Fluorinated Quinolines: Synthesis, Properties and Applications

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Contents

Abstract The data on the chemistry of fluorinated quinolines available in the literature of the last 10–15 years are presented. A variety of synthetic methods exploiting cyclization and cycloaddition reactions, displacements of halogen atoms or the diaza group, as well as direct fluorinations have been considered. Novel approaches to functionalization of polyfluorinated quinolines, including nucleophilic displacement of fluorine atoms, cross-coupling reactions, and synthesis on the basis of organometallic compounds are discussed. Selected representative examples of fluoroquinolines

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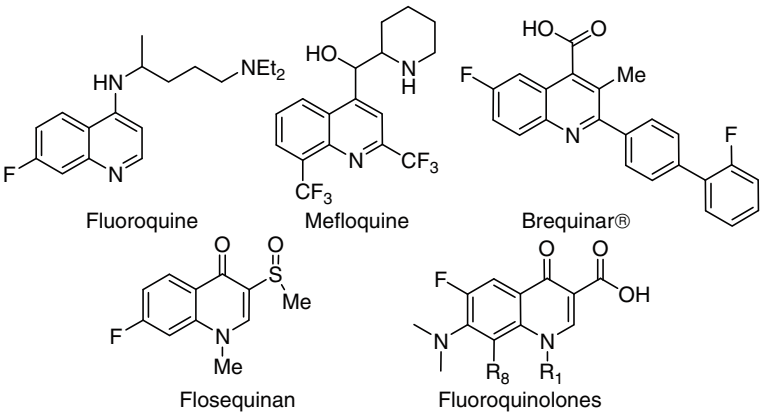
exhibiting a remarkable biological activity or those quinolines which have already found their applications in medicine will also be discussed in the text. The bibliography – 158 references.

Keywords Quinoline • Cyclocondensation • Nucleophilic substitution of fluorine atom • Cross-coupling reactions • Antibacterial activity • Enzyme inhibitor

1 Introduction

The quinoline ring system, the first representative of the family of benzazines bearing one nitrogen atom, is widespread in the nature. Alkaloid quinine has long been used traditionally as antimalarial drug, and it has happened to possess a toning effect. Oxamniquine is used for suppression of shistosoma, which is considered to cause many diseases in tropical regions. Being inhibitors of various enzymes, many synthetic quinolines proved to exhibit antibacterial, antineoplastic, and antiviral activities.

Incorporation of a fluorine atom into azaaromatics is known to enhance biological activity of fluorinated compounds, and provide some other unique properties. The quinoline skeleton has been used for a long time as a basic structure for search of synthetic antimalarial drugs, such as fluoroquine [7-fluoro-4-(diethyl-amino-1-methylbutylamino)quinoline] and mefloquine. The antineoplastic drug Brequinar® and its analogs proved to be useful in transplantation medicine, and also for treatment of rheumatic arthritis and psoriasis. Flosequinan is one of drugs of new generation for treatment of heart diseases. However, the most known drugs belong certainly to the family of fluoroquinolones exhibiting a broad spectrum of antibacterial activity (Scheme 1).



Scheme 1 Structure of fluorinated quinolones with unique properties

A number of fluorinated quinolines have found application in agriculture, and also as components for liquid crystals. Cyanine dyes on the basis of quinolines also make a considerable share in commercial production.

A growing interest in fluorinated derivatives of quinolines stimulates research studies aimed at development of novel methods of synthesis, studying of reactivity of fluorinated quinolines and their plausible practical applications, as indicated by numerous publications, including recent monograph and review articles [1–4].

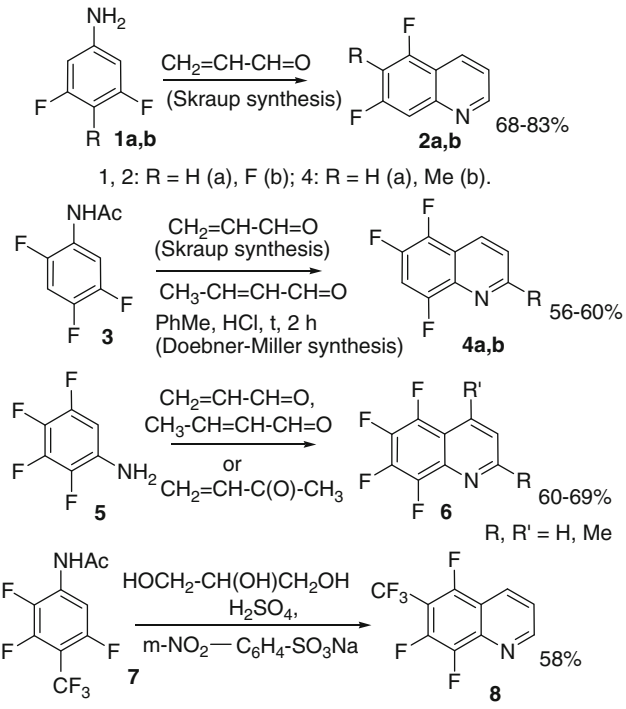
In the frames of this chapter we would like to outline briefly the recent data on fluorine-containing quinolines in which fluorine atoms are attached directly to carbons of the benzene or pyridine rings, and a special attention will be given to mono-fluorinated derivatives.

2 Synthesis and Structure

Cyclization reactions appear to be the most common synthetic method for obtaining of fluorinated derivatives of quinolines and their analogs (Scheme 2). The most important way of synthesis of quinolines, bearing fluorine atoms in benzene or pyridine rings, is ***condensation of anilines having no substituent at least in one of two ortho-positions with carbonyl compounds capable of donating a three-carbon fragment***.

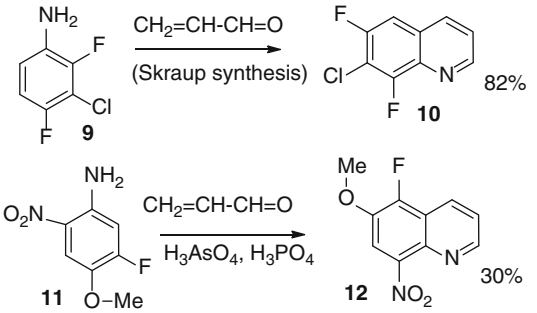
Scheme 2 Formation of pyridine ring of fluorinated quinolines

The Skraup reaction is a good illustration of this common approach, as illustrated by the series of syntheses of 5,7-difluoro- and 5,6,7-trifluoroquinolines **2a,b** proceeding in high yields on the basis of 3,5-difluoro- and 3,4,5-trifluoro-anilines **1a,b** (Scheme 3) [5]. In a similar way 5,6,8-trifluoroquinolines **4a,b** have been obtained from 2,4,5-trifluoro substituted acetanilide **3** and acrolein or crotonic aldehyde [6–8]. 5,7,8-Trifluoroquinoline has also been obtained from 2,3,5-trifluoroacetanilide, while 6-trifluoromethyl-5,7,8-trifluoroquinoline – from 2,3,5-trifluoro-4-trifluoromethyl acetanilide, respectively [6]. The Skraup cyclization is also an effective synthetic took to transform 2,3,4,5-tetrafluoro substituted aniline **5** into 5,6,7,8-tetrafluoroquinoline, 2-methyl-5,6,7,8-tetrafluoroquinoline and 4-methyl-5,6,7,8-tetrafluoroquinoline **6** by reacting aniline **5** with acrolein, crotonic aldehyde and methylvinylketone, correspondingly (Scheme 3). The reaction takes place even in the presence of a strong electron-withdrawing trifluoromethyl group, as shown by the synthesis of 6-trifluoromethyl-5,6,8-trifluoroquinoline **8** from 2,3,5-trifluoro-4-trifluoromethylacetanilide **7** (Scheme 3) [6].



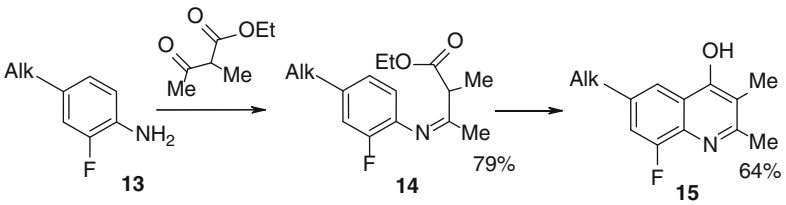
Scheme 3 Synthesis of quinolones **2**, **4**, **6**, **8**

Also the synthesis of 6,8-difluoro-7-chloroquinoline **10** has been performed in a high yield by means of the modified Skraup reaction from 3-chloro-2,4-difluoroaniline **9** [5]. Similarly 5-fluoro-6-methoxy-8-nitroquinoline **12** was obtained from 3-fluoro-4-methoxy-6-nitroaniline (Scheme 4) **11** [9].



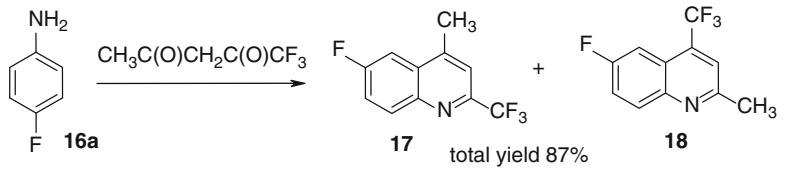
Scheme 4 Synthesis of quinolones **10**, **12**

There are some other synthetic methods to obtain fluorine-containing quinolines which are based on using of fluorinated anilines with a free *ortho*-position and three-carbon reagents. For instance, 8-fluoro-2,3,6-trialkyl substituted 4-hydroxyquinolines **15** were synthesized by the reaction of **13** with ethyl 2-methylacetoacetate and cyclization of the obtained enamines **14** into 8-fluoroquinolines **15** (Scheme 5) [10].



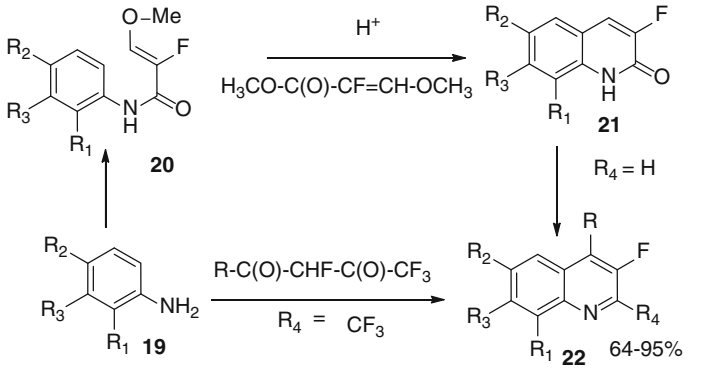
Scheme 5 Synthesis of 4-hydroxy-8-fluoroquinoline **15**

The reaction of 4-fluoroaniline **16** with trifluoromethyl diketone has been established to give a rise to 6-fluoroquinolines **17** and **18** in the ratio 1:1 (Scheme 6) [11].



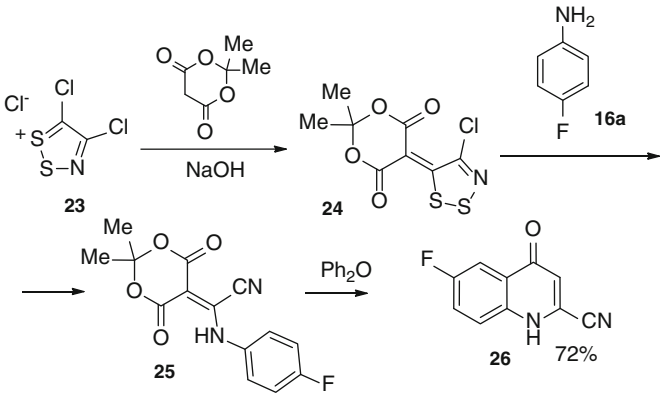
Scheme 6 Interaction of 4-fluoroaniline **16** with trifluoromethyl diketone

2-Fluoro-3-methoxyprop-2-enyl anilides **20** were obtained by condensation of anilines **19** with methyl 2-fluoro-3-methoxyacrylate. Compounds **20** can be transformed in the presence of strong acids into 3-fluoro-2-quinolines **22** (Scheme 7) [12]. A substituent in the *meta*-position relative to the amino group in starting anilines **19** directs the formation of a mixture of two regioisomers in the ratio 1:1, with 3-methoxy- and 3-fluoroanilines being exceptions [13]. 2-Trifluoromethyl-3-fluoroquinolines **22** were derived from anilines **19** and trifluoromethyl ketones [11].



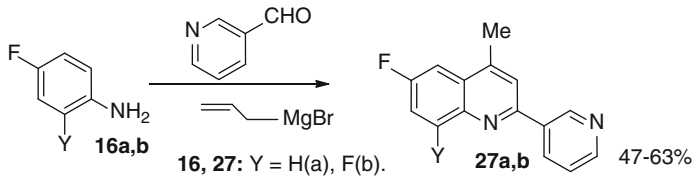
Scheme 7 Synthesis of 3-fluoroquinoline **22**

The synthesis of 6-fluoro-2-cyanoquinolone **26** from 4-fluoroaniline **16** is shown in Scheme 8. 4,5-Dichloro-5H-1,2,3-dithiazolium chloride **23** reacts with the Meldrum acid to form 5-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)-2,2-dimethyl-1,3-dioxan-4,6-dione **24**, which on treatment with 4-fluoroaniline **16** is transformed into 5-[(arylamino)(cyano)methylene]-2,2-dimethyl-1,3-dioxan-4,6-dione **25** in high yield. Heating of compound **25** in biphenyl ether results in the formation of 2-cyanoquinolone **26** [14, 15].



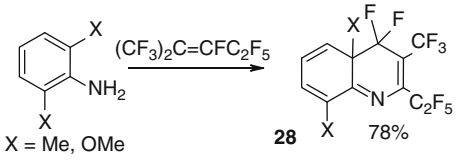
Scheme 8 Synthesis of 2-cyano-6-fluoroquinolone **26**

6-Fluoro- and 6,8-difluoro-4-methyl-2-(3-pyridinyl)-1,2,3,4-tetrahydroquinolines and the corresponding aromatic quinolines **27a,b** have been obtained from 4-fluoro- or 2,4-difluoroanilines **16a,b**, and pyridine-3-carbaldehyde and allylmagnesium bromide (Scheme 9) [16].



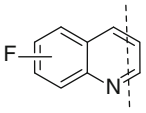
Scheme 9 Synthesis of quinolones **27**

The reaction of perfluoro-2-methylpent-2-ene with 2,6-dimethylaniline or 2,6-dimethoxyaniline has been shown to afford dihydroquinolines **28** (Scheme 10) [17].



