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Fluorine-containing quinazolines and their oxa and thia analogues: synthesis and biological activities †

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Abstract. Convenient methods for the synthesis of fluorine-containing quinazolines and their oxa and thia analogues are considered. The prospects for using these compounds in medicine are considered. The bibliography includes 129 references.

I. Introduction

Quinazolines [1–8] as well as their oxa and thia analogues [9–13] are important classes of heterocyclic compounds, among which antagonists of enzymes and of a number of receptors, compounds with antitumour, antiviral and antibacterial activity were found. A special place among these compounds is occupied by the fluorine-containing derivatives. Fluorine-containing heterocycles are widely used in the medicinal chemistry due to the unique properties of the fluorine atom, which is included in 20% of pharmaceuticals.[14] The good prospects of the search for new drugs among fluorine-containing quinazolines and benzothiazines are testified by the data published in the recent years in the scientific papers and patents (see, *e.g.*, Refs 15–21).

Quinazolin-4(3*H*)-ones monofluorinated at the benzene ring are of great interest. Promising compounds for the application in the clinical practice have been educed among them: 6-fluoroquinazolinones are effective for the obesity and diabetes treatment and are also neuroprotectors and inhibitors of 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptor, 5- and 7-fluoroquinazolones exhibit antitumour activity and 8-fluoroquinazolones are active against human cytomegalovirus.[22–25]

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This review generalizes the literature data obtained predominantly in the past 10–15 years and dealing with different approaches to the synthesis of the fluorine-containing quinazolines, their oxa and thia analogues. The biological activity of the most important representatives of this class of compounds is discussed.

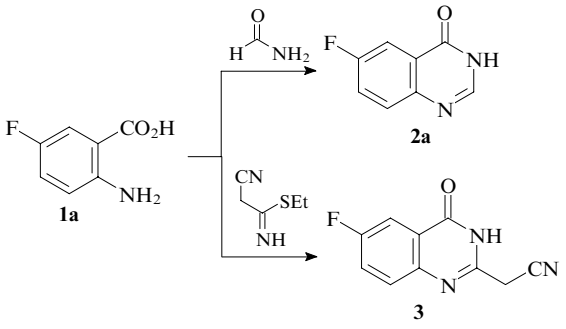
II. Fluorine-containing quinazolines

Several convenient one- and two-step methods for the preparation of the fluorine-containing quinazoline derivatives and their analogues based on the cyclocondensation reaction were suggested. The most important 'building blocks' in these reactions are fluorinated derivatives of anthranilic acid, *viz.*, nitriles, amides, acyl chlorides and hydrazides.

1. Cyclocondensation reactions

a. Cyclocondensation involving fluorine-containing anthranilic acids, their nitriles and amides

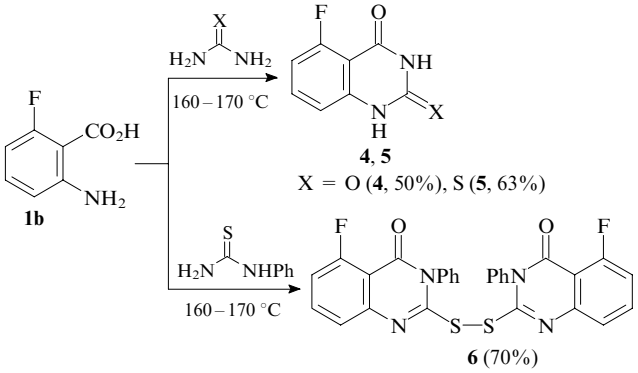
As a result of the cyclization of 2-amino-5-fluorobenzoic (5-fluoroanthranilic) acid (**1a**) and formamide, 6-fluoroquinazoline-4(3*H*)-one (**2a**) is formed.[22,23] A similar reaction of compound **1a** with ethyl α-cyanoiminothioacetate leads to 2-cyanomethyl-6-fluoroquinazoline-4(3*H*)-one (**3**).[26]



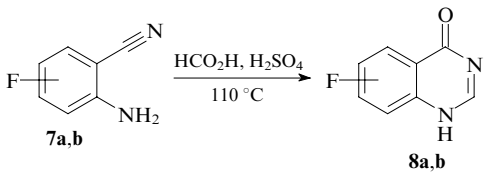
5-Fluoroquinazoline-2,4-dione (**4**) and its thio analogue (**5**) as well as 2,2′-dithiobis(3-phenyl-5-fluoroquinazoline-

† Dedicated to the member of the Russian Academy of sciences O N Chupakhin in connection with his 75th birthday.

4(3*H*)-one) (**6**) were obtained by the fusion of 6-fluoroanthranilic acid (**1b**) with urea, thiourea or phenylthiourea at the temperature of 160–170 °C. Most easily the reaction proceeds with phenylthiourea. For the interaction of acid **1b** with unsubstituted urea and thiourea a longer heating is required, while the corresponding products are obtained in lower yields. It should be noted that the introduction of the electron-withdrawing fluorine atom into anthranilic acid leads to the increase in its reactivity.[27,28]

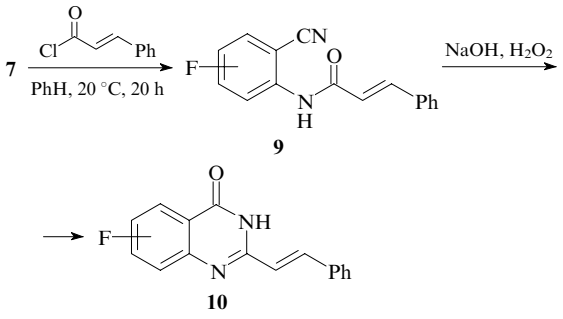


The treatment of 2-amino-3-fluorobenzonitrile (**7a**) with formic acid in the presence of sulfuric acid leads to 8-fluoroquinazolin-4(1*H*)-one (**8a**) in 88% yield.[29] Similarly 5-fluoroquinazolin-4(1*H*)-one (**8b**) was obtained from 6-fluoro isomer **7b**.[27]



Isomers: 3 (**a**), 6 (**b**) (hereafter indicate position of substituents in the initial compound).

The reaction of benzonitriles **7** with cinnamoyl chloride and subsequent oxidative cyclization of fluorine-substituted anilides of cinnamic acid (**9**) in the basic medium lead to 2-styrylquinazolin-4(3*H*)-ones **10**.[30,31]



The interaction of benzonitrile **7b** with phenyl isothiocyanate was studied.[28] Heating of the reactants at 100 °C for 3 h led to 2,2′-dithiobis(4-anilino-5-fluoroquinazoline) (**11**), its structure was confirmed by X-ray diffraction data (Fig. 1). The authors suggest that this reaction proceeds *via* intermediates **A** and **B**.

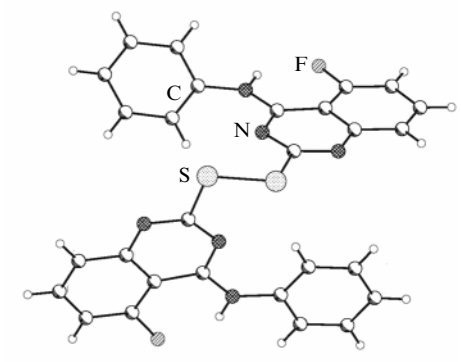
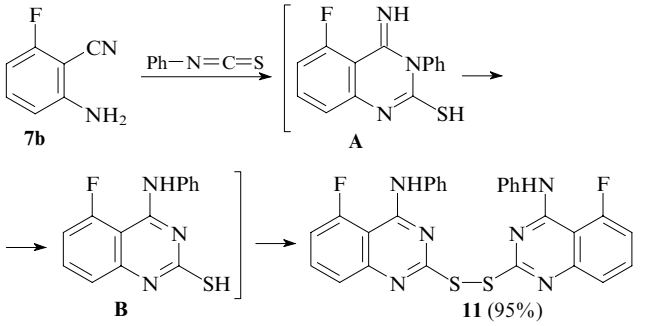
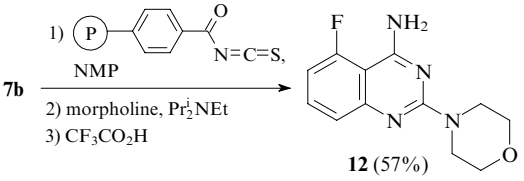


Figure 1. Molecular structure of dimer **11**.



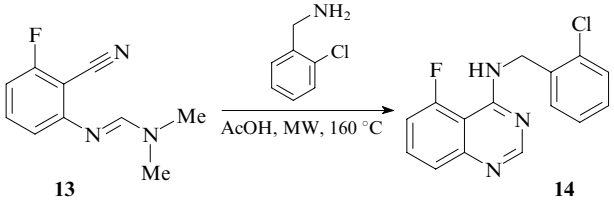
Fluorinated 4-oxo-2-thio-1,2,3,4-tetrahydroquinazolines are formed in the cyclization of fluorine-substituted methyl anthranilates with isocyanates or 2-(methoxycarbonyl)phenyl isothiocyanates with primary amines.[32]

The solid-phase synthesis of 2,4-diaminoquinazoline **12** was described [33] consisting in the condensation of 2-amino-6-fluorobenzonitrile (**7b**) with immobilized benzoyl isothiocyanate and morpholine. The product is detached from the polymeric support by the treatment with trifluoroacetic acid.



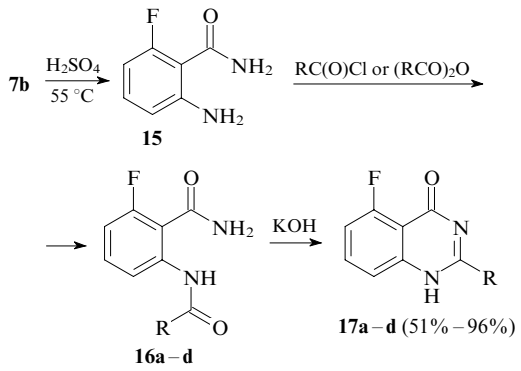
P is polymer, NMP is *N*-methylpyrrolidone.

The interaction of *N*,*N*-dimethyl-*N*′-(2-cyano-3-fluorophenyl)formamidine (**13**) with 2-chlorobenzylamine under microwave irradiation (MW) leads to *N*-substituted 4-aminoquinazoline **14**.[34]



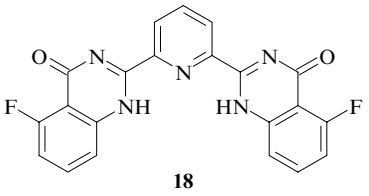
Diamides **16** are formed in the acylation of 6-fluoroanthranilamide obtained from benzonitrile **7b** with the

corresponding acyl chlorides or acid anhydrides. Diamides **16** are transformed into monofluorinated quinazolinones **17** by treatment with alkalies.[27]

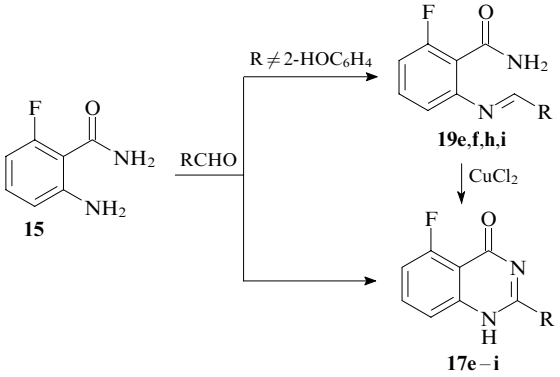


R = Me (**a**), Ph (**b**), 4-pyridyl (4-Py) (**c**), 3-Py (**d**).

Using 2 equiv. of amide **15** in the reaction with pyridine-2,6-dicarbonyl dichloride, it was possible to obtain 2,6-bis(5-fluoro-4-oxo(1*H*)-quinazoline-2-yl)pyridine (**18**).[27]

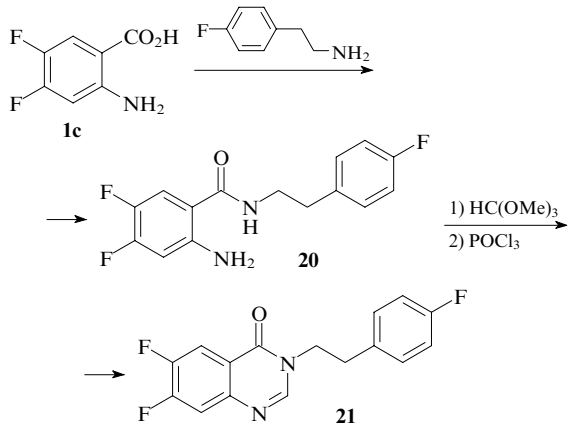


Monofluorinated quinazolinones containing (het)aryl substituents in position 2 were synthesized from amide **15** and aromatic or heterocyclic aldehydes. Imine **19e** is formed on heating furfural with amide **15** in ethanol, its oxidation by the treatment with $CuCl_2$ afforded 5-fluoro-2-(2-furyl)-quinazolinone **17e**.[27] The reactions with other (hetero)-aromatic aldehydes proceed in a similar manner. It should be noted that heating of salicylaldehyde (R = 2-HOC_6H_4) with amide **15** in ethanol gives directly 2-aryl-5-fluoroquinazolinone **17g**, while the corresponding Schiff base was not isolated.

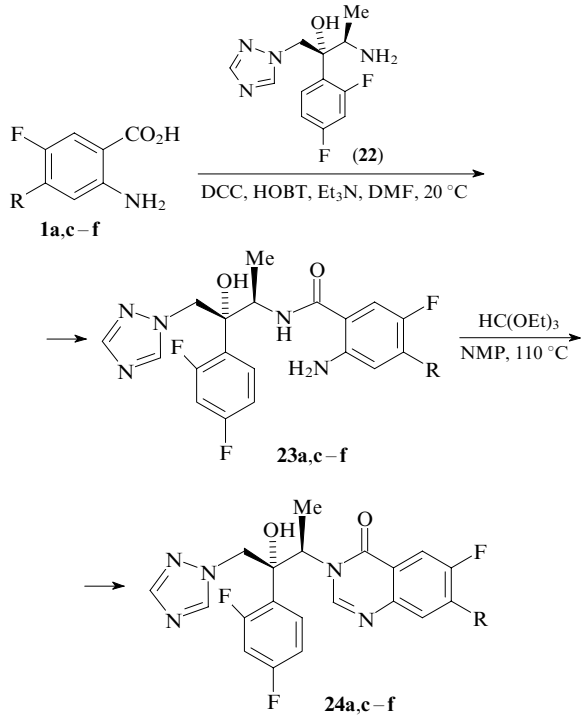


R = 2-furyl (2-Fu) (**e**), 2-Py (**f**), 2-HOC_6H_4 (**g**), 2-HO-5-$NO_2C_6H_3$ (**h**), 4-$MeOC_6H_4$ (**i**).

