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Review

Fluorinated azines and benzazines containing oxygen or sulfur atoms

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ABSTRACT

In the frames of this review article the recently obtained data on synthetic approaches to fluorinated oxa(thia)azines and benzazines, their chemical properties, structure, and biological activity have been analyzed.

Contents

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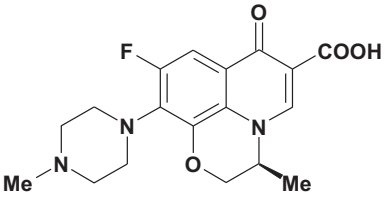
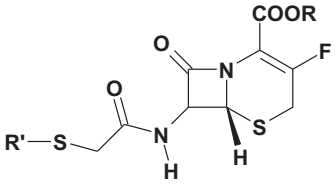
1. Introduction

The chemistry of heterocyclic compounds with incorporated fluorine atoms has been fast developing and rather promising area of research for the last two decades [1,2]. Due to unique properties of fluorine atoms (which enhance solubility of organic molecules in lipids, their ability penetrate through cell membranes, and to inhibit specific enzymes), fluorine-containing compounds have found wide application in medicinal chemistry; in particular, 20% of currently developed pharmaceuticals contain fluorine atoms in their structures [3]. For example, a rather important group of antibacterials is presented by the family of fluoroquinolones, which are derivatives of 4-quinolon-3-carboxylic acid [4–6]. Fluorinated 1,4-benzoxazine derivative proved to be the key intermediate for the synthesis of levofloxacin, one of the most effective fluoroquinolones, while a fluorinated 1,3-thiazine fragment is incorporated into the structure of cephalosporin antibiotics [7,8].



Levofloxacin

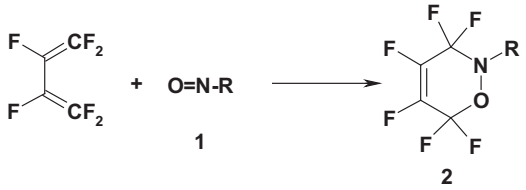


Cephalosporin antibiotics

Some thiadiazine derivatives are known as synthetic drugs. For instance, dichlothiazide, cyclomethyazide are used as diuretics [9]. Also, in the series of 1,2,4-thiadiazines a number of compounds, affecting blood coagulation and blood aggregation properties, have been discovered [10].

As a rule, compounds of natural origin scarcely bear in their structures the fragments of azines or benzazines with incorporated oxygen or sulfur atoms. At the same time, a whole number of derivatives with a various heteroatoms in different positions of a six-membered ring have been obtained synthetically. According to the recent review articles [11–15], the data on 1,2,4-, 1,3,4- and 1,3,5-oxa(thia)diazines are available in the literature. A few publications concern fluorinated azines and benzazines, bearing oxygen or sulfur atoms, while 1,3- and 1,4-oxa(thia)benzazines proved to be studied in a more detail.

In this review article we intend to discuss the literature data of the last decades concerning new methods for the syntheses of fluorinated oxa(thia)azines and benzazines, their chemical properties and biological activity.



R= CF_3, CF_2Cl, $CF_2CF_2NO_2$, $CF_2CF_2OSO_2F$.

Scheme 1.

2. Azines with oxygen or sulfur atoms incorporated in a six-membered ring

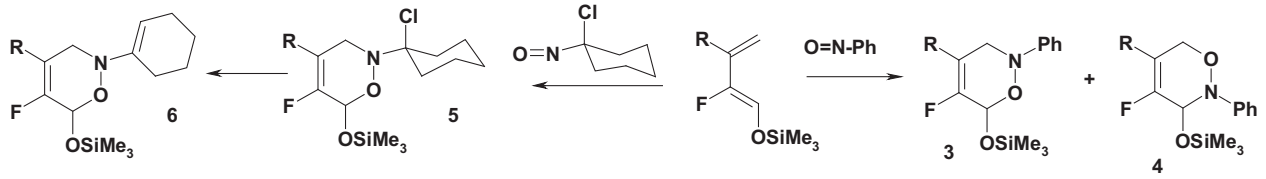
[4 + 2]-Cycloaddition, cyclocondensation reactions, targeted fluorination and other synthetic approaches represent the synthetic pathways for development of fluorinated oxa(thia)zines, thiadiazines and their annelated derivatives.

2.1. 1,2-Oxazines

An original synthetic approach to fluorinated 3,6-dihydro-1,2-oxazines **2** which is based on the reaction of the nitroso compounds **1** with hexafluorobutadiene has been advanced (Scheme 1) [16–18]. The reaction seems to proceed as the Diels–Alder process.

Also, 1-trialkylsiloxy-2-fluoro-1,3-diene is transformed into 6-hydroxy-3,6-dihydro-5-fluoro-1,2-oxazines through the same type of cycloaddition reactions [19].

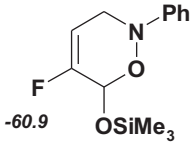
A mixture of two regioisomeric compounds, 3,6-dihydro-3-trimethylsilyloxy-2-phenyl-4-fluoro-1,2-oxazine (**3**, R = H) and 3,6-dihydro-6-trimethylsilyloxy-2-phenyl-5-fluoro-1,2-oxazine (**4**, R = H) has been isolated in the ratio 1:3 from the cycloaddition reaction of nitrozobenzene with 1-trimethylsilyloxy-2-fluoro-1,3-butadiene. It is worth noting that in case of their methyl analogue,

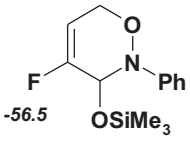


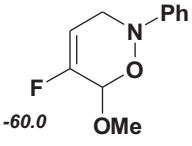
Scheme 2.

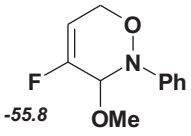
i.e. 1-trimethylsilyloxy-3-methyl-2-fluoro-1,3-butadiene, regioisomers (**3**, R = Me) and (**4**, R = Me) are formed in the ratio 3:1 (Scheme 2) [20]. The reaction of 1-nitrozo-1-chlorocyclohexane with 1-trimethylsilyloxy-2-fluoro-1,3-butadiene leads to the intermediate **5**, which undergoes spontaneous dehydrochlorination to give **6** (R = H, Me) [20].

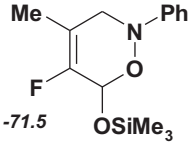
The ^{19}F chemical shifts in the ^{19}F NMR spectra of some 5-fluoro-3,6-dihydro-1,2-oxazines (see below) have been described in Ref. [20].

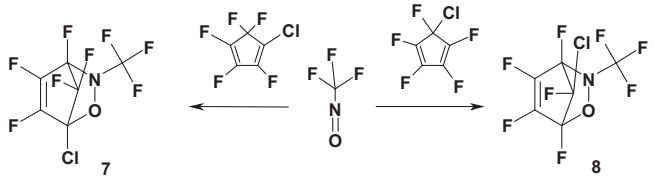












Scheme 3.

Tricyclic 3,6-dihydro-1,2-oxazines **7** and **8** were obtained by the reaction of 1(5)-chloropentafluoro substituted cyclopentadienes with trifluoro nitrozomethane (Scheme 3) [21,22].

Nucleophilic displacements of fluorine atoms in perfluoro-1,2-oxazines, in particular amino-defluorination reactions, have been studied. It has been established that perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine) reacts with ammonia at room temperature to give a mixture of 4- and 5-amino derivatives, while reacting with disubstituted amines in diethyl ester at −78 °C it affords only 5-amino compound [23].

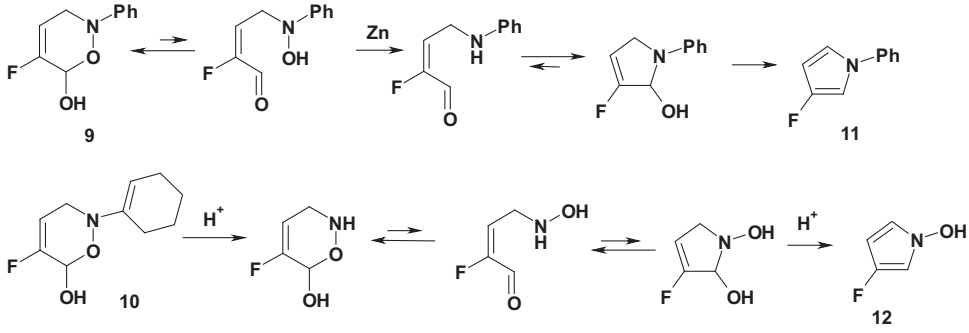
Dihydrooxazines **9** and **10** obtained from (**3**, R = H) and (**6**, R = H) by elimination of the trimethylsilyl group are able to undergo the ring transformation into pyrrole derivatives **11** and **12** (Scheme 4) [20].

2.2. 1,3-Oxazines

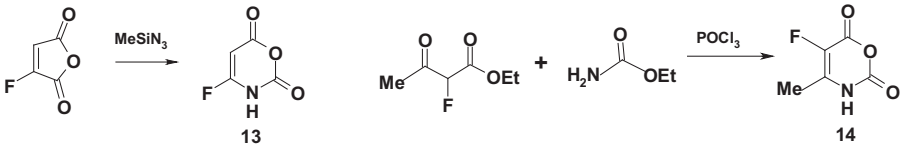
The synthesis of 2*H*-1,3-oxazine-2,6-diones using fluorinated maleic anhydride has been described. For instance, 4-fluoro-2*H*-1,3-oxazine-2,6-dione **13** was obtained by reacting fluoromaleic anhydride with trimethylsilyl azide on heating in chloroform for 30 min (Scheme 5) [24].

Another approach to 2*H*-1,3-oxazine-2,6-diones is illustrated by the reaction of 2-fluoroacetoacetate with ethyl carbamate which takes place on heating in the presence of $POCl_3$ and affords 5-fluoro-4-methyl-2*H*-1,3-oxazine-2,6-dione **14** (Scheme 5) [25].

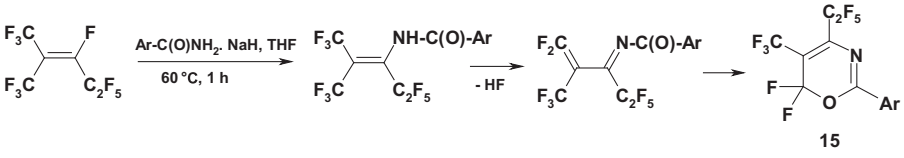
Mono- and disubstituted 2H-1,3-oxazin-2,6-dions, structural analogues of compounds **13** and **14**, appear to be intermediates for



Scheme 4.



Scheme 5.



Scheme 6.

preparation of pyridine-3-carboxamides; which can be used as active ingredients in plant disease controlling agents [26]. 2-Aryl substituted 6,6-difluoro-4-pentafluoroethyl-5-trifluoromethyl-6H-1,3-oxazines **15** were obtained by the reaction of perfluoro-2-methylpent-2-ene with benzamide in the presence of sodium hydride, followed by the intramolecular cyclization (Scheme 6) [27].

Treatment of 5-fluoro-1,3-dioxin-4-one **16** with dimethyl cyanamide on reflux in mesitylene for 30 min affords 2,3-dihydro-2-dimethylamino-5-fluoro-1,3-oxazin-4-one 17 due to the ring transformation reaction (Scheme 7) [28].

Fluorination of 5-substituted 1,3-oxazine-2,6(3*H*)-diones has been established to proceed as a stereoselective process to form chiral 5-fluoro-1,3-oxazine-2,6(3*H*)-diones **18**. These compounds have been tested as inhibitors of the tumor cell growth and have exhibited the activity comparable with that for some natural pyrimidines (Scheme 8) [29,30].

The features for direct fluorination of 2,6-dimethylmorpholine into the corresponding perfluorinated compound have been discussed in Ref. [31]. 4-Methylmorpholine undergoes fluorination by action of cobalt (III) fluoride to give 10 fluorinated derivatives [32]. Synthetic procedures to obtain perfluorinated N-carboxymethyl morpholine are given in the patent [33].

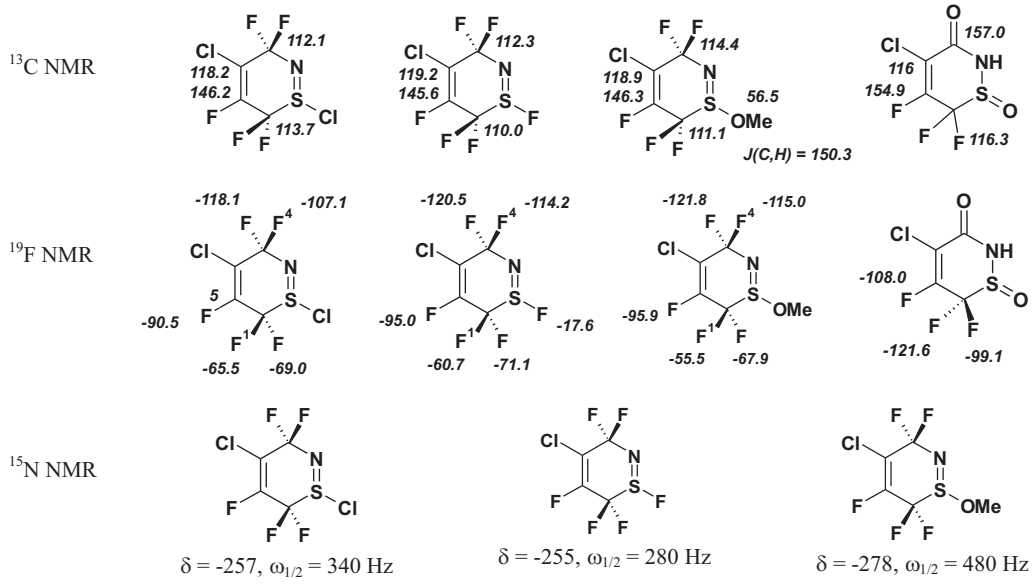
2.3. 1,2-Thiazines

The [4 + 2] cycloaddition reaction of perfluoro butadiene with halogeno thiazyls provides a synthetic way to fluorinated 1,2-thiazines (**19**, X = F) (Scheme 9) [34]. The chloro analogue (**19**, X = Cl) was obtained in a similar manner from 2-chloro-pentafluoro-1,3-butadiene [35].

