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(REVIEW ARTICLE)

Chemistry and synthetic methodologies of chalcones and their derivatives: A review

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Abstract

Due to the presence of keto ethylenic moiety, CO-CH=CH-, the chalcones and their derivatives are considered valuable moieties in the field of heterocyclic and synthetic organic chemistry. Chalcones and their derivatives have a wide range of antiproliferative, antifungal, antibacterial, antiviral, antileishmanial and antimalarial pharmacological activities because they contain a reactive α, β-unsaturated carbonyl group. Chalcones are also isolated from natural resources, especially from *Piper methysticum* as flavonoids and polyphenolic compounds. These derivatives are synthesized by using various conventional and greener approaches by employing different means of reactions, frequently by using Claisen-Schmidt condensation. In this review, information on the various synthetic methodologies, various approaches and techniques for the synthesis of chalcones and their derivatives are described. Thus, it will be useful to design and develop new novel drug-like candidates in the field of medicine.

Keywords: Chalcones; 1,3-diphenyl-2-propene-1-one; Claisen-Schmidt condensation; Microwave-assisted synthesis; Synthetic approaches

1. Introduction

Heterocyclic compounds are organic molecules that contain at least one carbon atom and at least one other heteroatom, such as N, O or S. They are crucial for the metabolism of living cells. They tend to have five or six members on average and some of their ring compositions exceed that of rings with three, four, seven or more members. Because of the huge diversity of pharmacological and therapeutic implications, heterocyclic chemistry has sparked a lot of attention toward pharmaceutical and synthetic organic chemistry [1]. Chalcones are one of the most important classes of heterocyclic compounds with wide therapeutic implications, which may be synthetic or obtained naturally as flavonoids. The chalcone is chemically 1,3-diphenyl-2-propene-1-one, which are polyphenolic compounds belonging to the flavonoid family. The chalcones are open-chained molecules with two aromatic rings, which are joined by the three carbon chains containing an α, β-unsaturated bond and a carbonyl group [2-4]. Chalcones, which greatly contribute to the colouration of the corolla of various plants, are mostly composed of polyphenolic compounds with colours ranging from yellow to orange. Moreover, these compounds are present in natural products such as insect hormones and plant allelochemicals. In addition to being utilized to create heterocyclic compounds, chalcones go through a variety of chemical processes. By coupling aromatic aldehydes with aryl ketones in the presence of the right quantity of condensing agents, it is feasible to synthesize a wide variety of chalcone derivatives. In numerous biosynthetic routes, chalcones serve as the first intermediate structure in the synthesis of flavonoids, isoflavonoids and aurones [5].

These chalcones and their derivatives have been reported to exhibit a wide variety of therapeutic and pharmacological applications including anticancer [6], antimicrobial [7], antitubercular [8], antioxidant [9], anti-inflammatory [10], larvicidal [11], anti-plasmodial [12], neuroprotective [13], cholinesterase inhibitors [14], antidepressant [15], anti-diabetic [16] and vitiligo treatment [17]. Among those therapeutic applications, chalcones and their derivatives have

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extended their interest in cancer and have the ability to regulate tumor neo-angiogenesis, as well as provide better anticancer potential through inhibiting different signaling pathways with immune enhancement and low toxicity towards normal cells [18,19].

Like chalcones, coumarins, hydroxy coumarins, chalconoids and curcuminoids are also naturally occurring moieties with an α, β-unsaturated carbonyl system extending their potential towards cancer i.e., the compounds containing hydrazide-hydrazone, acrylonitrile and 2-amino-3-cyanopyridine moieties exhibited significant anticancer potential [20]. The chalcones and their derivatives were synthesized by using various synthetic strategies including Claisen-Schmidt condensation [21], Knoevenagel condensation [22], Microwave-assisted synthesis [23], Ultrasonic-assisted synthesis [24], stirring at high temperature [25], Refluxing [26], Molecular hybridization approach [27] and base-catalyzed condensation reaction [28]. Among the various approaches, the chalcones and their derivatives were highly synthesized by employing the Claisen-Schmidt condensation approach.

In this review, only the literature indexed in Scopus, PubMed, Google Scholar, Embase, ResearchGate and Web of Science databases were collected by using the keywords such as chalcones, diphenyl propene-1-ones, synthetic approaches, Claisen-Schmidt condensation, Crossed Aldol condensation, Microwave-assisted synthesis and Conventional synthesis, individually and in combination between the time periods of 2016 to 2023. Here, we summarized the various synthetic approaches for the synthesis of novel and efficient chalcones and their derivatives.

2. Synthetic approaches of Chalcones and their derivatives

Aminochalcones were synthesized by the reaction between aminoacetophenone and benzaldehyde under a base-catalyzed condensation reaction in the presence of sodium hydroxide [2] (Scheme 1). 5-acetyl-2-hydroxybenzamide with different aldehydes in the presence of ethanol yielded the novel chalcones through Claisen-Schmidt condensation [20] (Scheme 2). The reaction between trifluoromethyl benzaldehyde and acetophenone with an aid of methanol under stirring conditions yielded an appropriate chalcone, (E)-1-phenyl-3-[2-(trifluoromethyl) phenyl] prop-2-en-1-one [22] (Scheme 3). The pyridyl-indole chalcone was synthesized by using the Knoevenagel condensation reaction. The condensation of indole-3-carboxaldehyde and 4-acetyl pyridine in presence of piperidine under reflux conditions yielded the respective pyridyl-indole chalcone [23] (Scheme 4). The benzimidazole-chalcone hybrid was synthesized by Zhou et al., 2020. On the condensation of (1H-Benzo[d]imidazol-2-yl)methanol and o-phenylenediamine with glycolic acid with an aid of hydrochloric acid resulted in the formation of substituted-(1-benzyl-1H-benzo[d]imidazol-2-yl)methanol. To the formed intermediate, benzyl bromide was added and upon the addition of bromoacetophenone, the corresponding chalcone was obtained as the result of Claisen-Schmidt condensation [26] (Scheme 5). The above-discussed schemes are given in Figure 1.

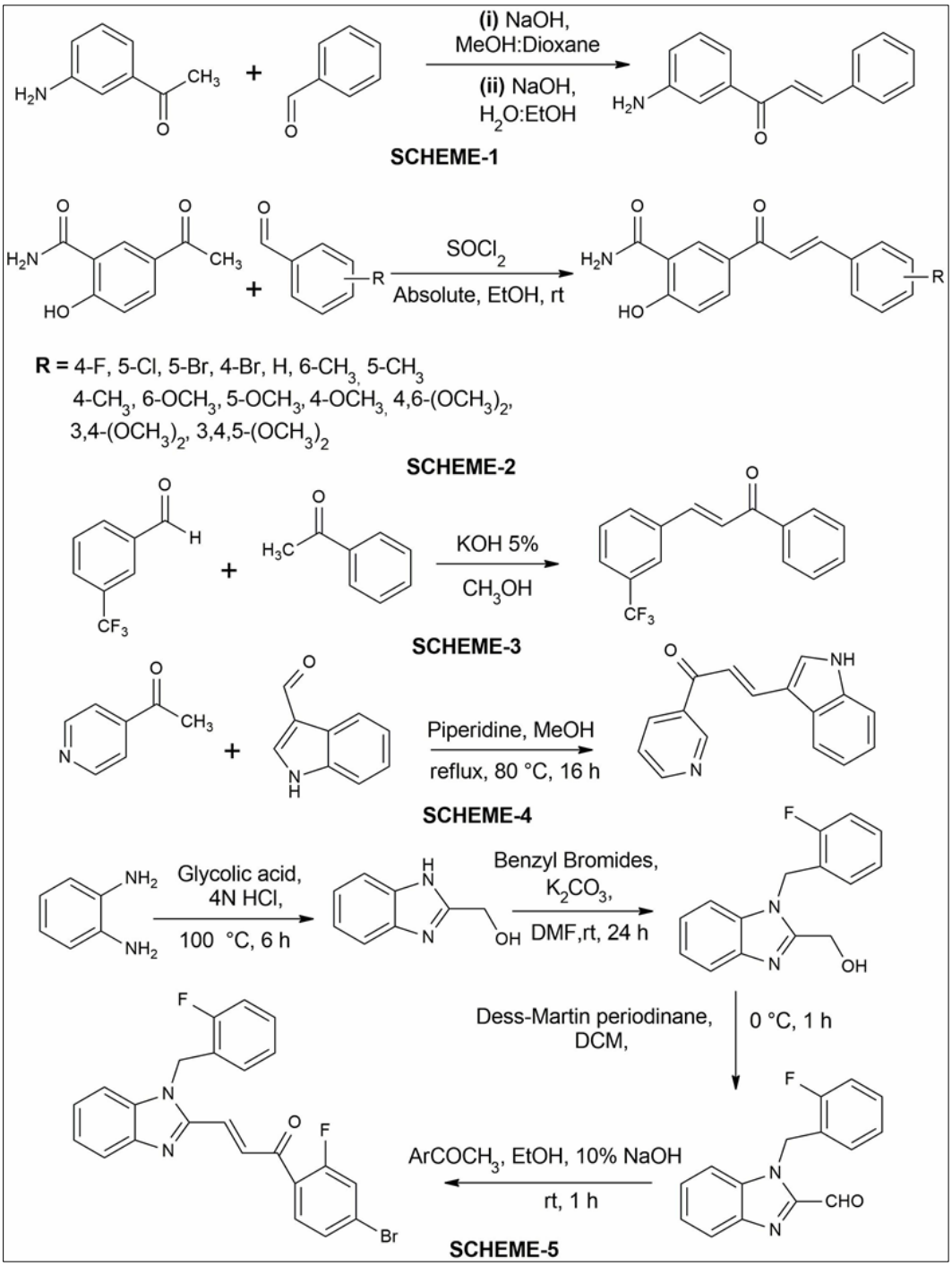

Figure 1 Synthesis of Aminochalcones (Scheme-1), 5-acetyl-2-hydroxybenzamide chalcone (Scheme-2), (E)-1-phenyl-3-[2-(trifluoromethyl) phenyl]prop-2-en-1-one (Scheme-3), pyridyl-indole chalcone (Scheme-4) and benzimidazole-chalcone (Scheme-5)

The naphthalene-chalcone derivatives were designed and synthesized by Wang et al., 2018. The reaction between different substituted benzaldehydes with 1-(4-methoxynaphthalen-1-yl)ethan-1-one under stirring conditions provided the naphthalene-chalcone compounds [29] (Scheme 6). Similarly, condensation of substituted benzaldehydes with 1-(2-methoxynaphthalen-1-yl)ethan-1-one, which was obtained by the alkylation of 1-(2-hydroxynaphthalen-1-yl)ethan-1-one in presence of potassium hydroxide at room temperature yielded the series of naphthalene-chalcone derivatives [30] (Scheme 7). Claisen Schmidt condensation of aromatic ketone with indole aldehydes with an aid of potassium hydroxide afforded corresponding chalcone derivatives [31] (Scheme 8). 2-naftaldehyde was stirred with various ketone derivatives obtained from the reaction between fluoroacetopheneone and piperazine derivatives, resulted in the formation of respective chalcones [32] (Scheme 9). The above-discussed schemes are given in Figure 2.

