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Synthesis of fluorine-containing 6,7-dihydrobenzisoxazolones from 2-(fluorobenzoyl)cyclohexane-1,3-diones and their methyl enol ethers

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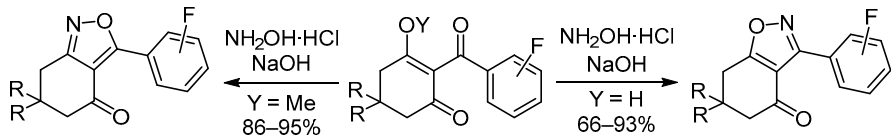


Regioisomeric fluorine-containing 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones and 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones were prepared by reactions of 2-(fluorobenzoyl)cyclohexane-1,3-diones or their methyl enol ethers with hydroxylamine.

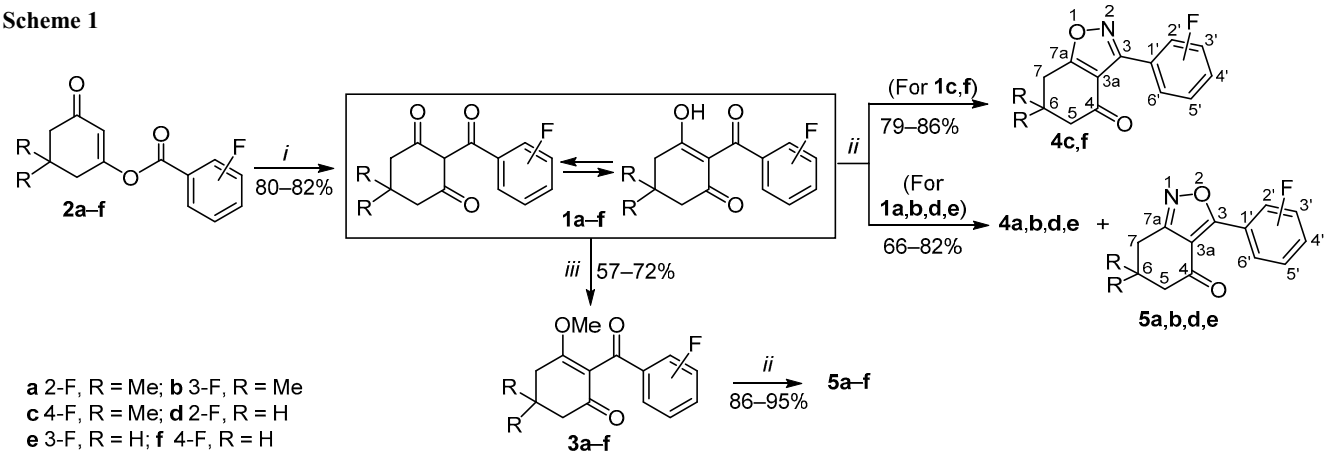
Keywords: 2-(fluorobenzoyl)cyclohexane-1,3-diones, 3-(fluorophenyl)-6,7-dihydrobenzisoxazolones, hydroxylamine hydrochloride, methyl enol ethers, cyclocondensation, nucleophilic vinylogous substitution.

Isoxazole ring and isoxazole-containing fused ring systems are found in a large variety of compounds, serving as the basis for many modern antiviral, antitumor, and anti-inflammatory drugs, and are also currently used as crop protection agents.[1] Selective introduction of fluorine substituents and fluoroalkyl groups in biologically active molecules can substantially affect their physicochemical properties, reactivity, biological activity and provides an effective strategy for the design of new pharmaceutical agents, as well as for enhancing the efficacy of established drugs.[2] The importance of this field is illustrated by the steadily increasing number of fluorinated active pharmaceutical ingredients that have been already approved for market, or currently undergo clinical trials.[3] Fluorine-containing isoxazoles show a broad spectrum of biological activity, including antitumor, anti-inflammatory, and other effects.[4] The active development of advanced synthetic methods provides access to various new fluorine-containing polyfunctional heterocyclic structures as potential drugs and crop protection agents.[5] One of the most promising approaches includes the use of polycarbonyl compounds as building blocks for the preparation of biologically active fluorine-containing organic compounds. The examples of such building blocks include cyclic fluoroacyl-β-diketones.[6] Due to their polyfunctionality, fluorinated 2-benzoylcyclohexane-1,3-diones **1**, similarly to their nonfluorinated analogs employed as powerful herbicides in agriculture,[7] as well as active molecules in medicinal chemistry,[8] can serve as effective building blocks for the construction of heterocyclic structures.

