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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 75th anniversary

Fluorine-Containing Heterocycles: XIX.* Synthesis of Fluorine-Containing Quinazolin-4-ones from 3,1-Benzoxazin-4-ones

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Abstract—Reactions of fluorine-containing 3,1-benzoxazin-4-ones with ammonium acetate, hydrazine, and heteroaromatic amines gave new 3*H*-, 3-amino-, and 3-hetarylquinazolin-4-ones, respectively. Differences in the conditions of formation of benzoxazinones from anthranilic acids with different fluorination patterns and in the reactions of fluorinated 3,1-benzoxazinones with nitrogen-centered nucleophiles were revealed.

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Due to unique properties of fluorine atoms (which ensure solubility in lipids and the ability to inhibit specific enzymes and penetrate through cell membranes) fluorine-containing organic compounds, including heterocyclic ones, have found wide application in medicinal chemistry; in particular, 20% of pharmaceuticals contain fluorine [2]. In the recent years, extensive studies have been performed on compounds of the quinazolinone series with a view to obtain highly efficient medicines [3–6]. In this respect, strong attention is given to 2,3-disubstituted quinazolin-4-ones, some of which were found to be useful in the treatment of obesity, diabetes, tumors, viral infections, and degenerative pathologies of central nervous system, including epilepsy and Parkinson's disease [7–9]. 2,3-Disubstituted quinazolin-4-ones can be synthesized in several ways [10–14], among which the procedure based on the transformation of 3,1-benzoxazin-4-ones by the action of amines or hydrazines [15–17] seems to be quite promising and fairly convenient.

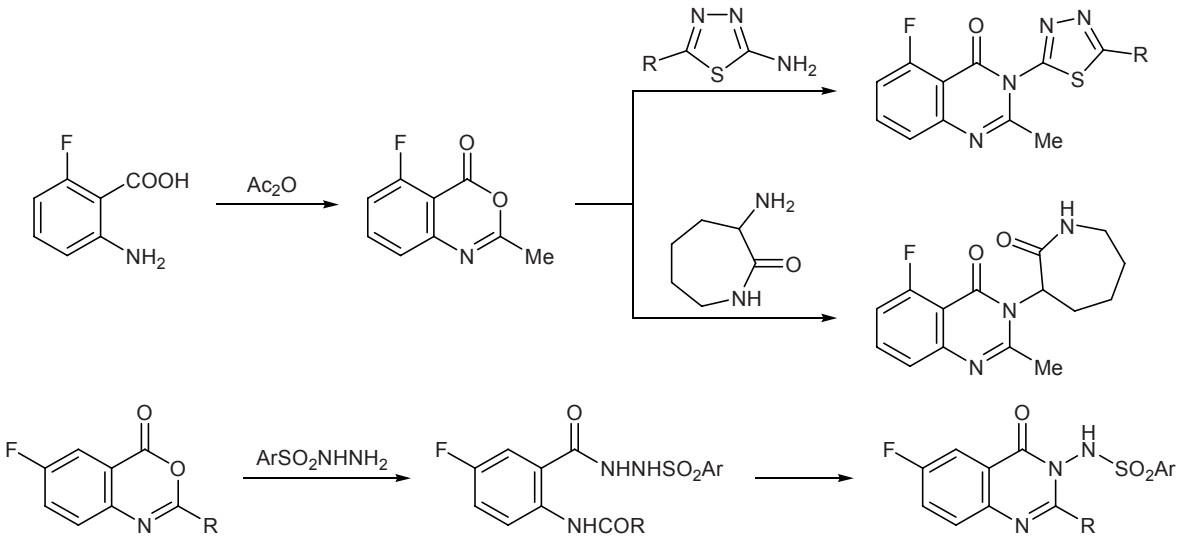
2-Methyl- and 2-phenyl-3,1-benzoxazin-4-ones can readily be synthesized from anthranilic acid derivatives and acetic anhydride or benzoyl chloride. The choice of this synthetic route was determined by high reactivity of 3,1-benzoxazin-4-ones, which makes it possible to vary substituent in the 3-position of the target quinazolinone. Published data on the synthesis of 5- or 6-fluoro-substituted quinazolin-4-ones according to the above procedure (Scheme 1) are very scanty [16, 17], whereas derivatives containing two or more fluorine atoms were not obtained in such a way.

We previously reported on the synthesis and properties of a series of 6,7,8-trifluoroquinazolin-4-ones, some of which were found to exhibit fairly strong tuberculostatic activity [18]. Taking into account that the presence of several fluorine atoms generally increases the toxicity, in the present work we synthesized a number of new 2- and 2,3-substituted quinazolin-4-ones having one to three fluorine atoms in the benzene fragment with a view to test the products for biological activity.

The procedures developed by us previously for the synthesis of fluorine-containing quinazolin-4(1*H*)-ones via cyclocondensation of *o*-fluorobenzoyl chloride with *S*-alkylisothioureas [18] or of 2-amino-5-fluoro-

* For communication XVIII, see [1].

Scheme 1.



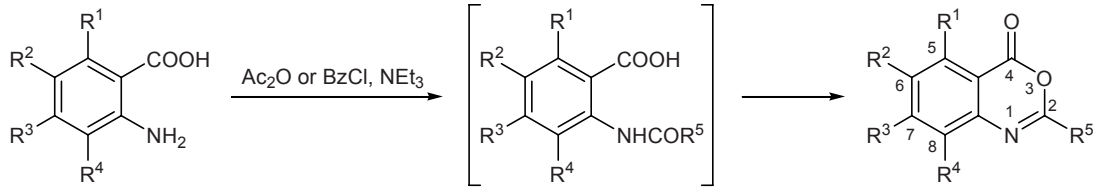
benzamide with carboxylic acid chlorides or aldehydes [19] are difficult to apply to the preparation of 6,7-difluoro derivatives. The reason is that the required initial compounds, such as 2,4,5-trifluorobenzoic acid and 2-amino-4,5-difluorobenzonitrile are difficultly accessible. Therefore, development of a convenient procedure for the synthesis of 6,7-difluoro-1*H*-quinazolin-4-one from accessible building blocks seems to be an important problem.