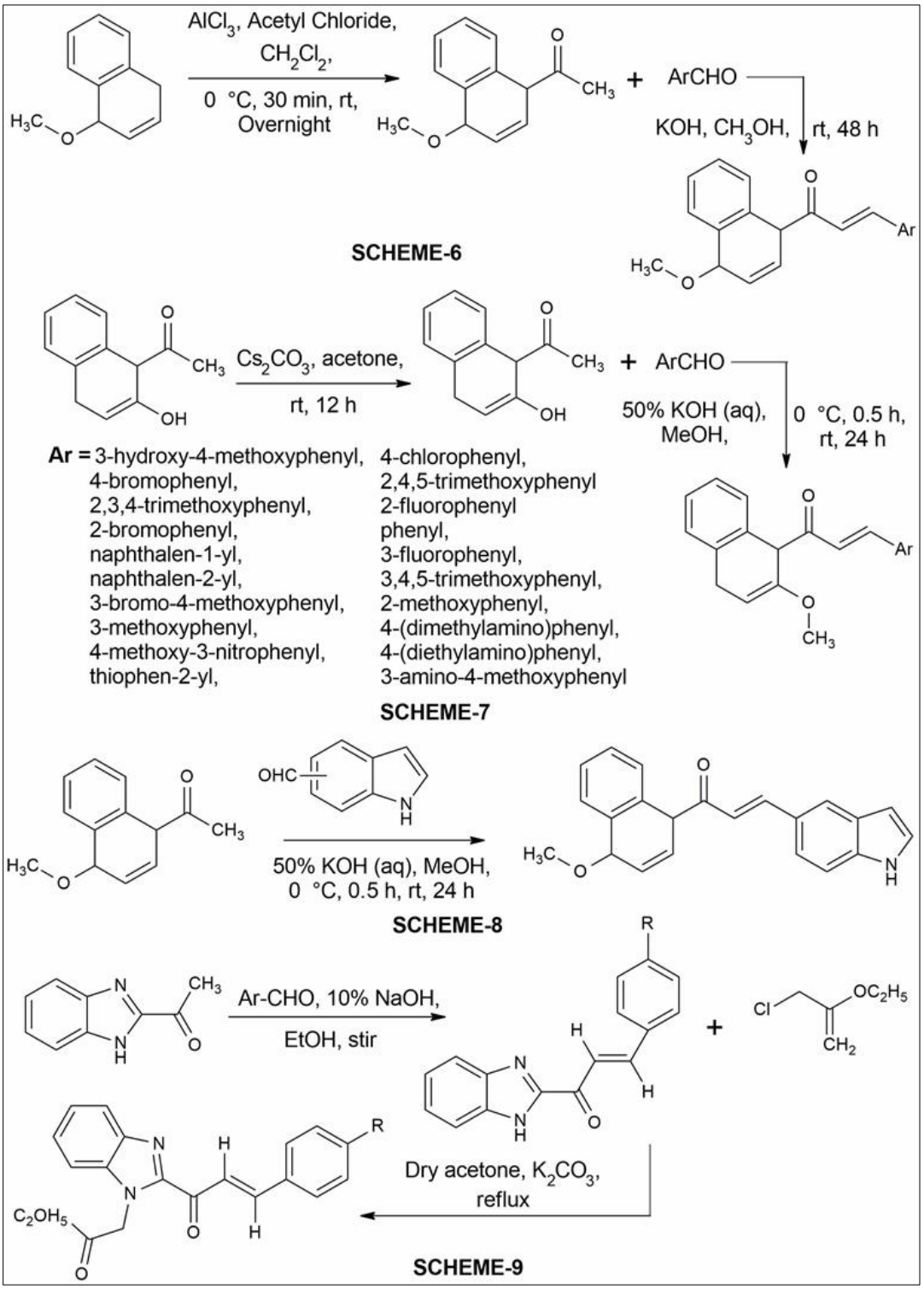

Figure 2 Synthesis of naphthalene-chalcone derivatives (Schemes-6 and 7), indole aldehyde-based chalcones (Scheme-8) and 2-naftaldehyde derived chalcones (Scheme-9)

The chalcone derivatives containing thieno [2,3-d]pyrimidin-2-yl group were synthesized by the reaction of 2-acteyl-6-methylthieno[2,3-d]pyrimidin-4(3H)-one with piperidine under stirring conditions for 30 min. To the resulted mixture, the appropriate aldehyde was added, which resulted in the corresponding chalcone derivatives [33] (Scheme 10). The mixture of acetophenone and 4-bromobenzaldehyde under stirring conditions at room temperature in the presence of sodium hydroxide afforded 6'-benzyloxy-4-bromo-2'-hydroxychalcone [34] (Scheme 11). The reaction between the 2-acetylbenzimadazole and benzaldehyde in presence of ethanol with an aid of sodium hydroxide, the corresponding chalcone was obtained [35] (Scheme 12). The above-discussed schemes are given in Figure 3.

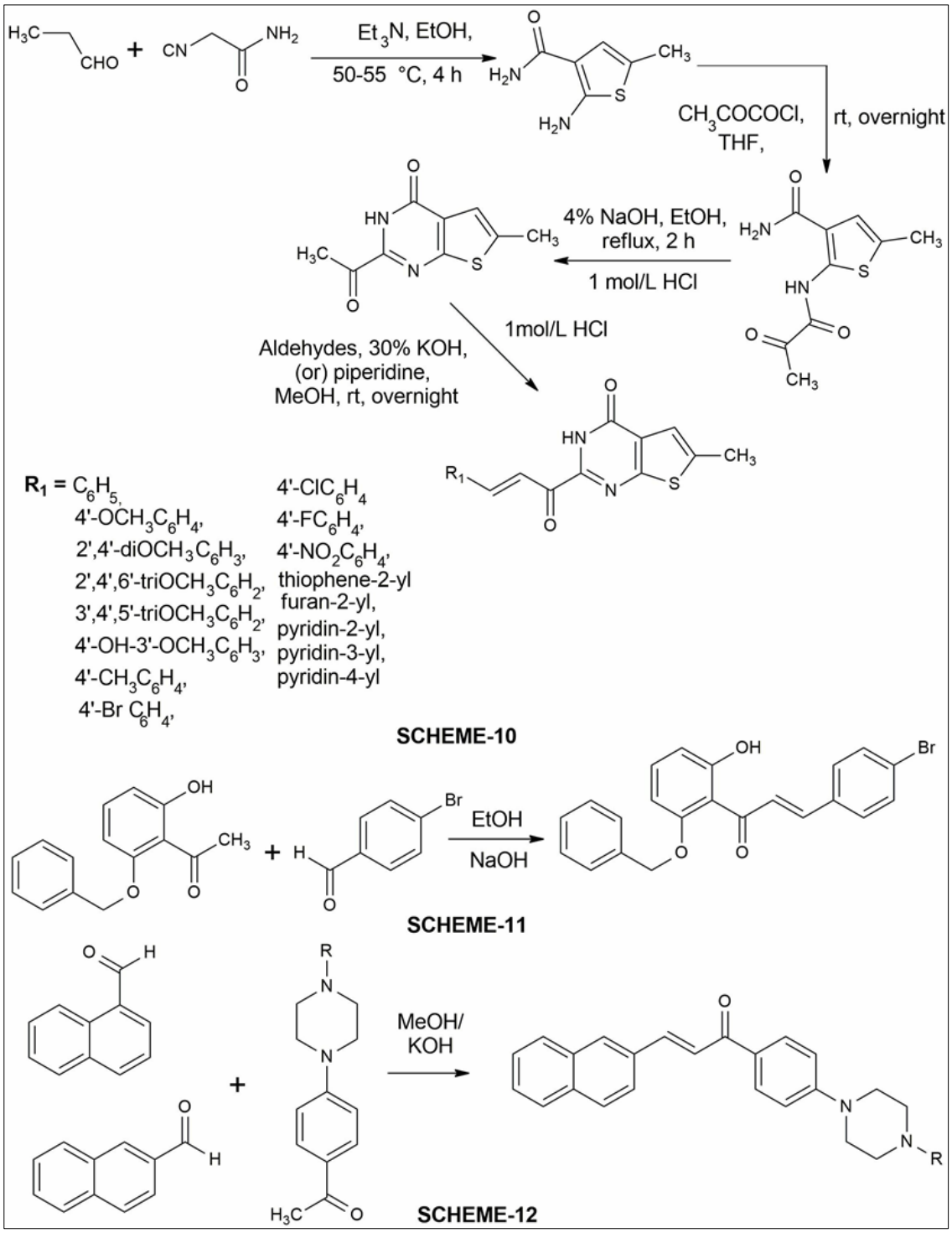

Figure 3 Synthesis of chalcone containing thieno [2,3-d]pyrimidin-2-yl group (Scheme-10), 6'-benzyloxy-4-bromo-2'-hydroxychalcone (Scheme-11) and acetylbenzimadazole-chalcone derivatives (Scheme-12)

2-hydroxy chalcone was synthesized by the Claisen Schmidt condensation of the 2-hydroxy acetophenone and benzaldehyde in presence of a base at high temperature [36] (Scheme 13). Chalcones containing 4-amino-5-cinnamoylthiazole derivatives were synthesized by the condensation of 1-(4-amino-2-(pyrrolidine-1-yl)thiazol-5-yl)ethanone with substituted benzaldehydes in methanol with an aid of sodium hydroxide in an ice bath yielded the corresponding chalcone derivatives [37] (Scheme 14). Flavokawain B type chalcone was synthesized by using Claisen Schmidt condensation reaction and also it can be isolated from the roots of *Piper methysticum*. The reaction between 2-hydroxy-4,6-dimethoxyacetophenone with aromatic aldehyde resulted in the formation of chalcone, (2-hydroxy-4,6-dimethoxypheyl)prop-2-en-1-one [38] (Scheme 15).

