Fluoroarenes in the synthesis of benzoannulated nitrogen-containing heterocycles

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Methods for the synthesis of fluoro-containing benzazoles and benzazines from fluoroarenes (fluoroanilines, fluorobenzoic acids, fluoroacetophenones, fluorophenols, *etc.*) are described. The potentialities of the most important synthons are considered. Ways of constructing heterocycles with fluorine atoms in the annulated benzene fragment are discussed.

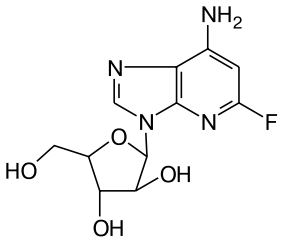
Key words: fluoroanilines, 4,5-difluoro-1,2-phenylenediamine, fluoro-containing 2-halobenzoyl chlorides, fluoro-containing benzamides, acetophenones, phenols, quinolines, quinazolines, benzotriazines, benzofuroxans, phenoxazines, benzimidazoles, benzoxazines, benzothiazines.

Introduction

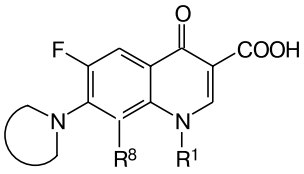
Interest in the creation of novel organofluorine compounds is due to their unique physicochemical and biological properties. Introduction of F atoms into organic molecules, especially into those fragments that are responsible for their biological activity, becomes an important aspect of pharmaceutical investigations, which in turn stimulates a search for new methodologies of the synthesis of diverse fluoro-containing compounds.[1—8]

The volume of the fluorine atom is close to that of the hydrogen atom; when the latter is replaced by a F atom, the primary metabolism of organic substances usually remains unchanged since enzymes in biological systems often do not distinguish between these compounds (mimicry effect). However, because C—F bonds are stronger than C—H bonds, their degradation is hindered and further metabolism proceeds anomalously.[2,9]

A well-known example of the inhibitors of nucleic exchange enzymes is 5-fluorouracil, which has become usual in oncological practice. This preparation is an antimetabolite of uracil, competes with it for thymidylate synthase, and breaks the formation of DNA. The recently obtained drug fludarabine inhibits DNA polymerase and is used to treat chronic lympholeucosis and lymphoma.[10] This compound is an analog of adenosine, in which the ribose residue is replaced by the arabinose residue and the purine ring bears the fluorine atom in position 2.



Fludarabine



Fluoroquinolones

Fluoroquinolones (6-fluoro-4-oxoquinoline-3-carboxylic acid derivatives[11—16]) constitute the most important class of antibacterial drugs. By inhibiting type II topoisomerase (DNA gyrase), they blockade the synthesis of RNA on the DNA matrix and, consequently, cause cells to perish.[17] The specific effect of fluoroquinolones on bacteria is that they inhibit DNA gyrase of bacteria but do not bind themselves to DNA topoisomerases of host cells. Leading pharmaceutical firms have already created and brought into medical practice a large group of drugs

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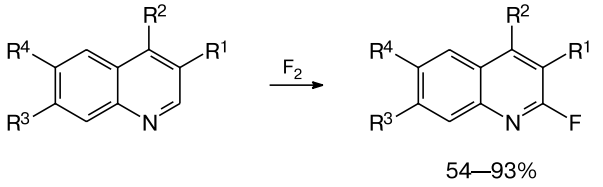
of this class such as pefloxacin, ciprofloxacin, levofloxacin, grepafloxacin, moxifloxacin, *etc.*[18]

In this review, we attempted to systematize the methods for the synthesis of benzazines and benzazoles containing fluorine atoms in the annulated benzene fragment with consideration for two fundamental approaches to the synthesis of fluoro-containing benzoannulated azaheterocycles. The first approach involves introduction of F atoms into a prepared heterocycle, while the second approach involves construction of cyclic systems from fluoro-containing synthons. The former approach has a number of limitations associated with the fact that selective introduction of F atoms into organic molecules is difficult. For instance, quinoline was directly fluorinated at the α-position[19,20] (Scheme 1), while electrophilic fluorination of its benzene ring was not selective (Scheme 2).[21,22]

Scheme 1



Reagents and conditions: 10% in nitrogen, I_2, CF_2Cl_2—$CFCl_2$.

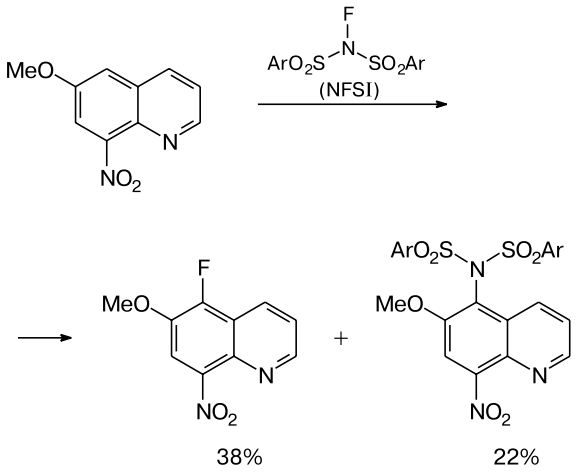
$R^1 = R^2 = R^3 = R^4 = H$ (**a**); $R^1 = R^4 = H$, $R^2 = R^3 = Cl$ (**b**);
$R^1 = Br$, $R^2 = R^3 = R^4 = H$ (**c**); $R^2 = Cl$, $R^1 = R^3 = R^4 = H$ (**d**);
$R^4 = Cl$, $R^1 = R^2 = R^3 = H$ (**e**); $R^1 = R^4 = H$, $R^2 = Cl$, $R^3 = CF_3$ (**f**)

Direct fluorination at position 5 of quinoline was described in Ref. 8 (Scheme 3). However, the yield of the target product was low and sulfone imide was isolated as a by-product.

A reaction of 1-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline with diethylaminosulfur trifluoride provides an example of selective fluorination giving a 6-fluoro derivative only.[23] However, the problem of selective fluorination still persists for a wide range of heterocycles.

In this context, we believe that the synthesis of fluoro-containing benzazoles and benzazines from fluoroarenes

Scheme 3



Conditions: 130 °C, 3 h.

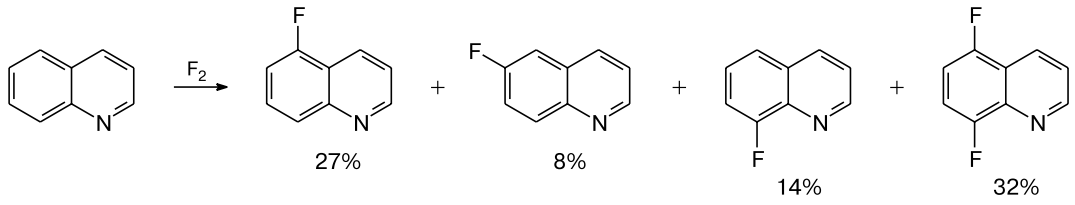
(fluoroanilines, fluorobenzoic acids, fluoroacetophenones, fluorophenols, *etc.*) is more promising. Here we considered the potentialities of the most important synthons and discussed ways of constructing, on their basis, heterocycles containing fluorine atoms in the benzene fragment. These ways can be represented by Scheme 4.

1. Fluorinated anilines and their derivatives in the synthesis of benzoannulated azaheterocycles

1.1. 2-Fluoro-, 3-fluoro-, and 4-fluoroanilines

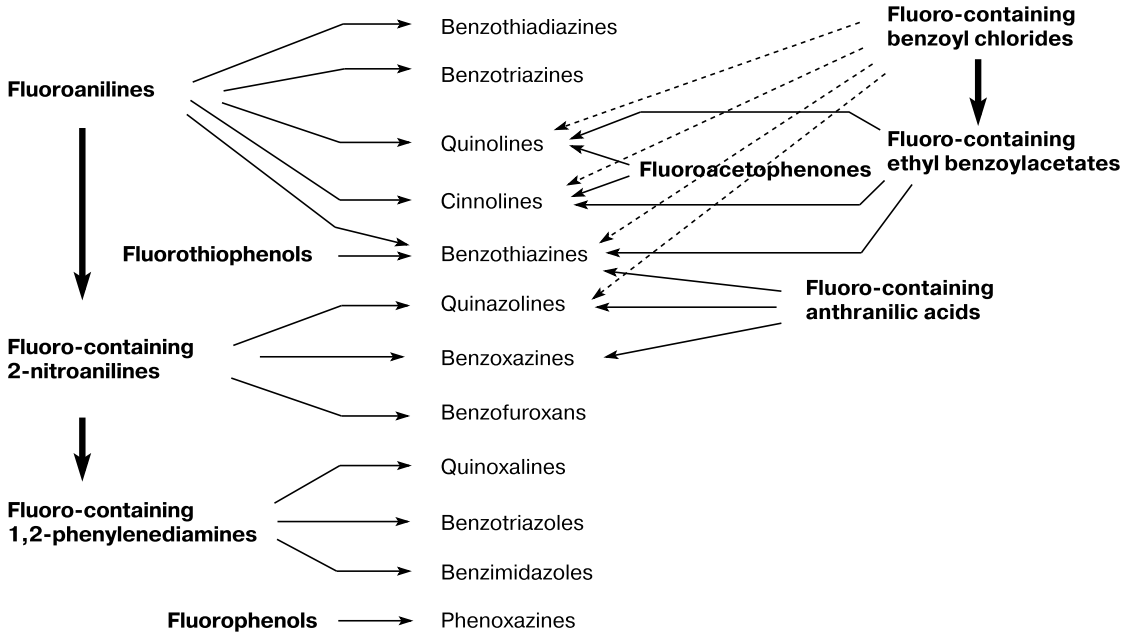
Monofluoroanilines are often used as synthons for the synthesis of benzazines containing a fluorine atom. For instance, reactions of 4-alkyl-2-fluoroanilines **1** with ethyl 2-acetylpropionate followed by cyclization of the resulting enamine **2** give 2,3,6-trialkyl-8-fluoro-4-hydroxyquinolines **3** (Scheme 5). Derivatives **3** are employed in agriculture.[24]

Scheme 2

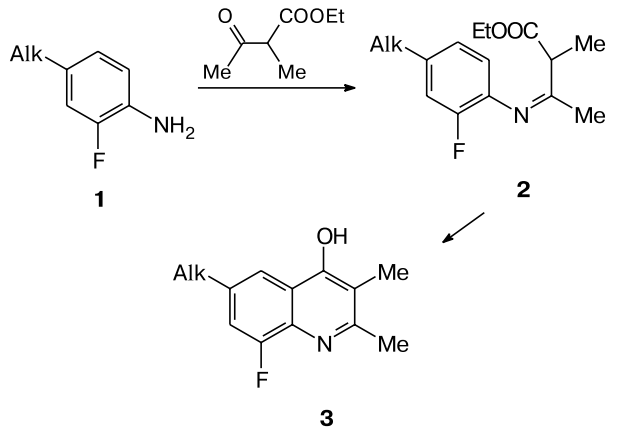


Reagents and conditions: N_2 (50 mL min^{-1}), 0 °C, H_2SO_4.

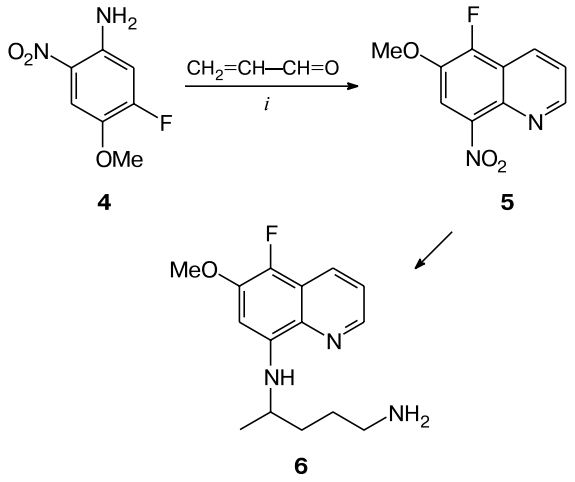
Scheme 4



Scheme 5



Scheme 6



i. H_3AsO_4, H_3PO_4.

The Skraup synthesis from 3-fluoroaniline **4** gives 5-fluoro-6-methoxy-8-nitroquinoline **5** (Scheme 6); compound **5** is used to prepare 5-fluoroprimaquine **6**, an analog of the known antimalaria drug.[25]

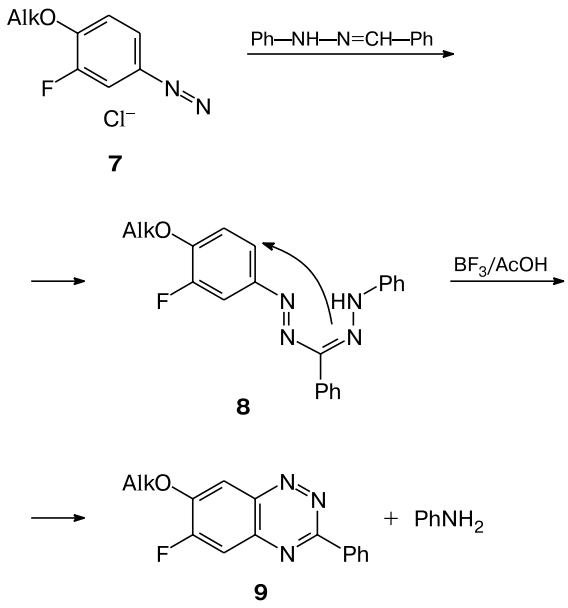
Diazotization of 3-fluoroanilines gives the corresponding 3-fluorobenzenediazonium chlorides **7**, which in turn can be transformed into 1,3,5-triphenylformazans **8**. In the BF_3/AcOH system, the latter undergo cyclization following an electrophilic attack with cleavage of the N—N bond and release of aniline. The final products are 7-alkoxy-6-fluoro-3-phenyl-1,2,4-benzotriazines **9** (Scheme 7). Fluoro-containing 3-phenyl-1,2,4-benzotriazines are of interest because of their antiviral effect (*e.g.*, on the smallpox virus[26]).

A reaction of 4-fluoroaniline **10** with 1,1,1-trifluoropentane-2,4-dione yields isomeric 6-fluoroquinolines **11** and **12** in the ratio 1 : 1 (Scheme 8).[27]

Amide **13a** obtained from 4-fluoroaniline (**10**) is thionated with Lawessonr's reagent. Cyclization of the resulting thioamide **13b** under UV light in the presence of $(Me_3Si)_3SiH$ (4 equiv.) in degassed benzene gives 1,3-dihydrofuro[3,4-*b*]quinoline **14** (Scheme 9).[28]

7-Fluoro-1-methyl-1,4-dihydro-9*H*-pyrazolo[4,3-*b*]-quinolin-9-one (**15**), which is the protein kinase C inhibitor, is obtained by cyclization of 4-[(4-fluorophenyl)-

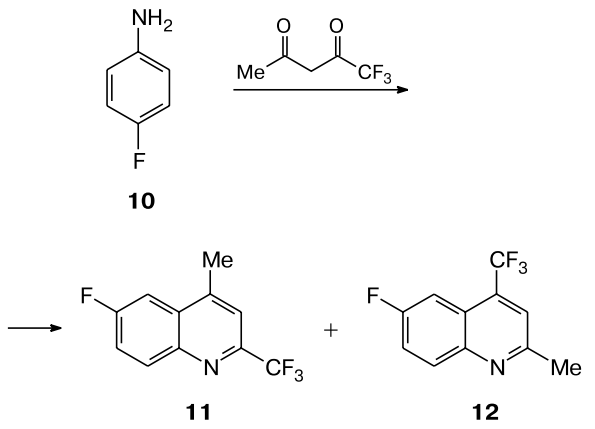
Scheme 7



amino]-1-methyl-1*H*-pyrazole-5-carboxylic acid (**16**). The latter is prepared from 4-fluoroaniline (**10**) and 4-iodo-1-methyl-1*H*-pyrazole-5-carboxylic acid (**17**) in water in the presence of a copper powder and sodium carbonate (Scheme 10).[29]

3-(Benzoxazol-2-yl)-4-fluoroaniline (**18**, X = O) and 3-(benzothiazol-2-yl)-4-fluoroaniline (**18**, X = S), which are obtained by condensation of 5-amino-2-fluorobenzoic acid (**19**) with 2-aminophenol or 2-aminobenzenethiol in polyphosphoric acid, are used to synthesize 7-benzoxazolyl- and 7-benzothiazolyl-6-fluoroquinolones **20** (Scheme 11).[30]

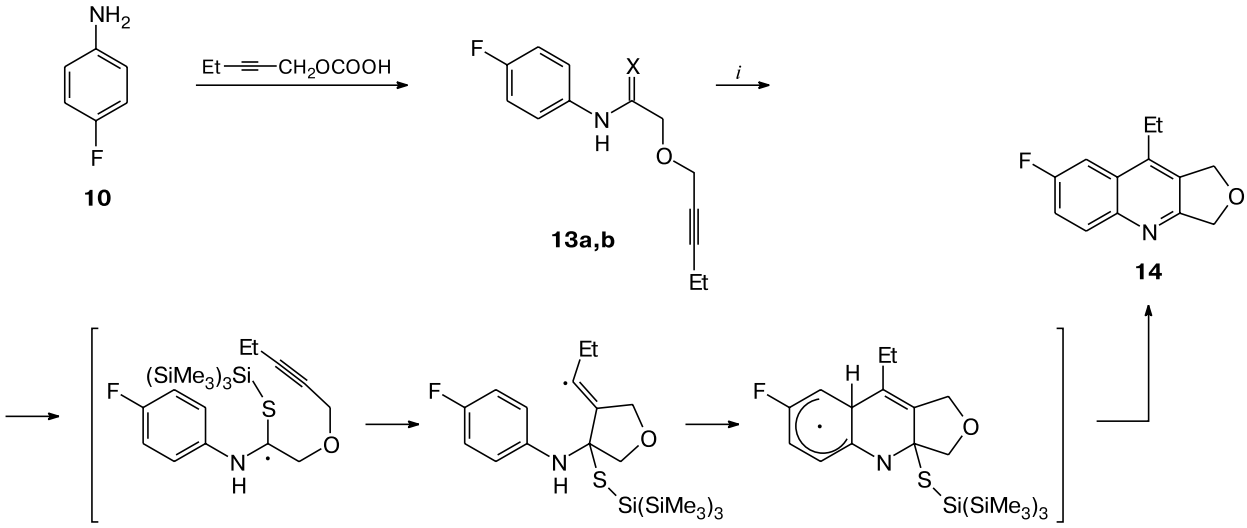
Scheme 8



Diazotization of 4-fluoroaniline (**10**) gives 4-fluorobenzenediazonium chloride (**21**), which undergoes coupling with ethyl acetoacetate to form hydrazone **22**. Intramolecular cyclization of the latter in chlorobenzene in the presence of $AlCl_3$ leads to 3-acetyl-6-fluoro-1*H*-cinnolin-4-one (**23**). Bromination of methyl ketone **23** under UV light yields 3-bromoacetyl-6-fluorocinnolone **24**, which reacts with thioamides to give 3-thiazolylcinnolones **25**, which exhibit antimicrobial activity (Scheme 12).[31,32]

Fluoro-containing cinnolin-4(1*H*)-ones, imidazo[2,1-*b*]thiazolylcinnolones, and pyrazolo[4,3-*c*]cinnolines that exhibit antibacterial and fungicidal effects are described in Ref. 33.

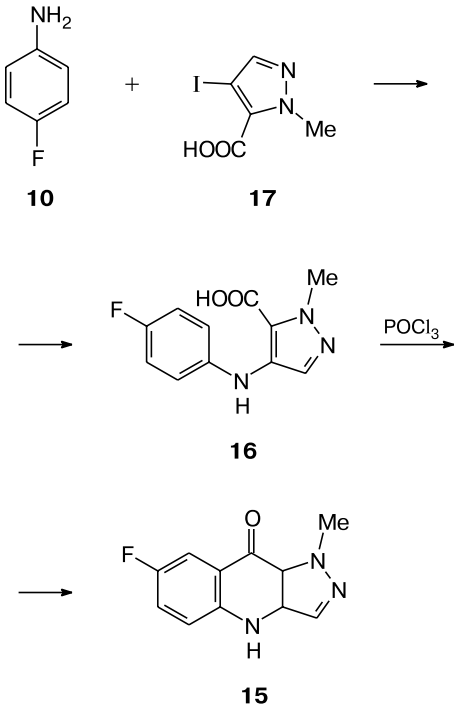
Scheme 9



i. 1) Lawesson´s reagent. 2) $(Me_3Si)_3SiH$, UV irradiation.