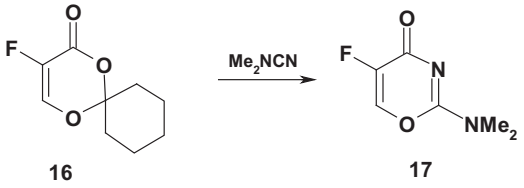
1,2-Thiazines (**19**, X = F) were found to react with MeOH and Me_3SiNMe_2 to form 1-methoxy- (**21**) or 1-dimethylamine derivatives; in particular 1,2-thiazine oxide was obtained from **19** and $(Me_3Si)_2O$ [36]. The reaction of **19** (X = Cl) with water leads to trifluoro-1,2-thiazine-3-one-1-oxide **20** (Scheme 9) [35].

The structure of 4-chloro-3,3,5,6,6-pentafluoro-3,6-dihydro-1-methoxy-1λ^4,2-thiazine was determined by X-ray crystallography (Fig. 1a) [35]. The compound was found to be in the envelope conformation with C^1–C^4 and N atoms located in the same plane. The sulfur atom deviates from it and forms the plane with C^4 and N atoms, the angle between these two planes proved to be 34.1°. Also, the six-membered ring structure with the envelope conformation was established for 4-fluoro-1-chloro analogue (Fig. 1b). Angle between the planes $N^1C^1C^4/N^1C^4S$ is 33.5° [36]. The S–Cl bond length is 0.2066 nm, and S–N bond length is 0.1544 nm. The pseudo-axial position of chlorine atom is also clear from the picture [37].

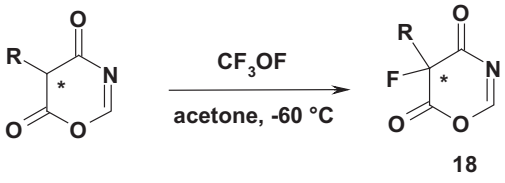
The ^{13}C, ^{19}F and ^{15}N NMR data for fluorinated 1,2-thiazines are presented below [35,36].



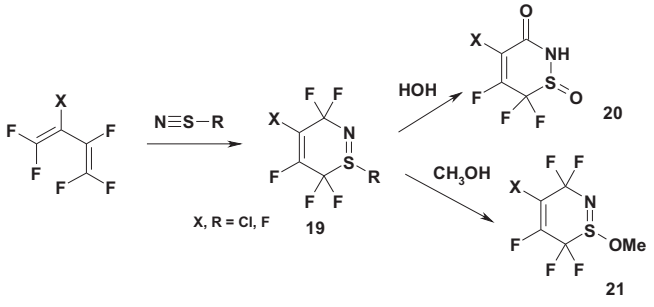
The formation of the six-membered ring as a result of the [4 + 2]-cycloaddition reaction of perfluorobutadiene with halogeno thiazyls is substantiated by the presence of five nonequivalent fluorine atoms in the structure (**19**, X = Cl); in case of X = F the structure contains six nonequivalent fluorine atoms (**19**, X = F), and



Scheme 7.



Scheme 8.



Scheme 9.

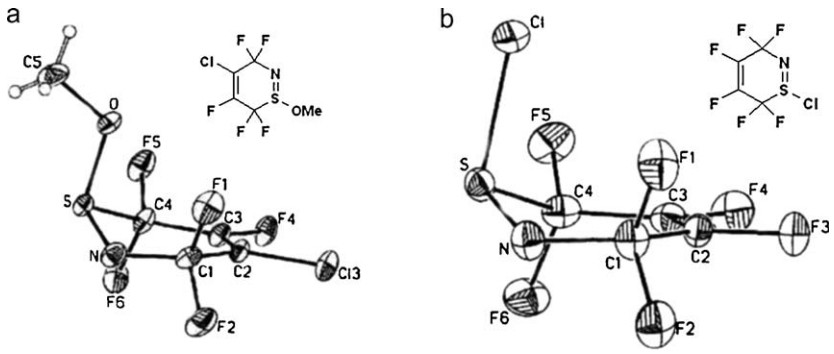
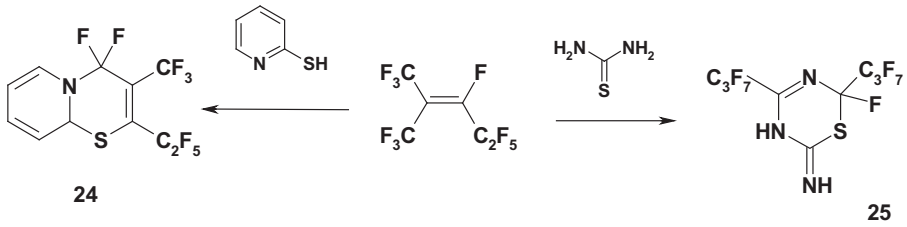


Fig. 1. Molecular structures of 4-chloro-3,3,5,6,6-pentafluoro-3,6-dihydro-1-methoxy-1λ^4,2-thiazine (a), and 1-chloro-3,3,4,5,6,6-hexafluoro-3,6-dihydro-1,2-thiazine (b).



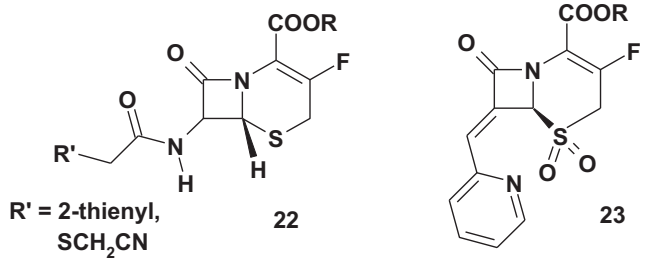
Scheme 10.

when X = R = F in the compound (**19**, X = R = F) one numbers 7 nonequivalent fluorine atoms.

1,2-Thiazines **19–21** have been characterized by mass spectrometry data, including the molecular ions and fragmentation peaks, which are caused by elimination of fluorine atoms and fluorinated fragments: $[M-F]^+$, $[C_4ClF_5]^+$, $[C_4ClF_5]^+$, $[M-F-Cl]^+$, $[M-2F-Cl]^+$, $[M-F-2Cl]^+$, $[C_3ClF_2]^+$ [35].

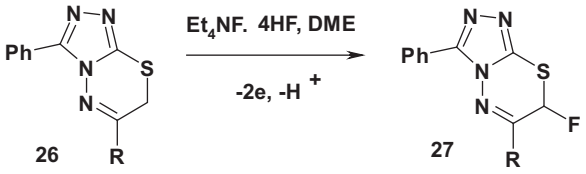
2.4. 1,3-Thiazines, thiadi(tri)azines

Only fused derivatives of fluorinated 1,3-thiazines have been described. For instance, 3-fluoro-1,3-thiazine fragment is incorporated in cephalosporin antibiotics **22** [7,8]. The fluorine atom was first introduced into compounds **22** by nucleophilic displacement of the methylsulphonyl group [7]; later on it has been reported [38] on a similar replacement of $SnMe_3$ group, proceeding fast (for 5 min) under very mild conditions (0 °C). Compounds **23** proved to be highly selective inhibitors for the class A β-lactamase [39].

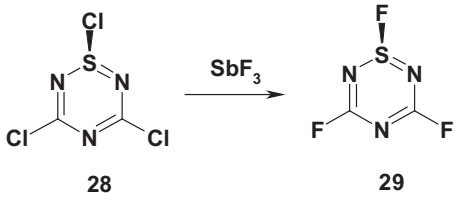


The reaction of perfluoro-2-methylpent-2-ene with 2-mercaptopyridine results in the formation of 1,3-thiazines **24**, a similar cyclization with thiourea affords 1,3,5-thiadiazines **25** (Scheme 10) [40].

Some novel procedures to incorporate the fluorine atom into thiadiazines have been reported. For instance, constant potential anodic oxidation of *s*-triazolo[3,4-*b*][1,3,4]thiadiazine **26** in DME containing $Et_4NF{\cdot}4HF$ gave the corresponding 7-fluoro compound **27** (Scheme 11) [41].



Scheme 11.



Scheme 12.

2,4,6-Thiatriazine **29** was obtained by reacting trichloro derivative **28** with SbF_3 (Scheme 12) [42].

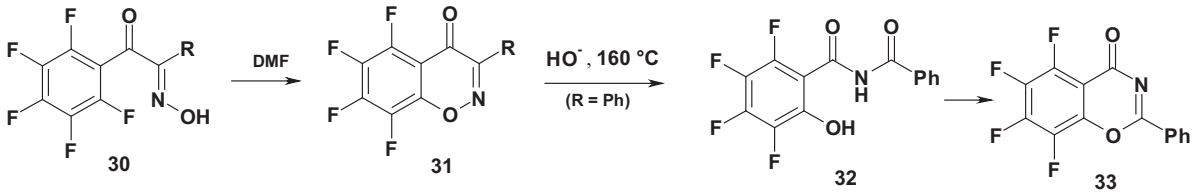
Replacement of fluorine atoms in **29** with nucleophiles, for example, by action of silylamine, is possible without destruction of the ring system. Also treatment of thiatriazines **29** with fluorinated Lewis acids provides rather stable salts [42].

3. Benzazines with oxygen or sulfur atoms incorporated in a six-membered azine ring

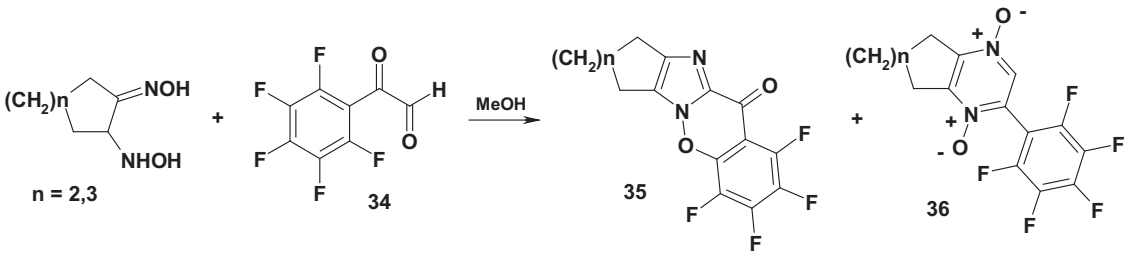
3.1. 1,2-, 1,3-, and 3,1-Benzoxazines

3.1.1. Synthesis

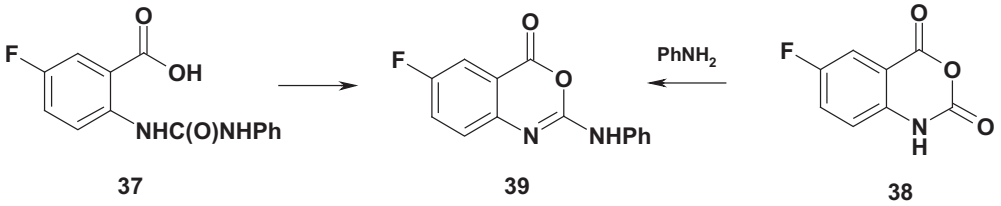
Cyclocondensations appear to be the key approach to fluorinated derivatives of 1,2-, 1,3-, 1,4-benzoxazines, 1,3- and 1,4-benzothiazines, benzothiadiazines and benzodithiadiazines, and a variety of substituted fluoroarenes are supposed to be versatile building blocks for those syntheses.



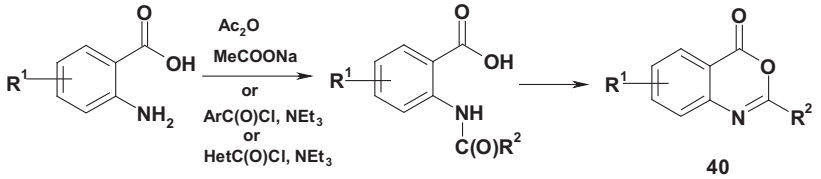
Scheme 13.



Scheme 14.



Scheme 15.



40, R^1= 6,7-difluoro, 7-fluoro, 6-fluoro, 6,7,8-trifluoro, 5,6,7,8-tetrafluoro;

R^2= aryl, substituted pyrazolyl, substituted isothiazolyl, thiophenyl, substituted pyridinyl

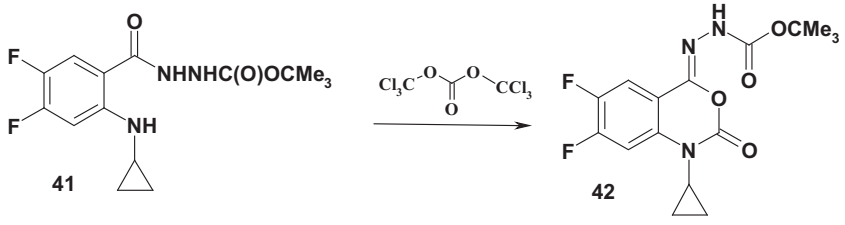
Scheme 16.