Previously we developed an effective method for the synthesis of 2-(fluorobenzoyl)cyclohexane-1,3-diones **1**,[9] which included O−C isomerization of 3-oxocyclohex-1-en-1-yl fluorobenzoates **2** by the action of acetone cyanohydrin in the presence of triethylamine in chloroform, providing access to such compounds and enabling further investigations of their reactivity. The types of chemical transformations known for fluorine-containing 2-benzoylcyclohexane-1,3-diones **1** include the reactions of these compounds or their enol derivatives with amines[10] and N,N-dinucleophiles.[11]

The aim of this work was to synthesize new 3-(fluorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones and 3-(fluorophenyl)-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones with potential biological activity. The most common methods for the preparation of nonfluorinated as well as fluorinated isoxazoles include the condensation of hydroxylamine with various 1,3-dienophiles (1,3-ketoaldehydes, 1,3-diketones, 1,3-ketonitriles, and other compounds) and 1,3-dipolar addition reactions of nitrile oxides to dipolarophiles – alkenes (followed by spontaneous or oxidative aromatization), alkynes,[4,12] 1,3-diketones[13] and their

Scheme 1



i: $Me_2C(OH)CN$, Et_3N, MeCN, rt, 3 h
ii: $NH_2OH·HCl$, NaOH, MeOH, rt, 20 h (for **1a–f**) or 8 h (for **3a–f**)
iii: CH_2N_2, Et_2O, 0°C, then rt, 3 h

derivatives. The result of the reaction between fluorine-containing 1,3-diketones and hydroxylamine depended on such factors as the nature of substituents and structure of β-diketone and the reaction conditions.[6] The main chemical transformations of cyclic β-triketones existing in enol form could occur at such reactive sites as the *exo*- and *endo*-cyclic carbonyl groups.[14] In order to obtain new regioisomeric fluorophenyl-substituted isoxazolones, we studied the reaction of hydroxylamine hydrochloride with 2-benzoylcyclohexane-1,3-diones **1a**–**f** containing fluorine atoms in the aromatic ring or with their methyl enol ethers **3a**–**f** (Scheme 1).

The treatment of 2-(fluorobenzoyl)cyclohexane-1,3-diones **1a**–**f** with an equimolar mixture of $NH_2OH·HCl$ and NaOH in methanol for 20 h at room temperature led to the formation of 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones **4a**–**f** as the major products. In the case of 2-(4-fluorobenzoyl)-cyclohexane-1,3-diones **1c**,**f**, the reaction was regio-selective, leading to the formation of only 1,2-benz-isoxazolones **4c**,**f** in high yields (89–93%), while the reactions with 2-(2-fluorobenzoyl)- and 2-(3-fluoro-benzoyl)cyclohexane-1,3-diones **1a**,**b**,**d**,**e** led to the formation of 1,2-benzisoxazolones **4a**,**b**,**d**,**e** as the major products, accompanied by 2,1-benzisoxazolones **5a**,**b**,**d**,**e** as the minor products (according to ^1H and ^{19}F NMR data, the following ratios were established – **4a**:**5a** = 17:1, **4b**:**5b** = 100:1, **4d**:**5d** = 3:1, **4e**:**5e** = 13:1). As the distance of the fluorine atom of the aromatic ring from the side chain carbonyl group was increased, the content of the minor 2,1-benz-isoxazolones **5a**,**b**,**d**,**e** was decreased. Compounds **4a**,**b**,**d**,**e** were isolated in 79, 82, 66, and 75% yields, respectively, while isoxazolone **5d** was obtained in 22% yield. The cyclocondensation of 2-(fluorobenzoyl)cyclohexane-1,3-diones **1a**–**f** with hydroxylamine hydrochloride under the indicated conditions proceeded mostly at the most electrophilic exocyclic carbonyl group, i.e., at the carbonyl carbon atom bonded to the fluorophenyl group.

