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Fluorinated Benzazoles and Benzazines

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ABSTRACT: *The review surveys the recently obtained data on the synthesis of fluorinated benzazoles and benzazines.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:579–594, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20281

INTRODUCTION

During the last two decades, the chemistry of fluorine-containing compounds has been developing quite extensively. Because of unique characteristics of fluorine atoms in organic molecules, they have a great influence on their physicochemical properties, and many fluorinated compounds have already found wide application as technical materials, pesticides, and effective drugs [1]. Also fluorine-containing heterocycles have gained the attention of chemists and biologists because many derivatives show a high biological potency in their ability to inhibit specific enzymes, their good solubility in lipids, and their ability to penetrate through cell membranes.

Anticancer 5-fluorouracil, antimicotic fluconazol, and antidepressant fluorobenzo-1,4-diazepine derivatives are just a few examples of these well-known series of fluorinated drugs. Also new antibacterials of the so-called fluoroquinolone family, derivatives of 6-fluoro-4-oxo-1,4-dihydroquinolin-3-carboxylic acid such as commercially available pefloxacin, ofloxacin, cyprofloxacin, marbofloxacin, etc. have been advanced [2]. A great deal of publications focus on structural modifications of fluoroquinolones as inhibitors of the DNA-gyrase (bacterial topoisomerase), the enzyme that is responsible for cleavage and renovation of the double helix of bacterial DNA [3–5]. It has been shown that fluoroquinolones can influence the eucariot cells, sometimes showing a high cytotoxicity, and thus being of interest as anticancer agents [6,7]. Some fluoroquinolones, for instance levofloxacin, exhibit a remarkable anti-HIV activity, acting as inhibitors of the HIV reverse transcriptase [8,9]. Also anti-HIV activity of some fluorinated quinoxalines as non-nucleoside inhibitors of the reverse transcriptase has been described in some literature [10,11].

Similarities between fluorinated arenas and DNA heterocyclic bases in electron density distribution and the ability for F · · · H hydrogen bond formation (Scheme 1) [12] make fluorinated benzazoles and benzazines as intriguing subjects for medicinal chemistry.

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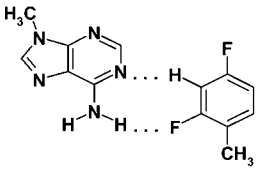
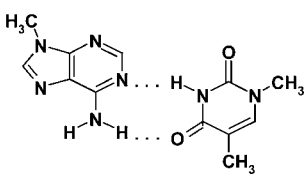
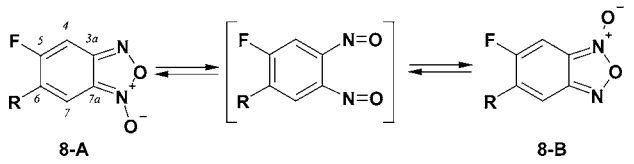




SCHEME 1



SCHEME 4

DISCUSSION

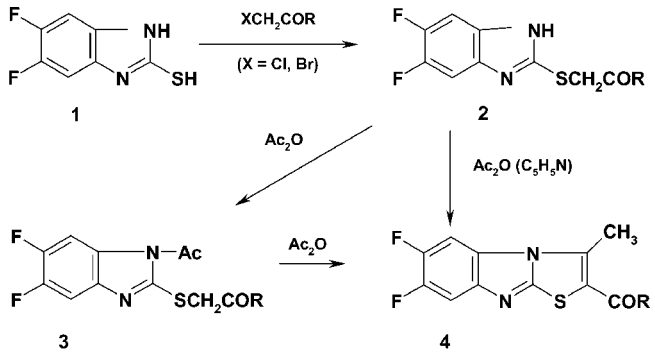
Fluorinated Benzazoles

Fluorinated Benzimidazoles. One of the most accessible compounds in the series of fluorinated benzimidazoles, 2-mercapto-5,6-difluorobenzimidazole **1** was prepared by condensation of 4,5-difluoro-1,2-phenylenediamine with CS_2. 2-Mercapto-5,6-difluorobenzimidazole **1** was shown to react with aromatic α-haloketones to give 2-phenacylthio-5,6-difluorobenzimidazoles **2**. The latter were transformed by acylation and cyclodehydration in an acetic anhydride–pyridine system into benzo[4,5]-imidazo[2,1-*b*][1,3]thiazoles **4** (Scheme 2) [13]. Biological tests revealed that compound **4** ($Ar = C_6H_5$) displayed a considerable activity toward the meastle virus [14].

By reacting with β-ketoesters, 1*H*-5,6-difluorobenzimidazol-2-acetonitrile **5** was transformed into pyrido[1,2-*a*]-benzimidazoles **6** and **7** (Scheme 3), which proved to be active against pathogenic orthopox viruses [15,16].

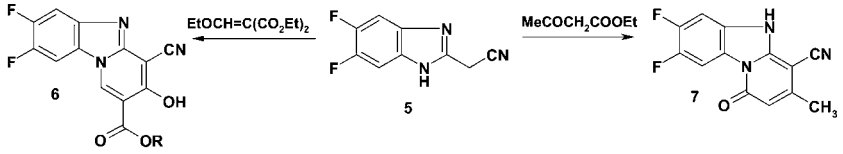
Fluorinated Benzofuroxanes. Features of tautomerism in the series of furoxanes **8** (R = F, morpholino) have been studied by ^1H, ^{13}C, and ^{19}F NMR methods. The factors affecting tautomeric equilibria as well as thermodynamic characteristics of both isomers have been determined (Scheme 4) [17,18].

Reacting with CH-active carbonyl compounds, enamines or nitriles 5,6-difluorobenzofuroxane **8** (R = F) was transformed into the corresponding 6,7-difluoroquinoxalin-1,4-dioxides **9** [19–21]. Nucleophilic displacement of a fluorine atom at C-6 in furoxane **8** allows one to modify the benzene ring, while the furoxane ring remains unchanged in this reaction (compounds **10**). Electrophilic substitution reactions on fluorinated benzofuroxanes and **8** bearing an electron-donating substituent R are accompanied with the Boulton–Katrizky rearrangement, resulting in the formation of nitro derivatives of benzofurazanes **11** and benzotriazoles **12** (Scheme 5) [18,22].



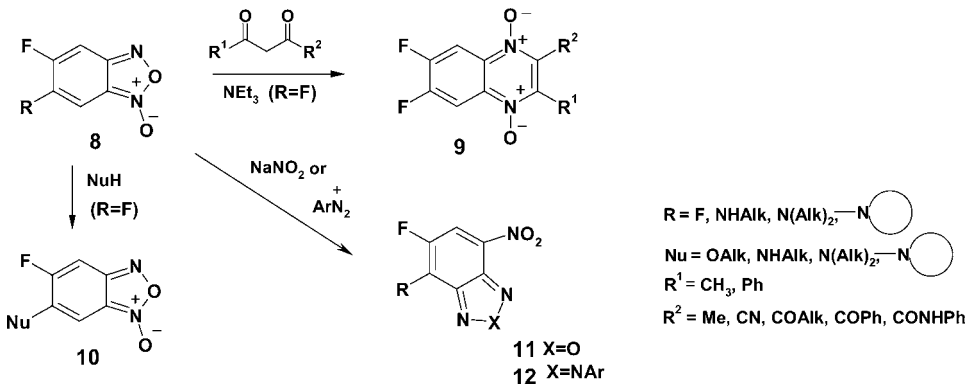
R = Ph, 2-$CH_3C_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$(CH_3O)_2C_6H_3$.

