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Research Article

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Recent Advances in Synthesis of Quinoline-4-Carboxylic Acid and their Biological Evaluation: A Review

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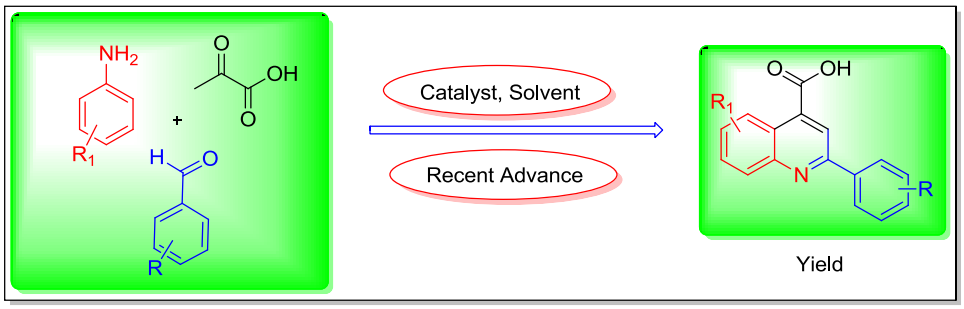
ABSTRACT

Quinoline-4-carboxylic acid is a very important structure in a synthetic medicinal chemistry. Compounds including a quinoline-4-carboxylic acid have a wide biological range as a pharmacophore in medicinal chemistry. Many methods have been developed for the synthesis of important quinoline moiety. However, some efficient methods have been found but methods are always correlate with the toxic, corrosive catalysts, poor yieldsand longer reaction time not environmentally friendly. In this review we have describe a methods which, some scientists are working under method developed in recent advances. Quinoline-4-carboxylic acid were evaluated in biological activities like antimicrobial, antifungal and tested against inhibitors.

Graphical abstract



Keyword: Quinoline-4-carboxylic acid; Doebner reaction; Pfitzinger reaction; Biological activity

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INTRODUCTION

Quinoline core is very important moiety because of their widely occurring drugs and natural products [1,2]. Quinolines moiety are very interested due to their broad spectrum as anti-malarial [3-6], anticancer [7, 8], antimicrobial [9], antibacterial [10,11], antifungal [12,13] and use as an inhibiting agent [14]. Quinoline based bacterial marketed drugs (Figure 1) and malarial marketed drugs (Figure 2) Many methods have developed for the synthesis of quinoline moiety.Cinchophenis a derivative of quinoline derivative, in which phenyl ring is in 2ndposition.Some quinoline and quinoline-4-carboxylic acid based derivatives make changes in the morphology of typical effect of Botrytis cinerea [15]. Cinchophen derivatives involvedimportantly in medicinal-drug chemistry as they show an important biological activity. Cinchophen (2-Phenylquinoline-4-carboxylic acid) and that type of derivatives have been proved a powerful antimicrobial agent [16]. Schiff bases of quinoline-4-carboxylic acid are associated with antifungal, antibacterial activities and have wide biological activities [17] as well as used as industrial antioxidants [18]. In Mannich base approach, the conjugation is made with secondary amines, which makes the compound water soluble and also to increase the antimicrobial activity of lead

compound [19]. Quinoline-4-carboxylicacids are used as the key structure for the synthesis of other useful quinoline derivatives [20].

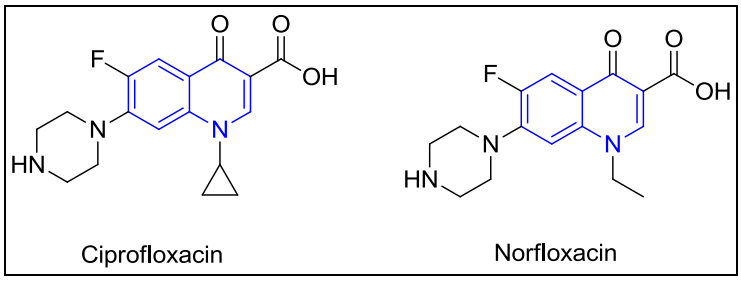


Figure 1: Quinoline analoge anti-bacterial marketed drugs

Therefore, the scientists have made to study the antifungal and antibacterial activity of Schiff base of cinchophen and its derivatives [21]. In the present investigation, cinchophen was synthesized from benzaldehyde, pyruvic acid and aniline by Doebner synthesis [21].The Skraup-Doebner quinoline synthesis [22], which generally carried out from the reaction of α,β-unsaturated carbonyl compounds with various anilines to give quinoline derivatives. One century ago great value of quinoline has been found in the research field [21]. Many methods have been developed for the synthesis of quinoline-based derivatives because of the involvement of quinolines as pharmaceuticals [23], functional materials and ligands [24]. It is well recorded that the Skraup-Doebner synthesis, which is generally carried out using aprotic acids, gives 2-substituted quinolones from the reaction of 3-substituted α, β-unsaturated carbonyl compounds [21,25]. One logical explanation for this selectivity is that the reaction process via 1,4-addition of anilines to α,β-unsaturated carbonyl compounds, followed by dehydrative oxidation or cyclization reaction. In this case, an added oxidant (such as nitrobenzene) or a Schiff's base caromatizes the 1,2-dihydro intermediate to the final quinolone [26]. Eisch and Dluzniewski have been studied the mechanism of the Skraup-Doebner quinoline synthesis and proposed that direct Schiff's base formation might be the most important step in the reaction mechanism [27,28] as a Skraup have suggested in the literature. Because directly heating the substrates under the conditions of the Skraup-Doebner quinolone synthesis first forms a Schiff's base, the 1,4-addition of aniline to the α,β-unsaturated carbonyl component is possibly only a minor pathway [29].

