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Review

2-Azidobenzaldehyde-Based [4+2] Annulation for the Synthesis of Quinoline Derivatives

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Abstract: Quinoline is a privileged heterocyclic ring which can be found in many drug molecules and bioactive compounds. The development of synthetic methods for making quinoline derivatives continuously attracts the interest of organic and medicinal chemists. This paper highlights 2-azidobenzaldehyde-based [4+2] annulation for the synthesis of quinoline derivatives including fused and spiro-quinolines, quinoline-4-ols, 4-aminoquinolines, and related compounds.

Keywords: quinolines; azidobenzaldehyde; [4+2] annulation; heterocyclic; bioactive

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1. Introduction

Quinoline is a privileged scaffold for bioactive molecules [1–6]. Shown in Figure 1 are some quinoline-containing drug molecules, including Mefloquine (antimalarial) [7–10], Brequinar (anticancer) [11–13], Pitavastatin (cholesterol-lowering) [14–16], Plaquenil (antimalarial) [17,18], Ciprofloxacin (antibacterial) [19–21], and Lenvatinib (anticancer) [22–24]. Other than these commercial drugs, a great number of quinoline derivatives have been reported or are under development as druggable molecules for anticancer [25,26], antibacterial [27–29], antifungal [30–32], antiviral [33–36], antimalarial [37–39], antioxidant [40–42], anti-inflammatory [43–45], CNS effect [46,47], cardiovascular, anticonvulsant, analgesic, and anthelmintic research [48–51].

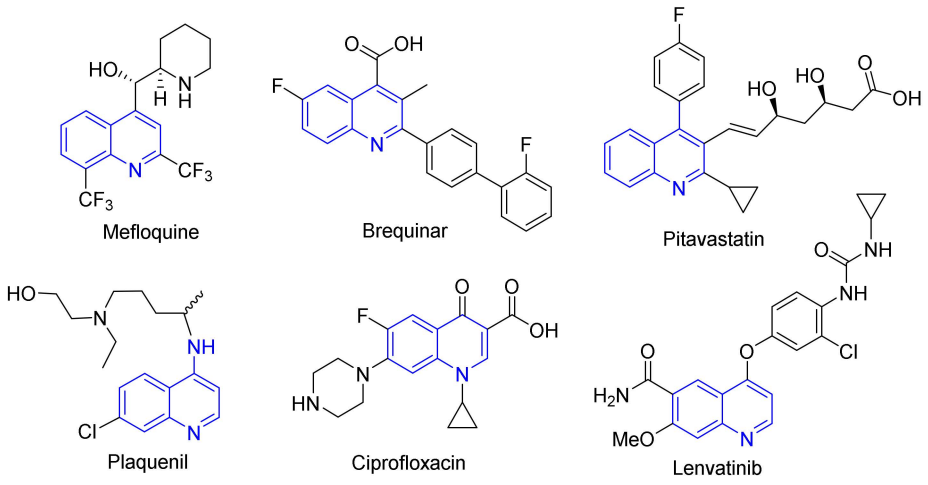
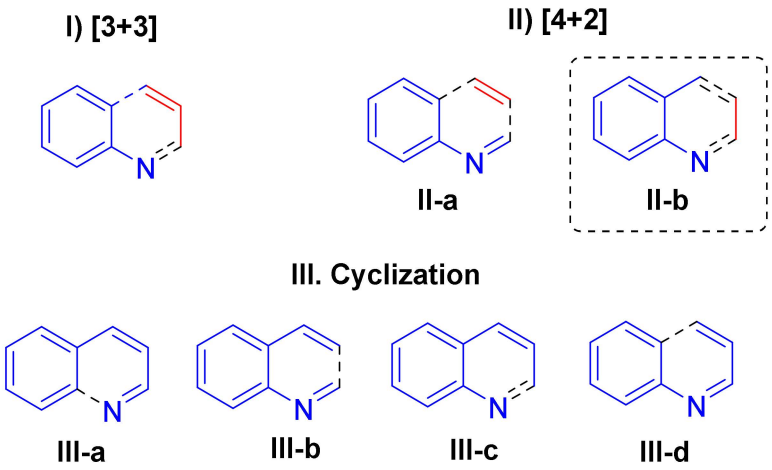


Figure 1. Representative structures of quinoline drugs.

The synthesis of quinolines has continuously attracted the interest of organic and medicinal chemists. Over the years, many methods including name reactions such as Skraup, Doebner–von Miller, Friedlander, Ptzinger, Conrad–Limpach, and Combes syntheses [52,53] have been developed for making quinolines. Alam and Patel have reviewed the general synthetic methods [54,55], which included new methods such as cascade reactions [56] and metal-free one-pot synthesis [57,58].

Shown in Scheme 1 are three general approaches to assembling the quinoline ring. (**I**) [3+3] Annulation. The early developed methods such as the Skraup, Doebner–von Miller, Conrad–Limpach, Gould–Jacobs, and Combes syntheses are in this category. The drawback of this approach is that it has a low regioselectivity for the synthesis of multi-substituted quinolines [52,54,57]. (**II**) [4+2] Annulation. There are two ways to put together the pyridine ring according to [4+2] annulation (**II-a** and **II-b**). The first one has low regioselectivity and a limited substrate scope [52,55,56]. The second one is more popular and uses readily available substrates to give products with a good regioselectivity. Reactions such as the Friedlander and Ptzinger reactions are in this category [52–55,58]. (**III**) Cyclization. In theory, there are four different ways to form the pyridine ring of quinolines (**III-a** to **III-d**) according to cyclization. But they have not been fully developed due to the difficult reaction process and the limited availability of the substrates [59,60].



Scheme 1. Common synthetic strategies for making quinolines.

Presented in this paper are azidobenzaldehyde-based [4+2] annulation reactions (**II-b** type) for the synthesis of substituted quinolines [61]. For example, [4+2] annulation could be accomplished using a direct Diels–Alder reaction or via sequential condensation and cyclization reactions. In addition to quinolines, versatile 2-azidobenzaldehydes **1** could be used for the synthesis of other heterocyclic rings such as indoles [62,63], 3,4-dihydroquinazolines [64,65], triazolobenzodiazepines [66], *2H*-indazoles [67], benzoxazepinones [68], and quinolines. Meanwhile, 2-azidobenzaldehydes could be easily prepared from commercially available 2-halobenzaldehydes, 2-aminobenzaldehydes, and 2-nitrobenzaldehydes [62,64,66–68]. Over 30 papers on the 2-azidobenzaldehyde-based synthesis of quinolines could be found in the literature and are summarized in this paper.

2. Results

2.1. Synthesis of 4-Unsubstituted Quinolines

There are many 4-nonsubstituted quinoline drugs and drug candidates (Figure 2), such as Bedaquiline for the treatment of active tuberculosis [69,70], Indacaterol for the treatment of chronic obstructive pulmonary disease [71,72], Brexpiprazole for the treatment of schizophrenia [73], Mardepodect for the treatment of schizophrenia [74], and Acridine carboxamide for the treatment of cancer [75].

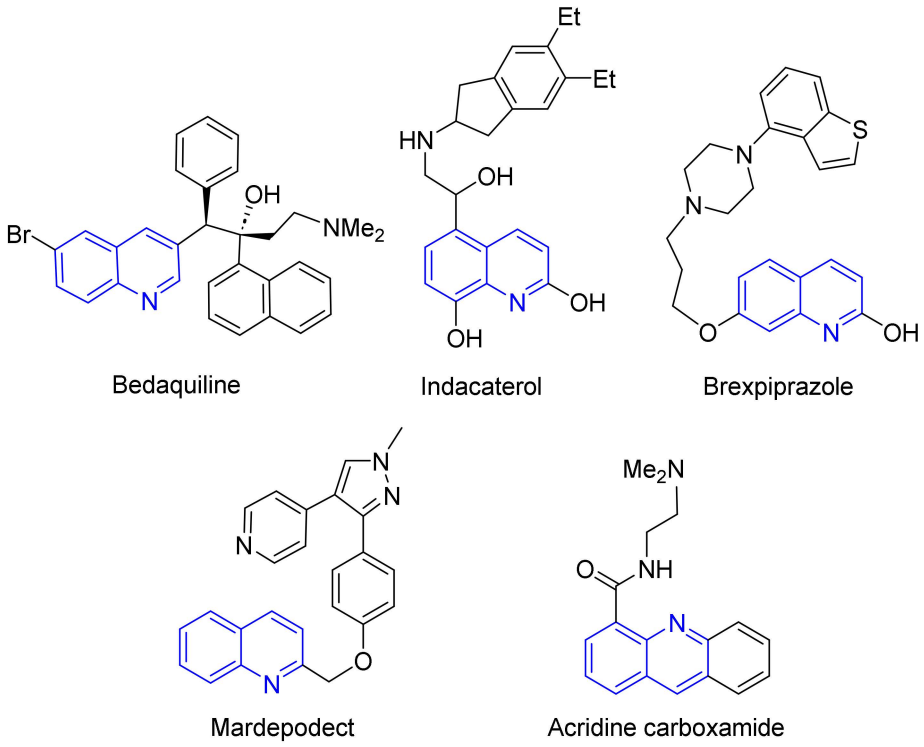
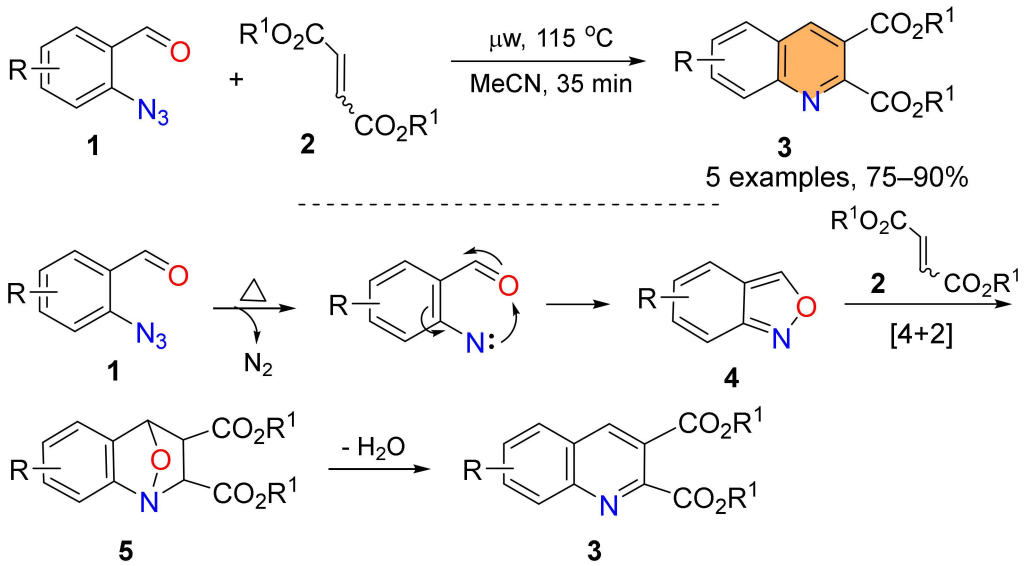