3-Substituted 6,7-difluoroquinazolin-4(3*H*)-one **21** was synthesized by cyclization of 2-aminobenzamide **20** with trimethyl orthoformate.[35] The starting amide is formed in the reaction of difluoroanthranilic acid **1c** with 4-fluorophenethylamine (carbodiimide method).



The interaction of fluoro-derivatives of anthranilic acid (**1a**,**c**–**f**) with amine **22** and the subsequent condensation of the amide intermediates **23** with triethyl orthoformate lead to fluoroquinazolin-4-ones **24a**,**c**–**f**, which contain an asymmetric centre.[36]

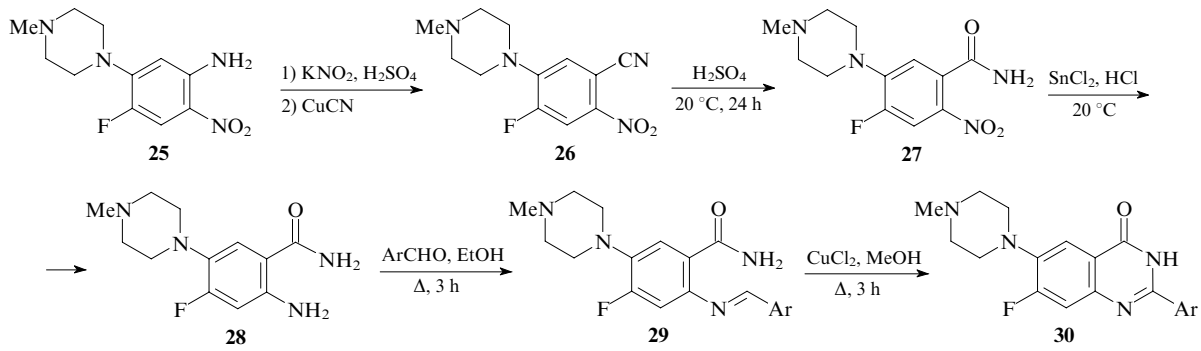


DCC is dicyclohexylcarbodiimide; HOBT is *N*-hydroxybenzotriazole; R = H (**a**), F (**c**), NH_2 (**d**), NMe_2 (**e**), $NHC(O)CF_3$ (**f**).

Fluorine-containing *o*-nitroaniline **25** was first converted into nitrile (**26**) and then into amide (**27**) of nitrobenzoic acid.[25] In the reduction of compound **27**, anthranilamide **28** is formed, which is coupled with aromatic aldehydes. In the final step, the oxidative cyclization of 2-arylideneimino-4-fluoro-5-(4-methypiperazin-1-yl)benzamides **29** leads to 2-arylquinazolinones **30** (Scheme 1).

Convenient routes to 3-*tert*-butoxyquinazoline-2,4-diones **31** were found based on the fluorine-containing *N*-alkoxyanthranilamides. The precursors are anthranilic acids with both free [**1**; R^1 = H (**c**), F (**g**), Cl (**h**)] and substituted (**32**) amino groups, while the key intermediates

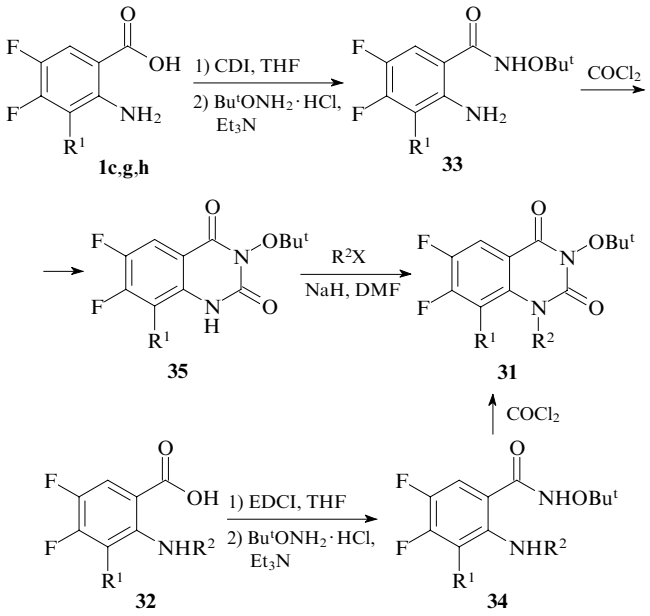
Scheme 1



Ar = 2-Fu, 2-thienyl (Th), 4-XC_6H_4 (X = H, F, Cl, Br, Me, MeO).

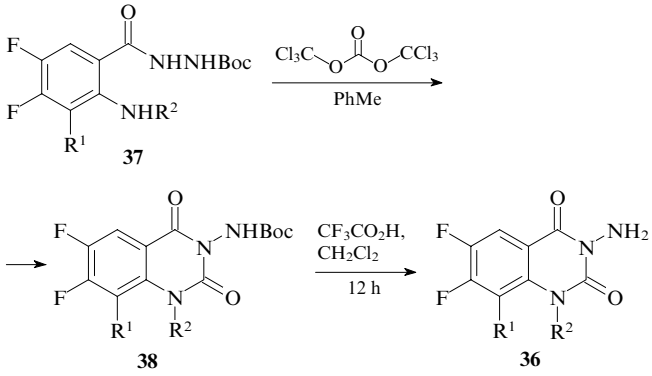
are the respective hydroxamates **33**, **34** (Scheme 2).[37] Thus, the reaction of compounds **1c**,**g**,**h** with carbonyldiimidazole gives anhydrides, which react with *O*-Bu^t-hydroxylamine hydrochloride in the presence of triethylamine. Hydroxamates **33** react with phosgene with cyclization yielding quinazolinediones **35**. The alkylation of the latter leads to compounds **31**. Thus one can introduce substituents into position 1, which are present at N(1) in known fluoroquinolone drugs. An alternative route to the synthesis of quinazolinediones **31** is the treatment of the *N*-substituted acid **32** with *O*-Bu^t-hydroxylamine hydrochloride and the cyclization of the resulting hydroxamate **34** with phosgene (see Scheme 2).

Scheme 2



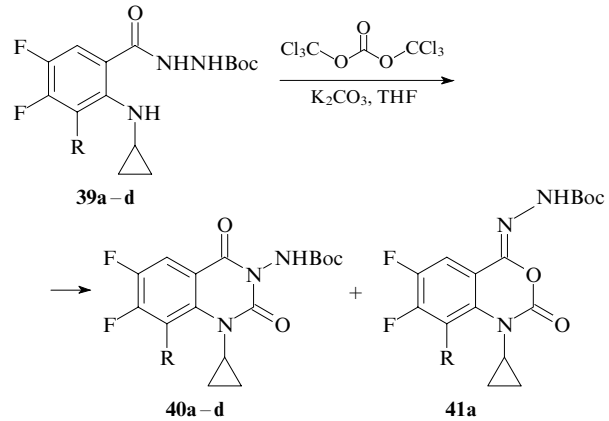
CDI is carbonyldiimidazole, EDCI is 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide; R^1 = H, F, Cl; R^2 = H, Me, Et, cyclo-Pr, Bn, 2,4-$F_2C_6H_3$; X = Cl, Br.

The synthesis of the fluorine-containing 3-aminoquinazolinediones **36** has some similarity with the assembly of the heterocycle in compounds **31**. The reaction of *N*-(2-amino-4-fluorobenzoyl)-*N*′-Boc-hydrazine **37** with triphosgene with the subsequent removal of the *tert*-butoxycarbonyl protecting group in the substituted 3-aminoquinazoline-2,4-diones **38** leads to derivatives **36**.[38]



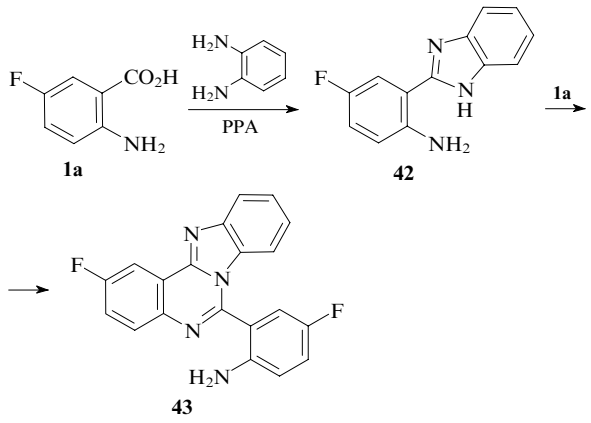
R^1 = H, F, Cl; R^2 = H, Me, Et, cyclo-Pr, Bn, 2,4-$F_2C_6H_3$.

Yet another example of the usage of fluorine-containing anthranilic acid hydrazides (**39**) for the synthesis of quinazolines was reported.[39] Thus in the reaction of trifluoro-substituted hydrazide **39a** (R = F) with triphosgene a mixture of quinazolinedione **40a** and benzoxazinone **41a** in the ratio of 80 : 20 is formed. In the case of difluorine-substituted hydrazides **39b**–**d** the only reaction products are the corresponding quinazolinediones **40b**–**d**.[39]



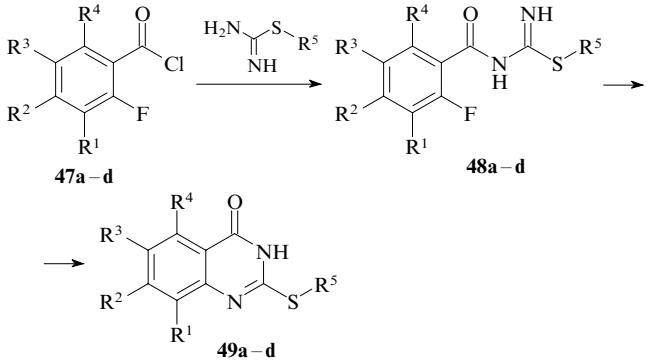
R = F (**a**), Cl (**b**), Me (**c**), OMe (**d**); Boc is *tert*-butoxycarbonyl.

Fluoro-anthranilic acid was also used to prepare condensed fluorine-containing quinazolones. In the reaction of *o*-phenylenediamine with 5-fluoroanthranilic acid (**1a**) in the presence of polyphosphoric acid (PPA), intermediate 2-(*o*-aminophenyl)benzimidazole **42** reacts with a second molecule of **1a** to give 6-(*o*-aminophenyl)benzimidazo-[1,2-*c*]quinazoline (**43**).[40]



1a **42** **43**

5 h results in their intramolecular cyclization to fluorine-containing 2-alkylthioquinazolin-4(3*H*)-ones **49a–d**.



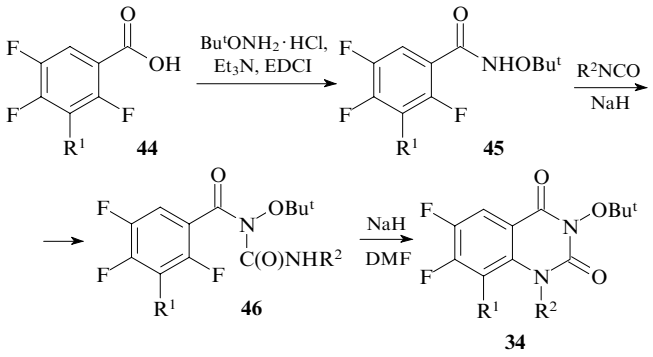
47a–d **48a–d** **49a–d**

$R^1 = R^3 = R^4 = H$, $R^2 = F$ (**a**); $R^1 = R^2 = R^3 = H$, $R^4 = F$ (**b**); $R^1 = R^4 = H$, $R^2 = Cl$, $R^3 = F$ (**c**); $R^1 = R^2 = R^3 = F$, $R^4 = H$ (**d**); R^5 = Me, Et.

b. Cyclocondensation using fluorine-containing derivatives of *o*-halobenzoic acids

One of the approaches to the synthesis of fluorine-containing quinazoline-2,4-diones **34** is based on the transformations of polyfluorobenzoic acids **44** (Scheme 3). First, they are converted to hydroxamates **45**, then to ureas **46**, which cyclize in the presence of the sodium hydride yielding quinazolinediones **34**.[37]

Scheme 3



44 **45** **46** **34**

R^1 = H, F, Cl; R^2 = H, Me, Et, cyclo-Pr, Bn, 2,4-$F_2C_6H_3$.