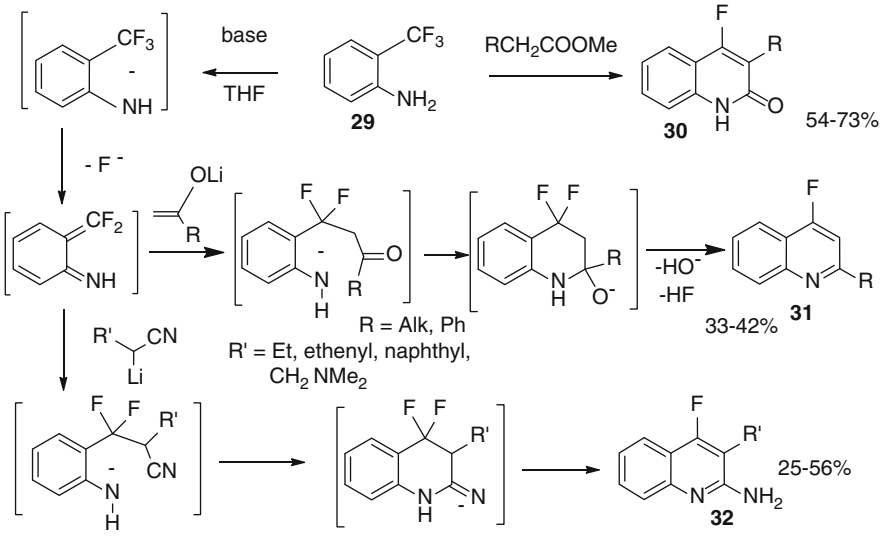
Scheme 10 Synthesis of compound **28**

Another synthetic approach to fluoroquinolines is based on ***cyclocondensations of fluorinated anilines bearing in the ortho-position a carbon-containing functional group*** (trifluoromethyl, nitrile, formyl, carbonyl groups, etc.), ***with reagents containing a two-carbon fragment*** (Scheme 11).



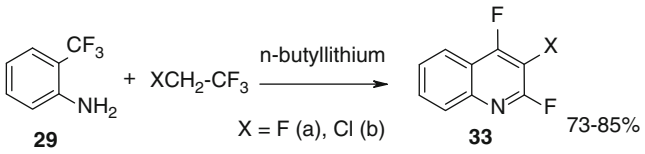
Scheme 11 Formation of fluorinated quinolones from two-carbon reagents

In accordance with this protocol 4-fluoroquinolones (**30**, R = Ar, N-methylindol-3-yl) were obtained by cyclocondensation of 2-trifluoromethylaniline **29** with methyl acetates in the presence of a base (Scheme 9) [18]. The lithium reagents, generated from methylketones, phenylacetylene and substituted acetonitriles, were allowed to react with 2-trifluoromethylaniline **29** to give the corresponding 4-fluoroquinolines **31, 32** (Scheme 12) [8, 19–21].



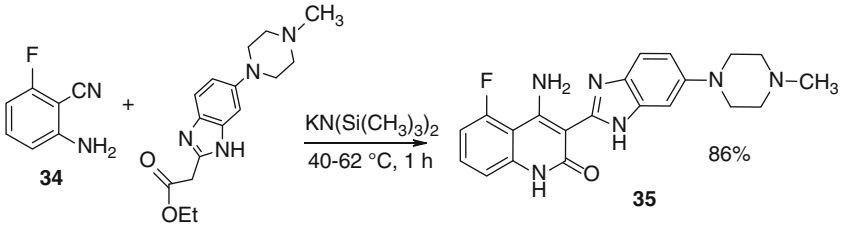
Scheme 12 Synthesis of 2-aminoquinoline **32**

Trifluorovinyl lithium (prepared from 1,1,1,2-tetrafluoroethane) was allowed to react with 2-trifluoromethylaniline **29** at −78 °C to give 1,2,3-trifluoroquinoline **33a** in moderate to good yield. In a similar cyclization with aniline **29** 1-chloro-2,2-difluorovinyl lithium (prepared from 1-chloro-2,2,2-trifluoroethane) afforded 2-chloro-1,3-difluoroquinoline **32b** (Scheme 13) [22].



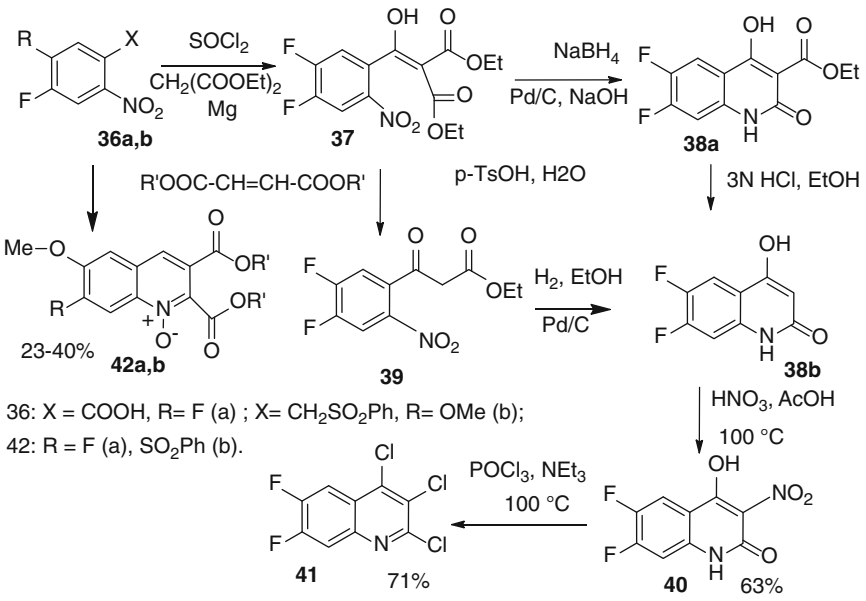
Scheme 13 Synthesis of 2,4-difluoroquinoline **33**

The reaction of 2-amino-6-fluorobenzonitrile **34** with ethyl 6-(4-methylpiperazinyl)-1H-benzimidazolyl acetate takes place in the presence of *bis*-(trimethylsilyl) amide, thus resulting in the formation of quinolin-2-one **35** (Scheme 14) [23].



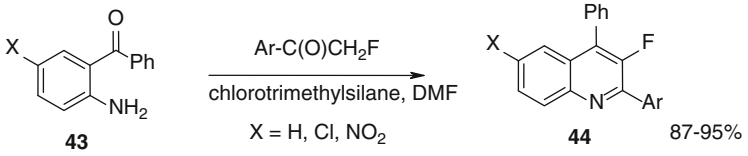
Scheme 14 Synthesis of quinolin-2-one **35**

The synthesis of 6,7-difluoro-3-nitro-4-hydroxy-2-quinolone **40** and 2,3,4-trichloro-6,7-difluoroquinolone **41** from 4,5-difluoro-2-nitrobenzoic acid **36a** is shown in Scheme 15. Diester **37** has been transformed smoothly into 4-hydroxyquinolone **38a** due to reductive cyclization proceeding in basic media in the presence of sodium borohydride. Diethyl 4,5-difluoro-2-nitrobenzoyl malonate **37** on treatment with *p*-toluolsulfonic acid affords ethyl 3,4-difluoro-2-nitrobenzoyl acetate **39**. Reductive cyclization of **39** was shown to take place in case of catalytic hydrogenation of the nitro group on Pd/C in ethanol, thus enabling one to obtain 6,7-difluoro-4-hydroxyquinolin-2(*1H*)-one **38b** in high yield. Decarboxylation of **38a** also affords 4-hydroxyquinolin-2(*1H*)-one **38b**. Compound **38b** can be nitrated into derivative **40**, followed by treatment of the latter with $POCl_3$ to form quinoline **41** [24]. In addition to condensation process, the reaction of **36b** with α,β-unsaturated esters (dimethyl fumarate and diethyl maleate) is accompanied by participation of the nitro group and desulfonisation leading to **42a**; finally displacement of fluorine atom and reduction of the N-oxide moiety afford a mixture of **42b** and **42b** in the ratio 1:2 [25].



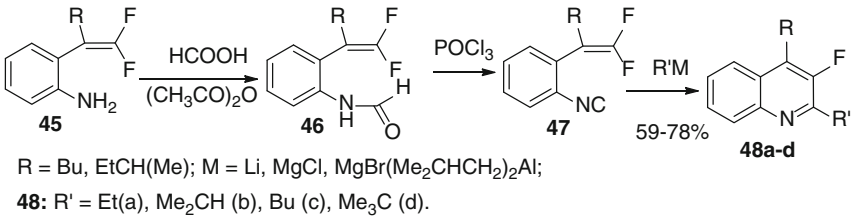
Scheme 15 Synthesis of 2,3,4-trichloroquinoline **41**

A convenient synthetic route to 3-fluoroquinolines **44** which exploits the organosilane-promoted Friedlander reaction of aromatic α-fluoroketones **43** has been suggested (Scheme 16) [26].



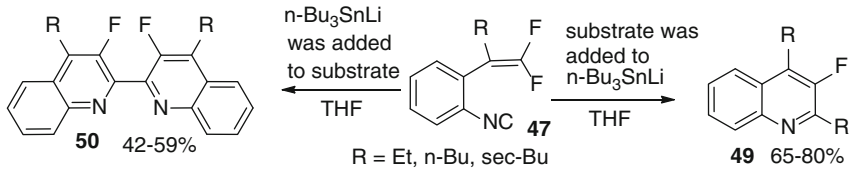
Scheme 16 Synthesis of 2,4-diarylquinoline **44**

To obtain quinolines bearing fluorine atoms in the pyridine ring, ***cyclizations of fluorinated ortho-vinylphenylnitriles and isonitriles*** proved to be an effective approach. Indeed, 3-fluoroquinolines **48a–d** have been obtained by cyclocondensation of organometallic reagents with 2-(2,2-difluorovinyl)phenyl substituted isonitriles **47** (Scheme 17). 2-(2,2-Difluorovinyl)anilines **45**, derived from the reaction of 2,2,2-trifluoroethyl tosylate, butyl magnesium salt of 2-iodoaniline, butyl lithium and trialkylborane, have been transformed into isonitriles **47** [27, 28].



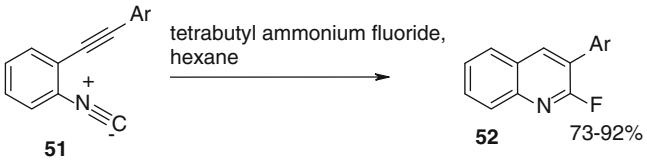
Scheme 17 Synthesis of 3-fluoroquinolines **48**

2,4-Disubstituted 3-fluoroquinolines **49** and 4,4′-disubstituted 3,3′-difluoro-2,2′-bisquinolines **50** have been obtained from *ortho*-isocyano substituted *β,*β-difluorostyrenes **47** through their reduction with tributylstannyl lithium, and intra-molecular arrack at the carbon of the isocyano group (Scheme 18) [29]. It is interesting to note that when compound **47** is added to a solution of n-Bu_3SnLi only quinoline **49** is formed, while the opposite order of mixing of reactants leads to bisquinoline **50** as the main product.



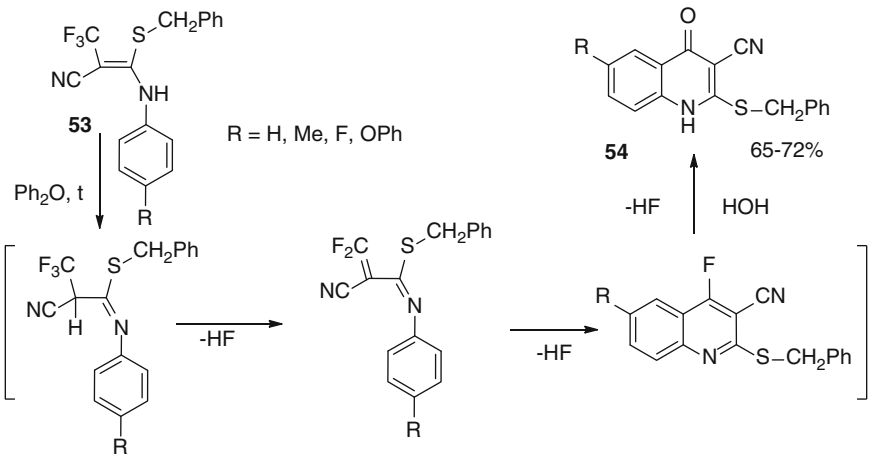
Scheme 18 Synthesis of 3-fluoroquinolines **49**

The intramolecular cyclization takes place on treatment of *ortho*-alkynyl substituted aryl isocyanides **51** with tetrabutyl ammonium fluoride affording the corresponding 2-fluorinated quinolines **52** in good to excellent yields (Scheme 19) [30].



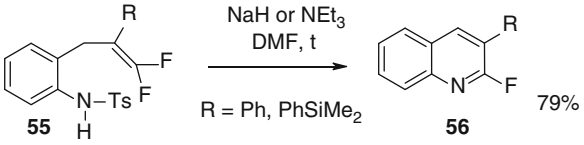
Scheme 19 Synthesis of 2-fluoroquinolines **52**

2-Benzylthio-3-cyanoquinolines bearing fluorine atom in position 4 have been obtained on heating of functionalized N-vinyl anilines **53**; the latter are prepared by condensation of the corresponding α-fluorine-containing vinyl sulfides with anilines (Scheme 20) [31]. Alkaline hydrolysis of the reaction products afforded the corresponding 3-cyanoquinolin-4-ones **54**.



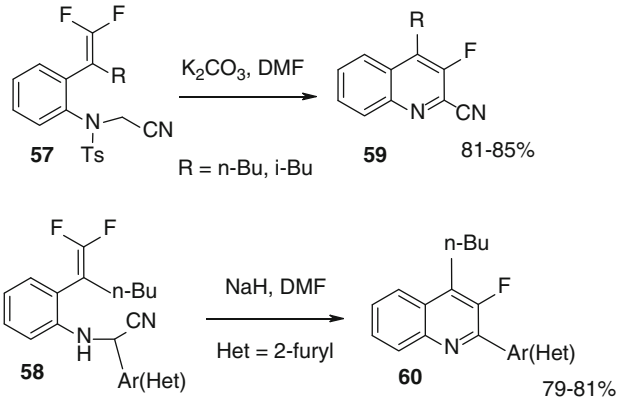
Scheme 20 Condensation of α-fluorine-containing vinyl sulfides with anilines

The intramolecular cyclization takes place smoothly in the 6-*endo-trig* fashion on treatment with a base (sodium hydride or triethylamine) of *N*-[*ortho*-(3,3-difluoroallyl)phenyl] substituted *p*-toluenesulfonamides **55**. As a result 2-fluoroquinolines **56** are formed in high yields (Scheme 21) [32].



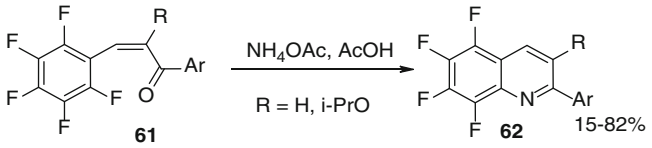
Scheme 21 Synthesis of 2-fluoroquinoline **56**

Intramolecular cyclization of *ortho*-cyanomethylamino-*β,β*-difluorostyrenes **57** and **58** have been observed to occur in the presence of K_2CO_3 or NaH to afford 2-substituted 3-fluoroquinolines **59, 60** (Scheme 22) [33, 34].