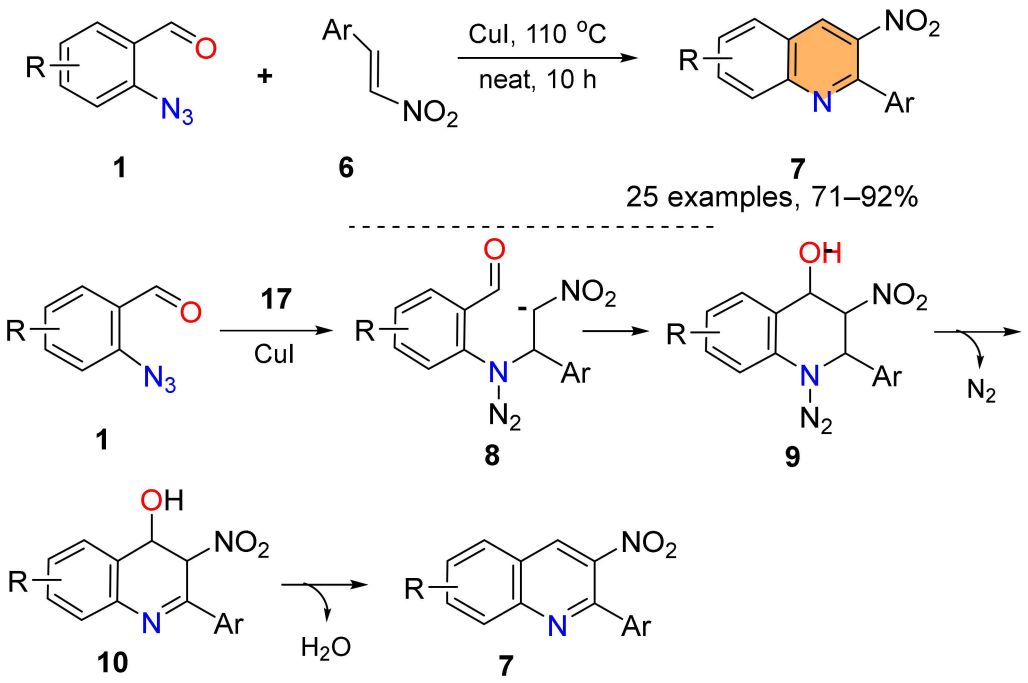
Figure 2. Examples of 4-unsubstituted quinoline-based marketed drugs and clinical candidates.

Utilizing the Diels–Alder reaction of benzisoxazole [76–78] as a key step, Zhang and co-workers developed a one-pot reaction involving the denitrogenation of 2-azidobenzaldehyde **1**, the formation of benzisoxazole **4**, [4+2] cycloaddition with fumarate ester **2**, and, finally, dehydrative aromatization of intermediate **5** for the synthesis of quinolinedicarboxylates **3** (Scheme 2) [79].



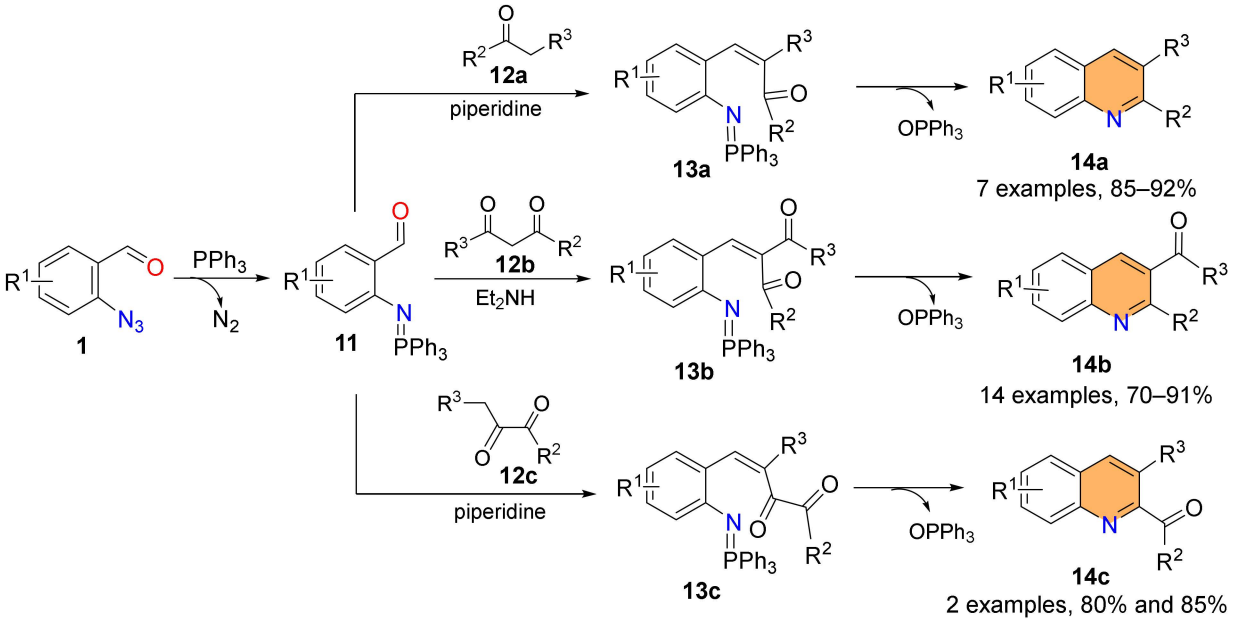
Scheme 2. Cascade reactions for quinolinedicarboxylates **3**.

Zeng and Chen reported the Cu-catalyzed synthesis of 3-NO_2 quinolines **7**. The addition of nitroalkene **6** to the azide group of **1** affords **8**, which then undergoes cyclization to form **9**. Proton transfer and the release of N_2 gas from **9** affords **10**, which leads to the formation of 3-NO_2 quinolines **7** after dehydration (Scheme 3) [80].



Scheme 3. Cu-catalyzed cascade reaction for 3-NO_2 quinolines **7**.

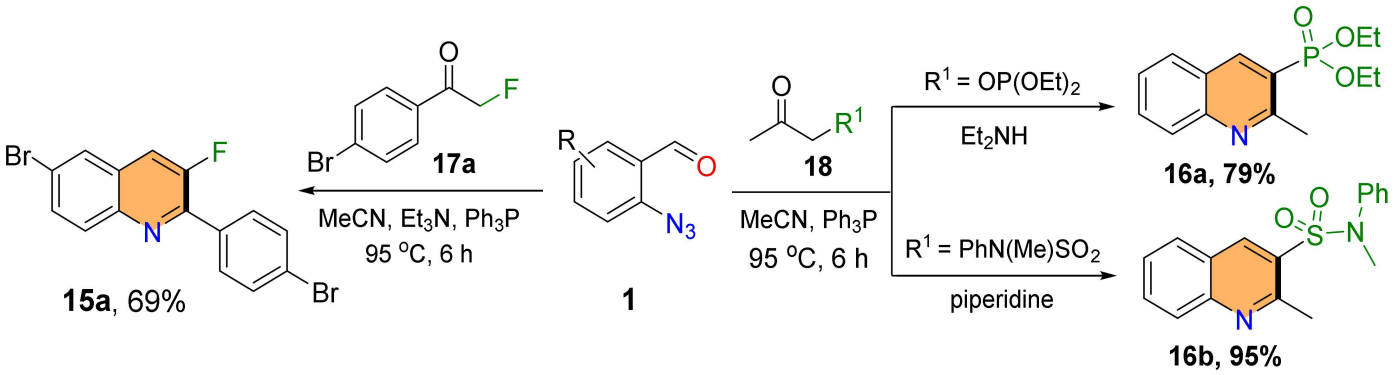
The intramolecular aza-Wittig reaction can be used for making *N*-heterocyclics [81,82]. Zhang and He reported the synthesis of 2,3-substituted quinolines **14** through a sequence involving the Staudinger, Knoevenagel, and aza-Wittig reactions [83,84]. The first intermediates **11** generated according to the Staudinger reaction of 2-azidobenzaldehydes **1** and PPh_3 undergo the Knoevenagel reaction with different carbonyl compounds **12a–c** to generate the corresponding intermediates **13a–c**. The intramolecular aza-Wittig reaction releasing $Ph_3P{=}O$ gives 2,3-substituted quinoline products **14a–c** (Scheme 4).



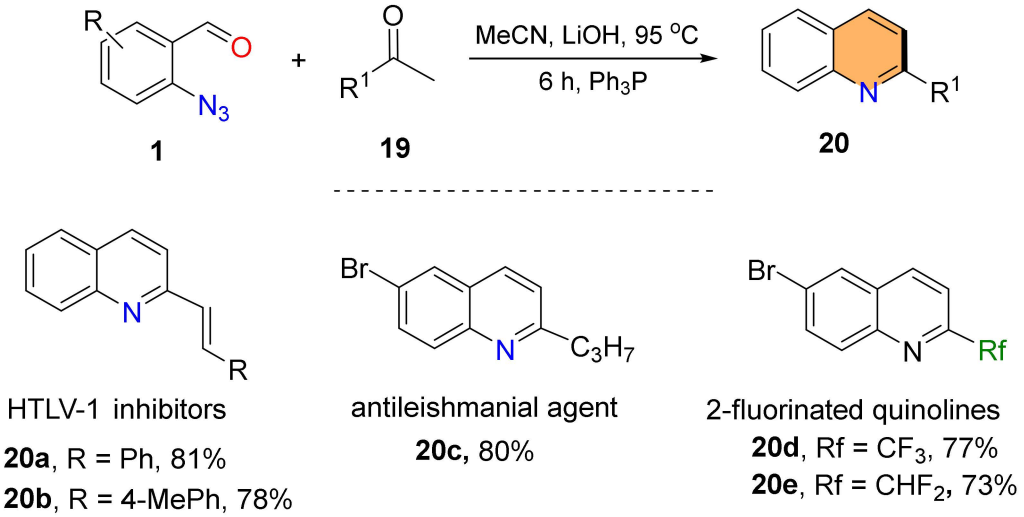
Scheme 4. Cascade synthesis of 2,3-substituted quinolines **14a–c**.

Zhang and co-workers expanded the scope of the aza-Wittig reaction for synthesizing 3-F quinoline **15a**, 3-phosphonylquinoline **16a**, and 3-sulfonylquinoline **16b** using **1** and **17a** or **18** as the substrates (Scheme 5) [83,85]. They also used 2-azidobenzaldehydes **1** and

1-substituted propan-2-ones **19** in the synthesis of bioactive 2-substituted quinolines such as HTLV-1 inhibitors **20a** and **20b**, antileishmanial agent **20c**, and CF_3- and CHF_2-substituted quinolines **20d** and **20e**, shown in Scheme 6 [86–88].