2-Methyl- and 2-phenyl-6,7-difluoro-4*H*-3,1-benzoxazin-4-ones **IIa** and **IIb** were synthesized by heating 4,5-difluoroanthranilic acid (**Ia**) with acetic anhydride for 1 h (**IIa**) or by reaction of **Ia** with benzoyl chloride in the presence of triethylamine in anhydrous methylene chloride (**IIb**, Scheme 2). According to the ^{1}H NMR data, the condensation of 3,4,5-trifluoroanthranilic acid (**Ib**) with acetic anhydride in the absence of a base gave a mixture of acid **A** and benzoxazinone **IIc** at a ratio of 27:73. When the reaction was performed by heating compound **Ib** with acetic anhydride in the presence of anhydrous sodium acetate (reaction time 2 h), benzoxazinone **IIc** was formed as the only product. Trifluoroanthranilic acid **Ib** reacted with benzoyl chloride in the presence of triethylamine at room temperature (4 h) to give the corresponding 2-phenylbenzoxazinone **IId**, as in the reaction with 4,5-difluoroanthranilic acid. Like trifluoro derivative **IIc**, 5-fluoro-3,1-benzoxazin-4-one (**IIe**) was synthesized by heating 6-fluoroanthranilic acid (**Ic**) with acetic anhydride in the presence of anhydrous sodium acetate. The reaction in the absence of sodium acetate lead to exclusive formation of 2-acetylamino-6-fluorobenzoic acid **A**. Thus, the condensation with acetic anhydride occurs most readily with 4,5-difluoroanthranilic acid, while the condensation of 3- and 6-fluoro-substituted anthranilic acids requires the presence of a base.

3,4,5-Trifluoroanthranilic acid (**Ib**) was synthesized by nitration of 3,4,5-trifluorobenzoic acid [20] with a mixture of concentrated nitric and sulfuric acids, followed by reduction of the nitro group with hydrogen over Pd/C.

The formation of oxazine ring in compounds **IIa** and **IIb** follows from the absence in their ^{1}H NMR spectra of broadened signals typical of protons in

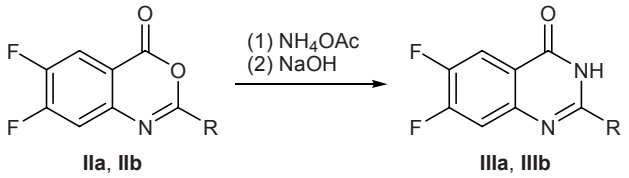
Scheme 2.



Ia–Ic **A** **IIa–IIe**

I, $R^1 = R^4 = H$, $R^2 = R^3 = F$ (**a**); $R^1 = H$, $R^2 = R^3 = R^4 = F$ (**b**); $R^1 = F$, $R^2 = R^3 = R^4 = H$ (**c**); **II**, $R^1 = R^4 = H$, $R^2 = R^3 = F$, $R^5 = Me$ (**a**), Ph (**b**); $R^1 = H$, $R^2 = R^3 = R^4 = F$, $R^5 = Me$ (**c**), Ph (**d**); $R^1 = F$, $R^2 = R^3 = R^4 = H$, $R^5 = Me$ (**e**).

Scheme 3.



IIa, **IIb** **IIIa**, **IIIb**

R = Me (a), Ph (b).

carboxy and amino groups, as well as from the presence of signals from protons in the methyl or phenyl group in position *2*. Signals from the 5-H and 8-H protons in the benzene fragment appear as doublets of doublets at δ 7.5–7.6 and 8.0 ppm, respectively. In the ^{1}H NMR spectra of 6,7,8-trifluoro-3,1-benzoxazin-4-ones **IIc** and **IId**, the 5-H proton resonated as a double doublet of doublets. The IR spectra of **IIa**–**IId** contained an absorption band at 1746–1767 cm^{-1}, which is typical of stretching vibrations of the C^4=O carbonyl group. Benzoxazin-4-ones **IIa** and **IIb** displayed molecular ion peaks in the mass spectra.

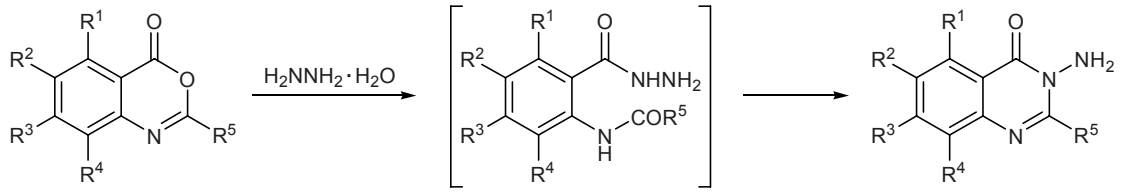
By fusion of benzoxazinones **IIa** and **IIb** with ammonium acetate and subsequent treatment of the reaction mixture with 5% aqueous sodium hydroxide on heating we obtained previously unknown 2-methyl- and 2-phenyl-6,7-difluoroquinazolin-4(3*H*)-ones **IIIa** and **IIIb** (Scheme 3). Their fluorine-free analogs were described in [10]. The structure of **IIIa** and **IIIb** was confirmed by the ^{1}H NMR and mass spectra.