In order to obtain fluorophenyl-substituted 6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones that are structural isomers of isoxazolones **4a**–**f**, it is necessary to alter the direction of nucleophilic attack by hydroxylamine. As known in the case of 2-acetylcyclohexane-1,3-diones,[15] this can be achieved by initially converting these triketones into methyl enol ethers, followed by a reaction of the latter with hydroxylamine. A range of methods have been proposed for the synthesis of methyl enol ethers of 2-acylcyclo-hexane-1,3-diones, including O-alkylation of their silver salts with iodomethane,[16] alkylation of sodium or tetrabutylammonium salts with dimethyl sulfate,[17] as well as treatment with diazomethane.[18] It should be noted, however, that this led to an intractable mixture of products in the case of 2-acetylcyclohexane-1,3-dione.[19] We obtained methyl enol ethers of 2-(fluorobenzoyl)cyclo-hexane-1,3-diones **3a**–**f** by treatment of triketones **1a**–**f** with diazomethane. The reaction was performed by adding an excess of ethereal diazomethane solution at 0°C to a solution of 2-(fluorobenzoyl)cyclohexane-1,3-dione **1a**–**f** in ether over 5 min, followed by stirring of the reaction mixture for 3 h at room temperature. Products **3a**–**f** were obtained in 57–72% yields. The treatment of methyl ethers **3a**–**f** with an equimolar mixture of $NH_2OH·HCl$ and NaOH in methanol for 8 h at room temperature provided 6,7-di-hydro-2,1-benzisoxazol-4(5*H*)-ones **5a**–**f** as the only pro-ducts in 86–95% yields. Under the indicated conditions, as well as in the case of nonfluorinated 2-acetylcyclohexane-1,3-diones,[14] the reaction of methyl enol ethers **5a**–**f** with hydroxylamine proceeded according to vinylogous substitution mechanism with subsequent intramolecular cyclization.

The structures of the synthesized compounds **1–5 a**–**f** were confirmed by using the data of elemental analysis, IR spectroscopy, as well as ^1H, ^{13}C, and ^{19}F NMR spectroscopy. IR spectra of methyl ethers **3a**–**f** contained characteristic absorption bands of two conjugated carbonyl groups (in the ranges of 1650–1680 and 1630–1640 cm^{-1}) and the carbon–carbon double bond (in the range of 1595–1610 cm^{-1}). ^1H NMR spectra ($CDCl_3$) featured a singlet in the range of 3.73–3.75 ppm, corresponding to the methoxy group protons. ^{13}C NMR spectra of compounds **4a**–**f** showed the signal of carbonyl carbon atom (C-4) and the signals of

C–O (C-7a) and C=N (C-3) carbon atoms at 190.9–192.3, 180.8–182.5, and 155.2–159.2 ppm, respectively, while the signals of C-4 (C=O), C-3 (C–O), and C-7a (C=N) carbon atoms in ^{13}C NMR spectra of isomeric isoxazolones **5a**–**f** were observed at 191.6–192.7, 166.2–169.8, and 163.8–165.1 ppm, respectively. The presence of fluorine atoms bonded to the aromatic ring in structures of compounds **3**–**5 a**–**f** was confirmed by the observation of a doublet signal in ^{13}C NMR spectra in the range of 160.0–165.0 ppm ($^1J_{CF}$ = 246–258 Hz) due to the carbon atom bearing a fluorine substituent, as well as the presence of fluorine signals in the range from –105.3 to –113.1 ppm in ^{19}F NMR spectra.

Additional spectral studies were performed in order to prove the structures of the synthesized isomeric benzisoxazolones **4**–**5 a**–**f**. The pair of regioisomers **4c** and **5c** was selected for spectral analysis using two-dimensional NMR experiments. The quaternary carbon signals and nitrogen signals in the benzisoxazole moiety were assigned based on HMBC data. The signal of C-7a carbon atom was identified by the presence of a cross peak with the proton bonded to the C-7 carbon atom, while the signal of C-3 carbon atom was recognized from its coupling to the *ortho* proton of aromatic ring. In the case of compound **4c**, the signal of C-7a nucleus was observed at lower field (182.0 ppm) than for its isomer **5c** (164.6 ppm). The opposite situation was observed for the nucleus of C-3 carbon atom: the signal of benzisoxazole **5c** was observed at lower field (169.5 ppm), while the analogous signal of compound **4c** – at stronger field (159.0 ppm). This trend was also evident for isomeric isoxazoles reported in the literature[20] and corresponded to the electron density distribution in the molecule. The assignment of signals was additionally confirmed by the results of two-dimensional ^{1}H–^{15}N HMBC experiments. In the case of compound **5c**, HMBC spectrum showed a strong cross peak (^3J) between the proton at C-7 carbon atom and the nitrogen nucleus. This cross peak was also observed for isomer **4c**, but it was significantly weaker (^4J). At the same time, no coupling between the nitrogen nucleus and the *ortho* proton of substituent at the C-3 carbon atom (^4J) was evident in the spectrum of compound **4c**.