SCHEME 2



R = C_2H_5, CH_3

SCHEME 3



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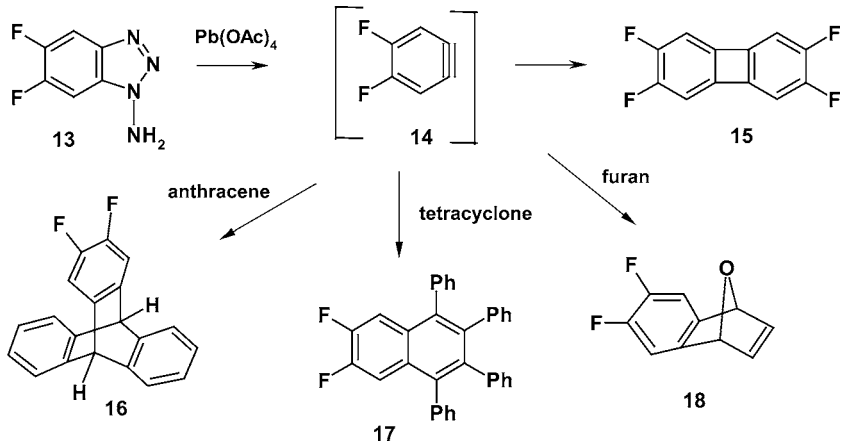

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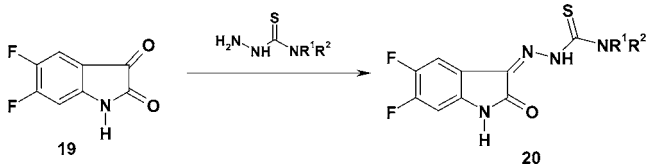
Fluorinated Benzotriazoles. 1-Amino-5,6-difluorobenzotriazole **13** was used to generate 4,5-difluoro-1,2-dehydrobenzene (DHB) **14**, and this intermediate **14** was allowed to react in situ with antracene, tetraphenyl-substituted cyclopentadienone (tetracyclone), and furan to give a number of fluorinated carbo- and heterocyclic compounds **15–18** (Scheme 5) [23,24].

Other Fluorinated Benzazoles and Condensed Azoles. Metisazone (thiosemicarbazone of *N*-methylisatin) is known as an antiviral agent that inhibits reproduction of the pox-type viruses. It can be used to prevent the infection caused by the smallpox virus as well as diminish the postvaccinative complications. This is why a number of fluorinated analogs of metisazone **20** have been obtained by reacting 5,6-difluoroisatin **19** with 4,4-cycloalkylimino-thiosemicarbazides (Scheme 7) [25].

Heating of ethyl 3-azolylamino-2-polyfluorobenzoyl acrylates **21** in acetonitrile in the presence of KF was shown to give the corresponding azolo[1,5-*a*]pyrimidines **22** (Scheme 8) [26].

Polyfluoroaryl fragments can be introduced into heterocyclic molecules by using the reactive



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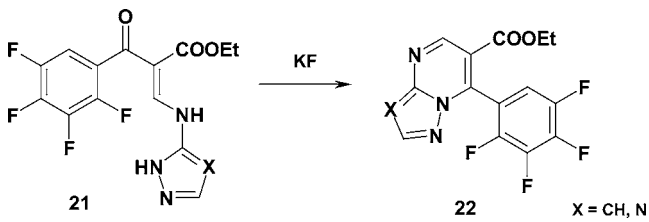

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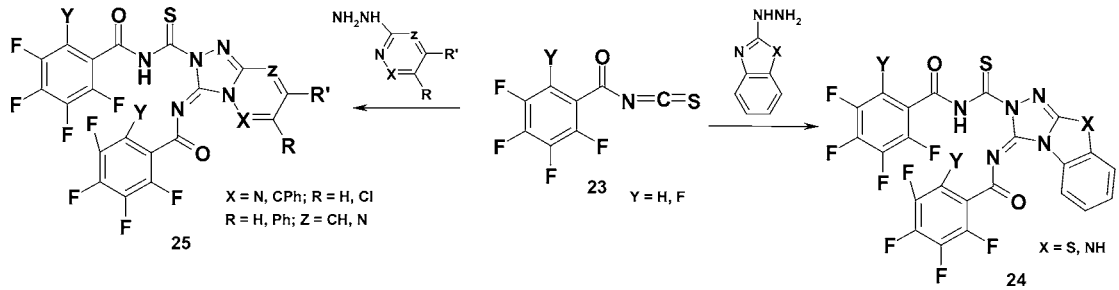

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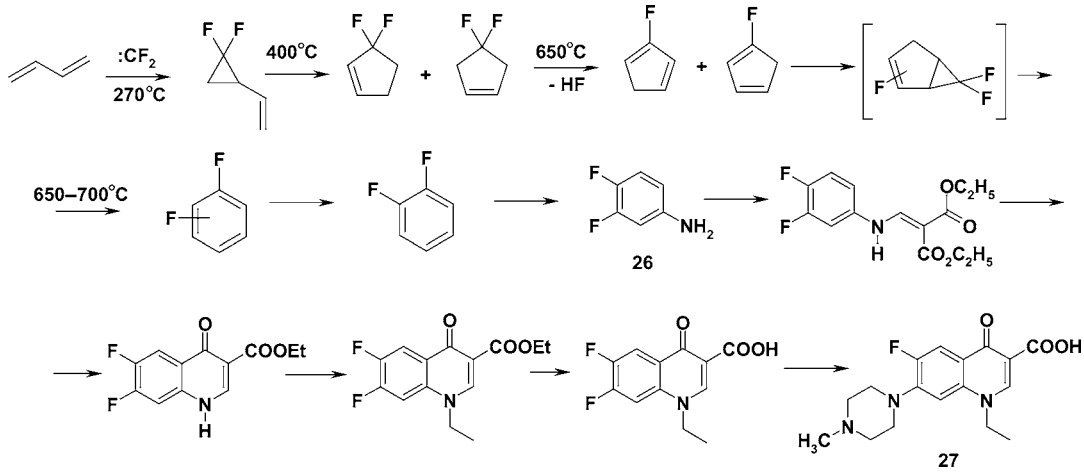


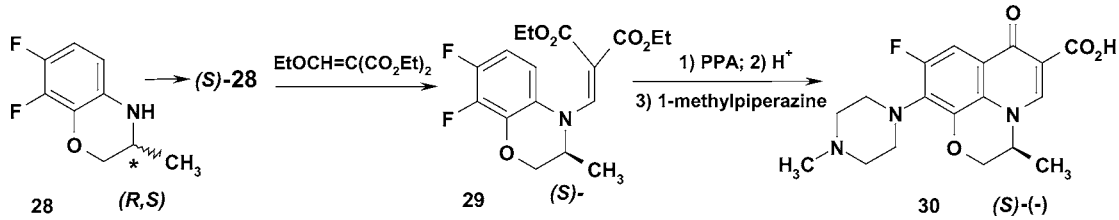
SCHEME 10

isothiocyanate moiety. In particular, the reaction of heteryl hydrazines with polyfluorobenzoyl isothiocyanates **23** affords triazolobenzazoles **24**, triazolopyrimidines, and triazolopyridazines **25** (Scheme 9).

Fluorinated Benzazines

Derivatives of Fluoroquinolonecarboxylic Acids. Pefloxacine, levofloxacine, and other fluoroquinolone antibacterials. A new approach for the synthesis of pefloxacin **27**, a representative of the fluoroquinolone family of antibacterials, has been advanced on the basis of the difluorocarbene methodology developed by Prof. O. Nefedov and co-workers [27], which enables one to obtain 3,4-difluoroaniline **26** followed by the known procedure [28] (Scheme 10).