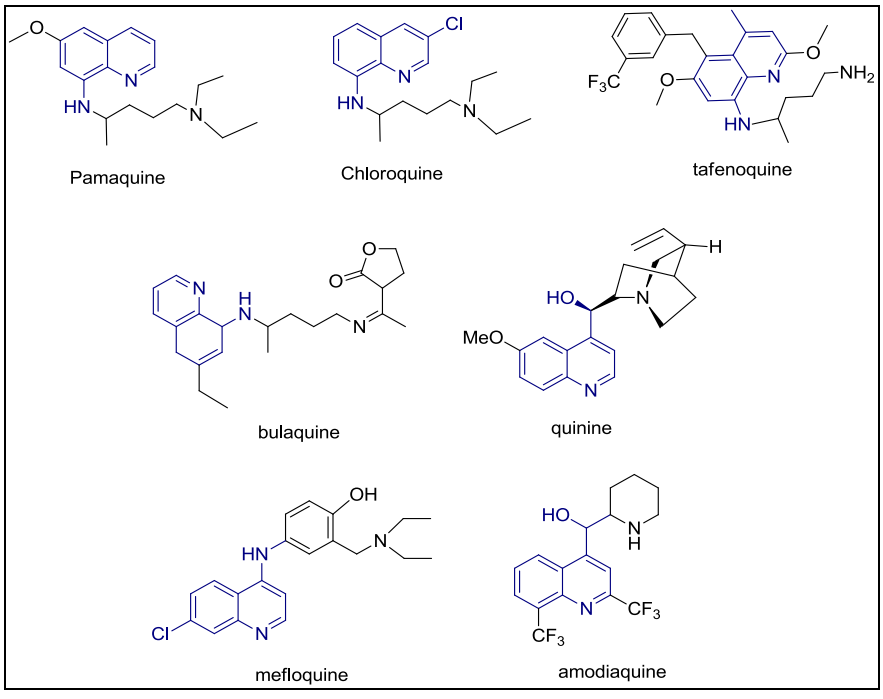


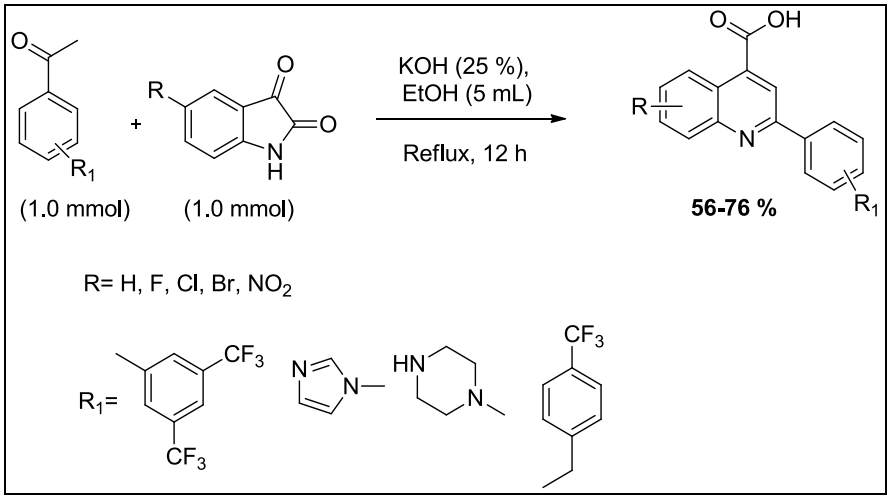
Figure 2: Quinoline analog anti-malarial marketed drugs

Literature review insertion of pharmacophore at 4th-position of quinoline with substituted amines complement its antituberculosis, antimicrobial activity [30]. Thus, many microwave irradiation (MWI) [31] as well as conventional synthesis involves the Pfitzinger reaction [25], Doebner reaction [32-34] However, these synthetic methods suffered from either low yields or long reaction time. Recently, there have been mild reports about modifying Skraup-Doebner reaction for synthesized quinoline-4-carboxylicacids via solid-phase synthesis [35].

However, these procedures are still restricted with some limits which involve the use of large amounts of organic solvents [36], the requirement of special apparatus, low yield or shorter reaction conditions. Therefore, the development of green and easy methods for the preparation of quinoline-4-carboxylic acid derivatives is still a challenging task. In recent years, rare earth metal catalysts have been gained in a variety of synthetic reactions because of their cheap advantages. Lewis acid-surfactants combined catalysts (LASCs) can be used to solubilise organic materials or form micelles due to water-stable Lewis acid type of property and structures in water [36]. Hence, these catalysts have been developed in detail for different reactions in universal aqueous solvent, which are cheap, safe and eco-friendly as well as green, environmentally friendly compared with hazardous organic solvents [37].With this Lewis acid-surfactants combined catalysts (LASCs) concept in mind [38].

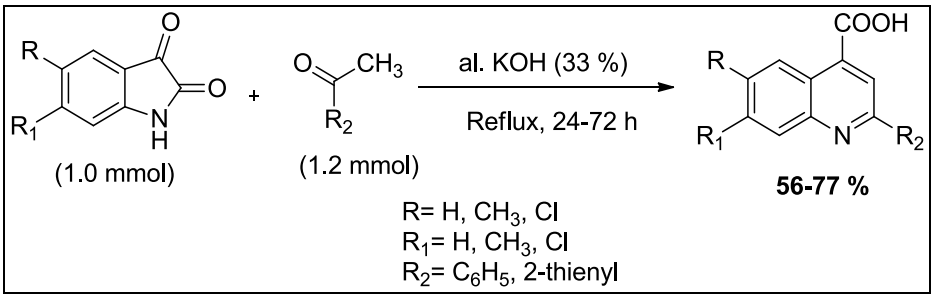
Various synthetic routes of quinoline-4-carboxylic acid and its derivatives

Erugu and associates have represented a synthesis of quinoline-4-carboxylic acids via Pfitzinger reaction of various aromatic ketones and various isatinsin the presence of aqueous potassium hydroxide in ethanol under reflux condition (Scheme 1).The superior advantages of this protocol are excellent yield, operational cleanness and formation of novel quinoline-4-carboxylic acid derivatives. The synthesized compounds were evaluated for antimicrobial activity. The antimicrobial activity against three Gram-negative bacterial strains (*Escherichia coli, Klebsiella pneumonia* and *Pseudomonas aeruginosa*), and three Gram-positive bacterial strains (*Bacillus subtilis, Bacillus licheniformis* and *Staphylococcus aureus*) of these quinoline-4-carboxylic acid derivatives were determined by the author [39]. In this study they have found a fluorine containing compound gives a higher activity against the *S. aureus* strains.



Scheme 1

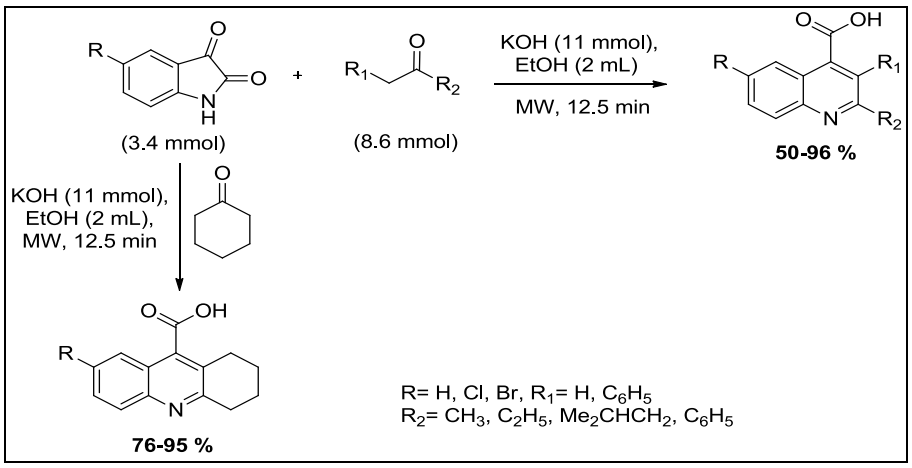
Zai-gang et al. have developed a synthesis of quinoline-4-carboxylic acid in good yield using various Isatin and allylic/cyclic ketone in the presence of the potassium hydroxide (KOH) in ethanol (EtOH) as a reaction medium (Scheme 2). Here, the reaction was completed within 24-72 h under ambient conditions. The synthesized products were evaluated for their primary anti-HIV properties against integrase reveal by the authors. The *in-vitro* anti-HIV study gives good results against the standard drugs. [40].



Scheme 2

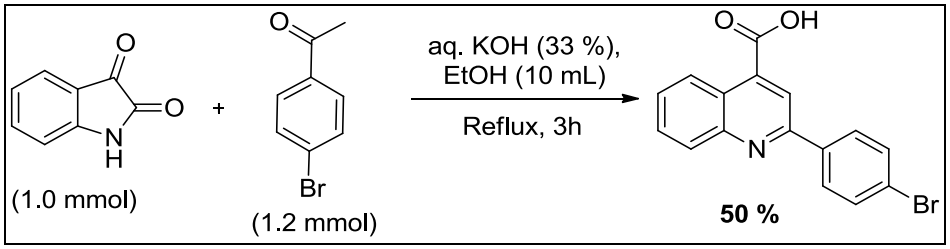
Ashry et al. have developed a facile, efficient and high-yielding synthesis of quinoline-4-carboxylic acid from the reaction of isatin with various acyclic and cyclic ketones under the microwave irradiation condition in the presence of catalytic amount of potassium hydroxide in ethanol as a solvent (Scheme 3). The reaction was completed within shorter period of time. By this transformation, the author got excellent yield of the quinoline-

4-carboxylic acid derivatives. In addition, 2-Hydroxyquinoline-4-carboxylic acid was also obtained by irradiating a mixture of isatin and malonic acid in acetic acid. From the acids, the esters of and their respective hydrazides were also prepared under MWI, by the author [41].