13: X = O (**a**), S (**b**)

Scheme 10



10 **17** **16** **15**

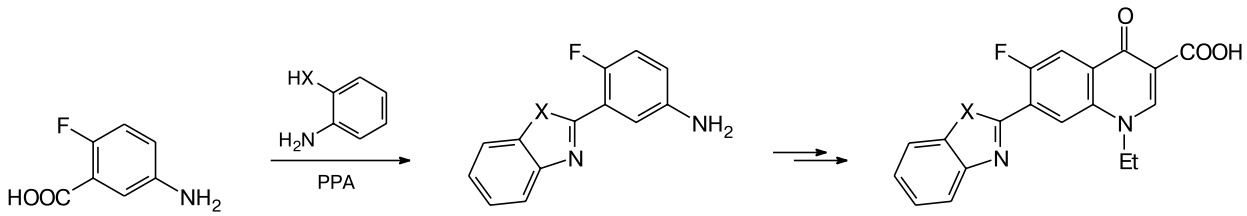
1.2. 3,4-Difluoro- and 3-chloro-4-fluoroanilines

One of the most important synthons for construction of fluoro-containing azaheterocycles is 3,4-difluoroaniline (**26**). Compound **26** can be prepared from *ortho*-difluorobenzene, a product of the difluorocarbene synthesis (Scheme 13).[34]

Condensation of 3,4-difluoroaniline (**26**) with ethyl ethoxymethylidenemalonate gives enamine **27**; its intramolecular cyclization leads to ester **28**, which is a key intermediate in the synthesis of some fluorooxoquinolinecarboxylic acids, including pefloxacin **29** (Scheme 14).[10]

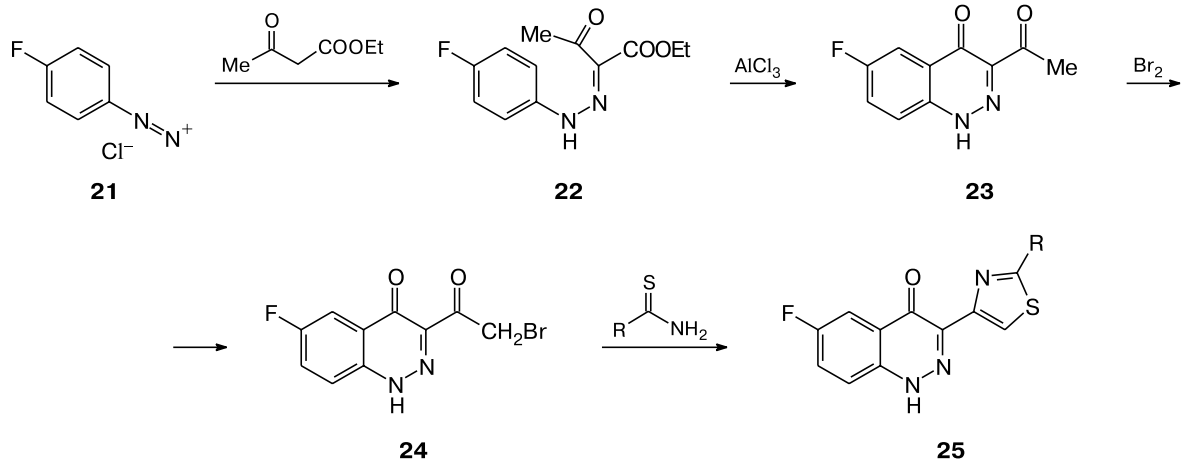
A search for new drugs of the fluoroquinolone series is in progress; an important way of modifying fluoroquinolones involves introduction of various substituents into their benzene ring. For instance, prior to the synthesis of 8-substituted fluoroquinolones, a desired substituent (SMe, Me, or CH_2OAc) should be introduced into position 2 of 3,4-difluoro-*N*-benzoylaniline.[35] For the synthesis of fluoroquinolones, 3-chloro-4-fluoroaniline is often used instead of 3,4-difluoroaniline and the cyclization is carried out by heating enamines in polyphosphoric acid or its ester.[36]

Scheme 11



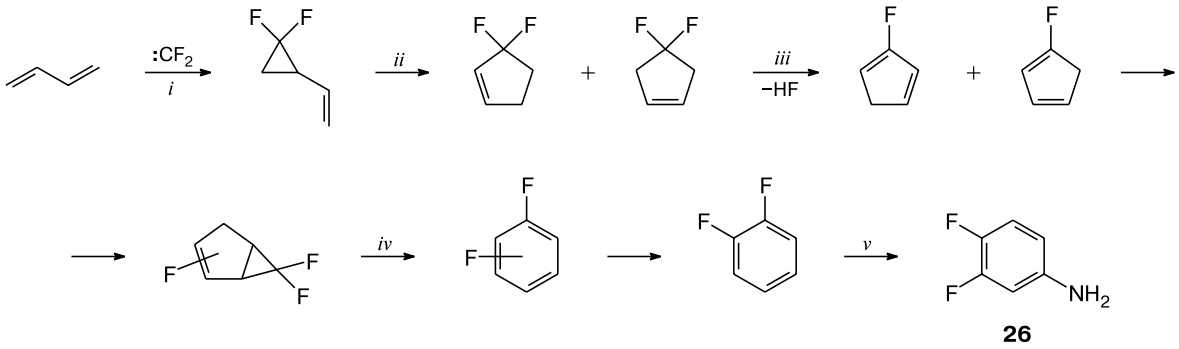
19 **18** **20**

Scheme 12



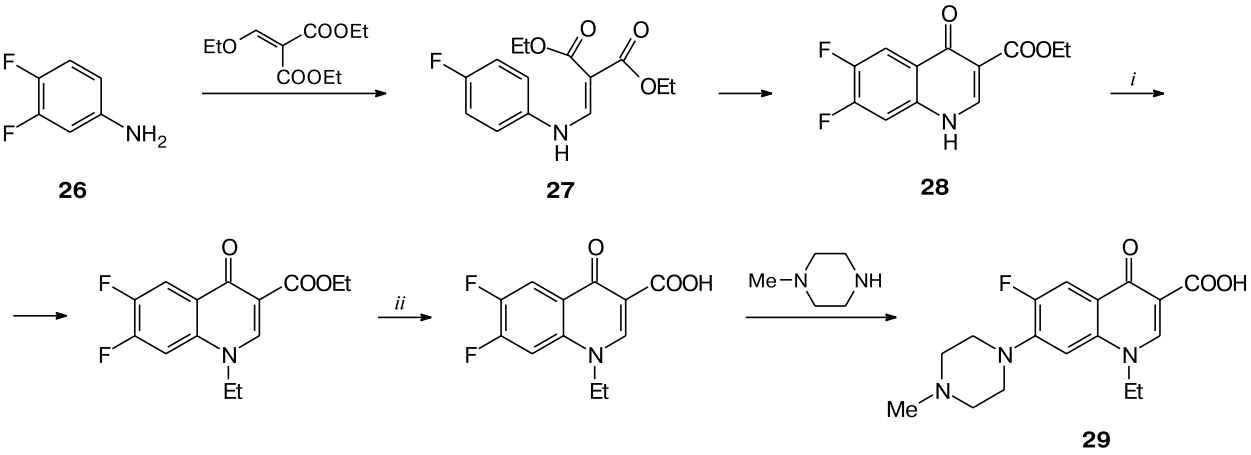
21 **22** **23** **24** **25**

Scheme 13



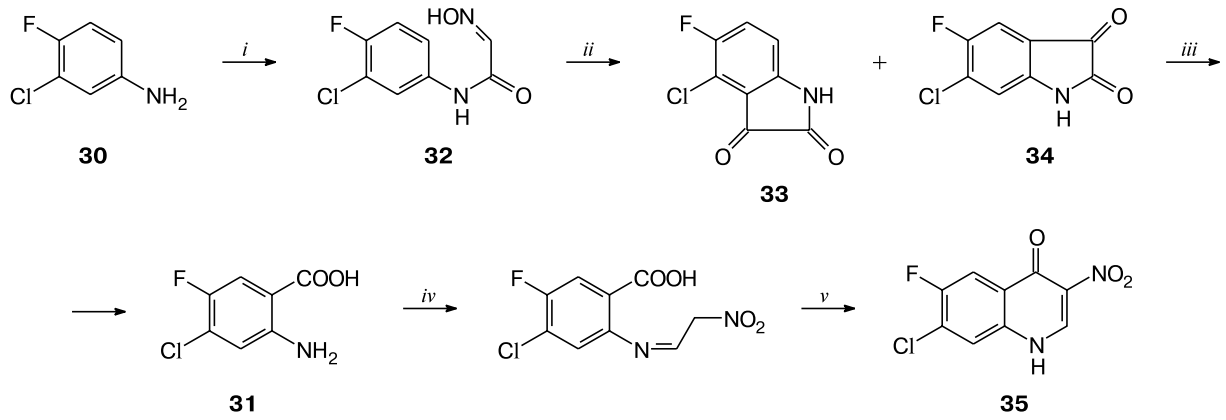
Reagents and conditions: *i*. 270 °C; *ii*. 400 °C; *iii*. 650 °C; *iv*. 650—700 °C; *v*. 1) HNO_3, H_2SO_4; 2) Sn, HCl.

Sceme 14



Reagents and conditions: *i*. EtBr, K_2CO_3; *ii*. HCl, AcOH, 110—120 °C.

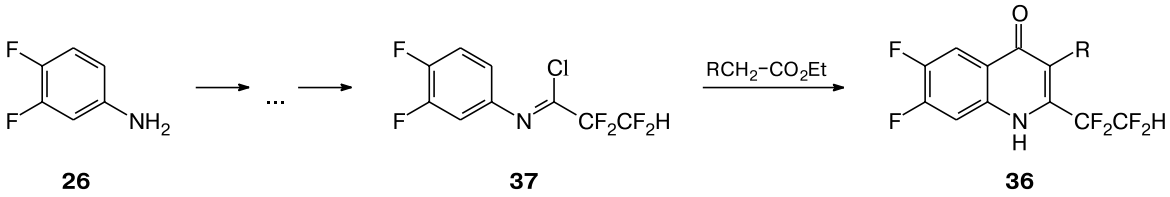
Scheme 15



Reagents: *i*. $CCl_3CH(OH)_2$, $NH_2OH \cdot HCl$; *ii*. H_2SO_4; *iii*. H_2O_2; *iv*. $HON{=}CHCH_2NO_2$; *v*. $(MeCO_2)_2O$, $MeCO_2Na$.

3-Chloro-4-fluoroaniline (**30**) can be easily transformed into 3-chloro-4-fluoroanthranilic acid **31**. A reaction of compound **30** with chloral hydrate and hydroxylamine yields isonitrosoacetanilide **32**; its cyclization in H_2SO_4 leads to a mixture of indole-2,3-diones **33** and **34** (Scheme 15).[37] Oxidation of this mixture with H_2O_2 gives

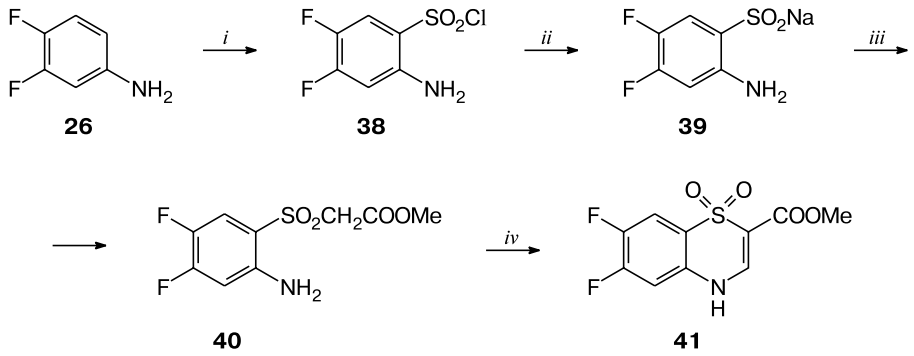
Scheme 16



26 **37** **36**

R = CN, COOEt

Scheme 17



26 **38** **39** **40** **41**

Reagents and conditions: *i*. HSO_3Cl, $SOCl_2$; *ii*. Na_2SO_3; *iii*. $BrCH_2COOMe$, EtOH; *iv*. $HC(OEt_3)$, 140 °C.

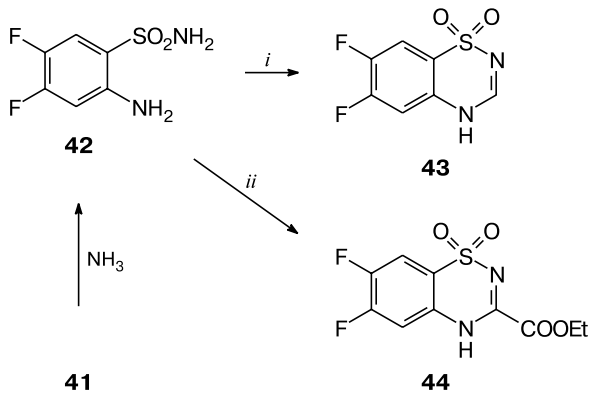
2-amino-4-chloro-5-fluorobenzoic acid (**31**), from which fluoroquinolone **35** was obtained. This way of constructing fluoroquinolones allows additional modifications of position 3 of the pyridone ring.

3,4-Difluoroaniline (**26**) is employed for the synthesis of 6,7-difluoro-2-polyfluoroalkylquinolones **36**. For this purpose, compound **26** is acylated with polyfluoroalkenoic anhydride and the resulting anilide is transformed into the corresponding imino chloride **37**. Cyclization of the latter with ethyl malonate or ethyl cyanoacetate yields quinolones **36** (Scheme 16).[38]

Using 3,4-difluoroaniline as a starting material, one can obtain sulfur analogs of fluoroquinolones: fluoro-containing 1,4-benzothiazines and 1,2,4-benzothiadiazines. Chlorosulfonation of 3,4-difluoroaniline (**26**) gives 2-amino-4,5-difluorobenzenesulfonyl chloride (**38**), which is reduced in a basic medium to the corresponding sodium sulfinate **39**. Alkylation of the latter with methyl bromoacetate in ethanol followed by condensation of intermediate **40** with triethyl orthoformate yields 6,7-difluoro-2-methoxycarbonyl-4*H*-1,4-benzothiazine 1,1-dioxide (**41**) (Scheme 17).[39]

Ammonolysis of sulfonyl chloride **38** gives sulfonamide **42**; its cyclization with triethyl orthoformate or ethyl oxalate affords 1,2,4-benzothiadiazines **43** and **44** (Scheme 18).[40]

Scheme 18



42 **43** **41** **44**

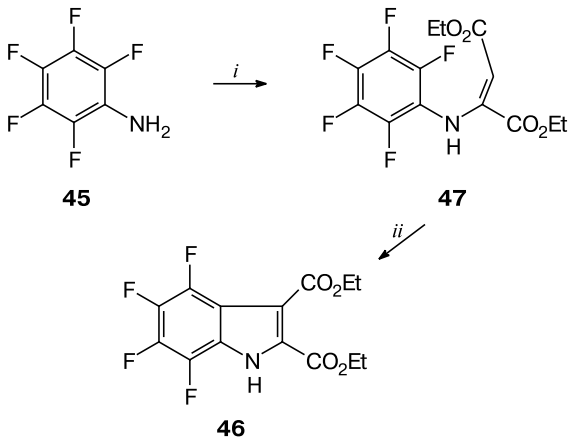
Reagents: *i*. $HC(OEt)_3$; *ii*. EtOOC—COOEt.

1.3. Polyfluorinated anilines and nitrobenzenes

The presence of a F atom in the *ortho*-position relative to the reactive group makes polyfluoroanilines and polyfluoronitrobenzenes convenient synthons for the synthesis of azaheterocycles *via* nucleophilic substitution of fluorine. For instance, pentafluoroaniline (**45**) serves as

a starting reagent for the preparation of polyfluorinated indole **46** according to Scheme 19 (see Ref. 41): aminofumarate **47** obtained from compound **45** and diethyl acetylenedicarboxylate undergoes intramolecular cyclization into indole **46**.

Scheme 19



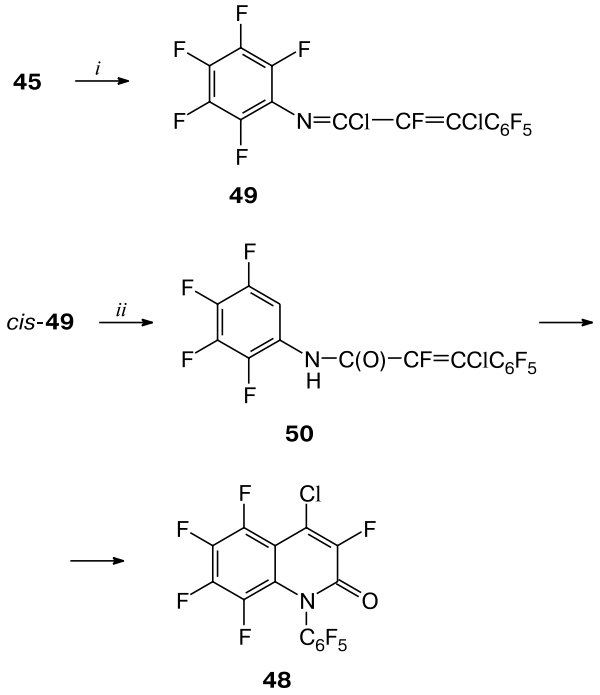
Reagents: *i*. NaH, THF, EtOOC—≡—COOEt; *ii*. NaH, DMF.

In Ref. 42, the synthesis of 4-chloro-3,5,6,7,8-pentafluoro-1-pentafluorophenylquinolin-2-one (**48**) is described. Pentafluoroaniline (**45**) reacts with *cis*-tetrachloro-2-fluoro-1-pentafluorophenylpropene in the presence of $AlCl_3$ to give a mixture of *cis*- and *trans*-aza dienes **49**. Hydrolysis of the mixture in a water—dioxane solution of K_2CO_3 yields the corresponding amides **50**. The amide obtained from the *cis*-isomer readily undergoes intramolecular cyclization into compound **48** (Scheme 20).

Electrochemical oxidation of pentafluoroaniline (**45**) gives a mixture of octafluorophenazine (**51**) and decafluoroazobenzene (**52**) (Scheme 21).[43]

Diazotization of polyfluoroanilines followed by reduction of the corresponding diazonium salts affords polyfluorophenylhydrazines **53**. After their acylation, the resulting hydrazides **54** are thionated with P_2S_5 to give polyfluorophenyl thiohydrazides **55**. Finally, cyclization of the latter yields 2-substituted 5,6,8-trifluoro- and 5,6,7,8-tetrafluoro-4*H*-1,3,4-benzothiadiazines **56** (Scheme 22).[44]

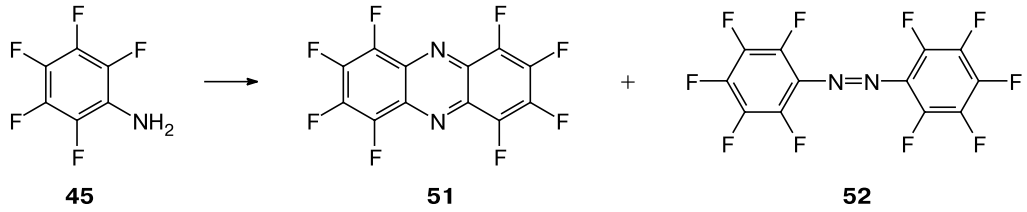
Scheme 20



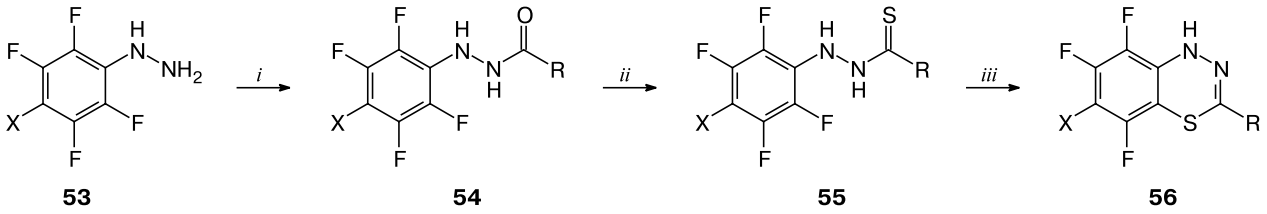
Reagents: *i*. *cis*-$C_6F_5CCl{=}CFCCl_3$, $AlCl_3$; *ii*. K_2CO_3.

2,3,4-Trifluoronitrobenzene (**57**) is a starting material for the preparation of (*S*)-(−)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-[1,4]benzoxazine (**58**), the most important intermediate in the synthesis of the antibacterial drug levofloxacin. Several routes to fluoro-containing stereoisomers of 3-methyl- and 2-methyl-2*H*-[1,4]benzoxazines were proposed.[45] For instance, compound **57** reacts with (*R*)-propane-1,2-diol in THF in the presence of NaH to give a mixture of (*R*)-3,4-difluoro-2-(2-hydroxypropoxy)-nitrobenzene and (*R*)-3,4-difluoro-2-(1-hydroxypropan-2-yloxy)nitrobenzene in the ratio 3 : 2. The mixture is transformed into mesylates **59** and **60**; this is followed by reduction of the nitro group, cyclization in the presence of potassium *tert*-butoxide, and separation of benzoxazines **58** and **61** by column chromatography (Scheme 23).

Scheme 21



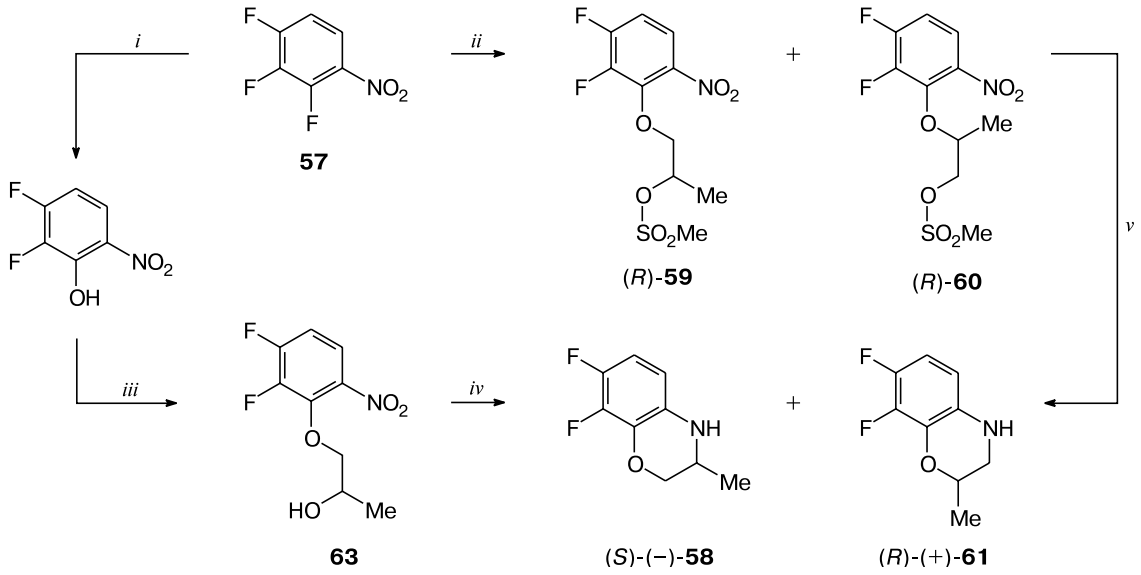
Scheme 22

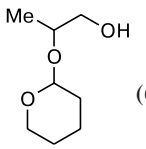


X = H, F; R = Me, Et, Ph

Reagents and conditions: *i*. $(RCO)_2O$ or PhCOCl, NEt_3; *ii*. P_2S_5; *iii*. DMF, 80—120 °C.

Scheme 23



Reagents and conditions: *i*. HO^-; *ii*. 1) (*R*)-$HOCH_2CH(OH)Me$, 2) $MeSO_2Cl$; *iii*. 1) (*S*)- or (*R*)-**62**,  (**62**), 2) removal of the tetrahydropyranyloxy group; *iv*. 1) $MeSO_2Cl$; 2) H_2, Pd/C; 3) Bu^tOK; *v*. 1) H_2, Pd/C; 2) Bu^tOK.

Another route to [1,4]benzoxazine **58** involves condensation of 2,3-difluoro-6-nitrophenol (prepared by hydrolysis of 2,3,4-trifluoronitrobenzene (**57**)) with (*S*)- or (*R*)-2-(tetrahydropyran-2-yloxy)propanol **62** (see Ref. 45). This is followed by elimination of the tetrahydropyranyloxy group on ion-exchange resin, transformation of the resulting compounds **63** into mesylates, reduction of the nitro group, and cyclization in the presence of potassium *tert*-butoxide. For construction of fluoro-containing benzoxazines, a reaction of 2,3,4-trifluoronitrobenzene (**57**) with (*R*)-2-(ethoxyethoxy)propan-1-ol or (*R*)-1-benzyloxypropan-2-ol is also used.[45]

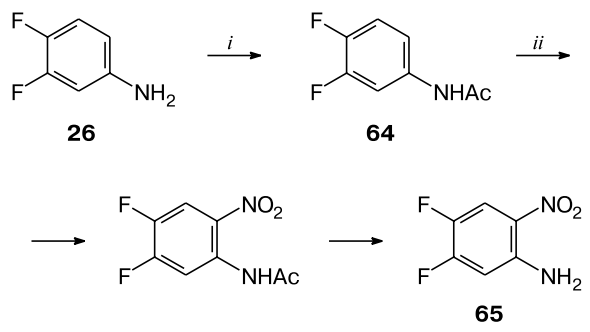
1.4. 4,5-Difluoro-2-nitroaniline

Nitration of 3,4-difluoroacetanilide **64** under usual conditions gives 4,5-difluoro-2-nitroaniline **65** (Scheme 24).

Diazotization of 4,5-difluoro-2-nitroaniline **65** followed by treatment of the diazonium salt with NaN_3 affords nitro azide **66**, which can be easily transformed into 5,6-difluorobenzofuroxan (**67**), an important intermediate in the synthesis of fused azaheterocycles (Scheme 25).[46]

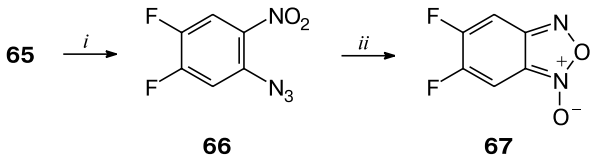
The Beirut reaction with 5,6-difluorobenzofuroxan (**67**) gives the corresponding 6,7-difluoroquinoxaline 1,4-dioxides **68**. For instance, 2-cyano-6,7-difluoro-

Scheme 24



Reagents: *i*. Ac_2O; *ii*. HNO_3/H_2SO_4.