Thus, 2-benzoylcyclohexane-1,3-diones containing fluorine atoms in the aromatic ring participated in cyclocondensation reactions with hydroxylamine preferentially at the most electrophilic exocyclic carbonyl group, forming 3-(fluorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones as the major products, while their methyl enol ethers reacted with hydroxylamine *via* vinylogous substitution mechanism followed by intramolecular cyclization, forming 3-fluorophenyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones as the only products.

Experimental

IR spectra were recorded on a PerkinElmer Spectrum 100 FTIR spectrometer in KBr pellets. ^{1}H, ^{19}F, ^{13}C, and ^{15}N NMR spectra were acquired on a Bruker Avance 500 instrument (500, 470, 125, and 50 MHz, respectively) by using a 5 mm probe (QNP) with Z-gradient at 293 K sample temperature in $CDCl_3$. Residual sovent signals were used as internal standards for ^{1}H and ^{13}C NMR spectra (7.26 ppm for ^{1}H nuclei and 77.16 ppm for ^{13}C nuclei). External standards were used for ^{19}F NMR (α,α,α-trifluorotoluene signal at –63 ppm) and ^{15}N NMR spectra ($MeNO_2$ signal at 380 ppm). The two-dimensional NMR spectra (^{1}H–^{13}C HSQC, COSY, ^{1}H–^{13}C HMBC, ^{1}H–^{15}N HMBC) were acquired and processed by using the standard software supplied by Bruker. Melting points were determined on a Boetius hot stage. Elemental analysis was performed on a EuroVector EA3000 CHNS-O analyzer. The reaction progress and purity of the obtained compounds were controlled by a TLC method on Silufol UV–254 plates, with EtOAc–hexane as eluent. Column chromatography was performed on silica gel (70–230 mesh).

2-(Fluorobenzoyl)cyclohexane-1,3-diones 1a–**f** were obtained as colorless crystals by O−C isomerization of (3-oxocyclohex-1-en-1-yl) fluorobenzoates **2a**–**f** by the action of acetone cyanohydrin in the presence of triethylamine in acetonitrile according to a published procedure.[9] The physicochemical characteristics of 2-(2-fluorobenzoyl)-5,5-dimethylcyclohexane-1,3-dione (**1a**), 2-(3-fluorobenzoyl)-5,5-dimethylcyclohexane-1,3-dione (**1b**), and 2-(4-fluorobenzoyl)-5,5-dimethylcyclohexane-1,3-dione (**1c**) were in agreement with the data reported in literature.[9] A compound, described in the work,[21] was assigned the structure of β-triketone **1e**. However the spectral data presented in that study did not confirm the claimed structure. ^{1}H NMR spectrum of the described compound lacked the signal of enol proton in the downfield region at 16–17 ppm, which would be characteristic for 2-benzoylcyclohexane-1,3-diones that exist in solutions as enol tautomers with a strong intramolecular bond.[9,22] At the same time, a signal was present at 6 ppm, which corresponded to the vinyl proton signal in compound **2e**. ^{13}C NMR spectrum contained signals of the carbonyl carbon atoms at 199.3 and 169.8 ppm, which also matched the signals in ^{13}C NMR spectrum of compound **2e**. Compounds **1d**,[23] **1f**[24] have been described in patents without characterization of their physicochemical properties.

2-(2-Fluorobenzoyl)cyclohexane-1,3-dione (1d). Yield 2.53 g (80%), mp 46–49°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1685 (C=O conjug.), 1610 (C=O chelate), 1550 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.06 (2H, quin, *J* = 6.4, CH_2); 2.49 (2H, t, *J* = 6.4, CH_2); 2.76 (2H, t, *J* = 6.4, CH_2); 7.03–7.06 (1H, m, H Ar); 7.20–7.24 (1H, m, H Ar); 7.41–7.48 (2H, m, H Ar); 16.89 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 19.2; 32.3; 37.8; 114.8; 115.4 (d, J_{CF} = 22); 124.2; 127.6 (d, J_{CF} = 15); 128.9 (d, J_{CF} = 1); 132.8 (d, J_{CF} = 8), 159.3 (d, J_{CF} = 251); 194.1; 194.2; 195.7. ^{19}F NMR spectrum, δ, ppm: –112.74 (m, F). Found, %: C 66.61; H 4.70. $C_{13}H_{11}FO_3$. Calculated, %: C 66.66; H 4.73.