For instance, 5,6,7,8-tetrafluoro-1,2-benzoxazin-4-one (**31**, R = COOEt) can be obtained by cyclization of ethyl 2-hydroxyimino-3-oxo-3-pentafluorophenyl-propionate (**30**, R = COOEt) [43], 3-phenyl-5,6,7,8-tetrafluoro-1,2-benzoxazin-4-one (**31**, R = Ph) is formed from *sin*-1-pentafluorophenyl-2-phenylethane-1,2-dione-2-oxime (**30**, R = Ph); amide **32** is formed by the ring opening of 1,2-benzoxazinone **31** under alkaline conditions. Since cyclization of **32** leads to 1,3-benzoxazinone **33** (Scheme 13) [44], the Scheme 13 demonstrates an opportunity to transform 1,2-benzoxazinones **31** into 1,3-isomers **33**.

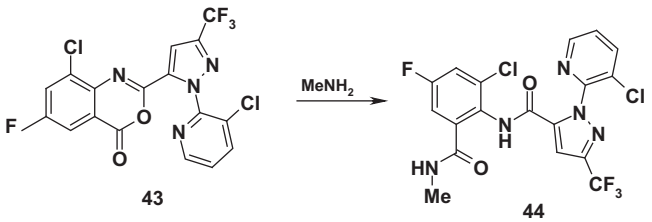
Tetrafluoro-*10H*-imidazo[1,2-*b*][1,2]-benzoxazin-10-ones **35** have been obtained by cyclocondensation of 2-hydroxyaminooximes with oxopentafluorophenyl acetaldehyde **34** in methanol. Fused 2-(pentafluorophenyl)pyrazine-1,4-dioxides **36** are by-products in this process (Scheme 14) [45].

Anthranilic acid derivative **37** or benzoxazinone **38** and aniline are versatile starting materials for their cyclizations into 6-fluoro-2-phenylamino-4*H*-3,1-benzoxazin-4-one **39** (Scheme 15) [46].

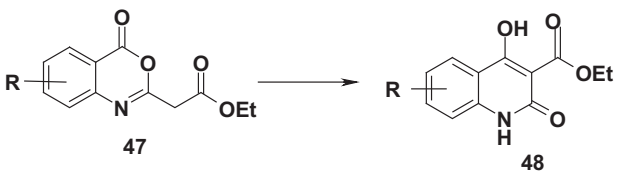
2-Substituted 4*H*-3,1-benzoxazin-4-ones **40** have been synthesized by the reaction of fluorinated antranilic acid derivatives with aroyl(hereroyl) chlorides (Scheme 16) [47–52].



Scheme 17.



Scheme 18.



Scheme 19.

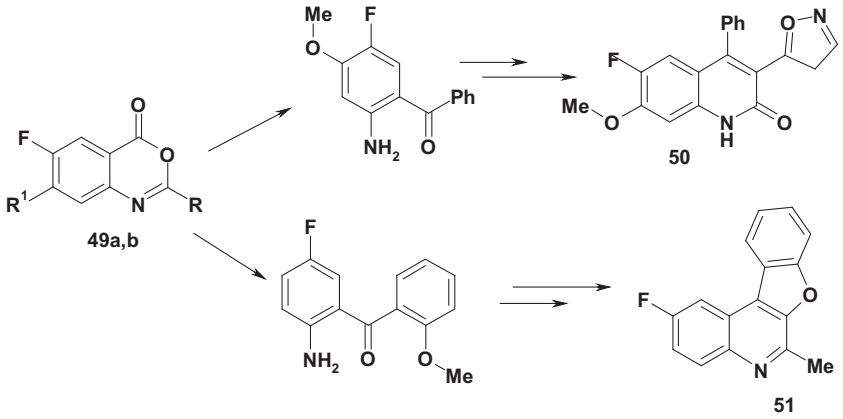
The reaction of difluoro substituted antranyl hydrazide **41** with triphosgene affords *tert*-butyl cyclopropyl-6,7-difluoro-2-oxo-1,2-dihydrobenzo[*d*][1,3]oxazin-4-ylidene)hydrazinecarboxylate a **42** (Scheme 17) [53].

3.1.2. Chemical properties and modifications

The ring-opening reactions of 5,6,7,8-tetrafluoro-1,2-benzoxazin-4-one under both acidic or alkaline conditions lead to oxo-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)-acetic acid or tetrafluoro-salicylic acid, respectively [54].

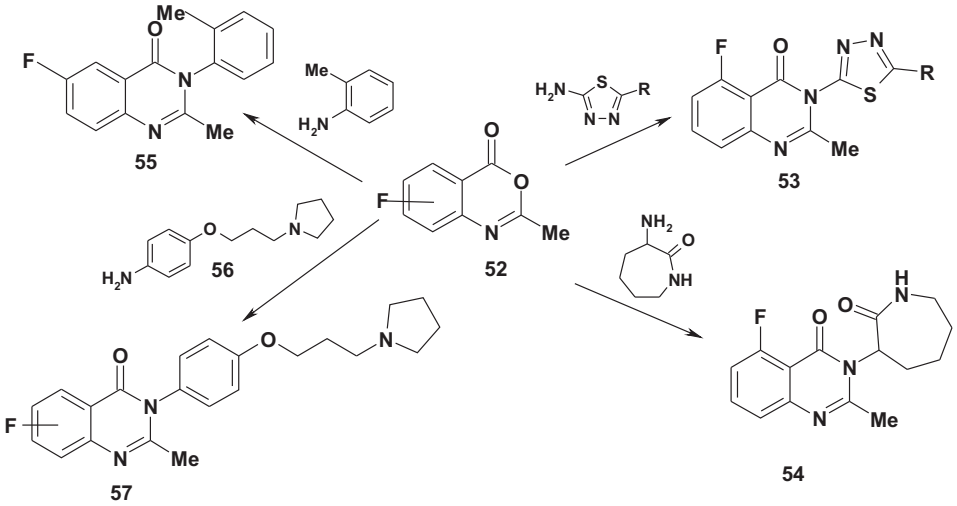
2-Substituted 6-fluoro-3,1-benzoxazin-4-ones by treatment with amines are easily transformed into the corresponding 2-amino-3,4,5,6-tetrafluorobenzamides. For instance, the reaction of benzoxazinone **43** with methylamine in THF at 20 °C yields the compound **44** (Scheme 18) [52]. This transformation is regarded by the authors as a new synthetic way to N-arylpyrazoles.

A similar approach has been suggested for preparation of N-[2-[[(cyclohexylmethyl)amino)carbonyl]-4-fluorophenyl]-1-naphthylcarboxamide by reacting 6-fluoro-2-(1-naphthyl)-4*H*-3,1-benzoxazin-4-one **45** with cyclo-hexylmethylamine [55], while N-(5-chloropyridin-2-yl)-5-fluoro-2-[(4-isopropylpyperazin-1-yl)amino]benzamide was obtained by interaction of 2-amino-5-chloropyridine with benzoxazinone **46** [56].

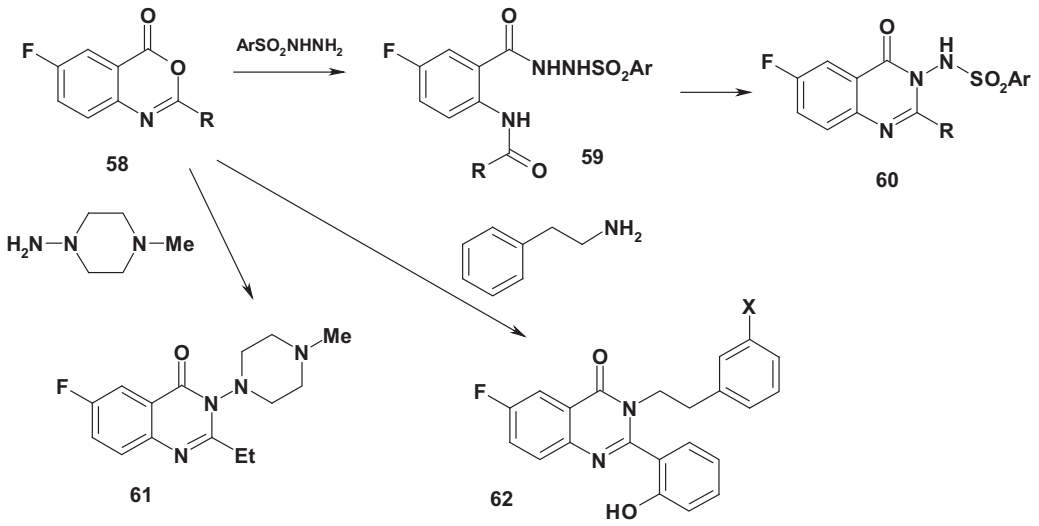


49a: R=Ph, R_1=F; **49b:** R=Me, R_1=H

Scheme 20.

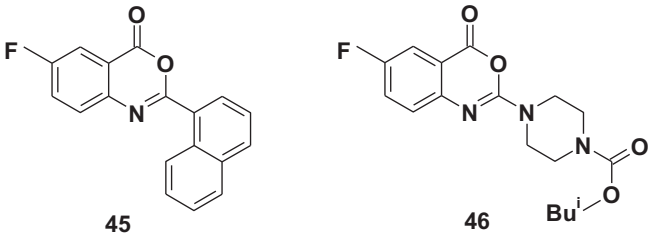


Scheme 21.



59, 60: R = $PhCH_2$, $PhCH_2CH_2$, 2-thiophenmethylene; **62**: X = H, F.

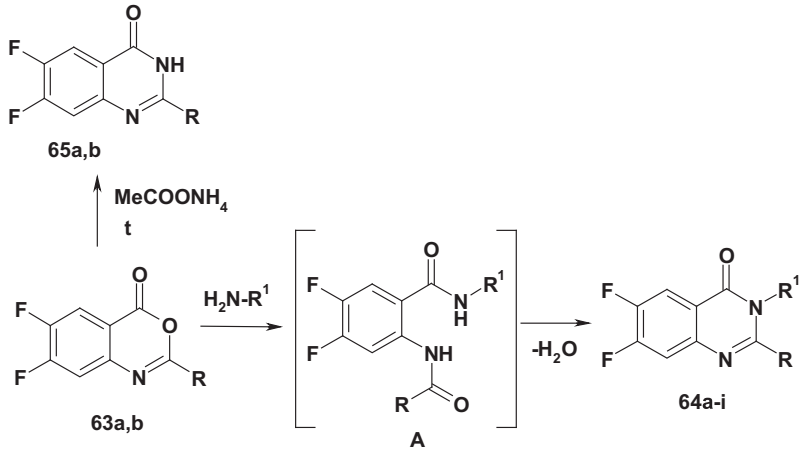
Scheme 22.



2-Ethoxycarbonylmethyl-3,1-benzoxazin-4-ones **47** were found to undergo recyclization into quinolin-3-carboxylates **48** by the reaction with triethylamine in absolute methanol (Scheme 19) [57].

2-Substituted 3,1-benzoxazin-4-ones are transformed by action of arylmagnesium bromides into the corresponding diarylketones, and further into quinolines. For instance, (2-amino-4-methoxy-5-fluorophenyl) phenylmethanone, which can be regarded as intermediate for the synthesis of 3-(3-methylisoxazol-5-yl)-7-methoxy-4-phenyl-6-fluoro-1*H*-quinolin-2-one **50** (known as the C-FMS kinasa inhibitor), was obtained by the reaction of 6,7-difluoro-2-phenyl-3,1-benzoxazin-4-one **49a** with phenylmagnesium bromide [58]. Also, (2-amino-5-fluorophenyl)-(2-methoxyphenyl)methanone, obtained from 2-methyl-6-fluoro-3,1-benzoxazin-4-one **49b** and 2-methoxyphenylmagnesium bromide, was transformed into 6-methyl-2-fluorobenzofuro[2,3-C]quinoline **51** (Scheme 20) [59].

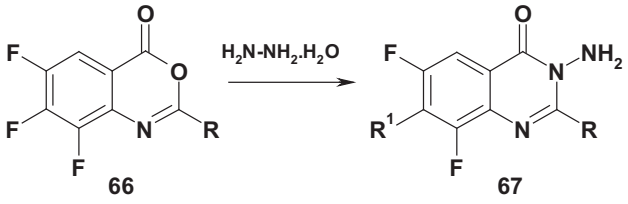
Transformations of fluorinated 3,1-benzoxazin-4-one into quinazolinones can be regarded as a special type of cyclocondensations. Indeed, 3-substituted quinazolin-4(*3H*)-ones **53** and **54** can easily be prepared by condensation of 5-fluoro-2-methyl-3,1-benzoxazin-4-one **52** with 5-substituted 2-amino-1,3,4-thiadiazoles or DL-α-amino-ε-capro-lactam on reflux in dry pyridine for



63: R = Me(a), Ph(b); **64:** R = Me, R^1 = NH_2 (a), 5-*t*-butylisoxazol-3-yl (b), thiazol-2-yl (c), triazol-3-yl (d), 5-methylpyrazol-3-yl (e), pyridin-2-yl (f), Ph (g), R = Ph, R^1 = NH_2 (h), R^1 = 5-*t*-butylisoxazol-3-yl (i);

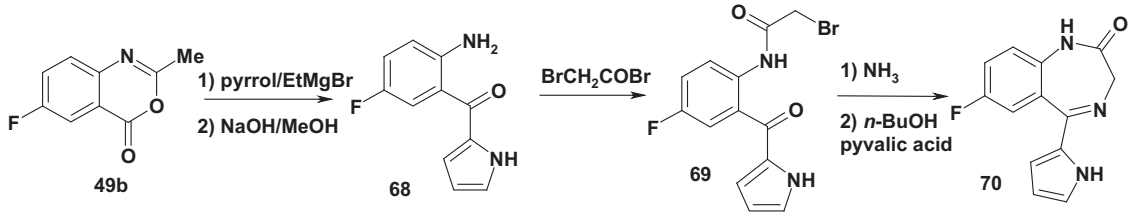
65: R = Me(a), Ph(b)

Scheme 23.