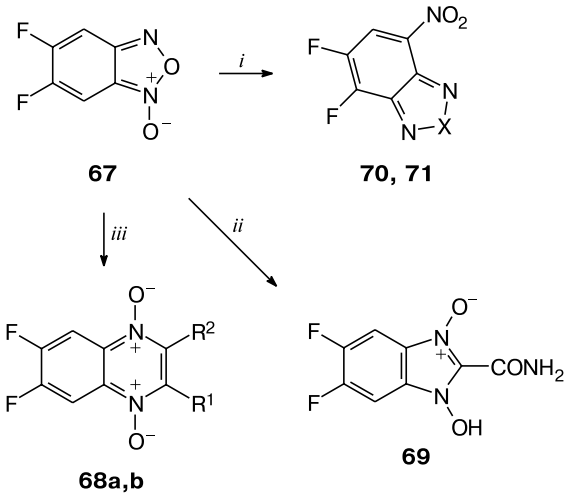
Scheme 25



Reagents: *i*. $NaNO_2$, NaN_3; *ii*. AcOH.

3-phenylquinoxaline 1,4-dioxide (**68a**) is obtained by treating furoxan **67** with benzoylacetonitrile in the presence of triethylamine and 6,7-difluoro-2,3-dimethylquinoxaline 1,4-dioxide (**68b**) results from a reaction of furoxan **67** with ethyl methyl ketone in DMF in the presence of ammonia (Scheme 26).[47] The reaction of compound **67** with cyanoacetamide leads to 2-carbamoyl-5,6-difluoro-1-hydroxybenzimidazole 3-oxide (**69**)

Scheme 26



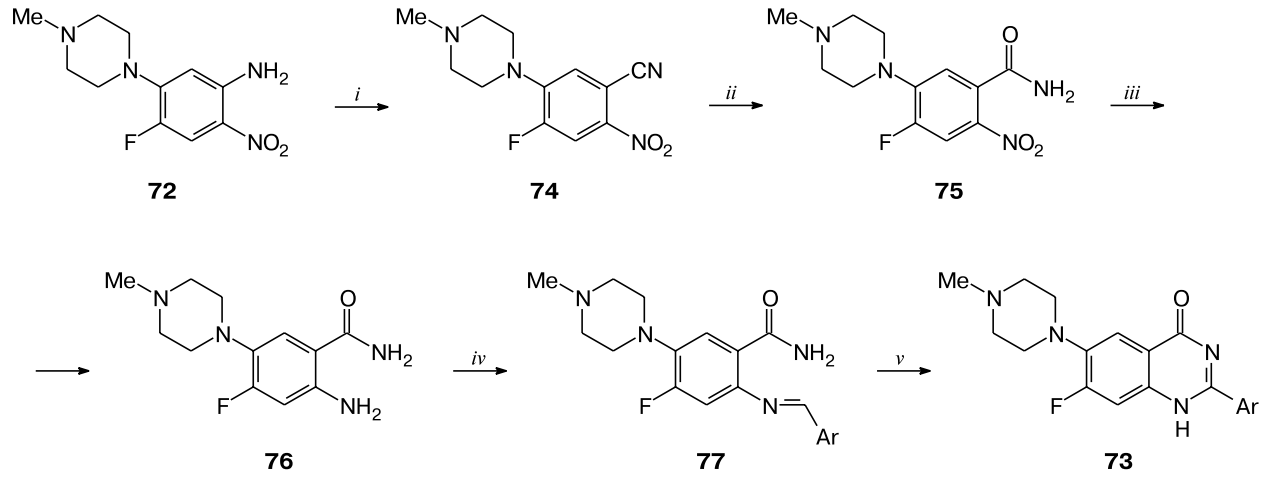
R^1 = CN, R^2 = Ph (**68a**); R^1 = R^2 = Me (**68b**)
X = O (**70**), N—Ar (**71**)

i. $NaNO_2$ or ArN_2^+; *ii*. $NCCH_2CONH_2$; *iii*. $R^1COCH_2R^2$.

(Scheme 26).[48] The Boulton—Katritzky rearrangement gives nitrobenzofurazans **70** and nitrobenzotriazoles **71**.[49,50]

4-Fluoro-2-nitroaniline **72** serves as a convenient synthon for the preparation of 2-aryl-7-fluoro-6-(4-methylpiperazin-1-yl)-4(3*H*)-quinazolin-4-ones **73** (Scheme 27).[51] The diazonium salt obtained from 2-nitroaniline **72** can be transformed into 2-nitrobenzonitrile **74** using the Sandmeyer reaction. Hydrolysis of the latter in H_2SO_4 gives benzamide **75**. Reduction of the nitro group in compound **75** with $SnCl_2$ followed by reactions of 2-aminobenzamide **76** with substituted

Scheme 27



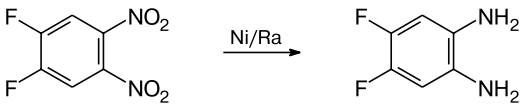
Reagents: KNO_2/H_2SO_4, CuCN; *ii*. H_2SO_4; *iii*. $SnCl_2$/HCl; *iv*. ArCHO/EtOH; *v*. $CuCl_2$.

benzaldehydes yields 2-arylideneamino-4-fluoro-5-(4-methyl-piperazin-1-yl)benzamides **77**. They undergo cyclization when heated in the presence of $CuCl_2$. It should be noted that 7-fluoroquinazolinones **73** exhibit antitumor activity.[51]

1.5. 4,5-Difluoro-1,2-phenylenediamine

Catalytic reduction of 4,5-difluoro-2-nitroaniline (**65**) gives 4,5-difluoro-1,2-phenylenediamine (**78**), an important intermediate in the synthesis of fluoro-containing benzazines and benzazoles (Scheme 28).[52]

Scheme 28



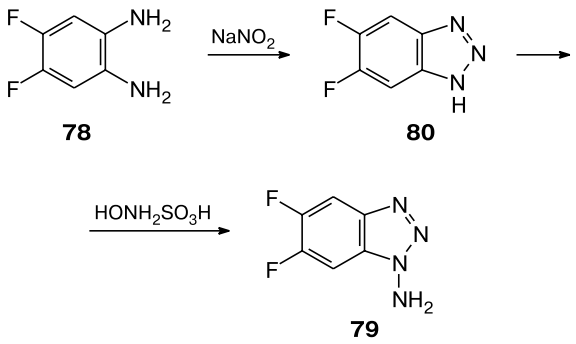
65 **78**

For instance, 1-amino-5,6-difluorobenzotriazole **79** is obtained from difluorophenylenediamine **78** by nitrosation in aqueous acetic acid and amination of product **80** with hydroxylamine-*O*-sulfonic acid at 65—80 °C (Scheme 29).[53]

4,5-Difluoro-1,2-dehydrobenzene **81** is generated in room-temperature oxidation of amine **79** with lead tetraacetate in dry CH_2Cl_2 (Scheme 30). Under these conditions, 4,5-difluoro-1,2-dehydrobenzene **81** dimerizes into tetrafluorobiphenylene **82**. Using anthracene, tetraphenylcyclopentadienone, and furan as "traps" for *in situ* released **81**, one can obtain adducts **83**—**85**.[53]

A reaction of 4,5-difluoro-1,2-phenylenediamine (**78**) with ethyl cyanoacetate gives 5,6-difluoro-1*H*-benzimidazol-2-ylacetonitrile (**86**). Its condensation with β-oxo esters yields pyrido[1,2-*a*]benzimidazoles **87** (Scheme 31). Some of compounds **87** have the effect on pathogenic *Orthopoxviruses*.[54] Condensation of diamine **78** with carbon disulfide in boiling ethanol in the presence of triethylamine gives 5,6-difluoro-2-mercaptobenzimidazole **88**. This compound smoothly reacts with aliphatic and aromatic ketones at room temperature in the presence of catalytic amounts of H_2SO_4 to give 2-R-6,7-difluoro-3-methylbenzimidazo[2,1-*b*]thiazoles **89** (see Scheme 31).[55]

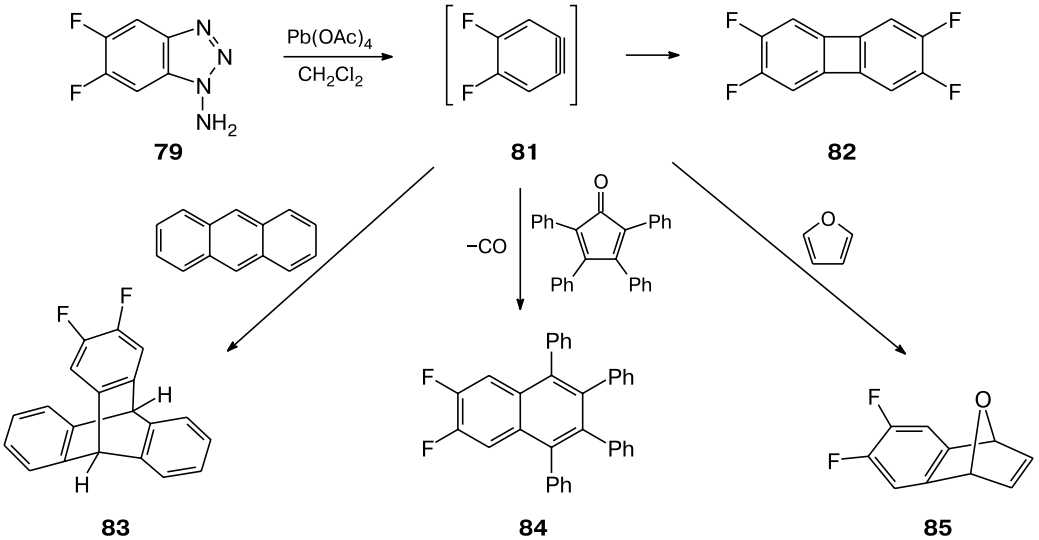
Scheme 29



78 **80** **79**

6,7-Difluoroquinoxaline (**90**) prepared by cyclization of diamine (**78**) with glyoxal[52] easily undergoes quaternization under the action of $Et_3O^+BF_4^-$ (Meerweinrs reagent) in CH_2Cl_2. Using 1-ethyl-6,7-difluoroquinoxalinium tetrafluoroborate (**91**), one can obtain a series of fused quinoxalines (Scheme 32).[52] For instance, reactions of quinoxalinium salt **91** with N-aryldithiocarbamic acids and β-oxo acids as enolates (bornyl acetoacetate and ethyl acetoacetate) give tetrahydrothiazolo[4,5-*b*]- and tetrahydrofuro[2,3-*b*]quinoxalines **92** and **93** (see Scheme 32).[56,57]

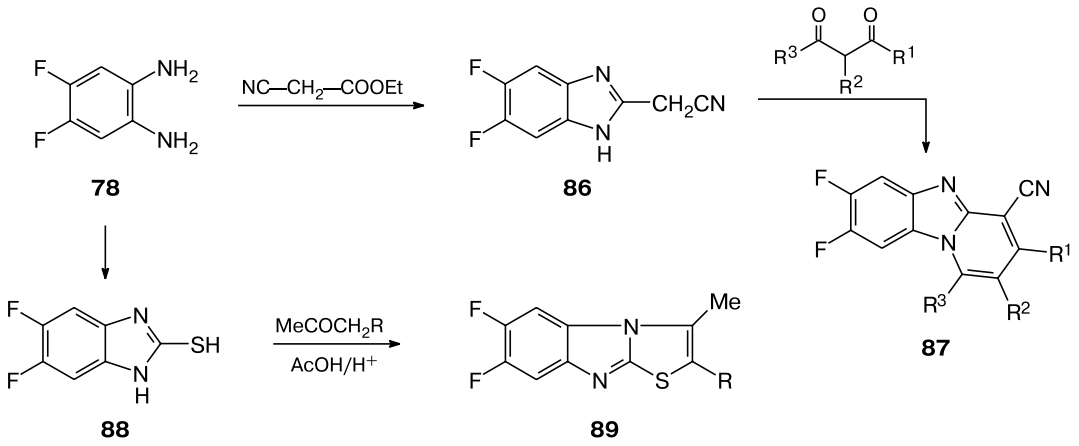
Scheme 30



79 **81** **82**

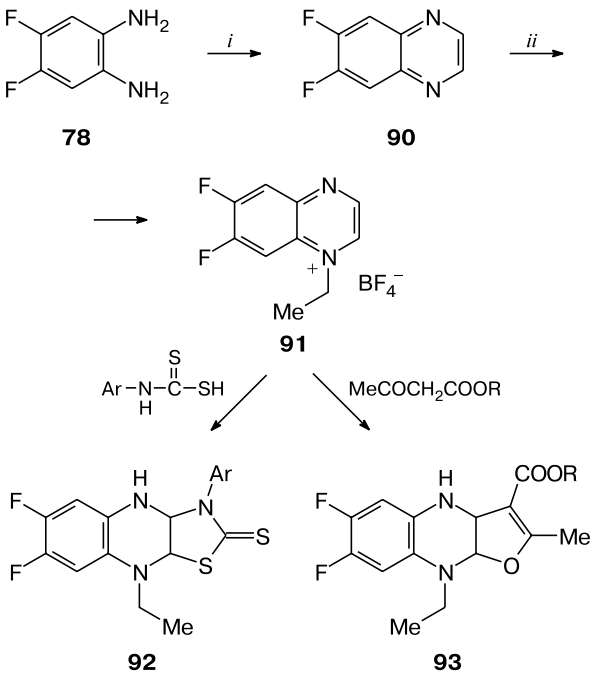
83 **84** **85**

Scheme 31



R = H, Me, COMe, COPh, COOEt; R^1 = OH, Me, CH_2Br; R^2 = H, COOAlk; R^3 = H, OH, OAlk, Cl, NR′R″

Scheme 32



R = Et, bornyl

i. H(O)C—C(O)H; *ii*. Meerweinr's reagent.

1.6. 4-Fluoro-1,2-phenylenediamine

6-Fluoroquinoxalinones **94** containing a trifluoromethyl group in position 3 are known to inhibit the reverse transcriptase of HIV-1. To obtain them, 4-fluoro-1,2-phenylenediamine (**95**) is treated with hexafluoropropylene oxide (HFPO) under basic conditions, the NH fragment is protected, and quinoxalinone **96** is made to react with lithium cyclopropylacetylenide. Then the NH group in compound **97** is alkylated (or acylated) and the protective groups are removed (Scheme 33).[58]

The synthesis of 3-anilinoquinoxalinone **98** from *N*-substituted 4-fluoro-1,2-phenylenediamine **99** involves cyclization of the latter with ethyl oxalate followed by treatment of the intermediate with $POCl_3$. The resulting quinoxaline **100** is used to obtain compound **98**, which is an efficient glycogen phosphorylase inhibitor (Scheme 34).[59]

The synthesis of 6-fluoro-3-methyl-1*H*-quinoxalin-2-one (**101**) from N-substituted 4-fluoro-1,2-phenylenediamine **102** was proposed in Ref. 60. 4-Fluoroaniline (**10**) is acylated with α-chloropropionyl chloride, compound **103** is nitrated at the *ortho*-position relative to the amide group, and the nitro group in compound **104** is reduced. Cyclization of compound **102** in the presence of $NaHCO_3$ followed by oxidation of compound **105** with H_2O_2 yields product **101** (Scheme 35).

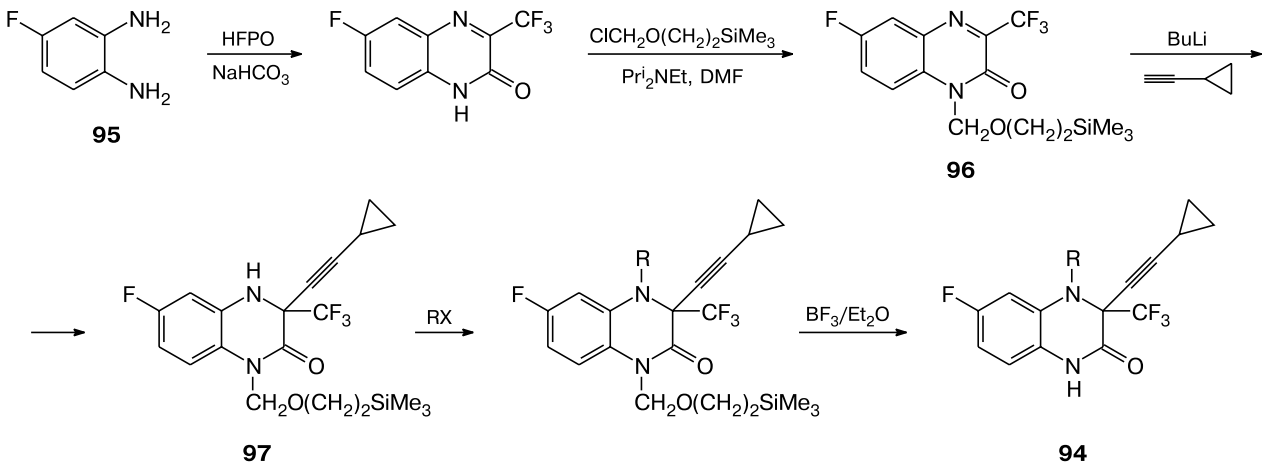
2. Fluoro-containing benzoic acid derivatives in the synthesis of benzoannulated azaheterocycles

2.1. Fluoro-containing benzoyl chlorides

Reactions of accessible fluoro-containing benzoyl chlorides with bifunctional nucleophiles provide a convenient route to a number of fluoro-containing heterocycles: fluoroquinolones, [*a*]- and [*b*]-annulated quinazolinones, and benzothiazinones.

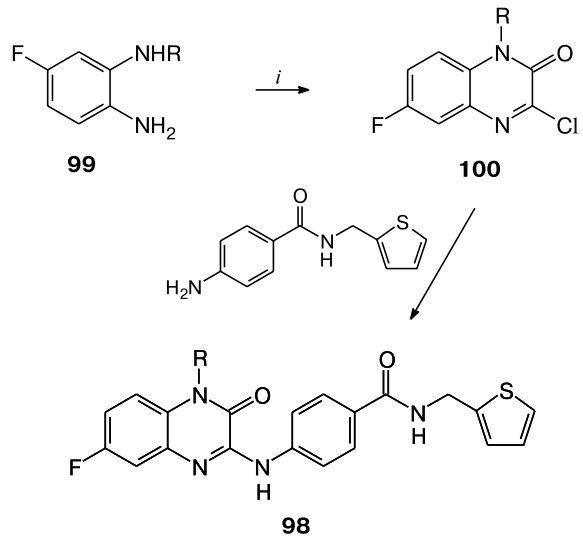
For instance, acylation of α-azaheterylacetonitriles **106** with acid chlorides **107a,b** in the presence of triethylamine gives cyano ketones **108**. Depending on the heterocyclic residue, compounds **108** can be transformed into thiazoloquinolones **109**, benzothiazoloquinolones

Scheme 33



R is allyl, cyclopropylmethyl, COORr, benzyl, propargyl, *etc*.

Scheme 34



i. 1) EtOOC—COOEt; 2) $POCl_3$, DMF.

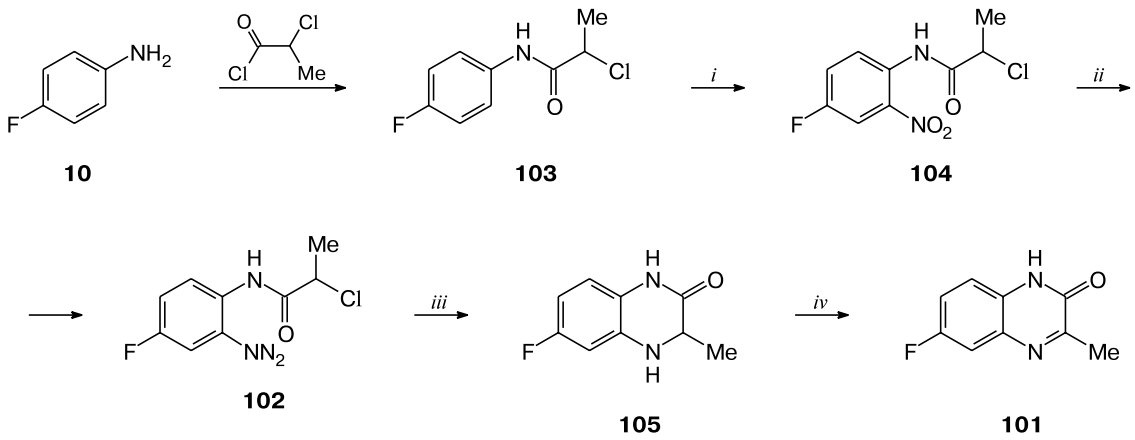
110, or benzimidazoquinolones **111** (heating in DMF), as well as into quinolinoquinolones **112** (reflux in acetonitrile in the presence of diazabicycloundec-7-ene (DBU)) (Scheme 36).[61,62]

Quinolones **113** can be obtained by reactions of 2,4,5-trifluorobenzoyl chloride (**114**) with enamines **115** as C,N-dinucleophiles; intermediate acylated enamines resist isolation (Scheme 37).[63]

Reactions of fluoro-containing benzoyl chlorides **116a,b** with *S*-ethylthiourea as an N,Nr-dinucleophile under mild conditions yield open-chain derivatives **117a,b**; when heated in DMF, they undergo cyclization into 1*H*-quinazolin-4-ones **118** (Scheme 38).[64]

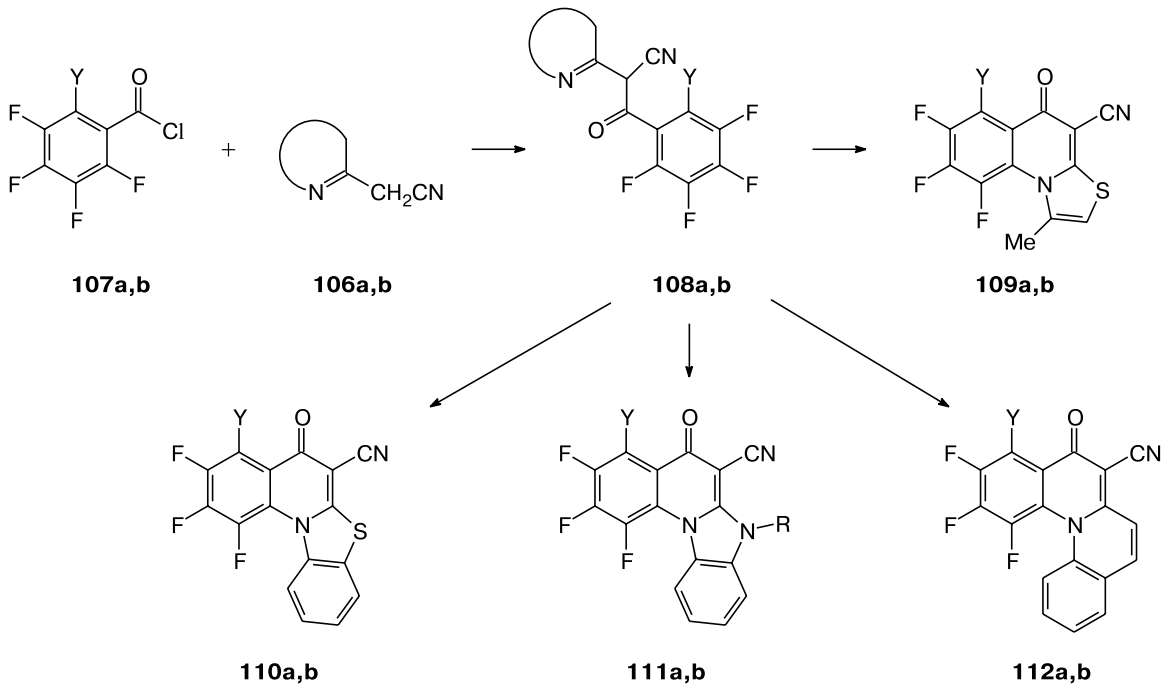
A distinctive feature of the reactions of tetrafluorobenzoyl chloride **107a** with 2-aminopyridines **119** is that acylation occurs at both endocyclic and exocyclic N atoms and that heating of diaroyl derivatives **120** in boiling toluene in the presence of triethylamine gives

Scheme 35



Reagents: *i*. HNO_3/AcO or KNO_3/H_2SO_4; *ii*. Fe/AcOH, H_2O/DMF; *iii*. NaI/$NaHCO_3$; *iv*. H_2O_2/NaOH.