Benzoxazin-4-ones **IIa**–**IIe** were brought into reaction with hydrazine hydrate as nucleophile (Scheme 4). Reactions of benzoxazinones **IIa** and **IIb** with hydrazine hydrate in boiling ethanol (reaction time 3 h) gave 3-amino-6,7-difluoroquinazolin-4(3*H*)-ones **IVa** and **IVb**, respectively. It is known that the transformation of benzoxazinones into quinazolinones involves intermediate *N*-acylanthranilic acid hydrazides **B** which under-go intramolecular cyclization to the corresponding 2,3-disubstituted quinazolin-4-ones **IV** [13]. The 5-H and 6-H protons in 2-methyl derivative **IVa** resonate in the same region of the ^{1}H NMR spectra as do analogous protons in benzoxazinones **IIa** and **IIb**. In the spectrum of 3-amino-6,7-difluoro-2-phenylqunazolin-4(3*H*)-one (**IVb**), the 5-H and 8-H signals are displaced downfield to δ 7.9 and 8.8 ppm, respectively. The amino group in position *3* of **IVb** gives rise to a broadened singlet at δ 12.9 ppm; the corresponding signal of 2-methyl derivative **IVa** is located in a much stronger field, at δ 5.7 ppm.

The reaction of 6,7,8-trifluoro-4*H*-3,1-benzoxazin-4-one (**IIc**) with hydrazine hydrate was accompanied by replacement of one fluorine atom in the benzene ring by hydrazino group, and the product was 3-amino-6,8-difluoro-7-hydrazino-2-methylquinazolin-4(3*H*)-one (**IVc**) whose structure was determined on the basis of its ^{1}H and ^{19}F NMR and mass spectra. The observed multiplicity of the 5-H signal in the ^{1}H NMR spectrum of **IVc** (δ 7.40 ppm, d.d, ^3J = 11.7, ^5J = 1.4 Hz) indicated that fluorine atom in position *7* was replaced. The ^{19}F NMR spectrum of **IVc** contained signals assignable to two fluorine atoms. Compound **IId** reacted with hydrazine hydrate under analogous conditions to give 3-amino-6,7,8-trifluoro-2-phenylquinazolin-4(3*H*)-one (**IVd**) which displayed signals from three fluorine atoms (d.d.d) in the ^{19}F NMR spectrum. In the mass spectra of **IVa**–**IVd** we observed the corresponding molecular ion peak. Stretching vibrations of the carbonyl group in compounds **IVa** and **IVc** gave rise to IR absorption at 1673–1681 cm^{-1}, and bands in the region 3206–3342 cm^{-1} were assigned to stretching vibrations of amino and hydrazino groups. The reaction of 5-fluoro-2-methyl-3,1-benzoxazin-4-one (**IIe**) with hydrazine hydrate in boiling ethanol stopped at the stage of formation of the corresponding hydrazide **B.**

We also examined reactions of benzoxazinones **IIa** and **IIb** with some heteroaromatic amines with a view to obtain quinazolin-4-one derivatives having a pharmacophoric heterocyclic substituent in the 3-position (Scheme 5). The reactions smoothly occurred on fusion of the reactants at 170–180°C over a period of 20–40 min, and the yield of 3-hetaryl-6,7-difluoroquinazolin-4(3*H*)-ones **Va**–**Vf** thus obtained ranged from

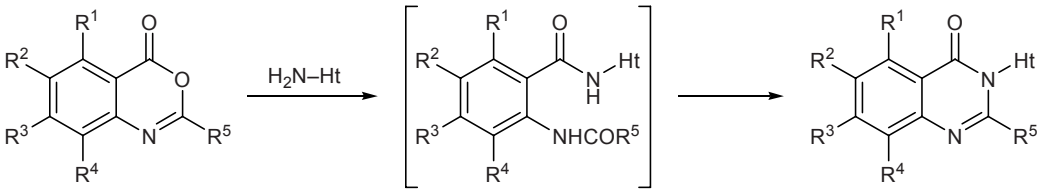
Scheme 4.



IIa–IIe **B** **IVa–IVd**

IV, $R^1 = R^4 = H$, $R^2 = R^3 = F$, R^5 = Me (**a**), Ph (**b**); $R^1 = H$, $R^2 = R^4 = F$, $R^3 = NH_2NH$, R^5 = Me (**c**), $R^3 = F$, R^5 = Ph (**d**).

Scheme 5.



V, $R^1 = R^4 = H$, $R^2 = R^3 = F$: R^5 = Me, Ht = 5-*tert*-butyl-1,2-oxazol-3-yl (**a**), 1,3-thiazol-2-yl (**b**), 1*H*-1,2,4-triazol-5-yl (**c**), 3-methyl-1*H*-pyrazol-5-yl (**d**), pyridin-2-yl (**e**); R^5 = Ph, Ht = 5-*tert*-butyl-1,2-oxazol-3-yl (**f**); R^1 = F, $R^2 = R^3 = R^4 = H$, R^5 = Me, Ht = 5-*tert*-butyl-1,2-oxazol-3-yl (**g**); **VI**, $R^1 = R^4 = H$, $R^2 = R^3 = F$, R^5 = Me, Ht = 4,6-dimethylpyrimidin-2-yl (**a**); R^1 = F, $R^2 = R^3 = R^4 = H$, R^5 = Me, Ht = pyridin-2-yl (**b**).

60 to 80%. The product structure was determined by ^{1}H NMR and mass spectrometry. The mass spectra of **Va**–**Vf** characteristically contained strong molecular ion peaks, as well as a peak with *m*/*z* 153 (**Vb**, **Vc**), belonging to the $[M - R^1 - NCO]^+$ ion. In the IR spectra of quinazolinones **Vb** and **Ve** the carbonyl absorption band appeared at 1678–1687 cm^{-1}.