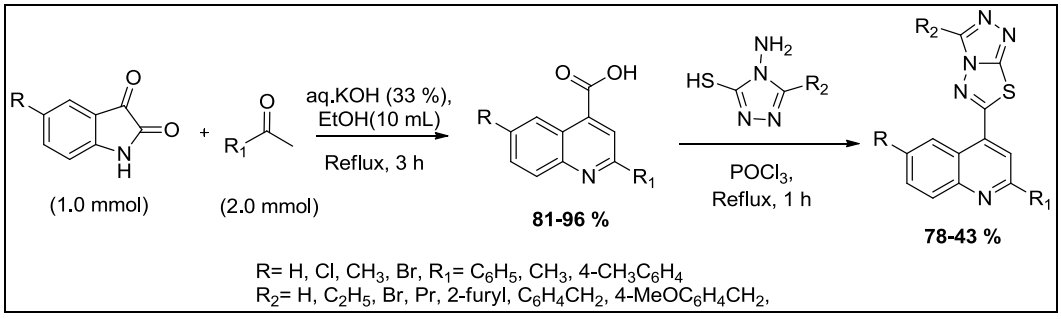
Scheme 3

Xiang et al. have reported an efficient synthesis of substituted quinoline 4-carboxylic derivatives using the condensation reaction between Isatin and substituted aromatic ketones in the presence of potassium hydroxide (KOH) in ethanol-water as a solvent under reflux conditions (Scheme 4). By this protocol products were obtained in very high purity with good yields. The author was evaluated this compound in *Candida albicans* over the human enzyme and their SAR study. In case some synthesized compounds give a good inhibition against *Candida albicans* [42]. SAR study and human enzyme study was show a better prediction in the pharmacophore generation.



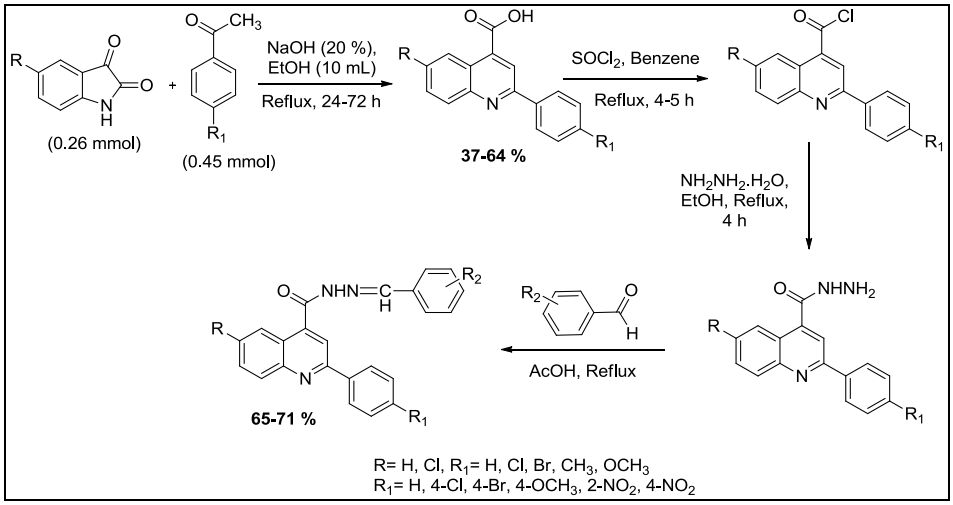
Scheme 4

Obushak and associates have represented a synthesis of quinoline-4-carboxylic acids via reaction of isatin with various ketonesin the presence of catalyticamount of aqueous potassium hydroxide in ethanol as a solvent (Scheme 5). Further, the author has carried out reaction between quinoline-4-carboxylic acids and4-Amino-5-R_1-4*H*-1,2,4-triazole-3-thiols in the presence of phosphoryl chloride to give 2-R_2-6-R_3-4-(3-R_1-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)quinolines and they were got a good yield in these reaction [43]. Green, efficient protocols were gives a facile, efficient and high-yielding synthesis of quinoline-4-carboxylic acid.



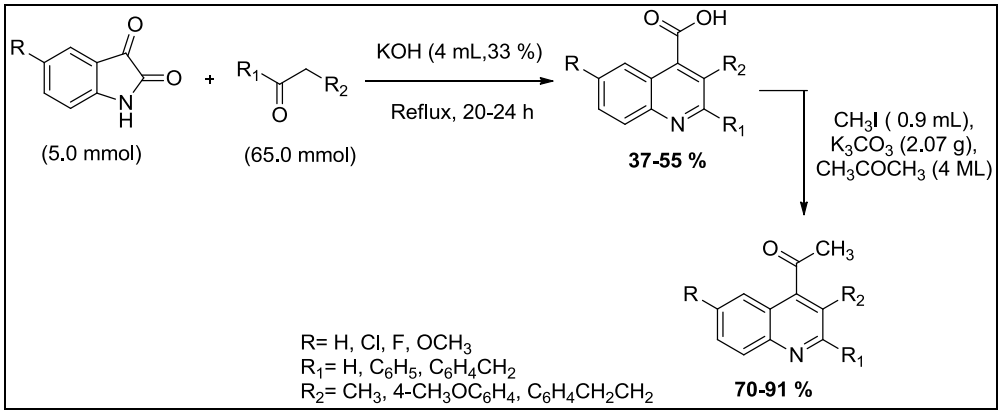
Scheme 5

Metwally et al. have discovered a facile, high-yielding and efficient synthesis of quinoline 4-carboxylic acid derivative using substituted Isatin and various aromatic ketones in the presence of potassium hydroxide in water as a solvent under reflux condition for 24-72 h (Scheme 6). With this protocol the author have improved the yield and purity of the products. A new series of 2-arylquinoline-4-carboxylic acid hydrazide–hydrazones was also synthesized from the reaction of quinoline-4-carboxylic acid derivative. All the target compounds were evaluated for their in vitro antimicrobial activity against *Staphylococcus aureus* as examplefor Gram-positive bacteria, *Escherichia coli* as an example for Gram-negative bacteria and *Candida albicans* as a representative of fungi. The minimum inhibitory concentration (MIC) was determined for test compounds as well as for reference standards. Among the compounds tested, compounds having nitro substituent at the arylidene moiety showed the most potent antifungal as well as antibacterial activities against *Candida albicans* and *Escherichia coli* respectively [44].



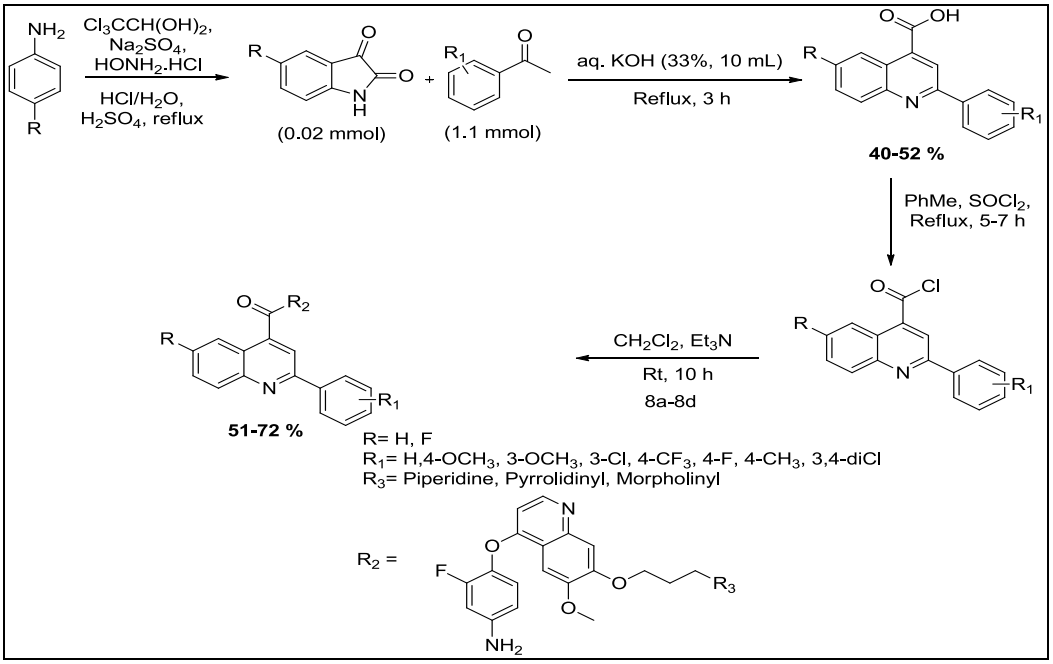
Scheme 6

Wu et al. have developed a synthesis for quinoline-4-carboxylic acid in goodyield via Pfitzinger condensation reaction of Isatin and various ketonesin the presence of aqueous potassium hydroxide (KOH) under reflux conditions (Scheme 7). Here, the reaction was completed within 20-24 h under ambient conditions. The author has evaluated this compound as human non pancreatic secretory phospholipase A2 (hnps-PLA2) inhibitors. Among the compounds they get hnps-PLA2 inhibitory activity in the in vitro bioassay and get the best Ic_{50}value compound. Also they have a performed a molecular docking study [45].