Scheme 36



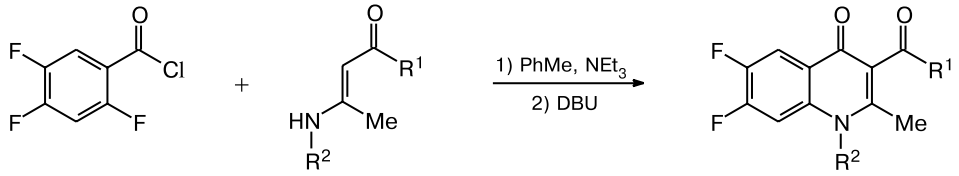
107a,b **106a,b** **108a,b** **109a,b**

110a,b **111a,b** **112a,b**

106—112: Y = H (**a**), F (**b**)

: pyridin-2-yl, quinolin-2-yl, 1*H*-benzimidazol-2-yl, 1-methylbenzimidazol-2-yl, benzothiazol-2-yl, 4-methylthiazol-2-yl.

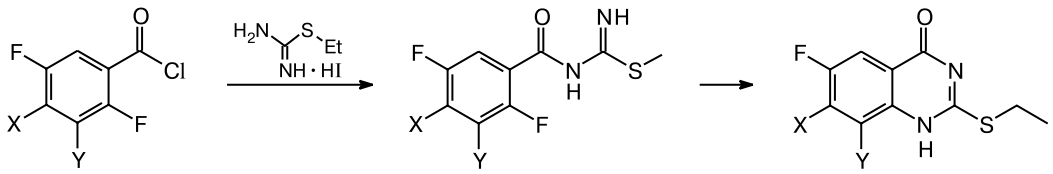
Scheme 37



114 **115** **113**

R^1 = Me, Ph; R^2 = Pr^n, Ph

Scheme 38

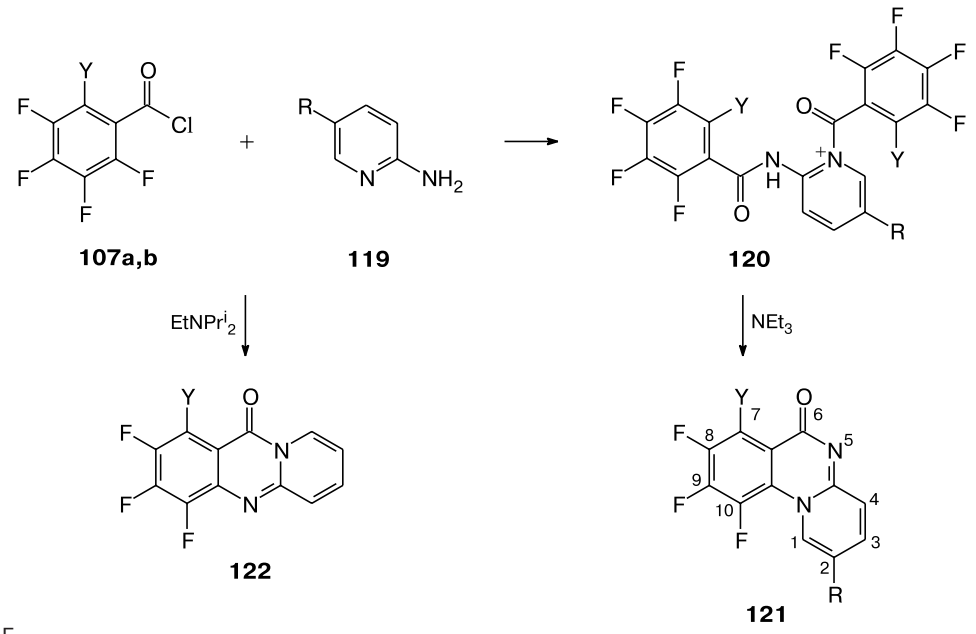


116a,b **117a,b** **118a,b**

116—118: X = Y = F (**a**); X = Cl, Y = H (**b**)

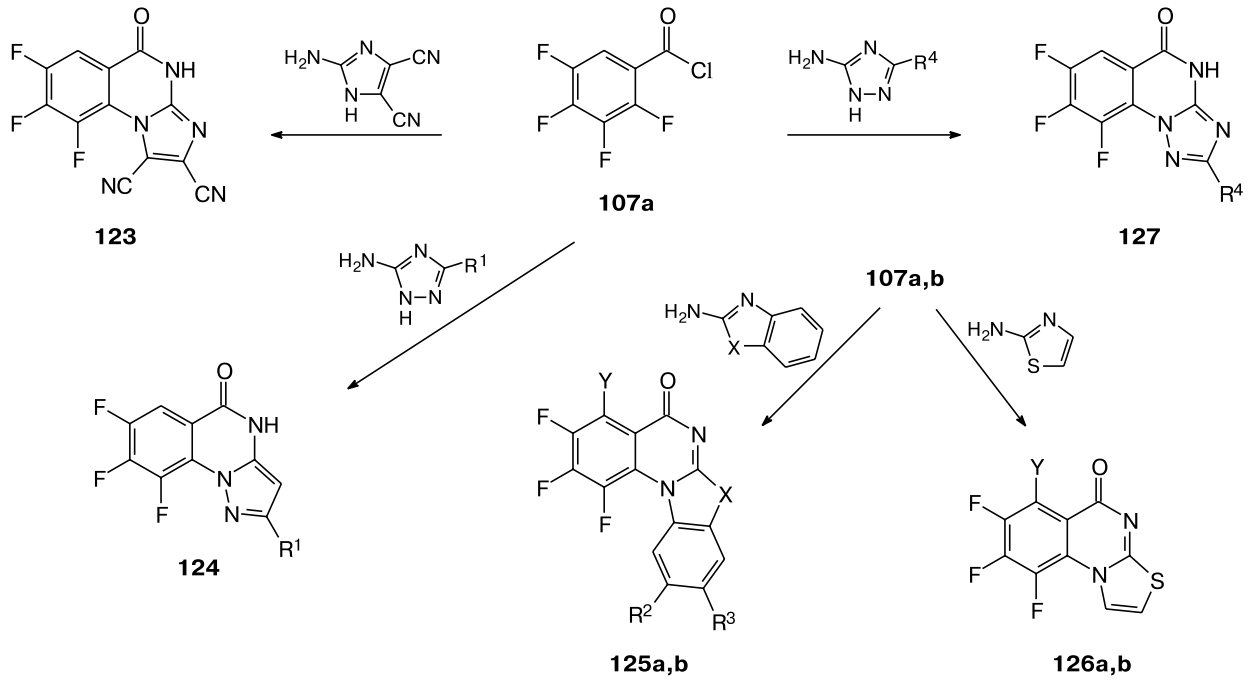
pyridoquinazolinones **121** (Scheme 39).[65] Angular structure **121** (Y = H) is confirmed by the coupling constants $J(F^{10},H^1)$ and $J(F^{10},H^2)$ in the ^{19}F NMR spectrum and by 2D heteronuclear experiments (HetCOR and HMBC). With pentafluorobenzoyl chloride (**107b**), this reaction yields a mixture of products **121** (Y = F) and **122** (Y = F). The use of ethyl(diisopropyl)amine as a base in reactions of polyfluorobenzoyl chlorides **107a,b** with 2-aminopyridine affords individual quinazolin-4-ones **122** (Y = H, F).[66]

Scheme 39



[*a*]-Annulated quinazolin-4-ones **123**—**127** are obtained from polyfluorobenzoyl chlorides **107a,b** and N,N´-dinucleophiles (aminoimidazoles, aminopyrazoles, aminotriazoles, or aminothiazoles). Heating of acid chlorides **107** with aminoimidazole, aminopyrazoles, or aminotriazoles yields benzamides, the exocyclic N atom being acylated. Cyclization of benzamides into tricyclic derivatives **123**, **124**, and **127** occurs in boiling toluene in the presence of NEt_3 or in boiling acetonitrile in the presence of DBU (Scheme 40).[67] The angular structure of

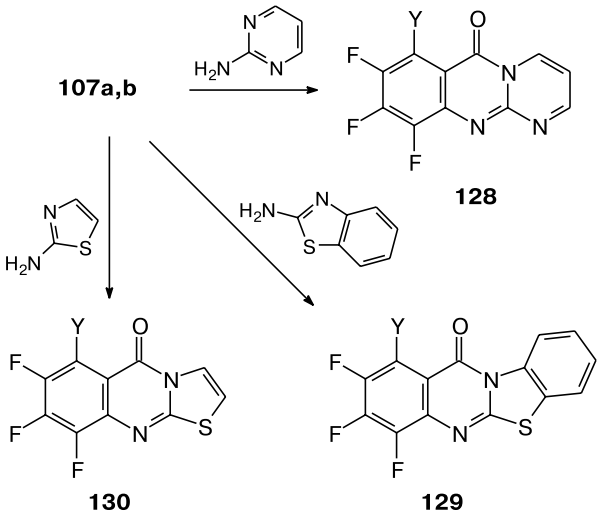
Scheme 40



derivatives **125** and **126** obtained by cyclization of acylated heterylamines in diphenyl ether was confirmed by the spin-spin coupling of the F atom in position 8 of the quinazoline ring with the proton of the thiazole or benzazole fragment (J = 4.5—6.8 Hz).

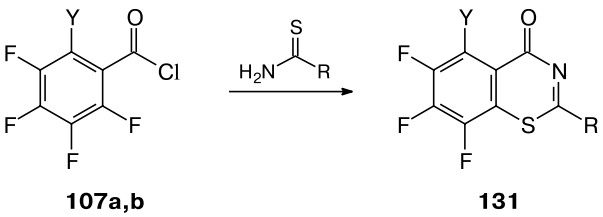
The synthesis of [*b*]-annulated 4(3*H*)-quinazolinones is described in Ref. 66. Compounds **128—130** are obtained by room-temperature cyclocondensation of 2-aminoazaheterocycles with polyfluorobenzoyl chlorides **107** in CH_2Cl_2 in the presence of ethyl(diisopropyl)amine (Scheme 41). The linear structure of compound **129** was proved by X-ray diffraction analysis; structure **128** is confirmed by the coupling constant $^3J_{C,H}$ for the carbonyl C atom and the proton of the pyrimidine ring.

Scheme 41



Heating of polyfluorobenzoyl chlorides **107a,b** with thioamides gives compounds **131** (Scheme 42); *N*-acylated intermediates cannot be isolated under these conditions.[68] It should be noted that this synthesis of various 2-substituted benzothiazinones is limited since many thioamides are not easily accessible.

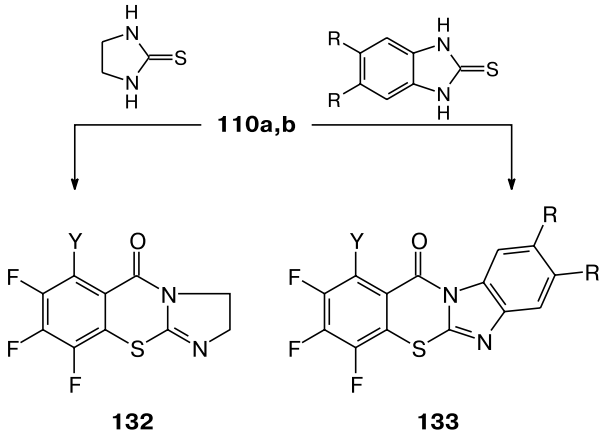
Scheme 42



Y = H (**a**), F (**b**), R = 4-Cl-C_6H_4, 4-Me-C_6H_4, 2-pyridyl

Reactions of acid chlorides **107a,b** with imidazolidine-2-thione in pyridine at 80 °C afford benzothiazinone **132**. Analogously, benzimidazole-2-thiones react with compounds **107a,b** under heating in toluene to give tetracyclic derivatives **137** (Scheme 43).[69]

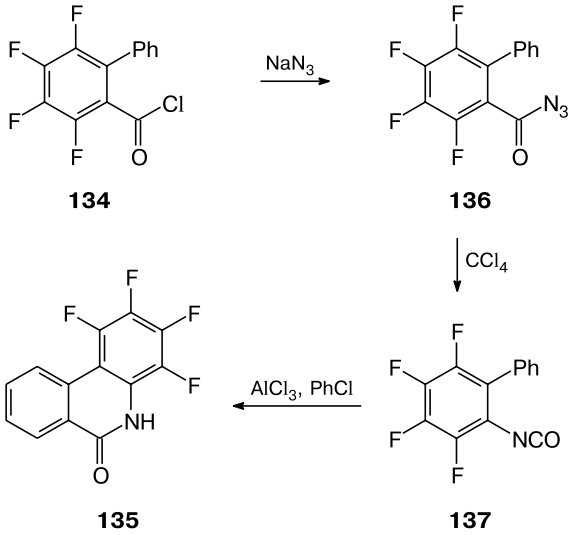
Scheme 43



Y = H, F; R = H, F, Cl, Me

Tetrafluorobenzoyl chloride **134** containing a phenyl substituent is employed for the synthesis of phenanthridin-6-one **135** (Scheme 44).[70] For this purpose, 3,4,5,6-tetrafluoro-2-phenylbenzoyl azide **136** (prepared from acid chloride **134**) is subjected to the Curtius rearrangement into isocyanate **137** and the latter undergoes cyclization into phenanthridin-6-one **135** on heating in the presence of $AlCl_3$ (see Scheme 44).

Scheme 44



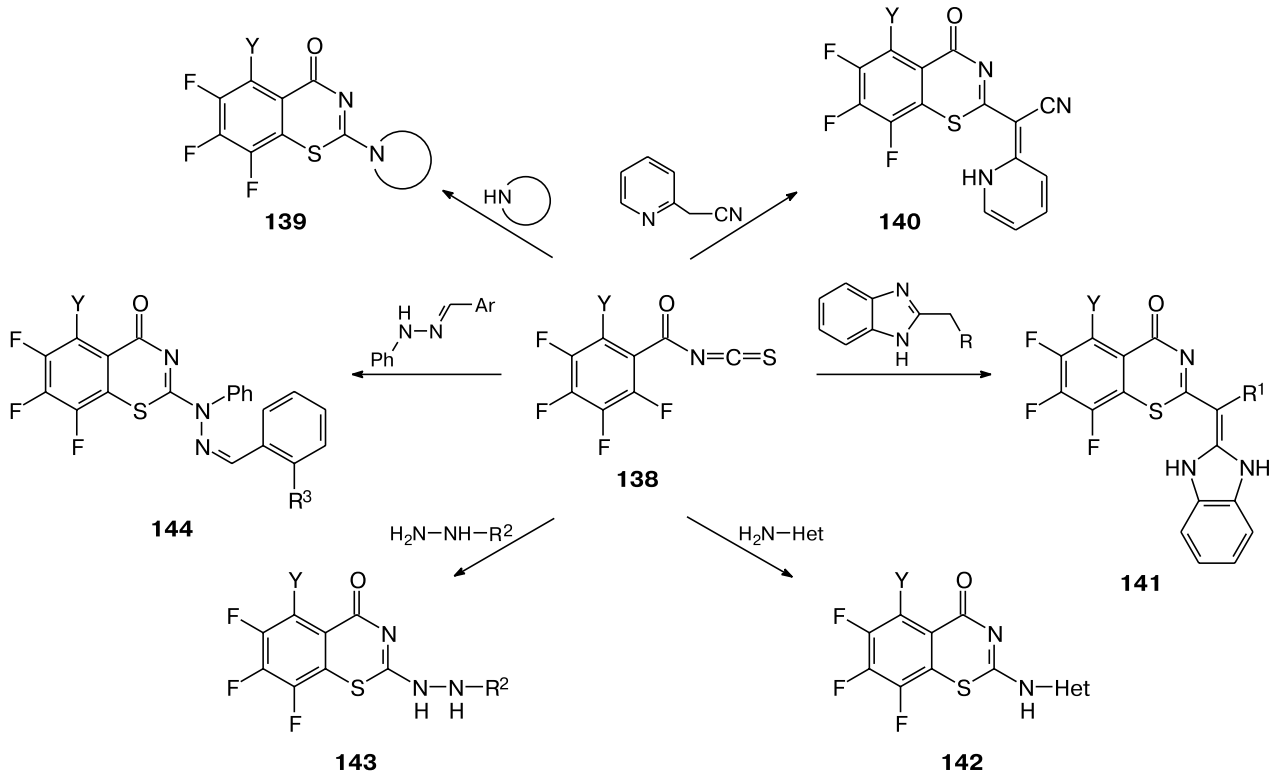
2.2. Polyfluorobenzoyl isothiocyanates

Polyfluorobenzoyl isothiocyanates **138** (prepared from appropriate benzoyl chlorides and ammonium thiocyanate) readily react with N- and C-nucleophiles at the C atom of the N=C bond, giving derivatives of thiocarbamic acid. Adducts of nucleophiles with isothiocyanates undergo intramolecular cyclization with replacement of the F atom to give 2-substituted [1,3]benzothiazin-4-ones **139**—**144** (Scheme 45).[71] This method allows wide variation of the substituent in position 2 of benzothiazinones.

2.3. Fluoro-containing benzamides and benzonitriles

The synthesis of quinazolinones **145** from polyfluorobenzamides **146** involves heating of the latter with oxalyl chloride in the presence of amines and intramolecular cyclization of the resulting ureas **147** in the presence of potassium bis(trimethylsilyl)amide and catalytic amounts of 18-crown-6. Amination of quinazolinedione **145** with *O*-(2,4-dinitrophenyl)-hydroxylamine in the presence of NaH yields compound **148** (Scheme 46).[72]

Scheme 45

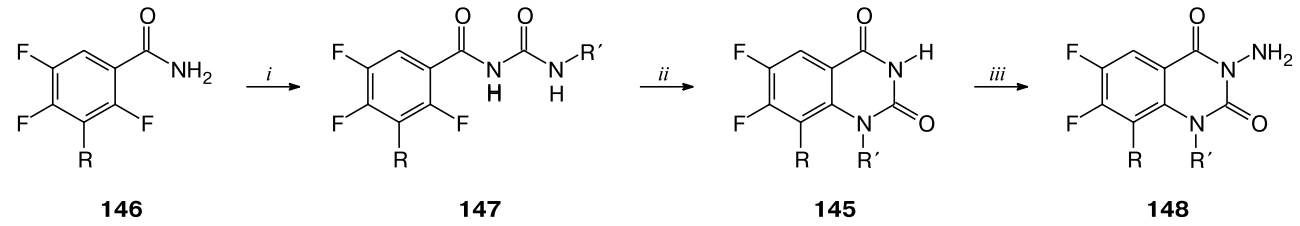


R^1 = COPh, CN; R^2 = 4-NO_2Ph, 2,4-dimethylpyridin-2-yl; R^3 = OH, H

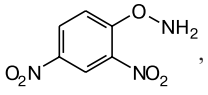
N—: morpholino, 4-ethoxycarbonylpiperazin-1-yl, hexamethyleneimino;

Het is pyridin-2-yl, 6-methylpyridin-2-yl, pyrimidin-2-yl, 4,6-dimethylpyrimidin-2-yl, 5-methylpyrazol-3-yl, 5-phenylpyrazol-3-yl.

Схема 46

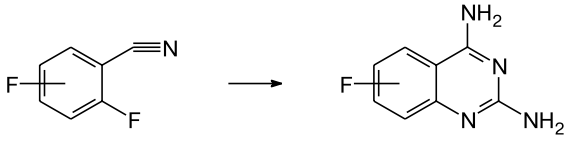


R′ = $CHMe_2$, *cyclo*-C_3H_5, Ph; R = H, Me, OMe

Reagents: *i*. $(COCl)_2$, R′NH_2; *ii*. $(Me_3Si)_2NK$, 18-crown-6; *iii*.  , NaH.

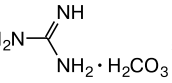
Reactions of *o*-fluorobenzonitriles with N,N´-dinucleophiles seem to be one of the most rational synthetic approaches to fluoro-containing 4-aminoquinazolines. Indeed, reactions of 2,3-difluoro-, 2,4-difluoro-, 2,5-difluoro-, or 2,6-difluorobenzonitrile **149** and pentafluorobenzonitrile with guanidine carbonate in dimethylacetamide at 140 °C give fluoro-containing 2,4-diaminoquinazolines **150a—e** in good yields (Scheme 47).[73]

Scheme 47



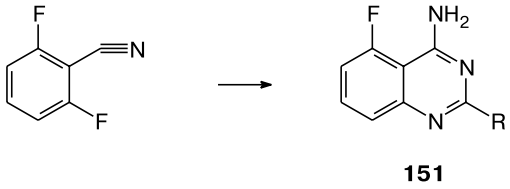
149 **150a—e**

150: 5-F (**a**), 6-F (**b**), 7-F (**c**), 8-F (**d**), 5,6,7,8-tetrafluoro (**e**).

Reagents and conditions:  , 140 °C.

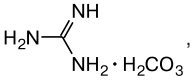
Analogously, a reaction of 2,6-difluorobenzonitrile with formamidine acetate or acetamidine acetate in *N*,*N*-dimethylacetamide under nitrogen at 150 °C leads to 4-amino-5-fluoroquinazolines **151** (Scheme 48).[74]

Scheme 48



151

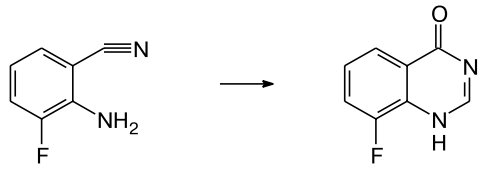
R = H, Me.

Reagents and conditions:  , 150 °C.

Treatment of 2-amino-3-fluorobenzonitrile (**152**) with formic acid in the presence of H_2SO_4 gives 8-fluoro-1*H*-quinazolin-4-one (**153**) in 88% yield (Scheme 49).[75] Apparently, the formation of the quinazolinone involves condensation of intermediate 2-aminobenzamide with formic acid.

A reaction of 2-amino-6-fluorobenzonitrile (**154**) with ethyl 5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-ylacetate (**155**) in the presence of potassium bis(trimethylsilyl)amide produces 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-quinolin-2-one (**156**) (Scheme 50).[76] Compound **156** is a dihydrofolate reductase inhibitor and has an effect on multiple myeloma.[77,78]

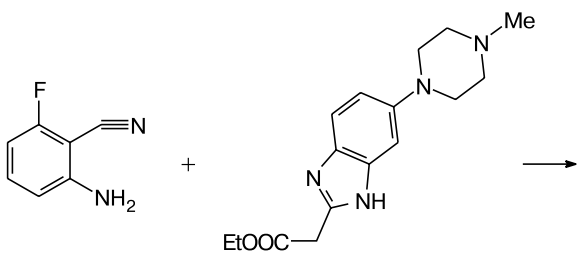
Scheme 49



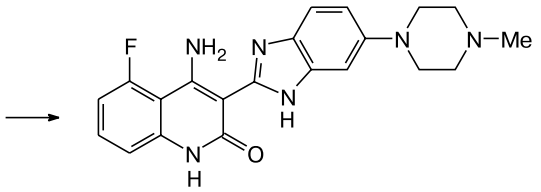
152 **153**

Reagents and conditions: HCOOH, H_2SO_4, 110 °C.

