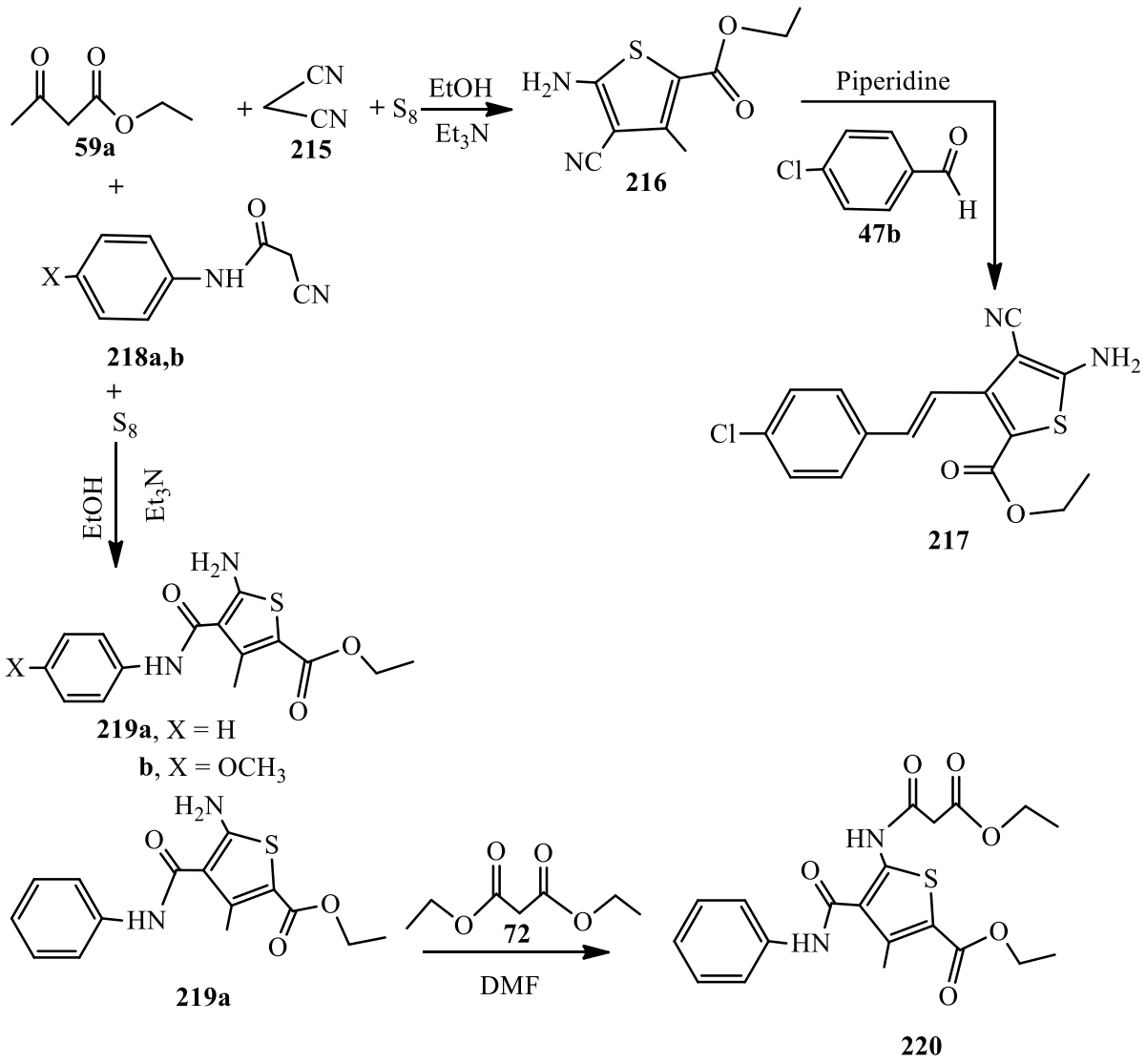
Havaldar et al. reported the syntheses of **214a-c**, which were outlined in (Scheme 61).[104] Compounds **214a-c** were screened for their antibacterial efficacy towards *E. coli, S. aureus, S. typhos*a and *B. subtilis*. The results indicated that compound **214b** exhibited the highest antibacterial activity towards all the used bacteria strains.[105]



214a, R = -H, R^1 = -NO_2
b, R = -H, R^1 = -CH_3
c, R = -OCH_3, R^1 = -H

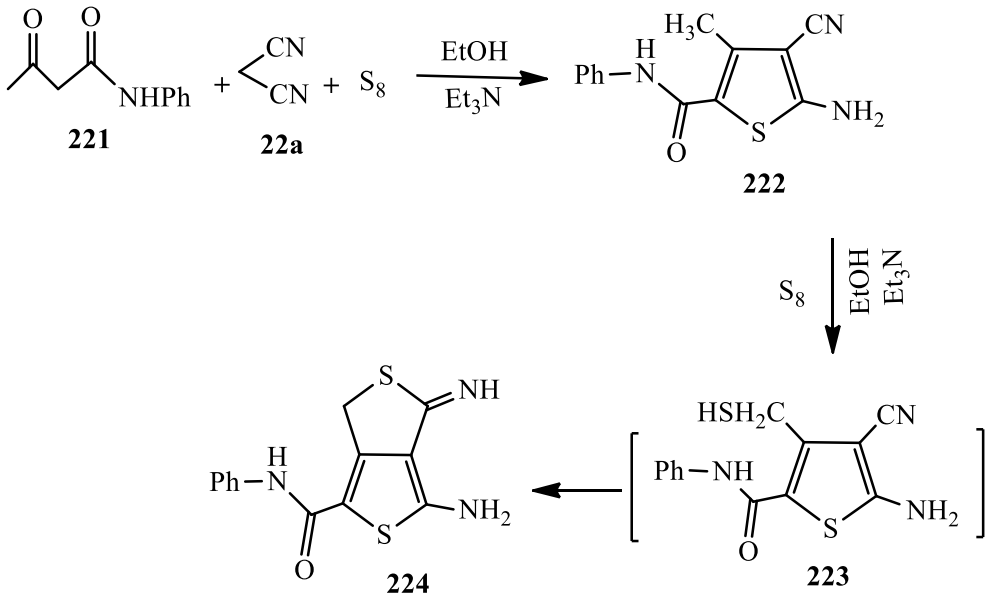
Scheme 61. Synthesis and antibacterial activity of thiophene derivatives **214a-c**