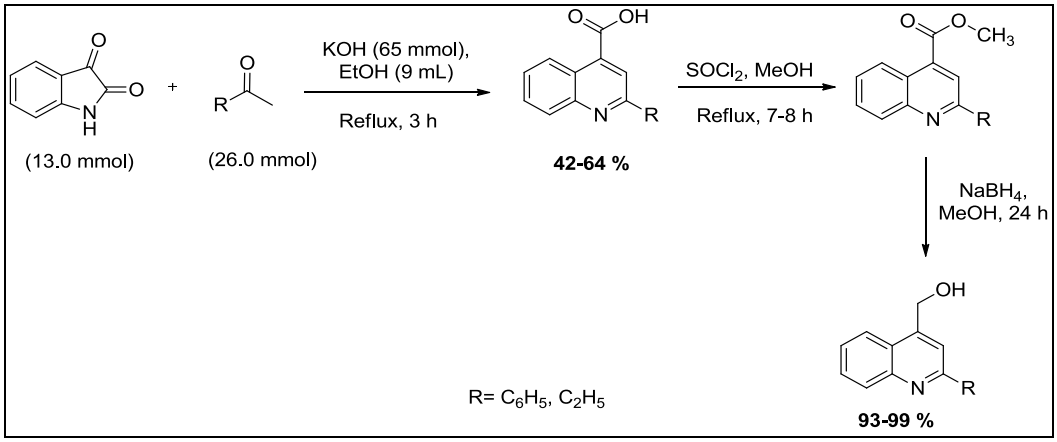
Scheme 7

Li et al. have discovered a facile, high-yielding and efficient, preparation of quinoline 4-carboxylic acid derivative from the reaction of substituted Isatins and various aromatic ketones in the presence of potassium hydroxide in water as a solvent under reflux conditions for the 3h (Scheme 8). Here, substituted Isatins were prepared from the reaction of various aniline with hydroxylamine hydrochloride in aqueous hydrochloric solution followed by addition into a solution of chloralic hydras in water and anhydrous sodium sulphate under the reflux condition (100 ^{0}C).Synthesized moiety was evaluated for their in vitro anti-tumour activities against a panel of five cancer cell lines (H460, HT-29, MKN-45, U87MG, and SMMC-7721) and all compounds shows high selectivity towards the H460 and MKN-45 cell lines get single-digit in *Ic50* value [46].



Scheme 8

Gupta and co-workers have reported a high-yielding synthesis of novel quinoline-4-carboxylic acid derivatives via condensation of Isatin with various allylic and aromatic ketones in the presence of a catalytic amount of potassium hydroxide (KOH) in ethanol (EtOH) under reflux condition for the 3h (Scheme 9). Synthesized compounds were evaluated for their TACE inhibitory activity and its docking study by the authors. They get good result in inhibition of TACE and computational study by the author [47]. In these protocols, they found a quinoline-4-carboxylic acids derivatives were good binding affinity with the protein. Docking study was also suggested that the synthesized compounds have potent activity against the TACE inhibition.