Scheme 22 Synthesis of 3-fluoroquinolines **59**, **60**

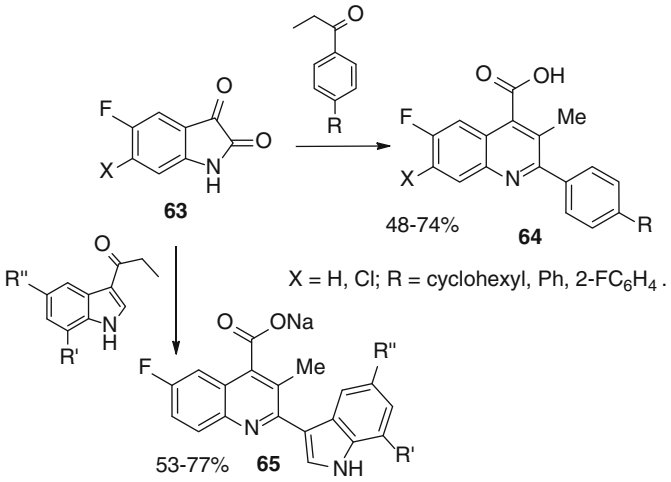
Also 2,3,4,5,6-pentafluorophenyl substituted chalcones **61** undergo the intramolecular cyclization into 5,6,7,8-tetrafluoroquinolines **62** on treatment with ammonium acetate in acetic acid (Scheme 23) [35].



61 **62**

Scheme 23 Synthesis of 5,6,7,8-tetrafluoroquinolines **62**

Fluorinated isatines appear to be important intermediates in the synthesis of fluoroquinolines. Indeed, 2-aryl- and 2-heteryl substituted derivatives **64, 65** were obtained from 5-fluoroisatines **63** (Scheme 24) [36].

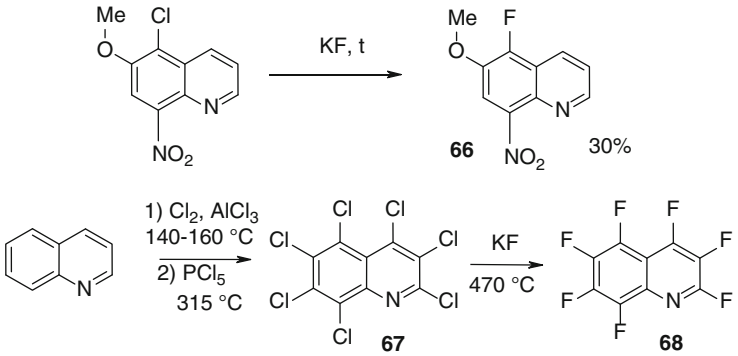


63 **64** **65**

Scheme 24 Reactions of 5-fluoroisatines **63**

Nucleophilic displacement of chlorine atoms with the fluoride ion is undoubtedly one of the most common methods to obtain fluorinated quinolines from their chloro analogues. For instance, treatment of perchloroquinoline with cesium fluoride in DMSO at 100° has resulted in a mixture of 2-fluoro-3,4,5,6,7,8-hexachloroquinoline, 4-fluoro-2,3,5,6,7,8-hexachloroquinoline, 4,5-difluoro-2,3,6,7,8-pentachloroquinoline and 2,4-difluoro-3,5,6,7,8-penta-chloroquinoline. In similar way 3,5,6,7,8-pentachloroquinoline was transformed into a mixture of 5-fluoro-3,6,7,8-tetrachloroquinoline,7-fluoro-3,5,6,8-tetrachloroquinoline,6,7-difluoro-3,5,8-trichloroquinoline and 5,7-difluoro-3,6,8-trichloroquinoline. Nucleophilic fluoro-dechlorination of 5,6,7,8-tetrachloroquinoline gave a mixture of

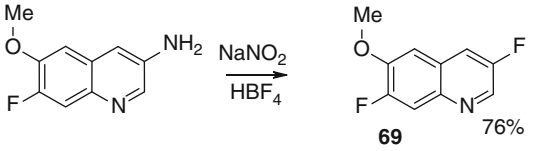
7-fluoro-5,6,8-trichloroquinoline, 5-fluoro-6,7,8-trichloroquinoline and 6,7-difluoro-5,8-dichloroquinoline, while 7-fluoro-4-chloroquinoline was obtained as the only product from 4,7-dichloroquinoline [37]. Also 5-fluoro-6-methoxy-8-nitroquinoline **66** was obtained by replacement of chlorine atom in 5-chloro-6-methoxy-8-nitroquinoline (Scheme 25) [9], and potassium fluoride proved to be an appropriate reagent to cause full transformation of heptachloroquinoline **67** into heptafluoroquinoline **68** (Scheme 25) [38].



Scheme 25 Nucleophilic displacement of chlorine atoms with the fluoride ion

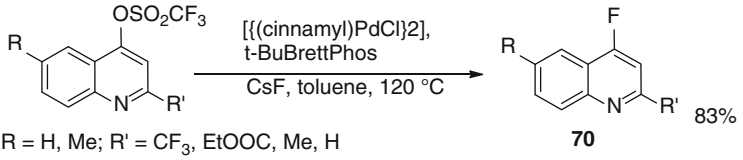
Heating of 4-chloroquinolines with potassium fluoride (tetrabutylphosphonium fluoride) in DMSO affords only low yields of the corresponding 4-fluoro compounds [39, 40], however use of microwave irradiation (300 W) results in the formation of 2-fluoroquinolines from 2-chloroquinolines in 60–62 % yields [41].

Replacement of the diaza group with the fluoride ion, the method which is widely used in heterocyclic chemistry, has also found its application to obtain fluoroquinolines, as illustrated, for instance, by the syntheses of 3-fluoroquinoline from 3-aminoquinoline [42] and 3,5-difluoroquinoline from 3-fluoro-5-aminoquinoline, respectively [43]. 3,7-Difluoro-6-methoxyquinoline **69**, one of the key intermediates for the synthesis of antibacterial agents, has been obtained by the reaction of 3-amino-7-fluoro-6-methoxyquinoline with sodium nitrite in the presence of hydrogen borotetrafluoride (Scheme 26) [44].



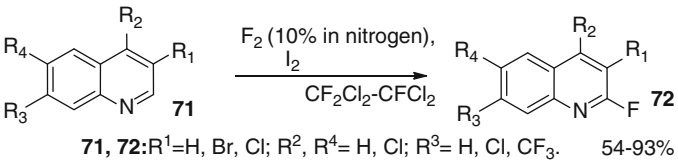
Scheme 26 Synthesis of 3,7-difluoroquinoline **69**

Replacement of other groups with the fluoride ion can be illustrated by the palladium-catalyzed C-F bond formation affording a number of 4-fluoro-quinolines **70** from the corresponding 4-susbstituted quinolines bearing OTf group (Scheme 27) [45].



Scheme 27 Synthesis of 4-fluoroquinoline **70**

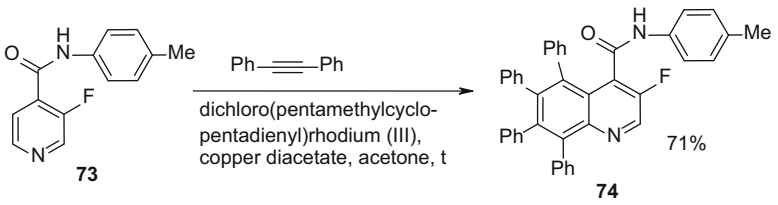
The direct fluorination of quinolines has a limited use since a low selectivity of the reaction, and also due to technological and ecological difficulties. However, there are several examples of selective syntheses of monofluorinated quinolines. For instance, 2-fluoroquinolines **72** were obtained by interacting quinoline **71** with elementary fluorine in the presence of I_2 [46], yields proved to be in the range of 54–93 %, ratio I_2-quinoline **71** was 1:1, and ratio F_2-quinoline **71** was 2:1 (Scheme 28). To obtain 2-fluoro-4-chloroquinoline and 2-fluoro-4,7-dichloroquinoline the reaction was carried out in the presence of triethylamine.



Scheme 28 The direct fluorination of quinolines

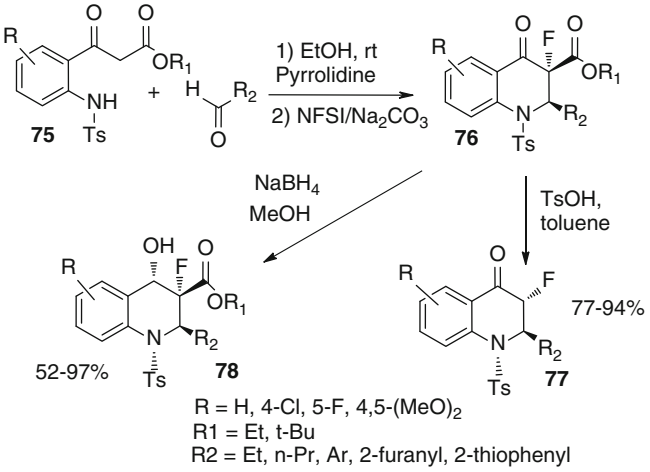
Also direct fluorination of quinoline **71a** under acidic conditions has been reported [47, 48]. Electrophilic substitution in the series of quinolines proceeds not selectively, therefore a mixture of 5-fluoroquinoline**,** 6-fluoroquinoline, 8-fluoroquinoline and 5,8-difluoroquinoline is formed. 6-Methoxyquinoline was shown to undergo direct fluorination at the position 5, and 5,5-difluoroquinolin-6-one was isolated in addition to the main 5-fluoro-6-methoxy compound [48]. 5-Fluoro-6-methoxy-8-nitroquinoline was obtained by the reaction of 6-methoxy-8-nitroquinoline with N-fluorobenzolsulphonamide [9]**.**

***Other methods*.** An unusual example of the synthesis of 3-fluoroquinoline system **74** through annelation of the benzene ring has been reported to occur in the Rh(III)-catalyzed oxidative condensation of 3-fluoropyridine **73** with two molecules of diphenyl acetylene [49] (Scheme 29).



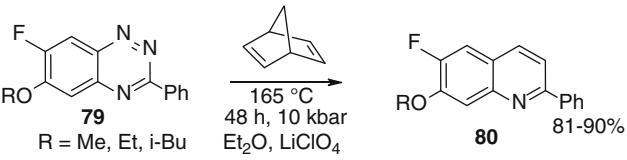
Scheme 29 Synthesis of 3-fluoroquinoline **74**

Stereoselective multi-steps synthesis of fluorinated 2,3-dihydroquinolin-4(1H)-ones proceeding as a one-pot transformation has been described [50]. The Ts-protected *β*-(2-anilino)-*β*-ketoesters **75** are capable of reacting with a variety of aldehydes under mild conditions to form fluorinated quinolines **76** in good yields (up to 98 %) and high diastereo selectivities (*dr* up to 99:1) (Scheme 30). The compounds **76** are considered as versatile synthetic intermediates, and, indeed, they can be transformed into functionalized heterocyclic derivatives. For example, decarboxylation of compounds **76** results in the formation of 3-fluoroquinolines **77**, while reduction with $NaBH_4$ affords *α*-fluoro-*β*-hydroxy esters **78**.



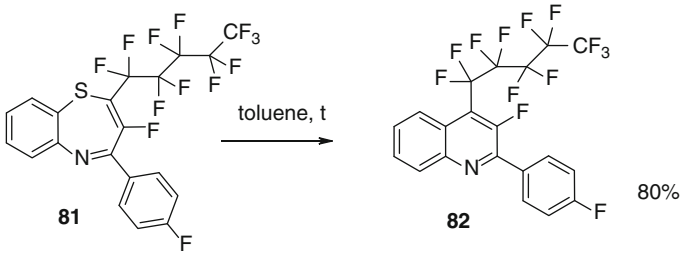
Scheme 30 Formation of compounds **77**, **78**

2-Phenyl-6-fluoroquinoline **80** has been obtained through the cycloaddition reaction of bicyclo[2.2.1]heptadiene on 1,2,4-benzotriazine **79**, taking place under high pressure conditions (Scheme 31) [51].



Scheme 31 Transformation of benzotriazine **79** into quinolone **80**

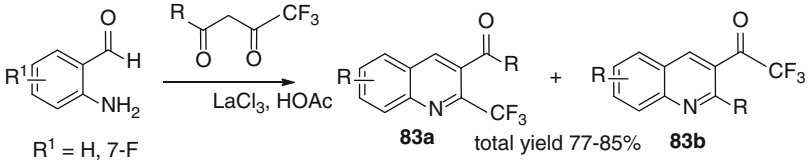
Ring transformation of the thiazepine ring in compound **81** bearing fluorine atom and perfluoroalkyl substituent into the pyridine one enabled to obtain the corresponding 3-fluoroquinoline derivative **82** (Scheme 32) [52].



Scheme 32 Synthesis of 3-fluoroquinoline **82**

Synthetic methods leading to **quinolines bearing the trifluoromethyl group** in the benzene ring are similar in many respects to those which are applied in the chemistry of fluoroquinolines, containing fluorine atoms in the benzene ring. As for quinolines containing the trifluoromethyl group in the pyridine ring, this series of fluorinated quinolines has been discussed in detail in the book [53]. Some recent examples are given below.

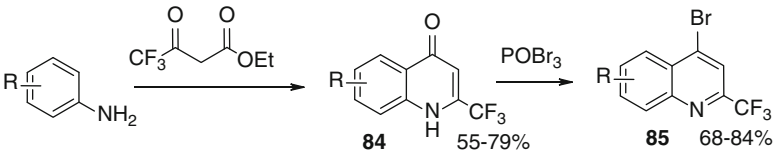
Various synthetic approaches to ***2-(trifluoromethyl)quinolines*** are based on use of the trifluoromethyl-containing reagents. In particular, 2-aminoaryl aldehydes (ketones) or *ortho*-vinyl substituted anilines are appropriate starting materials to be condensed with readily available trifluoromethyl 1,3-diketones or aldehyde hydrates respectively. For instance, the regioselective Friedlaender reaction of unsymmetrical trifluoromethyl 1,3-diketones with 2-aminoaryl aldehydes appears to be an efficient way to 2-trifluoromethylquinolines **83a** and **83b** (Scheme 33) [54].



83a/83b R = Ph 100:0, R = 2-thienyl 100:0 R = Me 89:11, R = naphthyl 100:0, R = t-Bu 100:0

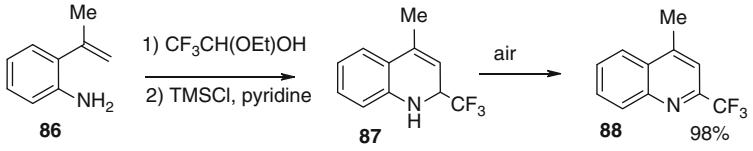
Scheme 33 Reaction of trifluoromethyl 1,3-diketones with 2-aminoaryl aldehydes

The acid-catalyzed condensation of anilines with ethyl 4,4,4-trifluoro acetoacetate affords 1,4-dihydro-2-trifluoromethyl-4H-4-quinolinones, which can easily be converted into 4-bromo-2-(trifluoromethyl)quinolines (Scheme 34) [55].



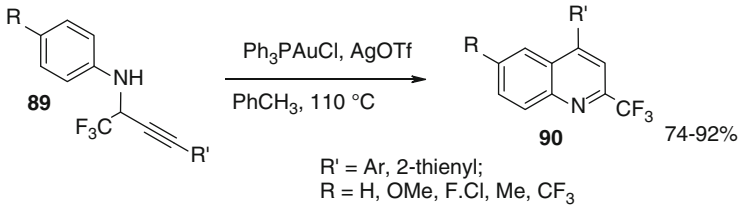
Scheme 34 Synthesis of 2-(trifluoromethyl)quinolones **85**

Also 2-(trifluoro-methyl)-4-methylquinoline **88** has been obtained through intermediacy of the corresponding imine derived from the reaction of *ortho*-vinylaniline **86** with perfluorinated carbonyl compounds taken in the forms of semiacetals or aldehyde hydrates (Scheme 35) [56].