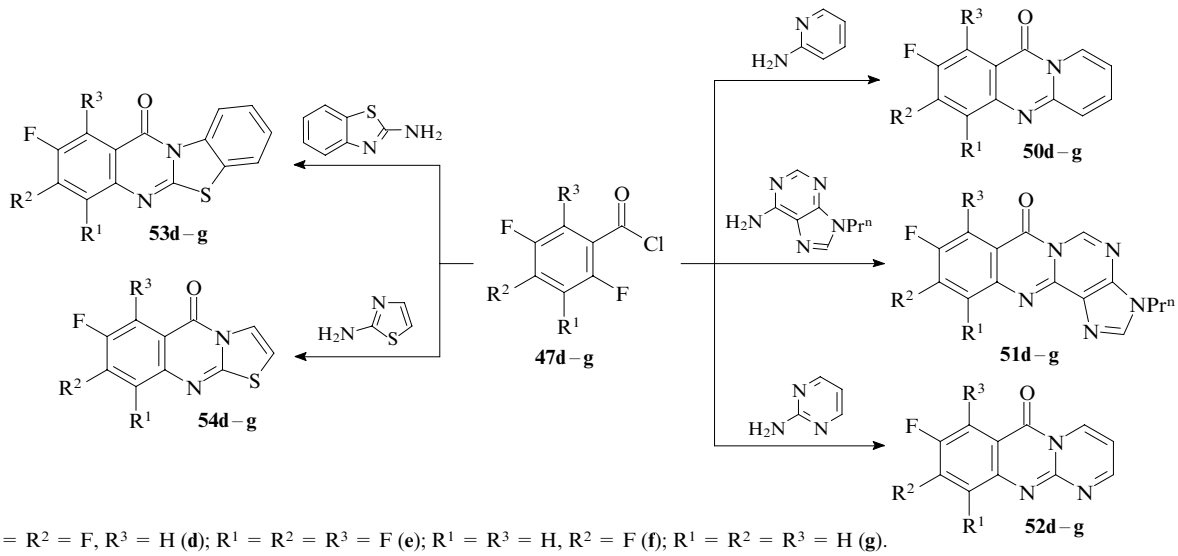
A method was proposed for the synthesis of fluoroquinazolin-4-ones from 2-fluoro-substituted benzoyl chlorides and *N*,*N*′-dinucleophiles. Thus coupling of acyl chlorides **47a–d** with *S*-alkylisothiourea afforded the *N*-aroylic derivatives of **48a–d**.[27,28,41] Refluxing of the latter in toluene in the presence of triethylamine or in dimethylformamide for

Since 2,6-difluorobenzoyl chloride (**47b**) is more reactive in the cyclocondensation than its 2,4-difluoro isomer **47a**, the corresponding quinazolinone **49b** was obtained in a higher yield. The application of this method for the synthesis of fluorine-containing quinazolinones with the use of 2-chloro-substituted benzoic acids (2-chloro-5-fluorobenzoyl chloride or 2-chloro-4,5-difluorobenzoyl chloride) was so far unsuccessful.[41]

The fluorine-containing annulated quinazolines are of great interest as they are analogues of the fluoroquinolones — highly active antibacterial agents. A number of compounds was found in the series of polycyclic fluoroquinolones (*e.g.*, levofloxacin, marbofloxacin), which are equally promising for medicinal chemistry as the bicyclic compounds. The most important method for the construction of the skeleton of [*a*]- and [*b*]annulated quinazolinones is the reaction of the polyfluorobenzoyl chlorides with *N*,*N*′-dinucleophiles.[42]

[*b*]Annulated quinazolin-4(3*H*)-ones **50–54** were obtained by the cyclocondensation of 2-aminoazaheterocycles with 2-fluorobenzoyl chlorides **47d–g** in dichloromethane in the presence of diisopropylethylamine at room temperature (Scheme 4). The linear annulation of the azole and azine fragments to the quinazolinone core in products

Scheme 4

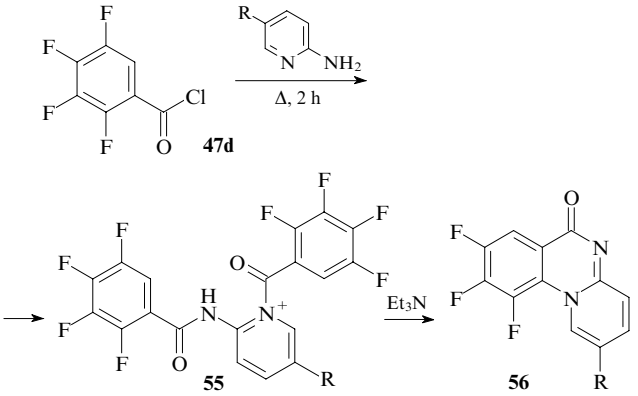


53d–g **54d–g** **47d–g** **50d–g** **51d–g** **52d–g**

$R^1 = R^2 = F$, $R^3 = H$ (**d**); $R^1 = R^2 = R^3 = F$ (**e**); $R^1 = R^3 = H$, $R^2 = F$ (**f**); $R^1 = R^2 = R^3 = H$ (**g**).

50–**54** was confirmed by ^{13}C NMR spectroscopy and X-ray diffraction data (by the example of compound **53e**).[43]

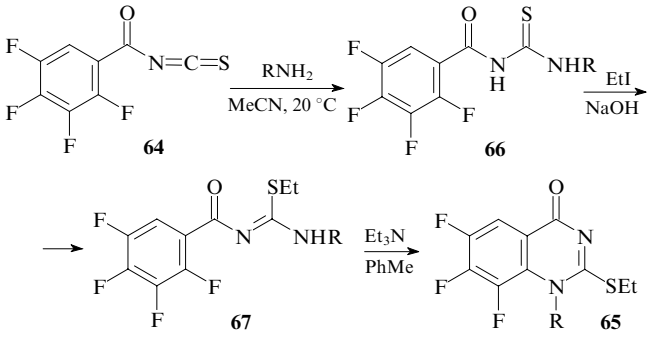
Upon the reaction of 2-aminopyridine and 2-amino-5-methylpyridine with tetrafluorobenzoyl chloride (**47d**) salts **55** are formed, which are transformed on refluxing in toluene in the presence of triethylamine into pyrido-[1,2-*a*]quinazoline-6(6*H*)-ones (**56**). The angular structure of the obtained tricyclic derivatives **56** was confirmed by the ^{19}F, ^{13}C NMR spectra as well as two-dimensional heteronuclear experiments HetCOR (Heteronuclear chemical shift CORrelation) and HMBC (Heteronuclear Multiple Bond Coherence).[44]



R = H (70%), Me (72%).

New approaches were developed to the synthesis of 2-iminoquinazolin-4-ones (**57**), imidazo[1,2-*a*]- (**58**), triazolo[1,5-*a*]- (**59**), pyrazolo[1,5-*a*]- (**60**) and thiazolo-[3,2-*a*]quinazolin-5-ones (**61**), benzothiazolo[3,2-*a*]- (**62**) and benzimidazo[3,2-*a*]quinazolin-7-ones (**63**) based on reactions of tetrafluorobenzoyl chloride **47d** with *N*,*N*′-dinucleophiles (Scheme 5).[45,46] In compounds **57**–**63**, the fluorine atom situated between two F atoms can easily be substituted by the amino group in the reactions with secondary cyclic amines.

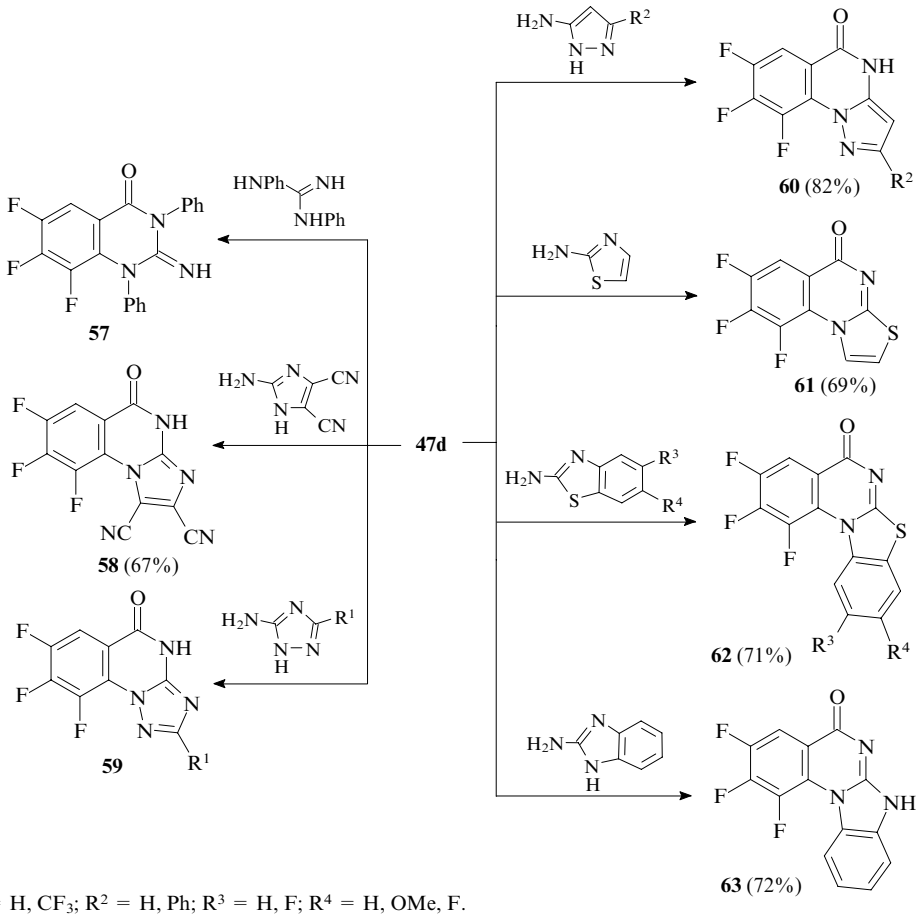
We were the first to use tetrafluorobenzoyl isothiocyanate (**64**) for the synthesis of fluorine-containing 1-arylquinazolin-4-ones **65**.[47] Tetrafluorobenzoylthioureas **66** were prepared by the reaction of isocyanate **64** with aromatic amines in acetonitrile at room temperature. S-Alkylation of thioureas **66** and the subsequent intramolecular cyclization of intermediates **67** in toluene in the presence of triethylamine for 3 h lead to *N*-arylquinazolinones **65**.



R = Ph, 4-MeC_6H_4, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$.

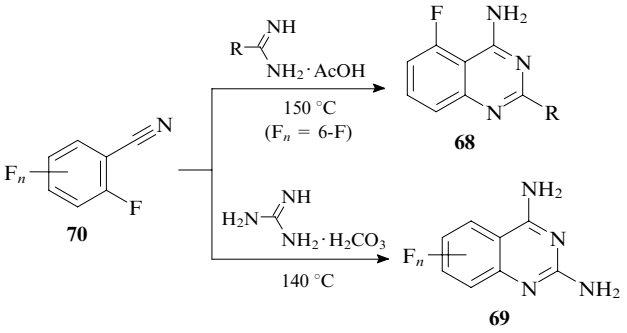
Fluorinated 4-aminoquinazolines **68**, **69** were synthesized from fluorine-containing benzonitriles **70.** The reac-

Scheme 5



R^1 = H, CF_3; R^2 = H, Ph; R^3 = H, F; R^4 = H, OMe, F.

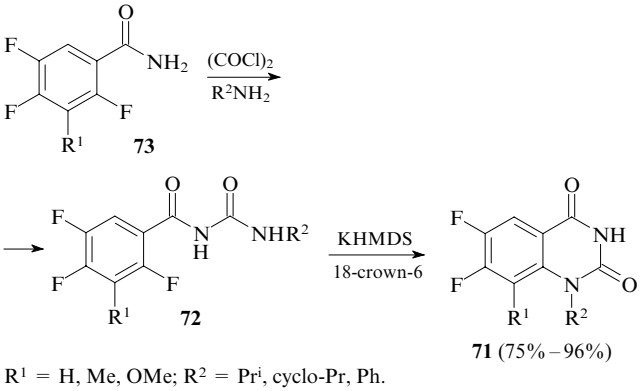
tion of 2,6-difluorobenzonitrile (**70**, F_n = 6-F) with formamidinium acetate or acetamidinium acetate in *N*,*N*-dimethylacetamide at 150 °C in the nitrogen atmosphere afforded 4-amino-5-fluoroquinazolines **68**.[48] The reactions of 2,6-difluoro-, 2,5-difluoro-, 2,4-difluoro-, 2,3-difluoro- and pentafluorobenzonitriles **70** with guanidinium hydrocarbonate in *N*,*N*-dimethylacetamide at 140 °C lead to the corresponding fluorine-containing 2,4-diaminoquinazolines **69**.[49]



F_n = 3-F, 4-F, 5-F, 6-F, 3,4-F_2, 4,5-F_2, 5,6-F_2, 3,4,5,6-F_4; R = H, Me.

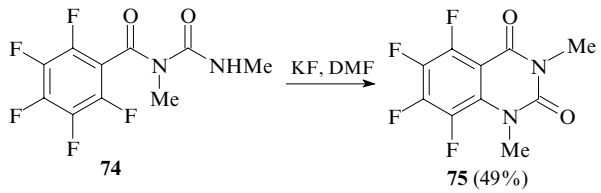
On the basis of trisubstituted benzonitriles **70** and guanidinium hydrocarbonate, 5,6-difluoro-, 6,7-difluoro- and 7,8-difluoro-2,4-diaminoquinazolines **69** were also synthesized. Note that 2,3,6-trifluorobenzonitrile is transformed under these conditions solely into 2,4-diamino-5,6-difluoroquinazoline, while 3-amino-2,6-difluorobenzonitrile is transformed into 2,4,8-triamino-5-fluoroquinazoline.[50]

Quinazoline-2,4-diones **71** are formed upon intramolecular cyclization of ureas **72** obtained from trifluorobenzamides **73**. Potassium hexamethyldisilazide (KHMDS) is used as the cyclization agent in the presence of catalytic amounts of 18-crown-6 ether.[39]

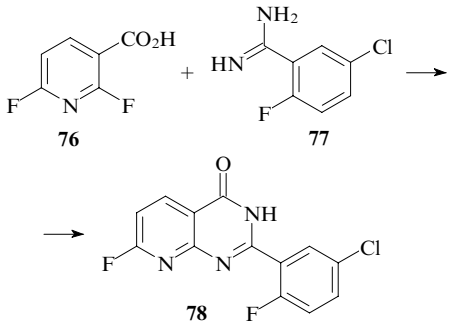


R^1 = H, Me, OMe; R^2 = Pr^i, cyclo-Pr, Ph.

1,3-Dimethyl-1-pentafluorobenzoylurea (**74**) gave tetrafluoroquinazoline-2,4-dione **75** on heating with potassium fluoride in *N*,*N*-dimethylformamide.[51]

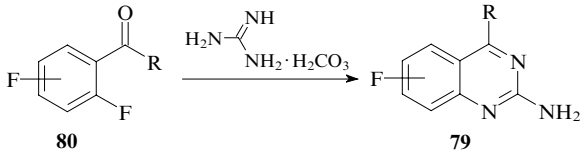


Using cyclocondensation of 2,6-difluoronicotinic acid (**76**) with amidine **77**, the aza analogue of fluorine-containing quinazolinones, *viz*., pyridopyrimidone **78**, was synthesized.[52]



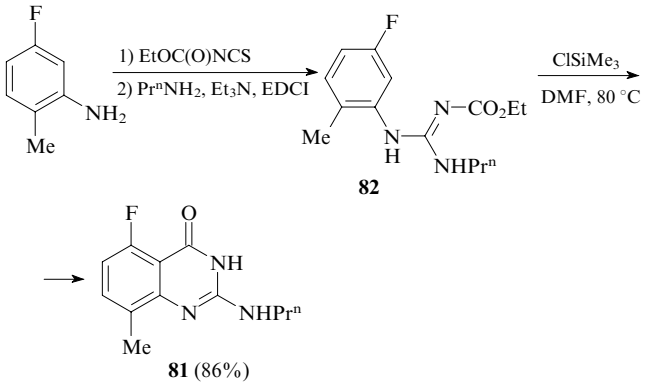
b. Cyclocondensation using other fluorine-containing synthons

The preparation of unsubstituted[53] and 4-substituted[54] fluorine-containing 2-aminoquinazolines **79** by heating of 2,6-, 2,5- or 2,4-difluoro-substituted benzaldehydes (**80**, R = H) and ketones (**80**; R = Me, Et, Ph) with guanidinium hydrocarbonate in *N*,*N*-dimethylacetamide was described.