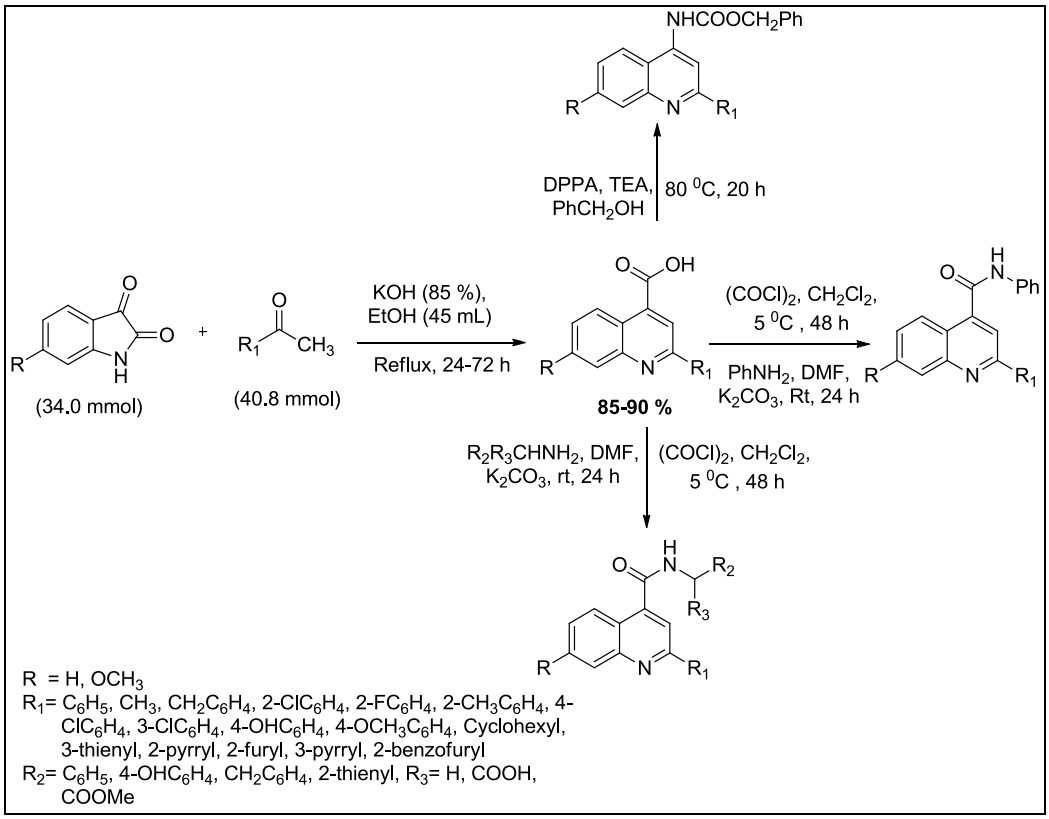


Scheme 9

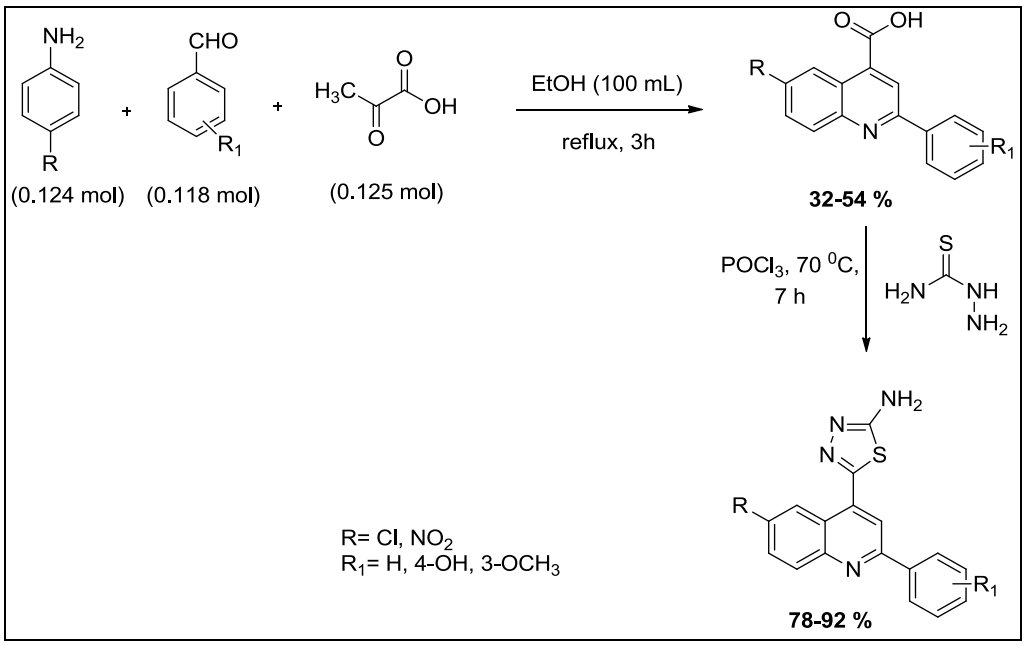
Giardina and co-workers have discovered an efficient synthesis of quinoline-4-carboxylic acid derivatives through an intermolecular condensation reaction of various Isatin with allylic and cyclic ketone (Scheme 10). This reaction was carried out in alcoholic potassium hydroxide in ethanol under the reflux condition for 24-72 h, which afforded good product yield. The authors were evaluated a synthesized compounds as a selective non-peptide *Tachykinin receptor 3*, among the some synthesized compounds shows a better activity against the stains [48].

Ramjith and their associates have synthesized quinoline-4-carboxylic acid derivatives by condensation reaction of substituted anilines, aromatic aldehyde and pyruvic acid compounds in the absence of a catalyst in ethanol (EtOH) under reflux condition as well as under microwave irradiation (MWI) to afford product in excellent yields (Scheme 11). Compared to conventional heating, microwave irradiation gave better results in term of product yields and reaction times. After the synthesizing of compounds, the authors were evaluated against

Bacillus subtilis, Staphylococcus aureus, Escherichia Coli, Pseudomonas aeruginosa as antimicrobial agents. In this study they were found a methoxy and nitrogen contained molecules active against the *E. Coli* [35].



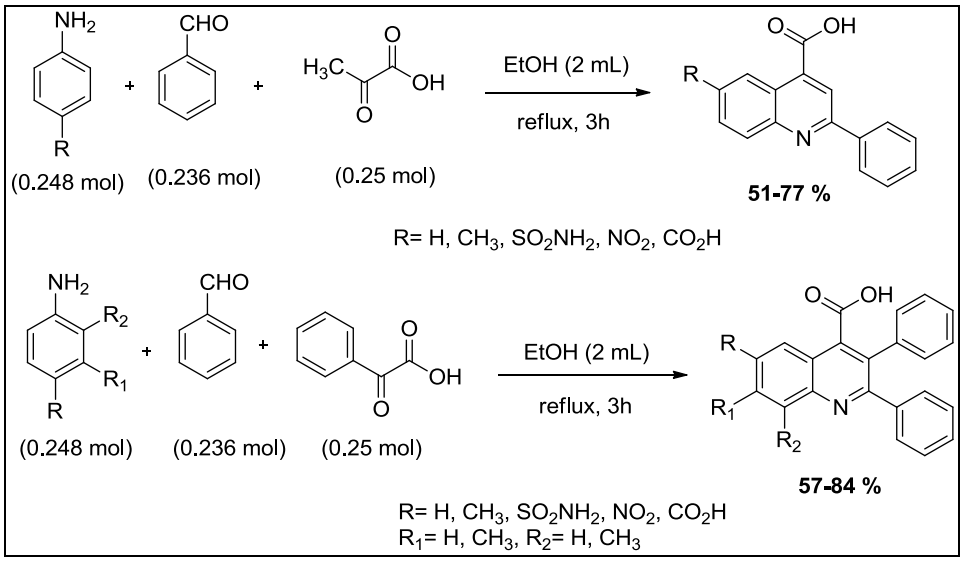
Scheme 10



Scheme 11

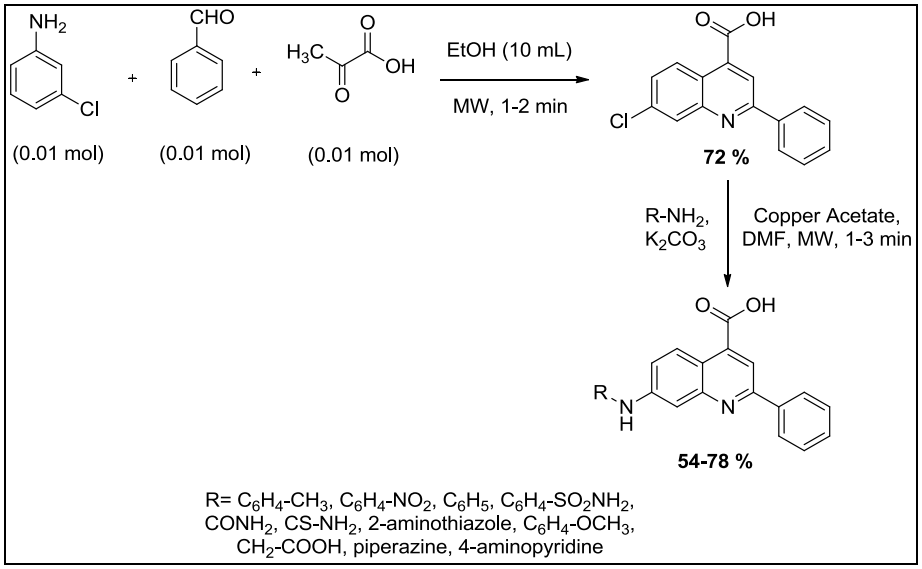
Saeed and co-workers have disclosed an efficient method for the synthesis of quinoline-4-carboxylic acid derivatives by condensation of substituted anilines, benzaldehyde and pyruvic acid in the absence of a catalyst in ethanol under reflux conditions (Scheme 12). Same reaction was carried out via phenyl pyruvic acid instead of the pyruvic acid under similar reaction conditions, which gave the best results in terms of product yields and reaction times. The authors have screened antibacterial activity of all synthesized compounds against the

standard bacterialstrains*B. subtilis*, *S. aureus*, *E. coli* and *P. vulgaris*. It is important to note that, 2,3-Diphenyl-6-sulfanilamidoquinolin-4-carboxylic acid showed the highest activity against the four tested strains [49].