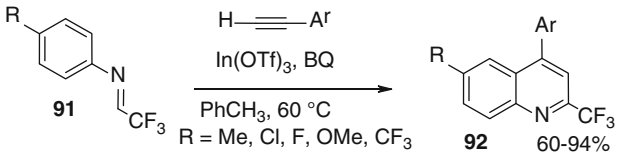
Scheme 35 Synthesis of 2-(trifluoromethyl)quinolone **88**

Cyclizations of alkynyl derivatives proved to be a synthetically convenient way to 2-(trifluoromethyl)quinolines. Indeed, the intramolecular cyclization of N-(α-trifluoromethyl)propargyl anilines **89** takes place with the gold(I) catalyst under extremely mild conditions to afford 2-trifluoromethylquinolines **90** (Scheme 36). The reaction mechanism has been suggested to involve cyclization and oxidation steps [57].



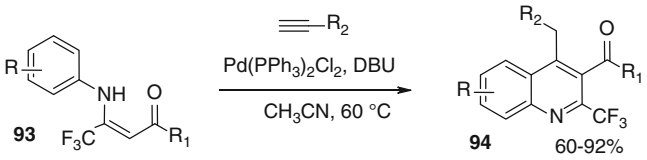
Scheme 36 Synthesis of 2-(trifluoromethyl)quinolones **90**

Also the indium(III)-catalyzed Diels-Alder reaction of N-aryl trifluoroethylimine **91** with a variety of readily available alkynes affords the corresponding 2-trifluoromethyl-4-arylquinolines **92** (Scheme 37) [58].



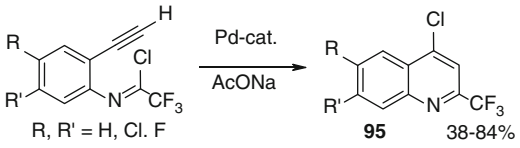
Scheme 37 Synthesis of 2-(trifluoromethyl)quinolones **92**

Rapid method to prepare 3,4-disubstituted 2-trifluoromethylquinolines **94** by a palladium catalyzed tandem Sonogashira-alkyne carbocyclization of β-trifluoromethyl β-enaminoketones **93** with arynes has been suggested (Scheme 38) [59].



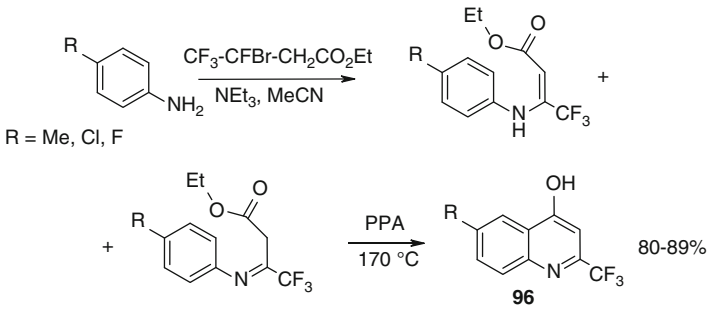
Scheme 38 Synthesis of 2-(trifluoromethyl)quinolones **94**

4-Chloro-2-trifluoromethyl quinolines **95** can be obtained from the corresponding N-aryl trifluoroacetimidoyl chlorides through the Rh(I)-catalyzed intramolecular cyclizations with the alkyne moieties (Scheme 39) [60, 61].



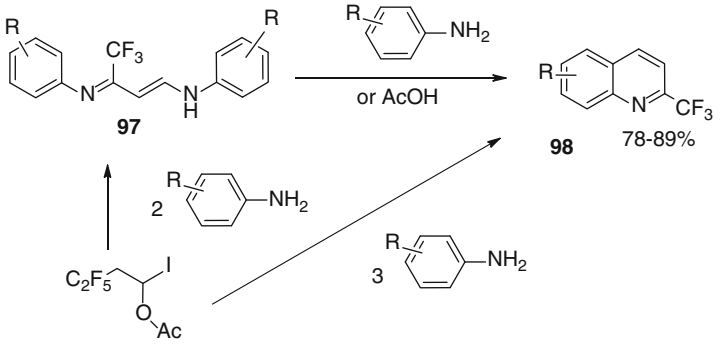
Scheme 39 Synthesis of 2-(trifluoromethyl)quinolones **95**

Treatment of ethyl 2,2-dihydrotrifluoropropionate with aromatic amines in acetonitrile at 70 °C in the presence of triethylamine affords a mixture of the corresponding enamines and imines, which undergoes cyclization on heating in polyphosphoric acid (PPA) at 170 °C to give 2-trifluoromethyl-4-hydroxyquinoline in a good yield (Scheme 40) [62].

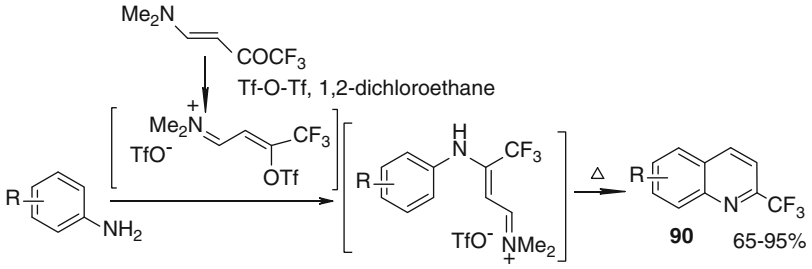


Scheme 40 Synthesis of 2-(trifluoromethyl)quinolones **96**

2-Trifluoromethylquinolines **98** were obtained by condensation of arylamines with fluoroalkyl gem-iodoacetoxy derivative, and the intermediate 1,5-diaryl-2-trifluoromethyl-1,5-diazapentadiene **97** was isolated (Scheme 41) [63]. Use of 3-trifloxy-3-trifluoromethyl propeniminium triflate for the synthesis of 2-trifluoromethylquinolines **90** has been discussed (Scheme 42) [64].

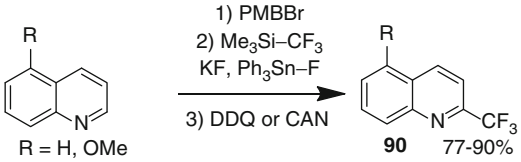


Scheme 41 Synthesis of 2-(trifluoromethyl)quinolones **98**



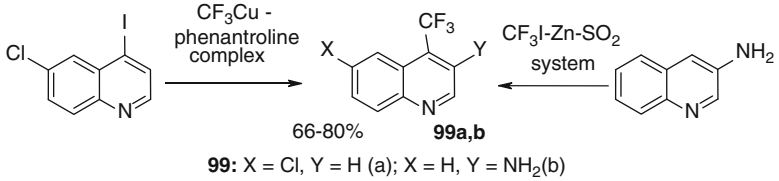
Scheme 42 Synthesis of 2-(trifluoromethyl)quinolones **90**

A three-step procedure for direct trifluoromethylation of quinolines by using the oxidative version of nucleophilic substitution of hydrogen in the pyridine ring by CF_3^- carbanion has recently been advanced (Scheme 43) [65]. The initial step in this process is addition of the CF_3^- carbanion (generated from Me_3SiCF_3 on treatment with KF in the presence of Ph_3SnF as a catalyst), to N-alkylquinolinium salts, resulting in relatively stable 2-trifluoromethyl-1,2-dihydroquinolines. Deprotection of the N-*para*-methoxybenzyl substituent and aromatization of the dihydropyridine ring on treatment with CAN [cerium(IV)ammonium nitrate] provides quinolines bearing CF_3 group in position 2.



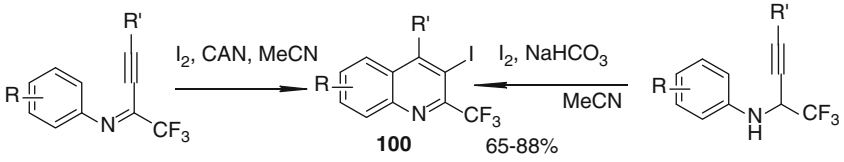
Scheme 43 Another approach to 2-(trifluoromethyl)quinolones **90**

The trifluoromethylation of 4-iodo-7-chloroquinoline by action of trifluoromethylcopper(I)phenanthroline complex represents a modern way to 4-trifluoromethyl-7-chloroquinoline **99a** (Scheme 44) [66]. 4-Trifluoromethyl substituted 3-aminoquinolines **99b** have also been obtained by the reaction of 3-aminoquinoline with trifluoroiodomethane-zinc-sulfur dioxide system (Scheme 44) [67].



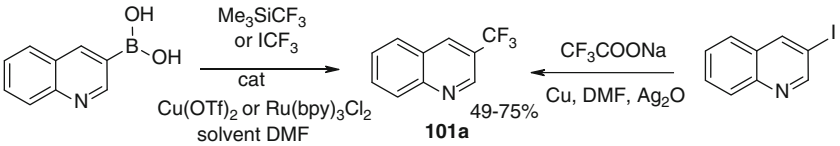
Scheme 44 Synthesis of 4-(trifluoromethyl)quinolones **99**

A series of highly substituted 2-trifluoromethyl-3-iodoquinolines **100** have been prepared in good to excellent yields under rather mild reaction conditions according to the method which involves iodocyclization of trifluoromethyl propargyl imines with I_2-CAN or I_2 and ICl. The starting trifluoromethyl propargyl amines can be obtained by means of the Sonogashira cross-coupling reaction of the corresponding readily accessible imidoyl iodides with alkynes followed by reduction with $NaBH_3CN$ (Scheme 45) [68].



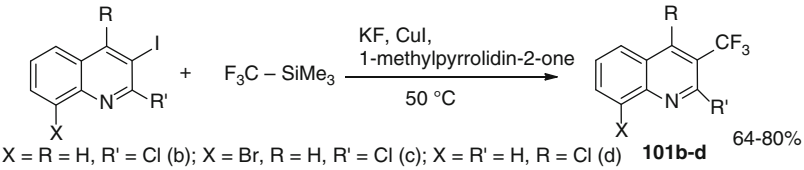
Scheme 45 Synthesis of 2-(trifluoromethyl)quinolones **100**

During the last decade the metal-catalyzed cross-coupling reactions proved to be one of the main methods for obtaining of ***3-(trifluoromethyl)quinolines***. For instance, the copper-catalyzed oxidative trifluoromethylation [Me_3SiCF_3, cat. $Cu(OTf)_2$] of quinolin-3-boronic acid results in the formation of quinoline **101** in 49 % yield (Scheme 46) [69]. Trifluoromethylation of quinolin-3-boronic acid with CF_3I leads to the same compound **101** in 67 % yield, as it has recently been described [70]. The ligand-free trifluoromethylation of quinolin3-boronic acid in the presence of the catalytic system $[Ph_2SCF_3]^+[OTf]^-/Cu(0)$ provides 75 % yield of compound **101** [71], while the copper-catalyzed trifluoromethylation of **100** with the Togni's reagent results in 3-trifluoromethylquinoline **101** in 53 % yield [72]. Also the ligand-free copper-catalyzed decarboxylative trifluoromethylation of 3-iodoquinoline with sodium trifluoroacetate using Ag_2O as a promoter has been reported (Scheme 46) [73].



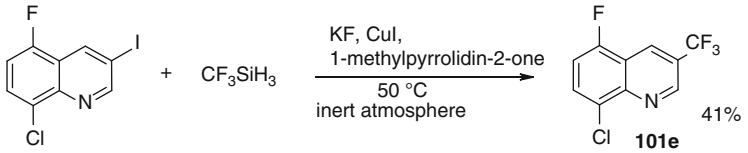
Scheme 46 Synthesis of 3-(trifluoromethyl)quinolone **101a**

2-Chloro- and 4-chloro-3-(trifluoromethyl)-quinolines were obtained from the corresponding iodoquinolines by action of Me_3SiCF_3 (Scheme 47) [74].



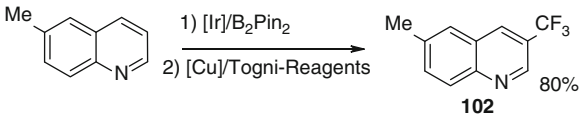
Scheme 47 Synthesis of 3-(trifluoromethyl)quinolone **101b-d**

The reaction of 3-iodo-5-fluoro-8-chloroquinoline with CF_3SiH_3, KF, and CuI proceeds rather smoothly in 1-methyl-pyrrolidin-2-one, leading to the formation of 3-trifluoromethyl-5-fluoro-8-chloroquinoline **101e** in 41 % yield (Scheme 48) [43].



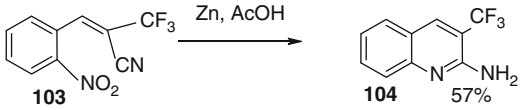
Scheme 48 Synthesis of 3-(trifluoromethyl)quinolone **101e**

2-Propyl-3-iodoquinoline has been transformed into 2-propyl-3-(trifluoromethyl) quinoline by action of $ClCF_2CO_2Me$, CuI, and KF on reflux in DMF [75]. An interesting example of highly selective trifluoromethylation of 6-methylquinoline by means of the iridium-catalyzed reaction is presented in Scheme 49 [76].



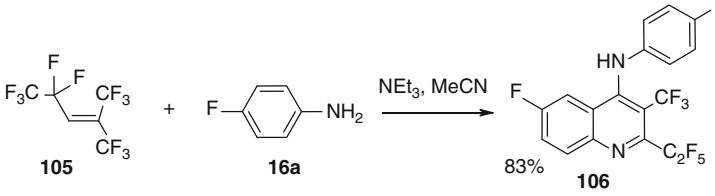
Scheme 49 Synthesis of 3-(trifluoromethyl)quinolone **102**

Another approach to 3-(trifluoromethyl)quinolines is based on cyclizations of trifluoromethyl-containing intermediates, as illustrated, for instance, by the synthesis of 2-amino-3-(trifluoromethyl)quinoline **103** by means of the Leimgruber-Batcho reaction (Scheme 50) [77].



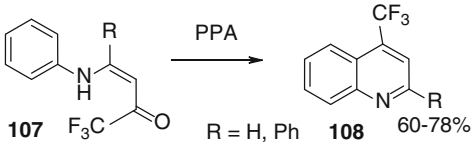
Scheme 50 Synthesis of 2-amino-3-(trifluoromethyl)quinoline **103**

The reaction of perfluoro-2-methylpent-2-ene **105** with 4-fluoroaniline in the presence of Et_3N illustrates one more approach to 3-trifluoromethylquinoline derivatives, in particular to the compound **106** (Scheme 51) [78].



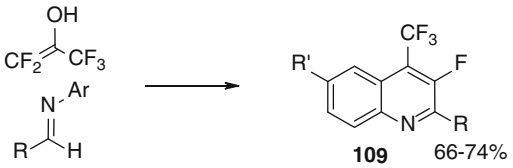
Scheme 51 Synthesis of 3-(trifluoromethyl)quinoline **106**

The synthesis of ***4-(trifluoromethyl)quinolines*** **108** can be realized through the cyclocondensation of oxotrifluoroalkenyl anilines **107** (Scheme 52) [79, 80].