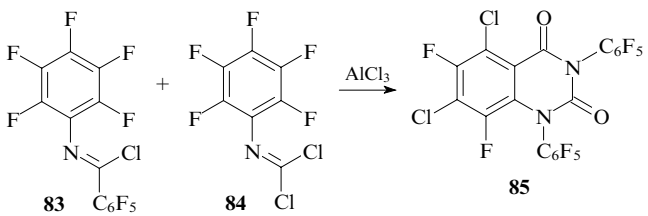


R = H, Me, Et, Ph; isomers: 2,4-F_2, 2,5-F_2, 2,6-F_2.

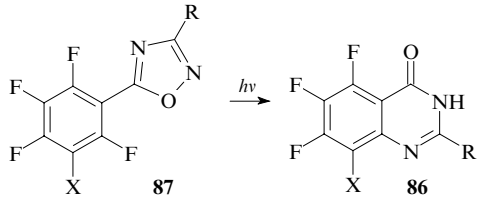
The key step of the new efficient method for the synthesis of 2-alkylaminoquinazolin-4(3*H*)-ones **81** is the intramolecular cyclization of *N*-ethoxycarbonyl guanidine **82**.[55]



The original synthon for the formation of the skeleton of fluorine-containing quinazoline-2,4-diones is *N*-pentafluorophenyl benzimidoyl chloride **83**. Its reaction with phosgene imine **84** in the presence of $AlCl_3$ yields 5,7-dichloro-6,8-difluoro-1,3-bis(pentafluorophenyl)quinazoline-2,4-dione (**85**).[56] Three products were obtained in the reaction of compound **83** with pentafluorobenzene in the presence of $AlCl_3$: quinazolinedione **85**, 1,3-bis(pentafluorophenyl)urea and $C_6F_5NHC(O)C_6F_5$. The structure of compound **85** was confirmed by the X-ray diffraction analysis.[56]

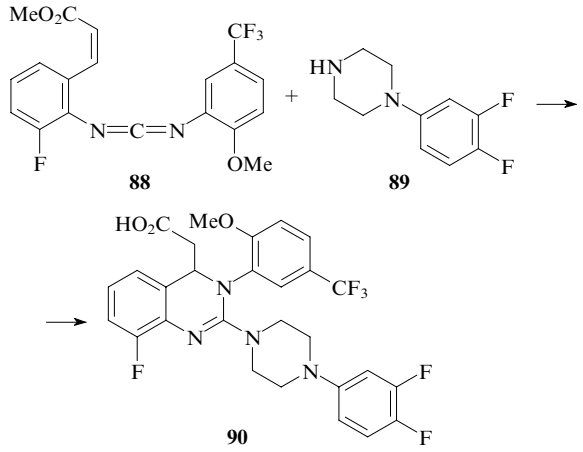


2-Methyl- and 2-phenylpolyfluoroquinazolin-4(3*H*)-ones (**86**) were synthesized by the photochemical conversion of 3-methyl(phenyl)-5-polyfluorophenyl-1,2,4-oxadiazoles **87** in anhydrous solvent (methanol, acetonitrile) in the presence of triethylamine (at $\lambda = 313$ nm) or pyridine (at $\lambda = 365$ nm).[57]

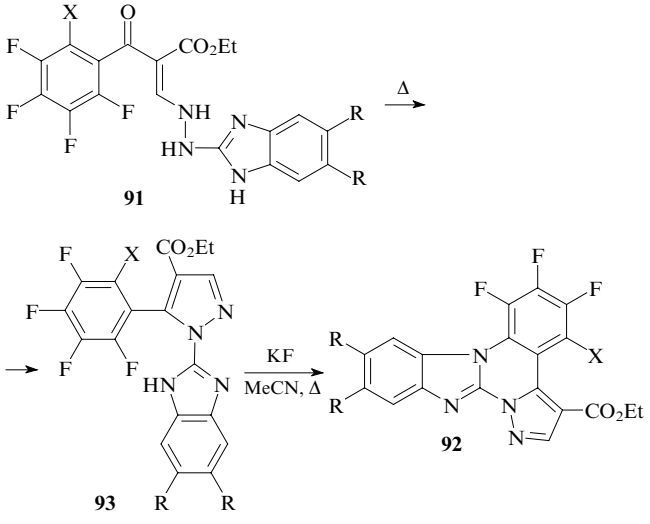


R = Me, Ph; X = H, F.

The condensation of diarylcarbodiimide **88** with 1-(3,4-difluorophenyl)piperazine (**89**) and the subsequent hydrolysis of the ester group leads to 8-fluoroquinazoline **90**.[58]



Fluorine-containing 2-benzoyl-3-(hetarylhydrazino)-acrylates are intermediates in the synthesis of the original pentacyclic derivatives of fluoroquinazoline. For example, benzimidazo[1,2-*a*]pyrazolo[1,5-*c*]quinazolines **92** were obtained by cyclization of ethyl 3-[-(benzimidazol-2-yl)-hydrazino]-2-(polyfluorinebenzoyl)acrylates (**91**) in boiling acetonitrile in the presence of potassium fluoride or benzyltriethylammonium chloride. The reaction proceeds through the formation of pyrazolyl-substituted benzimidazoles **93** as intermediates.[59,60] The structure of benzimidazopyrazoloquinazoline **92** (X = R = H) was confirmed by X-ray diffraction analysis.[60]

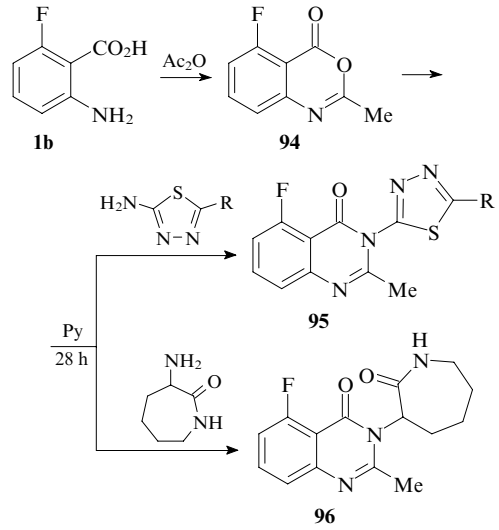


X = H, F; R = H, F, Cl.

d. Transformation of the fluorine-containing 3,1-benzoxazin-4-ones into quinazolinones

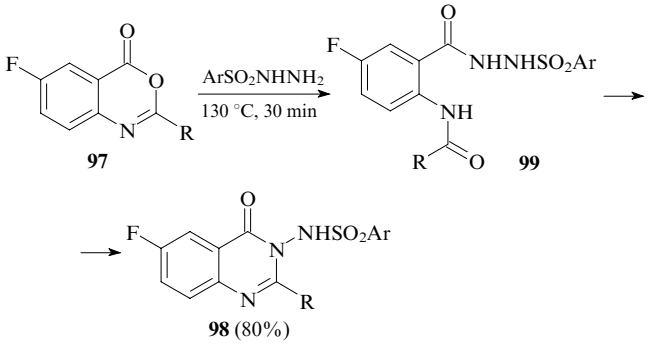
Refluxing of 2-methyl-5-fluoro-3,1-benzoxazin-4-one (**94**) with 2-amino-1,3,4-thiadiazoles or α-amino-ε-caprolactam in dry pyridine for 28 h leads to 3-substituted quinazolin-4(3*H*)-ones **95** or **96**, respectively (Scheme 6).[61]

Scheme 6



R = Et, cyclo-Pr, Bu^t, CF_3.

The fusion of sulfohydrazides with 6-fluoro-3,1-benzoxazines **97** at 130 °C for 30 min yields sulfonamides **98**.[62] The reaction proceeds through the formation of open intermediates **99**, which were isolated when the process was carried out under mild conditions.



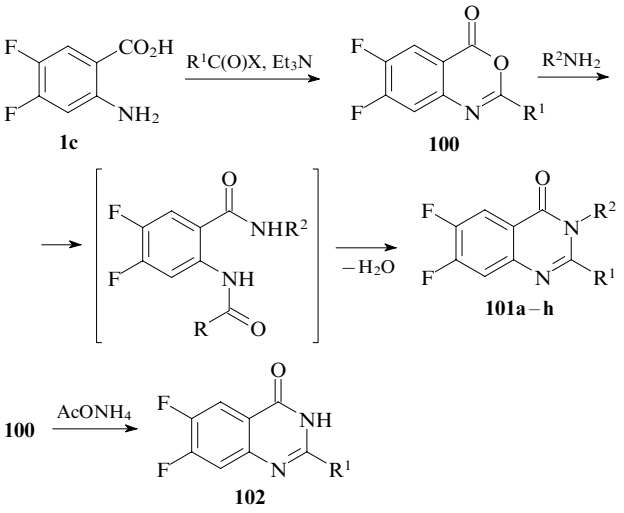
R = Bn, $Ph(CH_2)_2$, 2-$ThCH_2$.

2-Methyl- and 2-phenyl-6,7-difluorobenzoxazin-4-ones (**100**) were synthesized by our group from 4,5-difluoroanthranilic acid (**1c**) by refluxing with acetic anhydride for 1 h or by the reaction with benzoyl chloride in the presence of triethylamine in dry methylene chloride, respectively (Scheme 7).[63]

The reaction of benzoxazines **100** with hydrazine hydrate in boiling ethanol for 3 h leads to 3-amino derivatives of 6,7-difluoroquinazolin-4(3*H*)-ones **101a**,**g**. In order to obtain quinazolines with heterocyclic substituents in position 3, hetarylamines were introduced into the reactions with benzoxazinones **100** instead of hydrazine hydrate.

Fusion of reactants at 170–180 °C for 20–40 min gave the corresponding 3-hetaryl-6,7-difluoroquinazolin-4(3*H*)-ones **101b–f,h** in 60%–80% yields.[63] The fusion of benzoxazinones **100** with ammonium acetate leads to quinazolinones **102** (see Scheme 7).

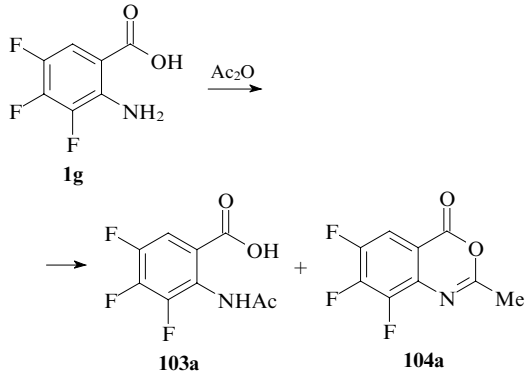
Scheme 7



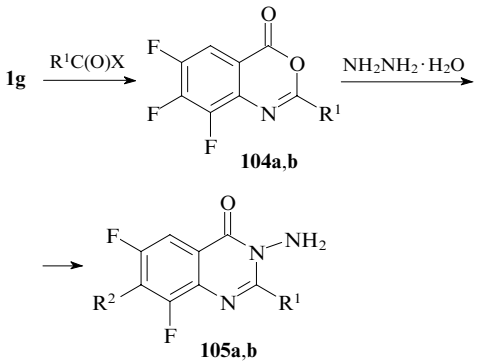
X = OAc, Cl;
R^1 = Me: R^2 = NH_2 (**a**), 5-*tert*-butylisoxazol-3-yl (**b**), thiazol-2-yl (**c**), triazol-2-yl (**d**), 5-methylpyrazol-3-yl (**e**), 2-Py (**f**);
R^1 = Ph: R^2 = NH_2 (**g**), 5-*tert*-butylisoxazol-3-yl (**h**).

Compounds **101c,e,f** were also obtained by refluxing benzoxazinone **100** (R^1 = Me) and the corresponding hetarylamines in dimethylformamide for 1 h, but their yields in this case were lower than upon fusion of the same reactants. It should be noted that in the reaction of compounds **100** with hetarylamines and hydrazine hydrate, the fluorine atoms in the benzene ring are preserved.

The condensation of the 3,4,5-trifluoroanthranilic acid (**1g**) with acetic anhydride in the absence of a base leads to a mixture of acyl derivative **103a** and benzoxazinone **104a** in which the latter predominates (27 : 73 ratio, according to the ^{1}H NMR spectroscopy data).



The use of a mixture of acetic anhydride with anhydrous sodium acetate as the condensation agent results in benzoxazinone **104a** solely (heating of the reactants for 2 h). The reaction of trifluoroanthranilic acid **1g** with benzoyl chloride at room temperature in the presence of triethylamine for 4 h leads to benzoxazinone **104b** (R^1 = Ph).

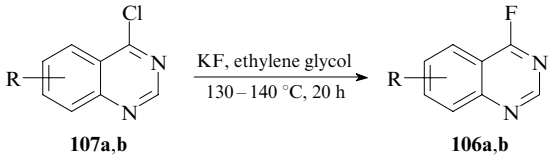


R^1 = Me, R^2 = $NHNH_2$ (**a**); R^1 = Ph, R^2 = F (**b**).

Compounds **104a,b** were introduced into the reaction with hydrazine hydrate. In the case of benzoxazin-4-one **104a**, the transformation of the benzoxazine ring into the quinazoline one occurs together with the replacement of the fluorine atom in the benzene ring by hydrazino group with the formation of 3-amino-6,8-difluoro-7-hydrazino-2-methylquinazolin-4(3*H*)-one (**105a**). Under the same conditions, benzoxazinone **104b** is transformed into 3-amino-2-phenyl-6,7,8-trifluoroquinazolin-4(3*H*)-one (**105b**).[63]

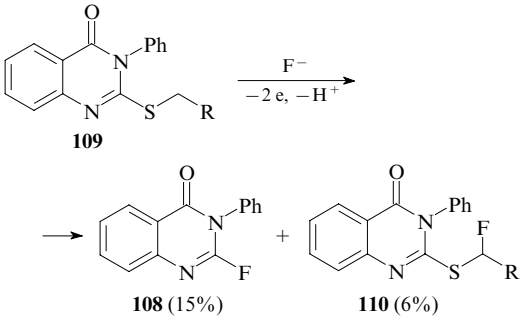
2. Modification of substituents in the heterocycle

4-Fluoroquinazolines **106a,b** containing chorine atom or nitro group in the benzene ring were synthesized by the fluorination of the corresponding 4-chloro derivatives **107a,b**.[64]



R = NO_2 (**a**), Cl (**b**).