A series of chalcone derivatives containing naphthalene and fluorine moieties were designed and synthesized by the reaction between alkylated naphthaldehyde with substituted acetophenones in the presence of few drops of piperidine under stirring conditions [39] (Scheme 16). A novel quinoxalinyl chalcone hybrids were synthesized by the reaction of quinoxaline-2-carbaldehyde (obtained from the reaction of glucose, phenylenediamine and hydrazine) and substituted aromatic acetophenones using Claisen Schmidt condensation under basic conditions [40] (Scheme 17). The above-discussed schemes are given in Figure 4.

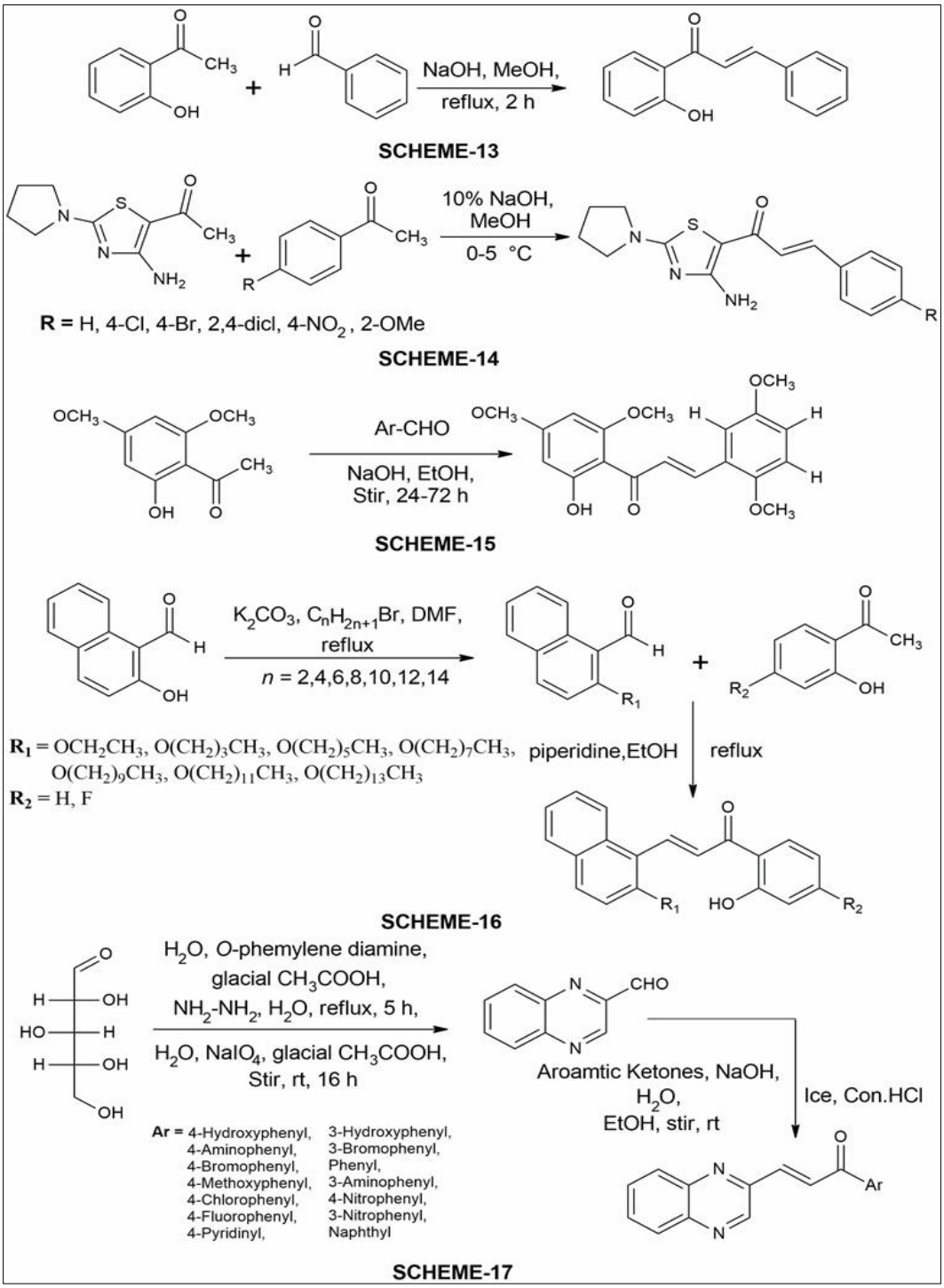

Figure 4 Synthesis of 2-hydroxy chalcone (Scheme-13), Chalcones containing 4-amino-5-cinnamoylthiazole derivatives (Scheme-14), Flavokawain B type chalcone (Scheme-15), chalcone derivatives containing naphthalene and fluorine moieties (Scheme-16) and quinoxalinyl chalcone hybrids (Scheme-17)

The chalcone-imide derivatives were synthesized by refluxing the amino-chalcone derivatives with maleic anhydride, toluene and diethylamine for 24 h [41] (Scheme 18). To a solution of heteroaryl methyl ketone, aryl/heteroaryl aldehyde was added with methanol and stirred for 60 min using a magnetic stirrer, the heteroaryl-chalcone derivatives were obtained [42] (Scheme 19). The thiazole-linked chalcones were synthesized by the mixture of 4-acetyl thiazole with appropriate aldehydes in ethanol under stirring conditions for 2 h [43] (Scheme 20). The above-discussed schemes are given in Figure 5.

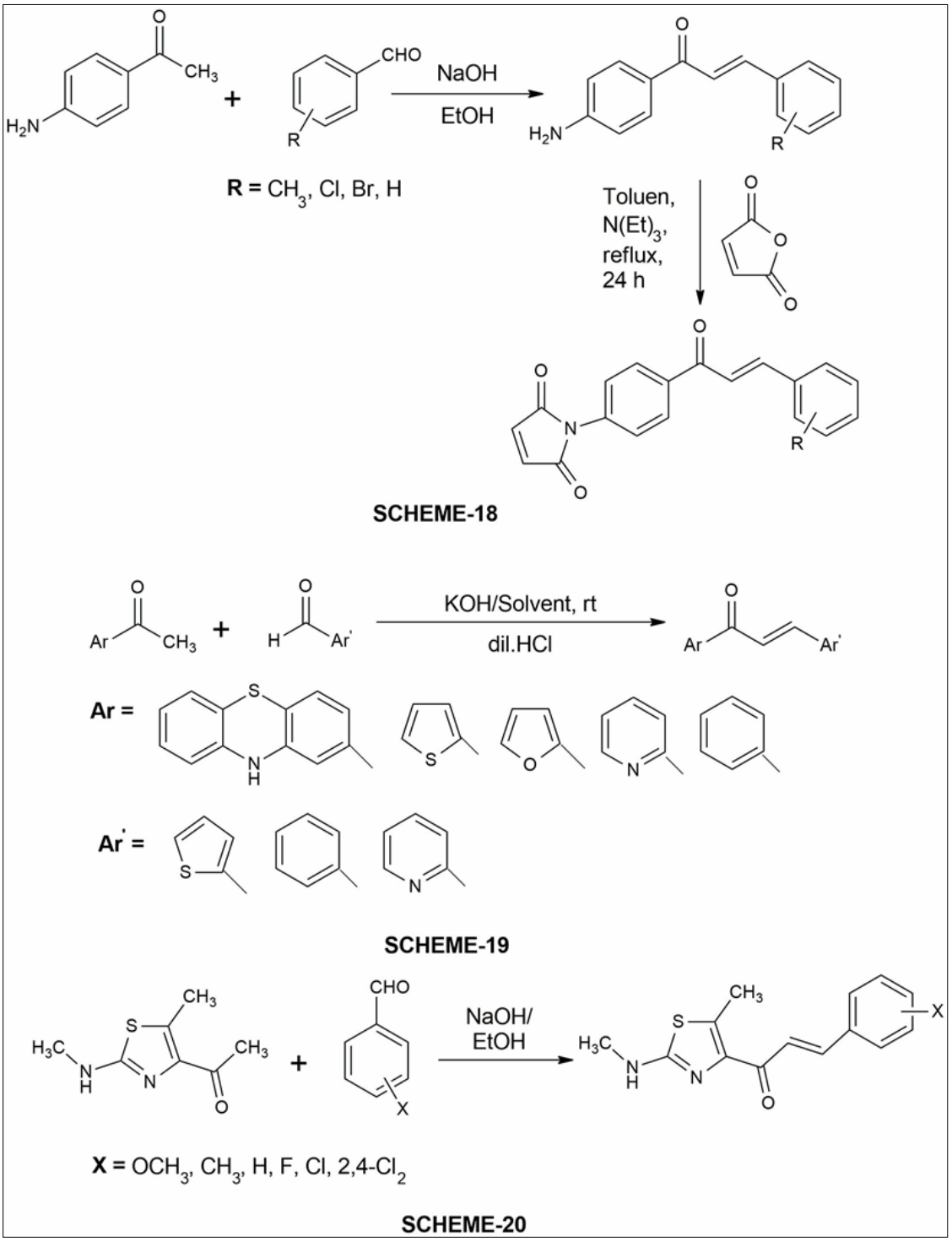

Figure 5 Synthesis of chalcone-imide derivatives (Scheme-18), heteroaryl-chalcone derivatives (Scheme-19) and thiazole-linked chalcones (Scheme-20)

3-aminomethyl pyridine chalcone derivatives were synthesized by the reaction between the cold solution of substituted bromoacetamide with 3-aminomethyl pyridine in presence of triethylamine under stirring conditions for 30 min [44] (Scheme 21). The bis-chalcones were synthesized by reacting 1,1'-(2-hydroxy-4,6-dimethoxy-1,3-phenylenediethanone) with various benzaldehyde derivatives in presence of potassium hydroxide under stirring conditions [45] (Scheme 22). These schemes are given in Figure 6.