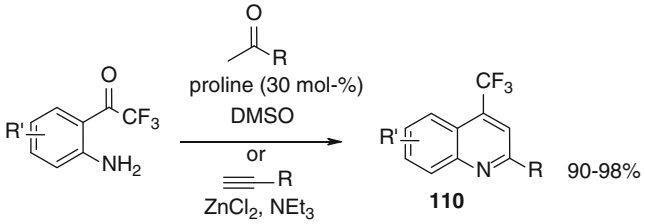
Scheme 52 Synthesis of 4-(trifluoromethyl)quinoline **108**

One-pot conversion of pentafluoropropen-2-ol into quinolines **109** involves the sequence of the Mannich addition to aromatic aldimines followed by the Friedel-Crafts cyclization and aromatization (Scheme 53) [81].



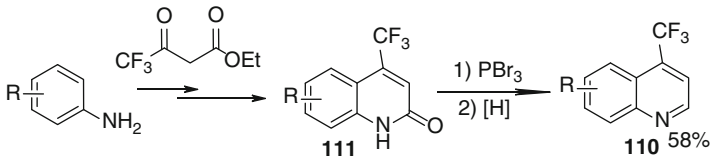
Scheme 53 Synthesis of 4-(trifluoromethyl)quinoline **109**

The proline-catalyzed Friedlander reaction has been used for the synthesis of 2-substituted 4-trifluoromethyl quinolines **110** (Scheme 54) [82]. Compounds **110** have also been obtained through the Zn(II)-mediated alkynylation-cyclization of *o*-trifluoroacetyl anilines (Scheme 54) [83].



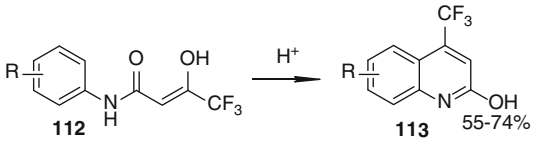
Scheme 54 Synthesis of 4-(trifluoromethyl)quinolines **110**

Condensation of anilines with ethyl 4,4,4-trifluoroacetoacetate have been established to give the corresponding 4,4,4-trifluoro-3-oxobutane substituted anilides, precursors in the synthesis of 4-(trifluoro-methyl)-2-quinolinones **111** [84]. Heating of these compounds with phosphoryl tribromide affords 2-bromo-4-(trifluoro-methyl)quinolines which can be converted into 4-(trifluoromethyl) quinolines **110** by reductive debromination (Scheme 55) [85].



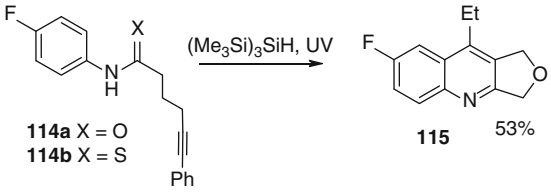
Scheme 55 Another approach to 4-(trifluoromethyl)quinolines **110**

4-Fluoroalkyl-2-quinolinols **113** were obtained regioselectively in moderate to good yields by acid-assisted intramolecular ring-closure reaction of the corresponding N-aryl-3-oxa-polyfluoroalkanamides **112** prepared from 2,2-dihydropolyfluoroalkanoic acids (Scheme 56) [86].



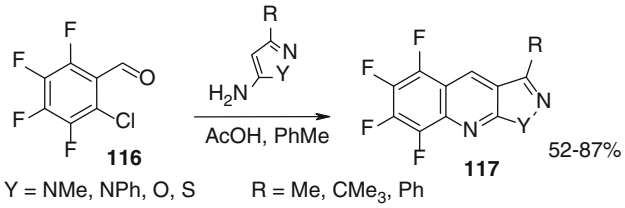
Scheme 56 Synthesis of 4-(trifluoromethyl)quinolines **113**

New approaches to **annelated quinolines** have also been developed, as illustrated by the synthesis of fluorinated tetrahydroquinoline **115** through the radical cyclization of thioamide **114b** by action of 4 equivalents $(Me_3Si)_3SiH$ in benzene on irradiation with UV light. Tioamide **114b** is easily accessible through thionation of amide **114a** with Louwesson's reagent (Scheme 57) [87].



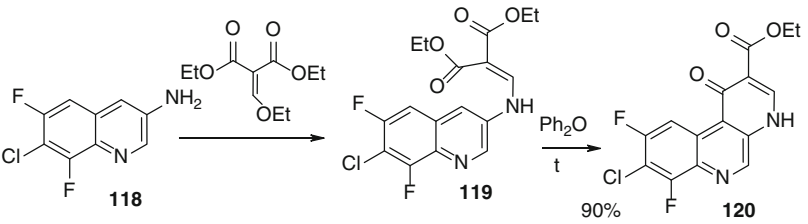
Scheme 57 Synthesis of compound **115**

A number of fluorinated azolo[*b*]quinolines **117** have been obtained by cyclocondensation of *ortho*-chlorobenzaldehyde **116** with 5-amino-1,2-azoles (Scheme 58) [88].



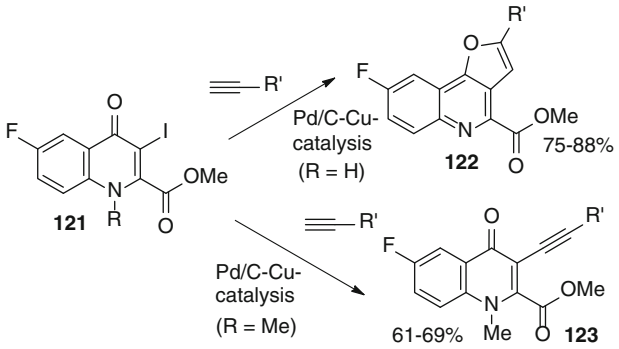
Scheme 58 Condensation of **116** with 5-amino-1,2-azoles

Tricyclic system of benzo[*f*][1,7]naphthyridone **120** was obtained through the Gould-Jacobs cyclization of enamine **119**, derived from 3-amino-6,8-difluoro-7-chloroquinoline **118** and diethyl ethoxymethylene malonate. The cyclization was carried out in diphenyl ether at 240 °C, providing a good yield of compound **120** (Scheme 59) [89].



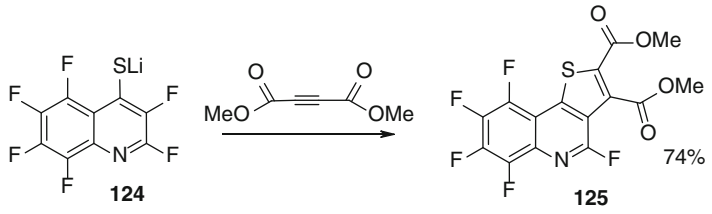
Scheme 59 Synthesis of compound **120**

The Pd/C-Cu catalyzed coupling of 3-iodo-1H-6-fluoroquinolin-4-ones **121** with the series of terminal alkynes proceeds regioselectively and results in the formation of furo[3,2-*c*]quinolines **122** in high yields (Scheme 60). 3-Alkynyl-quinolines **123** were isolated in those cases where the NH hydrogen in the starting 3-iodo-1H-quinolin-4-one **121** was replaced with the methyl group [90].



Scheme 60 Synthesis of compounds **122**, **123**

The action of dimethylacetylenedicarboxylate (DMAD) on lithium salt of 2,3,4,5,7,8-hexafluoro-4-quinolinthiole **124** leads to 74 % of 4,6,7,8,9-pentafluoro-thieno[3,2-*c*]quinoline **125** and 13 % dimethyl 1-(2,3,5,6,7,8-hexafluoro-4-quinolyl-thio)ethen-1,2-dicarboxylate (Scheme 61) [91].



Scheme 61 Synthesis of compound **125**

The structure of fluorine-containing quinolines has been elucidated in crystals and solutions. The data on X-ray crystallography analysis of a number of mono- and difluoroquinolines are available in the literature [47, 92]. In order to elucidate the phenomenon of π-stacking for polyfluoroaromatic rings the X-ray studies of some polifluoroquinolines have been carried out [93]. Main types of internal motives in organisation of these systems appear to be associated with π…π polyfluoroarene…poly-fluoroarene, polyfluoroarene…heteroarene, heteroarene…heteroarene interactions.

Fluorinated quinolines have been studied in detail by calculation methods. In particular, the quantum-chemical calculations of the series of difluoroquinolines have recently been performed [94]. The negative charge of the nitrogen atom extends also on fluorine atoms, because the nitrogen atom exhibits both σ- and π-electron withdrawing nature, while a fluorine atom is a strong σ-acceptor, but at the same it has a π-donative character. Charges on carbon atoms of the pyridine ring are in accordance with π-electron withdrawing effect of the nitrogen atom. Non-substituted carbon atoms of the benzene ring are charged negatively due to π-electron donating effect of fluorine atoms. 5,7-Difluoroquinoline has the lowest energy due to the fact that π-electron donating fluorine atoms are conjugated to the nitrogen atom. 6,8-Difluoroquinoline has a little higher energy, since the arrangement of fluorine atoms in this compound is similar to 5,7-difluoroquinoline, however both fluorine atoms aren't conjugated to the pyridine nitrogen atom. Besides that, a negative charge on nitrogen atom in 5,7-difluoriquinoline exceeds that in 6,8-difluoroquinoline. 6,7-Difluoroquinoline and 5,8-difluoroquinoline have a higher energy, than 5,7-difluoroquinoline and 6,8-difluoroquinoline, since effects of two *meta*-orientated fluorine atoms are in accord with each other.

^{1}H, ^{13}C and ^{19}F NMR spectra for the series of fluoroquinolines have been analysed. Incorporation of a fluorine into the pyridine ring of quinolines proved to cause the same changes in chemical shifts of signals, as in case of pyridine. Indeed, proton H^3 in 2-fluoroquinoline resonates in a higher field relative to the parent quinoline, while proton H^4 – in a lower field. Incorporation of fluorine into the benzene ring of quinolines results in upfield shifts for the resonance signals of H^6, H^7, H^8 of 5-fluoroquinoline and for H^5, H^7 signals in case of 8-fluoroquinoline (Fig. 1) [95]. It should be noted that coupling constant values $^{4}J(H^4,F)$ proved to exceed $^{3}J(H^3,F)$. Also ^{1}H NMR characteristics for quinolines bearing one or two fluorine atoms in the benzene ring have been established [47, 94].

The main features of the ^{13}C NMR spectra of 2-fluoroquinolines associated with the presence of a fluorine atom are similar to those of 2-fluoropyridines. Incorporation of a fluorine atom into positions 5 or 8 of the benzene ring results in upfield shifts of C^6-C^8 (or C^5-C^7) carbon resonances; the biggest shift value is observed for the C^6 signal in case of 5-fluoroquinoline and for C^7 resonance signal of 8-fluoroquinoline (Fig. 1) [94]. The data of ^{13}C NMR spectroscopy for fluoroquinolines with fluorine atoms in the benzene ring are well presented [47].

The resonance signal in the ^{19}F NMR spectrum of 2-fluoroquinoline (−63 ppm) is shifted down field relative to that for 2-fluoropyridine (−68 ppm). Downfield shifts in the ^{19}F NMR spectra of 2-fluoroquinolines, containing in the pyridine or benzene rings chloro, bromo, or trifluoromethyl substituents are even bigger [46].

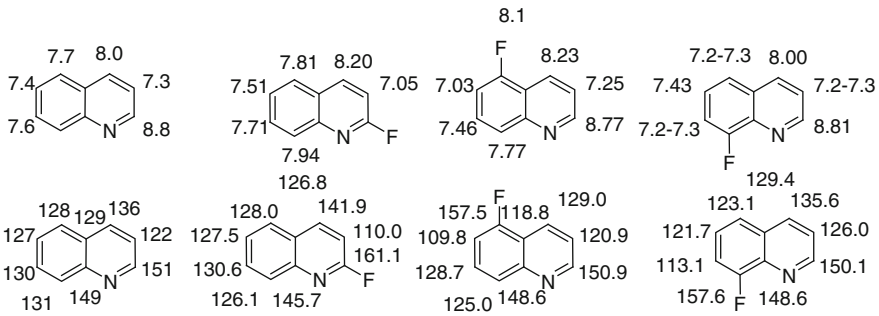


Fig. 1 NMR data of selected fluoroquinolines

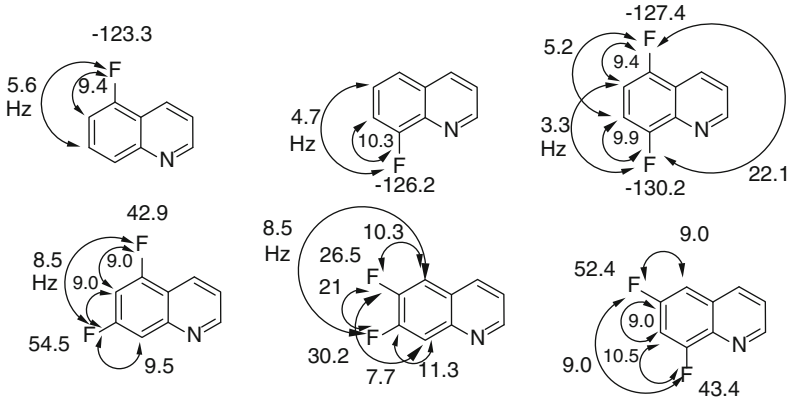


Fig. 2 Chemical shifts and $J_{F,H}$ и $J_{F,F}$ in the ^{19}F NMR spectra

The selected spectral ^{19}F NMR data for quinolines bearing one and two fluorine atoms in the benzene ring are given in Fig. 2 [47, 94]. These data illustrate mutual effects of fluorine atoms.

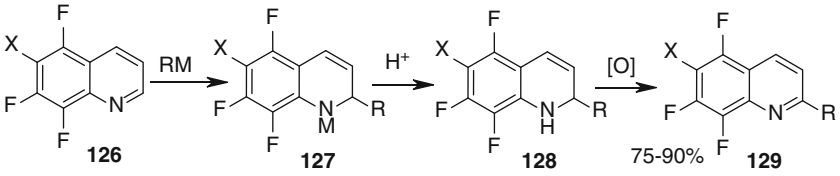
In the ^{19}F NMR spectrum of perfluoroquinoline the F^2 signal is observed in the weakest field; while coupling constants for fluorine atoms in the *peri*-position to each other have the biggest values. Also, the data of ^{19}F NMR spectroscopy are available for fluoroquinolines, bearing phosphorus groups in the benzene ring, and for 2-substituted quinolines with fluorine atoms in the benzene ring [92].

3 Chemical Properties

The quinoline system is of interest as an important building-block for the whole number of biologically active compounds; therefore development of new synthetic routes to fluorinated quinolines, capable of various transformations is a key task of heterocyclic chemistry. One of the most common approaches to functionalization of fluoroquinolines is based on their reactions with nucleophiles. In particular,

nucleophilic replacement of fluorine atoms with a variety of nucleophiles is of significant importance for synthetic use.