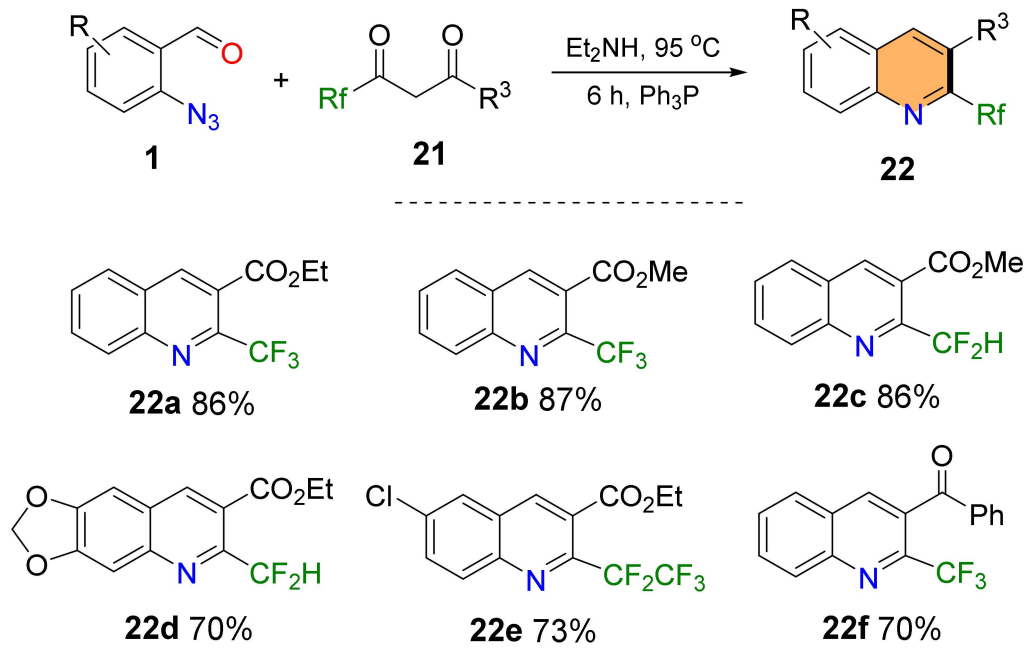


Scheme 5. Synthesis of 3-F quinolines **15a**, 3-phosphonylquinolines **16a**, and 3-sulfonylquinoline **16b**.

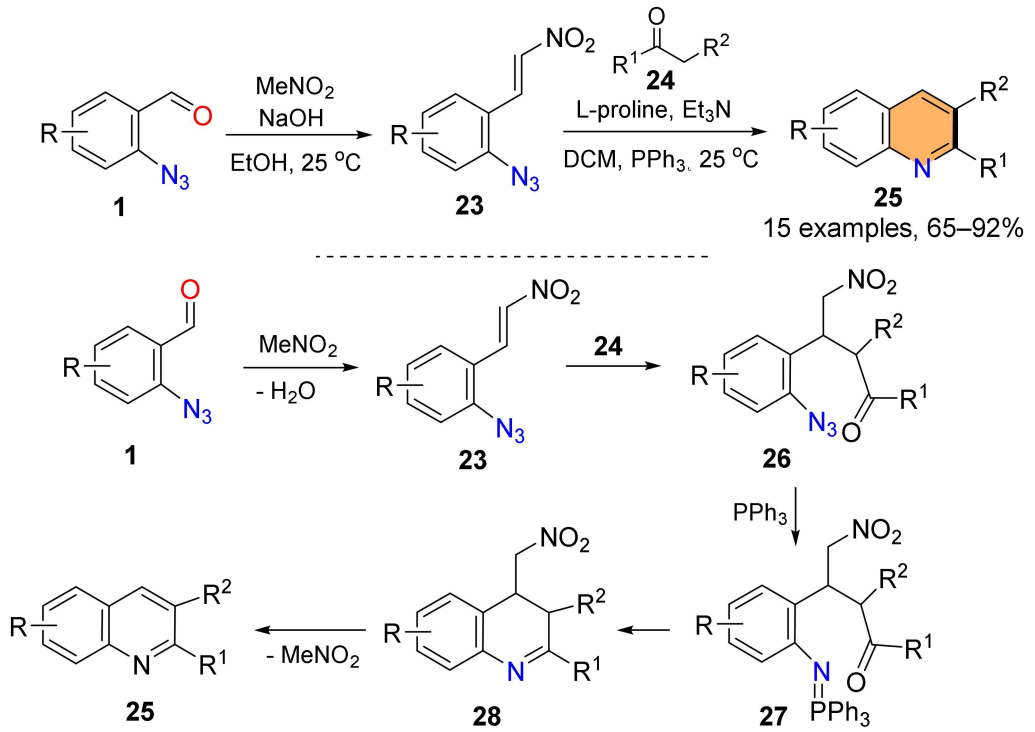


Scheme 6. Synthesis of bioactive 2-substituted quinolines **20**.

Due to the importance of F groups in drug molecules [89–93], the Zhang group introduced a reaction between compounds **1** and **21** for making 2-fluorinated quinolines **22a–f**, bearing CF_2, CF_3, and C_2F_5 at 70–87% yields (Scheme 7). These compounds are related to histone acetyltransferase (HAT) inhibitors [94–96]. Shi and co-workers reported the synthesis of 2,3-substituted quinolines **25** via a condensation/Michael/Staudinger/aza-Wittig/aromatization reaction (Scheme 8) [97]. The *ortho*-Azido-*β*-nitro-styrenes **23**, synthesized by the condensation of 2-azidobenzaldehydes **1** and $MeNO_2$, undergo the Michael addition with ketones **24** to form **26**, which then reacts with PPh_3 according to the Staudinger reaction to afford intermediates **27**. The intramolecular aza-Wittig reaction of **27** gives **28**, followed by the aromatic removal of $MeNO_2$ to afford **25** (Scheme 8).

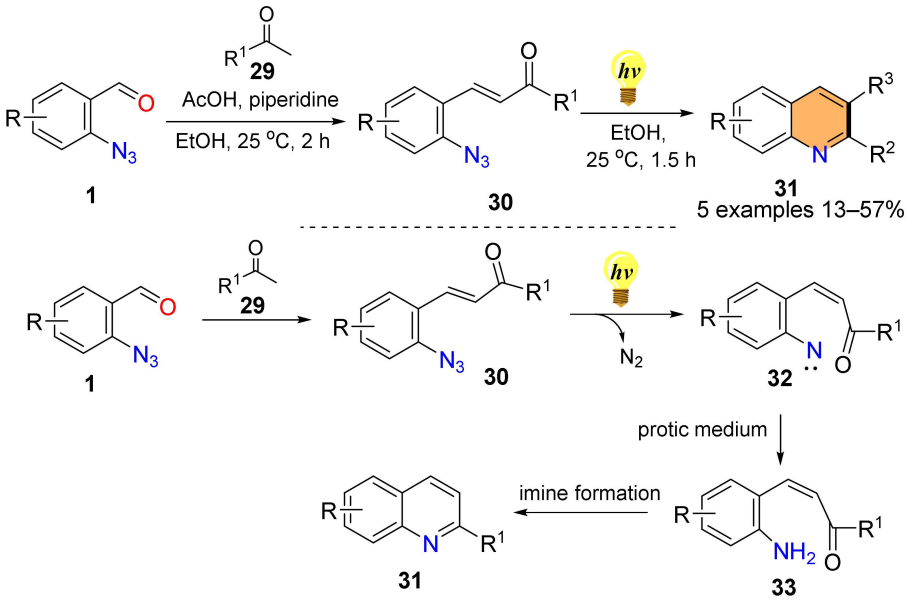


Scheme 7. Direct synthesis of 2-fluorinated quinolines **22**.



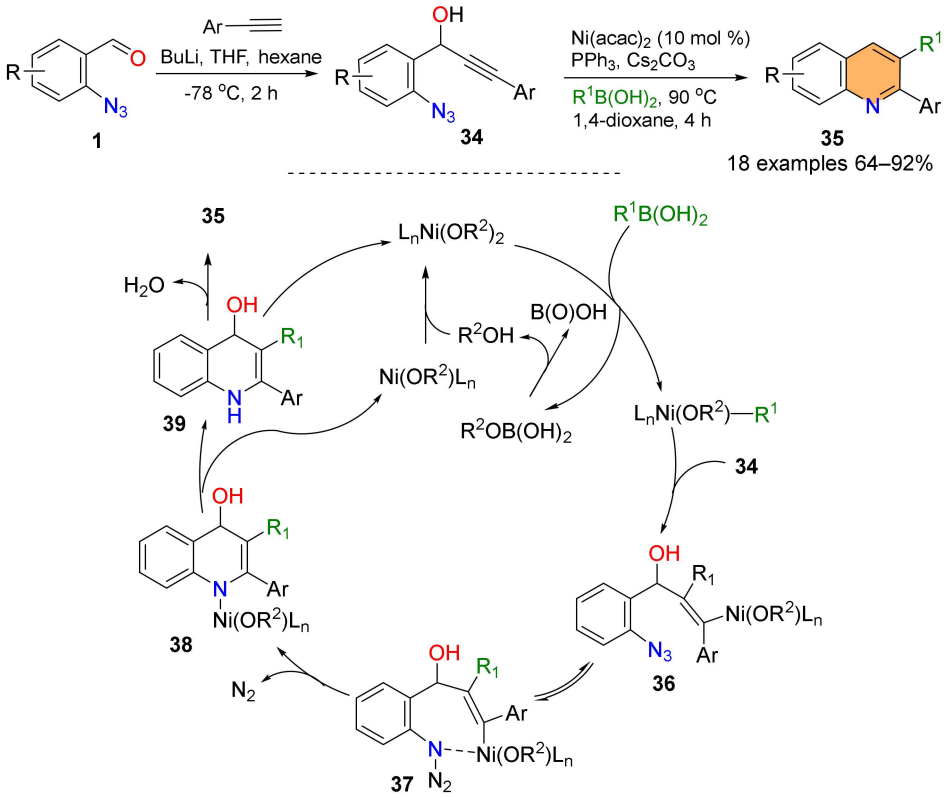
Scheme 8. One-pot synthesis of 2,3-substituted quinolines **25**.

In addition to aza-Wittig cyclization, for making quinolines, Chassaing and co-workers reported intramolecular imine formation of aldehyde and aniline for the synthesis of 2-substituted quinolines **31**. The reaction process involves the formation of *ortho*-azidocinnamoyl compounds **30** via the condensation of 2-azidobenzaldehydes **1** and ketones **29**. The irradiation of aryl azides **30** generates nitrenes **32**, which are then converted into amino intermediates **33** in protic media to give products **31** after imine cyclization (Scheme 9) [98].