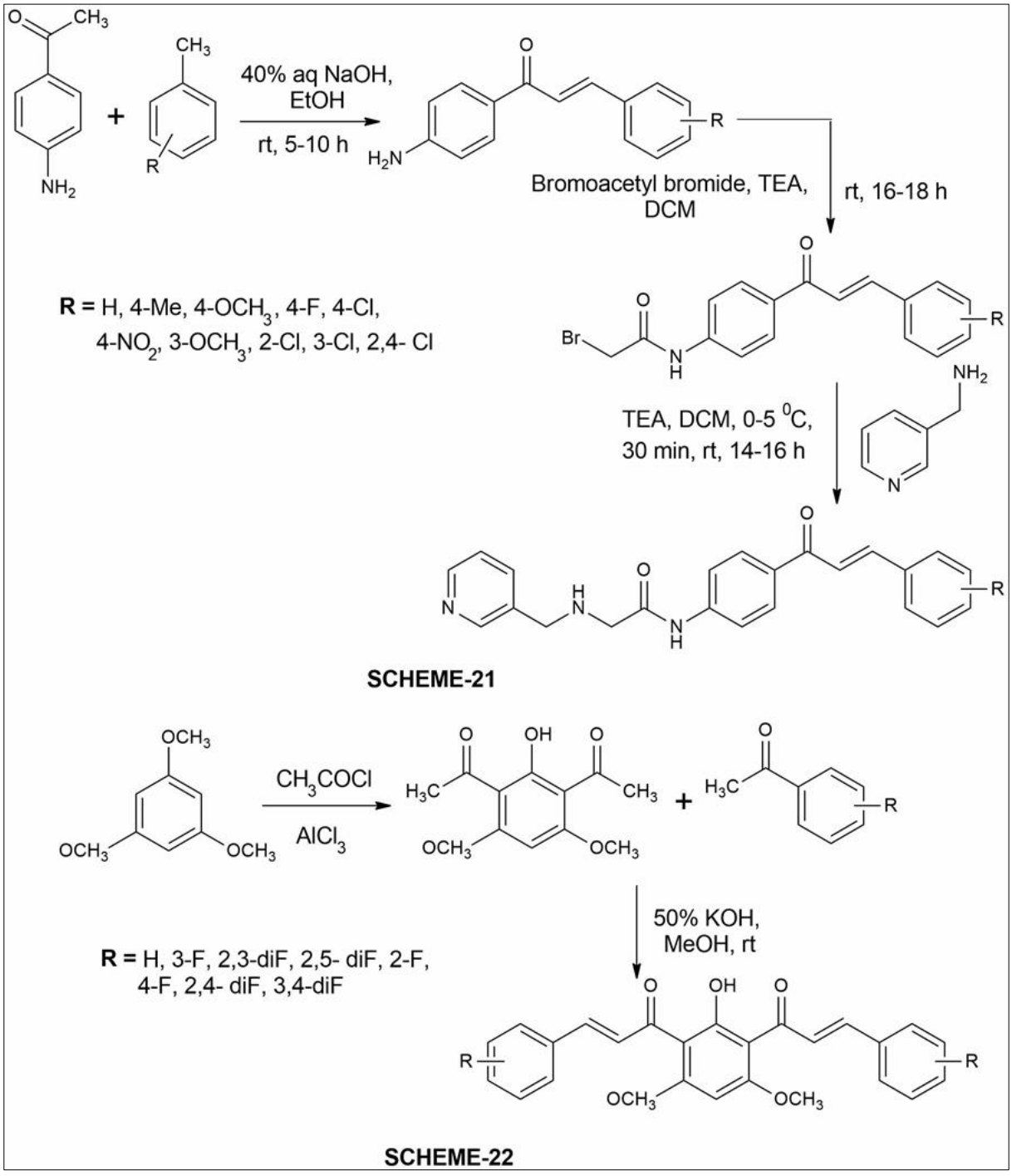

Figure 6 Synthesis of 3-aminomethyl pyridine chalcone derivatives (Scheme-21) and bis-chalcones (Scheme-22)

Chalcone-incorporated quinazoline derivatives were synthesized by the condensation of 4-(quinazolin-4-ylamino)benzaldehyde with various substituted acetophenones under reflux conditions for 6 h with an aid of piperidine [46] (Scheme 23). A novel chalcone-1,2,3-triazole derivative was synthesized by the reaction of 1-(4-(3-(4-(((1,3,4-Thiadiazol-2-yl)thio)methyl)-1H-1,2,3-triazol-1-yl)propoxy)phenyl)ethanone with appropriate aldehyde under stirring conditions at room temperature [47] (Scheme 24). These schemes are given in Figure 7.

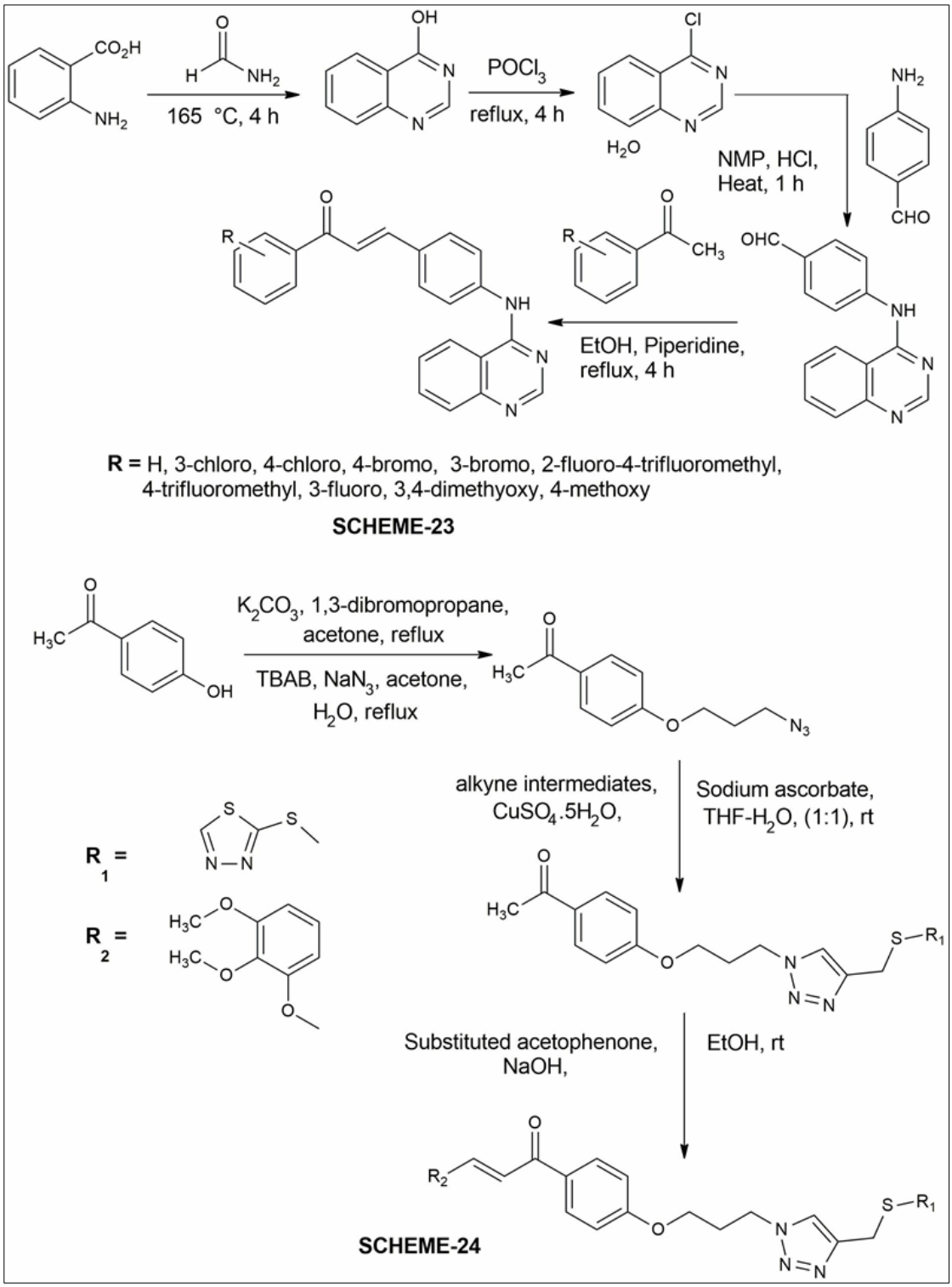

Figure 7 Synthesis of Chalcone-incorporated quinazoline derivatives (Scheme-23) and chalcone-1,2,3-triazole derivative (Scheme-24)

A series of extended conjugated δ-chloro-α-cyano substituted indolyl chalcones were prepared by reacting 3-cyanoacetylindole with 3-chloro-3-phenyl-propenal in the presence of piperidine by using Knoevenagel condensation reaction [48] (Scheme 25). To the substituted acetophenone, 4-O-propargylated benzaldehyde was added with ethanol in the presence of sodium hydroxide under stirring conditions for 30 min, the chalcone linked-1,2,3-triazoles were obtained [49] (Scheme 26). Halogenated phenoxychalcones were synthesized by the mixture of 4-(4-substitutedphenoxy)benzaldehyde with 4-substituted acetophenone in ethanol under stirring conditions for 5 h [50] (Scheme 27). These three schemes are given in Figure 8.