2-(3-Fluorobenzoyl)cyclohexane-1,3-dione (1e). Yield 2.59 g (82%), mp 52–55°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1655 (C=O conjug.), 1610 (C=O chelate), 1570 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (2H, quin, *J* = 6.2, CH_2); 2.50 (2H, t, *J* = 6.2, CH_2); 2.76 (2H, t, *J* = 6.2, CH_2); 7.17–7.21 (2H, m, H Ar); 7.26–7.28 (1H, m,

H Ar); 7.34–7.39 (1H, m, H Ar); 16.71 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 19.1; 32.3; 38.0; 113.2; 115.2 (d, J_{CF} = 23); 118.7 (d, J_{CF} = 21); 123.9 (d, J_{CF} = 2); 129.4 (d, J_{CF} = 8); 140.4 (d, J_{CF} = 7); 162.0 (d, J_{CF} = 247); 194.1; 196.2; 197.9. ^{19}F NMR spectrum, δ, ppm: –113.28 (m, F). Found, %: C 66.59; H 4.68. $C_{13}H_{11}FO_3$. Calculated, %: C 66.66; H 4.73.

2-(4-Fluorobenzoyl)cyclohexane-1,3-dione (1f). Yield 2.53 g (80%), mp 164–167°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1665 (C=O conjug.), 1595 (C=O chelate), 1565 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (2H, quin, *J* = 6.4, CH_2); 2.50 (2H, t, *J* = 6.4, CH_2); 2.74 (2H, t, *J* = 6.4, CH_2); 7.05–7.08 (2H, m, H Ar); 7.55–7.58 (2H, m, H Ar); 16.87 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 19.1; 32.4; 38.1; 113.1; 114.9 (d, J_{CF} = 22); 131.2 (d, J_{CF} = 9); 134.2 (d, J_{CF} = 22); 165.1 (d, J_{CF} = 253); 194.3; 196.2; 197.6. ^{19}F NMR spectrum, δ, ppm: –106.81 (m, F). Found, %: C 66.72; H 4.76. $C_{13}H_{11}FO_3$. Calculated, %: C 66.66; H 4.73.

3-Oxocyclohex-1-en-1-yl fluorobenzoates 2a–f were obtained as colorless crystalline products by *O*-acylation of dimedone or dihydroresorcinol with fluorobenzoyl chlorides in the presence of pyridine in chloroform according to a published procedure.[25] The physicochemical characteristics of 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 2-fluorobenzoate (**2a**),[9] 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 3-fluorobenzoate (**2b**),[9] 5,5-dimethyl-3-oxocyclohex-1-en-1-yl 4-fluorobenzoate (**2c**),[9] and 3-oxocyclohex-1-en-1-yl 2-fluorobenzoate (**2d**)[26] matched those reported in the literature.

3-Oxocyclohex-1-en-1-yl 3-fluorobenzoate (2e). Yield 4.31 g (92%), mp 40–43°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1735 (C=O ester), 1670 (C=O conjug.), 1590 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (2H, quin, *J* = 6.5, CH_2); 2.48 (2H, t, *J* = 6.5, CH_2); 2.69 (2H, td, *J* = 1.0, *J* = 6.5, CH_2); 6.06 (1H, br. s, H vinyl); 7.33–7.37 (1H, m, H Ar); 7.47–7.52 (1H, m, H Ar); 7.75–7.78 (1H, m, H Ar); 7.88–7.90 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.3; 28.4; 36.8; 117.1 (d, J_{CF} = 23); 118.0; 121.3 (d, J_{CF} = 21); 126.0 (d, J_{CF} = 2); 130.5 (d, J_{CF} = 8); 130.8 (d, J_{CF} = 8); 162.1 (d, J_{CF} = 2); 162.6 (d, J_{CF} = 248); 169.8; 199.4. ^{19}F NMR spectrum, δ, ppm: –111.70 (m, F). Found, %: C 66.60; H 4.68. $C_{13}H_{11}FO_3$. Calculated, %: C 66.66; H 4.73.