Scheme 50



154 **155**



156

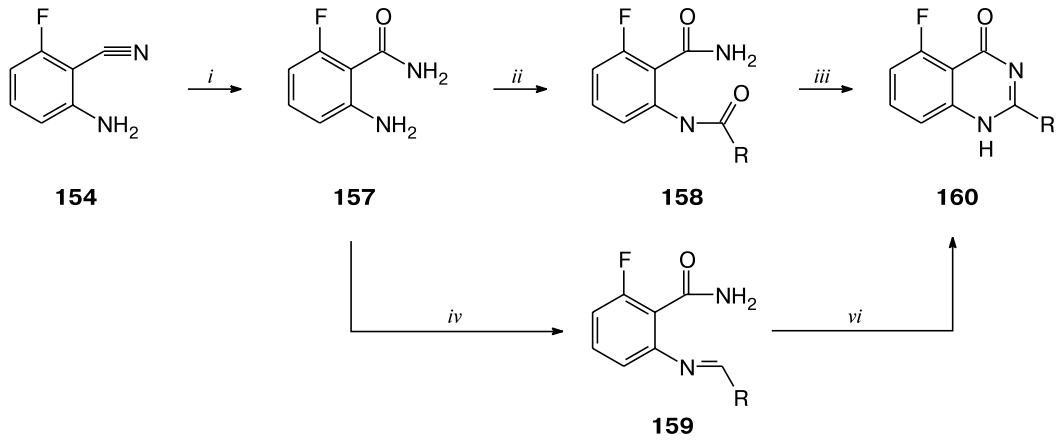
Reagents and conditions: $KN(SiMe_3)_2$, 40—62 °C, 1 h.

Acid hydrolysis of nitrile **154** leads to 2-amino-6-fluorobenzamide (**157**), which allows widely varying the substituent in position 2 of quinazolinones. Two approaches to the synthesis of 5-fluoroquinazolin-4-ones were proposed. These involve reactions of amide **157** with acid chlorides (anhydrides) or aromatic (heterocyclic) aldehydes followed by cyclization of intermediates **158** and **159** into quinazolin-4-ones **160** (Scheme 51).[79]

2.4. Polyfluorobenzoylacetic and acrylic acid esters

Fluoro-containing ethyl benzoylacetates **161** are important synthons for the preparation of [*a*]-annulated fluoroquinolones **162** and **163** (Scheme 51). Esters **161** are synthesized by base-catalyzed reactions of fluorobenzoyl halides **164** with ethyl malonate followed by hydrolysis of the resulting malonate **165** and decarboxyla-

Scheme 51



R = Me, Ph, 2-, 3-, 4-pyridyl, 2-furyl, 2-hydroxyphenyl, 2-hydroxy-5-nitrophenyl, 4-methoxyphenyl, 2,4-dihydroxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl.

Reagents and conditions: *i*. H_2SO_4, 55 °C; *ii*. RC(O)Cl or $(RCO)_2O$; *iii*. KOH; *iv*. RCHO; *vi*. $CuCl_2$.

tion.[80] Compound **161** can also be obtained directly by reactions of fluorobenzoyl halides **164** with potassium ethyl malonate in the presence of Et_3N and $MgCl_2$ (Scheme 52).[25]

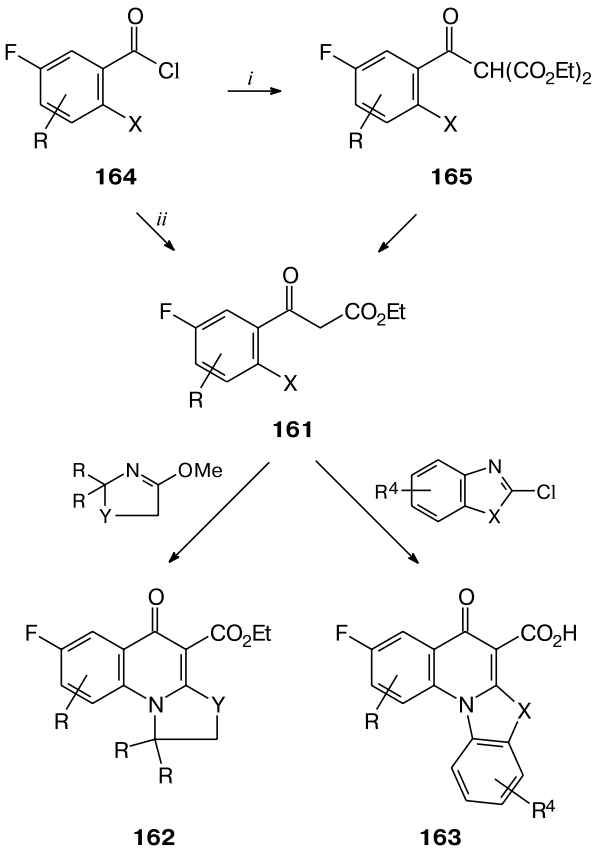
Condensation of compounds **161** with imino ethers gives tricyclic fluoroquinolones **162** (see Ref. 80). A reaction of compound **161** with 2-chlorobenzothiazole or 2-chlorobenzoxazole in diphenyl ether in the presence of NaH at 160 °C leads to benzothiazolo[3,2-*a*]quinolones and benzoxazolo[3,2-*a*]quinolones **163** (see Scheme 52).[80]

The synthesis of fluoroquinolone derivatives from 3,4-difluoroaniline is discussed in Section 1. The second method of constructing the quinolone system, which employs fluoro-containing ethyl acetates **161** as the starting reagents, has a greater synthetic scope. Condensation of fluoro-containing ethyl acetates with diazonium salts and hydroxylamine affords aza and oxo analogs of quinolonecarboxylic acids (Schemes 53, 54). For instance, ethyl pentafluorobenzoylacetate (**166**) reacts with benzenediazonium chloride in the presence of KOH at 0 °C to give hydrazone **167**; treatment of this compound with a weak solution of KOH yields 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-1-phenylcinnolin-4-one (**168**) (see Scheme 53).[81] 3-Ethoxycarbonyl-6,7-difluoro-1-methylcinnolin-4-one is obtained analogously from ethyl 4,5-difluorobenzoylacetate; in this case, the cyclization of intermediate hydrazone is promoted by heating with NaH.[82]

A reaction of ester **166** with hydroxylamine leads to oxime **169**, which undergoes cyclization into 5,6,7,8-tetrafluoro-1,2-benzoxazin-4-one **170** (see Scheme 54).[83]

Ethyl 3-ethoxy-2-polyfluorobenzoylacrylate **171** is the most important synthon for the synthesis of fluoroquinolones and their annulated analogs. This ester is

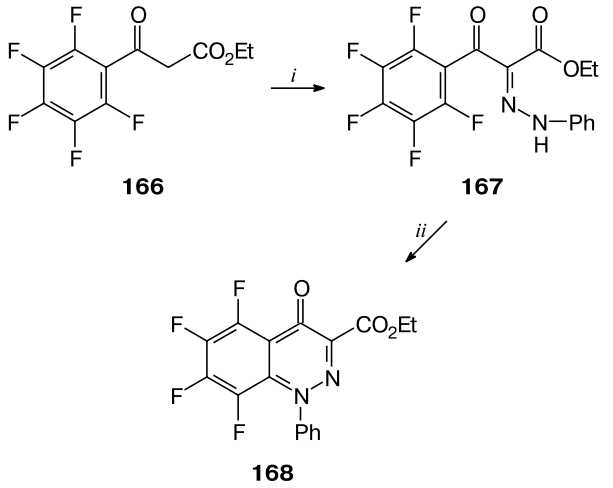
Scheme 52



X = S, O; R = H, Me; R = H, F, Cl, NR^1R^2, AlkS, AlkO, *etc.*; R^4 = COOH, CN, AlkO, AlkS, NH_2, AlkNH

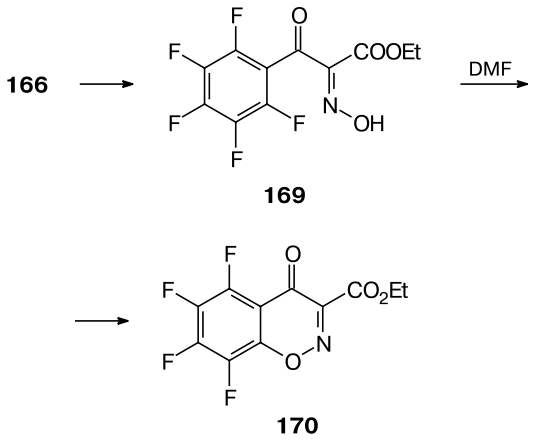
Reagents and conditions: *i*. $CH_2(COOEt)_2$; *ii*. $KOOC—CH_2—COOEt/NEt_3/MgCl_2$.

Scheme 53



i. 1) KOH, 2) PhN_2Cl; *ii*. KOH.

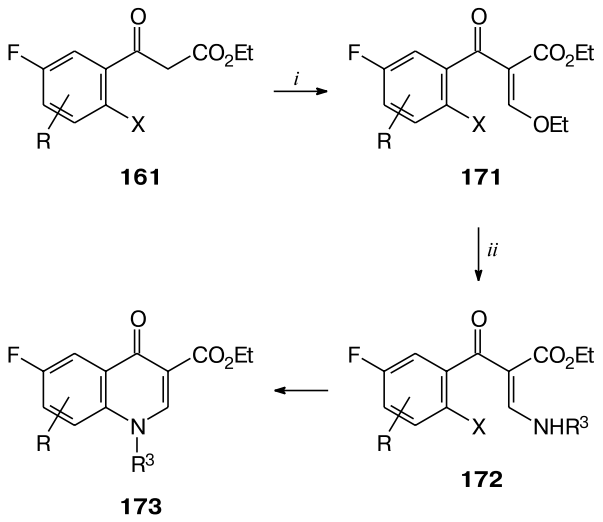
Scheme 54



prepared by condensation of ethyl aroylacetate **161** with ethyl orthoformate in acetic anhydride (Scheme 55).[25] Replacement of the ethoxy group in compounds **171** under the action of primary amines or hydrazines followed by base-catalyzed intramolecular cyclization of intermediates **172** yields the corresponding ethyl 6-fluoro-4-oxoquinoline-3-carboxylates **173** (see Scheme 55).[25]

Room-temperature reactions of ethyl 3-ethoxy-2-[tetra(penta)fluorobenzoyl]acrylates **174** with hydrazides (**175**, X = O), thiohydrazides (**175**, X = S), or amidrazones (**175**, X = NH) in ethanol lead to acrylates **176**. Their intramolecular cyclization gives 1,3,4-thiadiazino-[6,5,4-*i*,*j*]-, 1,3,4-oxadiazino[6,5,4-*i*,*j*]-, and 1,2,4-triazino[5,6,1-*i*,*j*]annulated quinolones **177**. For instance, reflux of acrylate **176a** (X = S) in toluene for 2 h yields thiadiazinoquinolones **177a** (X = S); bicyclic intermediates cannot be isolated under these conditions (Scheme 56).[84,85] Cyclization of acrylates **176** (X = O, NH) in toluene for

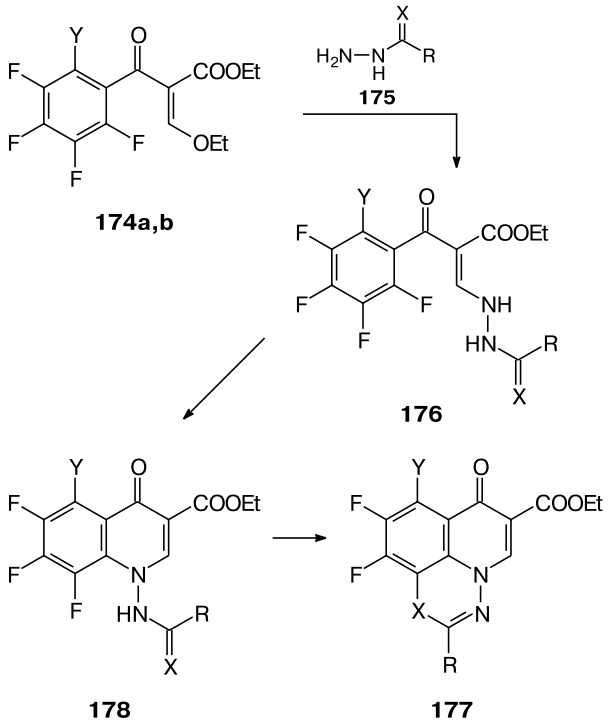
Scheme 55



i. $HC(OEt)_3$, Ac_2O; *ii*. R^3NH_2

2—3 h gives bicyclic derivatives **178**. Heating of the latter in acetic anhydride produces triazinoquinolones **177** (X = NH), while heating in boiling toluene in the presence of K_2CO_3 or in acetonitrile in the presence of KF gives oxadiazinoquinolones **177** (X = O) (Scheme 56).[86—88]

Scheme 56



174, 176—178: Y = H (**a**), F (**b**); X = S, O, NH; R = Ar, Het, cycloalkylimino

Room-temperature reactions of ethyl 3-ethoxy-2-[tetra-(penta)fluorobenzoyl]acrylates **174a,b** with heterylhydrazines in toluene yield compounds **179a—g** (Scheme 57).[89] The tendency of the latter toward amino-imine tautomerism allows cyclization with [*i*,*j*]-annulation of quinolines to the triazine ring. Pentacyclic derivatives **180a—g** are obtained by cyclization of acrylates **179a—g** in boiling acetonitrile in the presence of DBU, triethylbenzylammonium chloride (TEBAC), or KF, or by heating in dioxane in the presence of NaH. When acrylate **179a** was heated with TEBAC in acetonitrile, bicyclic derivative **181a** was isolated (Scheme 57).[89]

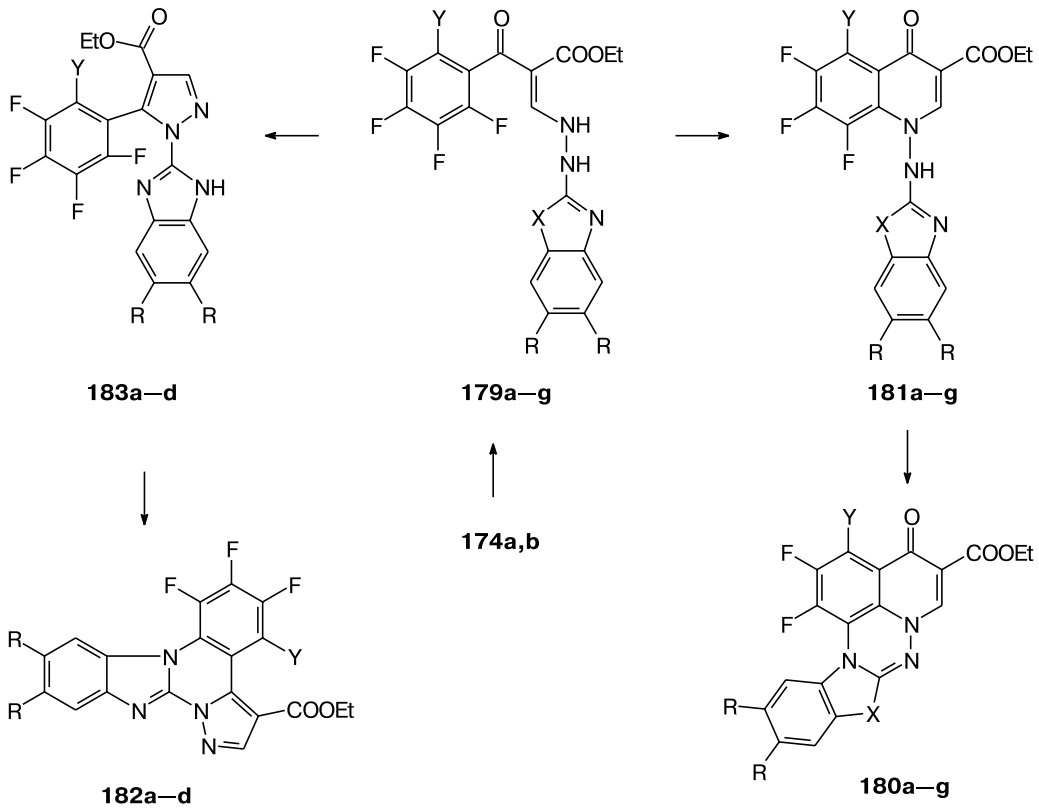
Alternative transformations of 3-benzazolylhydrazino-2-polyfluorobenzoylacrylates **179** involve the carbonyl group. For instance, reflux of acrylates **179** with KF in acetonitrile gives benzimidazo[1,2-*a*]pyrazolo[1,5-*c*]-quinazolines **182a—d**. Pyrazolyl intermediates **183a—d** can be isolated after short-time heating of acrylates **179a—d** in acetonitrile; heating of compounds **183** with KF for 4 h yields products **182a—d** (Scheme 57).[90,91]

Analogously, room-temperature reactions of acrylates **174** with aminoazoles **184** in ethanol give ethyl 3-azolylamino-2-polyfluorobenzoylacrylates **185**, which undergo cyclization in boiling acetonitrile in the presence of KF. For instance, 1-substituted quinolone **186** is obtained from ethyl 2-pentafluoro-3-(pyrazol-3-yl)aminobenzoylacrylate **185b**. Cyclization of tetrafluorobenzoyl derivatives **185a,c** follows a different pathway leading to pyrazolo[1,5-*a*]pyrimidines **187a,b** (Scheme 58).[92]

The synthesis of difluoro-1,2,4-oxadiazino[*i*,*j*]-quinolone **188** involves cyclization of acrylate **189** in DMF in the presence of K_2CO_3 (Scheme 59). Compound **189** is prepared by heating of ethyl 3-ethoxyacrylate **174a** with acetamide oxime **190** in acetic anhydride (see Scheme 59).[93]

Methyl 3-methoxy-2-pentafluorobenzoylacrylate (**191**) reacts with 4-amino-5-phenyl-4*H*-1,2,4-triazole-3-thiol (AMT) to give compound **192**. Heating of the latter in DMF at 120 °C in the presence of K_2CO_3 yields quinolone **193** (Scheme 60).[94]

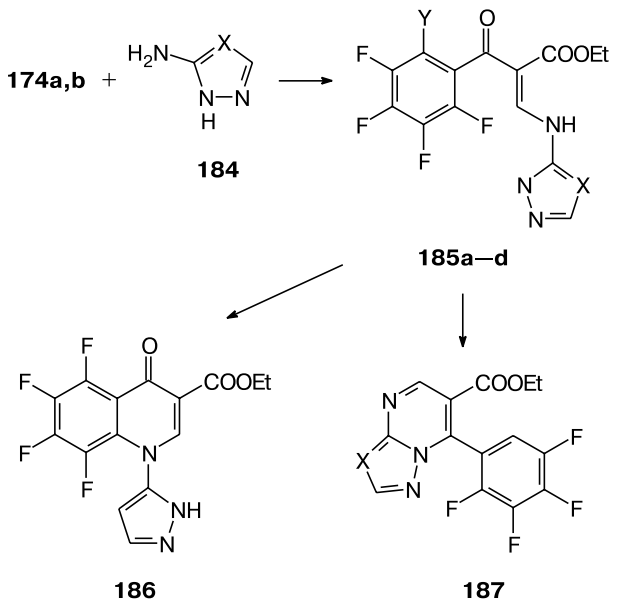
Scheme 57



179—181: X = NH, R = F, Y = F (**a**), X = NH, R = F, Y = H (**b**), X = NH, R = Y = H (**c**), X = NH, Y = F, R = NO_2 (**d**), X = NH, Y = F, R = Br (**e**); X = S, R = H, Y = F (**f**), R = H, Y = H (**g**)

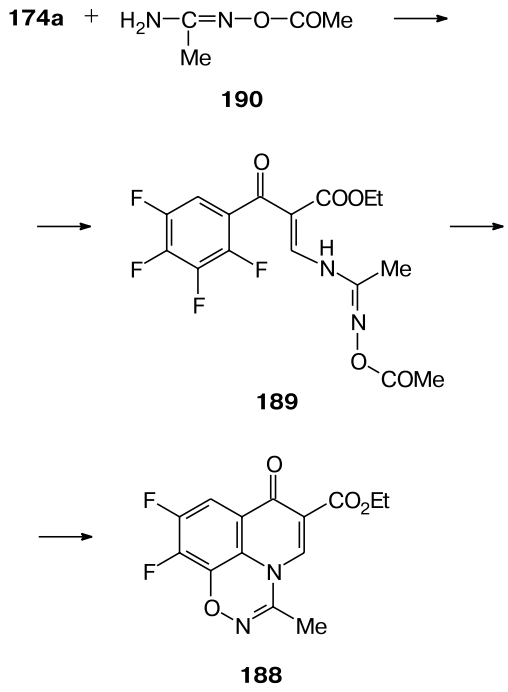
182, 183: Y = H, R = H (**a**), R = Br (**b**), R = F (**c**), Y = F, R = F (**d**)

Scheme 58

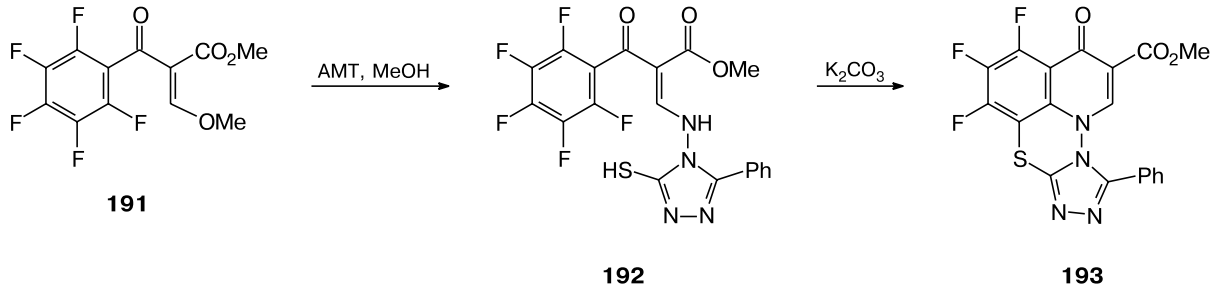


184: X = CH (**a**), N (**b**);
185: X = CH, Y = H (**a**), F (**b**), X = N, Y = H (**c**), F (**d**)

Scheme 59



Scheme 60



2.5. Fluoro-containing derivatives of anthranilic and 2-nitrobenzoic acids

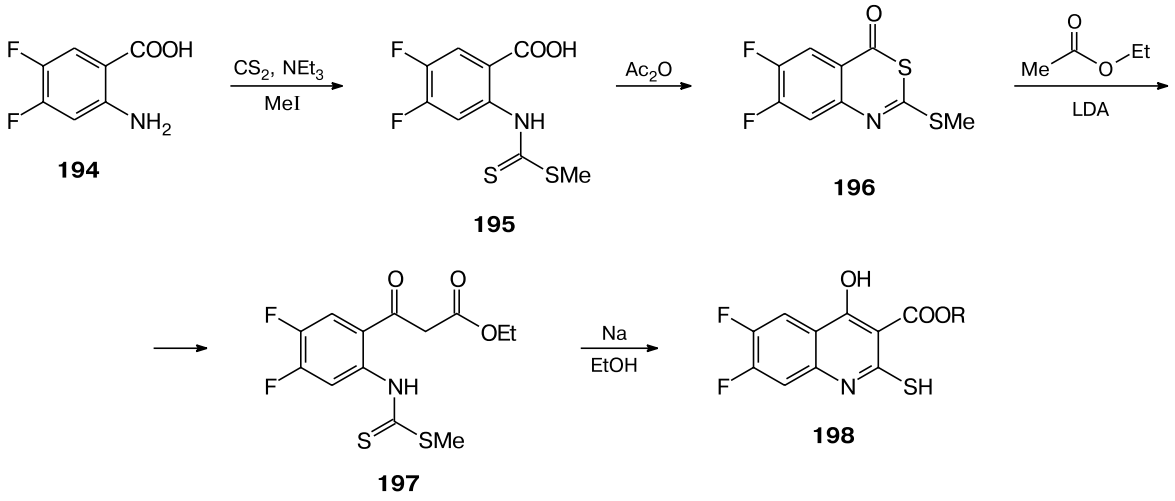
Derivatives of benzoic acids bearing an amino or nitro group in the *ortho*-position are widely used as synthons for the preparation of fluoro-containing benzazines.