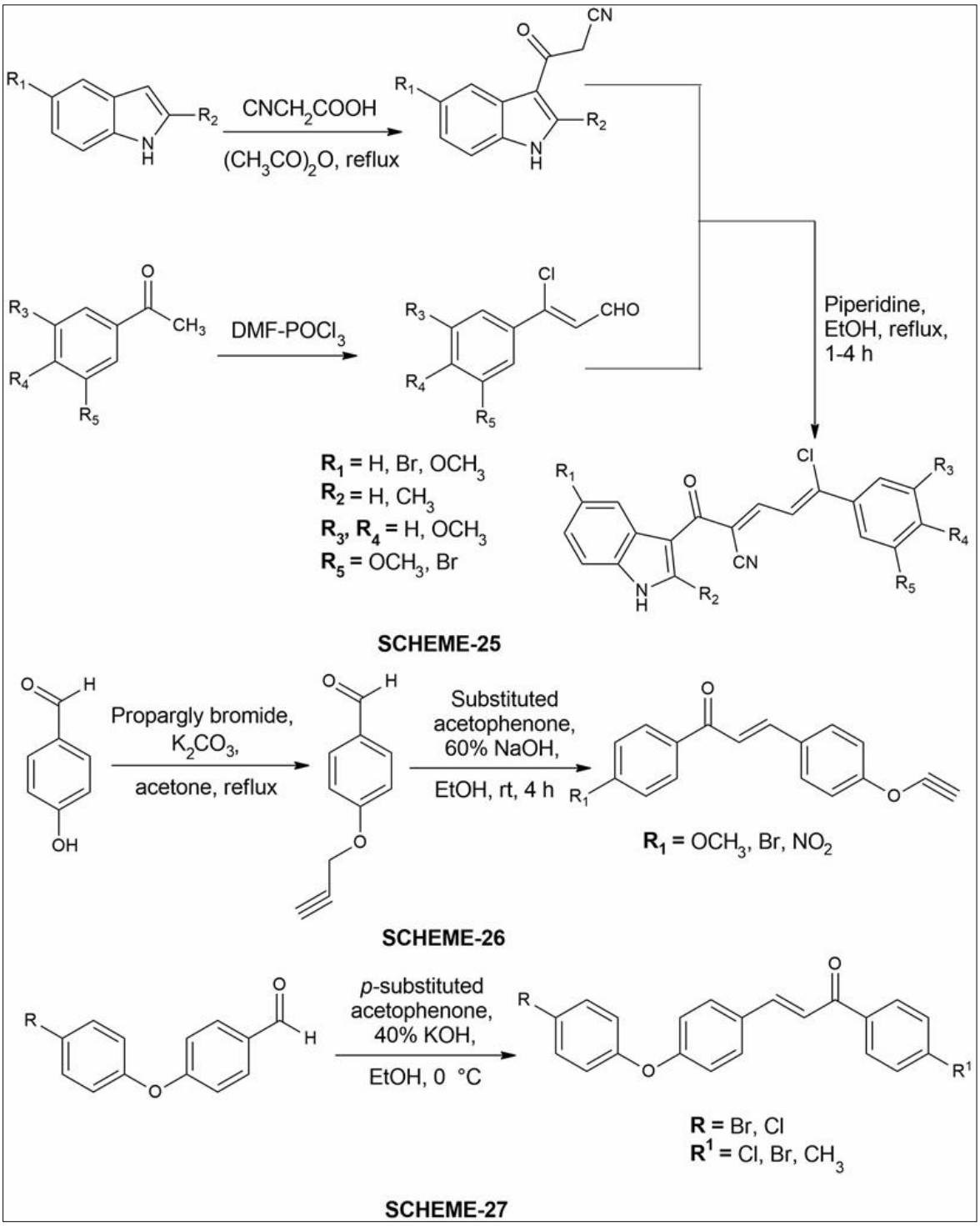

Figure 8 Synthesis of δ-chloro-α-cyano substituted indolyl chalcones (Scheme-25), chalcone linked-1,2,3-triazoles (Scheme-26) and halogenated phenoxychalcones (Scheme-27)

The novel β-carboline chalcone compound was synthesized by utilizing tryptamine as starting material. The 1-acetyl-β-carboline was prepared from the tryptamine by using the Pictet-Spengler reaction, which was deprotected and further reacted with respective aldehyde, yielded the corresponding chalcone [51] (Scheme 28). Chalcone-based phenothiazine derivatives were designed and synthesized by stirring 1-(10-Dodecylphenothiazin-2-yl)Ethan-1-one with appropriate aldehydes with an aid of 5 % alcoholic sodium hydroxide overnight at room temperature [52] (Scheme 29). Chalcone-linked sorafenib derivatives were synthesized by the condensation of 4-(4-acetylphenoxy)-N-methylpicolinamide and 4-(4-formylphenoxy)-N-methylpicolinamide with substituted benzaldehyde and substituted acetophenone, respectively [53] (Scheme 30 and 31). The above-discussed schemes are given in Figure 9.

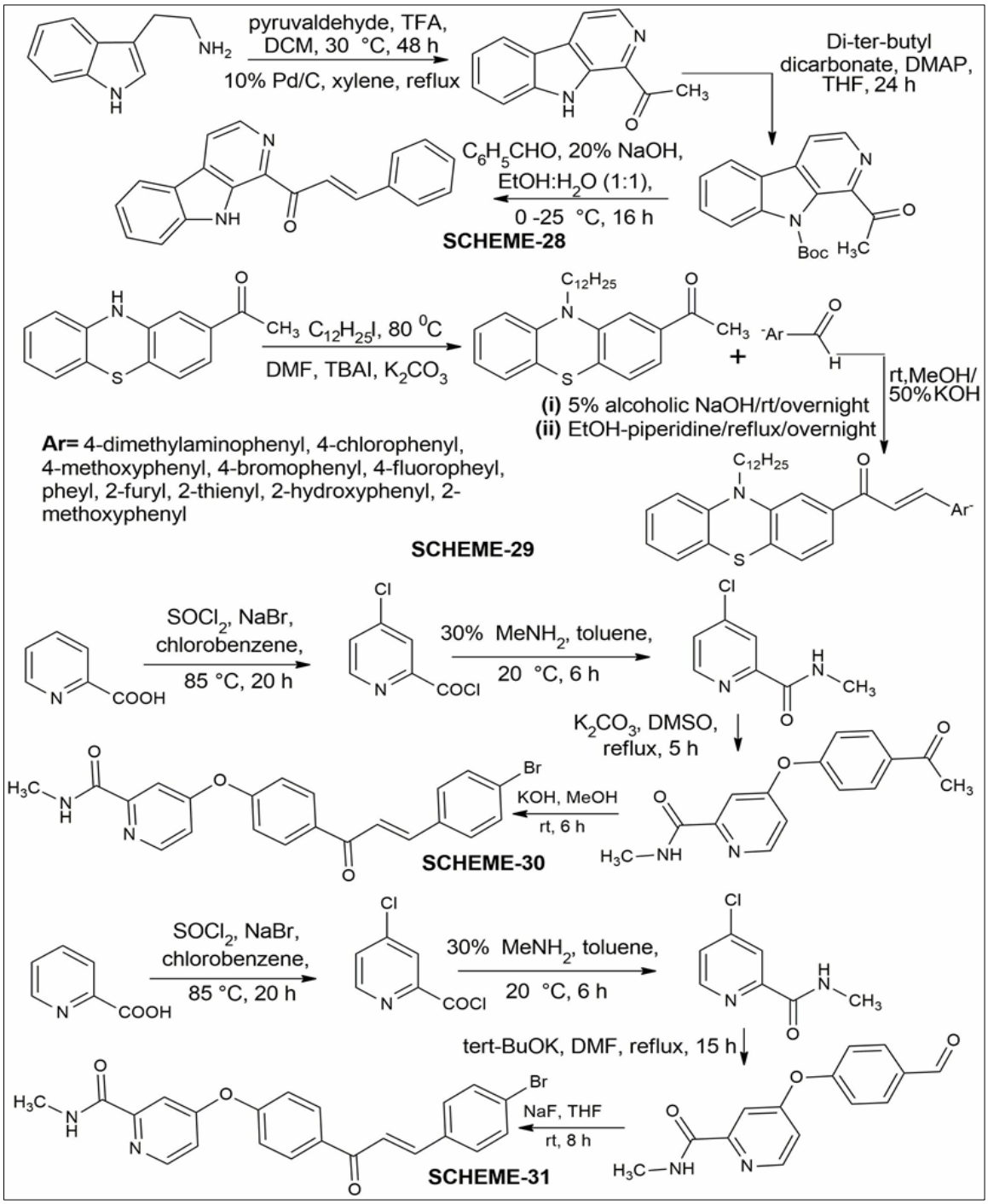

Figure 9 Synthesis of β-carboline chalcone (Scheme-28), Chalcone-based phenothiazine derivatives (Scheme-29) and Chalcone-linked sorafenib derivatives (Schemes-30 and 31)

The reaction between the 3-(4-benzyloxy)phenyl -1-phenyl-1H-pyrazole-4-carbaldehyde with appropriate acetophenone in ethanol in the presence of sodium hydroxide under stirring conditions for 24 h yielded a pyrazole hybrid chalcone derivative, (E)-3-(3-(4-benzyloxy)phenyl-1-phenyl-1H-1-pyrazol-4-yl)-1-phenylprop-2-en-1-one [54] (Scheme 32). The benzofuran-chalcone hybrid was synthesized by the reaction between the 2-hydroxychalcone derivative with an arylacetone at 80 °C for 2 h. The corresponding chalcone derivative was prepared by utilizing the mixture of 5-bromo-2-hydroxy-3-indoacetophenone with 4-fluorobenzaldehyde under stirring conditions for 48 h [55] (Scheme 33). On the reaction of 5-acetyl-6-methylfuro[2,3-d]pyrimidin-4(3H)-one with 4-chlorobenzaldehyde in ethanol with an aid of 20 % sodium hydroxide solution, afforded a novel furo[2,3-d]pyrimidine based chalcone derivative, (E)-5-(3-(substituted phenyl)acryloyl)-6-methylfuro[2,3-d]pyrimidin-4(3H)-one [56] (Scheme 34). These schemes are given in Figure 10.