Mohareb et al. disclosed that the thiophene derivative **216** was afforded *via* the reaction of ethyl acetoacetate **(59a**), malononitrile (**22a**) and elemental sulfur in ethanol.[106] The reaction of **216** with para-chlorobenzaldehyde (**47b**) in the presence of piperidine produced the thiophene derivative **217**. On the other hand, the thiophene derivatives **219a**,**b** were afforded through the reaction of ethyl acetoacetate **(59a**), 2-cyano-N-phenylacetamide (**218a**), 2-cyano-N-(4-methoxyphenyl)acetamide (**218b**) and elemental sulfur in ethanol in the presence of triethylamine. Furthermore, compound **219a** reacted with diethyl-malonate (**72**) to give the thiophene derivative **220** (Scheme 62). The synthesized compounds **217**, **219a-b** and **220** were evaluated against four tumor cell lines, NCI-H460 (non-small cell lung cancer), MCF-7 (breast adenocarcinoma), a normal fibroblast human cell line (WI-38) and SF-268 (CNS cancer), where doxorubicin was used as a positive control. The results displayed that compounds **217**, **219b** and **220** were the most active ones towards SF-268, NCI-H460 and MCF-7, while they showed less activity towards (WI-38). The higher cytotoxic activity of compounds **217**, **219b** and **220** were due to the presence of chloro, OCH_3 and two ethoxy groups, respectively.



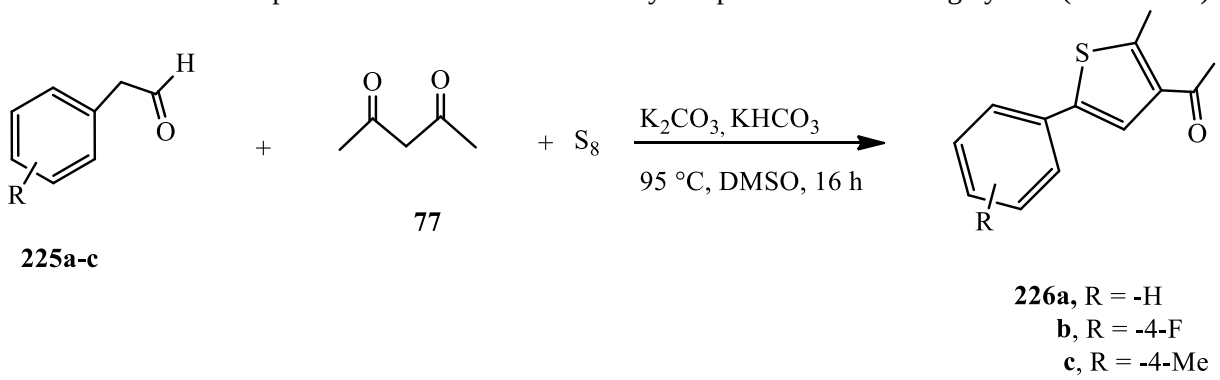
Scheme 62. Synthesis of thiophene derivatives **217**, **219a-b** and **220**

Acetoacetanilide (**221**) reacted with malononitrile (**22a**) and elemental sulfur in the presence of triethylamine to give the thiophene derivative **222**, which was then reacted with elemental sulfur in the presence of triethylamine to give the thieno[c]thiophene derivative **224**. The reaction took place through the initial reaction of the CH_3 group with elemental sulfur to give the thiol derivative **223**, which was followed by addition of the SH group to the CN group to give the thiophene derivative **224** (Scheme 63). The antiproliferative of the newly synthesized compounds was evaluated against the three cancer cell lines, namely, SF-268 (CNS cancer), MCF-7 (breast adenocarcinoma) and NCI-H460 (non-small cell lung cancer). The results showed that compounds **222** and **224** exhibited lower cytotoxic effect than the positive control doxorubicin against three cancer cell lines.[107]



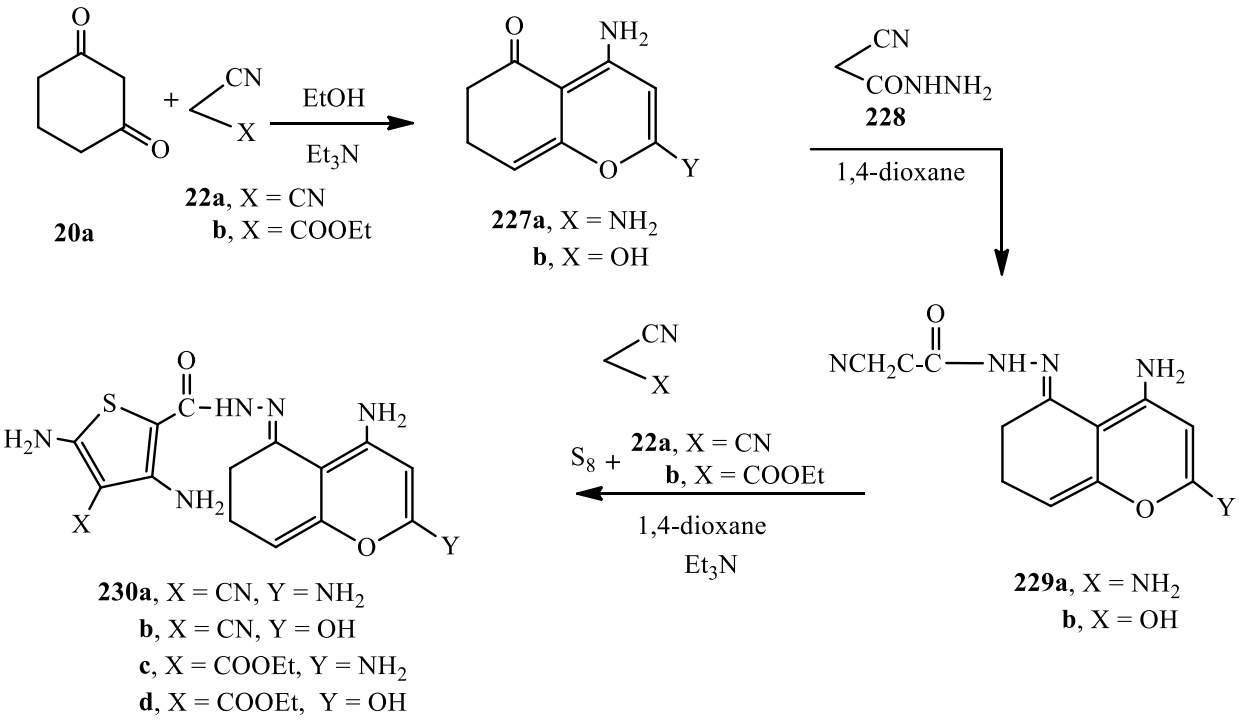
Scheme 63. Synthesis of thiophene derivatives **222**, **224**