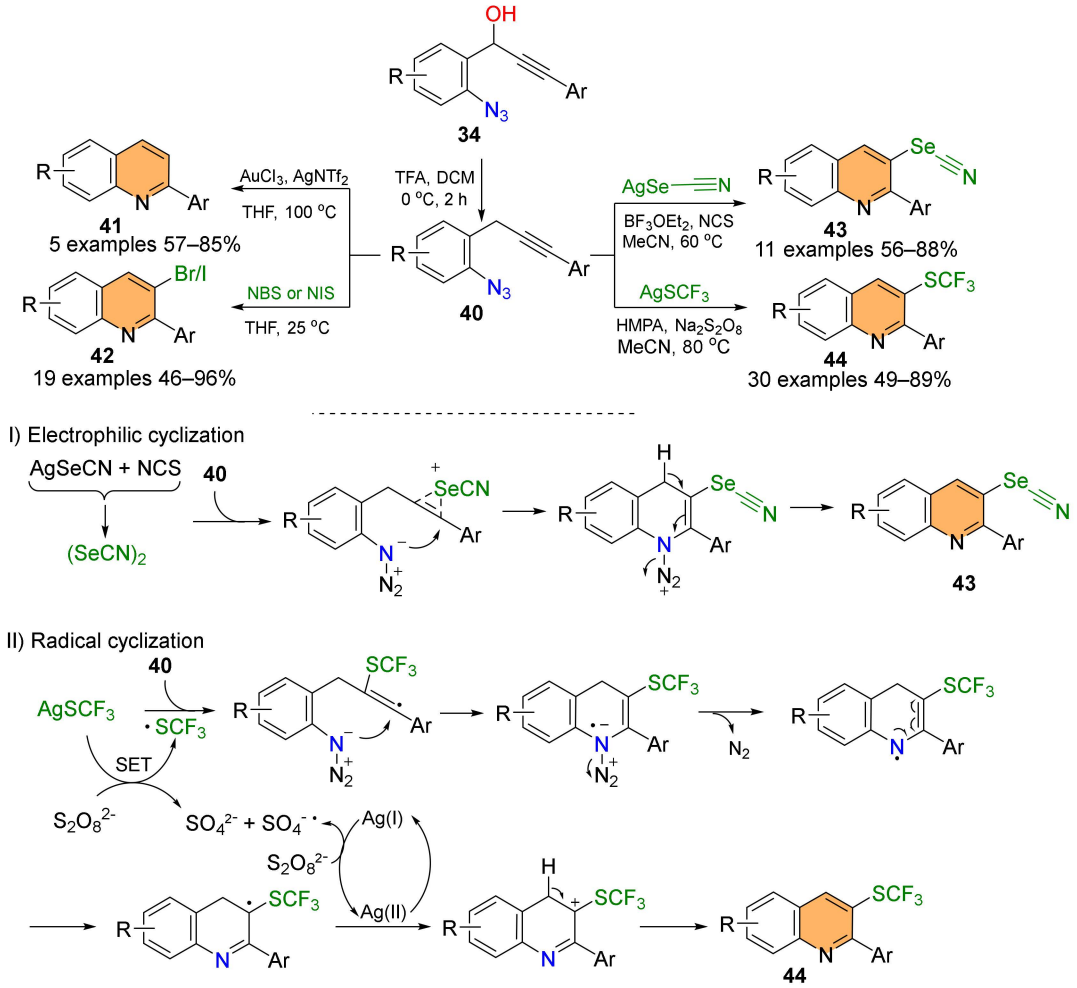
Scheme 9. Photosynthesis of 2-substituted quinolines **31**.

Reddy and co-workers reported a cyclization reaction of azidophenyl propargyl alcohol **34** for making 2,3-substituted quinolines **35** (Scheme 10) [99]. The azidophenyl propargyl alcohol **34**, generated according to the Favorskii reaction of 2-azidobenzaldehydes **1**, undergoes the Ni-catalyzed addition of its R^1 group to the propargylic system to form intermediates **36**, followed by *E*/*Z* isomerization to afford intermediate **37**. The stabilized azido group enables the subsequent denitrogenative cyclization into cyclic intermediates **38**. The denickelation of **38** under the photo conditions gives intermediate **39**, followed by dehydrative aromatization to afford 2,3-substituted quinolines **35**.



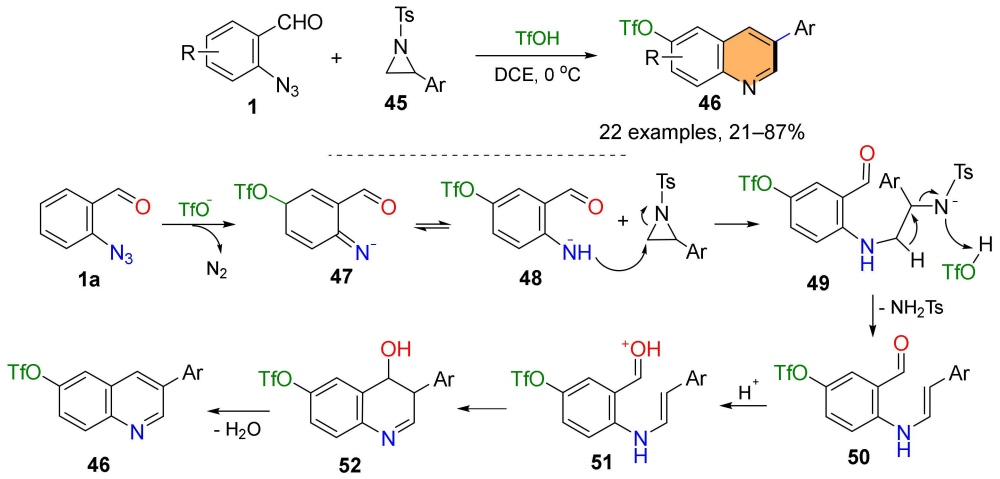
Scheme 10. Ni-catalyzed cyclization for making 2,3-substituted quinolines **35**.

The Yamamoto group utilized *o*–propargyl arylazides **40** derived from the dehydration of compound **34** for the synthesis of multi-substituted quinolines **41**–**44** (Scheme 11). The electrophilic cyclization of **40** in the presence of catalytic amounts of $AuCl_3/AgNTf_2$ affords products **41**. The method was applied to the synthesis of 3-Br/I quinolines **42** in the presence of I_2, Br_2, or NIS [100]. Zhou and co-workers extended the scope of electrophilic cyclization induced by pseudohalogen $(SeCN)_2$ for the synthesis of quinolylselenocyanates **43** [101]. Wang and Quan reported the synthesis of SCF_3-substituted quinolines **44** through radical cyclization of *o*–propargyl arylazides **40** [102].



Scheme 11. Alkyne–azide cyclization for making quinolines **41**–**44**.

The ring-opening of aziridines is a useful tool for the construction of N-heterocycles via cycloaddition or cyclization reactions [103–106]. Wan and co-workers utilized ring-opening and the cyclization of aziridines **45** for the synthesis of 3-substituted quinolines **46** (Scheme 12) [107]. The TfOH-promoted denitrogenation of the azide group of **1** gave intermediate **47** and then **48** after deprotonation. The addition of 48 to aziridines **45** forms **49**, followed by the cleavage of TsNH2 to afford **50**. Acid-promoted cyclization of **50** gives **51**, which is converted into 3-aryl quinoline **46** after aromatization (Scheme 12).



Scheme 12. Ring-opening and cyclization of aziridines for the synthesis of quinolines **46**.

2.2. Synthesis of Polycyclic Quinolines

Polycyclic quinolines can be found in a number of commercial drugs and other bioactive compounds, such as the natural alkaloid Mappicine [108], the poly ADP ribose polymerase (PARP) inhibitor for cancer Talazoparib [109], the antibacterial drug Levofloxacin [110], the natural product Flindersine [111], and the immune response modifier Imiquimod (Figure 3) [112]. The cyclization of 2-azidobenzaldehydes can be integrated into multistep synthesis, one-pot synthesis, or a multi-component reaction (MCR) to make *N*-heterocycles [63,68,113,114]. The aza-Wittig cyclization-based synthesis of polycyclic quinolines is covered in this section. Shown in Scheme 13 are two pathways for the synthesis of cyclohexane-fused quinolines **55** (ee up to 98%) and **57** involving Knoevenage/aza-Wittig/dehydration reactions and Mannich/aza-Wittig/deamination sequences, respectively [115,116].

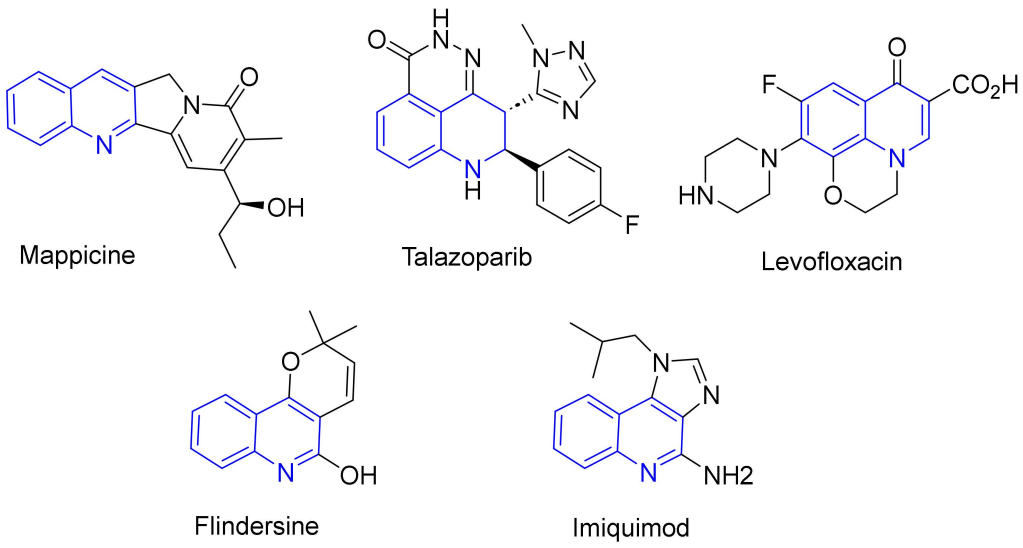
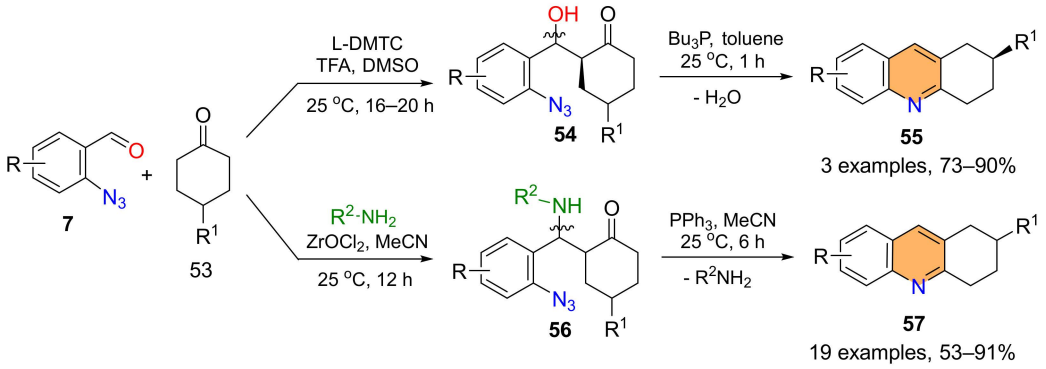
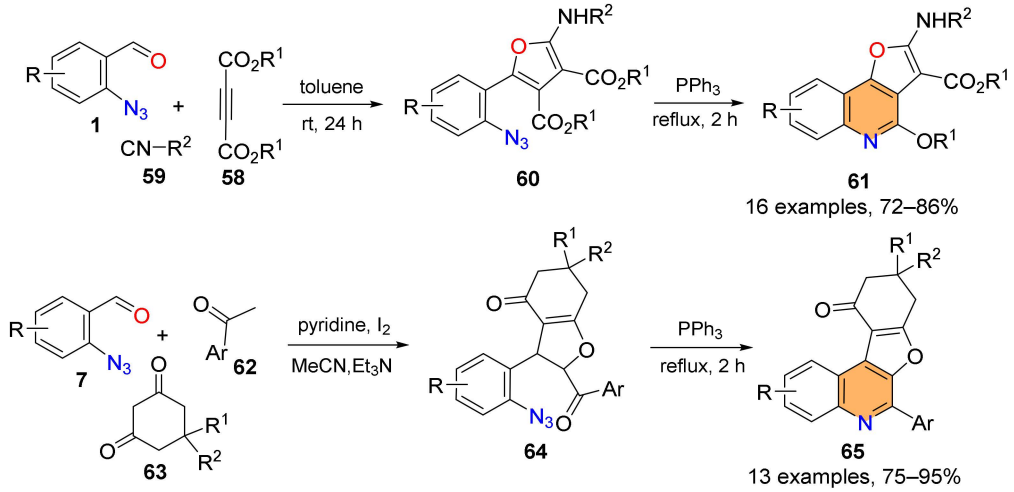