One of the key synthons is 4,5-difluoroanthranilic acid **194**. A reaction of compound **194** with carbon disulfide in the presence of triethylamine followed by methylation with methyl iodide gives dithiocarbamate **195**; treatment of the latter with acetic anhydride affords 4*H*-[3,1]-benzothiazin-4-one **196** in high yield. Treatment of compound **196** with a lithium salt of ethyl acetate gives β-oxo ester **197**, which undergoes cyclization into 2-mercaptoquinoline **198** under the action of sodium ethoxide in ethanol (Scheme 61).[95]

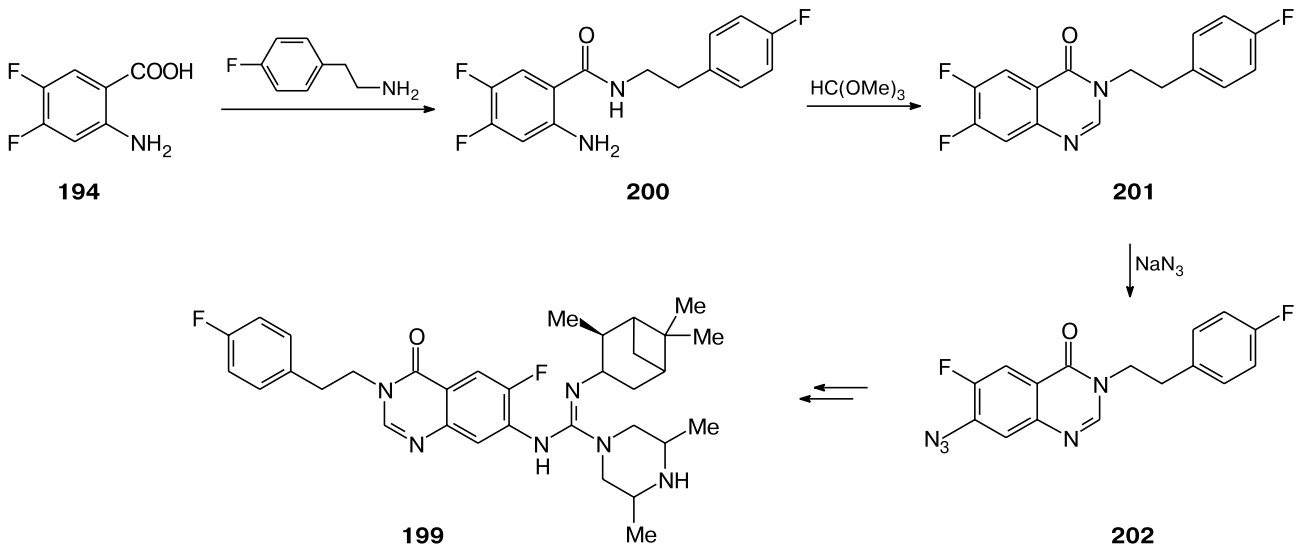
Anthranilic acid is known to be a convenient synthon for construction of the quinazoline system.[96] Using fluoroanthranilic acids, one can also synthesize fluoro-containing quinazolines according to well-developed procedures. This approach allows a greater variation of the substituents in the heterocycle compared to the synthesis of quinazolines from benzoyl chlorides (Section 2.1). This can be illustrated with the synthesis of 6-fluoro-7-guanidinoquinazolinones **199** (Scheme 62). 2-Cyclization of aminobenzamide **200** (prepared from acid **194**) with trimethyl orthoformate gives 3-substituted quinazo-linone **201** transformed further into azide **202**. The latter is treated with (1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo-[3.1.1]heptan-3-yl isocyanate in THF in the presence of PPh_3 and then with (6*S*,2*R*)-2,6-dimethyl-piperazine. The resulting quinazoline **199** is biologically active and can be used to treat obesity and type II diabetes.[97]

A reaction of *o*-phenylenediamine with 5-fluoro-anthranilic acid (**203**) in the presence of polyphosphoric acid yields 2-(2-aminophenyl)benzimidazole **204**. The latter can react with a second molecule of acid **203** to give 6-(2-aminophenyl)benzimidazo[1,2-*c*]quinazoline **205** (Scheme 63).[98]

Scheme 61



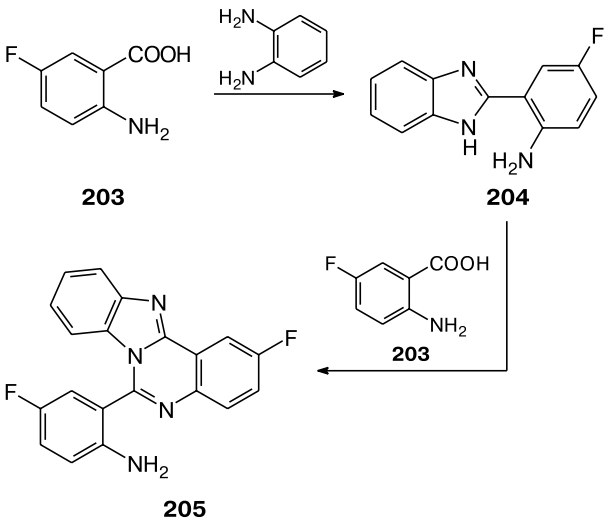
Scheme 62



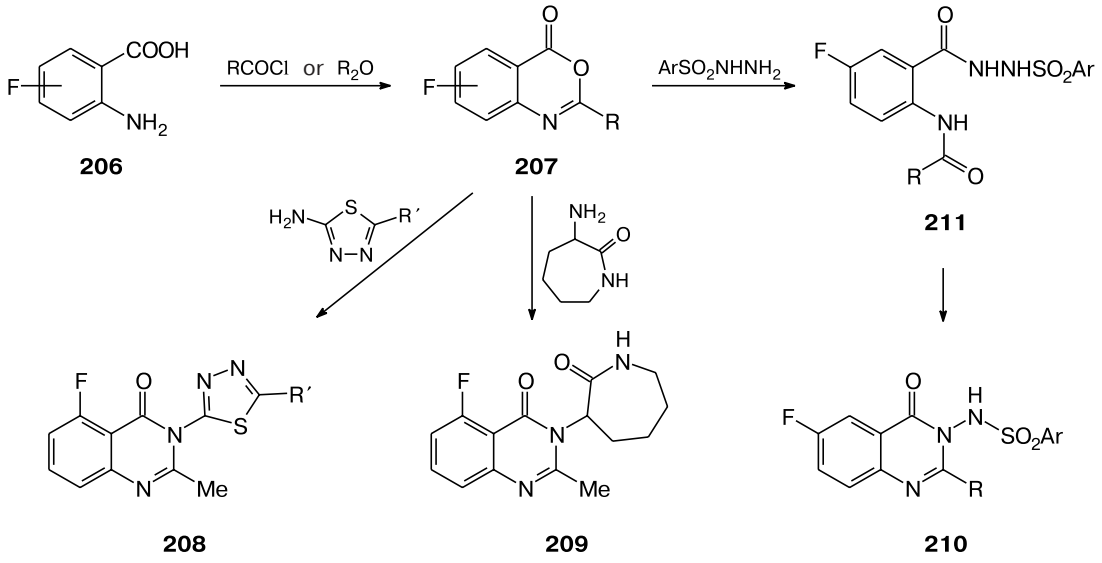
Heating of monofluoroanthranilic acids **206** with acetic anhydride or carboxylic acid chlorides leads to 2-substituted [3,1]benzoxazin-4-ones **207**. Reactions of 5-fluoro-2-methyl-3,1-benzoxazin-4-one with 2-amino-1,3,4-thiadiazoles and (*DL*)-α-amino-ε-caprolactam give 3-substituted quinazolin-4(3*H*)-ones **208** and **209**, respectively (Scheme 64).[99] Fusion of arenesulfonylhydrazides with 6-fluoro-3,1-benzoxazines **207** at 130 °C for 30 min or keeping of the reagents in DMF at room temperature for 22 h affords a number of sulfonamides **210** (see Ref. 100). The reaction proceeds through open-chain intermediates **211**, which can be isolated under mild reaction conditions.

In some cases, construction of fluoroquinazolinones involves the formation of intermediates containing an isothiocyanate group. For instance, cyclization of methyl anthranilates **212** with isothiocyanates and that of substituted 2-(methoxycarbonyl)phenyl isothiocyanates **213**

Scheme 63

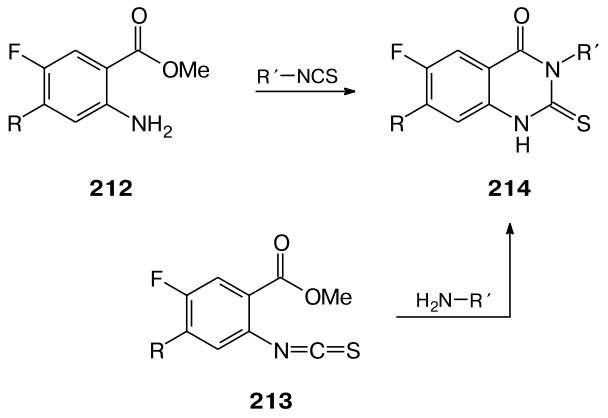


Scheme 64



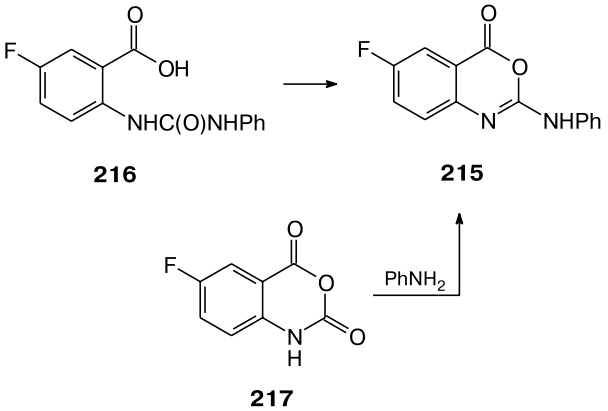
R = Me, $PhCH_2$, $PhCH_2CH_2$, thiophen-2-ylmethyl

Scheme 65



R = H, Cl, COOMe; R′ = $Et_2NCH_2CH_2$, cyclohexyl, CH_2Ph, 2-$H_2NC_6H_4$

Scheme 66

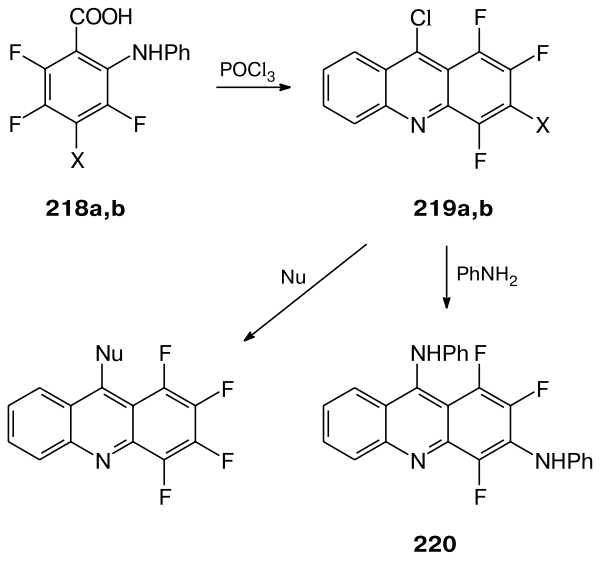


with primary amines lead to 4-oxo-1,2,3,4-tetrahydroquinazoline-2-thiones **214** (Scheme 65).[101]

It is reported that 6-fluoro-2-phenylamino-4*H*-3,1-benzoxazin-4-one **215** obtained by cyclization of compound **216** or by condensation of benzoxazinedione **217** with aniline (Scheme 66) is used to treat obesity.[102]

Reactions of 2-anilinopolyfluorobenzoic acids **218** with $POCl_3$ give 9-chloro-1,2,4-trifluoro- and 9-chloro-1,2,3,4-tetrafluoroacridines **219a,b**, in which the Cl atom is replaced by a nucleophile. Compound **219b** can be easily transformed into compound **220** in the presence of aniline (Scheme 67).[103]

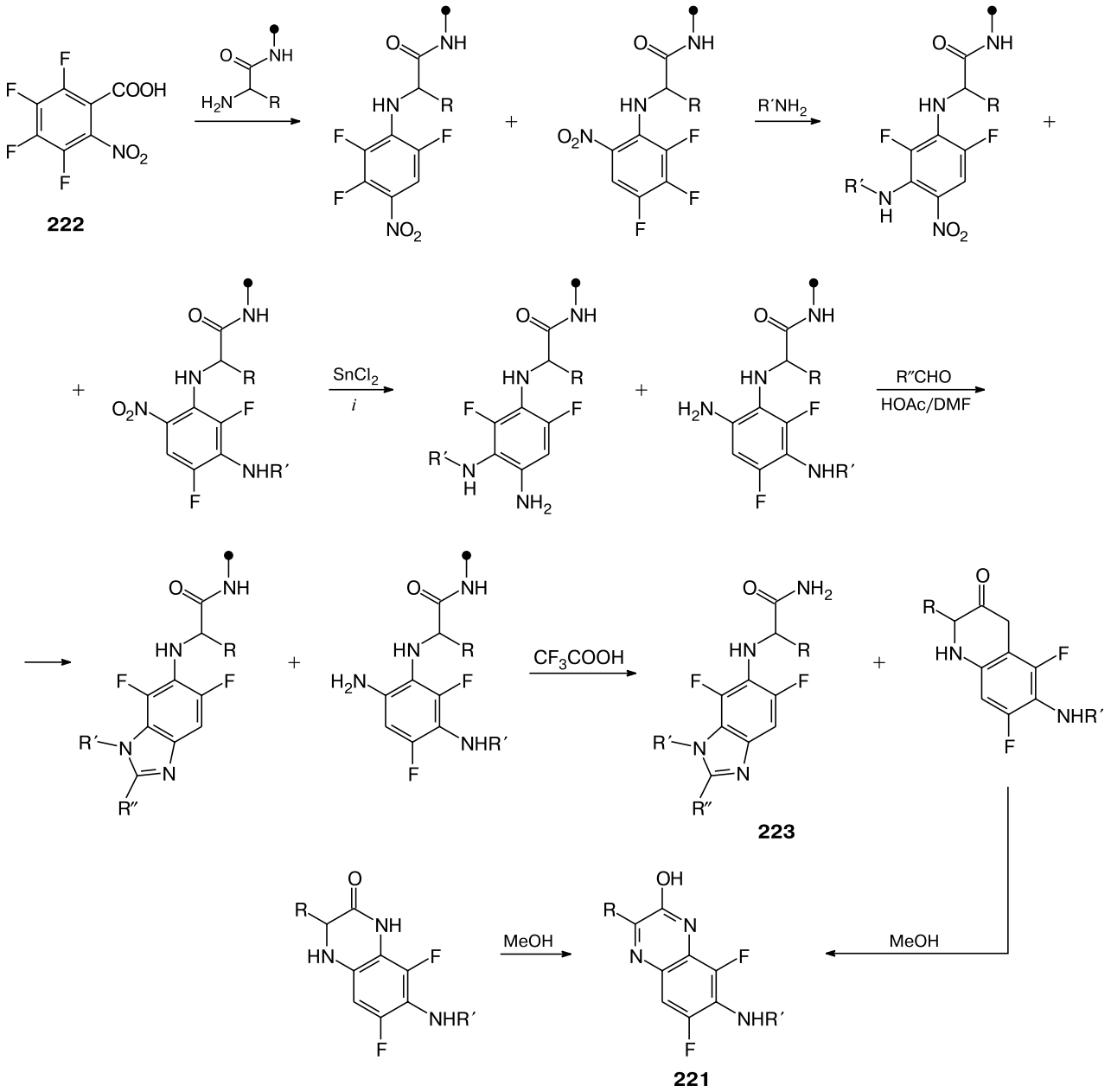
Scheme 67



218, 219: X = H (**a**), X = F (**b**)

Nu = MeNH, Me_2N, PhNH, NH_2NH, PhNHNH, C_6F_5NHNH.

Scheme 68

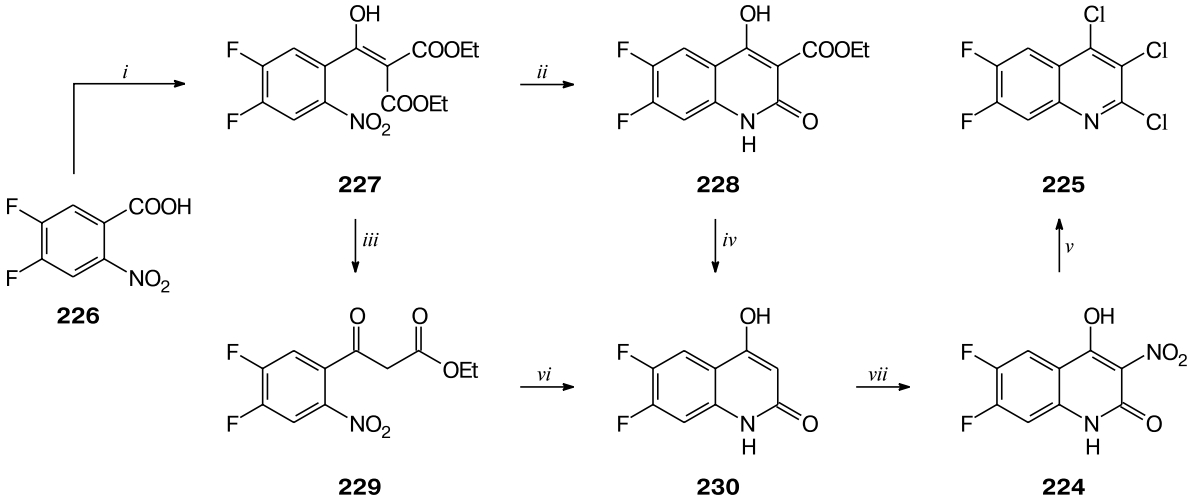


i. *N*-Methylmorpholine.

The solid-state synthesis of fluoro-containing 2-hydroxyquinoxalines **221** from 2,3,4,5-tetrafluoro-6-nitrobenzoic acid (**222**) was considered in Ref. 104 (Scheme 68); another product is 4,6-difluorobenzimidazole **223**.

The synthesis of 6,7-difluoro-4-hydroxy-3-nitroquinolin-2-one (**224**) and 2,3,4-trichloro-6,7-difluoroquinoline (**225**) from 4,5-difluoro-2-nitrobenzoic acid (**226**) is shown in Scheme 69. Malonate **227** is smoothly transformed into 4-hydroxyquinolone **228** in the presence of $NaBH_4$ in a basic medium. Treatment of compound **228** with *p*-toluenesulfonic acid gives ethyl 3,4-difluoro-6-nitrobenzoylacetate (**229**). Catalytic reduction of the nitro group in the latter on Pd/C in ethanol results in cyclization into 6,7-difluoro-4-hydroxy-quinolin-2(1*H*)-one (**230**) in high yield. Hydrolysis and decarboxylation of compound **228** also gives 4-hydroxy-quinolin-2(1*H*)-one **230**. Nitration of compound **230** yields 3-nitroquinolone **224**, which is transformed into 2,3,4-trichloroquinoline **225** under the action of $POCl_3$ (Scheme 69).[105]

Схема 69

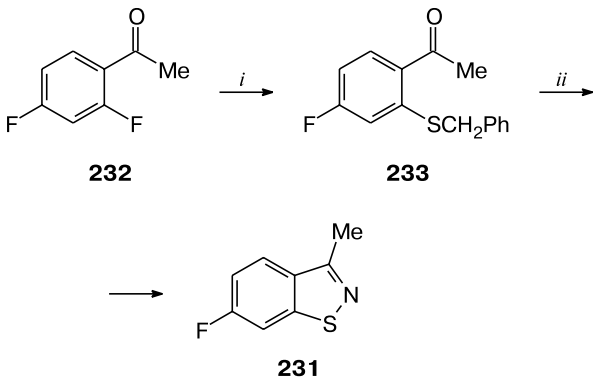


Reagents and conditions: *i*. $SOCl_2$, $CH_2(COOEt)_2$, Mg; *ii*. $NaBH_4$, Pd/C, NaOH; *iii*. *p*-TsOH, H_2O; *iv*. 3 *N* HCl, EtOH; *v*. POCl, NEt_3, 100 °C; H_2, *vi*. EtOH, Pd/C; *vii*. HNO_3, AcOH, 100 °C.

3. Fluoro-containing acetophenones in the synthesis of benzoannulated azaheterocycles

Fluoro-containing acetophenones are convenient synthons for construction of various benzoannulated azaheterocycles. For instance, 6-fluorobenzo[*d*]isothiazole **231** is obtained from 2,4-difluoroacetophenone (**232**).[106] A reaction of compound **232** with benzyl mercaptide gives sulfide **233** through selective replacement of the F atom in position 2. When treated with thionyl chloride, sulfide **233** is transformed into sulfenyl chloride, which reacts with ammonia to give sulfenamide undergoing spontaneous cyclization into benzoisothiazole **231** (Scheme 70).

Scheme 70



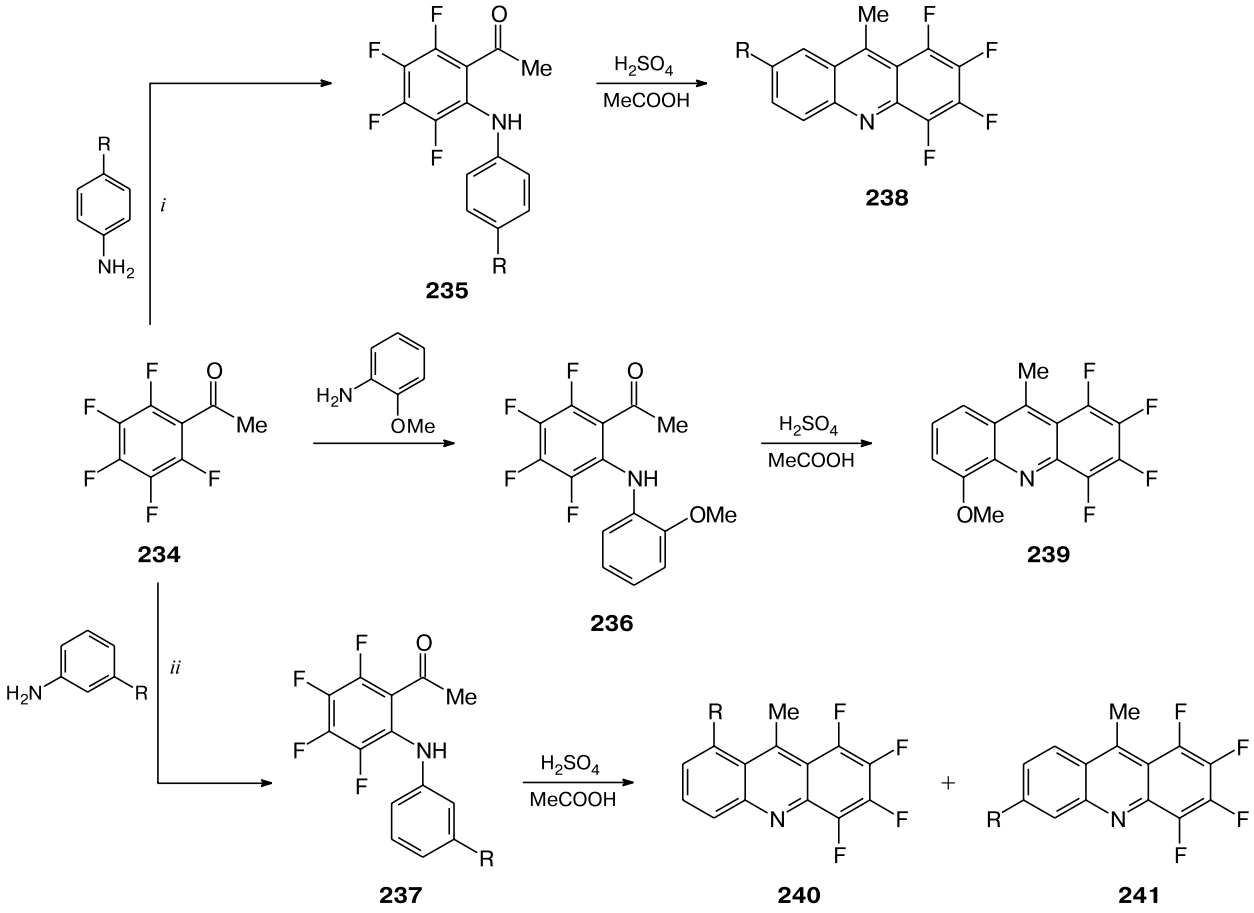
i. $PhCH_2SH$, $KOBu^t$, THF; *ii*. 1) $SOCl_2$; 2) NH_3, THF.