Synthetic approaches to other antibacterials of the fluoroquinolone family, such as norfloxacin, ciprofloxacin, and enantiomerically pure levofloxacin, have been worked out and patented [29–38]. It is worth noting that (*S*)-naproxen chloride, *N*-sulfonyl-substituted (*R*)-proline, and (2*S*)-(6-methoxynapht-2-yl)propionyl chloride were found to be appropriate agents for kinetic resolution of a racemic mixture of 7,8-difluoro-2,3-dihydro-3-methyl-4*H*[1,4]benzoxazine (*R,S*) **28**. The optically active (*S*)-isomer of 2-methyl-benzoxazine **29** was used as the key intermediate for the synthesis of levofloxacin (*S*)-(-) **30** (Scheme 11) [32, 39–42].



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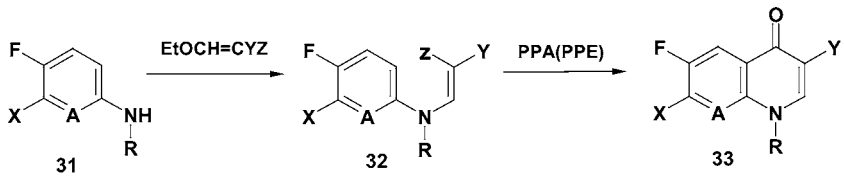


A = CH, CX, N; Y, Z = CO_2R, CN, COMe

SCHEME 12

Modification of bicyclic fluoroquinolones. Two principal approaches for the synthesis of bicyclic 4-pyridone-3-carboxylic acids are known from the literature [2,3,43–45]. The first one is based on using fluorinated anilines (**31**, A = CH, CF) or 2-aminopyridines (**31**, A = N) as starting materials. It involves a condensation with ethoxymethylene malonate, cyanoacetate, or acetoacetate to obtain enamines **32**. Intramolecular cyclization of compounds **32** by action of polyphosphorus acid (PPA) (the Gould–Jacobs reaction) affords the corresponding fluoroquinolones (**33**, A = CH, CF) or 1,8-naphthyridones (**33**, A = N) (Scheme 12).

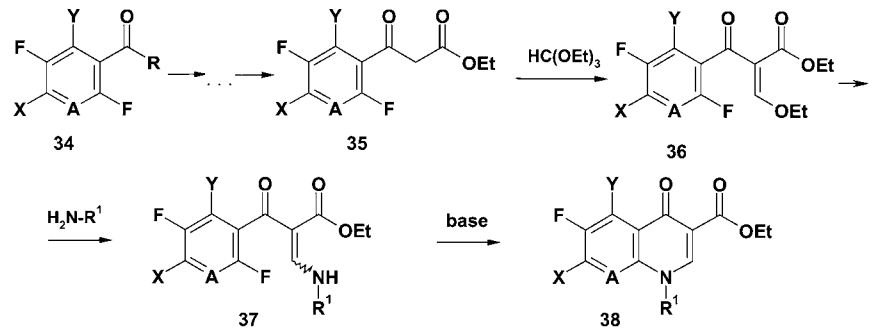
The second approach suggests using fluorinated benzoyl derivatives (**34**, A = CF, CH) or their nicotinoyl analogs (**34**, A = N) as starting materials and involves the formation of benzoyl acrylates **36** as the key intermediates (Scheme 13).

Compounds **36** can easily be modified to introduce substituents at position 1 of the fluoroquinolone skeleton. Indeed, the reactions of ethyl 3-ethoxy-2-polyfluorobenzoyl acrylates **36** (A = CF) with a variety of amines, hydrazines, or hydrazides followed by intramolecular cyclizations, hydrolysis of the ethoxycarbonyl group, and the displacement of fluorine atom at C-7 (Scheme 14) afford a variety of fluoroquinolones **39–43** [26,46,47].

The synthesis of 2-polyfluoroalkyl-6,7-difluoroquinolones **46** from 3,4-difluoroaniline **44** was achieved through acylation with anhydrides of polyfluoroalkanecarboxylic acids, followed by conversion of anilides obtained into the corresponding imino chlorides **45**. Finally, the expected cyclization of compound **45** can be caused by malonic or cyanoacetic esters to give quinolones **46** (Scheme 15) [48].

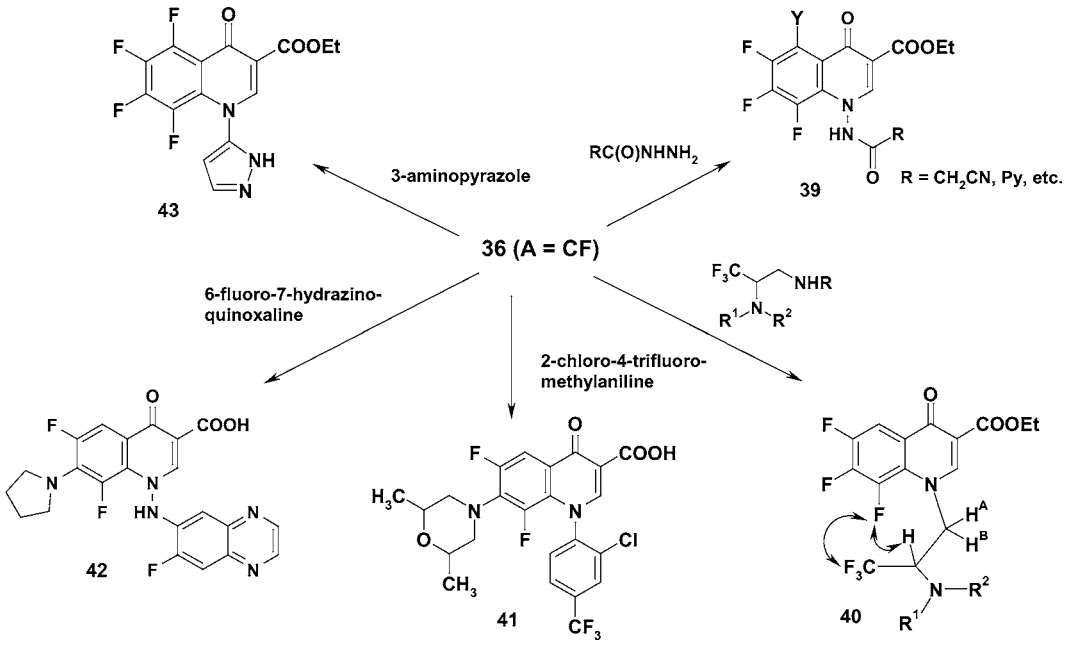
2-Amino-substituted 3-pentafluorobenzoyl acrylic acids **48** derived from pyruvic acid **47** were found to undergo an intramolecular cyclization into fluoro-4-quinolone-2-carboxylic acids **49** (Scheme 16) [49–51].

Using ethyl 4-(*R*-amino)-2-oxo-3-pentafluorobenzoyl-but-3-enoate **50**, obtained from copper chelate of ethyl pentafluorobenzoyl pyruvate, *N*-substituted 2-(4-oxo-5,6,7,8-tetrafluoro-1,4-dihydroquinolin-3-yl)glyoxylic acids and their esters **52** (Scheme 17) have been synthesized [52]. 3-Arylhydrazones of fluorinated 2,3,4-triketoesters (**51**, R = Ar), obtained by the coupling reaction of aryldiazonium chlorides with fluoroacyl(aroyl) pyruvates or their chelates, may be used for the synthesis of fluorinated cinnolines. Indeed, arylhydrazone **51** was converted to cinnolone **53** under heating in DMSO in the presence of K_2CO_3 and dibenzo-18-crown-6 or under reflux in chloroform in the presence of NEt_3[53,54]. Quinolones (cinnolones) **54, 55** bearing quinoxalone, benzoxazinone, or benzothiazinone fragments in position



A = CF, CH, N; X = F, Cl, Br; Y = F, H.