Figure 3. Polycyclic quinoline-based marked drugs and natural products.



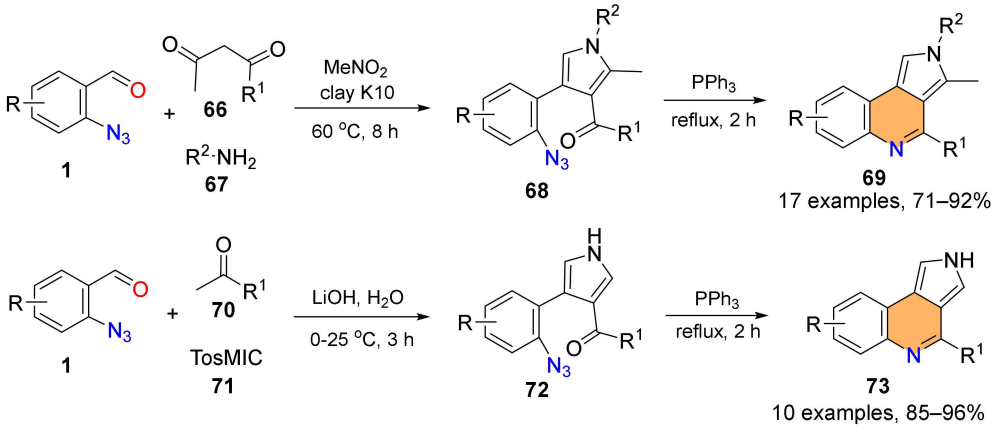
Scheme 13. One-pot synthesis of cyclohexane-fused quinolines **55** and **57**.

A three-component reaction (3-CR)-initiated synthesis of furan-fused quinolines was reported by Ding and co-workers (Scheme 14). Compounds **60** generated from the condensation of 2-azidobenzaldehydes **1**, dialkyl acetylenedicarboxylate **58**, and isocyanides **59** are used for Staudinger and aza-Wittig cyclization to make furan-fused quinolines **61** [117]. He's group reported sequential 3-CR/Staudinger/aza-Wittig cyclization/dehydroaromatization reaction processes for making furan-fused quinolines **65** (Scheme 14) [118].

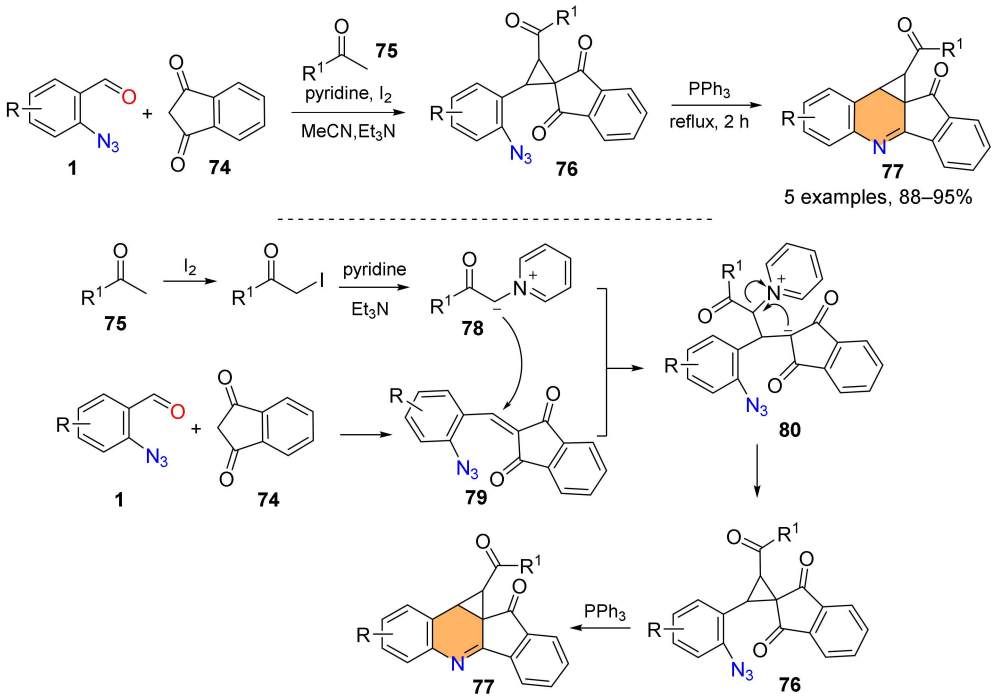


Scheme 14. MCR-initiated synthesis of furan-fused quinolines **61** and **65**.

He and Bharate's groups independently reported the reaction of aldehydes, 1,3-dicarbonyl compounds **66**, amines **67**, and nitroalkanes to make pyrrole-fused quinolines **69** (Scheme 15) [119,120]. He and co-workers also reported a 3-CR/Staudinger/aza-Wittig process for making pyrrole-fused quinolines **73** using **1**, acetyl compounds **70**, and TosMIC **71** as the starting materials (Scheme 15) [121]. Interestingly, an example of making cyclopropa[*c*]indeno [1,2-*b*]quinolines **77** was developed according to the 3-CR/Staudinger/aza-Wittig sequence. The products have a highly condensed ring system, including cyclopropane (Scheme 16) [122].

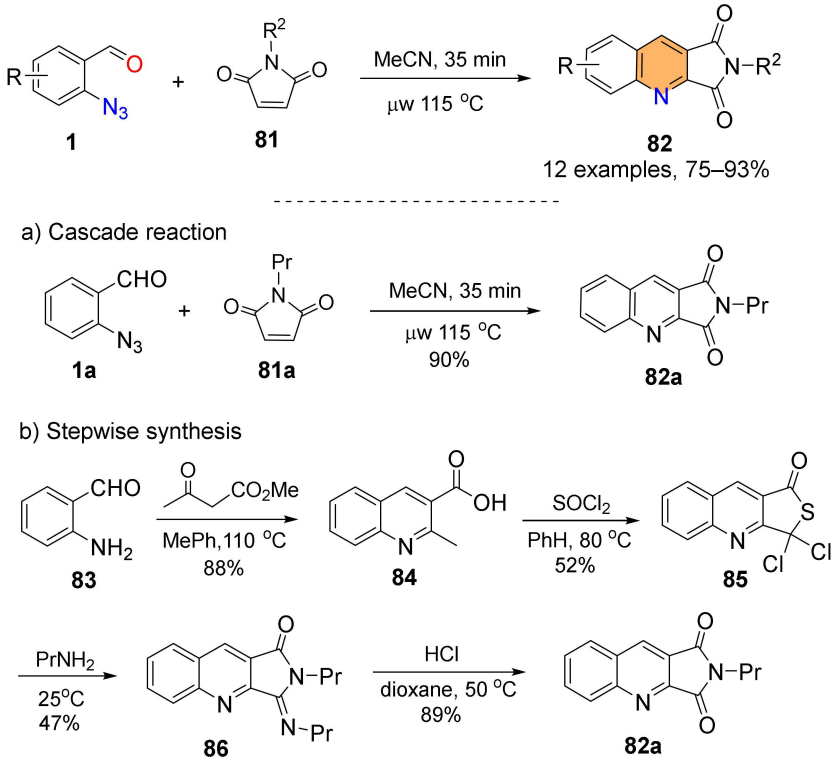


Scheme 15. MCR-initiated synthesis of pyrrole-fused quinolines **69** and **73**.

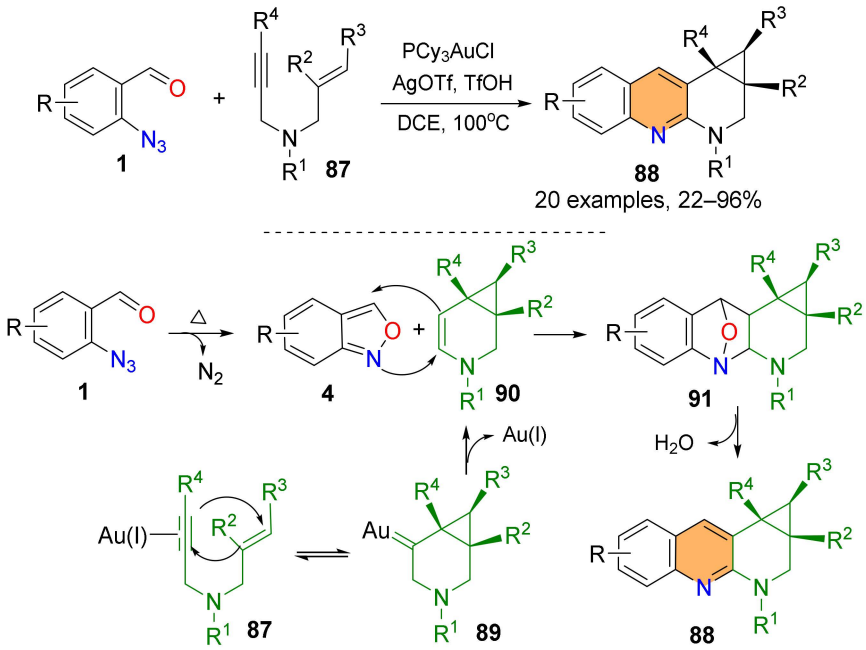


Scheme 16. MCR-initiated synthesis of highly condensed quinolines **77**.