Reactions of pentafluoroacetophenone (**234**) with aromatic amines in the presence of K_2CO_3 gives, through replacement of the F atom at the C(2) atom by the aniline residue, derivatives **235**—**237**. With highly basic amines ($pK_a > 4$), the yields of these products are sufficiently high. Heating of 2-arylamino-3,4,5,6-tetrafluoroacetophenones **235**—**237** in a mixture of sulfuric and acetic acids produces the corresponding 1,2,3,4-tetrafluoro-9-methylacridines **238**—**241** in high yields (Scheme 71).[107] The formation of 9-methyl-3-phenylamino- or 3-phenylamino-9-trifluoromethylacridine on heating of pentafluoroacetophenone **234** or perfluoroacetophenone with aniline was reported in Ref. 108.

The synthesis of fluoroquinolones and their analogs from ethyl 3-pentafluorobenzoylpyruvate (**242**) is well covered in the literature. Compound **242** is prepared by the Claisen condensation of pentafluoroacetophenone **234** and ethyl oxalate in the presence of LiH (Scheme 72).[109] Reactions of pyruvate **242** with 2-aminophenol and *o*-phenylenediamine in methanol at 20 °C afford 3-pentafluorobenzoylmethylidene-1,2,3,4-tetrahydrobenzoxazin-2-one (**243a**) and 3-pentafluorobenzoylmethylidene-1,2,3,4-tetrahydroquinoxalin-2-one (**243b**), respectively. Intramolecular cyclization of compound **243a** in DMSO at 200 °C without any base or at 80 °C in the presence of triethylamine yields 4,5,6-trifluoro-3*H*-pyrido[3,2,1-*k*,*l*]-phenoxazin-3-one (**244**) (Scheme 72).[110] Product **243b** is transformed into quinolone **245** on heating with triethylamine in DMSO (see Scheme 72).[111]

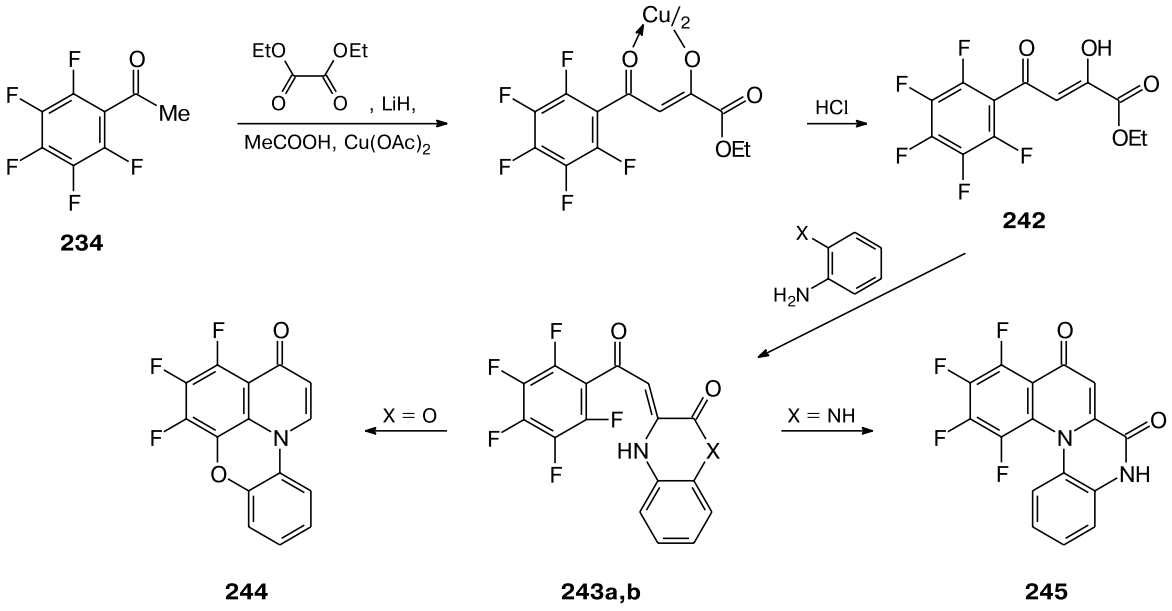
Hydrolysis of ester **242** leads to acid **246**, which reacts with primary amines to give 2-alkylamino(anilino)-3-pentafluorobenzoylacrylic acids **247a,b**. In the

Scheme 71



i. R = Me, OMe, Br, NMe_2; *ii*. R = Me, OMe.

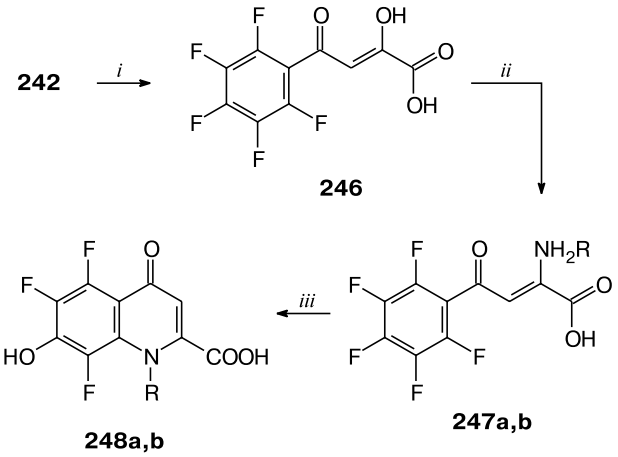
Scheme 72



243: X = O (**a**), NH (**b**)

presence of KOH, compounds **247a,b** are transformed into 1-substituted 5,6,8-trifluoro-7-hydroxy-4-oxoquinoline-2-carboxylic acids **248a,b** (Scheme 73).[109]

Scheme 73



247, 248: R = C_6H_{11} (**a**), Pr^i (**b**)

Reagents and conditions: *i*. HCl, 35—40 °C; *ii*. H_2NR, Δ; *iii*. KOH, 90—95 °C.

A reaction of pyruvate **242** with arenediazonium chloride gives ethyl 3-(arylhydrazino)pentafluorobenzoylpyruvate **249**. When heated in DMSO or refluxed in chloroform with a double excess of triethylamine, compound **249** undergoes cyclization into cinnolones **251** (Scheme 74).[112] The latter react with a double excess of *o*-phenylenediamine and *o*-aminophenol in boiling alcohols to give complex heterocyclic ensembles of hydrazones (**252**, X = NH, O). In a reaction of ester **249** (Ar = *p*-methoxyphenyl) with diethylenetriamine in ethanol at 20 °C, intramolecular nucleophilic substitution of the F atom is accompanied by an attack on the α-dicarbonyl fragment leading to polycyclic derivative **250** (Scheme 74).[113]

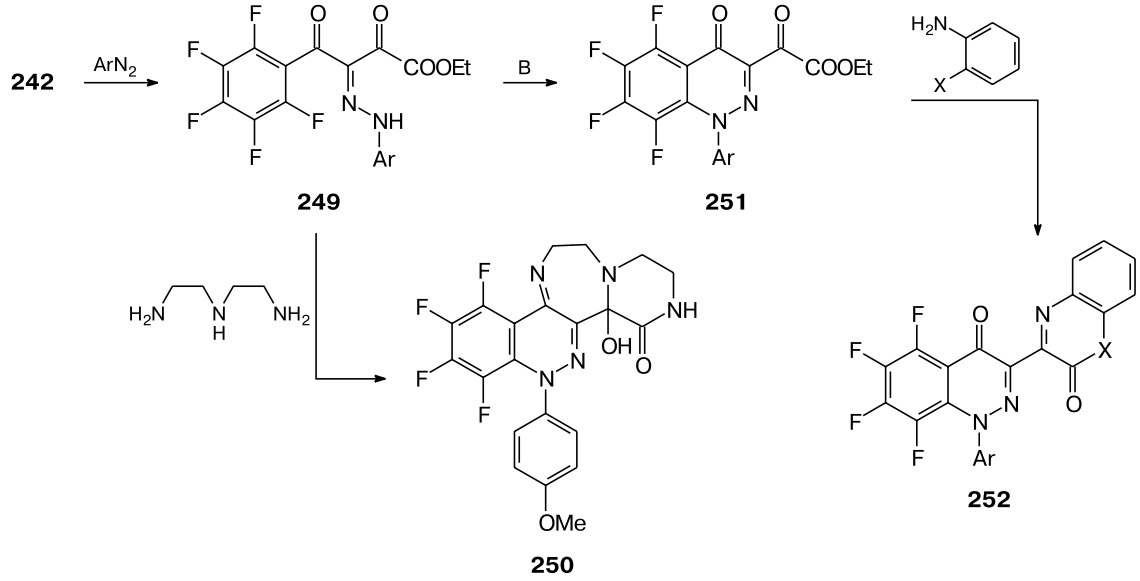
4. Fluoro-containing benzaldehydes and benzophenones in the synthesis of benzoannulated azaheterocycles

A number of fluoro-containing benzazoles and benzazines are obtained from appropriate benzaldehydes and benzophenones. For instance, a microwave-promoted reaction of 2-bromo-5-fluorobenzaldehyde (**253**) with phenylhydrazine gives hydrazone **254**, which undergoes cyclization into 1-phenyl-1*H*-indazole **255** on heating in the presence of CuI and K_2CO_3 (Scheme 75).[114]

Condensation of fluoro-containing *ortho*-halobenzaldehydes with C,N-dinucleophiles affords various quinolines. For instance, room-temperature reactions of pentafluorobenzaldehyde (**256b**) with substituted anilines give 1,2,3,4-tetrafluoroacridines **257** in quantitative yields and condensation of 2-chloro-3,4,5,6-tetrafluorobenzaldehyde (**256a**) with 5-amino-1,2-azoles yields azolo[*b*]-quinolines **258** (Scheme 76).[115]

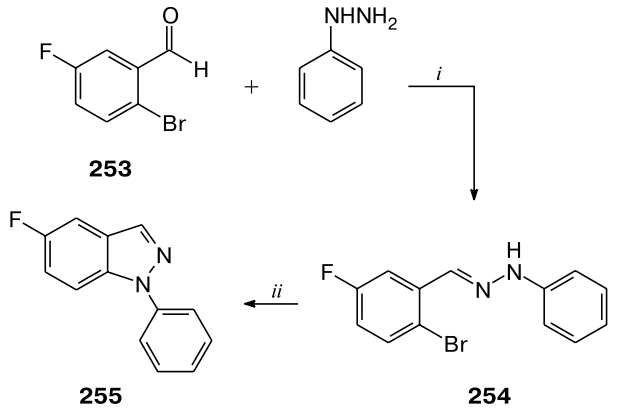
Analogously, pentafluorobenzaldehyde (**256b**) reacts with 6-amino-1,3-dimethyluracil in glacial acetic acid to give 5,6,7,8-tetrafluoro-1,3-dimethylpyrimidino[6,5-*b*]-quinoline-2,4-dione (**259**) (Scheme 77).[116]

Scheme 74



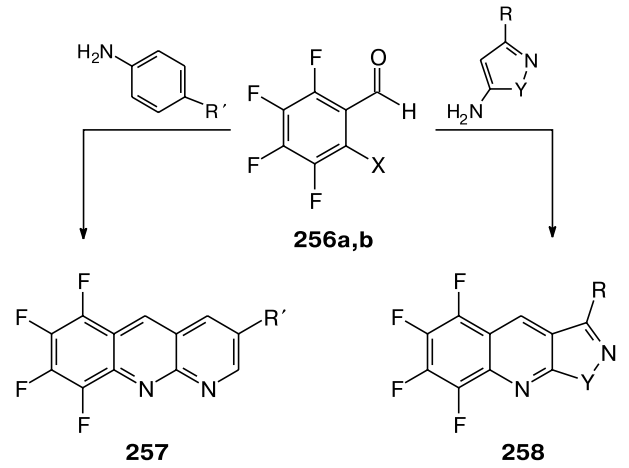
B is a base; Ar = *p*-$MeOC_6H_4$, X = NH, O

Scheme 75



Reagents and conditions: *i*. MW, 160 °C; *ii*. K_2CO_3, CuI, MW, 160 °C.

Scheme 76



272: X = Cl (**a**), F (**b**);

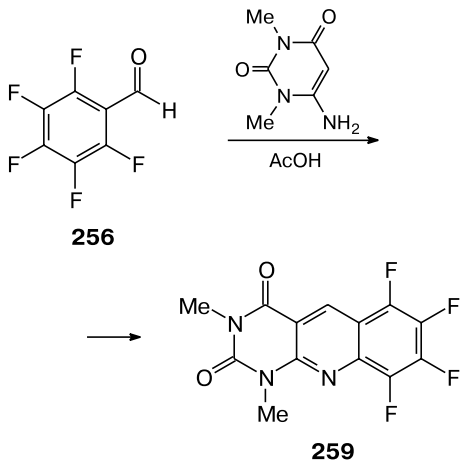
Y = NMe, NPh, O, S; R = Me, CMe, Ph; R′ = OMe, Me, H, F, Br.

Reactions of pentafluorobenzaldehyde (**256b**) with quinazolinylacetonitriles **260** yield compounds **261**, which undergo cyclization into polycyclic systems **262** on heating with NEt_3 in DMF (Scheme 78).[117]

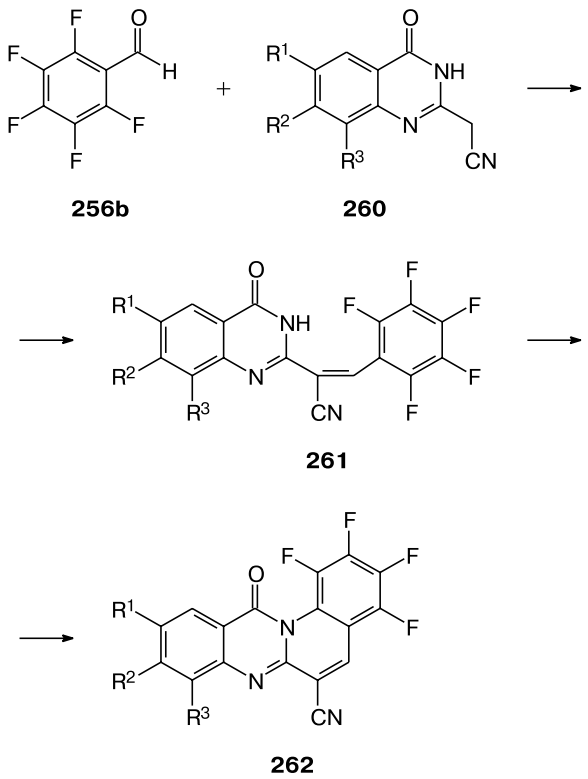
Base-catalyzed condensation of 2-amino-5-fluorobenzaldehyde (**263**) with 2-acetyl-1-methyl-5-nitroimidazole leads to 2-(1-methyl-5-nitroimidazol-2-yl)quinoline (**264**). This compound reacts with H_2O_2 in acetic acid to give derivative **265** transformed further into compound **266** under the action of $POCl_3$ (Scheme 79).[118] Condensation of aldehyde **263** with 2-acetyl-1-methyl-5-nitrobenzimidazole gives quinoline **267**.[119]

The patented[120,121] synthesis of 2-chloro-6-fluoroquinolines **268** and benzo[*b*]naphthyridines **269** from benzaldehydes **270** is shown in Scheme 80. Nitration of compound **270** with a mixture of nitric and sulfuric (or acetic) acids gives 2-nitrobenzaldehyde **271**. Condensation of this compound with ethyl malonate in the presence of a base (alkoxides, Na_2CO_3, or NaH) leads to ester **272**. Cyclization of malonates **272** followed by treatment of intermediates **273** with $POCl_3$ yields 2-chloro-6-fluoroquinolines **268**, from which benzo[*b*]naphthyridines **269** are obtained.

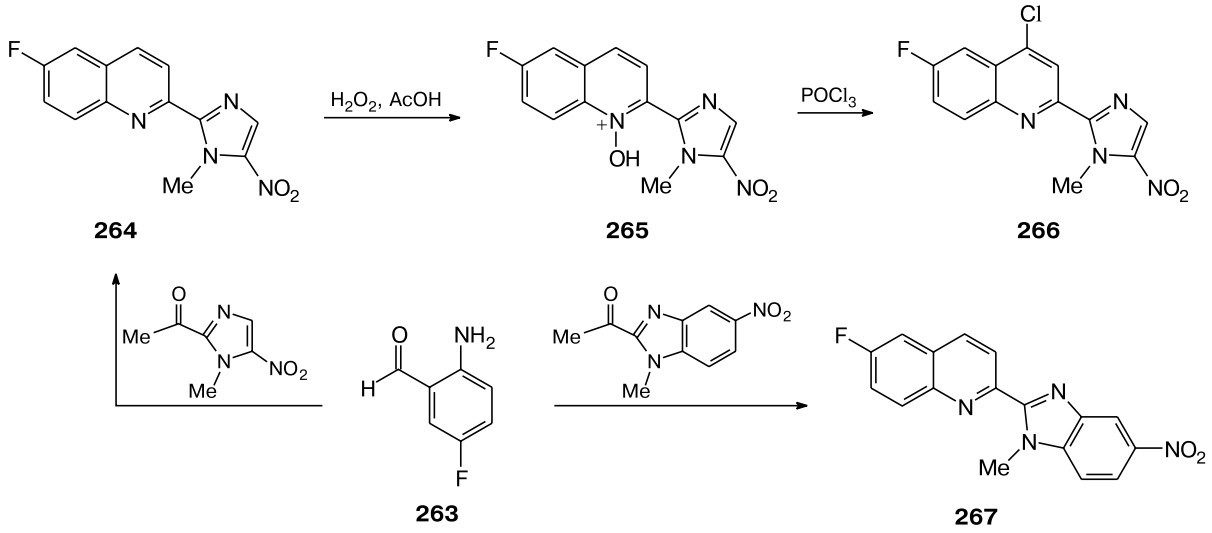
Scheme 77



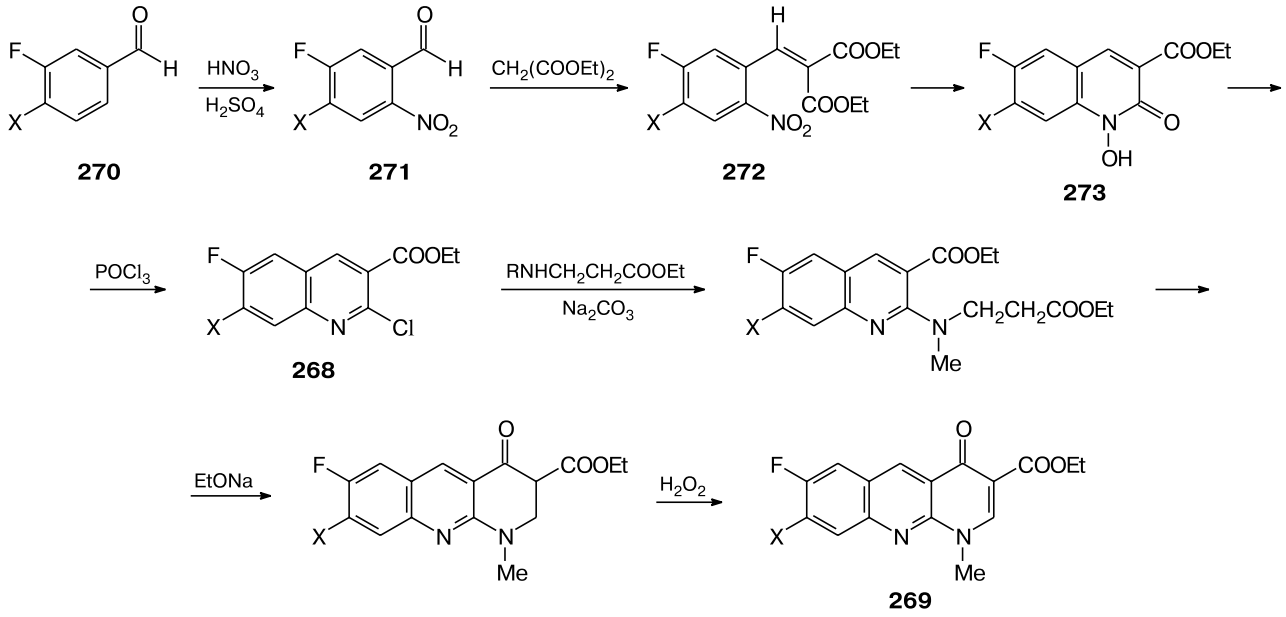
Scheme 78



Scheme 79



Scheme 80



R = Me, Et, *cyclo*-C_3H_5; **270:** X = F, Cl

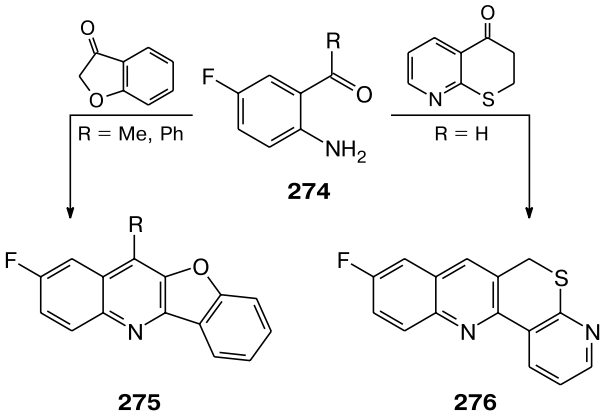
Replacement of the halogen atom X by the heterocyclic residues gives benzo[1,8]naphthyridines **269**, which exhibit antimicrobial activity.[122–125]

Condensation of 2-amino-5-fluorobenzaldehyde, acetophenone, or benzophenone **274** with 3(2*H*)benzofuranones or 3,4-dihydrothiopyrano[2,3-*b*]pyridin-4(2*H*)-one leads to benzofuro[3,2-*b*]quinolines **275** and 6*H*-pyrido[3r,2r:5,6]thiopyrano[4,3-*b*]quinolines **276** (Scheme 81).[126]

Fluoro-containing benzophenone **277** reacts with aniline in the presence of K_2CO_3 to give compound **278**, which can undergo cyclization into acridine **279** (Scheme 82).