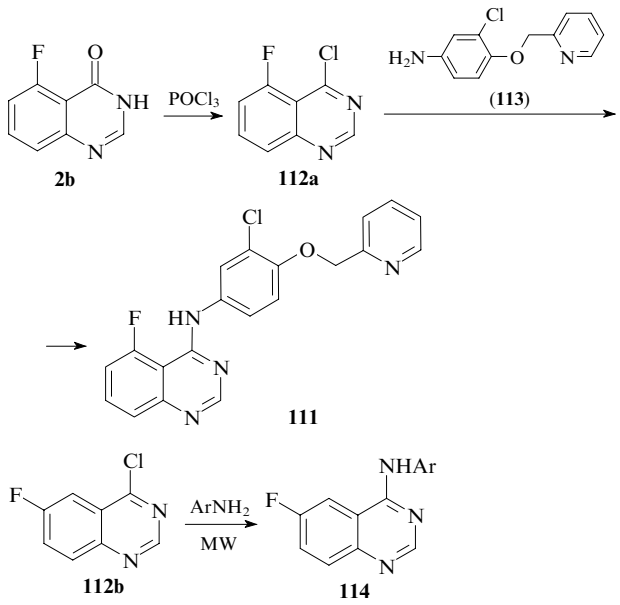
2-Fluoroquinazolinones **108** are formed by the electrochemical fluorination of sulfides **109**.[65] Quinazolinones **110** were isolated as by-products.



R = H, Ac, CO_2Et.

Numerous publications are devoted to the modification of fluorine-containing quinazolines at position 4. For example, with 4-arylamino derivative **111** was obtained by chlorodeoxygenation of 5-fluoroquinazolin-4(3*H*)-one (**2b**) with the subsequent amination of the chloro derivative **112a** with 4-(2-pyridilmethoxy)-3-chloroaniline (**113**) (Scheme 8).[66] The transformation of 4-chloro-6-fluoroquinazoline (**112b**) into 4-(*N*-arylamino)-6-fluoroquinazolines **114** was performed under microwave irradiation.[22]

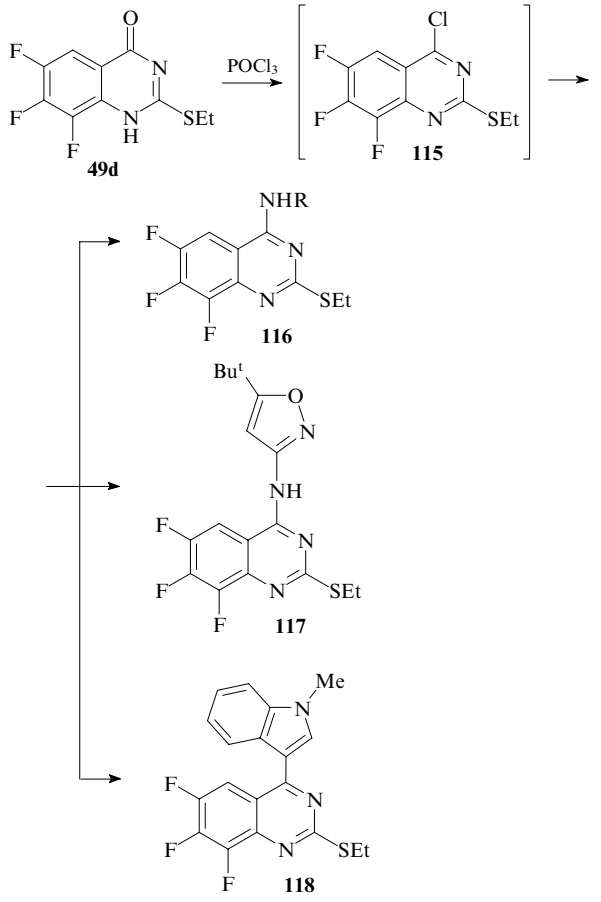
Scheme 8



Ar = 2-ClC_6H_4, 3,4-$F_2C_6H_3$.

As in the series of 4-anilinoquinazolines neuraminidase inhibitors[67] were found, it was of interest to obtain fluorinated 4-anilinoquinazolines. Sulfide **49d** was chosen as the starting compound (Scheme 9). Compound **49d** was treated with phosphorus oxychloride and the resulting 4-chlorine-containing intermediate **115** was introduced into reactions

Scheme 9

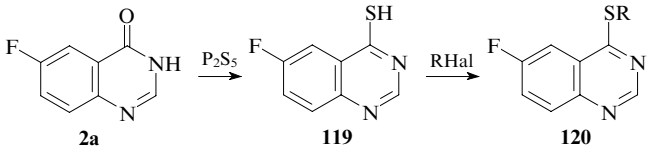


R = Bn, Ph, 2-ClC_6H_4, 3,4-$F_2C_6H_3$.

with different amines. Thus compounds **116** (R = Ph, 2-ClC_6H_4, 3,4-$F_2C_6H_3$, Bn) were obtained by the reaction with arylamines and benzylamine in acetonitrile, and quinazoline **117** was obtained by the reaction with 3-amino-5-*tert*-butylisoxazole. The reaction of the intermediate **115** with a C-nucleophile such as *N*-methylindole was also successful; this reaction gave 4-(indole-3-yl)quinazoline **118**.[41]

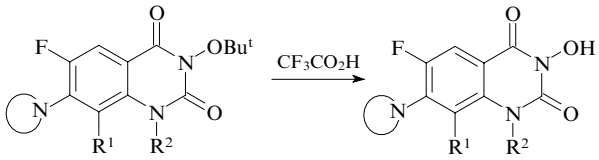
This method was used to prepare analogues of compounds **116** containing substituted indol-5-ylamino group in position 4 and a 4-[(decahydroxyquinolin-1-yl)carbonyl]-3-chloroaniline fragment.[68]

The treatment of compound **2a** with phosphorus pentasulfide and the subsequent reactions of quinazoline **119** with alkyl(aryl) halides lead to 4-alkyl(aryl)thio-6-fluoroquinazolines **120**.[23]



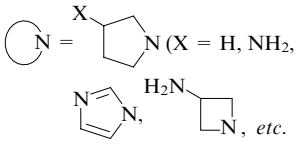
R = All, Bn, 2-chloropyridin-5-ylmethyl.

The synthesis of a large series of 3-substituted fluorine-containing quinazolines was performed. Thus 3-hydroxyquinazoline-2,4-diones **121** were obtained by hydrolysis of 3-*tert*-butoxy group in the fluorine-containing quinazolinediones **122**.[37]

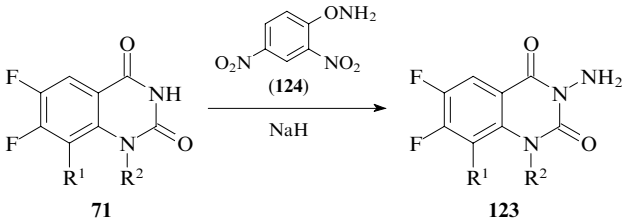


122 **121** (80%–90%)

R^1 = H, F, Cl; R^2 = H, Me, Et, cyclo-Pr, Bn, 2,4-$F_2C_6H_3$;



3-Aminoquinazoline-2,4-diones **123** are formed upon amination of quinazolinediones **71** with *O*-(2,4-dinitrophenyl)hydroxylamine (**124**) in the presence of sodium hydride.[39]

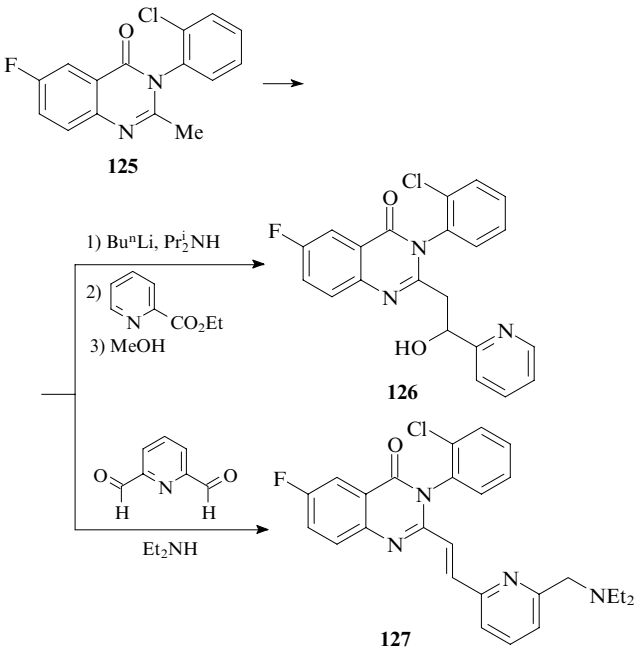


71 **123**

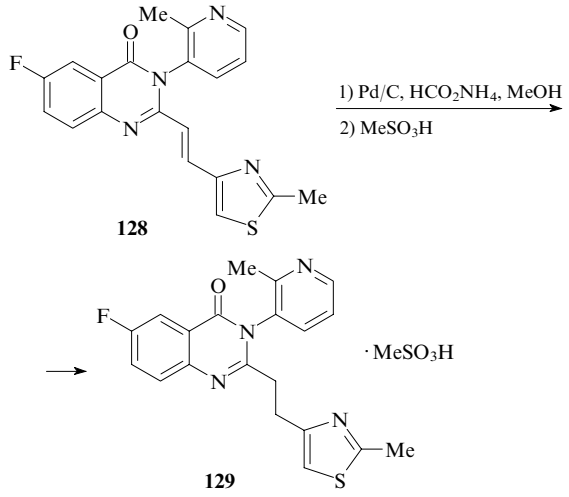
R^1 = H, Me, OMe; R^2 = Pr^i, cyclo-Pr, Ph.

One of modification routes for fluorine-containing quinazolines is their condensation involving the methyl group in position 2. For example, the reaction of 3-(2-chlorphenyl)-6-fluoro-2-methylquinazolin-4(3*H*)-one (**125**) with butyllithium leads to a carbanion which reacts with ethyl α-picolinate and then with methanol to give 2-[2-hydroxy-2-(2-pyridil)ethyl]-6-fluoro-3-(2-chlorophenyl)quinazolin-4(3-

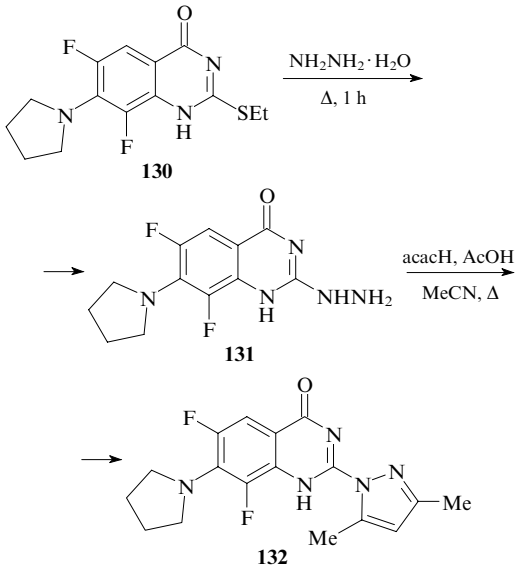
H)-one.[69] 2-[3-(2-Chlorophenyl)]-6-fluoro-[2-(2-pyridyl)vinyl]quinazolin-4(3*H*)-one (**127**) is formed in the reaction of compound **125** with pyridine-2,6-dicarbaldehyde in diethylamine.[70–75] Welch *et al.*[76] obtained a series of analogues of compound **127** containing different substituents in the pyridine fragment and in the *ortho*-position of the benzene ring at N(3) of quinazoline. In the same paper the dependences between the conformation of compound **127** and the inhibition of AMPA-receptor were studied. It was shown[77] that such derivatives are capable of atropoisomerism.



Due to the fact that 2-vinyl-substituted monofluorinated quinazolinones posses high biological activity, a large number of such compounds were synthesized and their modifications were studied. 6-Fluoro-3-(2-methylpyridin-3-yl)-2-[2-(2-methylthiazol-4-yl)ethyl]quinazolin-4(3*H*)-one mesylate (**129**) was obtained by refluxing 6-fluoro-3-(2-methylpyridin-3-yl)-2-[2-(2-methylthiazol-4-yl)vinyl]quinazolin-4(3*H*)-one (**128**) with ammonium formate and palladium black in methanol with subsequent interaction with methanesulfonic acid.[72]

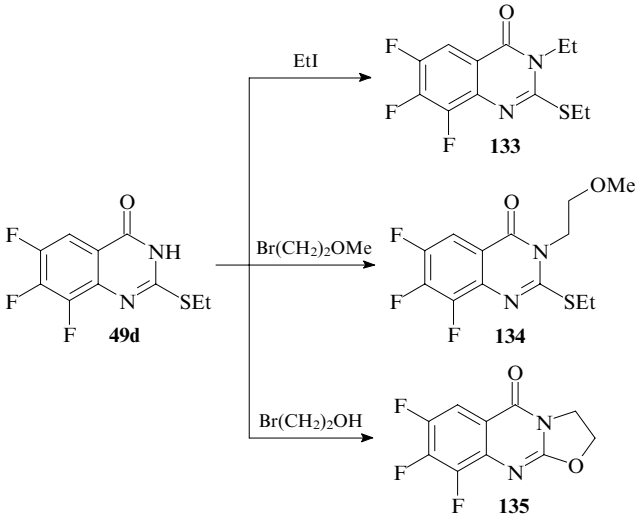


The ethylthio group in position 2 of quinazolines **130** can easily be substituted by the hydrazine one upon heating with hydrazine hydrate for 1 h. Product **131** can be used for the preparation of quinazolines containing heterocyclic substituent in position 2. For example, its reaction with acetylacetone (acacH) in boiling acetonitrile in the presence of acetic acid leads to 2-pyrazolylquinazolinone **132**.[41]



Examples of the modification of the fluorine-containing quinazolines at position 3 are mainly represented by the acylation reactions.[41] Quinazolin-4-one **133** is formed upon N-alkylation of quinazolinone **49d** with ethyl iodide in the presence of NaOH (Scheme 10), while compound **134** is

Scheme 10



formed upon the interaction with 2-bromoethyl methyl ether. As a result of reaction of quinazoline **49d** with 2-bromoethanol under the same conditions not only the alkylation takes place, but also the intramolecular nucleophilic substitution of the ethylthio group leading to the cyclic system, 2,3*H*-oxazolo[2,3-*b*]quinazolin-5-one **135**. The structure of compound **135** was established by the X-ray diffraction method (Fig. 2).