Quinazolinones **Vb**, **Vd**, and **Ve** can also be synthesized by heating benzoxazinone **IIa** with the corresponding hetarylamines in boiling DMF (1 h), but in this case the yield was lower than under solvent-free conditions. Weaker nucleophiles such as 2-aminopyrimidines failed to react with benzoxazinone **IIa** with formation of desired quinazolin-4-ones. The only product isolated in the reaction of compound **IIa** with 4,6-dimethylpyrimidin-2-amine was anthranilic acid amide **VIa** which did not undergo intramolecular cyclization to the corresponding quinazolinone, presumably due to steric hindrances created by the bulky 4,6-dimethylpyrimidinyl substituent. In the reaction of **IIa** with 2-aminopyrimidine, the former was recovered from the reaction mixture. The structure of **VIa** was confirmed by the ^{1}H NMR and mass spectra.

Fusion of 5-fluoro-2-methylbenzoxazin-4-one (**IIe**) with 5-*tert*-butyl-1,2-oxazol-3-amine (reaction time 1 h) resulted in the formation of a mixture of amide **VIc** (R^1 = F, $R^2 = R^3 = R^4 = H$, R^5 = Me, Ht = 5-*tert*-butyl-1,2-oxazol-3-yl) and quinazolinone **Vg** at a ratio of 1:1 (according to the ^{1}H NMR data). The reaction of 2-aminopyridine with 5-fluorobenzoxazinone **IIe** gave amide **VIb** as the only product. Compound **VIb** failed to undergo cyclization to the corresponding quinazolinone on heating in boiling anhydrous pyridine for 10 h or in DMF for 1 h. We can conclude that the presence of fluorine atom in position *5* of benzoxazinone hampers cyclization of intermediate benzamides to quinazolinones.

Thus we have studied the possibility of using mono-, di-, and trifluoroanthranilic acids in the synthesis of fluorinated 2- and 2,3-substituted quinazolin-4(3*H*)-ones through intermediate 3,1-benzoxazin-4-ones. Di- and trifluorobenzoxazin-4-ones were found to fairly readily undergo transformation into the corresponding quinazolin-4-ones, while reactions of trifluorobenzoxazin-4-ones with nitrogen-centered nucleophiles can be accompanied by replacement of the 7-fluorine atom by nucleophile residue, which makes it possible to introduce pharmacophoric groups into the 7-position of quinazolin-4(3*H*)-one.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6 on Bruker WM-250 and Bruker DRX-400 spectrometers at 250.14 and 400.13 MHz, respectively. The ^{19}F NMR spectra were measured on Bruker Avance 400 and Bruker DRX-500 instruments at 376.43 and 470.51 MHz, respectively. The chemical shifts were determined relative to tetramethylsilane (^{1}H) and $CFCl_3$ (^{19}F; C_6F_6 was used as secondary reference, δ_F –162.9 ppm). The mass spectra were obtained on a Varian MAT 311A mass spectrometer (electron impact, 70 eV; accelerating voltage 3 kV, cathode emission current 300 μA; direct sample admission into the ion source), as well as on a Shimadzu LCMS-2010 instrument (positive and negative ion detection; specified a.m.u. range scan, selected ion monitoring, profile scan; atmospheric pressure chemical ionization). The IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer with Fourier transform equipped with a diffuse reflectance adapter. The purity of the products was checked by TLC.

4,5-Difluoroanthranilic acid (**Ia**) was synthesized from 3,4-difluoroaniline according to the procedure described in [21] for 4-chloro-5-fluoroanthranilic acid

and was identical to commercially available product. 3,4,5-Trifluorobenzoic acid was prepared by hydrodefluorination of pentafluorobenzoic acid [20].

3,4,5-Trifluoroanthranilic acid (Ic). Fuming nitric acid (d = 1.54 g/cm^3), 15 ml, was carefully added under continuous stirring to 15 ml of concentrated sulfuric acid, 5 g (28.4 mmol) of 3,4,5-trifluorobenzoic acid was added in small portions, and the mixture was heated for 1 h on an oil bath at 90°C in a flask equipped with a reflux condenser. The mixture was then cooled to 20°C and poured onto 750 g of ice. When the ice melted, the mixture was extracted with methylene chloride (5×30 ml), the extracts were combined and dried over magnesium sulfate, and the solvent was distilled off to isolate 4.6 g (20.8 mmol, 73%) of 3,4,5-trifluoro-2-nitrobenzoic acid as colorless crystals with mp 185–187°C. ^{1}H NMR spectrum, δ, ppm: 7.84 d.d.d (1H, $^3J_{HF}$ = 9.8, $^4J_{HF}$ = 7.3, $^5J_{HF}$ = 2.0 Hz), 7.36 s (1H, COOH). ^{19}F NMR spectrum, δ_F, ppm: –145.0 d.d.d (1F, 3-F, $^3J_{FF}$ = 19.6, $^4J_{FF}$ = 9.9, $^5J_{HF}$ = 2.0 Hz), –148.2 d.d.d (1F, 4-F, $^3J_{FF}$ = 19.6, 19.8, $^4J_{HF}$ = 7.3 Hz), –127.5 d.d.d (1F, 5-F, $^3J_{FF}$ = 19.8, $^4J_{FF}$ = 9.9, $^3J_{HF}$ = 9.8 Hz). Found, %: C 38.05; H 0.95; N 6.22. $C_7H_2F_3NO_4$. Calculated, %: C 38.03; H 0.91; N 6.34.