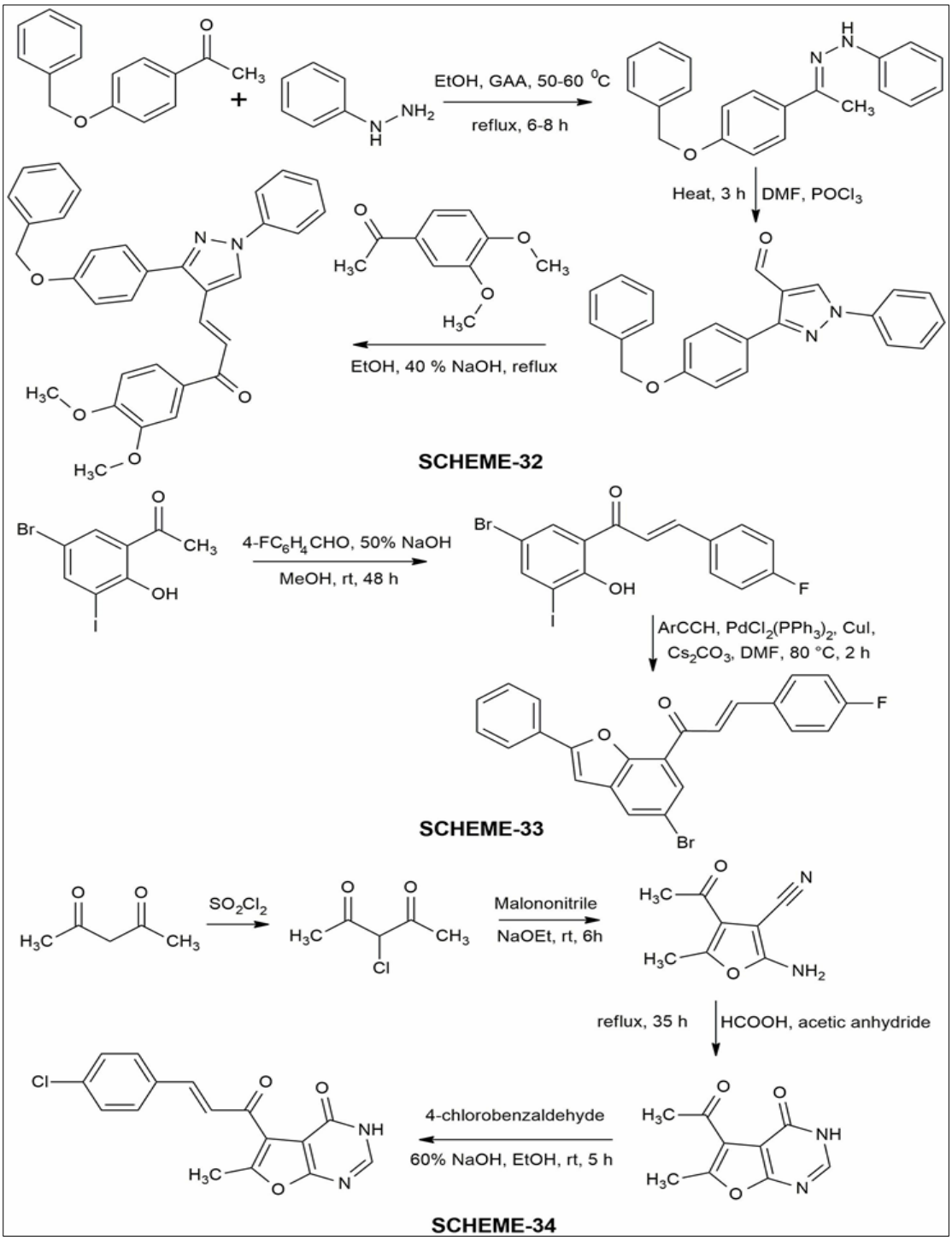

Figure 10 Synthesis of (E)-3-(3-(4-benzyloxy)phenyl-1-phenyl-1H-1-pyrazol-4-yl)-1-phenylprop-2-en-1-one (Scheme-32), benzofuran-chalcone hybrid (Scheme-33) and furo[2,3-d]pyrimidine based chalcone (Scheme-34)

Novel thienoquinoline-2-carboxamide chalcone derivatives were synthesized by heating the mixture of 2-mercapto-6-substituted quinoline-3-carbaldehyde and corresponding acylated derivatives of chalcones obtained from p-aminoacetophenone and appropriate benzaldehydes in ethanol [57] (Scheme 35). The mixture of 4-(1-benzimidazol-2-propene)benzoic acid, thionyl chloride and N,N-dimethylformamide was refluxed for 8 h, the substituted amines were added to the mixture and further reacted for an additional 4 h, afforded the aromatic amide-substituted benzimidazole derived chalcones [58] (Scheme 36). Acetyl 1,2,3-triazole was prepared by the reaction between aryl azide and aryl amine with sodium nitrite under acetic conditions. To the acetyl-1,2,3-triazole, 3,4-dimethoxy benzaldehyde was added under stirring conditions for 30 min, yielded the novel chalcone, (E)-1-[1-(4-Chlorophenyl)-5-methyl-triazol-4-yl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one [59] (Scheme 37). The above-discussed schemes are given in Figure 11.

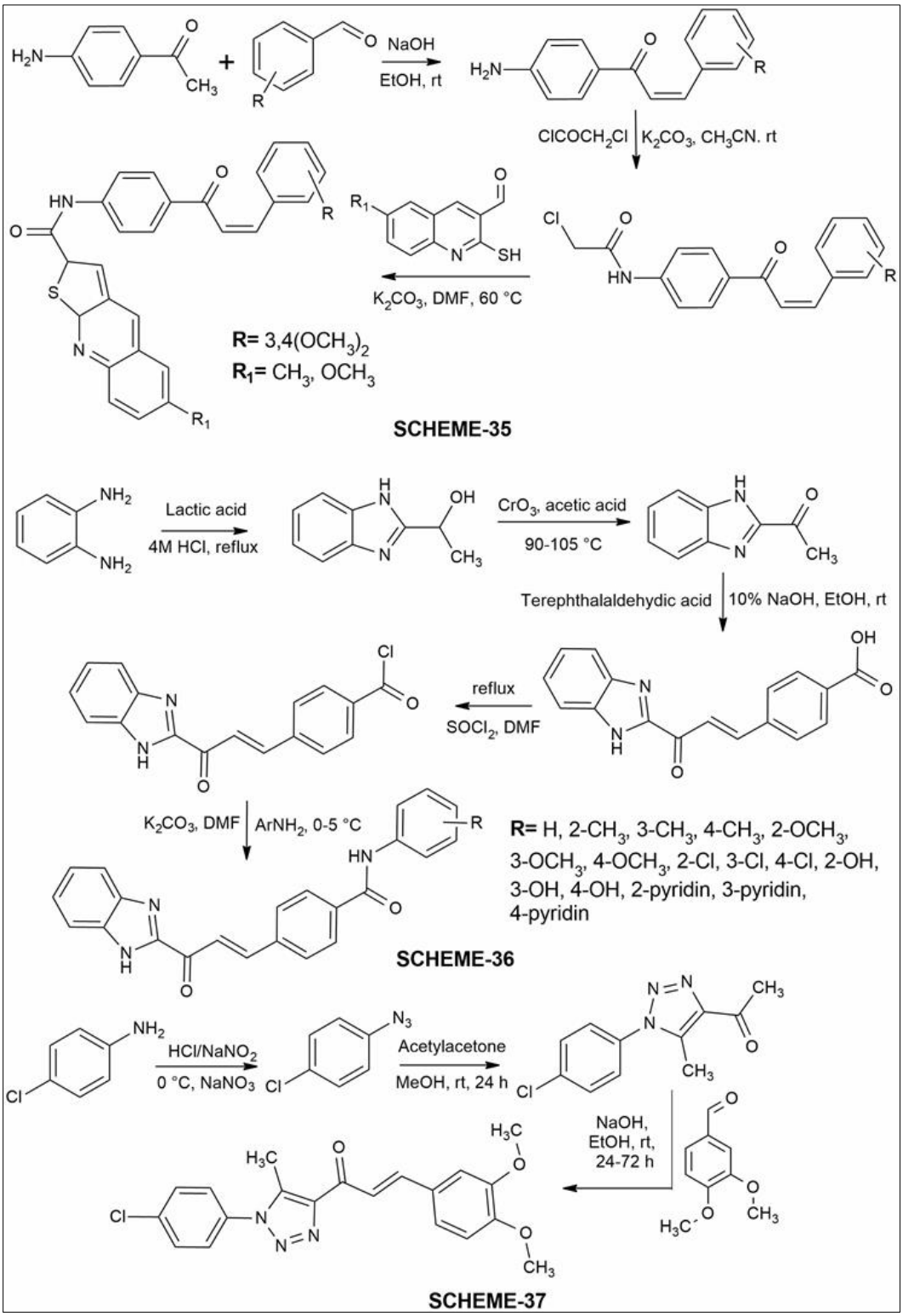

Figure 11 Synthesis of thienoquinoline-2-carboxamide chalcone derivatives (Scheme-35), aromatic amide-substituted benzimidazole derived chalcones (Scheme-36) and (E)-1-[1-(4-Chlorophenyl)-5-methyl-triazol-4-yl]-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (Scheme-37)

2-chloroquinolinyl chalcones were synthesized by the condensation of 2-chloro-3-formyl quinolines with respective acetophenones in the presence of the catalytic amount of sodium hydroxide under stirring conditions for 6-24 h [60] (Scheme 38). To a solution of 6-acetyl-2,2-dimethyl-2,3-dihydroquinolin-4(H)-one, different substituted benzaldehydes were added and stirred at room temperature for 48 h, resulted in the formation of the required quinolinoylchalcone derivatives [61] (Scheme 39). These two schemes are given in Figure 12.