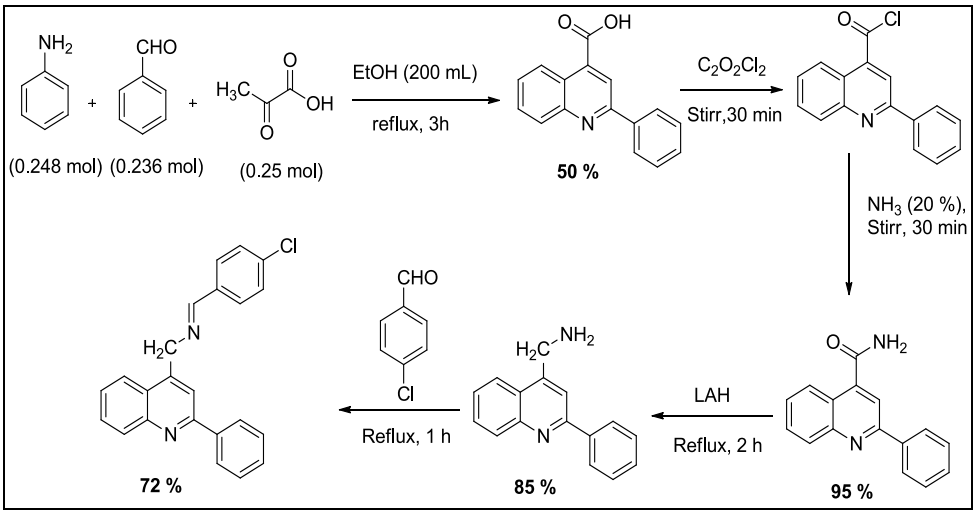
Scheme 12

Bhatt and co-workers have developed a synthesis method forquinoline-4-carboxylic acid from *m*-chloroaniline and pyruvic acid with suitable benzaldehyde in the presence of an ethanol (EtOH) as a solvent under microwave irradiation for 1-2 minutes (Scheme 13).The authors have carried out the synthesis of 2-phenyl-7-substitutedquinoline-4-carboxylic acid derivatives through both conventional and microwave-irradiated methods. However, by this methodology high product yields were obtained within shorter period of times. All the compounds were evaluated as an antimicrobial in *Streptococcus pyrogenes, Pseudomonas aeruginosa* by the authors. They have got extremely good results of some novel compounds [50].



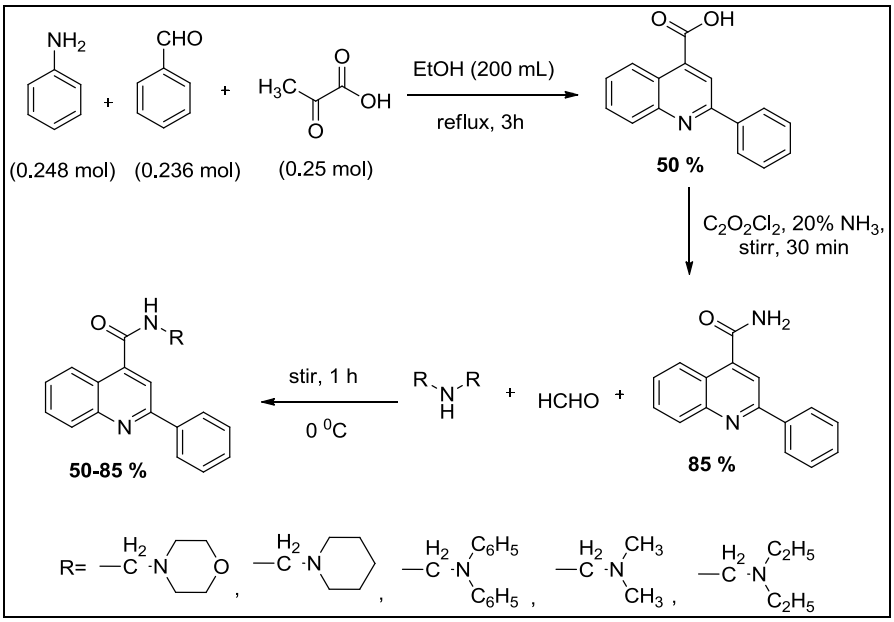
Scheme 13

Wadher et al. have disclosed an efficient methodology for the preparation of quinoline-4-carboxylic acid derivative by employing anilines, benzaldehyde and pyruvic acid in the presence of the ethanol (EtOH) as a solvent under the reflux condition for 3 h (Scheme 14). In this method quinoline-4-carboxylic acids were obtained in moderate yield. The authors have evaluated all compounds as an antimicrobial in *pathogenic bacteria*, *fungiin-vitro* activity. They have got good results in *fungi* with reference standard as a ciprofloxacin and fluconazole [21].



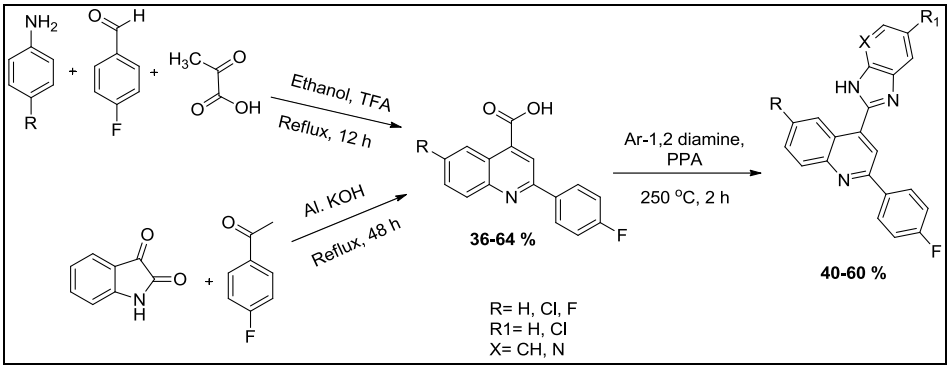
Scheme 14

Jumade et al. have discovered the similar protocol for the synthesis of quinoline-4-carboxylic acid derivative by employing aniline, benzaldehyde and pyruvic acid in the presence of the ethanol as n solvent under reflux condition for 3 h (Scheme 15). Then the quinoline-4-carboxylic acid was converted to cinchophen chloride, using oxalyl chloride. After that, cinchophen chloride was converted to cinchophen amide, using ammonia. The final compounds were synthesized via Mannich reaction by reaction of cinchophen amide with formaldehyde and secondary amines. The prepared Mannich bases were subjected to antibacterial screening against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and anti-fungal activity against *Candida albicans* and *Aspergillus niger* according to cup-plate method [51].



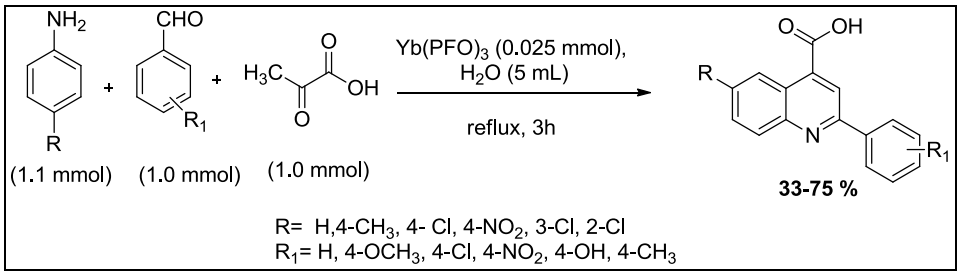
Scheme 15

Garuda chari and co-workers have reported a synthesis of various quinoline-4-caboxylic acids via a condensation reaction of 4-flourobenzaldehyde, various active *p*-anilines and pyruvic acid in the presence of trifluoroacetic acid as a catalyst in ethanol under reflux condition for the 3h (Scheme 16). It is important to note down that the better yield of the products within a short period of times were obtained, when reaction was carried out in the presence of trifluoroacetic acid as a catalyst. The author has synthesized two of quinoline incorporated benzimidazole derivatives by the reaction of 6-substituted-4-carboxyquinolines with substituted aromatic diamines in acidic media. The authorhas also screened these compounds for their *in-vitro* antibacterial and antifungal activity by well plate method (zone of inhibition) [52].