One-pot three-component reaction between arylacetaldehydes (**225a-c**), 1,3-dicarbonyl (**77**), and elemental sulfur in the presence of a base afforded 5-arylthiophenes **226a-c** in high yields (Scheme 64).[108]



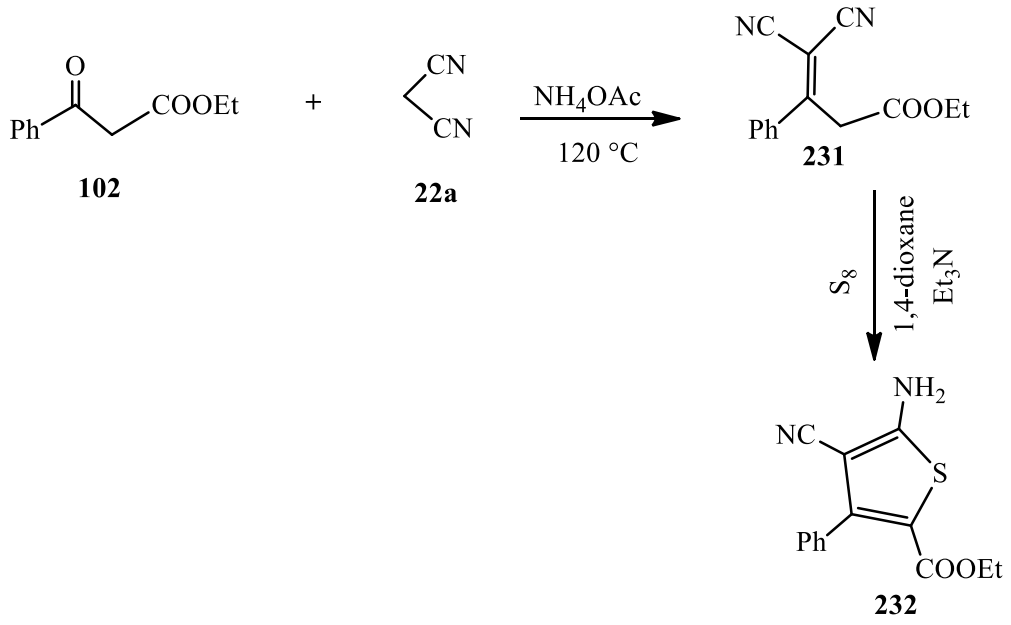
Scheme 64. Synthesis of thiophene derivatives **226a-c**

Chromene derivatives **227a,b** were afforded from the reaction between cyclohexan-1,3-dione (**20a**) and either of malononitrile (**22a**) or ethyl cyanoacetate (**22b**) in ethanol in the presence of a catalytic amount of triethylamine. They were then reacted with cyanoacetylhydrazine **228** in 1,4-dioxane to afford the hydrazidehydrazine derivatives **229b,a**, which were also reacted with either of malononitrile (**22a**) or ethyl cyanoacetate (**22b**) and elemental sulfur to give the thiophene derivatives **230a–d**, respectively (Scheme 65). The newly synthesized compounds were estimated towards three human tumor cell lines, namely, Huh7(hepatoma carcinoma cell), HCT116 (colon carcinoma cell) and MGC803 (gastric carcinoma cell). The results exhibited that compounds **227b**, **229b**, **230b** and **230d** showed higher cytotoxic activity compared with 5-fluorouracil (5-FU) towards MGC803 and HCT116 cell lines.[109]



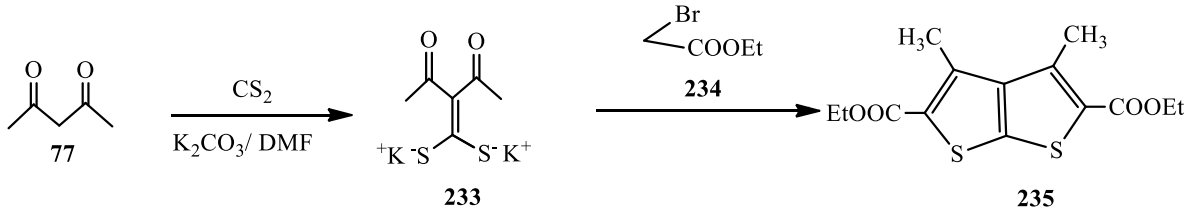
Scheme 65. Synthesis of chromen **227a,b**; **229a,b** and thiophene derivatives **230a-d**

Compound **231** was furnished from Knoevenagel condensation reaction between ethyl benzoylacetate (**102**) and malononitrile (**22a**) in the presence of ammonium acetate 120 °C. Furthermore, **231** was reacted with elemental sulfur in 1,4-dioxane and triethylamine to produce the thiophene derivative **232** (Scheme 66).[110]