A 100-ml round-bottom flask equipped with a magnetic stirrer was charged with 2.6 g (12 mmol) of 3,4,5-trifluoro-2-nitrobenzoic acid, 366 mg of palladium on Sibunit (1.8 wt %) and 25 ml of methanol were added, and the flask was triply evacuated to a residual pressure of 100–150 mm and filled with hydrogen. The flask was then connected to a gasholder filled with hydrogen, and the mixture was stirred until a required amount of hydrogen was absorbed (~810 ml). The catalyst was filtered off and washed with 5 ml of methanol, and the filtrate was evaporated under reduced pressure (water-jet pump) to isolate 1.61 g (8.42 mmol, 70%) of acid **Ic** as colorless crystals which gradually darkened on exposure to air. ^{1}H NMR spectrum, δ, ppm: 7.47 d.d.d (1H, $^3J_{HF}$ = 11.1, $^4J_{HF}$ = 8.6, $^5J_{HF}$ = 2.3 Hz). ^{19}F NMR spectrum, δ_F, ppm: –153.3 d.d.d (1F, 5-F, $^3J_{FF}$ = 21.7, $^3J_{HF}$ = 11.3, $^4J_{FF}$ = 2.3 Hz), –154.8 d.d.d (1F, 4-F, $^3J_{FF}$ = 21.7, 18.1, $^4J_{HF}$ = 8.6 Hz), –156.7 d.d.d (1F, 3-F, $^3J_{FF}$ = 18.1, $^4J_{FF}$ = 2.3, $^5J_{HF}$ = 2.0 Hz). Found, %: C 44.03; H 2.13; N 7.30. $C_7H_4F_3NO_2$. Calculated, %: C 43.99; H 2.11; N 7.33.

6,7-Difluoro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIa). Acetic anhydride, 4 ml, was added to 1 g (5.8 mmol) of 4,5-difluoroanthranilic acid (**Ia**), and the mixture was heated for 1 h under reflux. The mixture was cooled and evaporated, and the residue was washed with water and recrystallized from ethanol. Yield 0.98 g (86%), mp 164–166°C. IR spectrum: ν 1755 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 7.53 d.d (1H, 8-H, ^3J = 10.7, ^4J = 7.0 Hz), 8.00 d.d (1H, 5-H, ^3J = 9.7, ^4J = 8.7 Hz). Mass spectrum, m/z (I_{rel}, %): 197 (100) $[M]^+$, 182 (86) $[M - CH_3]^+$, 155 (75), 153 (64) $[M - CO_2]^+$, 112 (37) $[C_6H_2F_2]^+$. Found, %: C 54.71; H 2.56; N 6.96. $C_9H_5F_2NO_2$. Calculated, %: C 54.83; H 2.56; N 7.10. M 197.15.

6,7-Difluoro-2-phenyl-4*H*-3,1-benzoxazin-4-one (IIb). 4,5-Difluoroanthranilic acid (**Ia**), 0.7 g (4.1 mmol), was dissolved in 8 ml of anhydrous methylene chloride, 1.3 ml (8.2 mmol) of triethylamine and 0.6 ml (4.1 mmol) of benzoyl chloride were added, and the mixture was stirred for 4 h at room temperature using a magnetic stirrer. The precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 0.87 g (82%), mp 132–134°C. IR spectrum: ν 1755 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 7.5–7.7 m (4H, 8-H, Ph), 8.04 d.d (1H, 5-H, ^3J = 9.7, ^4J = 8.7 Hz), 8.20 m (2H, Ph). Mass spectrum, m/z (I_{rel}, %): 259 (44) $[M]^+$, 215 $[M - CO_2]^+$ (26), 105 (100) $[C_6H_5CO]^+$, 77 $[C_6H_5]^+$ (78). Found, %: C 64.70; H 2.75; N 5.44. $C_{14}H_7F_2NO_2$. Calculated, %: C 64.87; H 2.72; N 5.40. M 259.21.

6,7,8-Trifluoro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIc). Anhydrous sodium acetate, 1.4 g (17.1 mmol), was added to a solution of 0.7 g (3.7 mmol) of 3,4,5-trifluoroanthranilic acid (**Ib**) in 5 ml of acetic anhydride, and the mixture was heated for 2 h under reflux and evaporated. The residue was treated with 25 ml of water and extracted with ethyl acetate, the extract was dried over Na_2SO_4, and evaporated, and the residue was recrystallized from ethanol. Yield 0.56 g (71%), mp 125–127°C. IR spectrum: ν 1767 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 7.89 d.d.d (1H, 5-H, ^3J = 9.5, ^4J = 7.9, ^5J = 2.1 Hz). Mass spectrum, m/z (I_{rel}, %): 215 (95) $[M]^+$, 200 (66) $[M - CH_3]^+$, 171 (100) $[M - CO_2]^+$, 130 (63) $[M - CO_2 - CH_3 - CN]^+$. Found, %: C 50.34; H 1.93; N 6.44. $C_9H_4F_3NO_2$. Calculated, %: C 50.25; H 1.87; N 6.51. M 215.31.

6,7,8-Trifluoro-2-phenyl-4*H*-3,1-benzoxazin-4-one (IId) was synthesized as described above for compound **IIb**. Yield 0.81 g (79%), mp 191–193°C. IR spectrum: ν 1746 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 7.5–7.7 m (3H, Ph), 7.94 d.d.d (1H, 5-H, ^3J = 10.0, ^4J = 7.8, ^5J = 2.1 Hz), 8.25 m (2H, Ph). Mass spectrum, m/z (I_{rel}, %): 277 (34) $[M]^+$, 105 (100) $[C_6H_5CO]^+$, 77 (71) $[C_6H_5]^+$. Found, %: C 60.55;

H 2.12; N 5.03. $C_{14}H_6F_3NO_2$. Calculated, %: C 60.66; H 2.18; N 5.05. *M* 277.20.