Hydrolysis of the ether bond in the latter followed by intramolecular replacement of the F atom in DMF in the presence of KF completes the formation of the polycyclic system 6,7,8-trifluoro[1]benzopyrano[2,3,4-*k*,*l*]acridine (**280**) (see Scheme 82).[127]

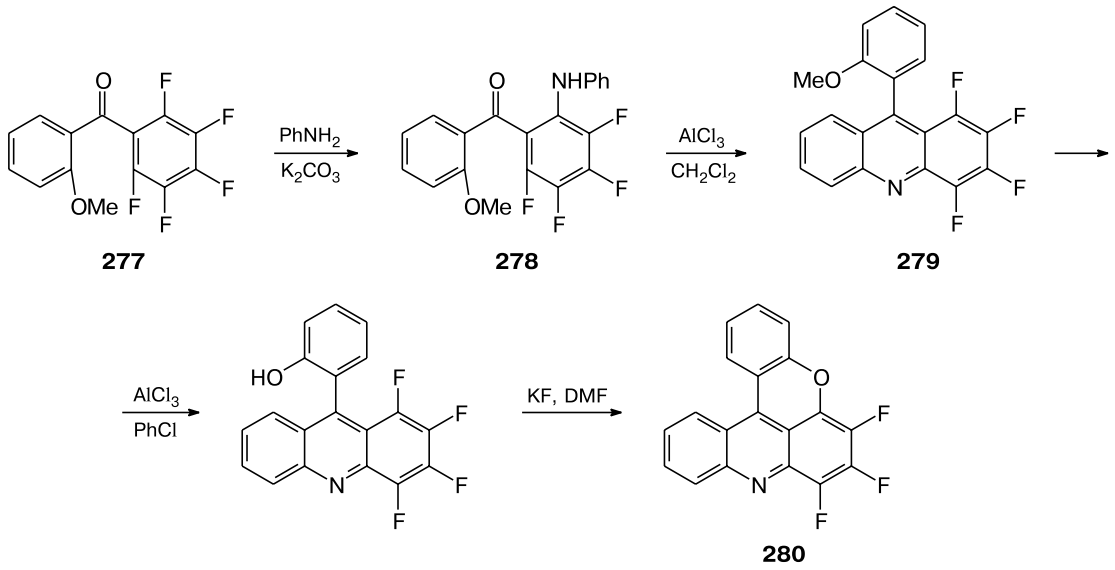
Scheme 81



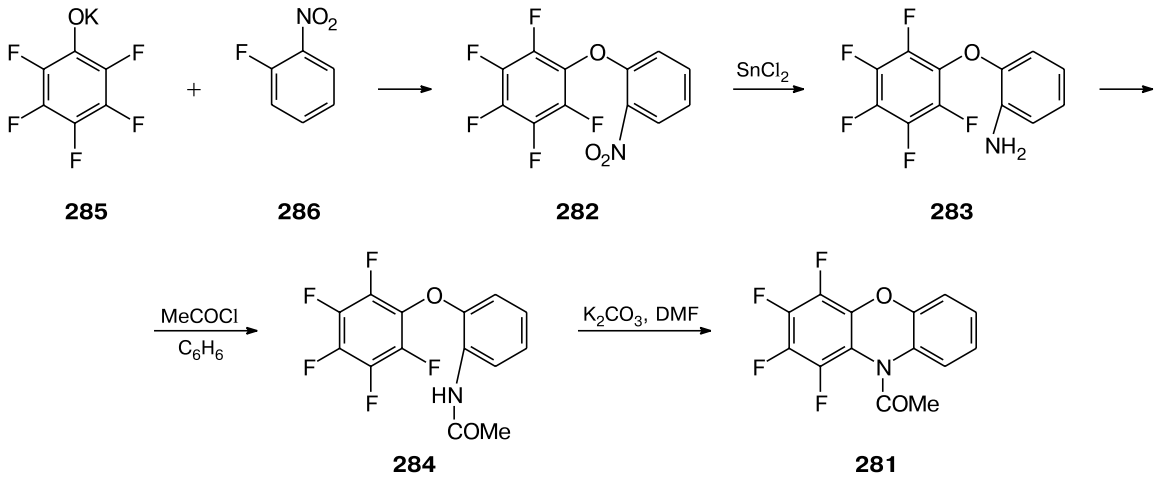
5. Fluoro-containing phenols and benzenethiols in the synthesis of benzoannulated azaheterocycles

Fluoro-containing phenols and benzenethiols find use in the synthesis of phenoxazines and [1,4]benzothiazines. Polyfluorodiphenyl ethers can serve as the starting materials for the preparation of polyfluorophenoxazines. For instance, 10-acetyl-1,2,3,4-tetrafluorophenoxazine (**281**) is obtained from pentafluoro-2-nitrodiphenyl ether **282**. Acid-catalyzed reduction of the latter with $SnCl_2$ gives 2-amino derivative **283**. *N*-Acyl derivative **284** undergoes cyclization into 10-acetyl-1,2,3,4-tetrafluorophenoxazine (**281**) on heating with anhydrous K_2CO_3 (Scheme 83). Ether **283** can be prepared either from potassium pentafluorophenolate (**285**) and 2-fluoronitrobenzene (**286**) or

Scheme 82



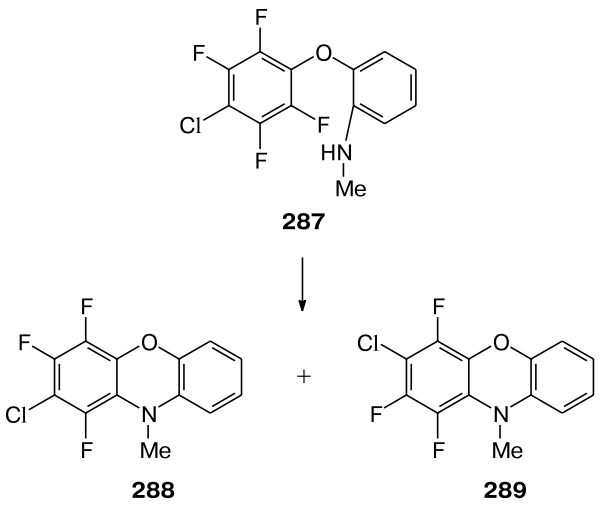
Scheme 83



from polyfluorobenzene and 2-aminophenol in pyridine in the presence of a base.[129]

Another example of the synthesis from polyfluorinated diphenyl ether **287** is provided by the formation of polyfluoro-10-methylphenoxazine **288** on heating of compound **287** in DMF for 3 h; the content of by-product **289** is 5% (Scheme 84).[130]

Scheme 84

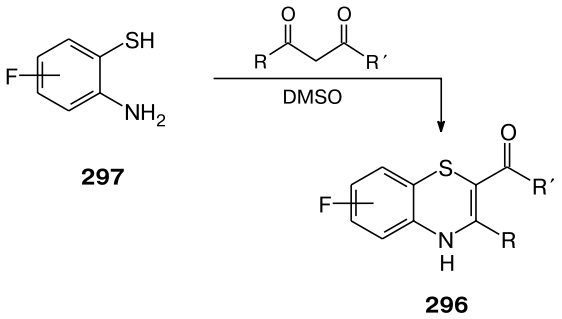


287 **288** **289**

2,3,4,5-Tetrafluorobenzenethiol (**290**) is used to obtain sulfur analogs of fluoroquinolones (**291** and **292**). Benzenethiol **290** is chlorinated and the resulting sulfenyl chloride reacts with ethyl 3-cyclopropylaminoacrylate in pyridine at 60 °C to give enamine **293**. Oxidation of the latter with chloroperoxybenzoic acid yields sulfoxide **294**; with a threefold excess of the oxidant, the oxidation product is sulfone **295**. Room-temperature cyclization of intermediates **294** and **295** in THF in the presence of NaH affords compounds **291** and **292**, respectively (Scheme 85).[131]

The single-step synthesis of fluoro-containing 4*H*-[1,4]benzothiazines **296** is effected by cyclization of 2-aminofluorobenzenethiols **297** with β-diketones in DMSO (Scheme 86).[132,133]

Scheme 86

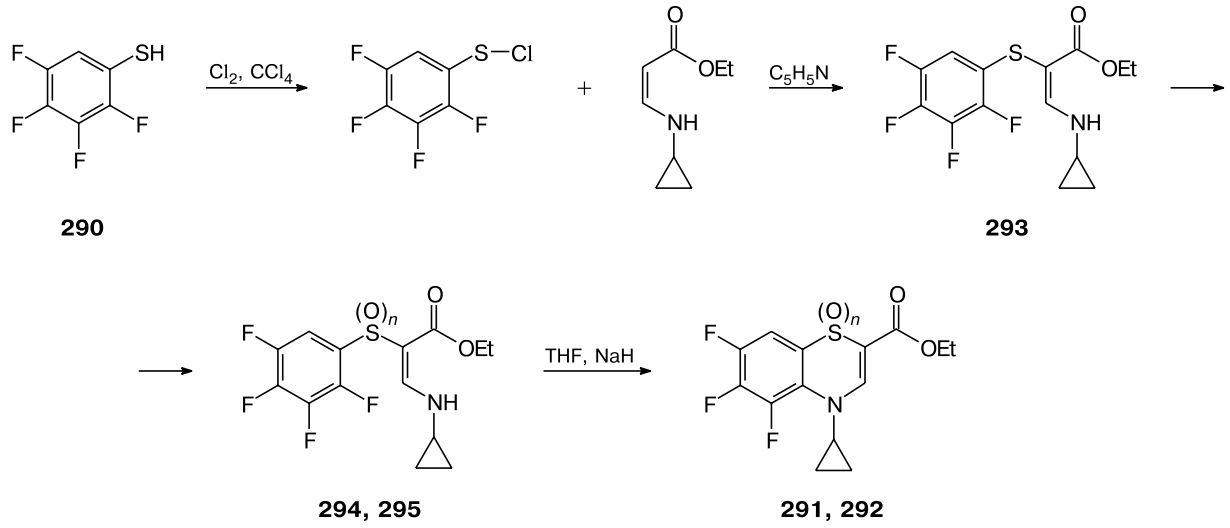


297 **296**

R = Me, R′ = Me, Ph, *p*-FC_6H_4, *p*-ClC_6H_4, EtO, MeO, *p*-$MeOC_6H_4$, *p*-MeC_6H_4; R = R′ = Ph

Fluoro-containing 2- and 3-methylbenzothiazines are used to obtain sulfur analogs of levofloxacin. An approach to optically active benzothiazines is shown in Scheme 87. (*S*)-7,8-Difluoro-3-methyl-3,4-dihydro-2*H*-[1,4]benzothiazine (**298**) is synthesized from 3,4-difluoro-2-mercaptonitrobenzene **299** and (*R*)-propylene oxide *via* intermediate (*R*)-**300** (see Scheme 87).[45]

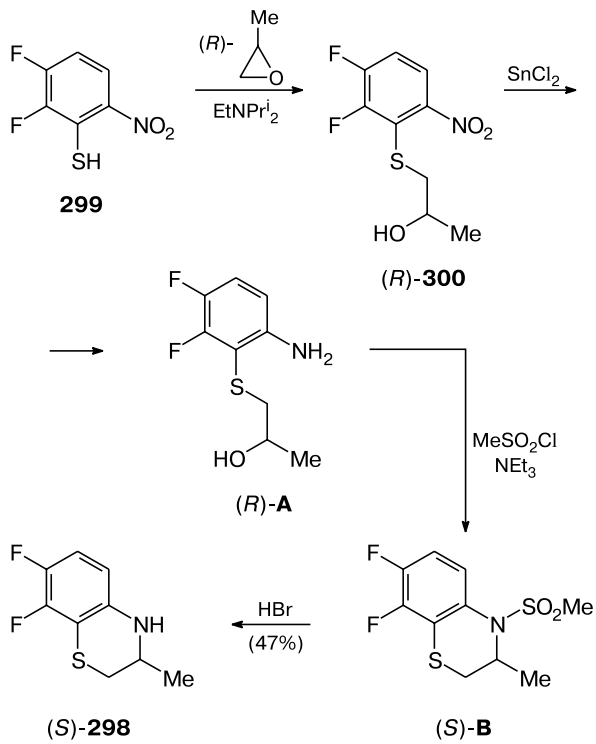
Scheme 85



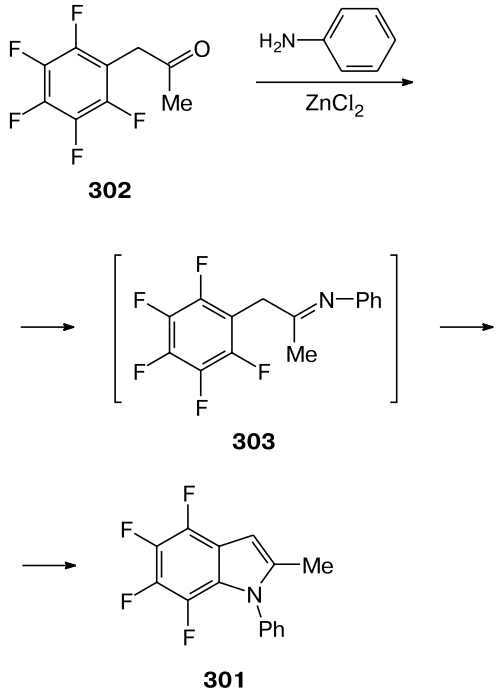
290 **293** **294, 295** **291, 292**

n = 1 (**291**, **294**), 2 (**292**, **295**)

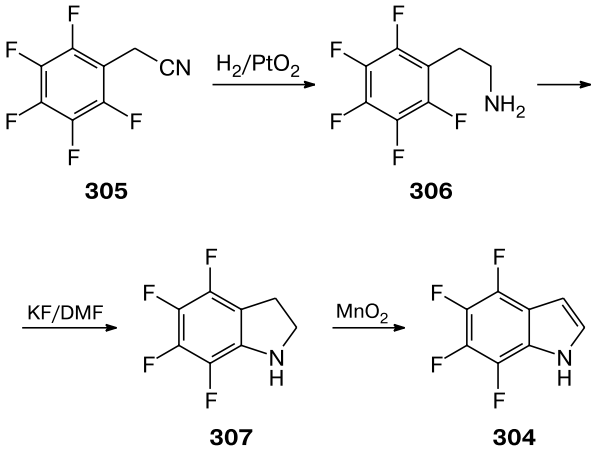
Scheme 87



Scheme 88



Scheme 89



6. Fluoro-containing arenes with other substituents

Apart from the synthons described above, other fluoroarenes containing substituents that can be involved in construction of azaheterocycles are of interest.

For instance, 4,5,6,7-tetrafluoro-2-methyl-1-phenylindole (**301**) is obtained by reaction of ketone **302** with an excess of aniline in the presence of anhydrous $ZnCl_2$ followed by intramolecular cyclization of the Schiff base **303** (Scheme 88).[134]

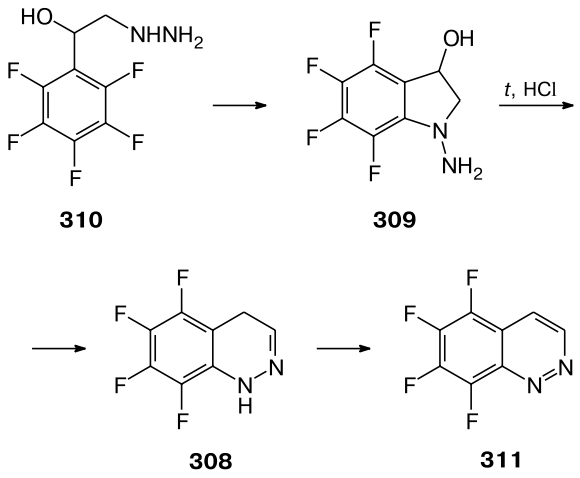
4,5,6,7-Tetrafluoroindole (**304**) is obtained as shown in Scheme 89. The synthesis involves reduction of pentafluorophenylacetonitrile (**305**) to amine **306**, intramolecular cyclization with replacement of the F atom, and smooth oxidation of dihydro derivative **307** with MnO_2 in benzene (Scheme 89).[135]

5,6,7,8-Tetrafluoro-1,4-dihydrocinnoline (**308**) is generated by heating of 1-amino-4,5,6,7-tetrafluoro-3-hydroxyindoline (**309**) (ring extension probably involves nitrene). In turn, compound **309** is prepared through intramolecular cyclization of hydrazine **310**. Dihydro derivative **308** is oxidized into 5,6,7,8-tetrafluorocinnoline (**311**) (Scheme 90; see Ref. 136).

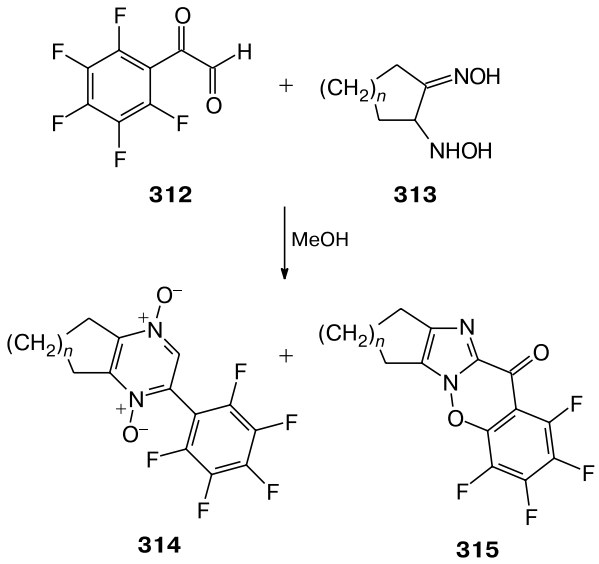
Reactions of pentafluorophenylglyoxal (**312**) with alicyclic 2-hydroxyamino oximes **313** in methanol give a mixture of annulated 2-(pentafluorophenyl)pyrazine 1,4-dioxides **314** and tetrafluoro-10*H*-imidazo[1,2-*b*]-[1,2]benzoxazin-10-ones **315** (Scheme 91).[137]

Pentafluorobenzyl bromide (**316**) reacts with benzimidazole-2-thione in the presence of NaH to give fused tetrafluoro derivative **317** (Scheme 92).[138] It should be noted that the cyclization pathway in this reaction differs from that in Scheme 43 and no analog of compound **133a** is formed. Apparently, benzimidazole-2-thione is initially alkylated at the S atom, while in the cyclocondensation with polyfluorobenzoyl chloride **107**, benzimidazole-2-thione is acylated at the N atom.

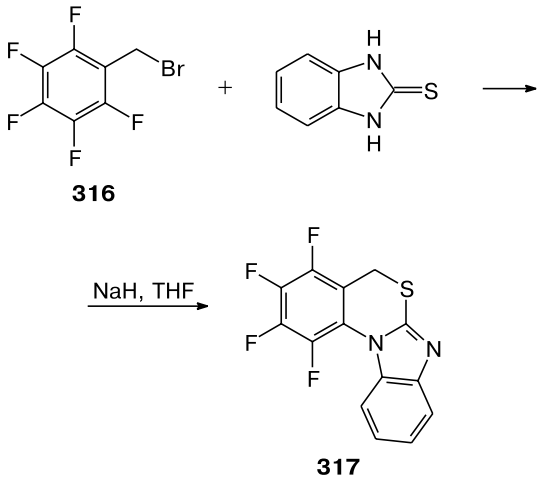
Scheme 90



Scheme 91

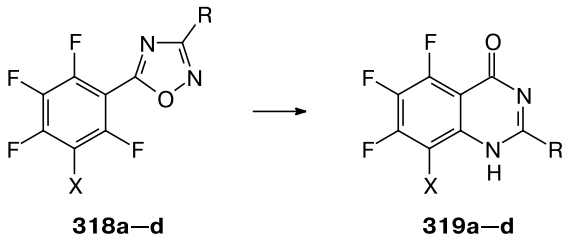


Scheme 92



Fluorinated quinazolin-4-ones can be conveniently obtained using a photochemical method.[139] Irradiation ($\lambda = 313$ nm) of 5-polyfluoroaryl-3-phenyl- or polyfluoroaryl-3-methyl-1,2,4-oxadiazoles **318** in dry methanol or acetonitrile in the presence of triethylamine gives the corresponding quinazolinones **319** (Scheme 93).

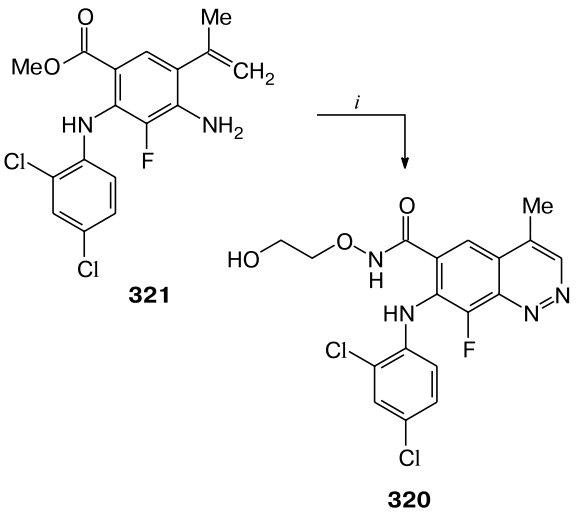
Scheme 93

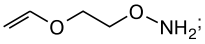


R = Ph, X = H (**a**), F (**b**); R = Me, X = H (**c**), F (**d**)

The synthesis of 8-fluorocinnoline **320** involves cyclization of methyl 4-amino-2-(2,4-dichlorophenylamino)-3-fluoro-5-propen-2-ylbenzoate (**321**) under the action of $NaNO_2$ and H_2SO_4, hydrolysis of the ester bond, and a reaction with *O*-(2-vinyloxyethyl)hydroxylamine (Scheme 94).[140] Hydrolysis of the ether group is carried out in a solution of HCl.

Scheme 94

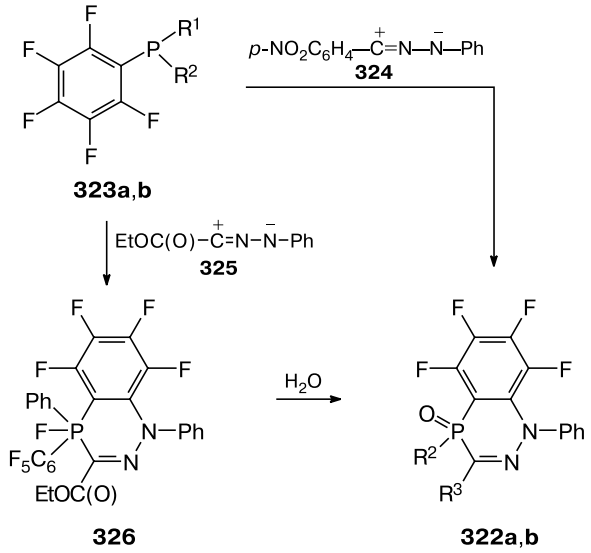


i. 1) $NaNO_2$, H_2SO_4; 2) 1 *M* LiOH; 3)  ; 4) 1 *M* HCl.

4-Ethoxy-5,6,7,8-tetrafluoro-3-(4-nitrophenyl)-4-oxo-1-phenyl-1,4-dihydrobenzo[*e*]-1,2,4-diazaphosphorine (**322a**) can be obtained by a reaction of diethyl pentafluorophenylphosphinate (**323a**) with *C*-(4-nitro-

phenyl)-*N*-phenylnitrile imine (**324**) under mild conditions (20 °C) (Scheme 95).[141] A reaction of polyfluorophenylphosphine **323b** with *C*-ethoxycarbonyl-*N*-phenylnitrile imine (**325**) under the same conditions gives polyfluorophosphorane **326** further hydrolyzed to 5,6,7,8-tetrafluoro-1,4-dihydrobenzo[*e*]-1,2,4-diazaphosphorine **322b** (see Scheme 95).[141]

Scheme 95



322: R^2 = OEt, R^3 = *p*-$NO_2C_6H_4$ (**a**), R^2 = C_6F_5, R^3 = COOEt (**b**);
323: R^1 = R^2 = OEt (**a**), R^1 = Ph, R^2 = C_6F_5 (**b**)

Conclusion

To sum up, the reviewed methods of constructing fluoro-containing azaheterocycles from fluoroarenes demonstrate that heterocyclization of fluoroarenes opens a route to a wide range of heterosystems. The great synthetic potential of fluoro-containing compounds makes them convenient synthons for the preparation of fluorinated heterocycles which are of interest for medicinal chemistry.

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