Other than aza-Wittig cyclization for the construction of quinolines, Zhang and co-workers reported cascade denitrogenation/aza-Diels–Alder/dehydrative aromatization reactions for the synthesis of pyrrolidine-2,5-dione-fused quinolines using 2-azidobenzaldehydes **1** and *N*-substituted maleimides **81** as the starting materials (Scheme 17) [79]. This method (Scheme 17a) is more efficient than stepwise synthesis for the synthesis of **82a** (Scheme 17b) [123]. In another case, Li and Wang's group utilized compounds **1** and 3-aza-1,6-enynes **87** as the substrates for making tetrahydrobenzo[*b*][1,8]naphthyridines **88** (Scheme 18) [124]. The reactions involved aza-Diels–Alder cycloaddition of intermediates **90** derived from the Au-catalyzed reaction of enynes **87** to form **91**, followed by dehydrative aromatization to give products **88**.



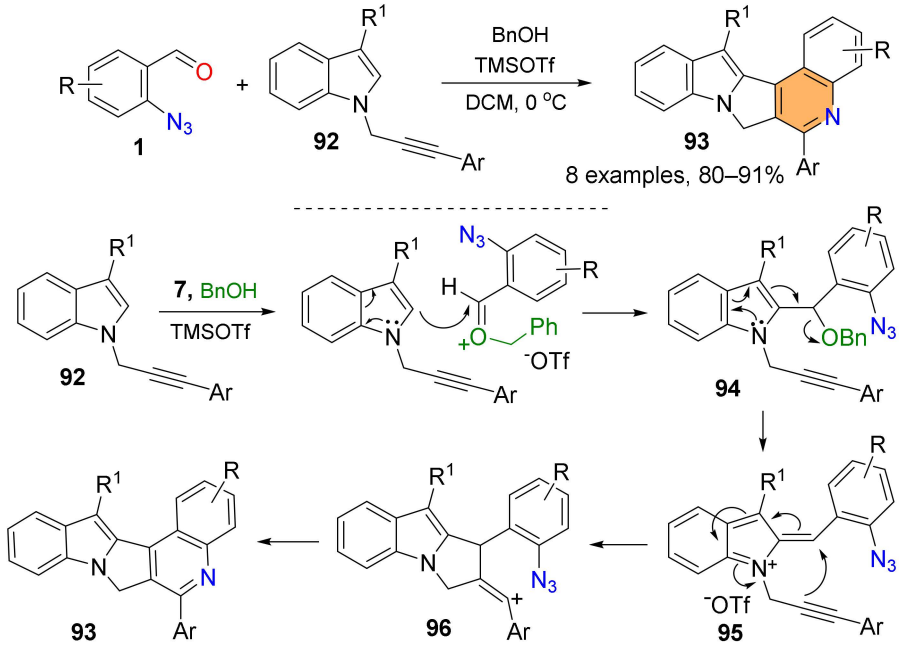
Scheme 17. Cascade reactions for pyrroloquinolinediones **82**.



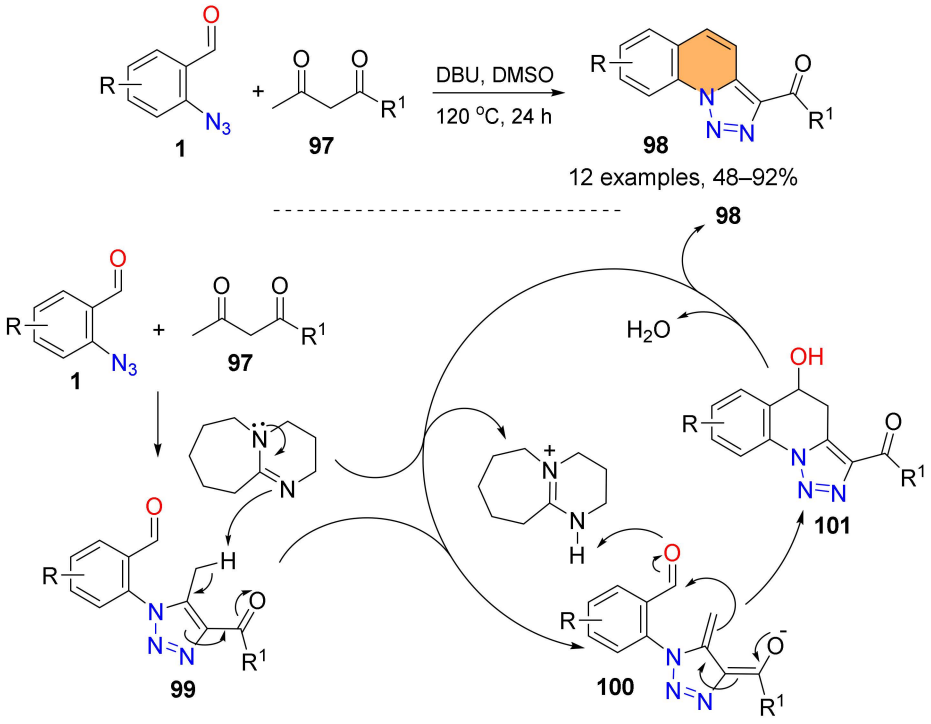
Scheme 18. Cascade reactions for tetrahydrobenzo[*b*][1,8]naphthyridines **88**.

Gharpure and co-workers introduced Lewis-acid-promoted cascade reactions involving Friedel–Crafts/alkyne indol-2-yl cation cyclization/vinyl cation trapping for the synthesis of pyrrolizino-quinolines **93** [125]. Benzyl alcohol and TMSOTf promote the Friedel–Crafts reaction of **1** and indoles **92** to form **93**, which undergoes alcohol elimination and cyclization to afford vinyl cations **96**. The trapping of the vinyl cations with the azide group generates pyrrolizino-quinolines **93** (Scheme 19) [125]. Alves and co-workers introduced sequential [3+2] cycloaddition and condensation reactions for making triazole-fused quinolines **98** (Scheme 20) [126]. The 1,3-dipolar cycloaddition of **1** and 1,3-dicarbonyl

compounds **97** leads to the formation of 1,2,3-triazoles **99**. The intramolecular condensation of enolates **100** generated from the DBU deprotonation of **99** affords **101** and then triazole-fused quinolines **98** after dehydration.



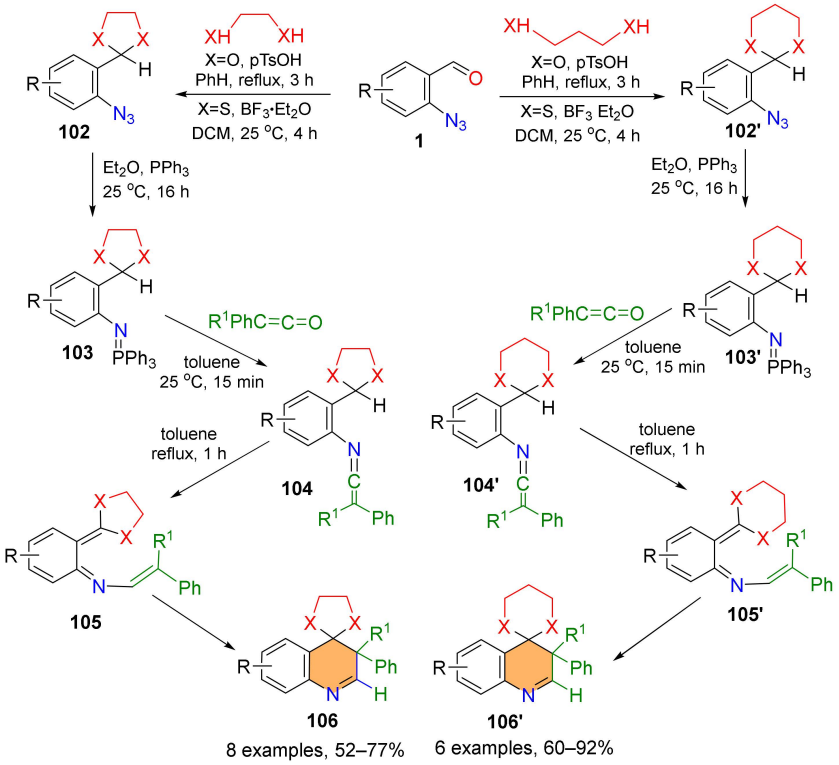
Scheme 19. Cascade synthesis of pyrrolizino-quinolines **93**.



Scheme 20. Direct synthesis of [1–3] triazolo[1,5-a] quinolines **98**.

Alajarin and co-workers reported the cyclization of ketenimines for making spiroquionlines **106** and **106′** using azides **102** and **102′** bearing five- and six-membered cyclic acetal functions (such as 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, and 1,3-dithiane) as the starting materials (Scheme 21) [127,128]. The treatment of azides **102** or **102′** with PPh_3 affords iminophosphorane **103** or **103′**, followed by aza-Wittig reactions with disubsti-

tuted ketenes giving ketenimines **104** or **104′** and then *ortho*-azaxylylenes **105** or **105′** after deprotonation. The cyclization of **105** or **105′** gives the products spiroquinolines **106** or **106′**.



Scheme 21. Tandem synthesis of spiroquinolines **106** and **106′**.

2.3. Synthesis of 4-Hydroxyquinoline Derivatives

There are some drugs and natural products that have 4-hydroxyquinoline moiety, such as the furoquinoline alkaloid Skimmianine, with anticancer and anti-inflammatory effects [129,130]; Cabozantinib, used for the treatment of medullary thyroid cancer [131]; Tasquinimod as an immunomodulator for the treatment of blood cancers [132]; AMG-208 as a clinical trial drug for cancer [133]; Anlotinib, with antineoplastic and anti-angiogenic activities [134,135]; and Delafloxacin as a fluoroquinolone antibiotic for the treatment of acute bacterial skin and skin structure infections (Figure 4) [136].