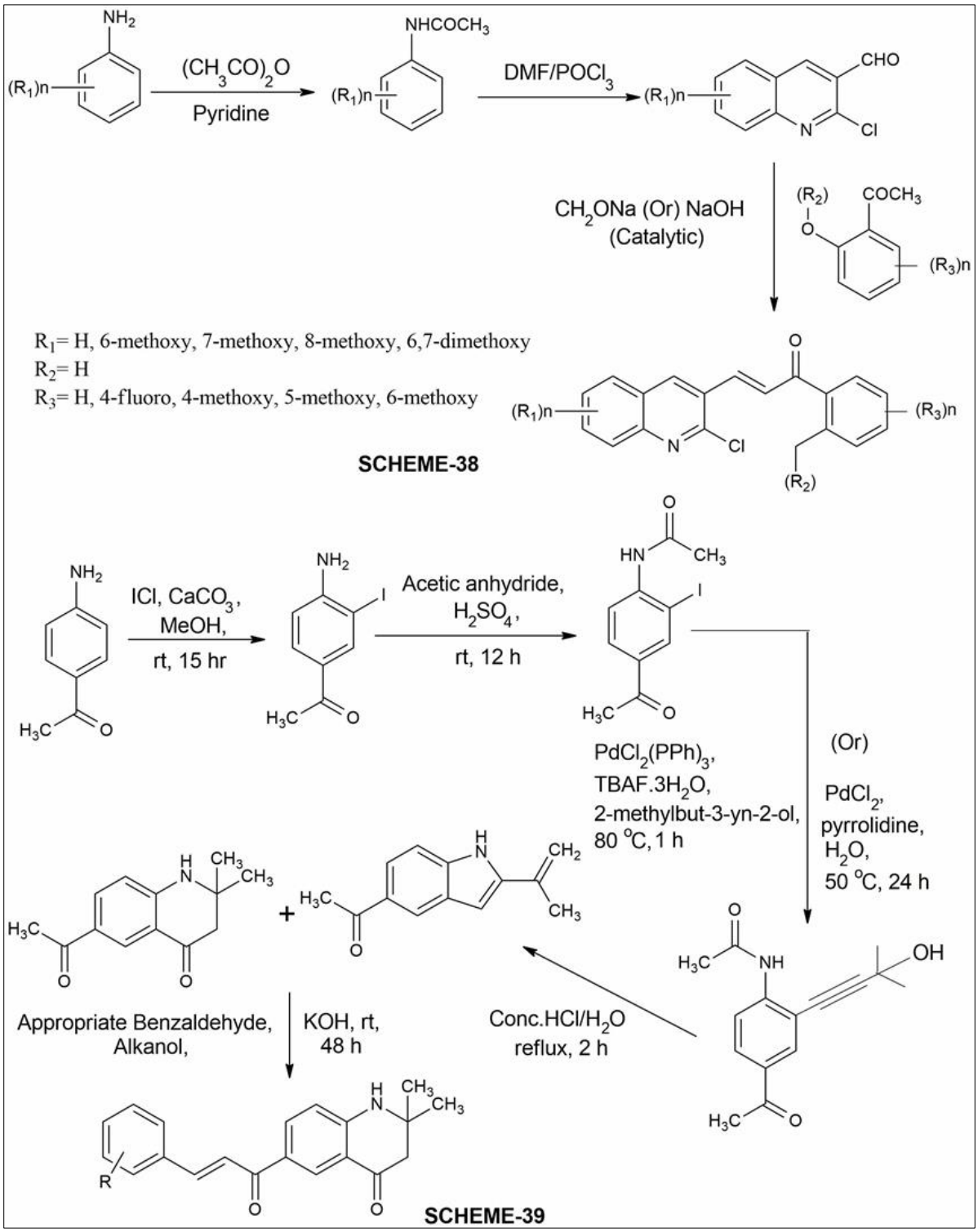

Figure 12 Synthesis of 2-chloroquinolinyl chalcones (Scheme-38) and quinolinoylchalcone derivatives (Scheme-39)

On the reaction between azo derivatives of 3-aminoacetophenone and 4-dimethylaminobenzaldehyde/4-fluoro benzaldehyde under stirring conditions for 72 h afforded the corresponding chalcones, respectively [62] (Scheme 40 and 41). 4-(2-bromo-3-(4-bromophenyl)-3-oxo prop-1-enyl) phenyl acrylate was prepared by the reaction of 2-bromo-1-(4-bromophenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one with methyl ethyl ketone and triethyl amine, followed by the addition of acryloyl chloride with constant stirring at room temperature for 5 h [63] (Scheme 42). To a stirred solution of 4-(2-(1-morpholino-2-oxopropylidene)hydrazinyl) benzenesulfonamide, different substituted benzaldehydes were added under stirring conditions for 5-6 h, which afforded 4-(2-((E)-1-morpholino-2-oxo-4-henylbut-3-enylidene) hydrazinyl) benzene-sulfonamide derivatives [64] (Scheme 43). The above-discussed schemes are given in scheme 13.

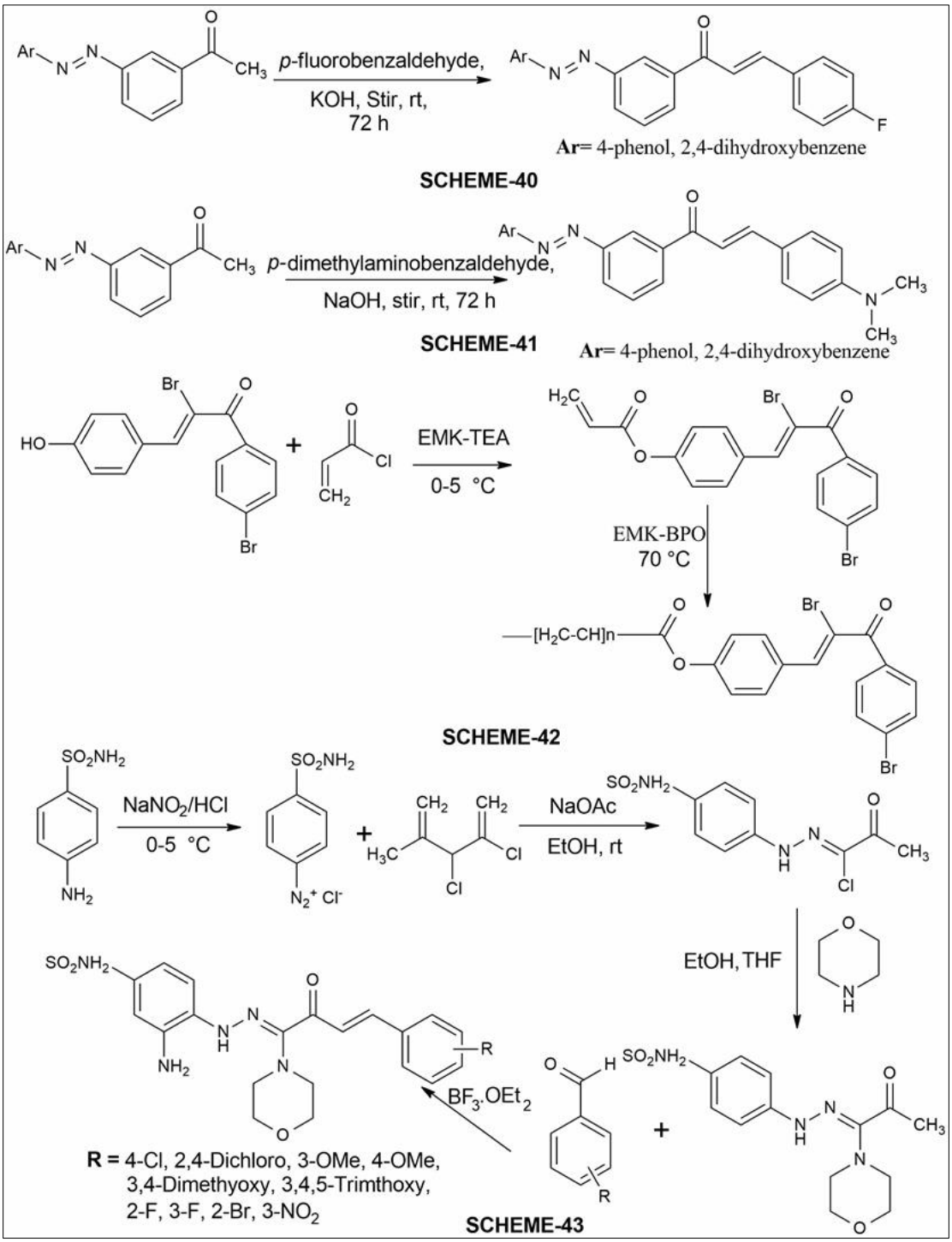

Figure 13 Synthesis of chalcones from azo derivatives (Schemes-40 and 41), 4-(2-bromo-3-(4-bromophenyl)-3-oxo prop-1-enyl) phenyl acrylate (Scheme-42) and 4-(2-((E)-1-morpholino-2-oxo-4-phenylbut-3-enylidene) hydrazinyl) benzene-sulfonamide derivatives (Scheme-43)

A novel dehydroabietic acid-chalcone hybrid was synthesized by the crossed aldol condensation of carboxaldehyde, aromatic methyl ketone and respective aldehyde in ethanol under stirring for 24-48 h at room temperature [65] (Scheme 44). The brominated chalcone derivative was obtained by the reaction of substituted hydroxy acetophenone with 4-methoxy benzaldehyde under reflux conditions for 4-6 h [66] (Scheme 45). The novel substituted [4-(2-(piperidine-1-yl)ethoxy)]chalcones were synthesized by utilizing two different methods viz., the reaction between chloroethyl piperidine and p-hydroxy substituted chalcone of p-hydroxy acetophenone and benzaldehyde (Scheme 46) and the other from the chalcone of p-hydroxy benzaldehyde and acetophenone [67] (Scheme 47). The schemes 44-46 are given in Figure 14.