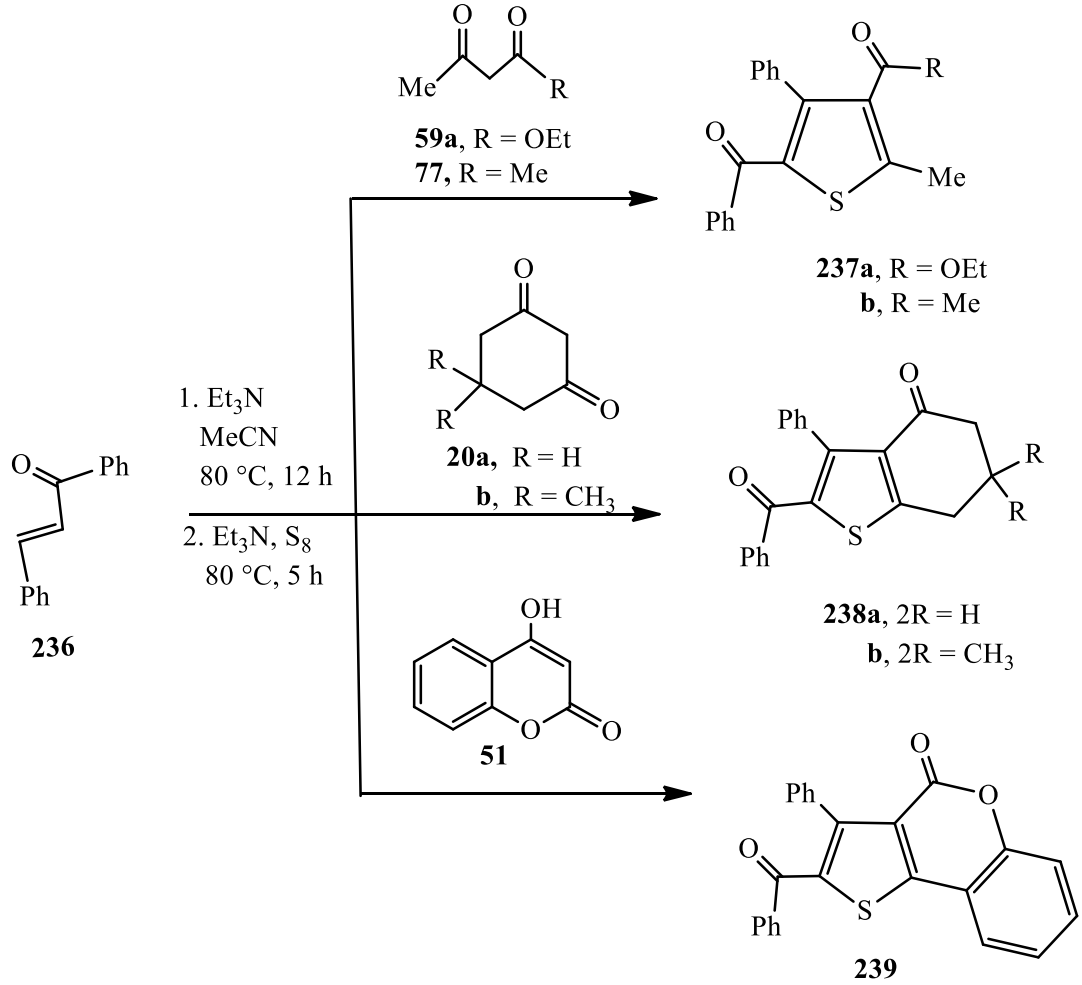
Scheme 66. Synthesis of ethyl 5-amino-4-cyano-3-phenylthiophene-2-carboxylate **232**

The reaction between pentan-2,4-dione (**77**) and potassium carbonate in dimethylformamide (DMF) was followed by dropwise addition of carbon disulfide under vigorous agitation. The mixture was cooled and ethyl bromoacetate (**234**) in DMF was added to form thiophene derivative **235** (Scheme 67).[111]



Scheme 67. Synthesis of diethyl thieno [2,3-b] thiophene-2,5-dicarboxylate **235**

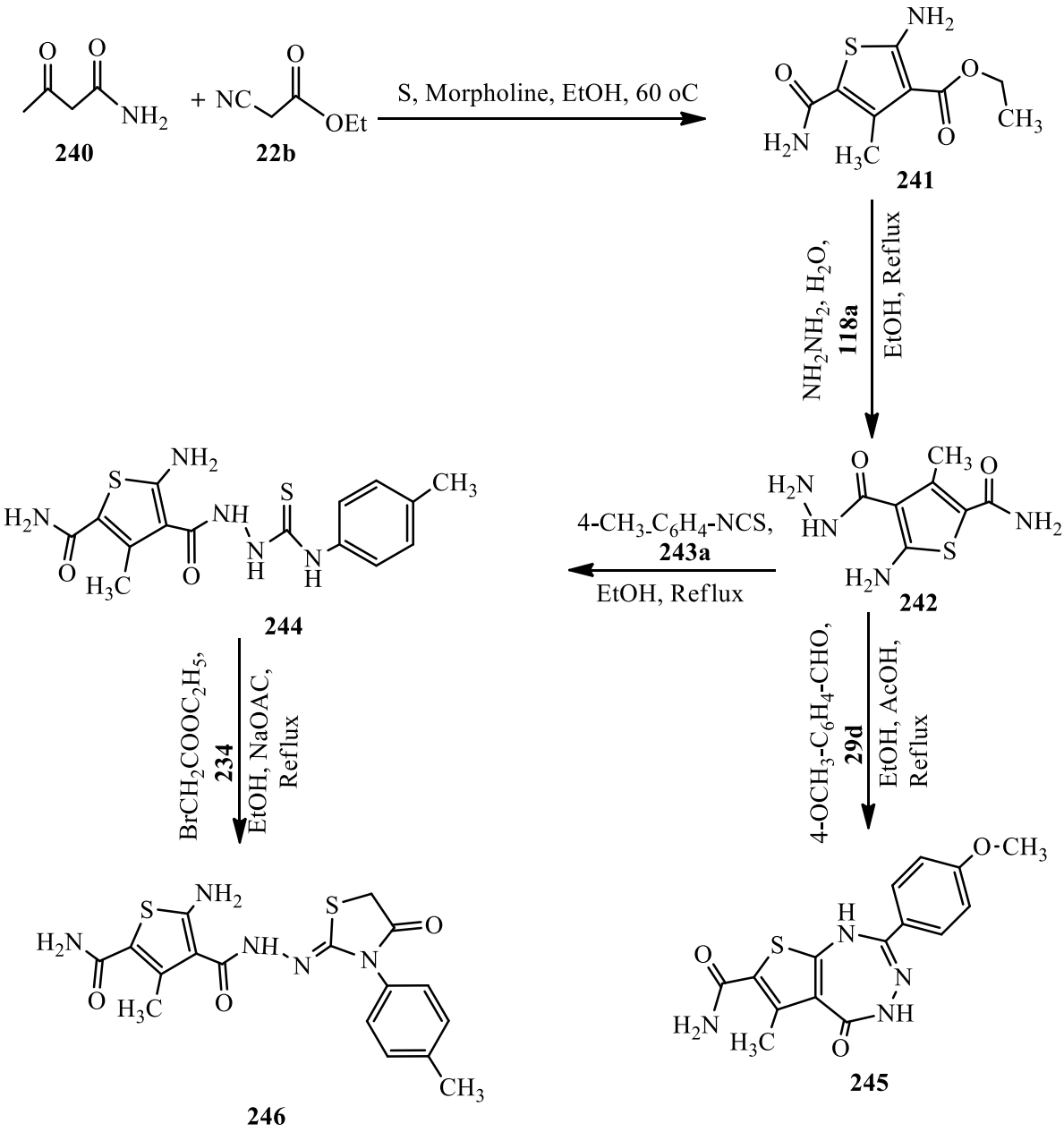
The reaction of chalcone (**236**) with β-dicarbonyl compounds as ethyl acetoacetate (**59a**), acetylacetone (**77**), 1,3-cyclohexanedione (**20a**), dimedone (**20b**), 4-hydroxycoumarin **51**, and elemental sulfur afforded corresponding substituted thiophenes **237a,b**, **238a,b** and **239** in an excellent yields (Scheme 68).[112,113]