66: R = Me (a), Ph (b), **67**: R = Me, R^1 = NH-NH_2 (a), R = Ph, R^1 = F (b).

Scheme 24.



Scheme 25.

28 h [60]. Also refluxing of **52** with *o*-toluidine or amine **56** in acetic acid afforded quinazolines **55** and **57** (5-F, 6-F, 7-F, 8-F) (Scheme 21) [61,62].

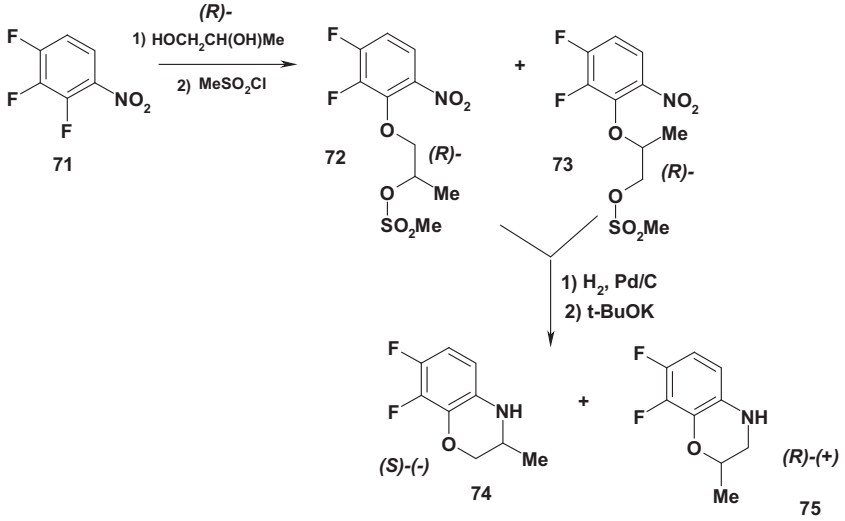
Sulfonamides **59** were obtained by reacting of sulfohydrazides with 6-fluoro-3,1-benzoxazines **58** in melt at 130 °C for 30 min or by heating of reagents in DMF at room temperature for 22 h (Scheme 22) [63]. The reaction was shown to proceed through the intermediates **59**, which were isolated in case the reaction was carried out under the above-mentioned mild conditions. There are reports concerning modification of the position 3 in quinazolinones with 4-methylpiperazine [64] and phenylethyl substituents [65].

2-Methyl- and 2-phenyl-6,7-difluoro-4*H*-3,1-benzoxazin-4-ones **63a,b** were obtained reaction represented at Scheme 16. The reaction of benzoxazinones **63** with hydrazine hydrate in refluxing ethanol (reaction time 3 h) gave the corresponding 3-aminoquinazolin-4(3*H*)-ones **64a–i**. By reacting with heteroaromatic amines benzoxazines **63a,b** were transformed into quinazolin-4-one derivatives **64** bearing a pharmacophoric substituent in 3-position. These reactions took place smoothly on heating of reactants in melt at 170–180 °C over a period of 20–40 min to give 3-hetaryl-6,7-difluoroquinazolin-4-ones in 60–80% yields. In a similar way, 2-methyl- and 2-phenyl-6,7-difluoroquinazolin-4(3*H*)-ones **65** were obtained by reacting of benzoxazines **64a,b** with ammonium acetate (Scheme 23) [66].

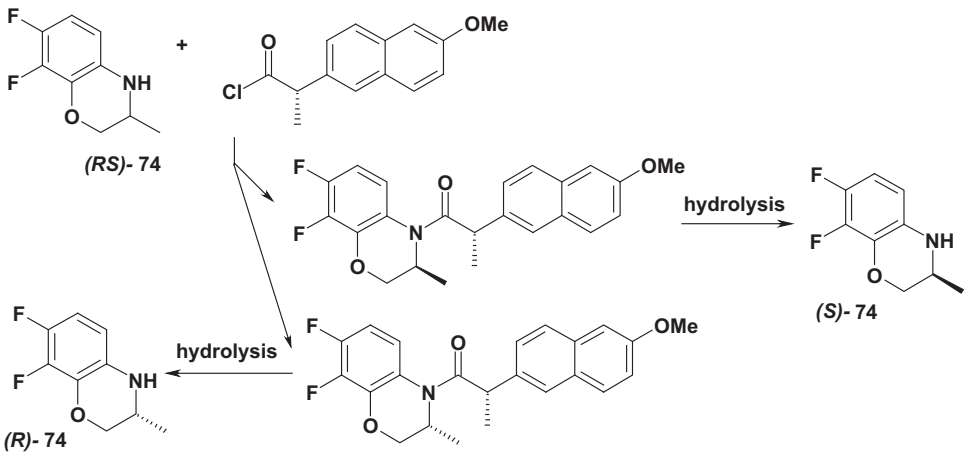
7-Fluoro-2-(*o*-nitrophenyl)-4*H*-3,1-benzoxazin-4-one was found to be transformed into the corresponding quinazoline on heating with urea at 180–190 °C [67]. At the same time transformation of 6-fluoro-2-ethyl-4*H*-3,1-benzoxazin-4-one into 3-unsubstituted quinazolinone proceeds at a milder conditions, on treatment with 25% ammonia solution for 10–12 h [68].

Benzoxazinones **66** react with hydrazine hydrate into 3-aminoquinazolin-4(3*H*)-ones **67**, and this ring transformation reaction is accompanied by replacement of a fluorine atom F^7 in the benzene ring with the hydrazine substituent (**69a**) (Scheme 24) [66].

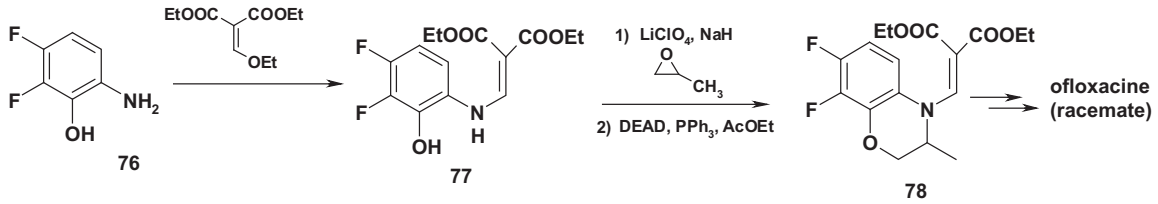
Transformations of substituted 3,1-benzoxazin-4-ones into benzodiazepines have been performed. In particular, 5-pyrrolyl-7-fluoro-1,3-dihydrobenzo[*e*][1,4]diazepine **70** was obtained from 2-methyl-6-fluoro-4*H*-3,1-benzoxazin-4-one **49b** through the intermediates **68**, **69** (Scheme 25) [69].



Scheme 26.



Scheme 27.



Scheme 28.

3.1.3. Biological activity

7-Fluoro-2-(2-iodophenylamino)-4*H*-3,1-benzoxazin-4-one, which was obtained by heating of methyl 2-[3-(2-iodophenyl)urea]benzoate in sulfuric acid, acts as a complement Clr protease inhibitor and anti-inflammatory agent [70]. 7-Fluoro-2-phenylamino-*4H*-3,1-benzoxazine-4-one has been recommended for treatment of adiposity [46]. Some derivatives of 2-amino-7-fluoro-4*H*-3,1-benzoxazin-4-ones **40** were found to exhibit a high selectivity as inhibitors of C1r Serine Protease [49]. 2-Aryl(pyridyl)6,7-difluoroderivatives **40** are effective as regulators for blood coagulation [47,50]. Amide **44** has exhibited insecticidal activity [52], while 5-heteryl substituted benzodiazepines, analogues of **70**, have demonstrated a profound antiviral properties [71].

3.2. 1,4-Benzoxazines

3.2.1. Synthesis

Condensation of *o*-hydroxy(halogeno) arylamines bearing fluorine atoms seems to be a rather common and convenient synthetic approach to 1,4-benzoxazines. Indeed, several methods for the synthesis of stereo isomers of fluorinated 2-methyl- and 3-methyl-*2H*-[1,4]benzoxazines have been developed [72]. Transformation of 2,3,4-trifluoronitrobenzene **71** into (*S*)-(−)-7,8-difluoro-3,4-dihydro-3-methyl-*2H*-[1,4]benzoxazine **74** is the process of great importance for the synthesis of levofloxacin, one of the most efficient antibacterial drug of the fluoroquinolone family (Scheme 26). Interaction of **71** with (*R*)-propan-1,2-diol in THF in the presence of sodium hydride leads to the formation of a mixture of (*R*)-3,4-difluoro-2-(2-hydroxypropoxy)nitrobenzene and (*R*)-3,4-difluoro-2-(1-hydroxyisopropoxy)nitrobenzene in the ratio 3:2. These products were transformed into a mixture of mesilates **72** and **73**, followed be reduction of the nitro-group, cyclization in the presence of *t*-BuOK and subsequent resolution of racemic benzoxazines **74** and **75** by means of chiral column chromatography.

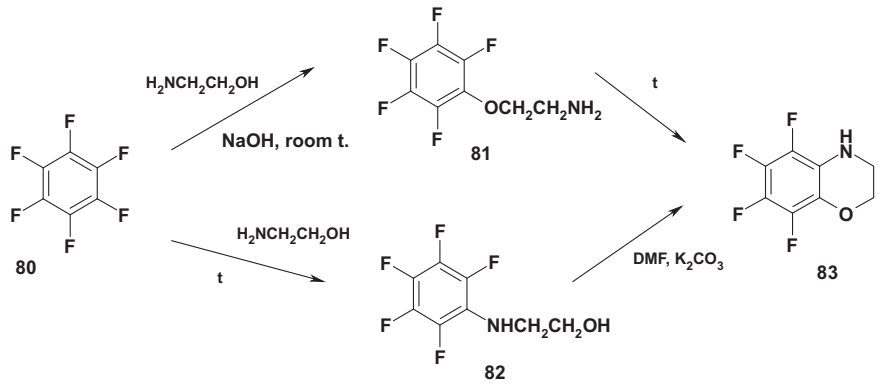
Another way to fluorinated 3-methyl-*2H*-[1,4]benzoxazines is based on the reaction of 2,3-difluoro-6-nitrophenol, derived from 2,3,4-trifluoronitrobenzene **71**, with (*S*)- or (*R*)-2-(2-tetrahydropyranyloxy)propanol [72]. The tetrahydropyranyl fragment has then to be eliminated with the assistance of an acidic ion-exchange resin, followed by the formation of the mesilate form, reduction of the nitro-group and cyclization in the presence of *t*-BuOK. The reaction of 2,3,4-trifluoronitrobenzene **71** with (*R*)-2-(ethoxyethoxy)-1-propanol or (*R*)-1-benzyloxy-2-propanol was also applied to obtain benzoxazine derivatives [72].

(*S*)-(−)-Isomer of **74** was obtained by the reaction of racemic (*RS*)-7,8-difluoro-2,3-dihydro-3-methyl-4H[1,4]benzoxazine derivative with (*S*)-2-(6-methoxynaphthyl-2-oyl)propionyl chloride at room temperature, followed by isolation of N-[(2*S*)-2-(6-methoxynaphthyl-2-oyl)propionyl]-(3*S*)-7,8-difluoro-2,3-dihydro-3-methyl-4H[1,4]benzoxazine using the kinetic resolution procedure (Scheme 27) [73].

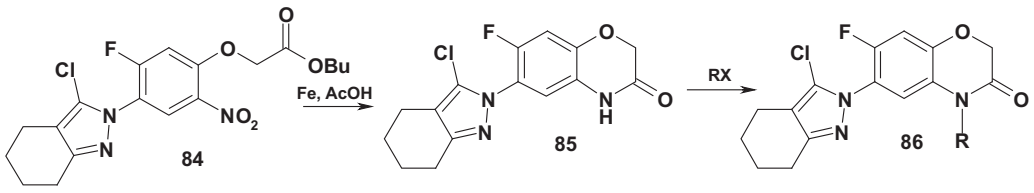
Cyclization of (*R*)-3,4-difluoro-2-(2-hydroxypropoxy)aniline into (*S*)-(-)-7,8-difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine **74** was proposed to carry out in CCl_4 in the presence of $ZnCl_2$ and PPh_3 [74]; patent [75] suggest obtaining of compound **74** by cyclization of N-(3-hydroxy-2-propyl)-2,3,4-trifluoroaniline in DMF in the presence of sodium hydride.

An original way for preparation of **78**, the key intermediate in the synthesis of ofloxacine, has been suggested [76]. According to this approach aminophenol **76** is transformed into enamine **77**, which reacts with methyloxyrane and undergoes the cyclization in

Scheme 29.