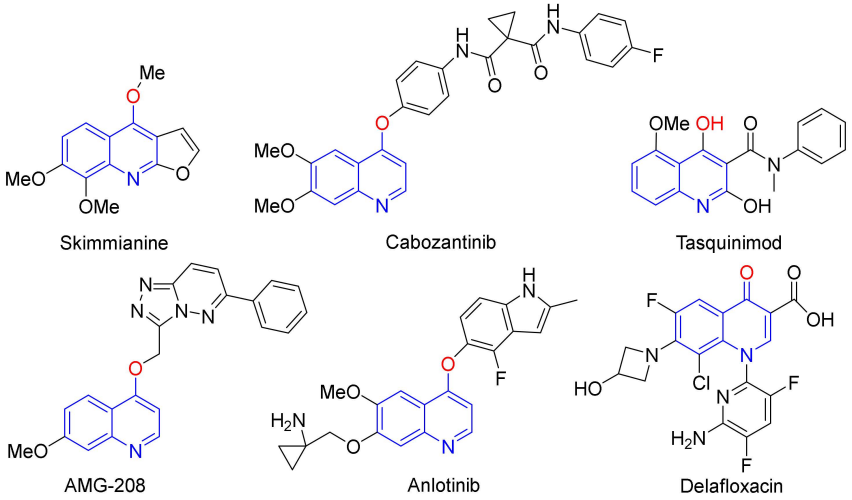
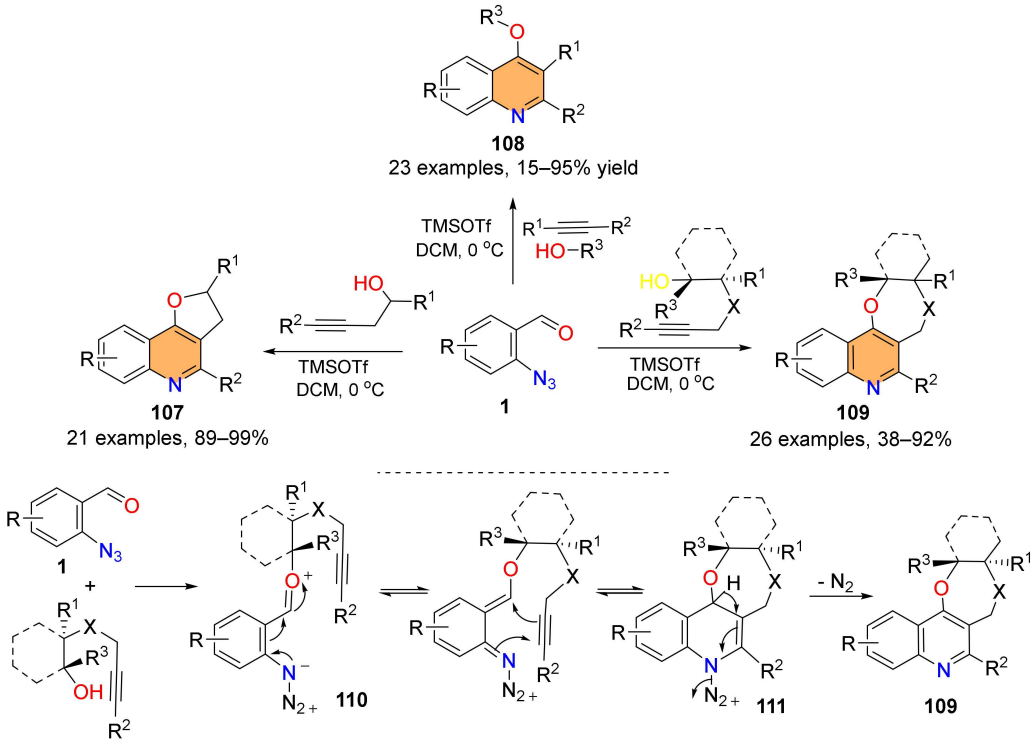


Figure 4. Examples of 4-hydroxy and related quinolines as drug molecules.

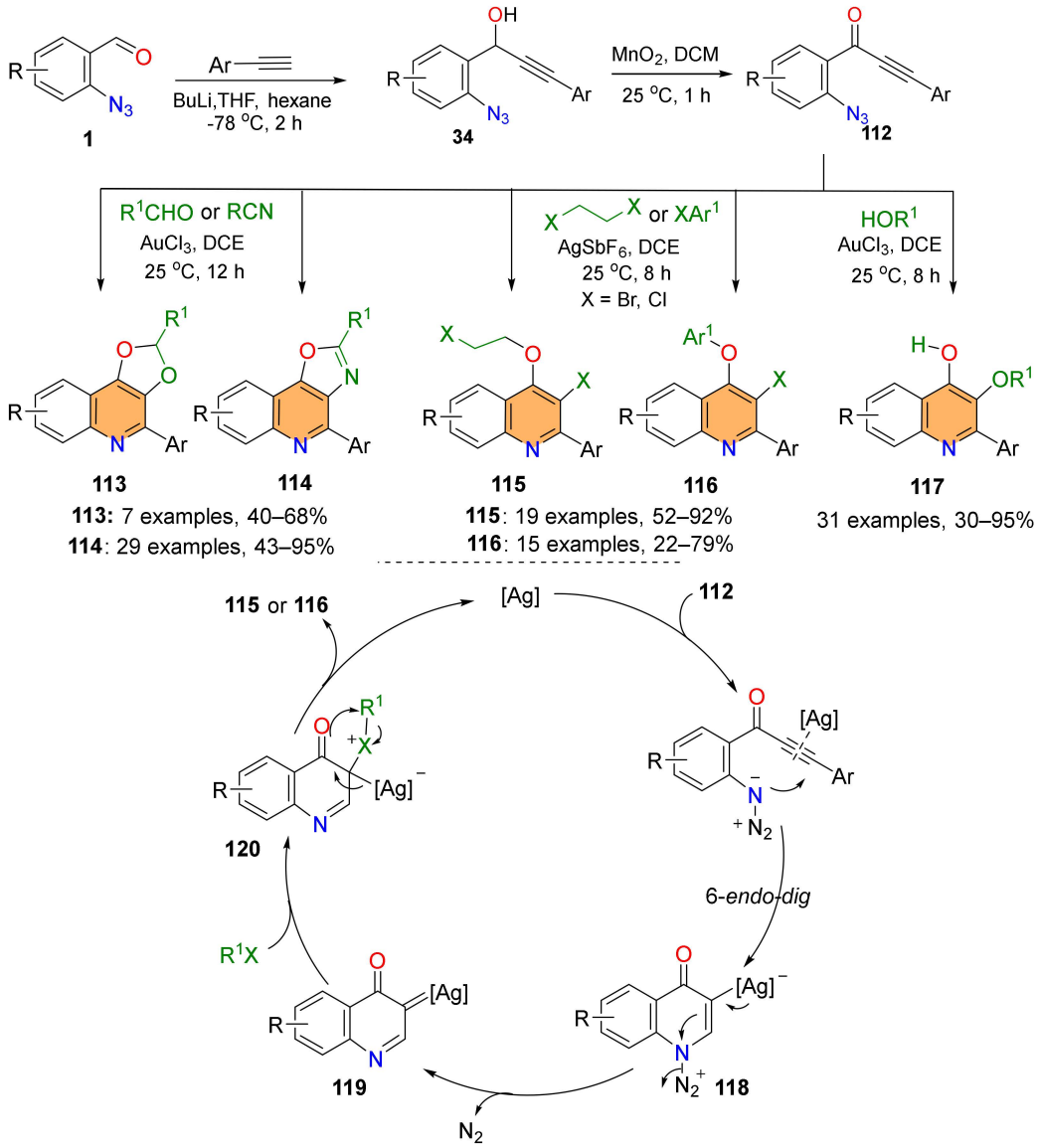
Other than aniline-based [3+3] annulation [137] and [4+2] annulation [138] reactions for making 4-hydroxyquinolines, 2-azidobenzaldehydes have also been employed for the [4+2] annulation-based synthesis of 4-alkoxy quinolines. Gharpure and coworkers reported the reactions of **1** with hydroxyalkynes for the synthesis of different kinds of 4-alkoxy quinolines, **107**, **108**, and **109** (Scheme 22) [139–141]. The synthesis first led to the formation of oxonium ions **110** followed by intramolecular [4+2] cycloaddition and aromatization to give 4-alkoxy quinolines **109**, with a new seven-membered heterocyclic ring (Scheme 22).



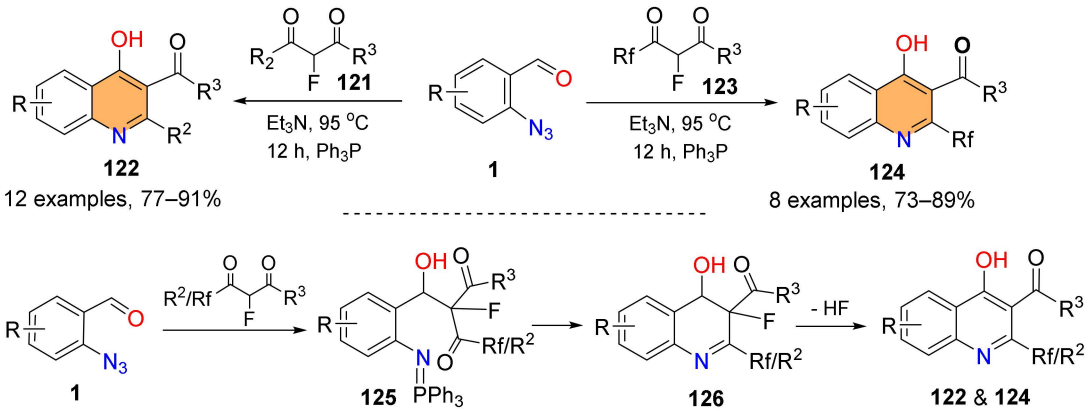
Scheme 22. Cascade synthesis of 4-alkoxy quinolines **107**, **108**, and **109**.

Metal-catalyzed 6-*endo*-dig azide–yne cyclization of azide-tethered alkynes **112** has been developed for the synthesis of multi-substituted 4-alkoxy quinolines **113**–**117** (Scheme 23) [142–144]. For example, Xu and coworkers synthesized **115** and **116** via the $AgSbF_6$-catalyzed cyclization of azide-tethered alkynes. The cyclization of Ag(I)-activated alkyne-tethered azides **112** affords **118**, followed by N_2 gas release from α-imino silver carbenes **119** and then reaction with R^1X to afford halonium zwitterions **120**. After a concerted rearrangement of **120**, product **115** or **116** is obtained.