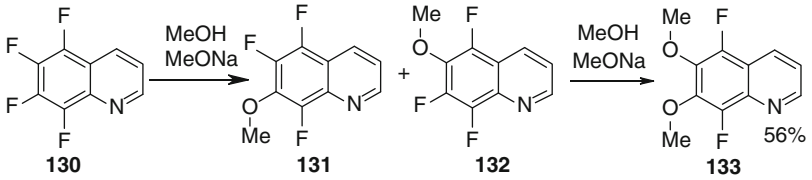
Systematic study on the problem of regioselectivity in the reactions of 6-X-5,7,8-trifluoroquinolines with nucleophiles has been carried out [92–96]. Depending on the nature of nucleophilic reagents either displacement of fluorine atoms takes place or competitive nucleophilic attack at position 2 and C-F bonds of the benzene ring has been shown to occur. Indeed, the reaction of 6-H-trifluoromethyl-5,7,8-trifluoroquinolines **126** (X=F, CF_3) **with rigid nucleophiles – organometal compounds RM** (MeLi, n-BuLi, PhLi and PhMgBr), followed by treatment with hydrochloric acid results in the formation of products of nucleophilic addition **128**. Compounds **128** are oxidized into 2-substituted 6-H-trifluoroquinolines **129** in high yields (75–90 %) using air oxygen or MnO_2 (Scheme 62) [92].



Scheme 62 Reaction of quinolines **126** with organometal compounds RM

In addition to nucleophilic substitution of hydrogen in **126**, as the main route of the reaction (leading to the S_N^H products **129**) [97–100], the second reaction pathway associated with substitution of fluorine atoms can be realized, especially with PhLi as nucleophilic reagent. Authors [92] reported that according to chromatomass spectrometry data product, in which one fluorine atom is replaced by phenyl group, was detected in reaction mixture.

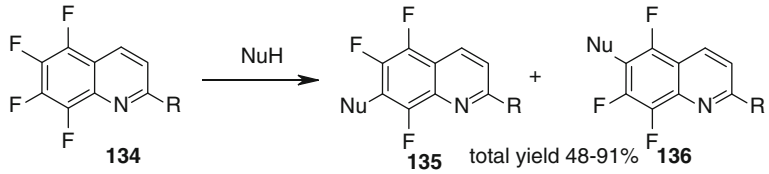
Interaction of polyfluoroquinolines with **O-nucleophiles** is illustrated by the reaction of 5,6,7,8-tetrafluoroquinoline **130** with sodium methoxide (Scheme 63) [92]. When the reaction was carried out in methanol, a mixture of 7-methoxy- and 6-methoxy derivatives **131** and **132** in the ratio 6:1 was obtained, while an excess of sodium methoxide provides a full conversion of both compounds, **131** and **132,** into 6,7-dimethoxy-5,8-difluoroquinoline **133**. The reaction of 5,6,7,8-tetrafluoroquinoline with sodium methoxide in the ratio 1:1.25, 1:1, or 1:0.5 has been established to afford 7-methoxy derivative **131** as the only product.



Scheme 63 Interaction of polyfluoroquinolines with O-nucleophiles

Treatment of 5,7-difluoroquinoline with sodium methoxide in liquid ammonia at 218–240 K results in a mixture of 5-methoxy-7-fluoroquinoline and 5-fluoro-7-methoxyquinoline. In a similar reaction of 6,7-difluoroquinoline 6-fluoro-7-methoxyquinoline and 6-methoxy-7-fluoroquinoline have been isolated. It is interesting to note that the reaction of 6,8-difluoroquinoline with sodium methoxide in liquid ammonia provides only 6-fluoro-8-methoxy derivative, while 5,8-difluoroquinoline doesn't react at all under the same reaction conditions. In case the reaction of 5,8-difluoroquinoline with sodium methoxide was carried out in DMSO at 298–378 K a mixture of 5-methoxy-8-fluoroquinoline and 5-fluoro-8-methoxyquinoline was isolated [95].

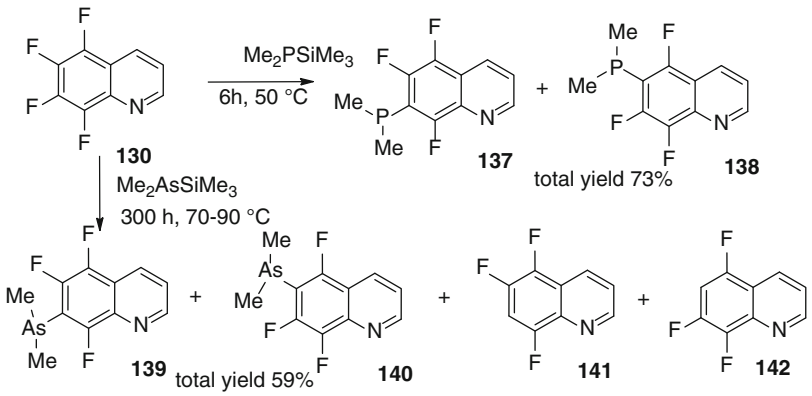
N-Nucleophiles (aqueous ammonia, piperidine, N_2H_4–H_2O in dioxane or sodium amide in liquid ammonia) react with 2-substituted 5,6,7,8-tetrafluoroqui-nolines **134** to form amino-defluorination products with substitution of F^6 and F^7 atoms **135** and **136** in the ratio from 5:1 to 3:1 (Scheme 64) [96, 101]. Interaction of N-nucleophiles with 2- or 4-methylsubstituted 5,6,7,8-tetrafluoroquinolines proceeds in a similar way.



Scheme 64 Amino-defluorination reactions of 5,6,7,8-tetrafluoroquinolines

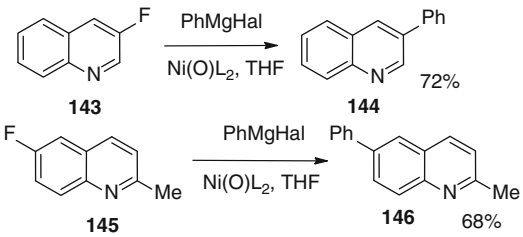
Amination of 5,7-difluoro- and 5,7,8-trifluoroquinoline, 5,7-difluoro-8-chloroquinoline and 6-trifluoromethyl-5,7,8-trifluoroquinoline leads to the formation of rather complicated mixtures of monoaminoquinolines [101]. The reaction of heptafluoroquinoline with **S-nucleophiles** (HS^-, PhS^-, MeS^-, PrS^- и $BuS)^-$ is very indicative, since it demonstrates a high regioselectivity, resulting in displacement of halogen at the position 4 [102].

When 5,6,7,8-tetrafluoroquinoline **130** reacts with P(As)-nucleophiles a mixture of two products is formed due to displacement of fluorine atoms at positions 6 and 7 [92]. Indeed, treatment of **130** with Me_2PSiMe_3 in benzene at 50 °C for 6 h gave 7-dimethylphosphano-5,6,8- and 6-dimethyl-phosphano-5,7,8-trifluoroquino-lines **137** and **138** in the ratio 4:1 (Scheme 65). The feature of the reaction of **130** with $Me_2AsSiMe_3$ is that, in addition to the expected arsines **139** and **140**, defluorination products **141** and **142** have been isolated. Preferable replacement of fluorine atoms in 6 and 7 positions indicates that, besides the ring nitrogen atom, the cooperative effect of four fluorine atoms plays an important role in stabilization of the intermediate σ-complex. Treatment of 6-trifluoromethyl-5,7,8-trifluoroquinoline or 5,7,8-trifluoroquinoline with Me_2PSiMe_3 resulted in the mixture of 7-, 5-, and 8-dimethylphosphano derivatives, while 7-dimethyl-phosphano-5,8-difluoroquinolines were transformed into 7,8-bis(dimethylphosphano)-5-fluoroquinoline [92].



Scheme 65 Reactions of quinoline **130** with P(As)-nucleophiles

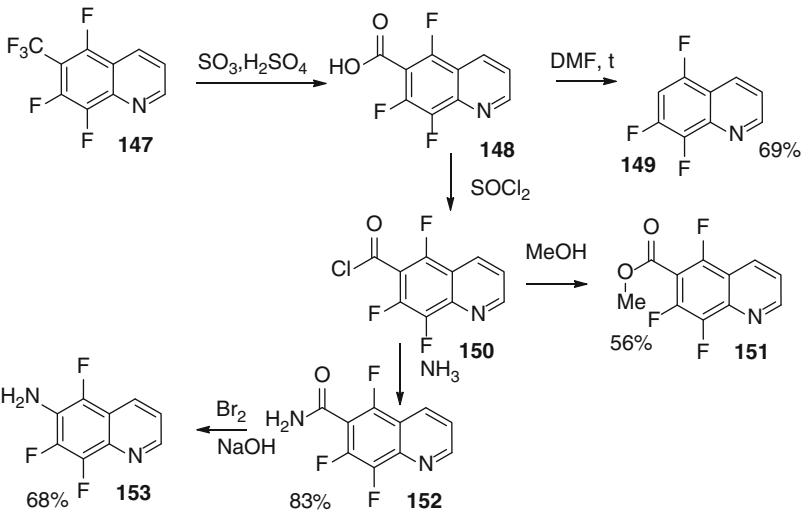
Cross-coupling reactions of fluoroquinolines is also an important synthetic tool to modify the structure of quinolines. Indeed, 3-fluoroquinolines proved to be useful intermediates in the synthesis of 3-substituted quinolines through nickel-catalyzed cross-coupling reactions [103]. For instance, 3-fluoroquinoline **143** can be transformed into 3-phenylquinoline **144** on treatment with phenyl-magnesium bromide in the presence of (1,2-*bis*-diphenylphosphoethane)nickel (II) dichloride or nickel (II) acetyl acetonate (Scheme 66) [103]. In a similar way the cross-coupling reaction of 6-fluoro-2-methylquinoline **145** leads to the formation of 6-phenyl derivative **146**.



Scheme 66 Nickel-catalyzed cross-coupling reactions

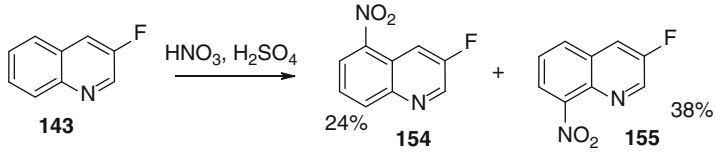
Reactions, ***not being accompanied by the displacement of fluorine atoms*** are also important for functionalization of fluorinated quinolines. For instance, 6-substituted 5,7,8-trifluoroquinolines **148–153** were obtained from 6-trifluoro-methyl-5,7,8-trifluoroquinoline **147** (Scheme 67) through hydrolysis of the CF_3 group in quinoline **147** followed by decarboxylation of 5,7,8-trifluoroquinoline-6-carboxylic acid **148** on heating in DMF [6]. From the acid **148** obtained is the acyl chloride **150**, which gives with methanol the methyl ester **151** and with ammonia – the amide of

5,7,8-trifluoroquinoline-6-carboxylic acid **152**. Involving the latter into the Hoffmann rearrangement leads to 6-amino-5,7,8-trifluoroquinoline **153**.



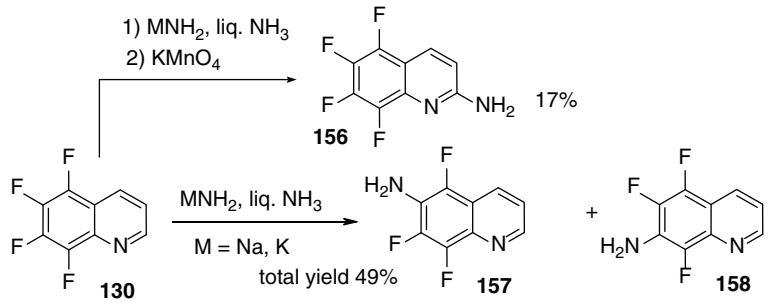
Scheme 67 Functionalization of fluorinated quinolines

The direct nitration of 3-fluoroquinoline **143** has been found to occur by action of a mixture of nitric and sulfuric acids, thus affording 24 % of 5-nitro-3-fluoro-quinoline **154** and 38 % of 8-nitro-3-fluoroquinoline **155** (Scheme 68) [101].



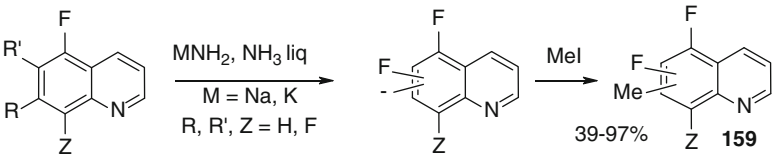
Scheme 68 The direct nitration of 3-fluoroquinoline **143**

Reactivity of 5,6,7,8-tetrafluoroquinoline **130** with the fully fluorinated benzene ring towards the amide anion has been studied [104]. The Chichibabin amination at C-2 has been shown to occur by action of sodium (potassium) amide in liquid ammonia in the presence of potassium permanganate, however only a low yield of the corresponding 2-aminoquinoline has been reached due to concurrent amino-defluorination reactions, taking place at positions 6 and 7 (Scheme 69).



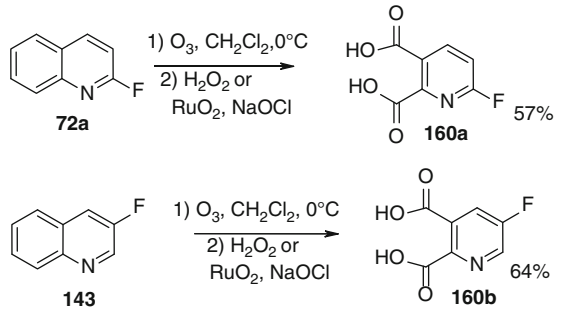
Scheme 69 Amination of quinolone **130**

It is worth mentioning that treatment of difluoro- or trifluoroquinolines with sodium (potassium) amide in liquid ammonia followed by the reaction with methyl iodide has been used to incorporate the methyl group into the benzene ring of these fluoroquinolones (Scheme 70) [101].



Scheme 70 Formation of quinolones **159**

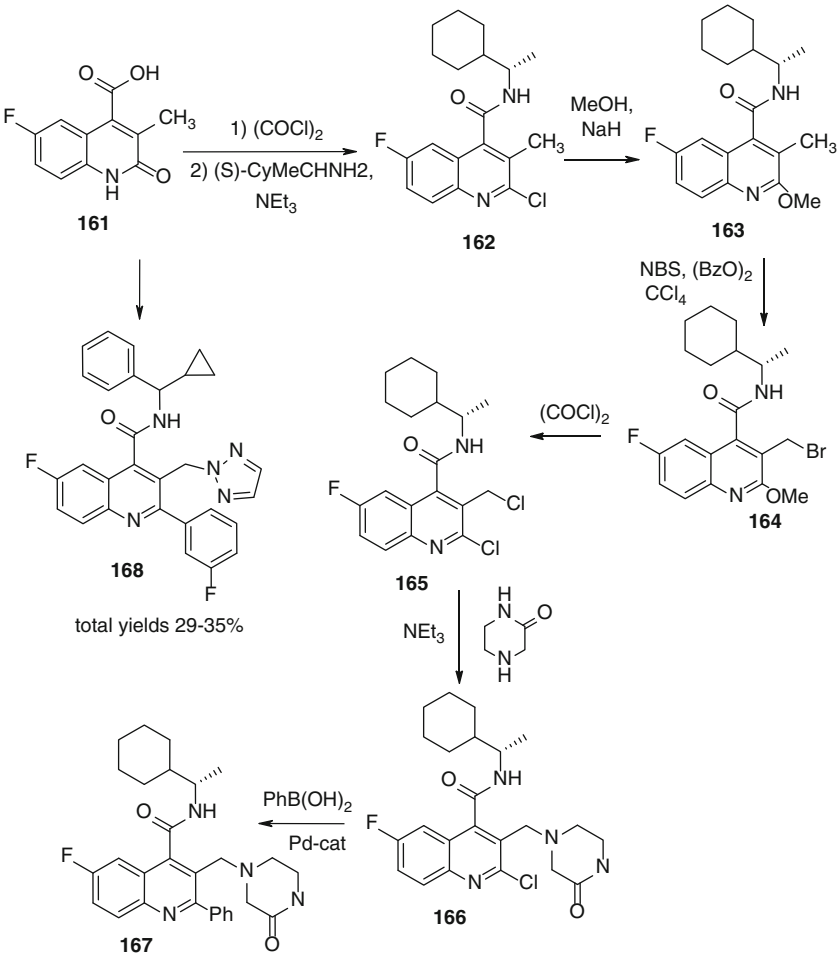
Oxidation of 2-fluoroquinoline **72a** with ozone and hydrogen peroxide or catalytic oxidation in the presence of ruthenium dioxide provides 2-fluoropyridin-5,6-dicarboxylic acid **160a** [105]. Under similar conditions 3-fluoroquinoline **143** is transformed into 3-fluoropyridine-5,6-dicarboxylic acid **160b** (Scheme 71) [104].