Scheme 68. Synthesis of thiophene derivatives **237a,b**, **238a,b**, **239**

The thiophene derivative **245** was synthesized through refluxing of 5-amino-4-(hydrazinecarbonyl)-3-methylthiophene-2-carboxamide **242** with 4-methoxy benzaldehyde (**29d**) in ethanol containing glacial acetic acid. On the other hand, thiophene derivative **246** was afforded from the cyclocondensation reaction between 5-amino-3-methyl-4-(2-(4-methylphenethyl)hydrazine-carbonyl)thiophene-2-carboxamide **244** with ethyl bromoacetate (**234**) in ethanol in the presence of anhydrous sodium acetate (Scheme 69). Compounds **245** and **246** were evaluated for their in vitro growth inhibitory activity towards *B. subtilis* and *S. aureus* (Gram-positive bacteria), *P. aeruginosa* and *E. coli* (Gram-negative bacteria) and

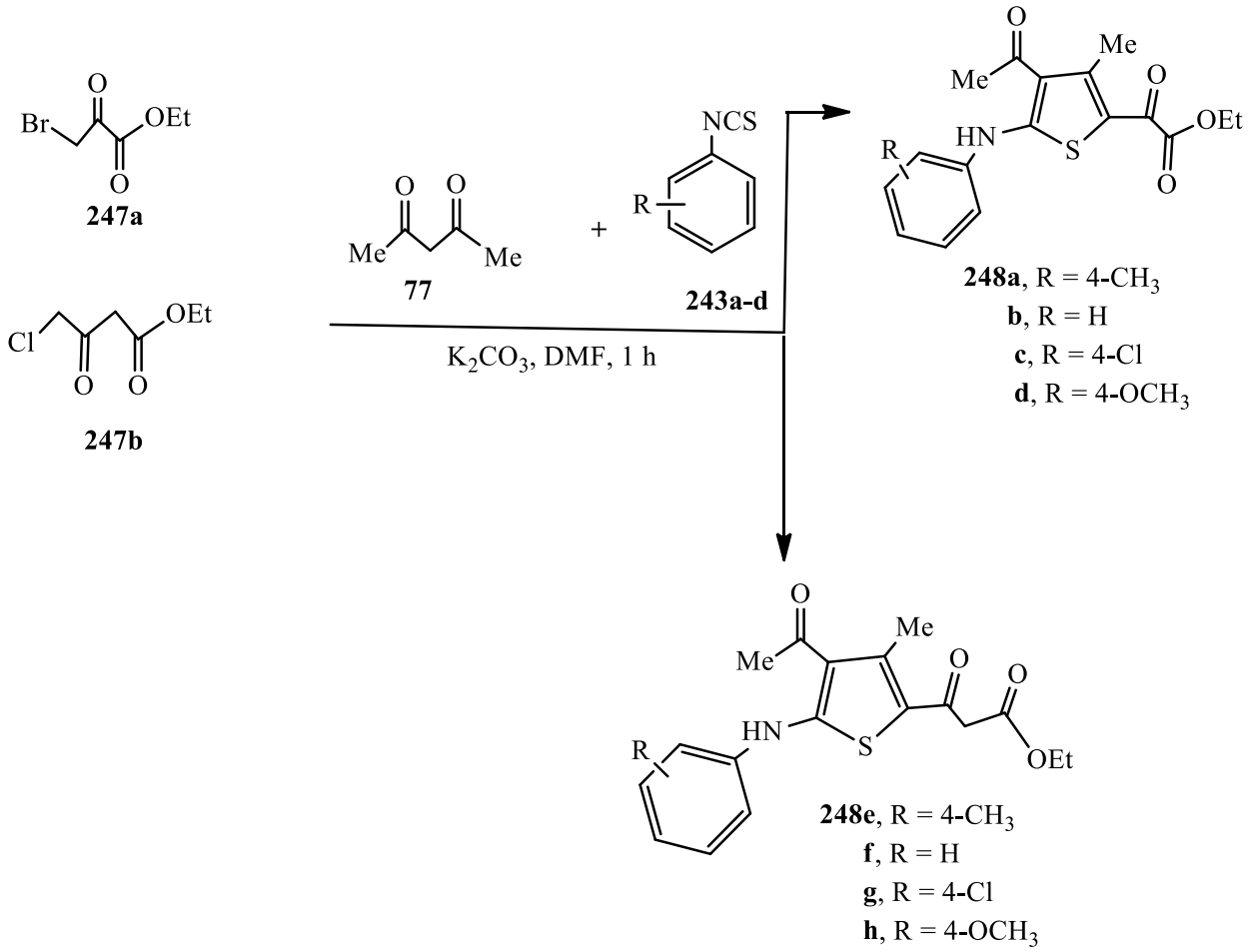
towards *C. albicans* (pathogenic fungi) employing ampicillin and clotrimazole as antimicrobial and antifungal references, respectively. Furthermore, they were tested for their in vitro anti-HCV activity towards hepatocellular carcinoma HepG2 cell line, infected with hepatitis-C virus, employing qualitative reverse transcription-polymerase chain reaction assay. The results revealed that thiophene derivatives **245** and **246** had interesting anti antimicrobial and anti-HCV activities.[114,115]