A number of investigations is devoted to the modification of the substituents in the benzene ring of fluoroquinazolines. Thus 2,4-diamino-8-fluoro-6-nitroquinazoline transforms, upon treatment with tin chloride, into 2,4,6-triamino-8-fluoroquinazoline. Similarly, 2,4-diamino-7-fluoroquinazoline is nitrated at position 6 and then reduced to 2,4,6-triamino-7-fluoroquinazoline. 2,4,6-Triaminoquina-

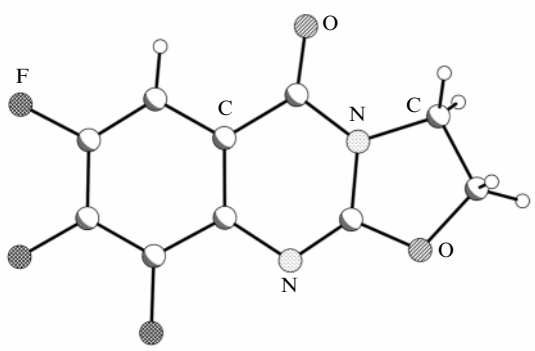
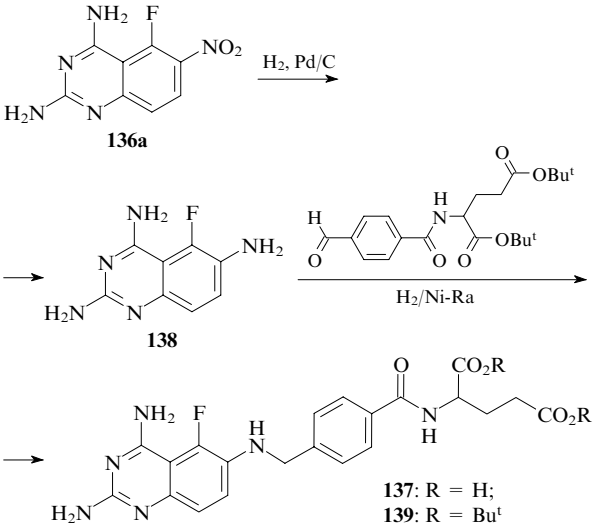


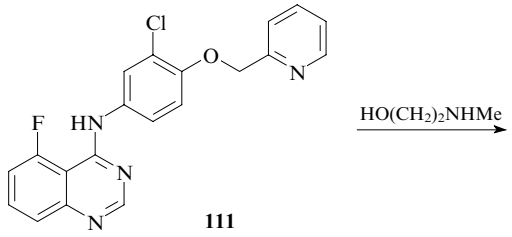
Figure 2. Molecular structure of compound **135**.

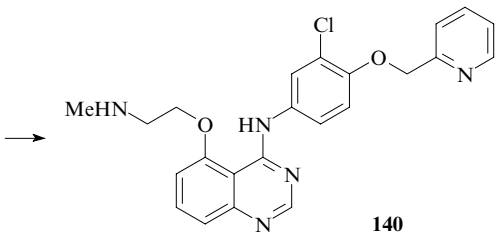
zolines thus obtained undergo the Sandmeyer reaction to give 2,4-diamino-6-chloro-8(or 7)-fluoroquinazolines, while 2,4,8-triamino-5-fluoroquinazoline is thus converted into 2,4-diamino-5-fluoro-8-chloroquinazoline.[50]

On the basis of 6-nitro isomer **136a**, 2,4,6-triamino-5-fluoroquinazoline **137** was synthesized, which can be regarded as 5,8-didesazaisoaminopterin.[78] Catalytic hydration of compound **136a** leads to 2,4,6-triamino derivative **138**. Di-*tert*-butyl ester **139** is formed as a result of the reductive condensation of quinazoline **138** with di-*tert*-butyl *N*-(4-formylbenzoyl)-L-glutamate in the presence of Raney nickel; compound **139** is hydrolyzed by trifluoroacetic acid to acid **137**.



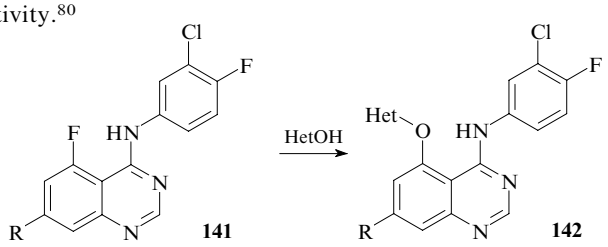
For the synthesis of compound **140**, a tyrosine kinase inhibitor, the replacement of the fluorine atom in 5-fluoroquinazoline **111** by the 2-(methylamino)ethanol residue was used.[66]





The heating of 7-fluoro-5-hydroxyquinazolin-4(3*H*)-one with 3-(*R*)-(+)-dimethylaminopyrrolidine in *N*-methylpyrrolidone yields the corresponding pyrrolidinylquinazolone.[79]

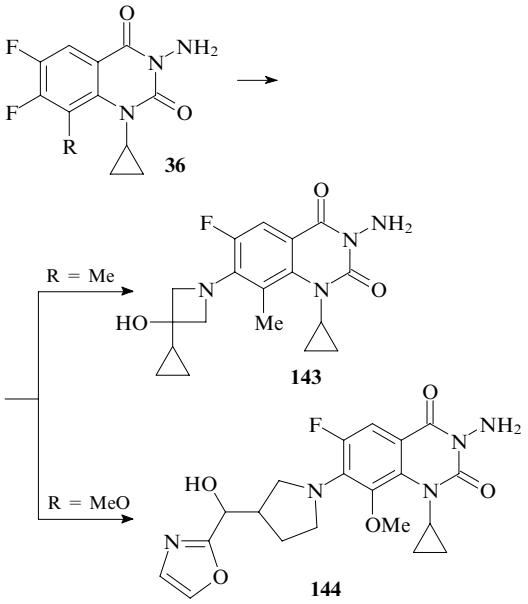
The replacement of the fluorine atom in 4-arylamino-5-fluoroquinazolines **141** by fragments of the heterocyclic alcohols gives compounds **142**, which possess antitumour activity.[80]



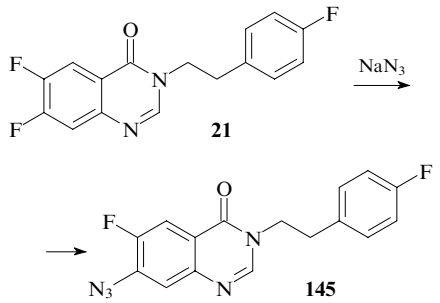
R = OMe, 2-methoxyethoxy, 3-(pyrrolidin-1-yl)propoxy;
Het is tetrahydrofuran-3-yl, 1-methylpiperidin-4-yl.

The nucleophilic substitution of the F atom in position 7 allowed introduction, into quinazolindiones **31**, of substituents (cyclic amines) that are present in fluoroquinolone antibacterial drugs.[37]

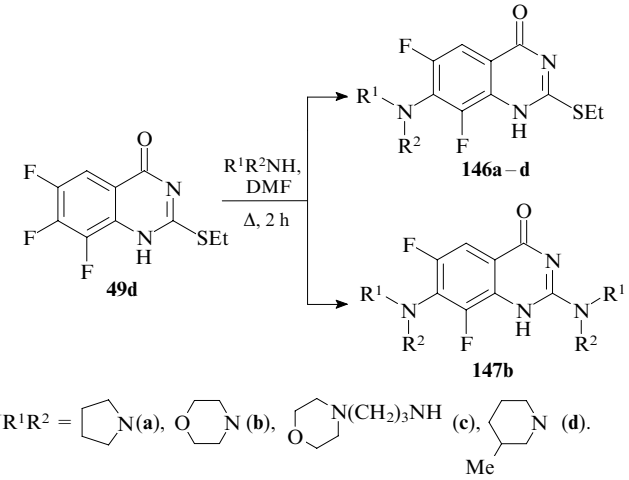
The reaction of 6,7-difluoro-8-methyl(or methoxy)quinazoline-2,4-diones **36** (R^1 = Me, OMe; R^2 = cyclo-Pr) with 3-cyclopropyl-3-hydroxyazetidine and with the pyrrolidine derivative yields 3-aminoquinazoline-2,4-diones **143**, **144**.[17, 18]



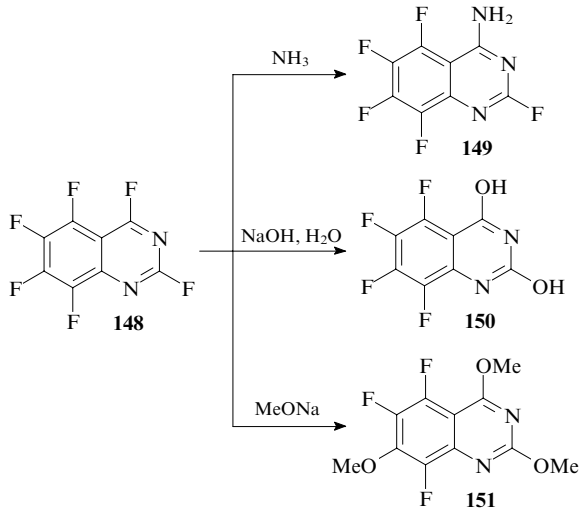
The replacement of F(7) atom in quinazolinone **21** by azido group gives azide **145**, which was used for the synthesis of compounds promising for the treatment of type II diabetes (see below).[35]



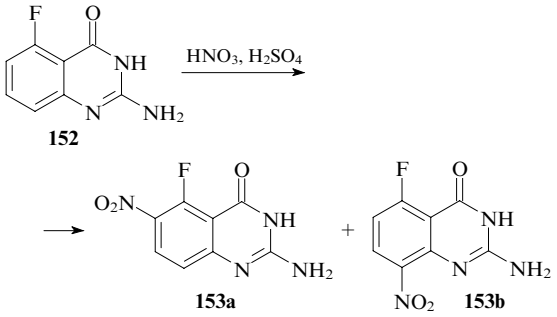
The heating of quinazolinone **49d** with pyrrolidine, 3-morpholino-1-propylamine and 3-methylpiperidine in anhydrous DMF for 2 h allows replacement of F(7) atom by the amine residue with the formation of compounds **146a**,**c**,**d**.[41] In the analogous reaction with morpholine, a mixture of 7-morpholino (**146b**) and 2,7-bis(morpholino) derivatives is formed (**147b**).



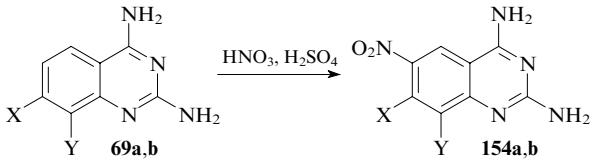
The nucleophilic substitution of amino, hydroxy and methoxy groups for the fluorine atoms in 2,4,5,6,7,8-hexafluoroquinazoline (**148**) was studied.[81] As a result of these reactions, fluorinated 4-amino (**149**), 2,4-dihydroxy (**150**) and 2,4,7-trimethoxy derivatives (**151**) of quinazoline were obtained.



The introduction of substituents into the benzene ring of quinazoline was performed using nucleophilic substitution reactions, first of all, nitration. Thus 6-nitro (**153a**) and 8-nitro derivatives (**153b**) are formed in a 4 : 1 ratio upon the nitration of 2-amino-5-fluoroquinazolin-4(3*H*)-one (**152**) with a mixture of nitric and sulfuric acids.[82]

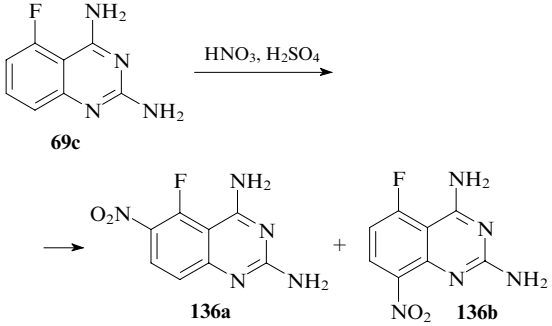


The nitration of 2,4-diamino-8(7)-fluoroquinazolines (**69a**,**b**) proceeds at position 6 with the formation of products **154a**,**b**, respectively.[50]



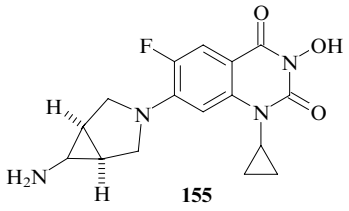
X = H, Y = F (**a**); X = F, Y = H (**b**).

At the same time, the nitration of diaminoquinazoline **69c** yields a mixture of 6- and 8-nitro derivatives **136a**,**b** in a 2 : 1 ratio, which were separated by chromatography.[78]



3. Biological activity of fluoroquinazoline derivatives

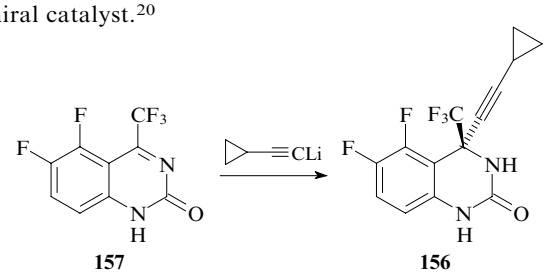
Compounds possessing antibacterial activity were found among fluorinated 3-hydroxyquinazoline-2,4-diones, but the activity for the majority of them is lower than that of ciprofloxacin. The highest antibacterial activity was found for compound **155**.[37]



Compounds **143**, **144**, derivatives of 3-aminoquinazoline-2,4-diones, were also shown to possess antibacterial activity.[17, 18, 83, 84]

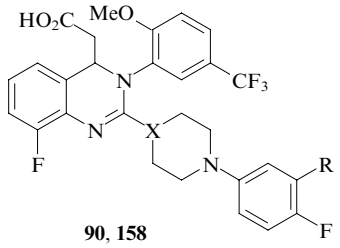
5,6-Difluoro-3,4-dihydroquinazolidin-2(1*H*)-one **156** inhibits HIV reverse transcriptase,[85, 86] this compound is synthesized by addition of cyclopropylacetylenide to 4-tri-

fluoromethylquinazolin-2-one **157** in the presence of a chiral catalyst.[20]



157 **156**

(8-Fluoro-3,4-dihydroquinzaolin-4-yl)acetic acid derivatives **90**, **158** are active against human cytomegalovirus.[24]

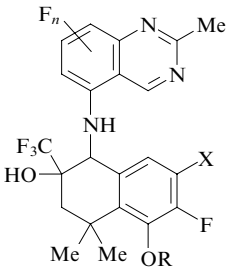


90, **158**

X = CH (**158**), N (**90**); R = Me, F.