Scheme 71 Oxidation of fluoroquinolines **72a** and **143**

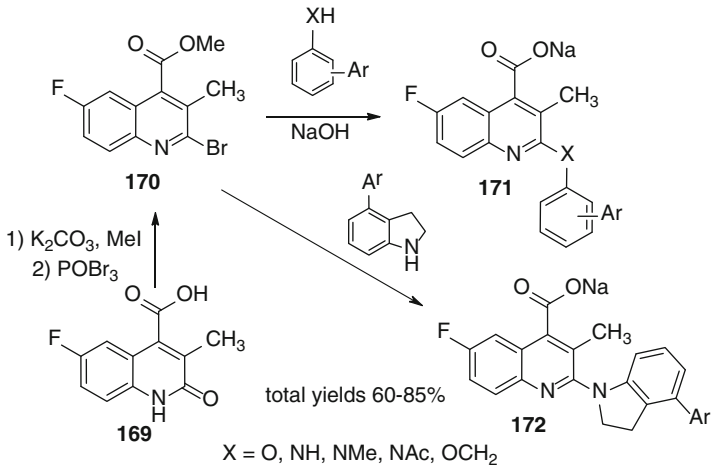
An interesting synthetic approach to 6-fluoro-3-(3-oxopiperazin-1-ylmethyl)-2-phenylquinolin-4-carboxylic acid [(*S*)-1-cyclohexylethyl]amide **167** – dual antagonist for NK2 and NK3 receptors – is presented in Scheme 72 [105]. The reaction

of compound **161** with oxalylchloride initiates conversion of the starting quinolinone into 2-chloroquinoline, while the carboxylic group is transformed first into the corresponding chloroanhydride, and then into amide **162** on treatment with (*S*)-1-cyclohexylethylamine. The next steps involve the formation of 2-methoxyquinoline **163** and 3-bromomethylquinoline **164**, the subsequent reaction of **164** with oxalylchloride and selective substitution of halogen with piperazin-2-one. Amide **166** undergoes the Suzuki cross-coupling reaction to give the corresponding 2-phenylquinoline **167.** Also a multi-steps synthesis of quinoline **168** has been performed [105] (Scheme 72).



Scheme 72 Synthesis of compound **167**

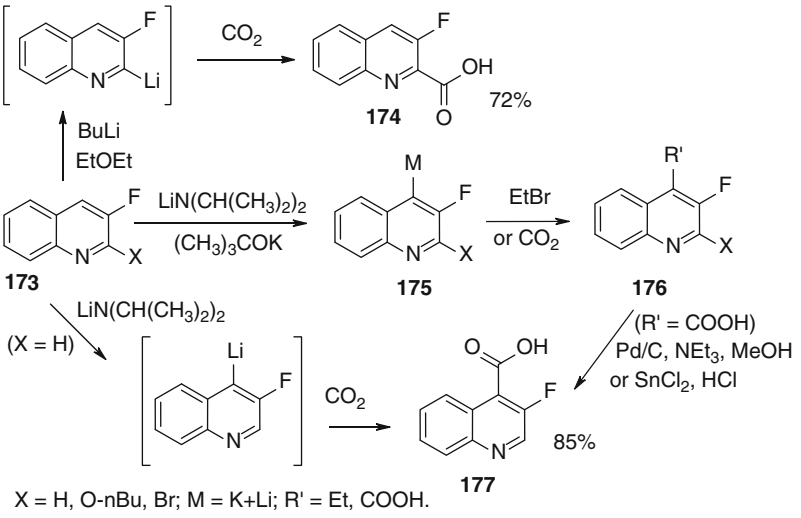
Quinolone **169** after esterification was transformed into bromoquinoline **170**; the latter reacts with aniline, phenol, alcohols or indoline to give 2-substituted 6-fluoroquinolines **171, 172** (Scheme 73) [36].



Scheme 73 Formation of compounds **171**, **172**

Syntheses on the basis of organometallic derivatives have found wide application in the chemistry of fluoroquinolines and their analogs.

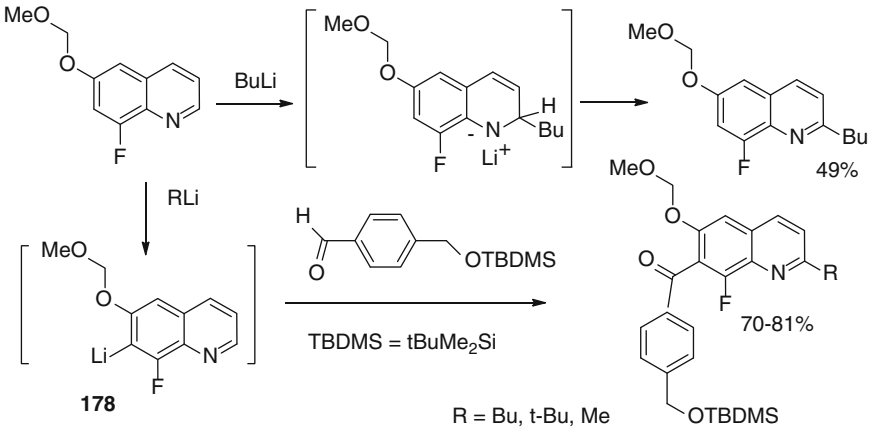
Being treated with a mixture of lithium diisopropylamide and potassium *t-butoxide*, 3-fluoroquinoline (**173**, X=H, $OCH_2CH_2CH_2CH_3$) undergoes the selective metallation of the C-H bond at position 4 of the heterocyclic ring. This reaction allows one to alkylate the position 4 of 3-fluoroquinoline (Scheme 74) [12]. 2-Bromo-3-fluoroquinoline (**173**, X=Br), derived from the reaction of 3-fluoro-quinolin-2(1H)-one with PBr_3, is easily lithiated and transformed into 3-fluoro-quinolin-2-carboxylic acid **174** on treatment of 2-lithium compound with dry carbon dioxide [106].



Scheme 74 Synthesis of quinolincarboxylic acids **174**, **177**

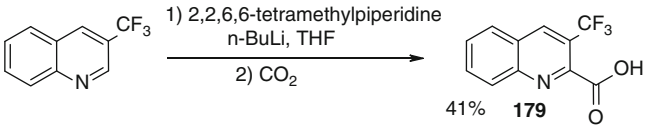
3-Fluoroquinoline (**173**, X=H) was obtained by reduction of 2-bromo-3-fluoroquinoline **173** (X=Br) with Pd/C and NEt_3 in methanol. Bromo derivative **176** (R'=COOH) has been shown to form the corresponding organomagnesium compound, which was transformed on treatment with DMF into aldehyde **176** [R'=COOH, X=C(O)H] and its thiosemicarbazone derivative **176** [R'=COOH, X=CH:NNHC(S)NH_2] [106]. In a similar way 2-bromo-3-fluoroquinolin-4-carbaldehyde and its 1,3-dioxalan were obtained from 4-lithium-3-fluoro-2-bromoquinoline and DMF.

8-Fluoro-6-(methoxymethoxy)quinoline in the reaction with MeLi undergoes a selective *ortho*-metallation at C-7, while BuLi also lithiates the *ortho*-position relative to fluorine atom, however the metallation process is accompanied by nucleophilic addition at C-2 (Scheme 75) [107].



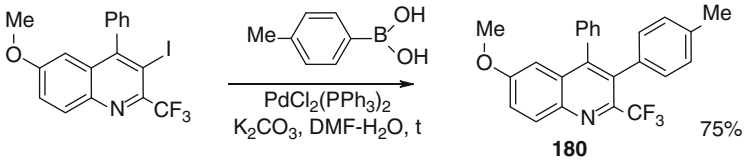
Scheme 75 Reaction of 8-fluoroquinoline with MeLi and BuLi

Use of the direct metallation reactions followed by further functionalization of the obtained organometallic intermediates has been reported for the synthesis of 3-trifluoromethylquinolin-2-carboxylic acid (Scheme 76) [108].



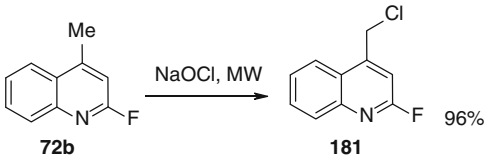
Scheme 76 Synthesis of 3-trifluoromethylquinolin-2-carboxylic acid **179**

The Suzuki -coupling, as well as dehalogenation and carboxylation reactions of 2-trifluoromethyl-3-iodoquinolines have been studied (Scheme 77) [68].



Scheme 77 Synthesis of compound **180**

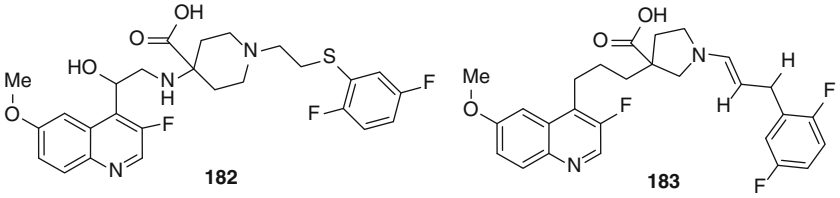
Rapid chlorination of side-chain Me group of 2-fluoro-4-methylquinoline **72b** is reported using sodium hypochlorite under microwave irradiation (Scheme 78) [109].



Scheme 78 Chlorination of Me group of 2-fluoro-4-methylquinoline **72b**

4 Selected Representatives of the Family of Fluoroquinolines

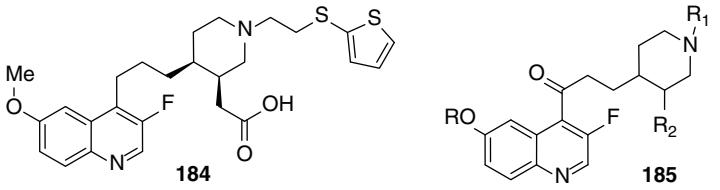
A great deal of fluoroquinolines have demonstrated various types of biological activity, and some of them have already found their applications in medicine. For instance, 3-fluoroquinolines **182** exhibit antibacterial activity against gram-positive and gram-negative bacteria. Compound **182** was obtained by the reaction of 1-(*t*-butyloxycarbonyl)-4-aminopiperidin-4-carboxylic acid with 3-fluoro-6-methoxy-4-(oxyran-2-yl)quinoline, followed be elimination of the protective BOC-group and alkylation of the piperidinyl fragment with 2-[(2-bromo-ethyl) sulphanyl]-1,4-difluorobenzene [110]. Another 3-fluoroquinoline **183** proved to be active against *Staphylococcus aureus IP8203* (Scheme 79) [111].



Scheme 79 Structure of quinolines **182**, **183**

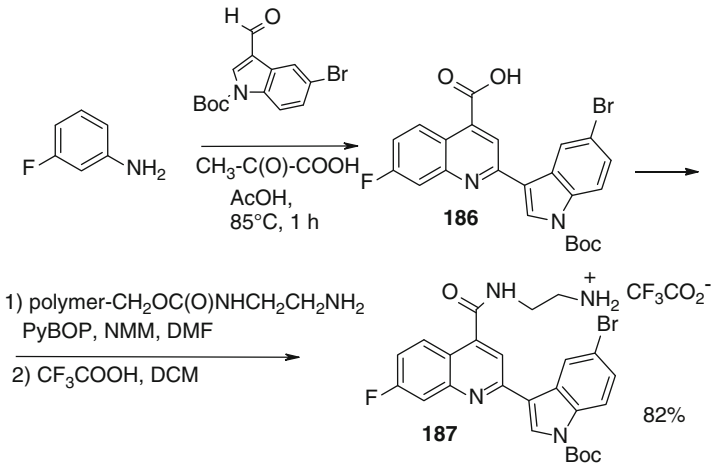
3-Fluoroquinoline **184**, also exhibiting antibacterial activity, has been obtained from 4-iodo-3-fluoro-6-methoxyquinoline through the Pd-catalyzed cross-coupling

reaction followed by N-alkylation with 2-(2-bromoethylthio)thiophene [112]. 3-Fluoroquinoline derivatives **185** have been shown to possess antimicrobial activity (Scheme 80) [113].



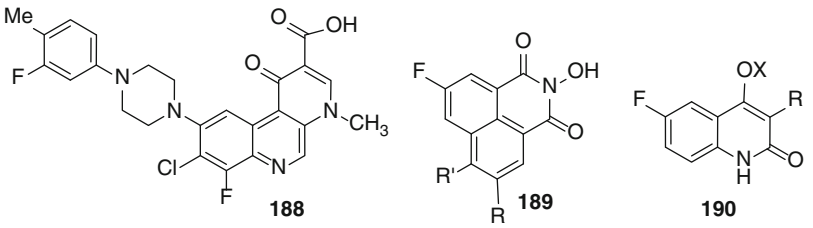
Scheme 80 Structure of quinolines **184**, **185**

The synthesis of 2-(1H-Indol-3-yl)-7-fluoroquinoline **187** from 3-fluoroaniline has been performed (Scheme 81); compound **187** is active against methicillin-resistant *Staphylococcus aureus* strains [114].



Scheme 81 Synthesis of 2-(1H-Indol-3-yl)-7-fluoroquinoline **187**

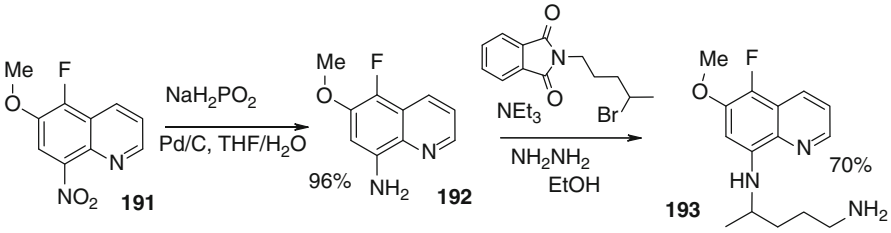
Tricyclic derivative **188** has been established to be active against multi-resistant gram-positive bacteria [90]. Also benzo annelated derivatives of fluorinated 3-hydroxyisoquinolindiones **189** exhibit antibacterial activity [115]. It is worth noting, that derivatives of 6-fluoro-2(1H)quinolinone **190** are of interest as non-nucleoside inhibitors of reverse HIV transcriptase (Scheme 82) [116].