Scheme 69. Synthesis of thiophene derivatives **245**, **246**

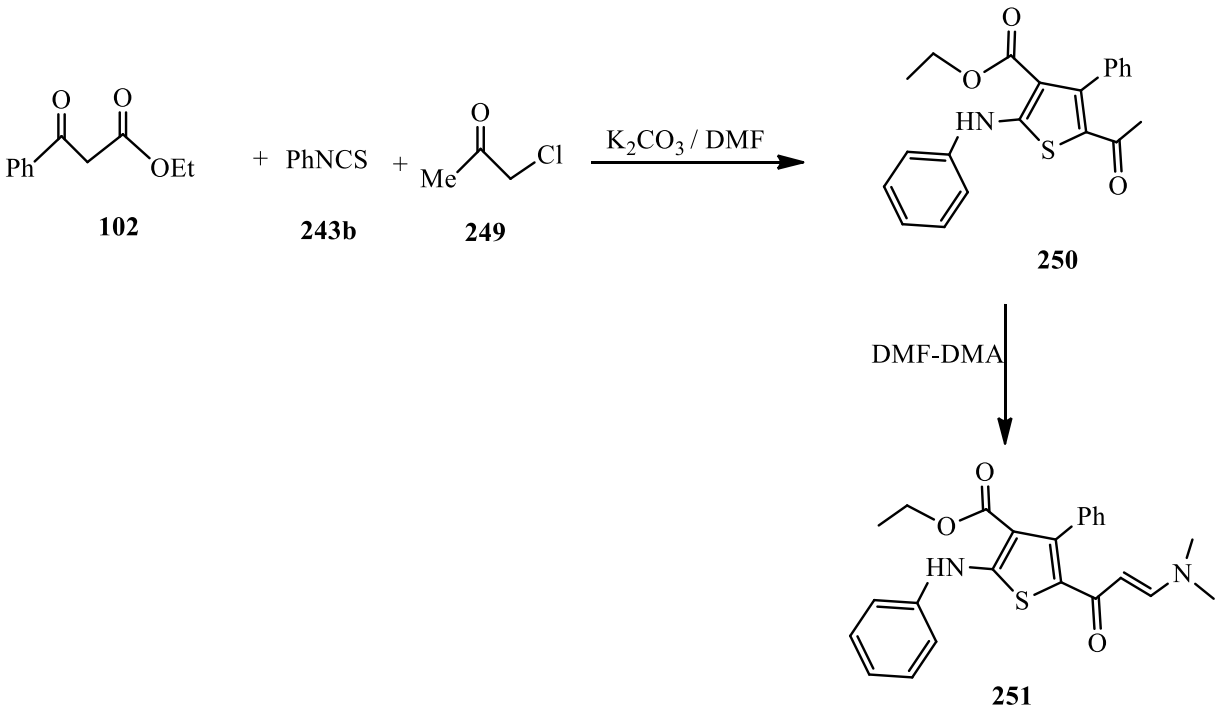
One-pot three-component reaction between acetylacetone (**77**), 2-chloro/bromo methyl derivatives **247a,b** and phenylisothiocyanates (**243a-d**) afforded the thiophene derivatives **248a-d** and **248e-h** (Scheme 70). The synthesized compounds were screened for their in vitro antibacterial activities towards *S. aureus, B. subtilis* (Gram-positive bacteria), and *E. coli, P. aeruginosa* (Gram-negative bacteria), employing azithromycin as a standard drug. The results indicated that compounds **248a-d** and **248e-h** displayed good to excellent activities towards *E. coli* and *P. aeruginosa* (Gram-negative bacteria) by minimum inhibitory concentration (MIC) values between 0.3 and 8.5 µM, and lower activity against *S. aureus* and *B. subtilis* (Gram-positive bacteria) by minimum inhibitory concentration (MIC) values between 0.1 and 9.5 µM. Furthermore, a change in the substituent might also affect the antibacterial

activity. For example, compounds with R = H/Cl were found to be more effective towards *S. aureus* (Gram-positive bacteria) and *E. coli*, *P. aeruginosa* (Gram-negative bacteria). The compounds with R = CH_3/OCH_3 appeared to have more potential toward *B. subtilis* (Gram-positive) and *E. coli*, *P. aeruginosa* (Gram-negative bacteria).[116,117]



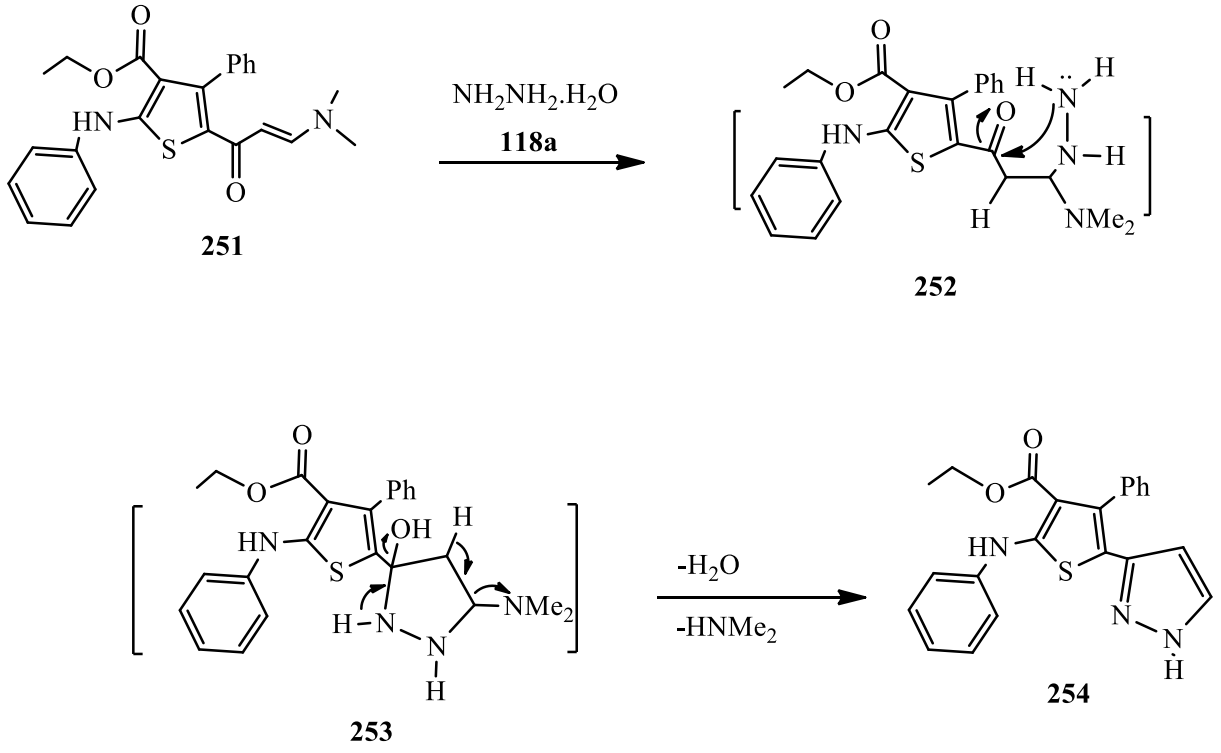
Scheme 70. Synthesis of fully substituted thiophene derivatives **248a-d** and **248e-h**