SCHEME 13



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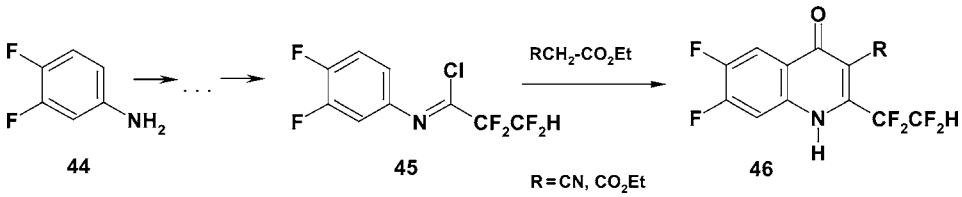

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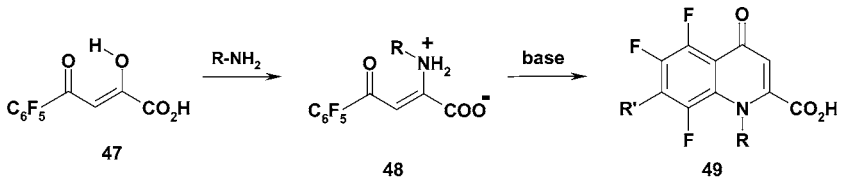


R = Ar, Alk; R′ = OH, morpholino.

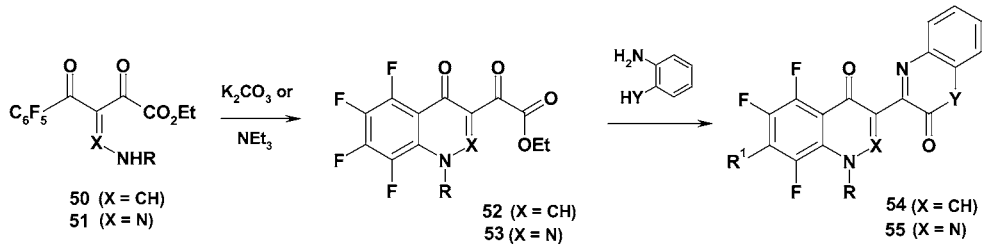
SCHEME 16

3 were obtained from **52, 53** and aromatic 1,2-dinucleophiles (Scheme 17) [55].

The carboxylic group in position 3 of fluoroquinolones can be replaced with other substituents to obtain new antibacterials [4], and many modifications of this type have been carried out. For instance, hydrazino derivatives of fluoroquinolones **57** were found to react with potassium ethylxantogenate to give 3-heteryl(oxadiazolyl) derivatives of quinolonecarboxylic acids **58** (Scheme 18) [56].

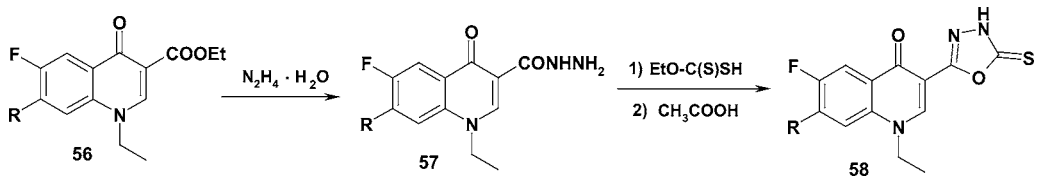
3-Nitro- and 3-bromo analogs of fluoroquinolones **61** were obtained by electrophilic nitration (bromination) of compound **60**, derived from decarboxylation of the corresponding carboxylic acid **59**. *N*-Alkylation or *N*-amination of **60** followed by nucleophilic substitution of fluorine atom at C-7 affording compounds **62** has been realized (Scheme 19) [57].

Position 7 in fluoroquinolones is often subjected to modification because a halogen atom at C-7



R = Alk, Ar; Y = NH, O, S.

SCHEME 17



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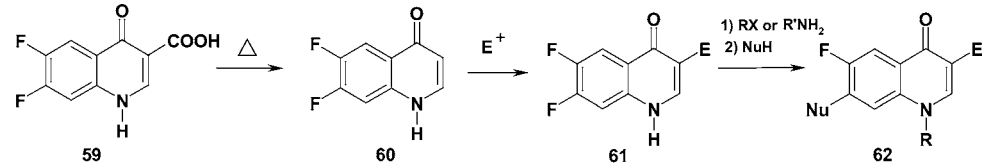


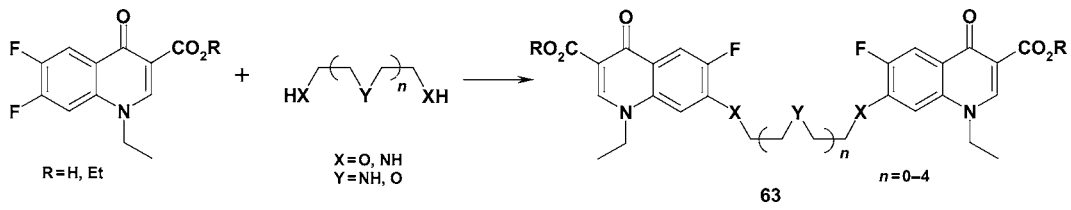
$E^+ = NO_2$, Br; R = Alk, NH_2.

SCHEME 19

can easily be substituted by the action of N-, S-, O-, and C-nucleophiles. In the case of 6-fluoro-7-halogeno- or 6,8-difluoro-7-halogenoquinolones, the displacement reaction proceeds selectively to form 7-substituted products [3,47,58]. Interaction of 5,6,7,8-tetrafluoroquinolones (cinnolones) with N-nucleophiles results in substitution of fluorine atoms at C-5 and/or at C-7 [49,59].

In order to improve the pharmacokinetic properties of fluoroquinolones, they were modified with aminoether or polyethyleneamine podand fragments, which are able to penetrate through cell membranes (Scheme 20) [60]. This modification gave derivatives **63** that proved to be specifically active against micobacteria under a low toxicity. It is noteworthy that tuberculostatic activity of compound **63** (R = H; X, Y = 0; $n = 4$) is five times higher than that of pefloxacin [61].

The 1,3-dipolar cycloaddition methodology is an effective synthetic tool to modify the structure of 6-fluoro-4-quinolon-3-carboxylic acids by introduction of a variety of heterocyclic fragments, such as triazoles, triazolines, isoxalidines, and others (Schemes 21 and 22) [58,62–65]. For instance, the reaction of 7-azido derivative of 6-fluoroquinolone **64** with enamines of cyclic ketones and norbornene