3-Oxocyclohex-1-en-1-yl 4-fluorobenzoate (2f). Yield 3.94 g (84%), mp 44–47°C (Et_2O–hexane). IR spectrum, ν, cm^{-1}: 1730 (C=O ester), 1670 (C=O conjug.), 1600 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): (2H, quin, *J* = 6.5, CH_2); 2.48 (2H, t, *J* = 6.5, CH_2); 2.70 (2H, t, *J* = 6.5, CH_2); 6.06 (1H, br. s, H vinyl); 7.16–7.21 (2H, m, H Ar), 8.10–8.14 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.6; 28.4; 36.8; 116.0 (d, J_{CF} = 22); 117.9; 124.9 (d, J_{CF} = 2); 136.0 (d, J_{CF} = 10); 162.2; 166.4 (d, J_{CF} = 256); 170.0; 199.4. ^{19}F NMR spectrum, δ, ppm: –103.46 (m, F). Found, %: C 66.74; H 4.78. $C_{13}H_{11}FO_3$. Calculated, %: C 66.66; H 4.73.

Preparation of 2-(fluorobenzoyl)-3-methoxycyclohex-2-en-1-ones 3a–f (General method). An ethereal diazomethane solution (concentration 0.48 mmol/ml) (3.6 ml, 1.7 mmol) was added over 5 min to a solution of triketone **1a–f** (1.15 mmol) in diethyl ether (30 ml) with stirring and cooling to 0°C. The reaction mixture was stirred for 3 h at room temperature, the solvent was removed by evaporation at reduced pressure, and the obtained residue was separated by silica gel column chromatography (eluent EtOAc–hexane, gradient from 1:10 to 1:3), providing methyl esters **3a–f** as colorless crystals. The products were recrystallized from an Et_2O–hexane mixture.

2-(2-Fluorobenzoyl)-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (3a). Yield 0.22 g (57%), mp 84–87°C. IR spectrum, ν, cm^{-1}: 1650 (C=O), 1640 (C=O), 1605 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.18 (6H, s, $2CH_3$); 2.31 (2H, s, CH_2); 2.52 (2H, s, CH_2); 3.75 (3H, s, OCH_3); 7.01–7.05 (1H, m, H Ar); 7.19–7.23 (1H, m, H Ar); 7.45–7.50 (1H, m, H Ar); 7.87–7.90 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.5; 31.9; 40.0; 50.4; 57.0; 116.4 (d, J_{CF} = 23); 121.1; 124.3 (d, J_{CF} = 3); 126.8 (d, J_{CF} = 10); 130.9; 134.5 (d, J_{CF} = 9); 161.7 (d, J_{CF} = 256); 173.6; 190.8; 196.3. ^{19}F NMR spectrum, δ, ppm: –113.06 (m, F). Found, %: C 69.50; H 6.17. $C_{16}H_{17}FO_3$. Calculated, %: C 69.55; H 6.20.

2-(3-Fluorobenzoyl)-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (3b). Yield 0.23 g (59%), mp 114–117°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 1630 (C=O), 1605 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.22 (6H, s, $2CH_3$); 2.35 (2H, s, CH_2); 2.55 (2H, s, CH_2); 3.73 (3H, s, OCH_3); 7.21–7.25 (1H, m, H Ar); 7.38–7.42 (1H, m, H Ar), 7.52–7.55 (1H, m, H Ar); 7.60–7.62 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.7; 32.2; 39.9; 50.3; 56.8; 115.6 (d, J_{CF} = 22); 118.3; 120.2 (d, J_{CF} =22), 124.9 (d, J_{CF} = 2); 130.2 (d, J_{CF} = 8); 139.8 (d, J_{CF} = 6); 162.8 (d, J_{CF} = 247); 173.7; 194.0; 196.3. ^{19}F NMR spectrum, δ, ppm: –112.7 (m, F). Found, %: C 69.61; H 6.24. $C_{16}H_{17}FO_3$. Calculated, %: C 69.55; H 6.20.