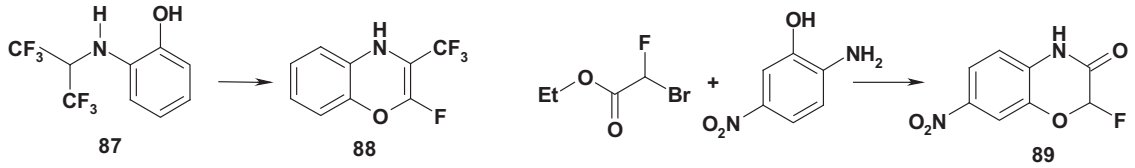


Scheme 30.



R = Et, propargyl, allyl, alkenyl, haloalkyl, haloalkenyl.

Scheme 31.



Scheme 32.

the presence of triethylphosphine and diethyl azodicarboxylate (DEAD) to give **78** (Scheme 28).

Another intermediate for the synthesis of **78** (compound **79**, Scheme 29) has been suggested [77].

2-Acetylmethoxy-3,4-difluoronitrobenzene was also used in the synthesis of benzoxazine **78** [78].

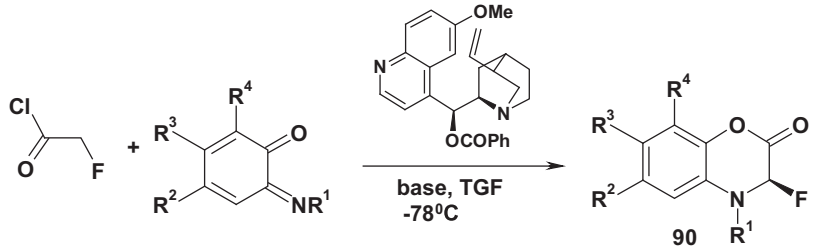
By reacting hexafluorobenzene **80** with aminoethanol in DMF at room temperature in the presence of NaOH 2-(pentafluorophenoxy)ethylamine **81** was obtained, however heating of reagents without a base yields aniline derivative **82**. Cyclizations of both compounds, **81** and **82**, lead to tetrafluorobenzoxazine **83** (Scheme 30) [79,80].

7-Fluoro-*2H*-1,4-benzoxazin-3(*4H*)-ones **85** have been obtained from butyl [4-(3-chloro-4,5,6,7-tetrahydro-indazol-2-yl)-5-fluoro-2-nitro-phenoxy]acetate **84** (Scheme 31) [81]. Alkylation of compounds **85** affords 4′-substituated 6-(3-chloro-4,5,6,7-tetrahydro-indazol-2-yl)-7-fluoro-4-alkyl-4H-benzo[1,4]oxazin-3-ones **86** (Scheme 31) [81].

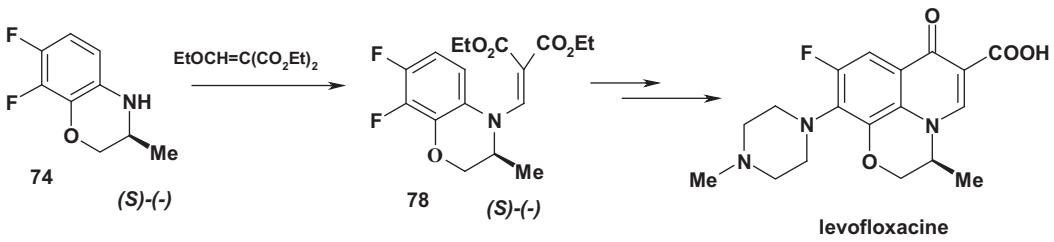
In order to obtain 1,4-benzoxazines bearing fluorine atoms in their heterocyclic part, cyclizations of *ortho*-hydroxyarylamines can be used, provided fluorine atoms are located in the side chain of N-substituted *ortho*-aminophenols or are supposed to be brought with the second component. Indeed, 3-trifluoromethyl-2-fluoro-1,4-benzoxazine **88** was obtained by heating of *ortho* aminophenol **87** with triethylamine in THF for 1 h [82]. The second approach is illustrated by the synthesis of 7-nitro-2-fluoro-1,4-benzoxazin-3-on **89** from 2-amino-5-nitrophenol and ethyl bromofluoroacetate in DMF in the presence of KF (Scheme 32) [83].

Asymmetric synthesis of 1,4-benzoxazinones **90** is based on a highly enantioselective [4 + 2]-cycloaddition of *ortho*-benzoquinonimides with chiral ketenes enolate generated from acyl chloride in the presence of the alkaloid-like catalyst (Scheme 33) [84,85].

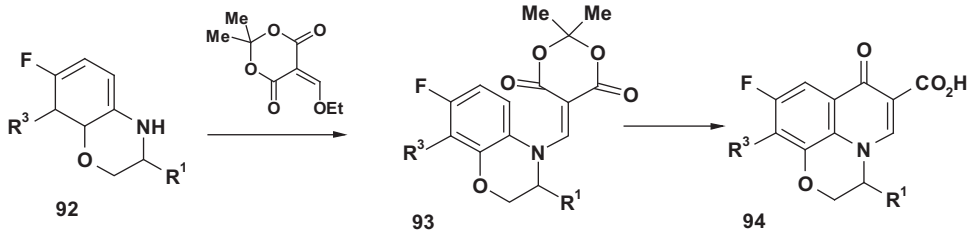
4-Substituted 2-fluoro-*2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one **91** was obtained in a regioselective manner by the direct



Scheme 33.

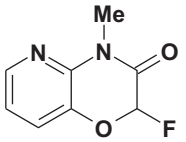


Scheme 34.



Scheme 35.

electrochemical fluorination of *2H*-1,4-pyrido[3,2-*b*]-1,4-oxazin-3(*4H*)-one in dimethoxyethane containing Et_4NF and 4HF [86]. Earlier [87] the same group of authors have synthesized 2-fluorosubstituted 4-R-*2H*-1,4-oxazin-3(*4H*)-ones under similar conditions.



91

3.2.2. Chemical properties and modifications

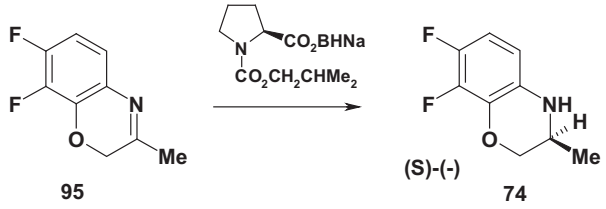
Condensation of **74** with diethylethoxymethylene malonate results in the formation of N-substituted derivative **78**, followed by its cyclization into the corresponding fluoroquinolone (Scheme 34) [88].

The synthesis of ofloxacin analogues **94** was suggested to perform through the reaction of fluorinated benzoxazine **92** with 2,2-dimethyl-5-ethoxymethylene-1,3-dioxane-4,6-dione, followed by cyclization of the intermediate **93** (Scheme 35) [89].

One more synthetic approach to (*S*)-(−)-7,8-difluoro-2,3-dihydro-3-methyl-*4H*-1,4-benzoxazine **74** is the asymmetric reduction of the derivative **95** by optically active sodium triacyloxyborohydride (Scheme 36) [90].

3.2.3. Biological activity

A great deal of 7-fluoro-1,4-benzoxazin-3-ones were found to exhibit herbicidal activity [91,92]. Condensation of 6-amino-7-fluorobenzoxazinone with phthalic anhydride, followed by the N-alkylation with propargyl bromide have been used for the synthesis of a number of derivatives [93,94]. Applications of various fluorobenzoxazines and fluorobenzothiazines in agriculture have been reported in the paper [94].



Scheme 36.

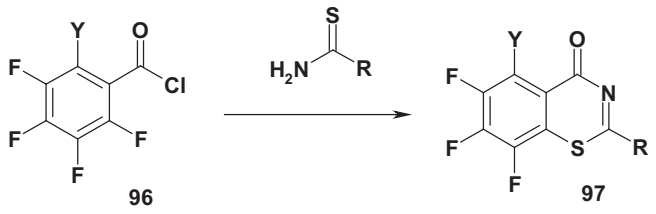
3.3. 1,3-Benzothiazines

3.3.1. Synthesis and the structure

A number of syntheses of fluorinated [1,3]benzothiazin-4-one derivatives have been carried out using cyclocondensation reactions based on polyfluorobenzoyl chlorides as starting materials. For instance, a series of fluorinated 2-substituted [1,3]benzothiazin-4-ones **97** have been obtained in 59–80% yields by heating of compound **96** with thioamides in toluene for 3 h. It should be noted, that attempts to isolate the intermediate N-acyl derivatives under these conditions have failed (Scheme 37) [95,96].

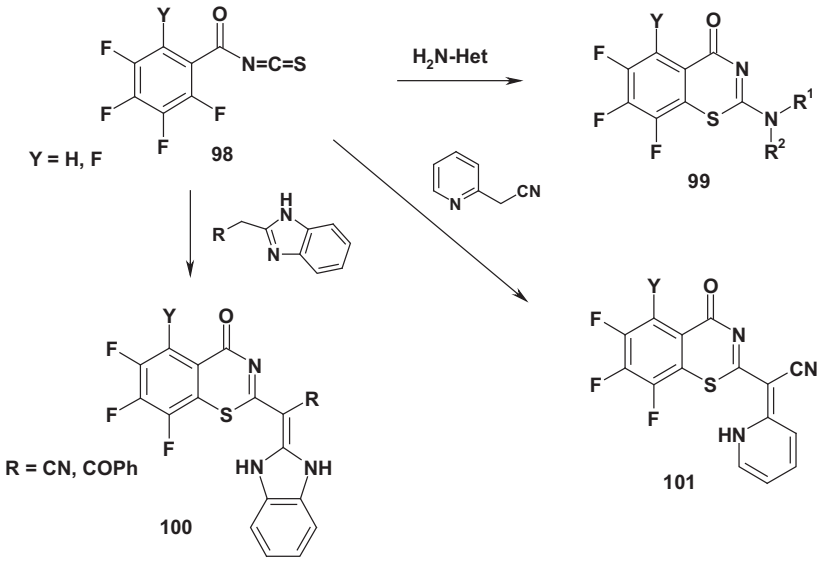
Polyfluorobenzoyl isothiocyanates **98** have been used as building blocks for the preparation of fluorinated [1,3]benzothiazin-4-ones. Indeed, compounds **98** react with cyclic amines, 2-aminoheterocycles, CH-active pyridines and benzimidazoles to yield 2-substituted [1,3]benzothiazin-4-ones **99–101** (Scheme 38) [95,97–99].

Interaction of tetrafluorobenzoyl isothiocyanate (**98**, Y = H) with hydrazines and hydrazones has been shown to form the fluorinated [1,3]benzothiazin-4-ones **102–105** (Scheme 39) [100]. Benzothiazinone **105** was formed as a result of amino-nitrile cleavage of the N-(4,6-disubstituted pyrimidinyl)hydrazone which is analog of **104** and subsequent reaction with the second isothiocyanate molecule.



Y = H, F; R = Ph, 4-Cl-C_6H_4, 4-Me-C_6H_4, 2-pyridyl

Scheme 37.



Scheme 38.

In the ^{1}H NMR spectra of 2-substituted 6,7,8-trifluoro[1,3]-benzothiazin-4-ones **97**, **99** (Y = H) the characteristic proton resonance of H^5 is observed at δ 7.97–8.24 ppm with the coupling constants J(H, F): ^{3}J 9.8–10.6, ^{4}J 6.8–7.7, ^{5}J 2.0–2.3 [95,99].

The ^{19}F NMR data for the series of 2-substituted 6,7,8-trifluoro[1,3]benzothiazin-4-ones **97** and **99** (Y = H), including characteristic coupling constants $^{3}J(F^7, F^6)$ 22.5, $^{3}J(F^7, F^8)$ 21.1–21.5, $^{4}J(F^8, F^6)$ 6.2–6.3, have been reported [95,96,99].

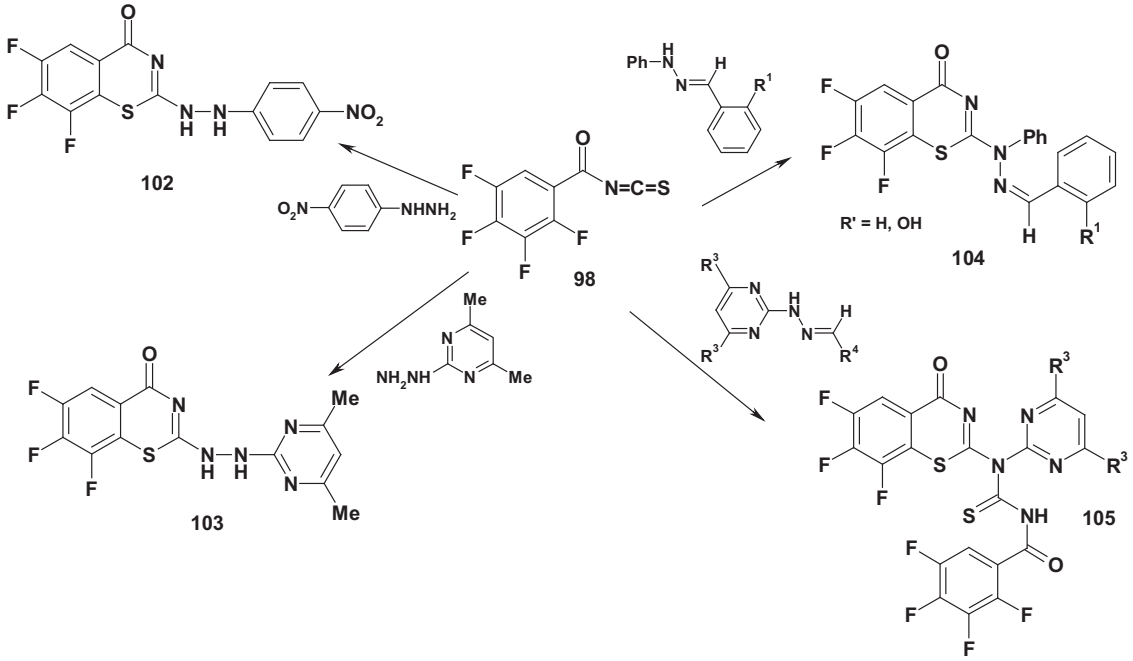
Molecular ion peaks in the mass spectra of compounds **97** and **99** (Y = H) proved to have a relatively small intensivities (4–11%), while the most intensive peak m/z 190 (100%) is caused by elimination of the fragment RCN from M^+ [95,99].