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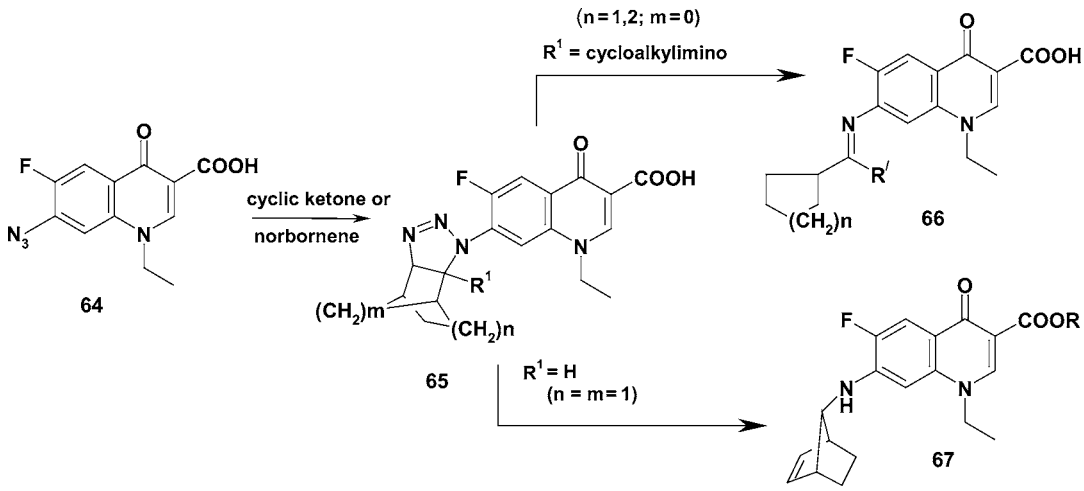

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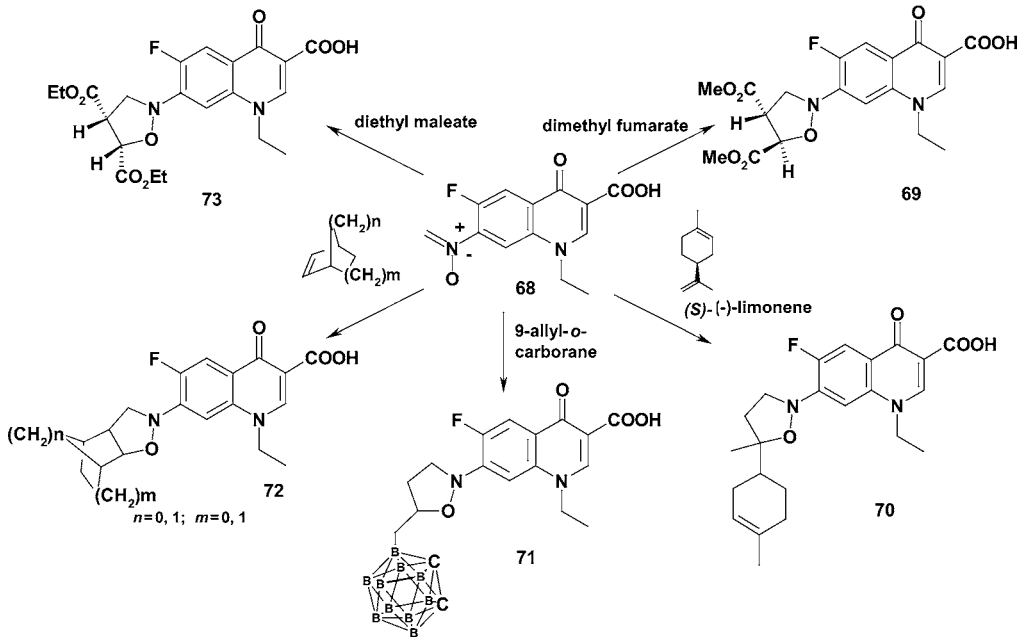


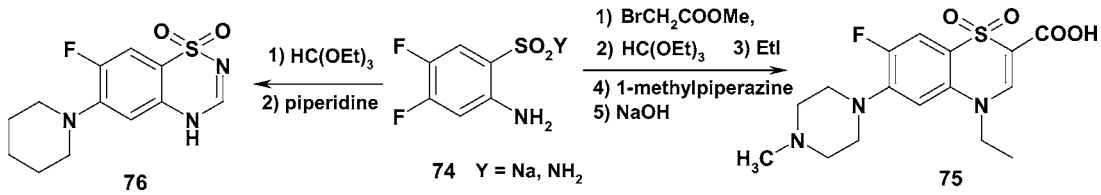
SCHEME 22

was shown to proceed smoothly, thus yielding the corresponding *exo*-1,2,3-triazolines **65**. These cycloadducts undergo cationic rearrangements, which are accompanied by extrusion of nitrogen and 1,2-sigmatropic shift, thus resulting in amidines **66** or aminonorbornane **67** (Scheme 21) [58,62].

Also, the cycloaddition reaction of azomethinoxide **68** with alkenes proceeds in a regio- and stereoselective manner, thus representing a general method for the synthesis of a variety of stereoisomeric 7-isoxazolidines **69–73** (Scheme 22) [63–65].

Thioanalogs of pefloxacin, fluorinated 4*H*-1,4-benzothiazin-1,1-dioxides **75**, and 1,4-benzothiadiazine-1,1-dioxides **76** have been prepared by using 2-amino-4,5-difluorobenzene sulfone derivatives **74** (Scheme 23) [66,67].

Annelated fluoroquinolones. Interaction of thiosemicarbazides, heterylhydrazides, or amidrazones with 3-ethoxy-2-polyfluorobenzoyl acrylates results in the formation of ethyl 3-(*R*-thiocarbonylhydrazino)-, 3-(*R*-carbonylhydrazino)-, and 3-(*R*-imidoylhydrazino)-substituted 2-polyfluorobenzoyl acrylates **77** (X = S, O, NH), which can be converted into fluoroquinolones **78** (X = S, O, NH). The latter are capable of further intramolecular cyclizations into tricyclic



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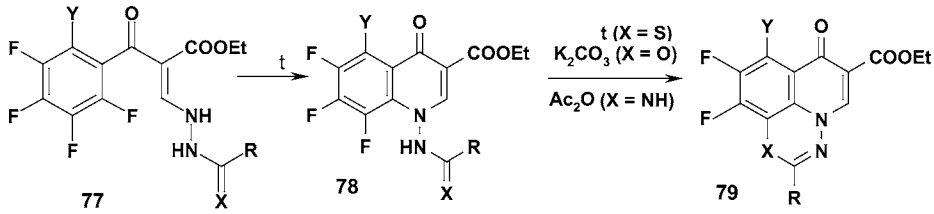


X = S, O, NH.

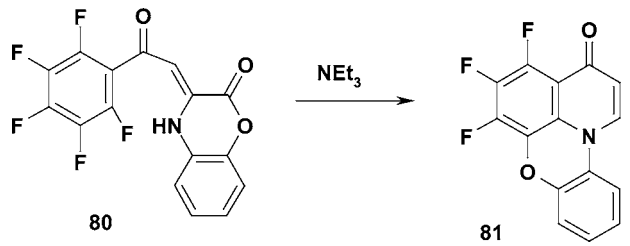
SCHEME 24

1,3,4-oxa(thia)diazino[6,5,4-*i*,*j*]quinolines **79** (X = S, O) and 1,2,4-triazino[5,6,1-*i*,*j*]quinolines **79** (X = NH) (Scheme 24) [68–73].

An alternative cyclization of acrylates **77a** leads to pyrazoles [74]. Fluoroquinolones **79** (X = S, O) and their 8- and 10-amino compounds are of special interest, because many derivatives of this series are associated with a wide range of pharmaceutical properties and exhibit tuberculostatic, antibacterial, and antitumor activities [47,75,76].

Intramolecular cyclization of 3-pentafluorobenzoylmethylen-3,4-dihydro-2*H*-1,4-benzoxazin-2-one **80** takes place in DMSO at 200°C without any base; in the presence of triethylamine it proceeds at 80°C, thus producing 3-oxo-4,5,6-trifluoro-3*H*-pyrido[3,2,1-*k*,*l*]phenoxazin-3-one **81** in a good yield (Scheme 25) [77].