2-(4-Fluorobenzoyl)-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (3c). Yield 0.24 g (60%), mp 115–118°C. IR spectrum, ν, cm^{-1}: 1675 (C=O), 1640 (C=O), 1600 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.22 (6H, s, $2CH_3$); 2.35 (2H, s, CH_2); 2.54 (2H, s, CH_2); 3.73 (3H, s, OCH_3); 7.09–7.12 (2H, m, H Ar); 7.86–7.90 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.7; 32.2; 39.8; 50.3; 56.7; 115.7 (d, J_{CF} = 22); 118.5; 131.8 (d, J_{CF} = 9); 134.1 (d, J_{CF} = 2); 165.9 (d, J_{CF} = 255); 173.5; 193.6; 196.4. ^{19}F NMR spectrum, δ, ppm: –105.3 (m, F). Found, %: C 69.62; H 6.25. $C_{16}H_{17}FO_3$. Calculated, %: C 69.55; H 6.20.

2-(2-Fluorobenzoyl)-3-methoxycyclohex-2-en-1-one (3d). Yield 0.22 g (63%), mp 122–124°C. IR spectrum, ν, cm^{-1}: 1665 (C=O), 1640 (C=O), 1610 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (2H, quin, *J* = 6.0, CH_2); 2.42 (2H, t, *J* = 6.7, CH_2); 2.66 (2H, t, *J* = 6.2, CH_2); 3.75 (3H, s, OCH_3); 7.00–7.04 (1H, m, H Ar); 7.19–7.22 (1H, m, H Ar); 7.45–7.49 (1H, m, H Ar); 7.87–7.91 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 20.4; 26.1; 36.5; 56.9; 116.6 (d, J_{CF} = 23); 122.5; 124.4 (d, J_{CF} = 3); 126.6 (d, J_{CF} = 9); 131.1; 134.7 (d, J_{CF} = 9); 162.0 (d, J_{CF} = 256); 174.8; 191.0; 196.5. ^{19}F NMR spectrum, δ, ppm: –112.6 (m, F). Found, %: C 67.80; H 5.31. $C_{14}H_{13}FO_3$. Calculated, %: C 67.73; H 5.28.

2-(3-Fluorobenzoyl)-3-methoxycyclohex-2-en-1-one (3e). Yield 0.25 g (72%), mp 156–159°C. IR spectrum, ν, cm^{-1}: 1675 (C=O), 1640 (C=O), 1610 (C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.11–2.17 (2H, m, CH_2); 2.45 (2H, t, *J* = 6.6, CH_2); 2.69 (2H, t, *J* = 6.2, CH_2); 3.73 (3H, s, OCH_3); 7.20–7.24 (1H, m, H Ar); 7.37–7.41 (1H, m, H Ar); 7.52–7.54 (1H, m, H Ar); 7.61–7.63 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 20.6; 25.8; 36.4; 56.7; 115.7 (d, J_{CF} = 22); 119.6; 120.3 (d, J_{CF} = 22); 125.0 (d, J_{CF} = 2); 130.3 (d, J_{CF} = 8); 139.6 (d, J_{CF} = 6); 163.0 (d, J_{CF} = 247); 175.5; 194.1; 196.5. ^{19}F NMR spectrum, δ, ppm: –112.5 (m, F). Found, %: C 67.68; H 5.24. $C_{14}H_{13}FO_3$. Calculated, %: C 67.73; H 5.28.

2-(4-Fluorobenzoyl)-3-methoxycyclohex-2-en-1-one (3f). Yield 0.25 g (72%), mp 102–104°C. IR spectrum, ν, cm^{-1}: 1675 (C=O), 1635 (C=O), 1595 (C=C). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.13 (2H, quin, *J* = 6.0, CH_2); 2.45 (2H, t, *J* = 6.7, CH_2); 2.69 (2H, t, *J* = 6.2, CH_2); 3.73 (3H, s, OCH_3); 7.06–7.10 (2H, m, H Ar); 7.85–7.89 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 20.6; 25.8; 36.5; 56.6; 115.7 (d, J_{CF} = 22); 119.7; 131.9 (d, J_{CF} = 9); 134.0 (d, J_{CF} = 2); 166.0 (d, J_{CF} = 255); 175.2; 193.8; 196.5. ^{19}F NMR spectrum, δ, ppm: –112.5 (m, F). Found, %: C 67.65; H 5.23. $C_{14}H_{13}FO_3$. Calculated, %: C 67.73; H 5.28.