Another promising "building block", fluoroanthranilic acid, seems to expand opportunities for the syntheses of [3,1]-benzothiazin-4-ones. Indeed, 4,5-difluoroantranilic acid **106** proved to react with carbon disulphide in the presence of triethylamine, followed by methylation with methyl iodide to give dithiocarbamate **107**. Treatment of this compound with acetic anhydride afforded to *4H*-[3,1]-benzothiazin-4-one **108** in a high yield (Scheme 40) [101,102].

3.3.2. Fused benzothiazines

Heating of benzimidazole-2-thiones or imidazolidine-2-thiones with tetra- or pentafluorobenzoyl chlorides in toluene or pyridine has been found to give rise to fluorinated derivatives of imidazo[2,1-*b*][1,3]benzothiazines **109** and **110** (R = F) (Scheme 41) [103].

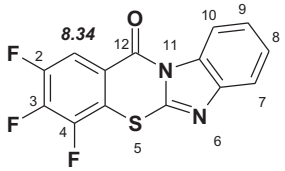
According to the X-ray crystallography data (Fig. 2) the compound **109** (R, R′ = F, R″ = H) has a linear tetracyclic system build up by fusion of benzimidazole and benzothiazine fragments along the C^1–N^2 bond; therewith all atoms are located actually in the same plane (the mean deviation is 0.02 Å) [103].



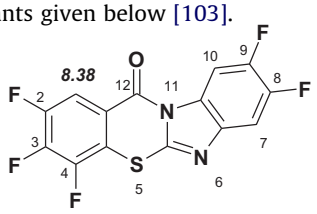
R^3 = Me, Ph, R^4 = Ph, 4-$MeOC_6H_4$.

Scheme 39.

In the ^{1}H NMR spectra of fluorinated derivatives **109** (R′ = H) the characteristic H^1 resonance signal is observed as doublet of doublets with the coupling constants given below [103].

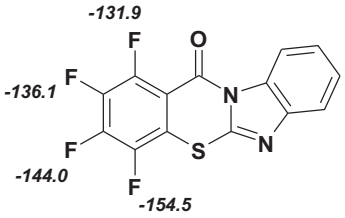


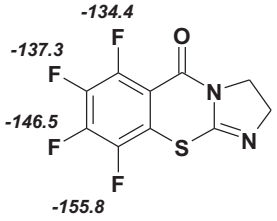
^3J 10.7, ^4J 7.3, ^5J 1.2

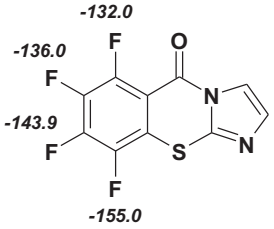


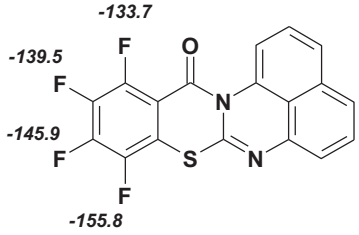
^3J 10.6, ^4J 7.4, ^5J 1.5

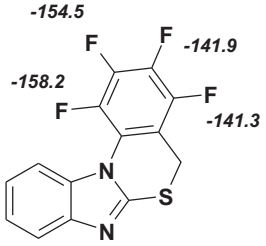
The ^{19}F NMR data for some condensed tetrafluoro benzothiazines are presented below ($CDCl_3$, standard $CFCl_3$) [104].











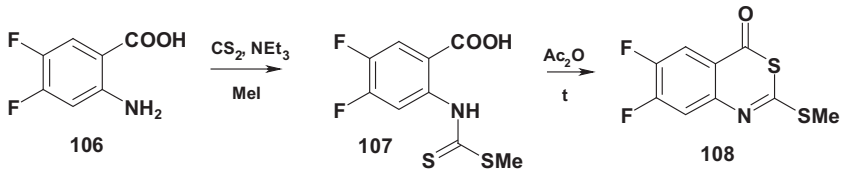
The ^{19}F NMR data for tetrafluorobenzimidazo annelated benzothiazinones **109** have been collected and discussed [103]. The following values of ^{19}F chemical shifts have been established for the series of 2,3,4-trifluoro derivatives **109** (X = H): δ_F (F^2) −134 to 135 ppm, δ_F (F^3) −149 to 151 ppm, δ_F (F^4) −133 to 134 ppm; and for 1,2,3,4-tetrafluoro compounds **109** (X = F) δ_F (F^1) −144 to 147 ppm, δ_F (F^2) −137 to 139 ppm, δ_F (F^3) −155 to 157 ppm, δ_F (F^4) −135 to 136 ppm [103].

Imidazo[2,1-*b*][1,3]benzothiazin-4-ones **111** have been obtained by the reaction of 4,5-disubstituted 2-mercaptoimidazoles with aroyl chloride **96** (Y = F) on heating in pyridine (Scheme 42) [105]. The dianion generated from perimidin-2-thione by action of *n*-BuLi reacts with pentafluorobenzoyl chloride **96** (Y = F) to form the compound **112**, a representative of the fused system of benzothiazinoperimidine [104].

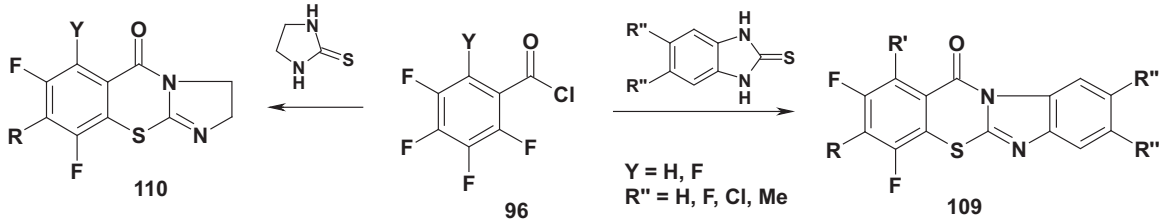
The formation of fused tetrafluoro derivative **114** is described to proceed in two steps: firstly, substitution of the bromine atom of pentafluorobenzyl bromide **113** under reaction with 2-mercaptobenzimidazol leads to the intermediate 2-benzylthiobenzimidazole, which then is cyclized by treatment with NaH in THF (Scheme 43) [104].

3.3.3. Chemical properties and modifications

Transformation of fluorinated [3,1]-benzothiazine into quinoline has been studied. When the compound **108** was treated with the lithium salt of ethyl acetate dithiocarbamate **115** is formed, the last is cyclized by treatment in ethanol in the presence of sodium ethoxide into 2-mercaptoquinoline **116** (Scheme 44) [101,102].



Scheme 40.



Scheme 41.

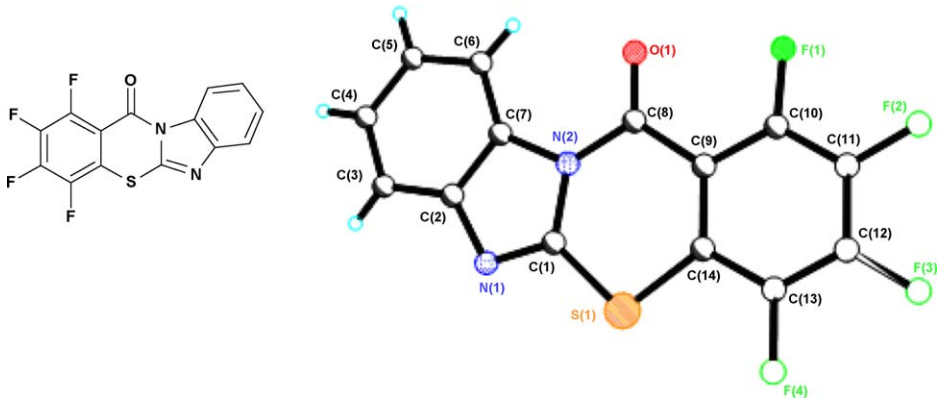
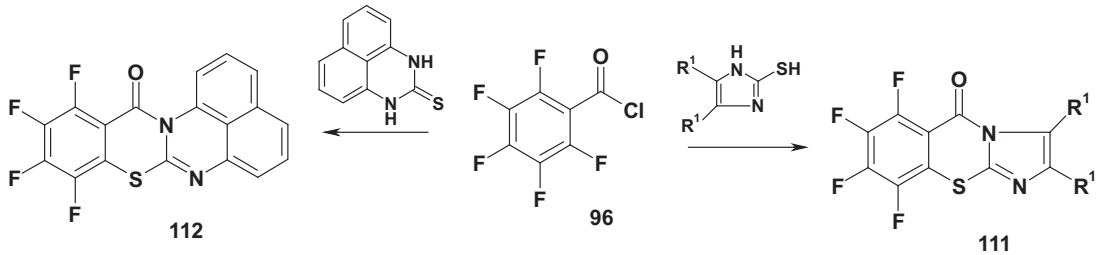
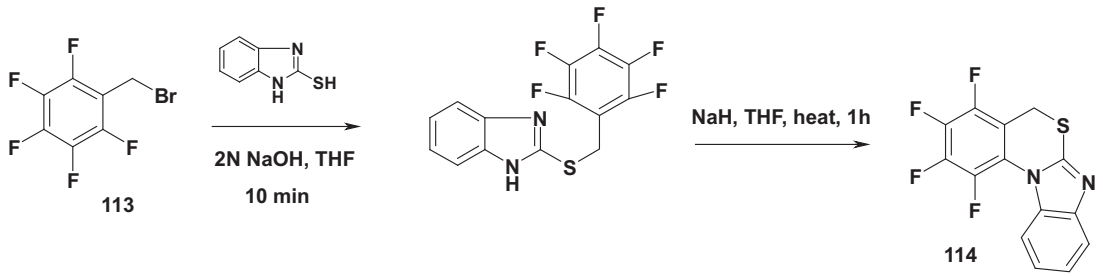


Fig. 2. 1,2,3,4-Tetrafluoro-*6a,10a*-dihydro12H-benzo[*e*]benzo[4,5]imidazo-[2,1-*b*][1,3]-thiazin-12-one.

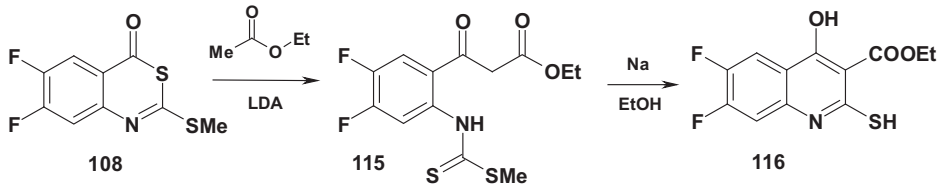


R^1 = H, Me, Ph.

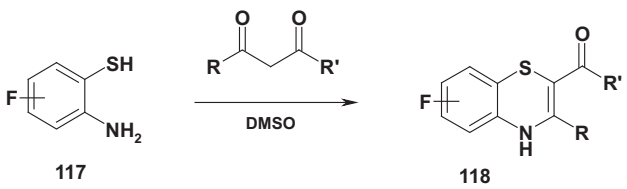
Scheme 42.



Scheme 43.

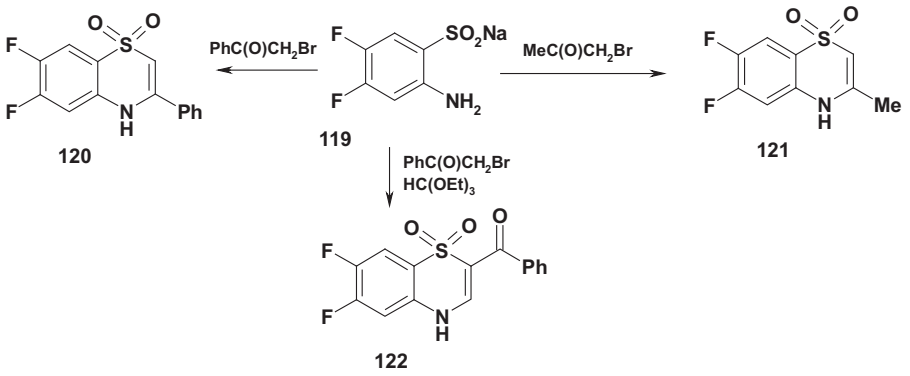


Scheme 44.