Heating of ethyl 3-[β-(benzazol-2-yl)hydrazino]-2-(polyfluorobenzoyl)acrylates **82** in acetonitrile with DBU yields derivatives of a novel heterocyclic system, 4-oxo-4*H*-benzazolo[2′,3′:3,4][1,2,4]triazino[5,6,1-*i*,*j*]quinoline-5-carboxylic acids **84** (Scheme 26) [78,79].

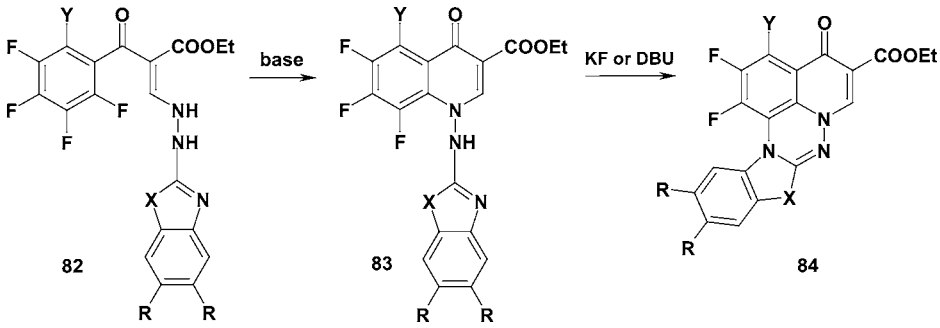


SCHEME 25

In pentacyclic derivatives **84**, the long-range ^{1}H–^{19}F and ^{19}F–^{19}F coupling constants $^{6}J(F, H) = 2.0$–3.0 Hz, $^{7}J(F, F) = 3.5$–4.0 Hz, and $^{9}J(F, H) = 3.0$–3.5 are observed in ^{19}F NMR of **84** spectra. Leaving abilities of fluorine atoms in the amino-defluorination reaction of fused fluoroquinolones **84** are also different relative to bi- and tricyclic analogs [80]. Also it is worth mentioning that compounds **84** proved to possess tuberculostatic and antitumor activities [75,81].

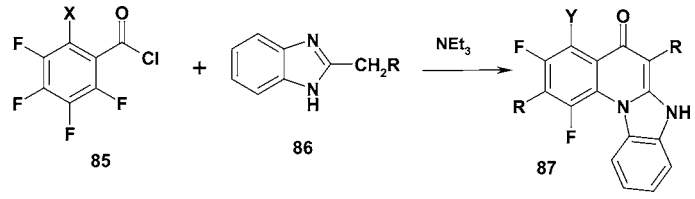
Condensations of 2-cyanomethylbenzimidazole or 2-benzoylmethylbenzimidazole **86** with polyfluorobenzoyl chlorides **85** provided new fluorinated benzimidazo[1,2-*a*]quinolones **87** (Scheme 27) [82].

The cycloaddition reaction of ylides generated from *N*-(ethoxycarbonyl)methyl-substituted ethyl 6,7-difluoro-, 6,7,8-trifluoro-, and 5,6,7,8-tetrafluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates **88** on the C=C bond of methyl metacrylate results in the [3 + 2] adducts, hexahydropyrrolo[1,2-*a*]quinolones **90** (Scheme 28) [83]. Another approach to [*a*]-fused fluoroquinolones is illustrated by the reaction of *N*-aminoquinolones **89** with acetylacetone and its derivatives, thus affording pyrazolo[1,5-*a*]quinolines **91** (Scheme 28) [84]. In the reaction of 3-acetyl (benzoyl)-substituted 5-oxo-7,8-difluoro-5,9*a*-dihydropyrazolo[1,5-*a*]quinolin-4-carboxylates and 5-methoxy derivative **91** with bromine, the *ipso*-substitution of acetyl (benzoyl) group takes place [85,86].



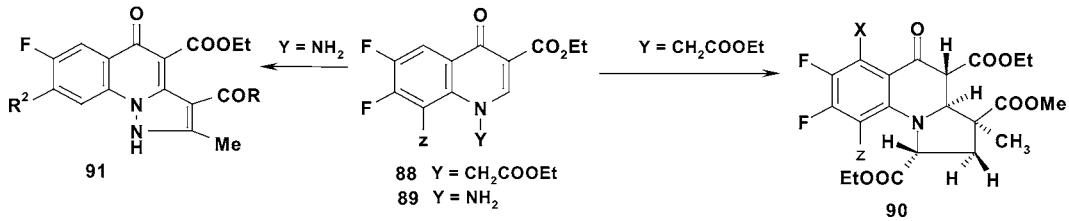
Y = H, F; X = NCH_3, X = S; R = H, F, NO_2, Br.

SCHEME 26



X = H, F; R = CN, COPh.

SCHEME 27

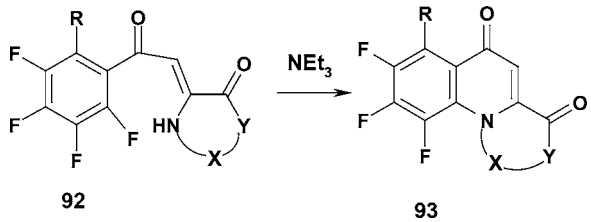


SCHEME 28

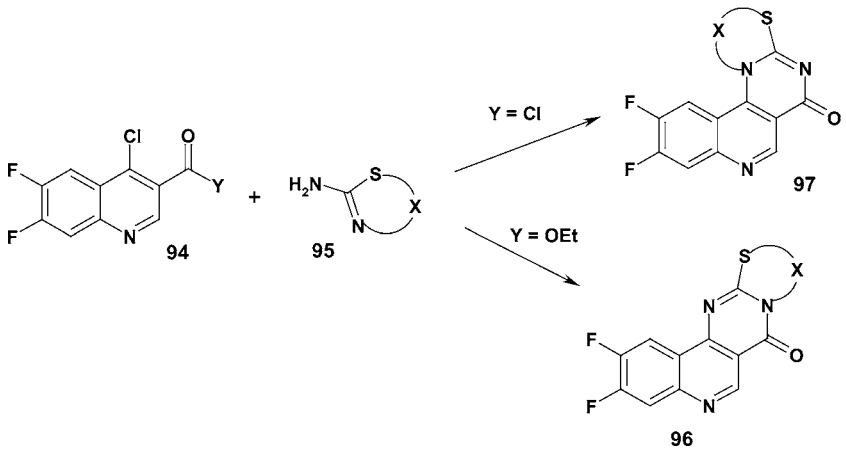
1,4-Oxazin-2-one **92** (Y = O, X = CH_2CH_2, R = F), obtained by condensation of pentafluorobenzoyl pyruvic acid with ethanolamine in refluxing dioxane, is able to undergo cyclization into 1,2,4,5-tetrahydro[1,4]oxazino[4,3-*a*]quinolin-4,6-dione **93** (Y = O, X = CH_2CH_2, R = F) [50]. On heating **92** (Y = NH, X = benzo, R = OH) in DMSO in the presence of NEt_3, the formation of 1,2,3-trifluoro-4-hydroxy-(5*H*)-5-oxoquinolino[1,2-*a*]-8*H*-quinoxalin-7-one **93** (Y = NH, X = benzo, R = OH) takes place (Scheme 29) [87].

The reaction of ethyl 4-chloro-6,7-difluoroquinolin-3-carboxylate **94** (Y = OEt) with 2-aminothiazoles **95** leads to pyrimido[*c*]-annelated quinolines **96**. Analogously, fluorinated thiazolo[2′,3′:2,3]pyrimido[4,5-*c*]quinolines **97** are formed from 4-chloro-6,7-difluoroquinolin-3-formyl chloride **94** (Y = Cl) and 2-aminothiazoles **95** (Scheme 30) [88,89].