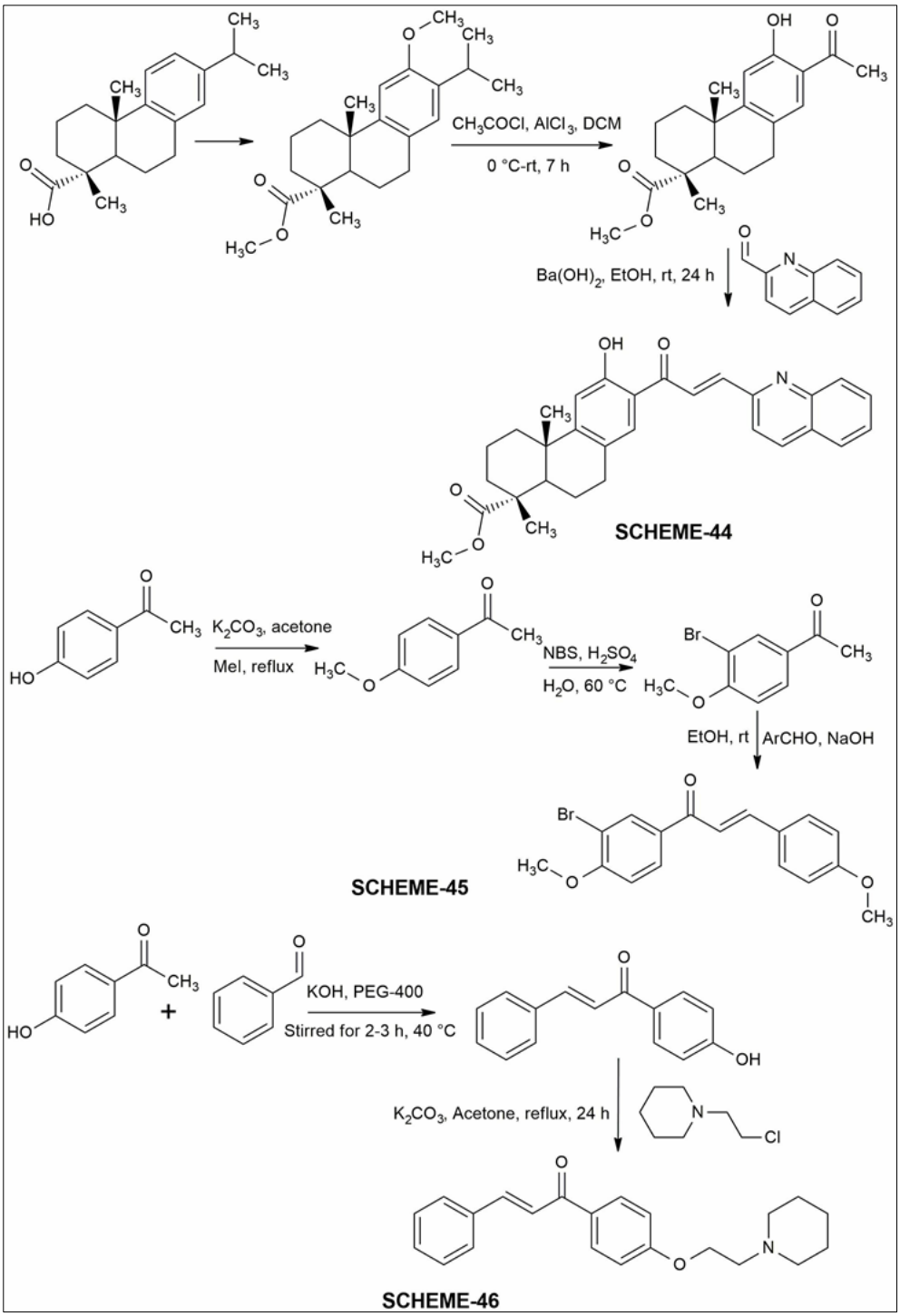

Figure 14 Synthesis of dehydroabietic acid-chalcone (Scheme-44), brominated chalcone derivative (Scheme-45), substituted [4-(2-(piperidine-1-yl)ethoxy)]chalcones (Scheme-46)

To the mixture of 4-hydroxy-3-methoxyphenyl benzaldehyde in ethanol, the substituted acetophenone was added, resulted in the formation of the corresponding chalcone, (E)-1-(4-hydroxy-3-(3-methylbut-2-en-1-yl) phenyl)-3-(4-hydroxy-3-methoxyphenyl)-prop-2-en-1-one [68] (Scheme 48). The novel 4-Boc-piperidone chalcones were synthesized by reacting a substituted benzaldehyde and 4-Boc-piperidone with LiOH in ethanol at room temperature for 24 h [69] (Scheme 49). (E)-1-(4-((1-allyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-3-(2,4-dichlorophenyl)prop-2-en-1-one was synthesized by the reaction between 3-azidoprop-1-ene, propargyl bromide and hydroxy chalcone derivative in the presence of copper sulphate, sodium ascorbate and tetrahydrofuran under stirring conditions for 10 h at room temperature [70] (Scheme 50). The above-discussed schemes are given in Figure 15.

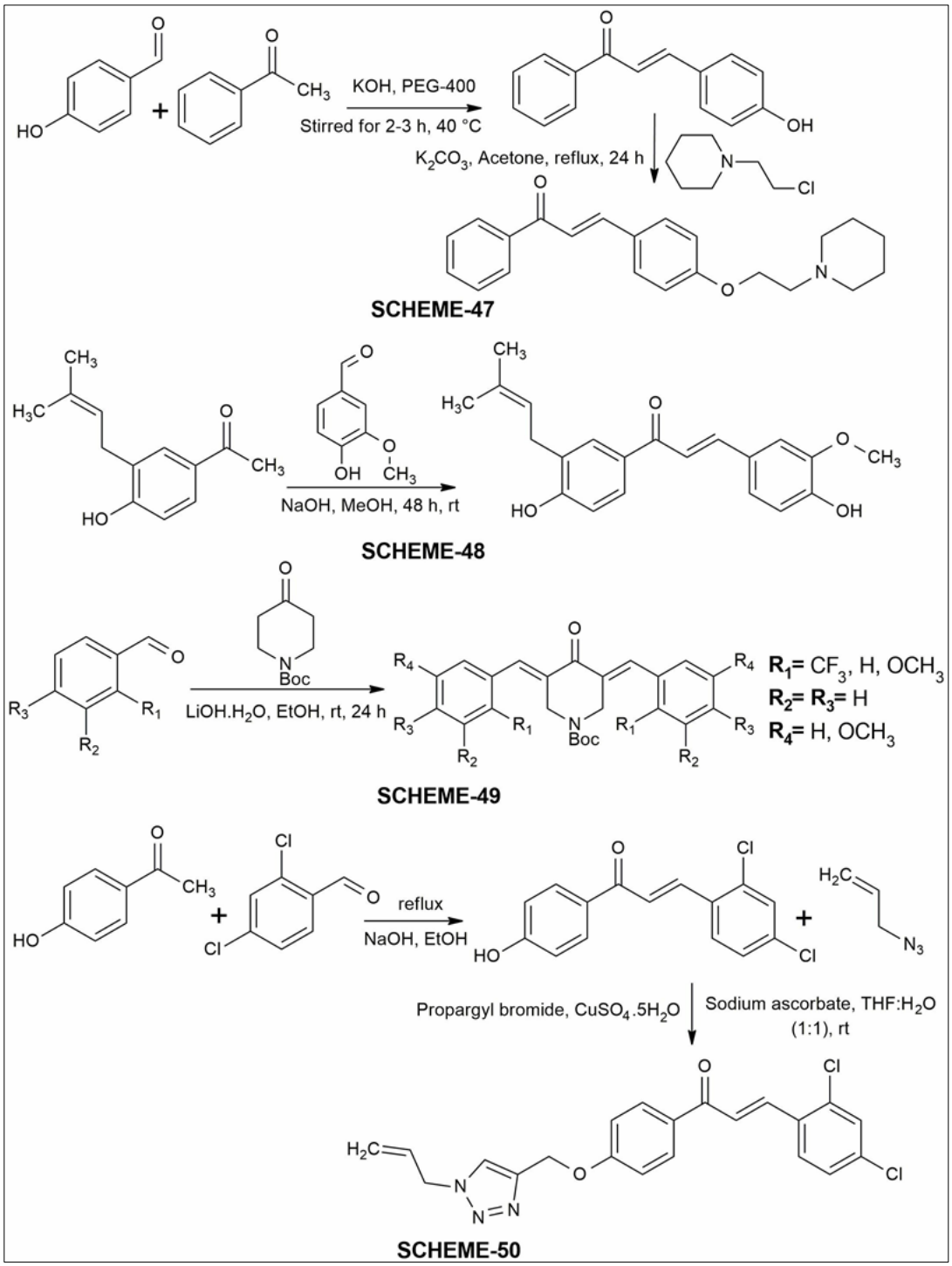

Figure 15 Synthesis of substituted [4-(2-(piperidine-1-yl)ethoxy)]chalcones (Scheme-47), (E)-1-(4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl)-3-(4-hydroxy-3-methoxyphenyl)-prop-2-en-1-one (Scheme-48), 4-Boc-piperidone chalcones (Scheme-49) and (E)-1-(4-((1-allyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-3-(2,4-dichlorophenyl)prop-2-en-1-one (Scheme-50)

3. Conclusion

Chalcones have a variety of pharmacological characteristics and are flexible scaffolds for synthetic modification. Research on chalcones and their derivatives is becoming more popular around the world for the creation of pharmacological substances because of their improved bioavailability and high tolerance in the body. Several methodologies and approaches were reported for the synthesis of chalcones and their derivatives. Claisen-Schmidt

condensation is the most frequently and commonly used approach for the synthesis of these derivatives. Thus, this review highlights and discusses the various synthetic approaches of medicinally significant chalcones and their derivatives. Claisen-Schmidt condensation, Knoevenagel condensation, Crossed Aldol condensation, Microwave-Assisted synthesis, Ultrasonic-mediated synthesis, refluxing using an oil bath and stirring at high temperatures are the approaches and techniques employed in the synthesis of chalcones and their derivatives. Beyond these, novel methods for the synthesis of these derivatives must be developed in the future based on the green chemistry approach to exhibit potential therapeutic applications and for the management of various ailments. Thus, this review will be useful in the further development of novel derivatives of chalcones with potential effects in the future.

Compliance with ethical standards

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Authors Contributions

All the authors have contributed equally.

Disclosure of conflict of interest

The authors declare no conflict of interest.

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