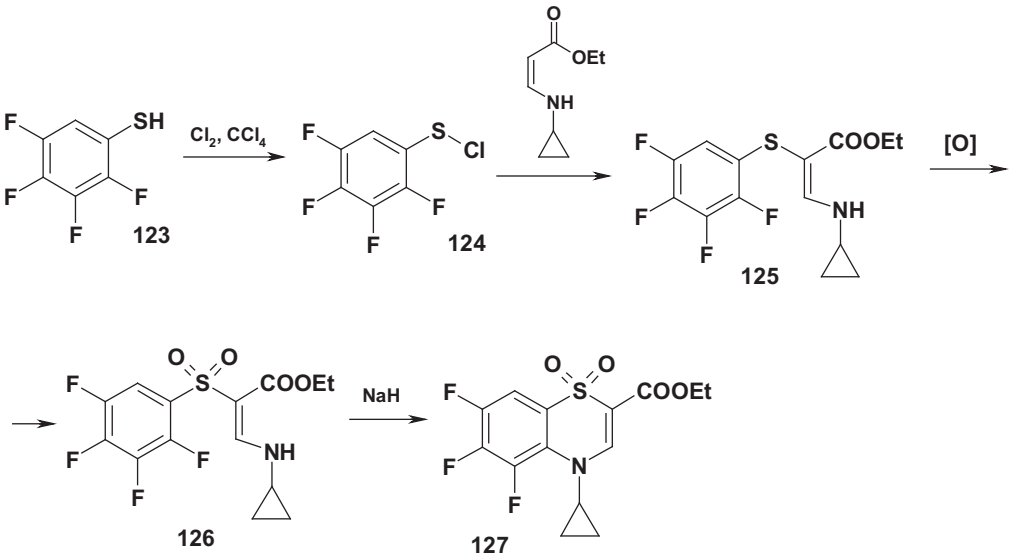


R = Me, R' = Me, Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, EtO, MeO, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$; R = R' = Ph

Scheme 45.



Scheme 46.



Scheme 47.

Nucleophilic amino-defluorination reactions in the series of fluorinated 1,3-benzothiazin-4-ones **97**, **100**, and **101** (Schemes 37 and 38), including [*b*]-annelated derivatives **109** and **110** (R = F), have been studied (Scheme 41) [98,99,103].

3.3.4. Biological activity

A number of 2-substituted tri(tetra)trifluoro[1,3]benzothiazin-4-ones **97**, **99**, and **100** were found to exhibit from moderate to high activity against *Micobacterium tuberculosis* $H_{37}R_V$ [106].

3.4. 1,4-Benzothiazines

3.4.1. Synthesis and the structure

Fluorinated aminothiophenols were used as precursors for the synthesis of the corresponding 1,4-benzothiazinones. For instance, a one pot synthesis of fluorinated *4H*-benzothiazinones **118** was carried out through condensation of fluorinated 2-aminothiophenols **117** with β-diketones in DMSO followed by oxidative cyclization (Scheme 45) [107–110].

In the ^{19}F NMR spectra the signals of fluorine atoms for 2-acyl-5-chloro-7-fluoro-3-methyl-4*H*-benzo-[1,4]thiazines **118** are registered at −104.3 to (−121.7) ppm; in the IR spectra the valence fluctuations of the C–F bond are observed at 1075–1090 cm^{-1} [109].

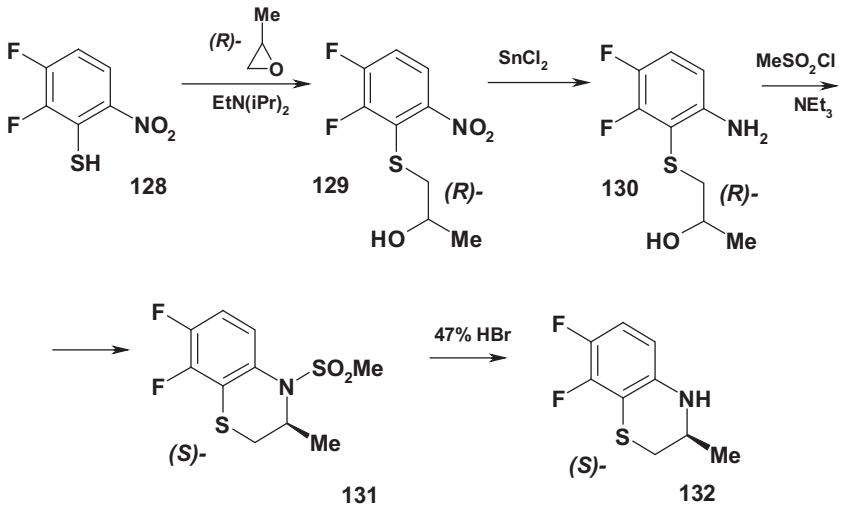
Fluorinated *4H*-1,4-benzothiazinesulfones have been obtained through oxidation of compounds **118** with 30% hydrogen peroxide in acetic acid [109].

Another way to a variety of 1,4-benzothiazin-1,1-dioxides is described [111]. Chlorosulfonation of 3,4-difluoroaniline gave 2-amino-4,5-difluorobenzenesulfonyl chloride which was converted into the corresponding sodium sulfinate **119**, which reacts with different bromocontaining ketones to give fluorinated 1,4-benzothiazin-1,1-dioxides **120–122** (Scheme 46).

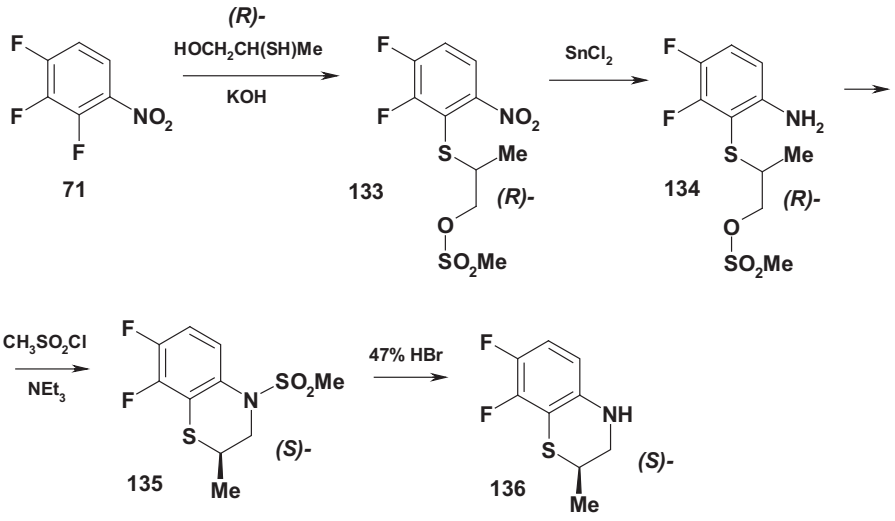
Thia-analogues of fluoroquinolones, the well-known class of antibacterial drugs, have been prepared. Chlorination of **123** affords sulfenyl chloride **124** which reacts with ethyl 3-(cyclopropylamino)-2-propenoate into enamines **125** as a mixture of (*Z*)- and (*E*)-isomers. Oxidation of **125** with 3.1 equiv. of *m*-chloroperoxybenzoic acid gave the sulfone **126**. Ring closure of **126** was carried out in THF solution with sodium hydride to give benzothiazine dioxide **127** (Scheme 47) [112]. The synthesis of 1,4-benzothiazin-2-carboxylic acid 1-oxide has been performed by means of the cyclyzation of fluorophenylsulfinyl acrylate [113].

The resonance signal of H^3 proton in the ^1H NMR spectra of benzothiazin-1-oxides is observed in a lower field than the correspondent signal in 1,1-dioxide **127** [112].

Fluorinated 2- and 3-methyl-1,4-benzothiazines can be used for the synthesis of levofloxacin thia-analogs. Synthetic



Scheme 48.



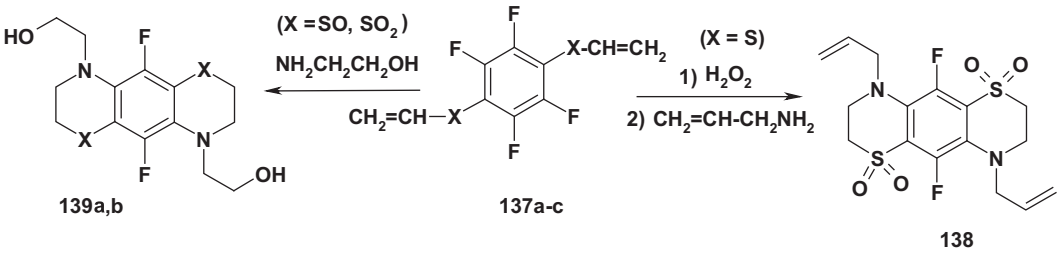
Scheme 49.

approaches to optically active benzothiazines are shown in Schemes 48 and 49. Reaction of 3,4-difluoro-2-mercaptonitrobenzene **128** with (*R*)-propylene oxide results in compound **129**, which was reduced into **130**. The compound **130** was cyclized to give derivative **131**, which was hydrolized into (*S*)-7,8-difluoro-3,4-dihydro-3-methyl-*2H*-1,4-benzothiazine **132** (Scheme 48) [72].

(*S*)-7,8-Difluoro-3,4-dihydro-2-methyl-*2H*-1,4-benzothiazine **136** was prepared from 2,3,4-trifluoronitrobenzene **71** and (*R*)-2-mercapto-1-propanol (Scheme 49) [72].

The presence of two vinylthio groups in fluorobenzenes **137** affords one to obtain the fused compounds **138**, **139** bearing two fragments of 1,4-benzothiazine. For instance, compound **138** was obtained by reacting 1,2,4,5-tetrafluoro-3,6-*bis*(vinylthio)benzene **137a** with hydrogen peroxide, followed by interaction of the oxidized product with allyl amine (Scheme 50) [114]. Compounds **137b** and **137c** react with aminoethanol in DMF at 50–55 °C to give fluorobenzo-1,4-thiazinoxides **139a,b** (Scheme 50) [115].

According to the X-ray crystallography data (Fig. 3) both six-membered heterocycles in compound **139a** have the conformation



137: X = S (**a**), SO_2 (**b**), SO (**c**); **139**: X = SO_2 (**a**), SO (**b**).

Scheme 50.

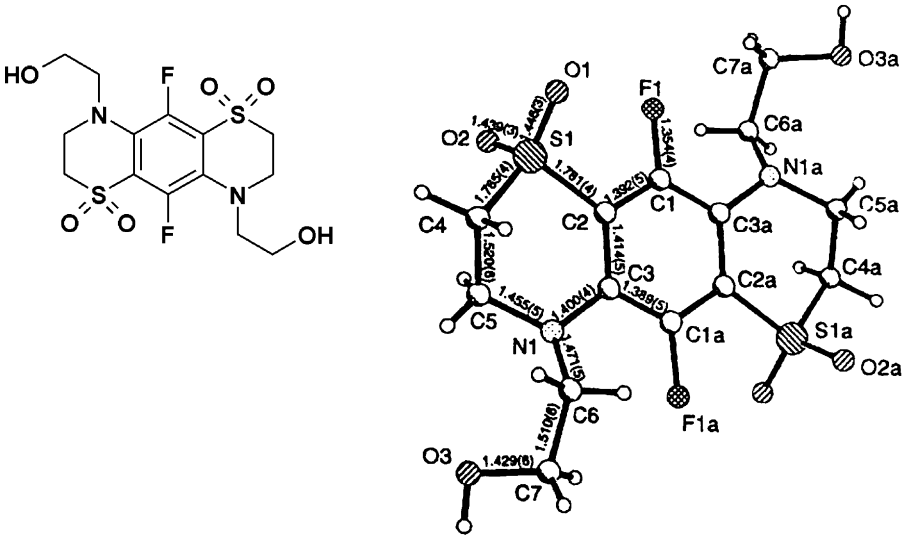
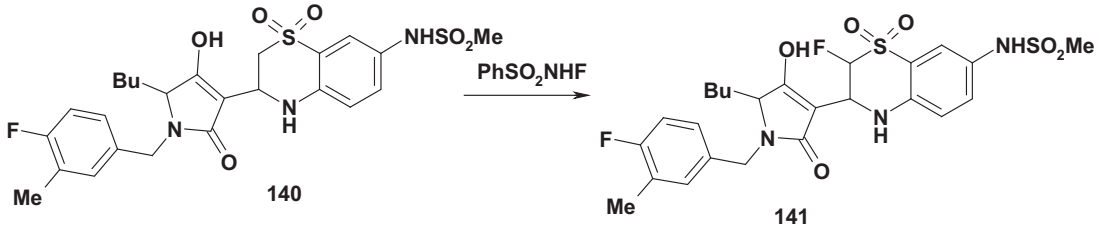
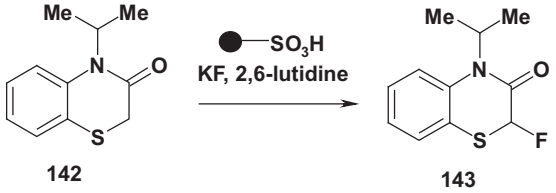


Fig. 3. Molecular structure of 4,9-bis(2-hydroxyethyl)-5,10-difluoro-1,2,3,4,6,7,8,9-octahydrobenzo[1,2-*b*;5,4-*b*]di-1,4-thiazin-1,1,6,6-tetraoxide **139a**.



Scheme 51.