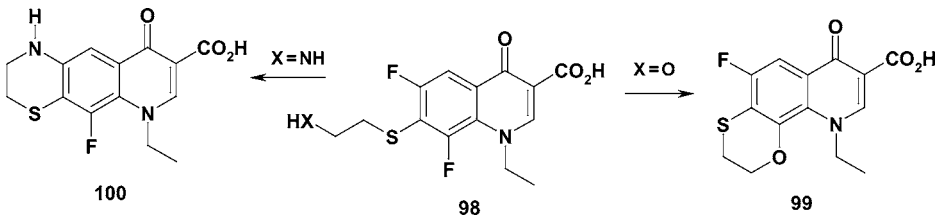
7-Thiosubstituted 6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxilic acids **98** were obtained by interaction of the corresponding 7-fluoro compound with 2-aminoethanthiol or 2-mercaptoethanol; the intramolecular cyclization of compounds **98** leads to [*g*]- and [*h*]-annelated fluoroquinolones **99** and **100** (Scheme 31) [90].



SCHEME 29



SCHEME 30

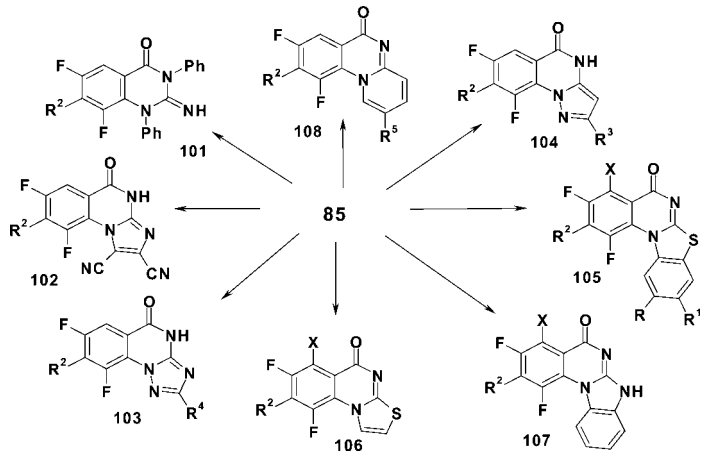


SCHEME 31

Fluorinated Quinazolinones. New synthetic ways to 2-iminoquinazolin-4-ones **101**, imidazo[2,1-*a*]-, pyrazolo-[1,5-*a*]-, and triazolo[1,5-*a*]quinazolin-5-ones **102–104**, thiazolo[3,2-*a*]-, benzthiazolo[3,2-*a*]-, and benzimidazo[3,2-*a*]quinazolin-5-ones **105–107** as well as pyrido[1,2-*a*]quinazolin-6-ones **108** have been proposed based on the reaction of tetrafluorobenzoyl chloride **85** with *N*,*N*′-binucleophiles (Scheme 32) [88,91,92].

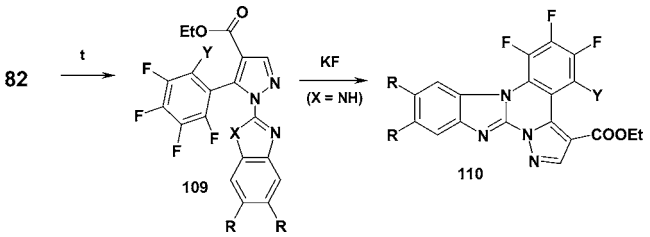
Cyclizations of ethyl 3-[β-(benzimidazol-2-yl)-hydrazino]-2-(polyfluorobenzoyl)-acrylates **82** caused by action of potassium fluoride or triethylbenzylammonium chloride in refluxing acetonitrile afford benzimidazo[1,2-*a*]pyrazolo[1,5-*c*]quinazoline **110** through the intermediate pyrazol-1-yl-substituted benzimidazoles **109** (Scheme 33) [93,94].

Some derivatives **110** were found to possess antitumor and tuberculostatic activities [75,81].



R = H, F; R^1 = H, OCH_3, F; R^2 = F, cycloalkylimino;
R^3 = H, Ph, R^4 = H, CF_3; R^5 = H, CH_3.

SCHEME 32

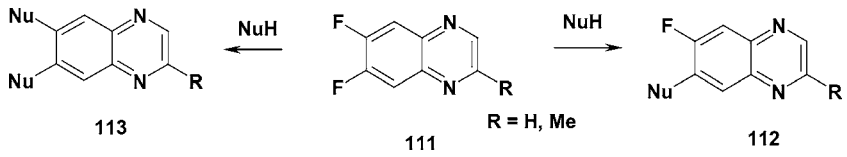


SCHEME 33

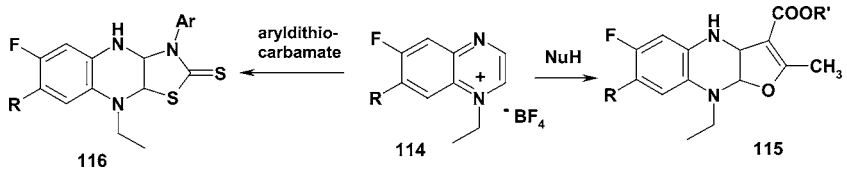
Fluorinated Quinoxalines. 6,7-Difluoroquinoxalines have been obtained from the corresponding 1,2-diamino-4,5-difluorobenzene and glyoxal, and quaternization of 6,7-difluoroquinoxalines by action of the Meervein reagent has been studied [95]. The reaction of 6,7-difluoroquinoxalines **111** with cycloalkylimines, hydrazine, sodium hydroxide as well as alkoxides was found to be dependent on the nature of nucleophile, thus resulting in the displacement of one or two fluorine atoms (Scheme 34) [96]. Also, the features of nucleophilic substitution of fluorine atoms in 2,3-disubstituted 6,7-difluoroquinoxalines by action of amines, sodium azide, and methoxide have been established [97]. As far as the amino-defluorination reaction is concerned, the leaving ability of fluorine atoms in 6,7-difluoroquinoxalin-1,4-dioxides is higher than that of the corresponding quinoxalines.

New methods for the synthesis of furo[2,3-*b*]- and thiazolo[4,5-*b*]-annelated tetrahydroquinoxalines **115, 116** have been proposed on the basis of the tandem nucleophilic addition A_N–A_N reactions of the quaternary quinoxalinium salts **114** with 1,3-bifunctional nucleophilic reagents (Scheme 35) [98].