5-Fluoro-2-methyl-4*H*-3,1-benzoxazin-4-one (IIe) was synthesized as described above for compound **IIc** from 2-amino-6-fluorobenzoic acid (**Ic**). Yield 92%, mp 111–113°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 7.24–7.35 m (2H, 7-H, 8-H), 7.84 d.d.d (1H, 6-H, ^3J = 7.4, 10.7, ^4J = 2.5 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 179 (59) $[M]^+$, 164 (100) $[M - CH_3]^+$, 135 (68) $[M - CO_2]^+$, 94 (33) $[C_6H_3F]^+$. Found, %: C 60.25; H 3.22; N 7.73. $C_9H_6FNO_2$. Calculated, %: C 60.34; H 3.38; N 7.82. *M* 179.15.

6,7-Difluoro-2-methylquinazolin-4(3*H*)-one (IIIa). A mixture of 1.7 g (8.5 mmol) of benzoxazinone **IIa** and 1.3 g (17 mmol) of anhydrous ammonium acetate was fused at 160°C over a period of 15 min, 15 ml of ethanol and 2.5 ml of a 30% solution of sodium hydroxide were added, and the mixture was heated for 15 min under reflux. The mixture was cooled and neutralized to pH 7.0 with dilute acetic acid, and the precipitate was filtered off and recrystallized from DMSO. Yield 1.27 g (76%), mp 232–234°C. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 7.64 d.d (1H, 5-H or 8-H, *J* = 11.6, 7.2 Hz), 7.97 d.d (1H, 8-H or 5-H, *J* = 10.0, 9.2 Hz), 12.4 br.s (1H, NH). Mass spectrum: *m*/*z* 195 (I_{rel} 100%) $[M - H]^+$. Found, %. C 55.11; H 3.09; N 14.23. $C_9H_6N_2F_2O$. Calculated, %: C 55.11; H 3.08; N 14.28. *M* 196.16.

6,7-Difluoro-2-phenylquinazolin-4(3*H*)-one (IIIb) was synthesized in a similar way. Yield 72%, mp 225–227°C. ^{1}H NMR spectrum, δ, ppm: 7.50 m (3H, Ph), 7.57 d.d (1H, 5-H or 8-H, *J* = 11.2, 7.2 Hz), 7.95 d.d. (1H, 8-H or 5-H, *J* = 9.6, 9.2 Hz), 12.7 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 257 $[M - H]^+$ (89), 276 $[M + H_2O]^+$ (100). Found, %: C 65.00; H 3.07; N 10.89. $C_{14}H_8N_2F_2O$. Calculated, %: C 65.12; H 3.12; N 10.85. *M* 258.23.

3-Amino-6,7-difluoro-2-methylquinazolin-4(3*H*)-one (IVa). Benzoxazinone **IIa**, 0.4 g (2 mmol), was dissolved in 10 ml of ethanol, 0.2 ml (4 mmol) of 98% hydrazine hydrate was added, and the mixture was heated for 3 h under reflux. After cooling, the precipitate was filtered off and recrystallized from ethanol. Yield 0.4 g (95%), mp 217–219°C. IR spectrum, ν, cm^{-1}: 3303 (NH_2), 1673 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.49 s (3H, CH_3), 5.72 s (2H, NH_2), 7.45 d.d (1H, 8-H, ^3J = 11.3, ^4J = 7.5 Hz), 7.97 d.d (1H, 5-H, ^3J = 10.2, ^4J = 8.6 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 211 (100) $[M]^+$, 182 (81) $[M - 29]^+$, 153 (38) $[M - CO - N_2H_2]$, 112 (43) $[C_6H_2F_2]^+$. Found, %: C 51.17; H 3.25; N 19.90. $C_9H_7F_2N_3O$. Calculated, %: C 51.19; H 3.34; N 19.90. *M* 211.17.

Compounds **IVb–IVd** were synthesized in a similar way from the corresponding benzoxazinones **II** and hydrazine hydrate.

3-Amino-6,7-difluoro-2-phenylquinazolin-4(3*H*)-one (IVb). Yield 89%, mp 201–203°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 7.57 m (3H, Ph), 7.88 d.d (1H, 5-H, ^3J = 12.0, ^4J = 8.7 Hz), 8.0 m (2H, Ph), 8.76 d.d (1H, 8-H, ^3J = 13.8, ^4J = 7.9 Hz), 12.9 br.s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 273 (6) $[M]^+$, 103 (100) $[C_6H_5CN]^+$, 77 (79) $[C_6H_5]^+$. Found, %: C 57.36; H 3.71; N 14.24. $C_{14}H_9F_2N_3O \cdot H_2O$. Calculated, %: C 57.73; H 3.81; N 14.43. *M* 273.24.

3-Amino-6,8-difluoro-7-hydrazino-2-methylquinazolin-4(3*H*)-one (IVc). Yield 0.81 g (79%), mp 202–204°C. IR spectrum, ν, cm^{-1}: 3342 (NH_2), 3275 (NH_2), 3206 (NH), 1681 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.59 s (3H, CH_3), 4.38 br.s (2H, NH_2), 5.61 br.s (2H, NH_2), 6.70 br.s (1H, NH), 7.41 d.d (1H, 5-H, ^3J = 11.7, ^5J = 1.4 Hz). ^{19}F NMR spectrum, δ_F, ppm: –143.43 m (1F), –126.85 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 241 (100) $[M]^+$, 196 (44) $[M - CH_3 - N_2 - H_2]^+$, 142 (21) $[M - CH_3 - CN - N_2 - H_2 - CO]^+$. Found, %: C 44.70; H 3.62; N 28.60. $C_9H_9F_2N_5O$. Calculated, %: C 44.82; H 3.76; N 29.04. *M* 241.20.