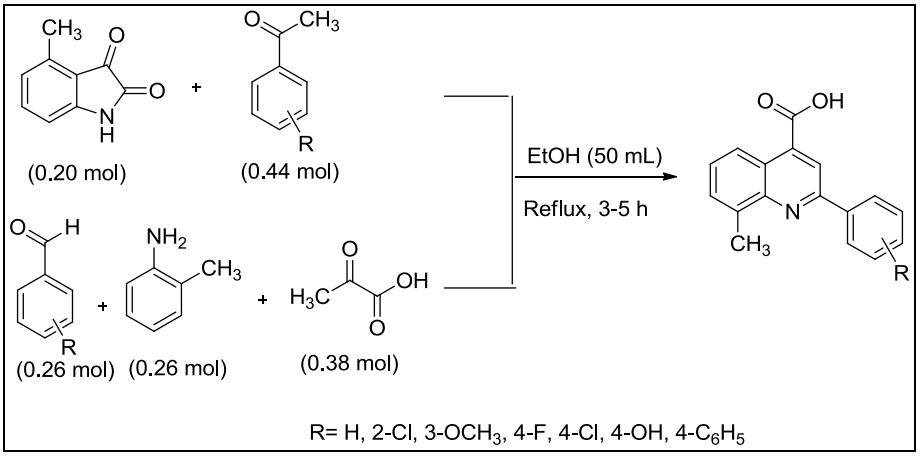
Scheme 16

The reaction of substituted aniline, various aldehyde and pyruvic acid in water using a small amount of Ytterbium perfluorooctanoate [$Yb(PFO)_3$] as a catalyst under reflux condition, which afforded quinoline-4-carboxylic acid in good yield (Scheme 17).The author has been carried out these reaction under the various catalytic condition, such as $Yb(PFO)_3$, $La(PFO)_3$, $Fe(PFO)_3$, $Zn(PFO)_2$, $Yb(CF_3CO_2)_3$, $C_7F_{15}COOH$, $Yb(OTf)_3$, $AlCl_3$, $ZnCl_2$. However, the best result was obtained in the case of Ytterbium perfluorooctanoate [$Yb(PFO)_3$] in terms of the yield of the product. The process is operationally simple and environmentally benign and the catalyst has readily been recycled for several times with consistent activity, these are the added features of this transformation [53].



Scheme 17

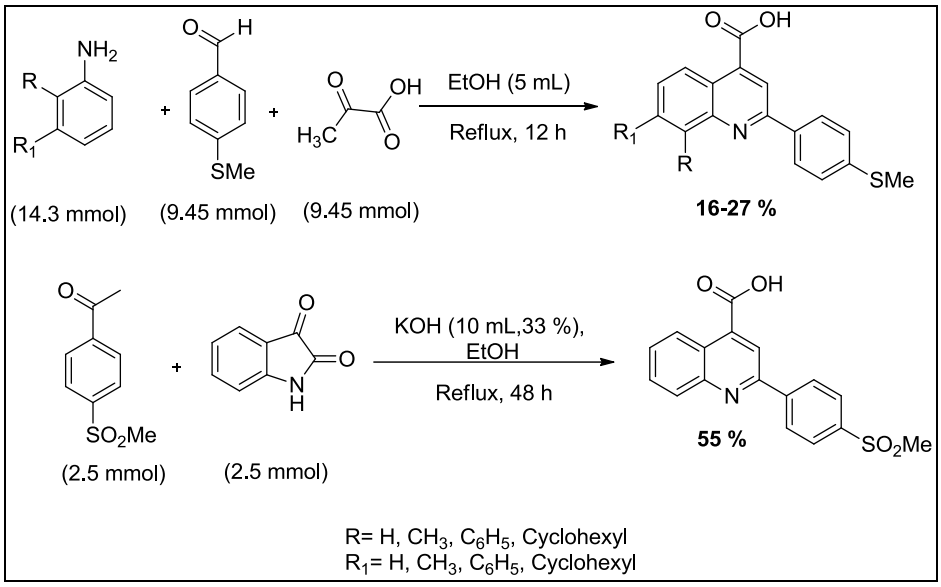
Atwell and co-workers developed an efficient preparation of quinoline-4-carboxylicacids using various aromatic aldehyde and 2-methylaniline with pyruvic acid in ethanolunder reflux conditions for 3-5 h, which afforded good yields of the products. The same product was obtained by the reaction of 4-methylisatin with various allylic and aromatic ketones inethanol under reflux condition at 80 ^{0}C for the 3-5 h (Scheme 18) [54].



Scheme 18

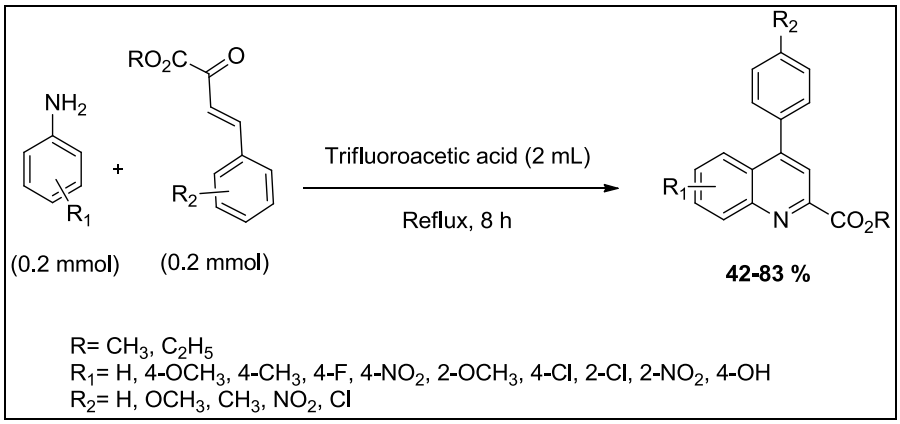
Zarghi et al. have discovered a facile, efficient and high-yielding synthesis of a quinoline-4-carboxylic acid using various aniline, 4-methylthio-benzaldehyde and pyruvic acid in the presence of ethanol under reflux conditions at the 80^{o}C for 12 h (Scheme 19). Furthermore Here, another method for the synthesis of a quinoline-4-carboxylic acid was described by the author, in which Isatin was reacted with1-(4-(methylsulfonyl)phenyl)ethanone in the presence of potassium hydroxide in ethanol as a solvent under the reflux

condition for the 48h. *In-vitro* COX-1/COX-2 structure–activity relationships were determined of all compounds and docking study by the authors [55].



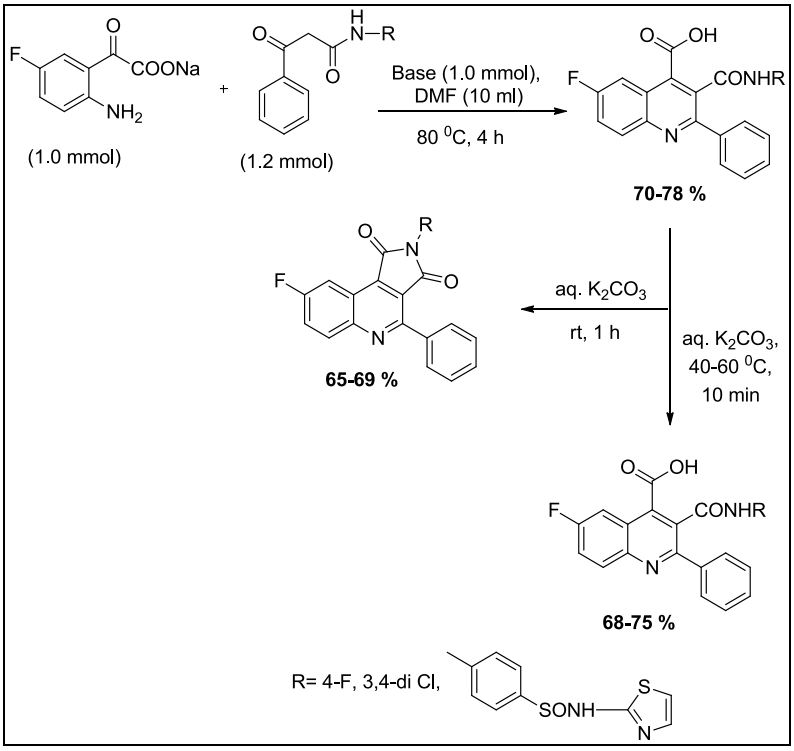
Scheme 19

Wu et al. have reported a mild and efficient method for the synthesis of quinoline-4-carboxylic acid derivatives using various aniline and various (*E*)-2-oxo-4-phenylbut-3-enoatein the presence of trifluoroacetic acid as a catalyst in ethanol under reflux condition for 8 h, which afforded good yield of the products (Scheme 20). This reaction proceeded via enolate intermediate and then it was reacted with various aromatic aldehyde afforded the desired products in good yield. The author has demonstrated various catalysts such as acetic acid, formic acid, TFA, H_2SO_4, $Hf(OTf)_4$ and HCl for this synthesis. However, excellent product yield was obtained, when TFA was used as a catalyst [19].