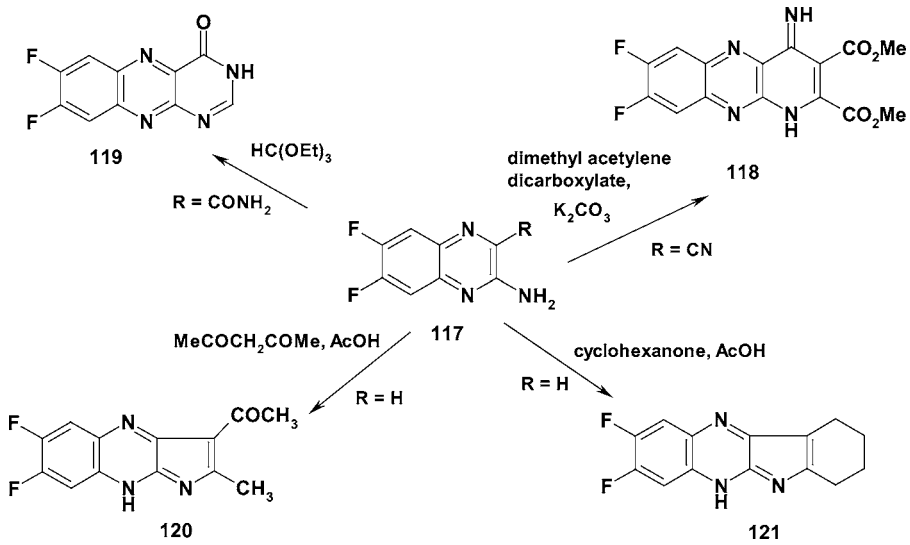
Fluorine-containing pyrido[2,3-*b*]- and pyrimido-[4,5-*b*]quinoxalines **118, 119** were obtained by condensations of 2-amino-3-cyano- and 2-amino-3-(aminocarbonyl)-6,7-difluoro quinoxalines **117** with dimethyl acetylene dicarboxylate and triethyl orthoformate, respectively (Scheme 36). A new approach



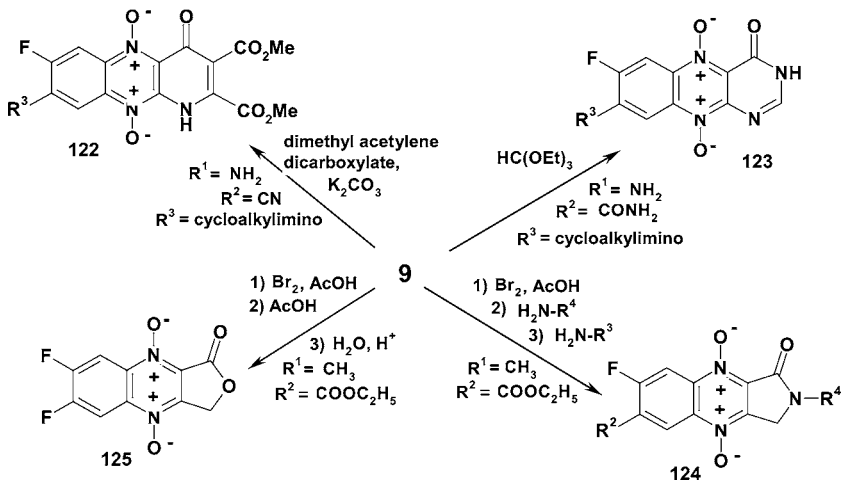
SCHEME 34



SCHEME 35



SCHEME 36



SCHEME 37

for the synthesis of pyrrolo[2,3-*b*]- and indolo[2,3-*b*]quinoxalines **120, 121** from 2-aminoquinoxalines **117** has been proposed by using the methodology of intramolecular substitution of hydrogen at C-3 in aminovinyl-substituted quinoxalines [99,100].

Fluorinated pyrido[2,3-*b*]quinoxalin-5,10-dioxides **122** and pyrimido[4,5-*b*]quinoxalin-5,10-dioxides **123** have been synthesized from 2,3-substituted quinoxalin-1,4-dioxides **9**. Hydrolysis of **9** (R = COOEt, $R^1 = CH_2OCOCH_3$) with HCl results in the formation of furo[3,4-*b*]quinoxalin-*N*,*N*-dioxide **125**. The reaction of **9** (R = COOEt, $R^1 = CH_2Br$) with primary alkylamines affords pyrrolo[3,4-*b*]quinoxalin-*N*,*N*-dioxides **124**, and the cyclization reaction is accompanied with the substitution of fluorine atom at C-7 (Scheme 37) [20,21,99].

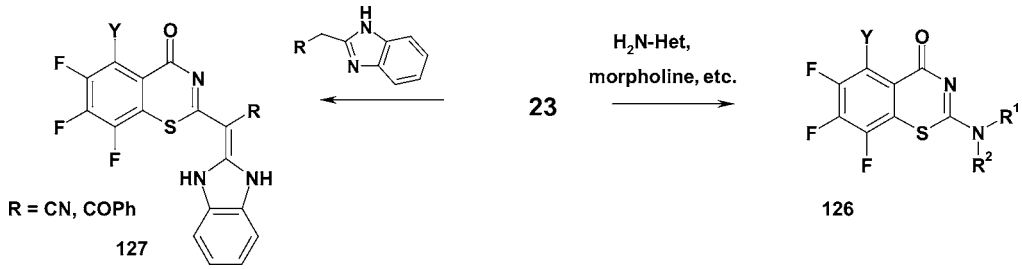
Fluorinated [1,3]benzothiazin-4-ones. The synthesis of fluorinated 2-substituted [1,3]benzothiazin-4-ones **126, 127** has been performed through interaction of polyfluorobenzoyl isothiocyanates **23** with cycloalkylimines or CH-active benzimidazoles (Scheme 38) [101].

Analogously, [1,3]-benzothiazinones **128** and their imidazo[2,1-*b*]-annelated derivatives **129** were obtained by reacting polyfluorobenzoyl chlorides **85** with *S*,*N*-dinucleophiles (Scheme 39) [101,102].

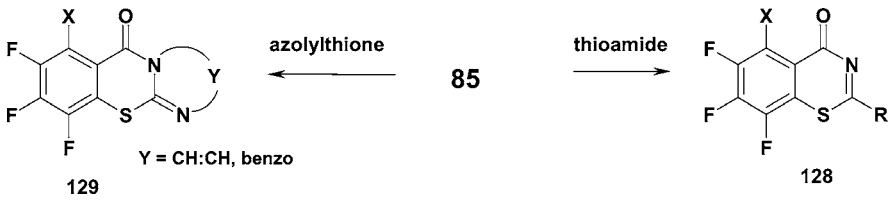
Fluorinated Benzotriazines. Fluorinated 3-phenyl-6-R_1-7-R_2-1,2,4-benzotriazines **131** (R_2 = F, R_1 = OAlk) have recently been obtained by means of cyclization of the corresponding 1,3,5-triphenylformazanes **130** in $HOAc/H_2SO_4$ mixture. The synthesis of benzotriazines **132** (R_1 = $OAlk_1$, R_2 = $OAlk_2$) can be performed by reacting 3-phenyl-6-R_1-7-fluoro-1,2,4-benzotriazines with sodium alkoxide (Scheme 40). Fluorinated 3-phenyl-1,2,4-benzotriazines and their derivatives proved to be active against severe diseases caused by smallpox and other pathogenic viruses [103].

CONCLUSION

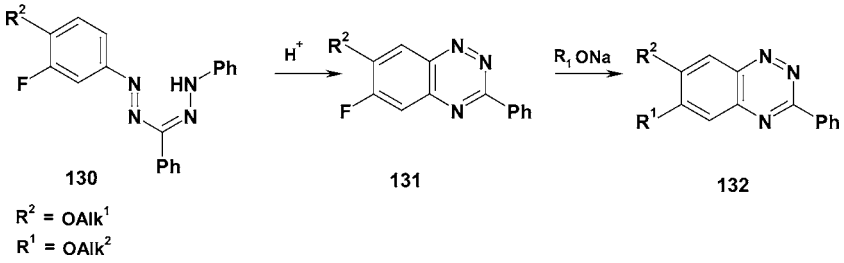
In a short review article, it is hardly possible to discuss in detail all aspects of the chemistry of fluorinated benzazoles and benzazines. Our interest toward this subject comes from the fact that fluorinated azaheterocycles are associated with a broad range of biological activities and a high potency exhibited by its many derivatives. This field of



SCHEME 38



SCHEME 39



SCHEME 40

heterocyclic chemistry appears to be an intriguing subject for further research and development of new drugs.

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