3-Amino-6,7,8-trifluoro-2-phenylquinazolin-4(3*H*)-one (IVd). Yield 0.81 g (79%), mp 180–181°C. ^{1}H NMR spectrum, δ, ppm: 7.40–7.59 m (4H, 5-H, Ph), 7.98 m (2H, Ph), 10.37 br.s (2H, NH_2). ^{19}F NMR spectrum, δ_F, ppm: –157.11 m (1F), –137.34 m (1F), –136.27 m (1F). Mass spectrum, *m*/*z* (I_{rel}, %): 291 (100) $[M]^+$, 290 (90) $[M - H]^+$, 262 (37) $[M - H - N_2]^+$, 130 (28) $[C_6HF_3]^+$, 77 (66) $[C_6H_5]^+$. Found, %: C 58.05; H 2.82; N 14.43. $C_{14}H_8F_3N_3O$. Calculated, %: C 57.74; H 2.77; N 14.43. *M* 291.23.

2-Acetylamino-6-fluorobenzohydrazide (B) was synthesized as described above for compound **IV** from benzoxazinone **IIc** and hydrazine hydrate. Yield 86%, mp 150–152°C. ^{1}H NMR spectrum, δ, ppm: 2.05 s (3H, CH_3), 5.5 br.s (2H, NH_2), 6.68 m (1H, H_{arom}), 7.16 m (1H, H_{arom}), 8.16 m (1H, H_{arom}), 11.5 br.s (1H, NH), 12.1 br.s (1H, NH). Found, %: C 51.05; H 4.62; N 19.83. $C_9H_{10}FN_3O_2$. Calculated, %: C 51.18; H 4.77; N 19.90.

6,7-Difluoro-2-methyl-3-(1,3-thiazol-2-yl)quinazolin-4(3*H*)-one (Vb). *a*. A mixture of 0.5 g (2.6 mmol) of benzoxazinone **IIa** and 0.4 g (3.4 mmol) of 1,3-thiazol-2-amine was heated for 30 min at 170–180°C.

The mixture was cooled, 4 ml of ethanol was added, and the product was recrystallized. Yield 75%, mp 226–228°C. IR spectrum: ν 1687 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 7.58 d.d (1H, 8-H, ^3J = 11.1, ^4J = 7.6 Hz), 7.86 d (1H, thiazole, ^3J = 3.1 Hz), 7.9–8.0 m (2H, 5-H, thiazole). Mass spectrum, *m*/*z* (I_{rel}, %): 279 (100) $[M]^+$, 179 (27), 153 (32) $[M - C_3H_2NS - NCO]^+$, 112 (83) $[C_6H_2F_2]^+$. Found, %: C 51.48; H 2.49; N 14.98. $C_{12}H_7F_2N_3OS$. Calculated, %: C 51.61; H 2.53; N 15.05. *M* 279.27.

Compounds **Va** and **Vc**–**Vf** were synthesized in a similar way from benzoxazinone **IIa** and 5-*tert*-butyl-1,2-oxazol-3-amine, 1*H*-1,2,4-triazol-5-amine, 3-methyl-1*H*-pyrazol-5-amine, and pyridin-2-amine, respectively.

b. A solution of 0.7 g (3.6 mmol) of benzoxazinone **IIa** and 0.56 g (5.5 mmol) of 1,3-thiazol-2-amine in 7 ml of DMF was heated for 1 h under reflux. The mixture was cooled and diluted with 6 ml of water, and the precipitate was filtered off and recrystallized from ethanol. Yield 68%.

Compounds **Vd** and **Ve** were synthesized in a similar way.

3-(5-*tert*-Butyl-1,2-oxazol-3-yl)-6,7-difluoro-2-methylquinazolin-4(3*H*)-one (Va). Reaction time 20 min. Yield 80%, mp 140–142°C (from ethanol). ^1H NMR spectrum, δ, ppm: 1.43 s (9H, *t*-Bu), 2.29 s (3H, CH_3), 6.45 s (1H, 4′-H), 7.56 d.d (1H, 8-H, ^3J = 11.1, ^4J = 7.3 Hz), 7.96 d.d (1H, 5-H, ^3J = 10.2, ^4J = 8.5 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 319 (74) $[M]^+$, 262 (85) $[M - C(CH_3)_3]^+$, 112 (31) $[C_6H_2F_2]^+$, 57 (100) $[C(CH_3)_3]^+$. Found, %: C 59.99; H 4.64; N 13.10. $C_{16}H_{15}F_2N_3O_2$. Calculated, %: C 60.18; H 4.74; N 13.16. *M* 319.31.

6,7-Difluoro-2-methyl-3-(1*H*-1,2,4-triazol-5-yl)-quinazolin-4(3*H*)-one (Vc). Reaction time 40 min. Yield 64% (from ethanol), mp > 300°C (from DMSO). ^1H NMR spectrum, δ, ppm: 2.18 s (3H, CH_3), 7.59 d.d (1H, 8-H, ^3J = 11.0, ^4J = 7.0 Hz), 7.99 m (1H, 5-H), 8.67 s (1H, 3′-H), 14.5 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 263 (100) $[M]^+$, 236 (20) $[M - CN]^+$, 153 (28) $[M - C_2H_2N_3 - NCO]^+$, 112 (53) $[C_6H_2F_2]^+$. Found, %: C 49.82; H 2.68; N 26.64. $C_{11}H_7F_2N_5O$. Calculated, %: C 50.20; H 2.68; N 26.61. *M* 263.21.

6,7-Difluoro-2-methyl-3-(3-methyl-1*H*-pyrazol-5-yl)quinazolin-4(3*H*)-one (Vd). *a*. Reaction time 35 min, yield 78%; *b*. Yield 74%. mp 200–202°C (from ethanol). ^1H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 2.50 s (3H, CH_3), 6.03 s (1H, 4′-H), 7.52 d.d (1H, 5-H, ^3J = 10.3, ^4J = 8.8 Hz), 7.94 d.d (1H, 8-H, ^3J = 11.3, ^4J = 7.6 Hz), 12.8 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 276 (100) $[M]^+$, 261 (34) $[M - CH_3]^+$, 235 (29) $[M - CH_3 - CN]^+$, 112 (54) $[C_6H_2F_2]^+$. Found, %: C 56.61; H 3.57; N 20.10. $C_{13}H_{10}F_2N_4O$. Calculated, %: C 56.52; H 3.65; N 20.28. *M* 276.25.