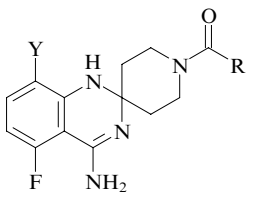
4-Arylamino derivatives of 6,7,8-trifluoro-2-methylthioquinzaolines (of **116** type) exhibit activity towards the family of pox viruses.[87]

8-Fluoro, 7-fluoro and 7,8-difluoro derivatives of 5-amino-2-methylquinazoline **159** in which the amino group contains 2-hydroxy-4,4-dimethyl-2-trifluoromethyl-1,2,3,4-tetrahydronaphtalene residue as a substituent as well as spiro-compounds **160** possess antiinflammatory activity.[88,89]



159

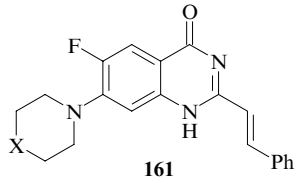
X = Me, Cl; R = H, Me; F_n = 7-F, 8-F, 7,8-F_2.



160

Y = H, F; R = 2-Th, 4-NCC_6H_4.

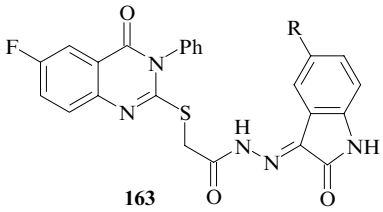
2-Styryl-6-fluoroquinzaoline-4(1*H*)-ones **161** and **162**, which contain a heterocyclic substituent in position 7, exhibit antitrypanosomal activity.[90]



161

X = CH_2 (**161**), NMe (**162**).

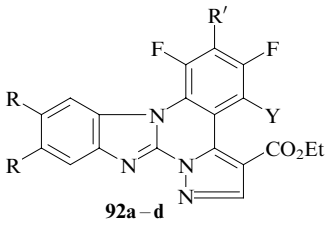
4-(*N*-Arylamino)-6-fluoroquinazolines and fluoroquinazolinones **30** are active against some lines of tumour cells (PC3, BGC823, BCap-37, *etc.*).[22,25] The activity of 5-fluoro-5,8-didesazaisoaminopterin **137** against leukemia L1210 is comparable to activity of methotrexate.[78] The antitumour activity was found also for compounds **50e**, **52e** and 2-mercaptoquinazolin-4-ones **163**.[43,91]



163

R = H, Cl, F, Br, Me.

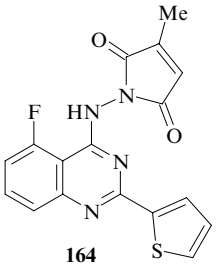
Derivatives **92a–d** exhibit high antitumour activity, especially against SK-Mel-5 (melanoma) and ACHN (renal cancer) tumours.[92]



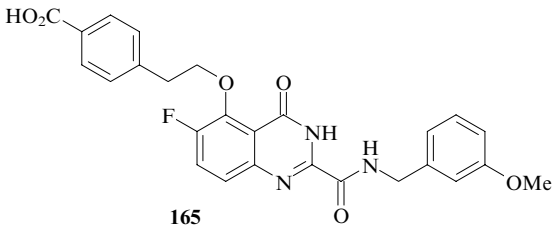
92a–d

Y = R = H: R′ = F (**a**); Y = R = R′ = F (**b**); Y = H, R = Br, R′ = F (**c**); Y = R = H, R′ is 4-methylpiperazin-1-yl (**d**).

4-Amino-5-fluoro-2-(2-thienyl)quinazoline **164** containing 3-methyl-1-pyrroline-2,5-dione fragment at the amino group is effective for the arthritis treatment.[15]



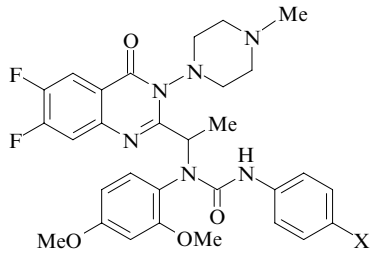
164



165

Compound **165** obtained in the reaction of 5,6-difluoro-*N*-(3-methoxyphenyl)methyl-4-oxo-(3*H*)-quinazoline-2-carboxamide with 4-(2-hydroxyethyl)benzoic acid can be used for the treatment of osteoarthritis and rheumatoid arthritis.[19] 2-(2-Hydroxyphenyl)-3-phenylethyl-7-fluoroquinazolin-4(3*H*)-one is recommended for the treatment of osteoporosis.[93]

Quinazolinones **24** possess antifungal activity against *Aspergillus fumigatus* due to the fragment in position 3. The same fragment is contained in the antifungal drugs fluconazole and itraconazole.[36] 6,7-Difluoroquinazolinones **166** and their analogues can be used for the treatment of fungal infections caused by *Candida albicans* and *C. glabrata*.[94–96]

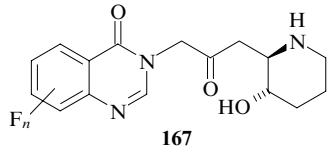


166

X = F, Cl.

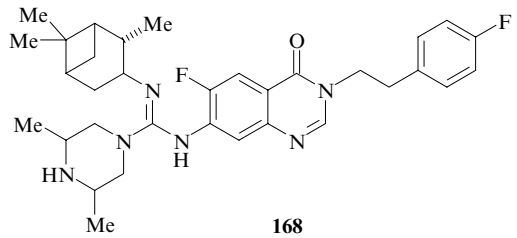
4-Alkyl(aryl)thio-6-fluoroquinazolines exhibit fungicidal activity, these compounds are highly effective for the suppression of *Fusarium oxysporum* cell growth. 4-Ethylthio-6-fluoro-quinazoline and 3-ethyl-6-fluoroquinazolin-4(3*H*)-one surpass hymexazol in the inhibitory action.[23, 97]

5(6)-Fluoro- and 5,6-difluoroquinazolin-4(3*H*)-ones **167** possess antimalarial activity.[98] The derivative of 7-guianidinoquinazolinone **168** can be used for the treatment of obesity and type II diabetes.[35]



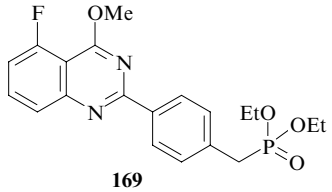
167

F_n = 5-F, 6-F, 5,6-F_2.

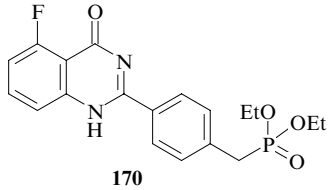


168

5-Fluroquinazoline diethylphosphonates (**169**, **170**) lower the triglyceride and overall cholesterol levels in blood.[99]

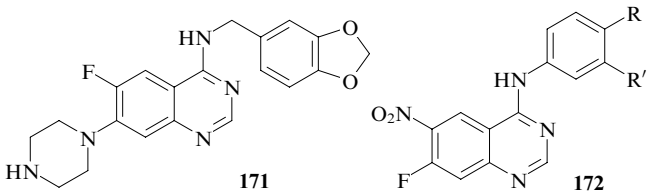


169



170

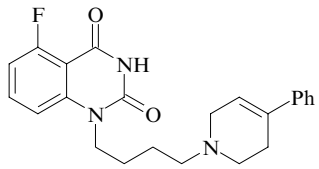
6-Fluoro-7-pyperazinoquinazoline derivative **171** inhibits the production of α-TNF and the proliferation of T-cells.[16] 4-Arylamino-7-fluoro-6-nitroquinazolines **172** are inhibitors of tyrosine kinase.[100, 101] Among 7-fluoro-4-piperazinoquinazolines, antagonists of PDGFR-tyrosine kinase were found.[102]



171 **172**

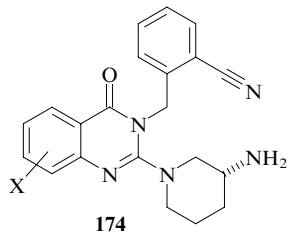
R = H, F; R′ = Me, Cl, Br.

5-Fluoroquinazoline-2,4-dione **173** inhibits poly(adenosine diphosphate ribose) polymerase-1.[103]



173

Fluorine-containing quinazolin-4(3*H*)-ones **174** (X = 5-F, 6-F) inhibit dipeptidyl peptidase-4, the binding of 3-cyanobenzyl-2-[3-(*R*)-aminopiperidine]quinazolin-4-one **174** (X = H) to the active site of the enzyme is shown in Fig. 3.[104]



174

X = H, 5-F, 6-F.

It was shown that 6,7-difluoro-4-[(1*S*)-1-methyl-2,2-diphenylethylamino]quinazoline (**175**) inhibit scytalone dehydratase. The investigation of the inhibitor–enzyme complex led to the conclusion about the formation of a hydrogen bond between quinazoline and the amine group of

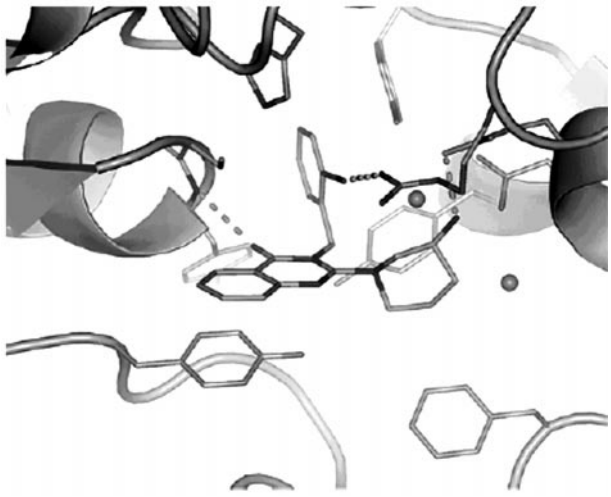
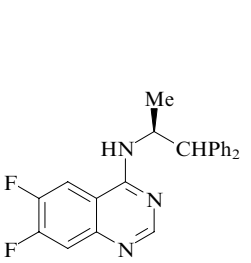
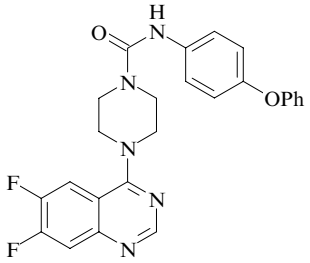


Figure 3. The binding of 3-cyanobenzyl-2-[3-(*R*)-aminopiperidino)-quinazolin-4-one **174** (X = H) with the active site of dipeptidyl peptidase-4.[104]

the Asn131 residue of the peptide chain.[105] 4-Pyperazino derivative of 6,7-difluoroquinazoline **176** inhibits the phosphorylation of the growth factor PDGFR.[106]



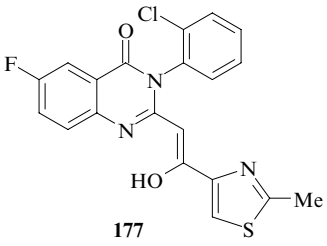
175



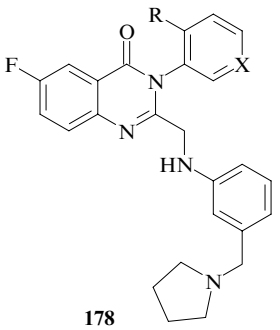
176

Fluorine-containing derivatives of diaminoquinazoline, which inhibit dihydrofolate reductase, are described.[107]

2-(Hetarylvinyl)-3-(2-chlorophenyl)-6-fluoroquinazolin-4(3*H*)-ones including compounds **127**[70–75] and **177**[30,108–110] are neuroprotectors and antagonists of AMPA-receptor. They are of interest as a basis for the creation of pharmaceuticals for epilepsy and Parkinson's disease treatment. Compounds **178** possess neuroprotective properties,[111] while derivatives **179** are antagonists for the 5-hydroxytryptamine (5-HT_7) receptor.[112]

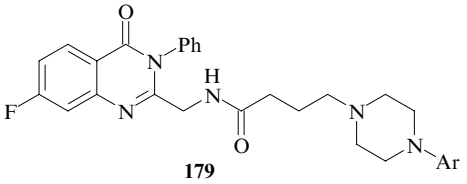


177



178

X = CH, N; R = Cl, F.

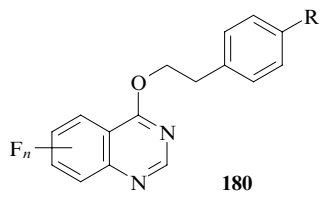


179

Fluorinated quinazolines, which contain substituted indol-5-ylamino group or 4-[(decahydroquinolin-1-yl)carbonyl]-3-chloraniline fragment in position 4 are antagonists of CB1-receptors.[80]

A number of fluorine-containing quinazolines (**6**, **49**, **92**, **101**, **116**, **132**, **149**) exhibited tuberculostatic activity against *Micobacterium tuberculosis* $H_{37}R_V$. The minimum inhibiting concentrations (MIC) are 0.36–0.75 μg ml^{-1} (Refs 113 and 114).