The reaction between ethyl benzoylacetate (**102**) with chloroacetone (**249**) and phenylisothiocyanate (**243b**) in the presence of dimethylformamide and potassium carbonate furnished 2-acetylthiophene **250**.[118] The reaction of thiophene **250** with N,N-dimethylformamide-dimethyl acetal gave the thiophene derivative **251** (Scheme 71).



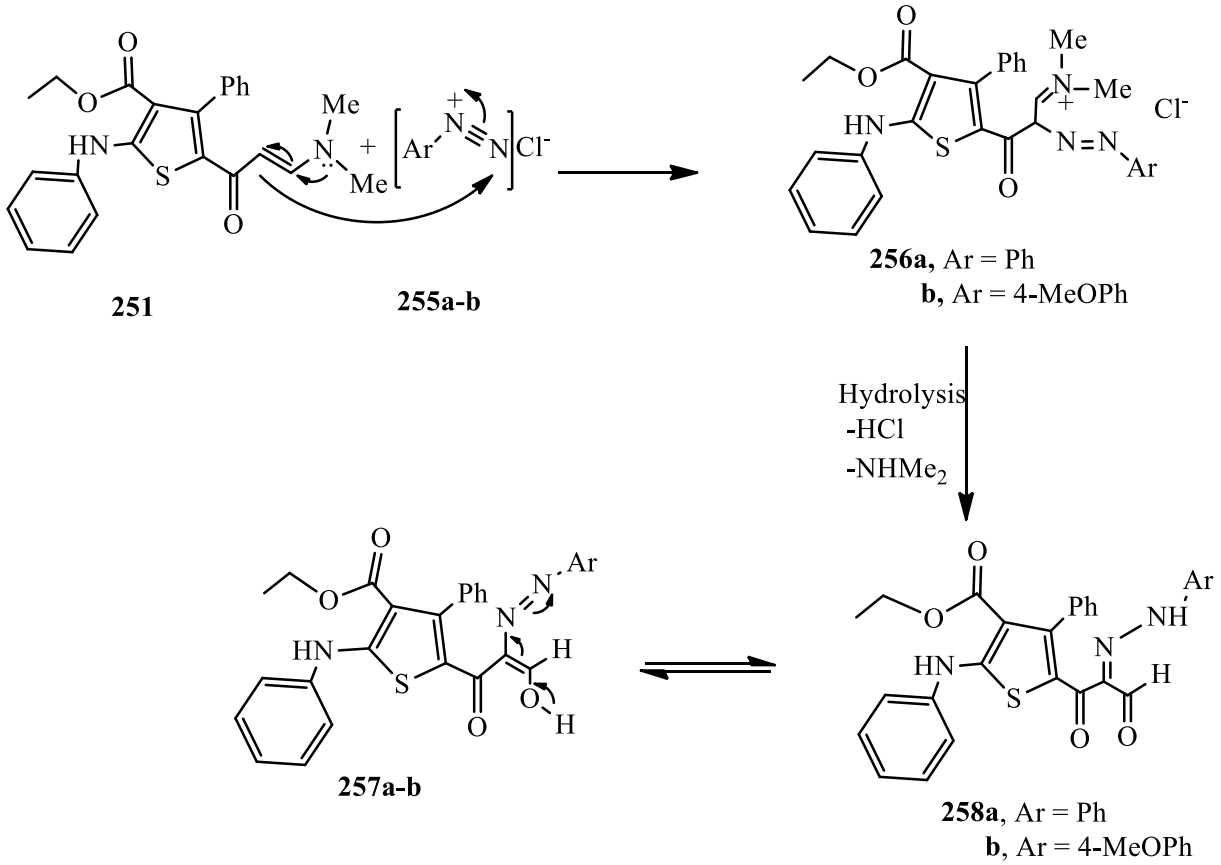
Scheme 71. Synthesis of thiophene derivative **251**

Treatment of the enaminone **251** with hydrazine hydrate (**118a**) afforded the pyrazole thiophene derivative **254** (Scheme 72). The authors suggested that compound **254** was synthesized through intramolecular cyclization of the intermediate **253**, which was afforded from an initial addition of the amino group of hydrazine **118a** to the double bond of the enaminone **251**.