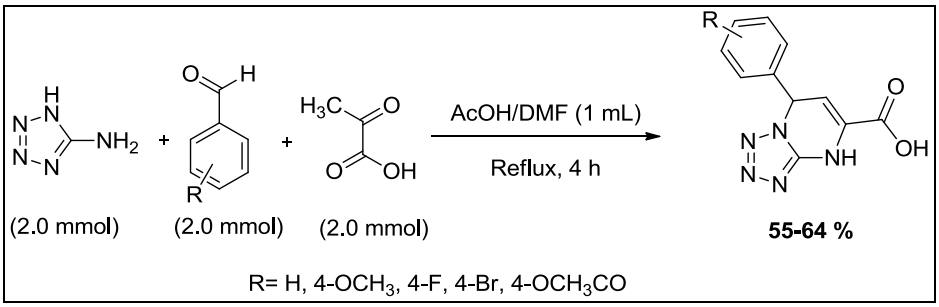
Scheme 20

Highly efficient syntheses of novel fluorine bearing quinoline-4-carboxylic acids and the related compounds had been achieved from cyclocondensation of sodium salt of 2-amino-5-fluorophenyl glyoxylic acid with various 3-oxo-3-phenylpropanamide in DMF at 80^{o}C. Which was discovered by Mohammed and co-workers (Scheme 21). Decarboxylation of quinoline-4-carboxylic acids produced 6-fluoro-2-phenyl-3-(substituted amino)-keto-quinolines in good yield, while that reaction underwent refluxing in the presence of aqueous K_2CO_3, afforded 7-fluoro-1-(aryl)-3-phenyl-pyrrolo[3,4-*c*] quinoline-2,9-diones in moderate yield. All synthesized compounds show the high to moderate activity against some *Aspergillus fungi* as amylolytic agents [56].



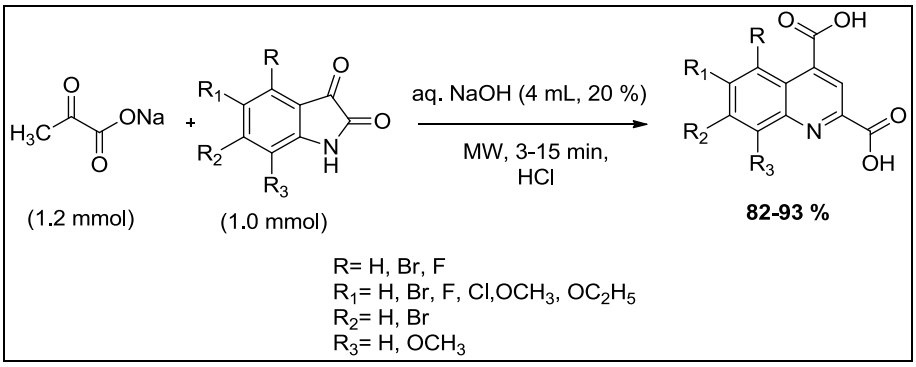
Scheme 21

Chebanov et al. have discovered an efficient protocol for the synthesis of quinoline-4-carboxylic acid via facile and efficient three-component condensation of aromatic aldehydes, some aminoazoles and pyruvic acid in acetic acid or dimethyl formamide under reflux conditions affording excellent yield of the products (Scheme 22). In one pot synthesis DMF is better solvent than the acetic acid due to the polarity of solvent. In this protocols they were found a DMF a better solvent for the synthesis [57].



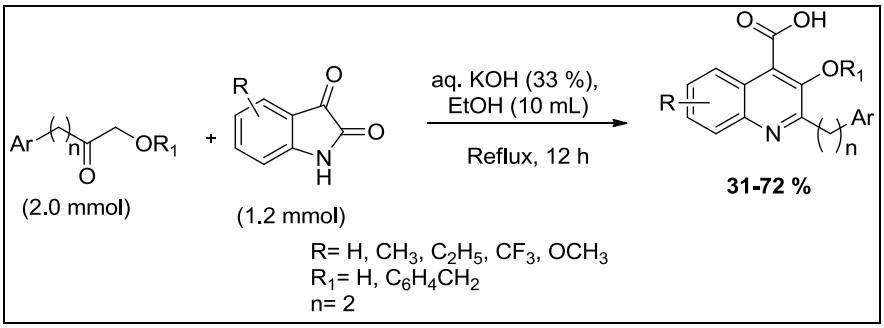
Scheme 22

Zhu et al. have reported an efficient method for the preparation of quinoline-2,4-dicarboxylic acids via the Pfitzinger reaction of isatins with sodium pyruvate in the presence of sodium hydroxide in water as a solvent under microwave irradiation for 3-15 min to get a high yield of product (Scheme 23) [58]. Green chemistry point of view the microwave synthesis was promoting a higher yield, time consuming and no by-products. In this study they have define a quinoline-2,4-dicarboxylic acids synthesis via microwave reaction.



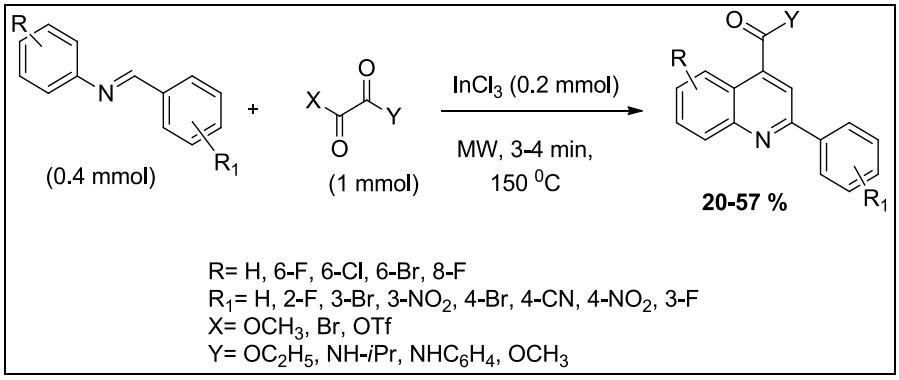
Scheme 23

Kaila et al. have discovered an efficient protocol for the synthesis ofquinoline-4-carboxylic acid derivatives by the reactionofvarious ketones and substituted isatins in the presence of a catalytic amount of potassium hydroxide in ethanolfor the 12 h reflux, which afforded good yield of theproduct (Scheme 24) [59].



Scheme 24

Duvelleroy et al. have discovered a novel, rapid and facile method for the preparation of quinoline-4-carboxylic acid derivatives via a 2-methoxy acrylates oracrylamides with *N*-arylbenzaldimines in acetonitrile in the presence of $InCl_3$as a catalyst under microwave irradiation (Scheme 25). In this protocol they have afforded a good yield of the products [60].



Scheme 25

CONCLUSION

Thisreview shows the recent advance synthetic method and different biological activities of quinoline-4-carboxylic derivativesand synthesis routs using via a various catalyst, and different solvents. These protocols have been developed for improving purity, selectivity and yield of the product. We have described here green method for synthesis of quinoline-4-carboxylic acid derivatives and their yield was still challenging task in the literature.This review will be useful to the researchers working in this field and help them to develop a new green, efficient, economical methods, with increasing higher yields, increasing environmental concerns, non-toxic, green catalyst and reagent. These are research areas that are grown and no doubts, in future we have a number of novel methods for the synthesis of quinoline-4-carboxylic acid.

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