Quinazolines that are promising for the application in agriculture should also be mentioned. For example, 8-fluoro-4-(2-{4-[4-(trifluoromethyl)phenoxy]phenyl}ethoxy)quinazoline (**180**, R = 4-$CF_3C_6H_4O$; F_n = 8-F) exhibits herbicidal activity.[115] Other derivatives of **180** are capable of preventing wheat mildew.[116]



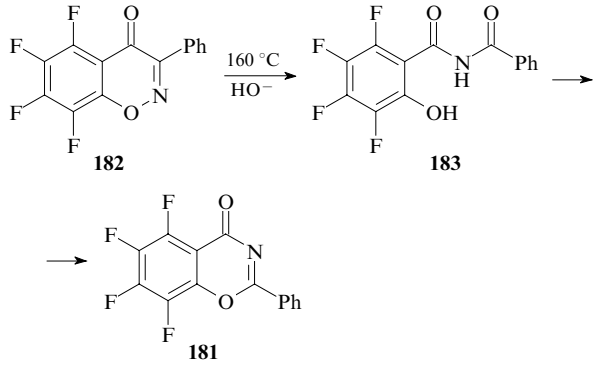
180

F_n = 5-F, 6-F, 7-F, 8-F, 6,7-F_2;
R = Bu^t, Ph, CF_3CH_2O, 4-MeC_6H_4O, 4-$CF_3C_6H_4O$.

III. Oxa and thia analogues of quinazolines

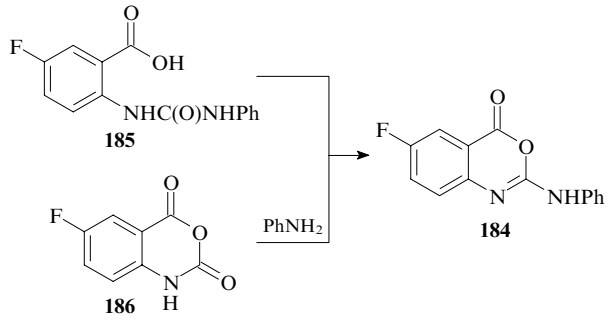
1. Synthesis of the fluorine-containing 1,3- and 3,1-benzoxazines

The information on the synthesis of fluorine-containing 1,3- and 3,1-benzoxazines is very scarce. For example, 5,6,7,8-tetrafluoro-1,3-benzoxazin-4-one **181** is obtained from the corresponding 1,2-benzoxazinone **182** upon ring opening in an alkaline medium and the subsequent cyclization of the intermediate **183**.[117]



182 **183** **181**

2-Anilino-6-fluoro-3,1-benzoxazin-4-one (**184**) was prepared by two routes: by the cyclization of the anthranilic acid derivative **185** and by the reaction of benzoxazinedione **186** with aniline.[118]



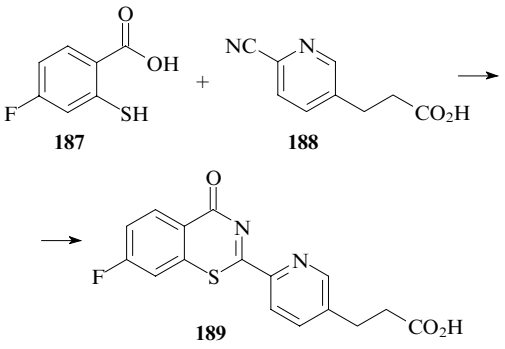
185 **186** **184**

The reaction of protected anthranilic acid hydrazide (**39e**, R = H) with triphosgene gives regioselectively 3,1-oxazine **41e** (R = H) (see Section II.1.a).[39]

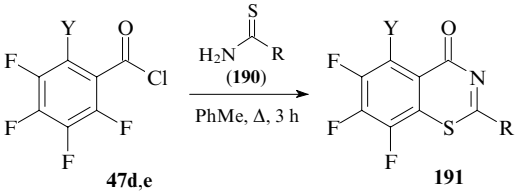
3,1-Benzoxazin-4-ones that contain different number of fluorine atoms in the benzene ring were synthesized in our work and used as intermediates for the synthesis of quinazolinones (see compounds **94**, **97**, **100**, **104**).

2. Synthesis of fluorine-containing 1,3-benzothiazines

The reaction of 2-mercapto-4-fluorobenzoic acid (**187**) with the substituted pyridine-2-carbonitrile **188** yielded 7-fluoro-1,3-benzothiazin-4-one derivative **189**.[21]



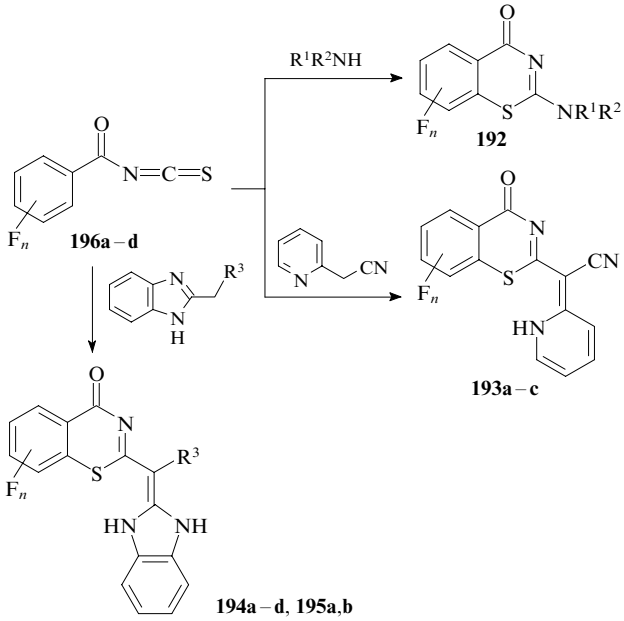
A number of polyfluorobenzothiazines was synthesized. Thus by heating tetra(penta)fluorobenzoyl chlorides (**47d**,**e**) with thioamides **190** in toluene for 3 h we obtained 2-substituted polufluoro-1,3-benzothiazin-4-ones **191** in 59%–80% yields.[119,120] In should be mentioned that we did not succeed in isolating the intermediate *N*-acylated derivatives under these conditions.



Y = H (**47d**), F (**47e**); R = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 2-Py.

Fluorobenzoyl isothiocyanates **196a**–**d** were used as precursors for the synthesis of the fluorine-containing 1,3-benzothiazin-4-ones **192**–**195**. The reactions of compounds **196** with amines, as well as with benzimidazoles and pyridines containing active methylene group, are given in Scheme 11.[119,121–123] Using a similar method it was possible to obtain also the monofluoro derivatives **193c** and **194c**,**d**.[27]

Scheme 11

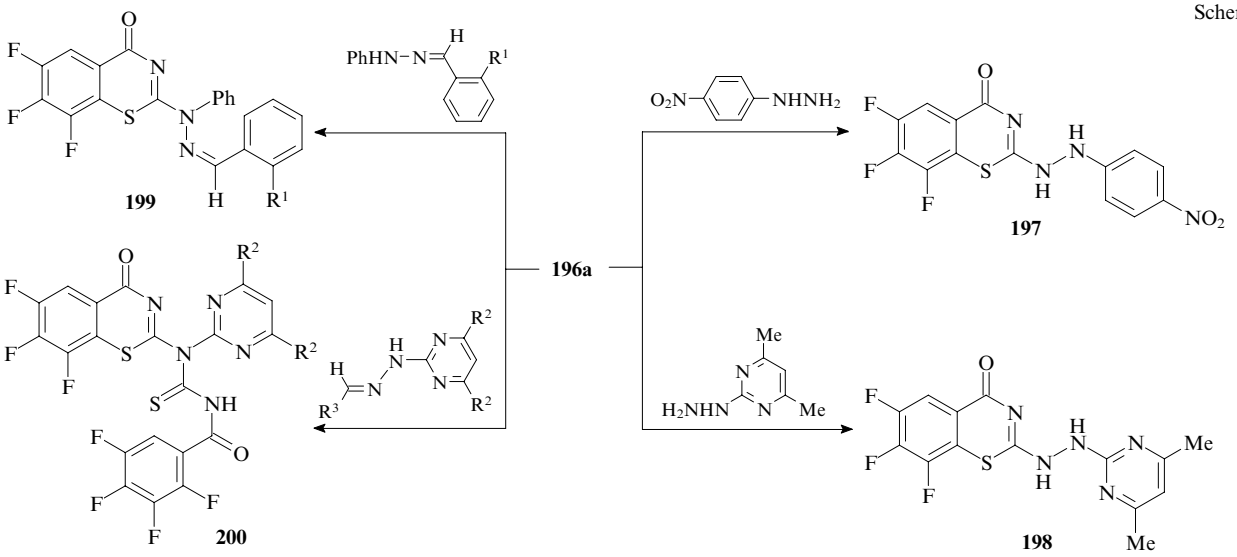


F_n = 2,3,4,5-F_4 (**a**), 2,3,4-F_3 (**b**), 4-F (**c**), 2-F (**d**);
R^1R^2NH = $HetNH_2$, morpholine, *etc.*; R^3 = CN (**194**), Bz (**195**).

Fluorine-containing benzothiazinones **197**–**200** are obtained by the reaction of tetrafluorobenzoyl isothiocyanate **196a** with hydrazines and hydrazones (Scheme 12).[124]

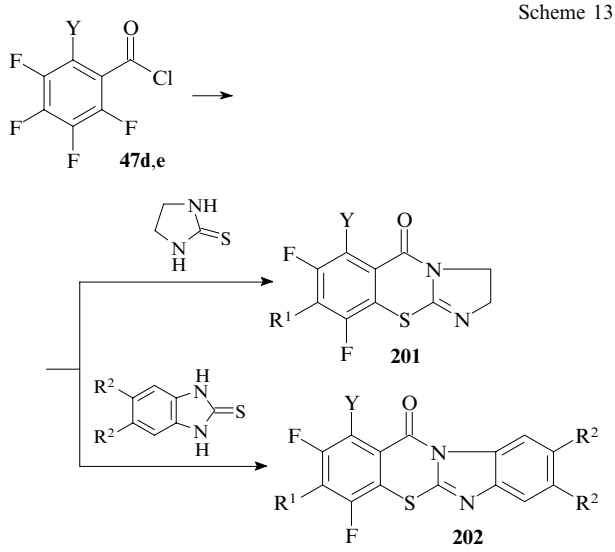
We obtained imidazo- (**201**, R^1 = F) and benzimidazoannulated 1,3-benzothiazin-4-ones (**202**, R^1 = F) in the reaction of polyfluorobenzoyl chlorides **47d**,**e** with imidazolidine-2-thione and benzimidazoline-2-thiones as S,N-dinucleophiles. The reaction proceeds on heating the reactants in toluene or pyridine. A series of derivatives **201**, **202** (R^1 = Nu, where Nu is a fragment of a secondary cyclic amine) was synthesized by the nucleophilic substitution of the fluorine atoms in position 7 (Scheme 13).[125]

Scheme 12



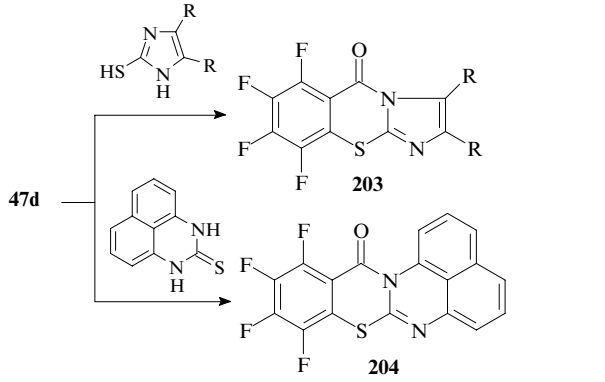
R^1 = H, OH; R^2 = Me, Ph; R^3 = Ph, 4-$MeOC_6H_4$.

Scheme 13



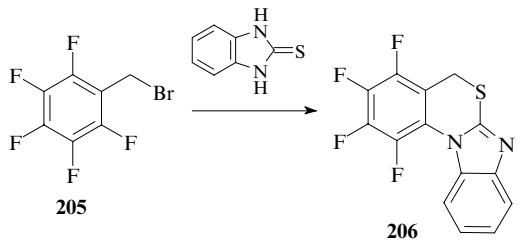
Y = H, F; R^1 = F, Nu; R^2 = H, F, Cl, Me.

Imidazo[2,1-*b*]-1,3-benzothiazin-4-ones **203** were obtained by the reaction of 4,5-disubstituted 2-mercaptoimidazoles with acyl chlorides **47d** upon heating in pyridine.[126] The reaction of compound **47d** with dianion generated from perimidine-2-thione under the action of n-butyllithium, leads to a fused system of benzothiazinoperimidine **204**.[127]



R = H, Me, Ph.

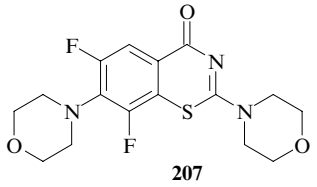
Pentafluorobenzyl bromide (**205**) reacts with benzimidazoline-2-thione in the presence of sodium hydride with the formation of a fused tetrafluoro derivative **206**.[127]



3. Biological activity of the fluorine-containing oxa and thia analogues of quinazoline

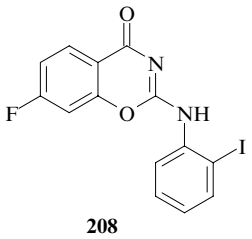
Compounds exhibiting tuberculostatic activity were found among fluorinated 1,3-benzothiazin-4-ones.[128] Below the values of MIC for such derivatives against *Mycobacterium tuberculosis* $H_{37}R_V$ are given.

Compound	Substituents	MIC /μg ml^{-1}
191	Y = H, R = 2-Py	0.3
194b	–	0.36
201	Y = H, R^1 is morpholino	0.1
207	–	0.36



2-Pyridine-substituted 7-fluoro-1,3-benzothiazin-4-one **189** is a promising drug for the treatment of cardiac and CNS diseases.[21]

7-Fluoro–2-(2-iodoanilino)-1,3-benzoxazin-4-one (**208**) inhibits protease C1r of the complement and can be used for curing of inflammatory processes.[118]



The application of different fluorobenzoxazine, fluorobenzothiazine and fluoroquinoxaline derivatives in agriculture is reported.[129]

* * *

Data provided in the present review demonstrate that cyclocondensation reactions based on fluorinated 'building blocks' are effective for the synthesis of fluorine-containing quinazolines and quinazolinones as well as their aza and thia analogues. The perspectives of the application of the fluorine-containing benzazines for the practical purposes, first of all, as pharmaceuticals, stimulates the development of the synthetic routes to these heterocycles as well as the investigation of the ways for their modification.

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