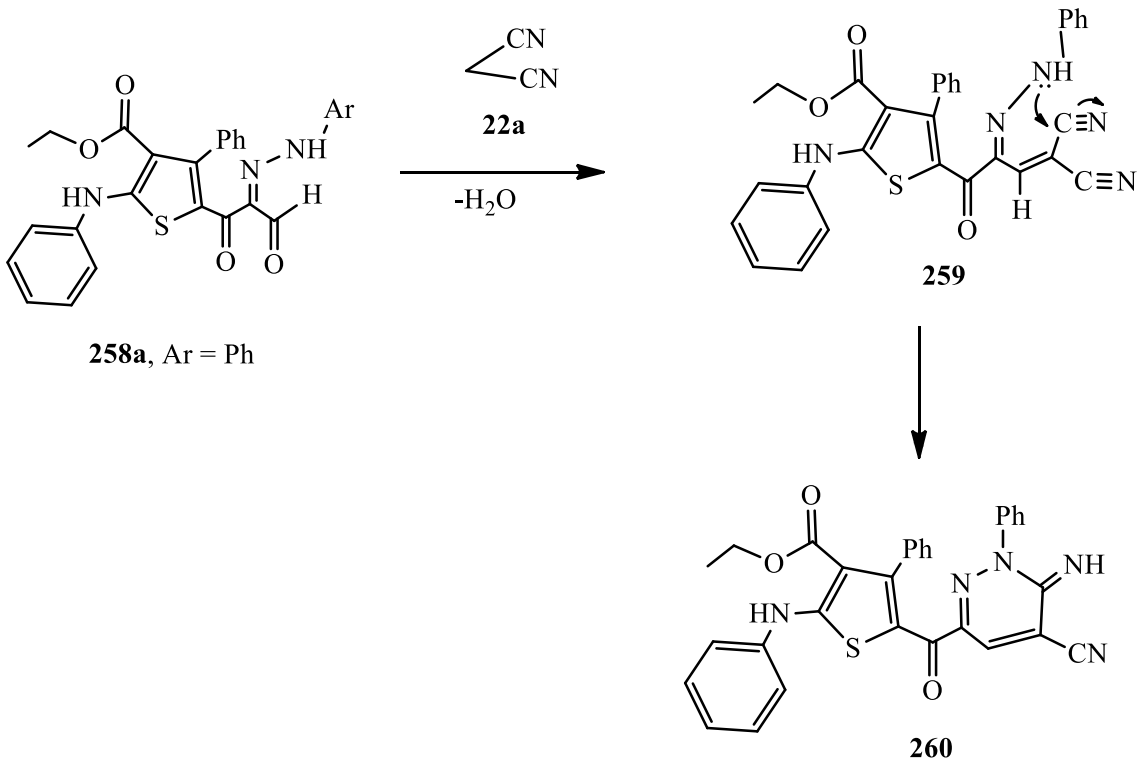
Scheme 72. Synthesis of thiophene derivative **254**

Hydrazones **258a,b** were obtained from the coupling of enaminone **251** with the diazonium salt of aniline or 4-methoxyaniline (**255a,b**) (Scheme 73).



Scheme 73. Synthesis of thiophene derivatives **258a,b**

The reaction between malononitrile (**22a**) and hydrazone **258a** produced thiophene derivative **260** (Scheme 74).



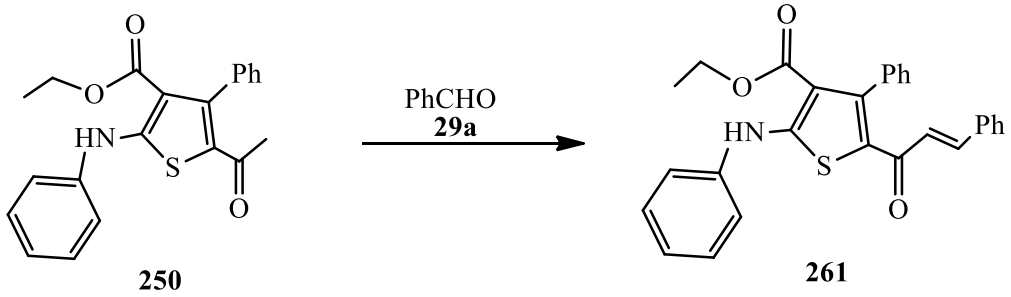
258a, Ar = Ph

259

260

Scheme 74. Synthesis of thiophene derivative **260**

The reaction between benzaldehyde (**29a**) and thiophene **250** in the presence of zinc chloride furnished chalcone **261** (Scheme 75).

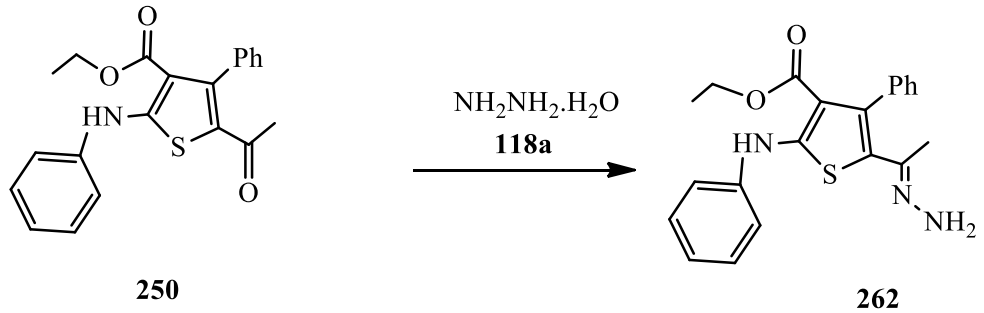


250

261

Scheme 75. synthesis of the thiophene derivative **261**

Treatment of hydrazine hydrate (**118a**) with thiophene **250** afforded hydrazone derivative **262** (Scheme 76).[119]



250

262

Scheme 76. Synthesis of the thiophene derivative **262**

9. Conclusion

In this review, chromen, coumarin, pyridine, pyrimidine, pyrazole, thiazole, thiophene derivatives were synthesized from β-diketones according to various reactions included Knoevenagel condensation, Michael addition, Hantzsch reaction, and Gewald's reaction in the presence of different catalysts as Fe_3O_4@GO-N-(pyridin4-amine) nanofilm, supported ionic liquid catalyst as heterogeneous catalyst (SILC), (DABCO), DMAP, DBU, ALAM, Cinchonine, Ni(II)-Schiff base/SBA-15 as environmentally benign catalyst, a new deep eutectic solvent (DES), saccharose, low transition temperature mixture (LTTM), OPC-SO_3H. Many compounds showed biological activity towards different tumor cell lines, and toward Gram-positive and Gram-negative bacteria, also some synthesized compounds exhibited important advanced glycation end-products (AGEs) formation inhibitory efficacy and important acetylcholinesterase (AChE) inhibitory efficacy.

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