190: R = i-Pr, n-Pr, OEt, Et, iBu, Me; X= (cyclopropyl)-C≡C, cyclopentyl, CH_2-(cyclobutyl), Et(Me)CH-C≡C,CF_3CH_2.

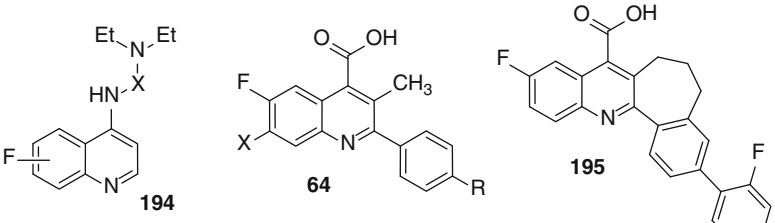
Scheme 82 Structure of quinolines **188–190**

The synthesis of 5-fluoroprimaquin **193**, an analog of the known antimalarial drug, has been reported from compound **191** (Scheme 83) [9].



Scheme 83 Synthesis of 5-fluoroprimaquin **193**

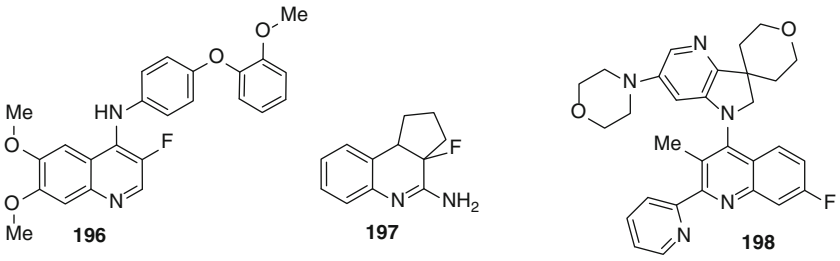
6-Fluoro-, 8-fluoro- and 6,8-difluoro derivatives of 4-aminoquinoline (**194**, X=$(CH_2)_3$, $CHMe(CH_2)_2$) are active against malaria, and can be used for treatment of the diseases caused by chloroquin-resistant strains of *P. falciparum W2* [117]. Also antiplazmodium activity of 7-fluoro derivatives [**194**, $(CH_2)_n$, n = 2, 3, 10, 12 and $CHMe(CH_2)_2$] has recently been reported [118]. 6-Fluoroquinoline-4-carboxylic acids **64** inhibit the melanoma B16 at mice; the sodium salt of **64** (X=H, R=2-FC_6H_4) has been launched by Dupont as Brequinar® drug [119]. The structure-activity relationship for analogs of Brequinar® has been thoroughly investigated [119–123]. Several analogues of this drug are used in transplantation medicine, as well for treatment of rheumatic arthritis and psoriasis. Quinoline **195** proved to be a highly effective immunosuppressant (Scheme 84) [124, 125].



64: X = H, Cl; R = cyclohexyl, phenyl, 2-fluorophenyl.

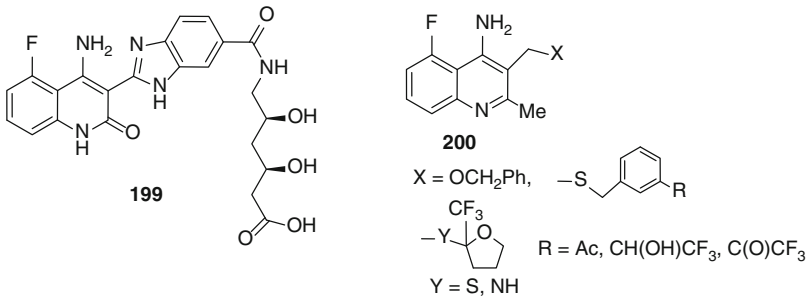
Scheme 84 Structure of quinolines **64**, **194**, **195**

During the recent decade a growing interest in 3-fluorosubstituted quinolines has been observed, since it has been shown that 3-fluoroquinolines, unlike their 5-fluoro analogues, are neither mutagenic not cancerogenic compounds, and can be used in medicine and agriculture [126]. Derivative of 3-fluoroquinoline **196** was shown to act as mitogen-activated protein kinase kinase (MEK) inhibitor [127], while compound **197** – as NOS (nitrogen oxide synthetase) inhibitor [128]. Compound **198** represents a novel type potent phosphoinositide 3-kinase (PI3K) inhibitors, it's valuable for treatment of rheumatoid arthritis (Scheme 85) [129].



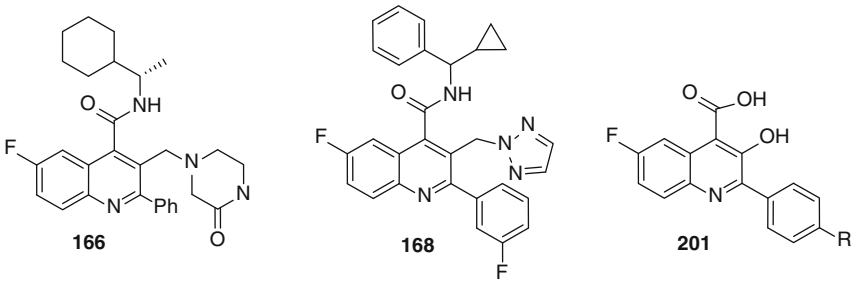
Scheme 85 Structure of quinolines **196–198**

5-Fluoro-2-quinolone **199** proved to be a highly effective protein-kinase inhibitor [130]. Also 5-fluoroquinoline derivatives **200** are inhibitors of acetylcholine esterase, and they are important for treatment of Alzheimer's disease (Scheme 86) [131].



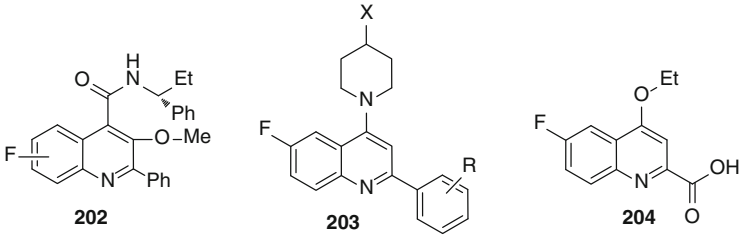
Scheme 86 Structure of quinolines **199**, **200**

Derivatives **166** and **168** are antagonists of neurokinine 3 (NK3) and can be applied to treatment of diseases of the central nervous system [107, 132]. Quinolines **201** are antagonists of P-selectine (Scheme 87) [133].



Scheme 87 Structure of quinolines **166, 168**, **201**

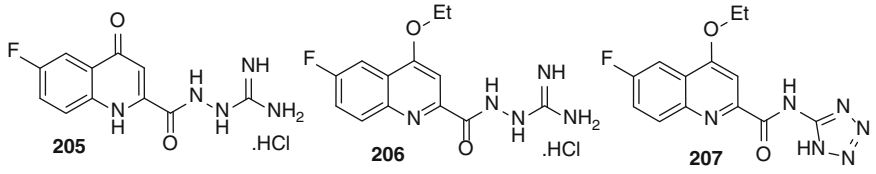
4-Quinolincarboxamides **202**, bearing a fluorine atom in 6, 7 or 8, proved to act as ligands for the NK-3 receptors [134]. Among 2-aryl-4-pyperidinyl-6-fluoro-quinolines **203** ligands of the benzodiazepine receptors have been revealed, and the 1,2,4-oxadiazole fragment appears to act in this case as heterocyclic analogue of COOH and COOR functional groups [135, 136]. 6-Fluoro-4-ethoxyquinolin-2-carboxylic acid **204** can be used for treatment of hyperglycemia, obesity and diabetes (Scheme 88) [137].



203: R = 2-Cl, 2-OMe, 4-F, 4-Cl, 2-OH;
X = $C(O)NH_2$, 3-methyl-1,2,4-oxadiazol-5-yl, COOEt, CN

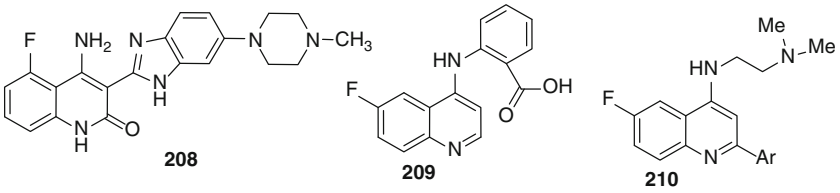
Scheme 88 Structure of quinolines **202–204**

In order to develop new antidiabetic agents, guanidine and tetrazole substituted amides of 6-fluoroquinolin-2-carboxamides **205, 206** and **207** have been obtained [138]. Compound **207** acts as fibroblast growth factor receptor 3 ($FGFR^3$) inhibitor and can be used for treatment of multiple myeloma (Scheme 89) [139, 140].



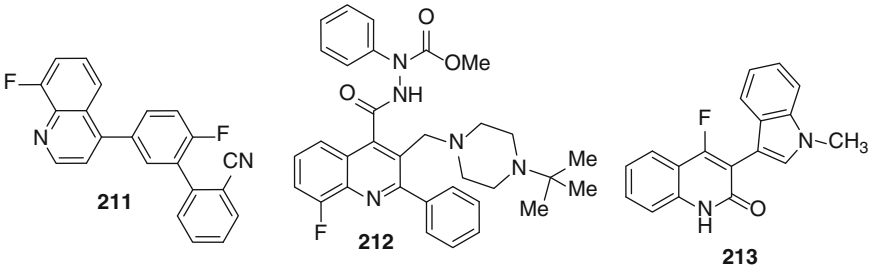
Scheme 89 Structure of quinolines **205–207**

Salt of **208** with lactic acid has been shown to be an effective inhibitor of various kinases, such as receptors for vascular endothelial growth factor 2 (VEGFR2), fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor-beta (PDGFRβ) [141, 142]. 6-Fluoroquinolinyl substituted anthranilic acid **209** is used for treatment of metabolic diseases of bones [143]. 6-Fluoro-2-arylquinolin-4-amines **210** are antagonists of immunostimulator CpG-oligonucleotides (Scheme 90) [144].



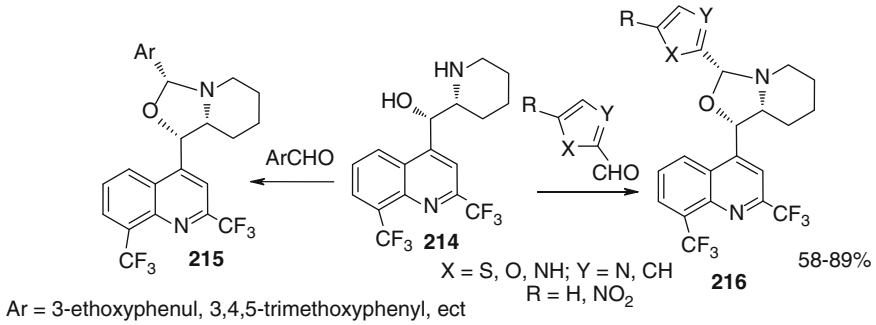
Scheme 90 Structure of quinolines **208–210**

8-Fluoroquinoline derivative **211** is capable of binding with γ-aminobutyric acid receptors, and can be used for treatment of convulsions, mental disturbances, and disorders of memory [145]. Compound **212** is antagonist of NK3 receptor [146], substituted 2-quinolone **213** – inhibitor of tyrosine-kinase vascular endothelial growth factor (VEGF) receptor (Scheme 91) [147]. 2-(Piperazin-1-yl)-5-fluoro-6-nitroquinoline labelled with fluorine-18 was shown to be useful for potential positron-emission-tomography (PET) tracer for imaging the serotonin transporter [148].



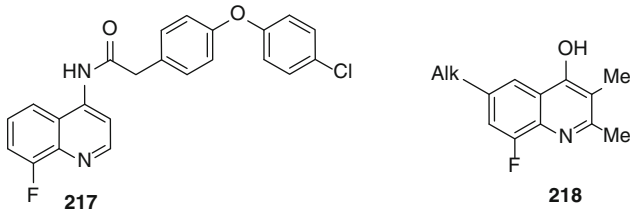
Scheme 91 Structure of quinolines **211–213**

An improved synthesis of mefloquine has been advanced [149]. Also the asymmetric total synthesis of the (+)-enantiomer of mefloquine hydrochloride has been described [150]. Modifications of mefloquine aimed at development of novel biologically active compounds, including antituberculosis drugs, have extensively been performed (Scheme 92) [151]. Compounds **215, 216** were more active than mefloquine against *M. tuberculosis* (MIC 11.9–33 μM), some of derivatives have a better tuberculostatic activity than the first line tuberculostatic agent ethambutol (MIC = 15.9) [151].



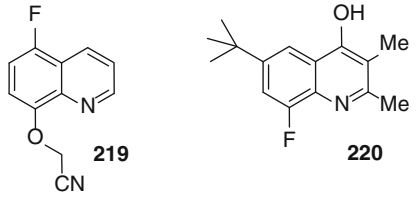
Scheme 92 Modifications of mefloquine

Compound **217** active against nematodes, insects, mites, and plant pathogens [152]. Derivative of 8-fluoroquinoline **218** useful as an agricultural chemical (Scheme 93) [10].



Scheme 93 Structure of quinolines **217**, **218**

5-Fluoro-8-cyanomethoxyquinoline **219** possesses herbicidal activity [153]. 2,3-Dimethyl-4-hydroxy-6-t-butyl-8-fluoroquinoline **220** is useful as rise blast control agent (Scheme 94) [154].



Scheme 94 Structure of quinolines **219**, **220**

2-Amino substituted 6,7-dimethoxy-4-(trifluoromethyl)quinolines have been shown to possess fluorescent properties [155]. 8-Hydroxyquinoline, its numerous derivatives and especially metal chelates on their basis attracted attention of many researchers since publication of the first data on electro-luminescence of the aluminum complex with 8-hydroxyquinoline which possesses thermal stability, high

efficiency of green luminescence, and rather good electronic mobility [156]. Influence of fluorine atoms in various positions of the quinoline system on luminescent characteristics of metal complexes of 8-hydroxyquinoline has been elucidated [157]. Due to specific properties of fluorine atom complexes of 8-hydroxyquinoline with metals proved to have an enhanced electronic mobility, a low temperature of sublimation, a good stability on air, and a wide energetic gap. 2-Methyl-6,7-difluoro-8-oxyquinoline, its stiryl derivatives and Zn (II) complexes have recently been obtained to study luminescence of these compounds [158].

In conclusion it is worth to mention that quinolines and their fluorinated derivatives continue to be one of the most important class of heterocyclic compounds. The medicinal chemistry remains one of the main fields for their applications, and special attention during the last decades is paid to the family of 6-fluoro-1,4-dihydroquinolin-4-oxo-3-carboxylic acids which will be discussed in a separate chapter. Derivatives of 8-hydroxyquinoline have found wide application in analytical, coordination chemistry, while their metal chelates are of interest as the basis to develop new materials.

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