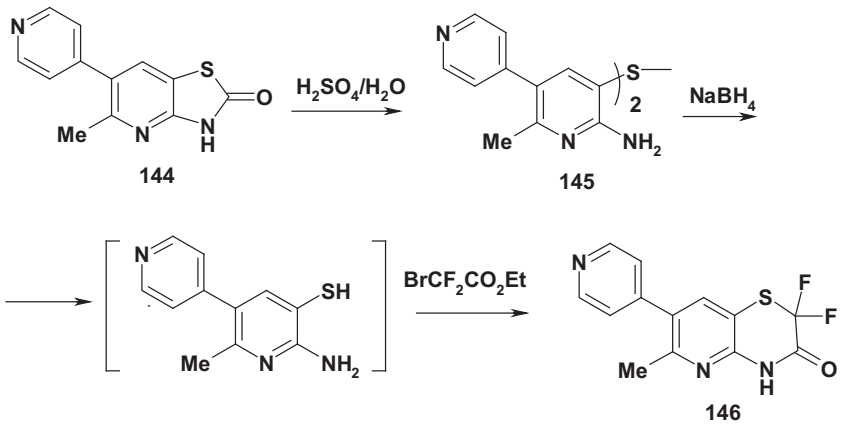
Scheme 52.

of semiarmchair: deviations of C^4 and C^5, C^{4a} and C^{5a} from the plane of other atoms are −0.0371 and 0.0446 nm, 0.0371 and −0.0446 nm, respectively. The planar fragment includes the benzene ring and S^1, N^1, F^1, S^{1a}, N^{1a}, F^{1a} atoms [114,115].

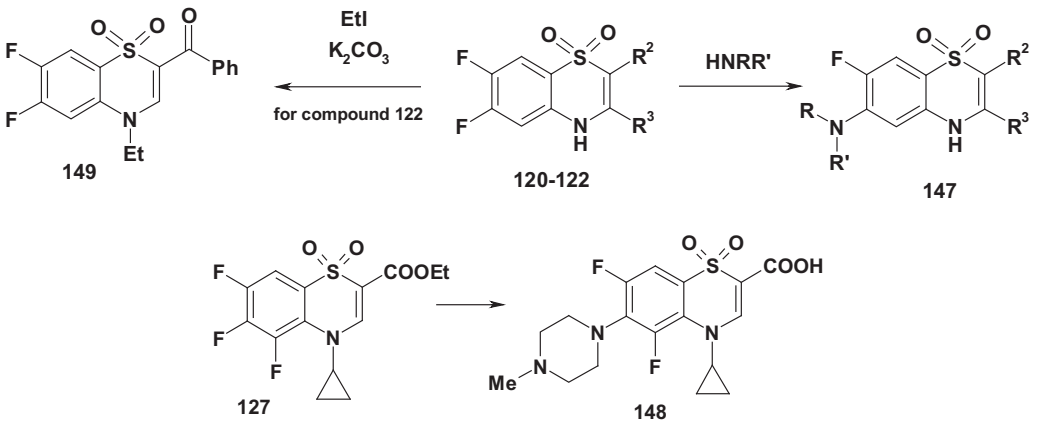
A limited number of fluorinated 1,4-benzothiazines are known up to now. Fluoro compound **141** has been obtained through the displacement of hydrogen in position 2 of 3,7-disubstituted 1,1-dioxybenzothiazine **140** (Scheme 51). This compound was found to exhibit antiviral activity [116].

2-Fluorobenzothiazin-4-on **143** was formed by anodic fluorination of 1,4-benzothiazinone **142** based on a cation-exchange reaction between alkali-metal fluorides and solid-supported acids (Scheme 52) [117].

Synthesis of 2,2-difluoro-6-methyl-7-(4-pyridinyl)-*2H*-pyrido[3,2-*b*]-1,4-thiazin-3(*4H*)-one **146** takes place on reflux of compound **144** under acidic conditions through opening of the thiazole ring, followed by reduction of disulfide **145** and condensation of 2-amino-3-mercaptopyridine derivative with ethyl bromodifluoroacetate (Scheme 53). Pyridothizinone **146** was studies as potential inhibitor of phosphodiesterase III [118].

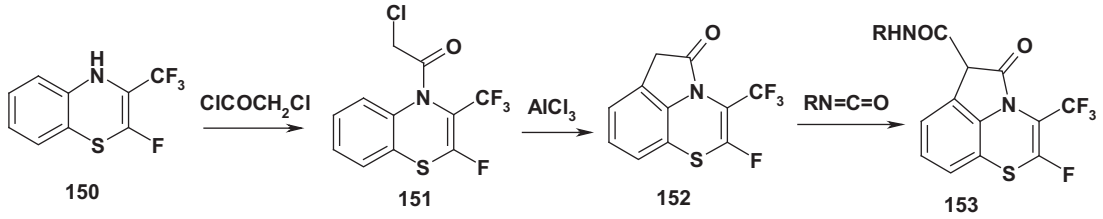


Scheme 53.

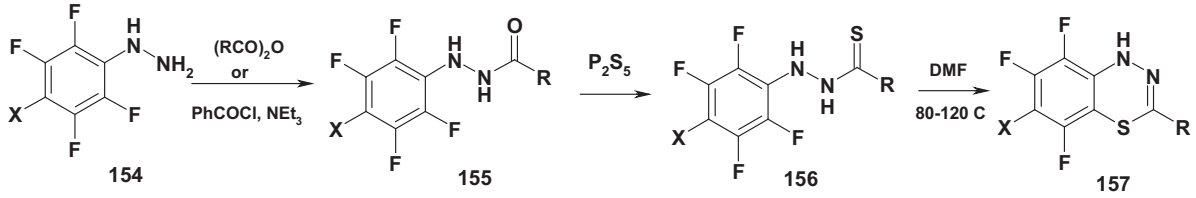


120: R^2 = H, R^3 = Ph; **121**: R^2 = H, R^3 = Me; **122**: R^2 = C(O)Ph, R^3 = H.

Scheme 54.



Scheme 55.



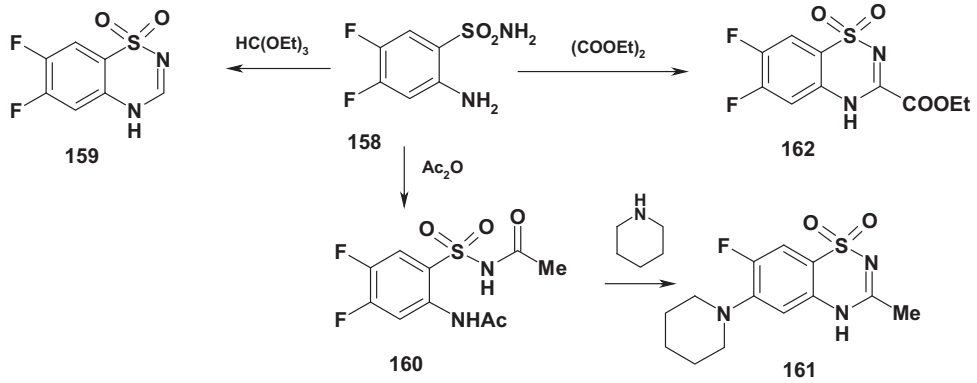
X = H, F; R = Me, Et, Ph

Scheme 56.

3.4.2. Chemical properties

6,7-Difluoro-1,4-benzothiazin-1,1-dioxides **120-122** react with cycloalkylimines to give compounds **147** as a result of nucleophilic displacement of F^6 atom (Scheme 54) [111]. Acid **148**, derived from the ester **127** through the displacement of F^6 atom with N-methylpiperazine and basic hydrolysis of the ethoxycarbonyl group, was subjected to biological trials as an inhibitor of DNA gyrase (Scheme 54) [112]. Alkylation of sulfone **122** with ethyl iodide in the presence K_2CO_3 afforded compound **149** (Scheme 54) [111].

3-Trifluoromethyl-2-fluoro-1,4-benzothiazine **150** prove to be a convenient starting material for the synthesis of tricyclic pyrrolobenzothiazine carboxamide **153** (Scheme 55), exhibiting anti-inflammatory activity [119].



Scheme 57.

3.5. Benzothiadiazines

2-Substituted 5,6,8-trifluoro- and 5,6,7,8-tetrafluoro-4*H*-1,3,4-benzothiadiazines **157** were prepared by intramolecular cyclization of polyfluorophenylthiohydrazides **156**, which have been obtained by the reaction of the corresponding hydrazides **155** with P_2S_5 (Scheme 56) [120,121].

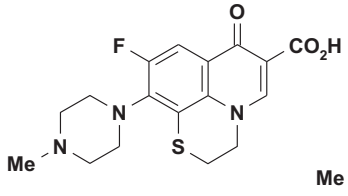
Sulfamide **158** under reaction with triethyl orthoformate or diethyl oxalate undergoes the cyclization to give fluorinated 1,2,4-benzothiadiazines **159**, **162** (Scheme 57) [111]. Interaction of **158** with acetic anhydride results in diacetyl derivative **160**, which under reflux with pyperidine undergoes not only cyclization but also amino-defluorination process to give **161**.

4. Conclusions

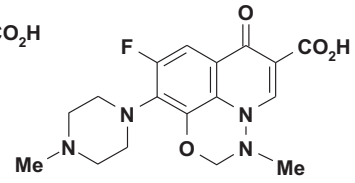
Analysis of the data presented in this review article and the reference list shows that a considerable body of synthetic methods to obtain fluorine-containing thia(oxazines) and benzothia(oxazines) have been developed over the last two decades, and recent publications demonstrate the continuing interest in these groups of compounds.

One of the main approaches to fluorinated azines and benzazines bearing oxygen or sulfur atoms is based on incorporation of fluorine atoms into a heterocyclic moiety, while the second approach suggests construction of a cyclic system from the available fluorine-containing building blocks through cyclocondensation or cycloaddition reactions. The first approach is not well-spread since selective incorporation of fluorine atoms into organic molecules has many limitations.

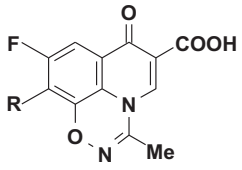
A number of fluorine-containing thia(oxazines) and benzothia(oxazines) can find their applications in pharmacology. Indeed, pyrido annelated benzoxazines, benzothiazines, benzoxa(thia)diazines are of great importance for medicinal chemistry. In addition to levofloxacin mentioned above, rufloxacin [122], marbofloxacin [123], and the series of 1,2,4-oxadiazino[*i*,*j*]-annelated fluoroquinolones **162** [124], as well as their tetracyclic derivatives **163** [125,126] belong certainly to a very promising group of antibacterials.



rufloxacine



marbofloxacine



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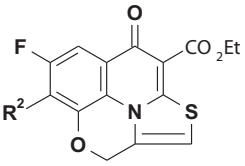

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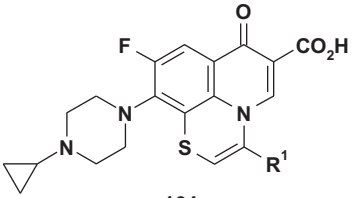
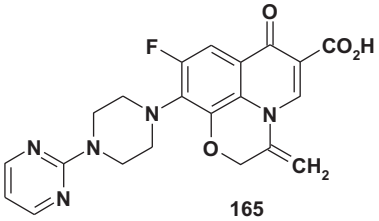
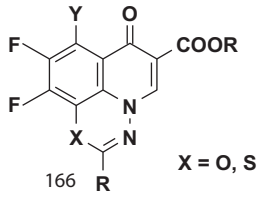
Compound **164** [127] proved to possess a high activity against hepatitis B virus, compound **165** [128,129] – against HIV virus. Also 1,3,4-thiadiazino[6,5,4-*i*,*j*]- and 1,3,4-oxadiazino[6,5,4-*i*,*j*]-annelated quinolones **166** have demonstrated a wide spectrum of biological activity (tuberculostatic, antibacterial and antitumor) [130–132].



164

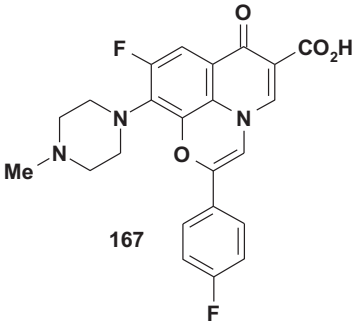


165

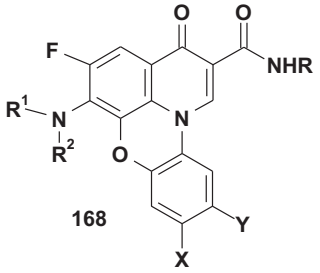


166

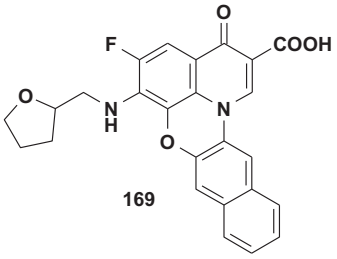
Three-, tetra- and pentacyclic derivatives of 1,4-oxazine 1**67–170** were found to possess antitumor activity [133–136].



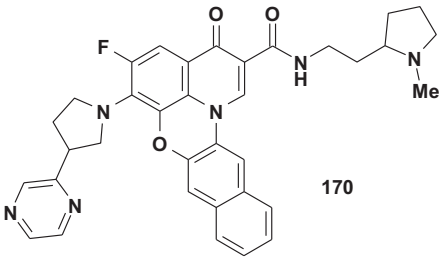
167



168



169



170

Synthetic approaches leading to pyridoannelated derivatives have thoroughly been discussed in previous review articles [137,138], therefore these data are omitted from consideration.

In conclusion, we would like to express a hope that systematic data on the synthesis of fluorine-containing thia(oxazines) and benzothia(oxazines) might be of interest for organic chemists and specialists working in the fields of fluorine and heterocyclic chemistry.

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