6,7-Difluoro-2-methyl-3-(pyridin-2-yl)quinazolin-4(3*H*)-one (Ve). *a*. Reaction time 40 min, yield 73%; *b*. Yield 68%. mp 208–210°C (from DMSO). IR spectrum: ν 1678 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 2.14 s (3H, CH_3), 7.55–7.62 m (3H, pyridine), 7.96 m (1H, 8-H), 8.06 d.d (1H, 5-H, ^3J = 9.7, ^4J = 8.5 Hz), 8.66 m (1H, pyridine). Mass spectrum, *m*/*z* (I_{rel}, %): 273 (32) $[M]^+$, 272 (100) $[M - H]^+$, 112 (22) $[C_6H_2F_2]^+$, 78 (62) $[C_4H_4N]^+$. Found, %: C 61.31; H 3.52; N 15.27. $C_{14}H_9F_2N_3O$. Calculated, %: C 61.54; H 3.32; N 15.38. *M* 273.24.

3-(5-*tert*-Butyl-1,2-oxazol-3-yl)-6,7-difluoro-2-phenylquinazolin-4(3*H*)-one (Vf). Reaction time 20 min. Yield 83%, mp 181–183°C (from ethanol). ^1H NMR spectrum, δ, ppm: 1.27 s (9H, *t*-Bu), 6.38 s (1H, 4′-H), 7.29–7.45 m (5H, Ph), 7.72 d.d (1H, 8-H, ^3J = 10.7, ^4J = 7.0 Hz), 8.07 d.d (1H, 5-H, ^3J = 10.3, ^4J = 8.8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 381 (27) $[M]^+$, 324 (43) $[M - C(CH_3)_3]^+$, 296 (100) $[M - C(CH_3)_3 - CO]^+$, 57 (53) $[C(CH_3)_3]^+$. Found, %: C 65.65; H 4.39; N 10.95. $C_{21}H_{17}F_2N_3O_2$. Calculated, %: C 66.14; H 4.49; N 11.02. *M* 381.39.

2-Acetylamino-*N*-(5-*tert*-butyl-1,2-oxazol-3-yl)-6-fluorobenzamide (VIc) and 3-(5-*tert*-butyl-1,2-oxazol-3-yl)-5-fluoro-2-methylquinazolin-4(3*H*)-one (Vg) (1 : 1 mixture) were synthesized as described above (method *a*) from benzoxazinone **IIe** and 5-*tert*-butyl-1,2-oxazol-3-amine (reaction time 1 h).

Compound **Vg**. ^1H NMR spectrum, δ, ppm: 1.37 s (9H, *t*-Bu), 2.28 s (3H, CH_3), 6.67 s (1H, CH), 7.21 m (1H, 6-H), 7.78 m (1H, 8-H).

Compound **VIc**. ^1H NMR spectrum, δ, ppm: 1.32 s (9H, *t*-Bu), 2.06 s (3H, CH_3), 6.45 s (1H, 4′-H), 6.98–7.75 m (3H, H_{arom}), 9.60 br.s (1H, NH_2), 11.30 br.s (1H, NH_2).

2-Acetylamino-*N*-(4,6-dimethylpyrimidin-2-yl)-4,5-difluorobenzamide (VIa). Yield 79%, mp 190–192°C (from DMSO). ^1H NMR spectrum, δ, ppm: 2.21 s (3H, CH_3), 2.30 s (6H, CH_3), 6.30 s (1H, 5′-H), 6.37 br.s (1H, NH), 7.86 d.d (1H, 5-H, ^3J = 11.3, ^4J = 9.5 Hz), 8.56 d.d (1H, 8-H, ^3J = 13.8, ^4J = 7.7 Hz), 11.43 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 155 (83) $[M - HtNH - COCH_3]^+$, 123 (100) $[HtNH]^+$, 112 (21) $[C_6H_2F_2]^+$. Found, %: C 56.30; H 4.48; N 17.42.

$C_{15}H_{14}F_2N_4O_2$. Calculated, %: C 56.25; H 4.41; N 17.49. *M* 320.30.

2-Acetylamino-6-fluoro-*N*-(pyridin-2-yl)benzamide (VIb) was synthesized from benzoxazinone **IIc** and pyridin-2-amine. Yield 81% (*a*), 76% (*b*); mp >250°C.

c. Pyridin-2-amine, 0.3 g (3 mmol), was added to a solution of 0.3 g (1.8 mmol) of compound **IIc** in 6 ml of anhydrous pyridine, the mixture was heated for 10 h under reflux and cooled, and the precipitate was filtered off and recrystallized from DMSO. Yield 0.51 g (91%), mp 210–212°C. ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 7.16 d.d.d (1H, 5′-H, ^3J = 8.0, 5.0, ^4J = 0.5 Hz), 7.29 d.d (1H, 3′-H, ^3J = 8.0, ^4J = 0.5 Hz), 7.81 t.d (1H, 4′-H, ^3J = 8.0, ^4J = 1.5 Hz), 7.87 m (1H, FC_6H_3), 8.08 m (1H, FC_6H_3), 8.41 d.d (1H, 6′-H, ^3J = 5.0, ^4J = 1.5 Hz), 9.08 m (1H, FC_6H_3), 11.5 br.s (1H, NH), 13.7 br.s (1H, NH). Found, %: C 61.45; H 4.32; N 15.43. $C_{14}H_{12}FN_3O_2$. Calculated, %: C 61.53; H 4.43; N 15.38.

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