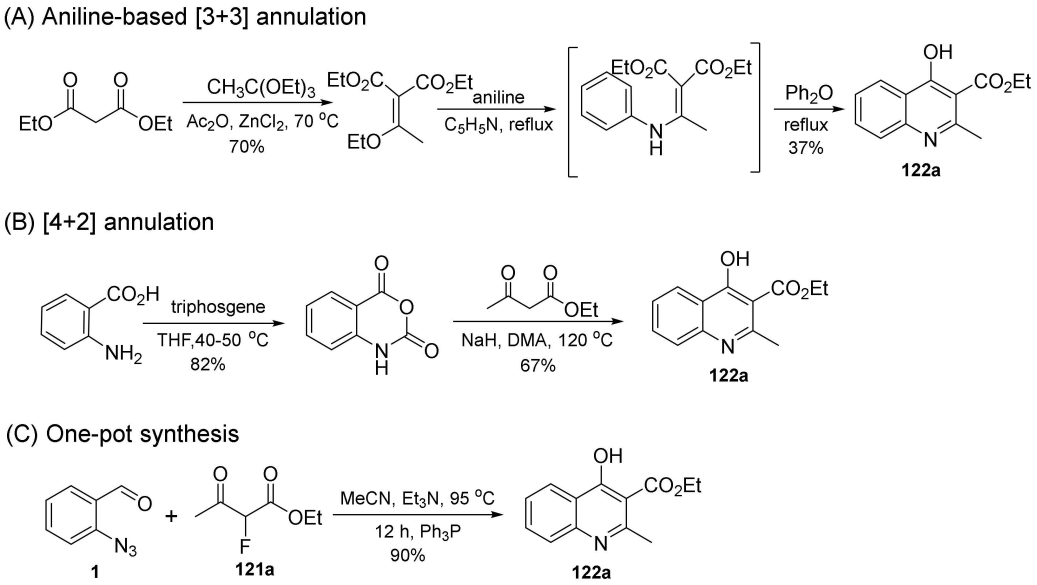
Zhang and coworkers reported the direct synthesis of quinolin-4-ols, which are structurally related to histone acetyltransferase (HAT) inhibitors [145] and the key intermediates for making HMG-CoA reductase inhibitors [146]. The reaction of **1** and α-fluoro-β-ketoesters **121** or **123** via sequential aldol, aza-Wittig, and dehydrofluorinative aromatization reactions gives quinolin-4-ols **122** or **124** (Scheme 24) [83]. Green chemistry metrics analysis for this one-pot synthesis and two reported multi-step syntheses [138] of HAT inhibitor **144a** was conducted [79,82,147] to validate synthetic efficiency and low waste generation (Scheme 25).



Scheme 23. Metal-catalyzed synthesis of diverse 4-alkoxy quinolines **113**–**117**.



Scheme 24. One-pot synthesis of quinolin-4-ols **122** and **124**.



Scheme 25. Three methods for making **122a**.

2.4. Synthesis of 4-Amino-Quinolines

Shown in Figure 5 are some 4-amino-quinoline drugs and drug candidates such as Chloroquine, Amodiaquine, Bosutinib, Amsacrine, and Dovitinib for the treatment of malarial [148–150], leukemia [151,152], and cancer diseases [153]. Common methods in the literature for the synthesis of 4-aminoquinolines are aniline-based multi-step reactions [96,154–156]. Sharada and coworkers employed azides **1** and amines **127** for the synthesis of 4-aminoquinolines **129** through the aza-Diels–Alder reaction of intermediates **128** with dimethylacetylenedicarboxylate (DMAD) (Scheme 26) [157]. Shown in Scheme 27 are two examples of quinoline synthesis using 2-azidobenzaldehyde-based [4+2] cycloadditions. In the first case of using fumarate esters as the dienophiles, quinolines **3** are generated from dehydrative aromatization involving C-O bond cleavage. In the second case of using DMAD as a dienophile for cycloaddition with **128**, 4-aminoquinolines **129** result from the aromatization via the N-N bond cleavage of **130** [79,157].

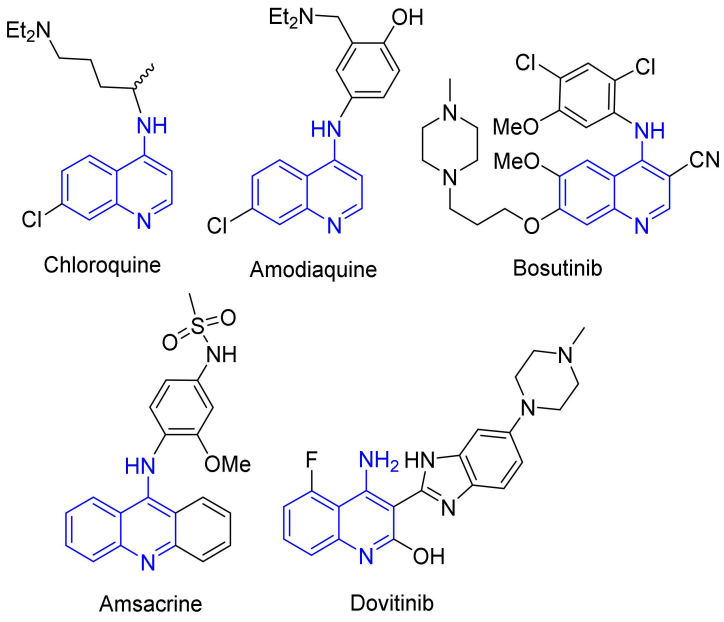
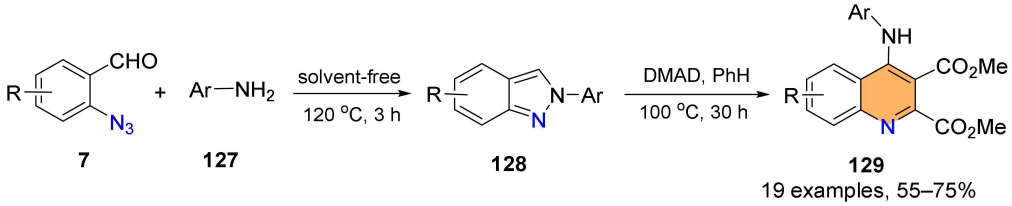
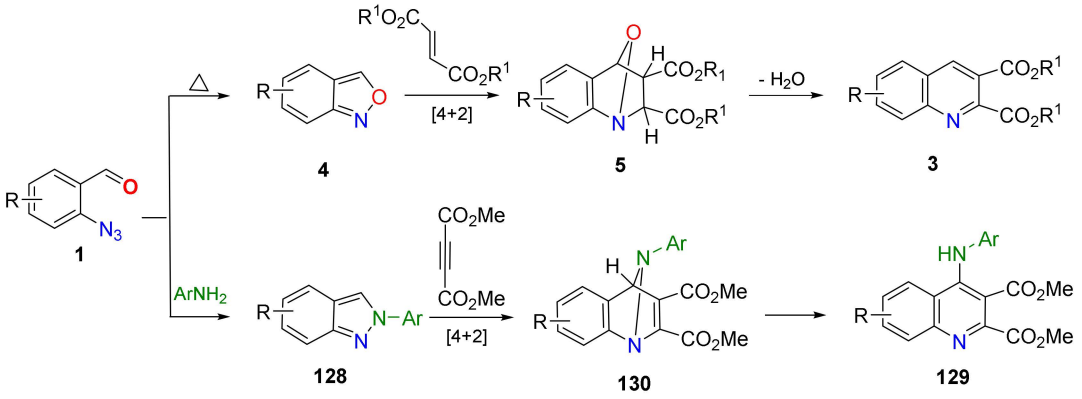


Figure 5. 4-Aminoquinoline-based drugs and drug candidates.

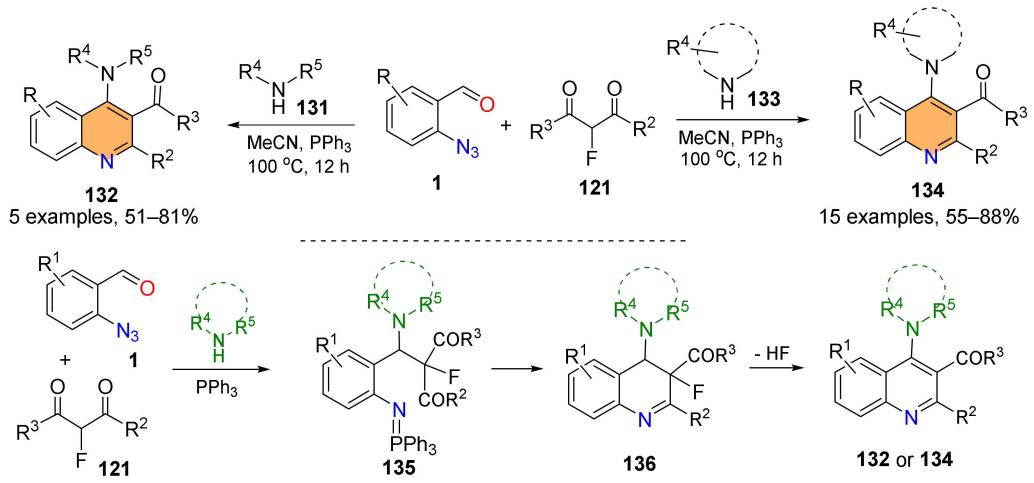


Scheme 26. One-pot synthesis of 4-aminoquinolines **129**.

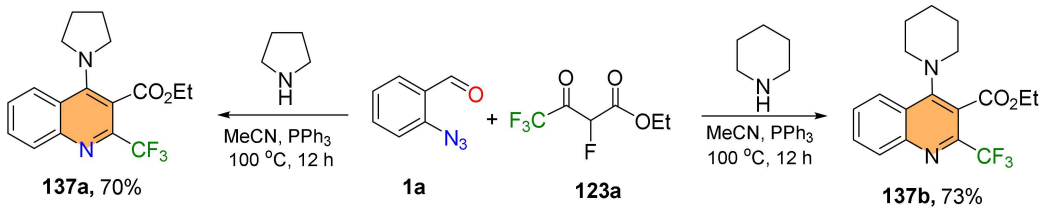


Scheme 27. Comparison of [4+2] cycloaddition for making compounds **3** and **129**.

Zhang and co-workers reported a three-component reaction of azides **1**, *α*-fluoro-*β*-ketoesters **121**, and amines **131** or **133** for the synthesis of 4-aminoquinolines **132** and **134** involving Mannich, aza-Wittig and dehydrofluorinative aromatization reactions (Scheme 28) [158]. They also applied this method to the synthesis of 2-CF_3 quinolines **137a** and **137b** with a pyrrolidine or a piperidine at the 4-position (Scheme 29).



Scheme 28. Three-component reaction to make 4-aminoquinolines **132** and **134**.



Scheme 29. One-pot synthesis of CF_3-containing 4-aminoquinolines **137a** and **137b**.

3. Conclusions

Presented in this paper are 2-azidobenzaldehyde-initiated reactions for the synthesis of diverse quinoline compounds, including fused, spiro-, and polycyclic quinolines, as well as substituted quinolines such as quinoline-4-ols and 4-aminoquinolines. These biologically significant quinoline compounds could be well utilized in medicinal chemistry programs for drug discovery. Also, 2-azidobenzaldehyde-initiated synthesis can be developed as one-pot stepwise synthesis or a multicomponent reaction for operation simplicity, process efficiency, and economizing in terms of steps, pots, and atoms. Some of the synthetic methods presented in this paper provide novel pathways for making quinolines which could also be used for the synthesis of other heterocyclic compounds.

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