Preparation of 3-(fluorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones 4a–f and 3-(fluorophenyl)-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-ones 5a–f (General method). $NH_2OH·HCl$ (1.0 mmol) and NaOH (1.0 mmol) were added to a solution of the appropriate triketone **1a**–**f** or methyl ether **3a**–**f** (1.0 mmol) in MeOH (5 ml) with stirring. The reaction mixture was stirred at room temperature for 20 h (reactions with triketones) or 8 h (reactions with methyl ethers). The solvent was removed by evaporation at reduced pressure, and the residue was dissolved in $CHCl_3$ (50 ml), washed with saturated $NaHCO_3$ solution (2×15 ml), water (15 ml), and dried over anhydrous Na_2SO_4. The solvent was removed by evaporation at reduced pressure and the obtained residue was separated by silica gel column chromatography (eluent EtOAc–hexane, gradient from 1:10 to 1:3), providing isoxazolones **4a**–**f** or **5a**–**f** as colorless crystals. The products were recrystallized from Et_2O–hexane mixture. Compounds **4d**,**f** have been mentioned in patents without a description of their physicochemical properties.[26,27]

3-(2-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4a). Yield 0.21 g (79%), mp 87–91°C. IR spectrum, ν, cm^{-1}: 1695, 1620, 1600, 1525, 1480. ^1H NMR spectrum, δ, ppm: 1.19 (6H, s, $2CH_3$); 2.46 (2H, s, CH_2); 2.94 (2H, s, CH_2); 7.17–7.27 (2H, m, H Ar); 7.46–7.50 (1H, m, H Ar); 7.61–7.65 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.3; 35.4; 36.9; 52.7; 114.1; 115.8 (d, J_{CF} = 14); 116.0 (d, J_{CF} = 21); 124.0 (d, J_{CF} = 3); 131.2; 132.2 (d, J_{CF} = 8); 155.2 (C-3); 160.4 (d, J_{CF} = 253, C-2'); 180.8 (C-7a); 190.9 (C-4). ^{19}F NMR spectrum, δ, ppm: –112.38 (m, F). Found, %: C 69.56; H 5.48; N 5.46. $C_{15}H_{14}FNO_2$. Calculated, %: C 69.49; H 5.44; N 5.40.

3-(3-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4b). Yield 0.21 g (82%), mp 77–80°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 1625, 1590, 1515, 1480. ^1H NMR spectrum, δ, ppm: 1.20 (6H, s, $2CH_3$); 2.50 (2H, s, CH_2); 2.93 (2H, s, CH_2); 7.16–7.20 (1H, m, H Ar); 7.41–7.46 (1H, m, H Ar); 7.88–7.94 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.2; 35.1; 37.0; 53.2; 113.1; 116.2 (d, J_{CF} = 24); 117.5 (d, J_{CF} = 21); 124.9 (d, J_{CF} = 2); 129.4 (d, J_{CF} = 9); 130.0 (d, J_{CF} = 8); 158.8 (d, J_{CF} = 1, C-3); 162.6 (d, J_{CF} = 246, C-3'); 182.0 (C-7a); 191.5 (C-4). ^{19}F NMR spectrum, δ, ppm: –112.70 (m, F). Found, %: C 69.57; H 5.49; N 5.48. $C_{15}H_{14}FNO_2$. Calculated, %: C 69.49; H 5.44; N 5.40.

3-(4-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4c). Yield 0.22 g (86%), mp 70–73°C. IR spectrum, ν, cm^{-1}: 1680, 1610, 1585, 1530, 1460. ^1H NMR spectrum, δ, ppm: 1.20 (6H, s, $2CH_3$); 2.49 (2H, s, 5-CH_2); 2.92 (2H, s, 7-CH_2); 7.13–7.17 (2H, m, H-3',5'); 8.13–8.16 (2H, m, H-2',6'). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.4 ($2CH_3$); 35.2 (C-6); 37.2 (C-7); 53.3 (C-5); 113.1 (C-3a); 115.7 (d, J_{CF} = 22, C-3',5'); 123.7 (d, J_{CF} = 3, C-1'); 131.5 (d, J_{CF} = 9, C-2',6'); 159.0 (C-3); 164.3 (d, J_{CF} = 251, C-4'); 182.0 (C-7a); 191.8 (C-4). ^{19}F NMR spectrum, δ, ppm: –109.90 (m, F). ^{15}N NMR spectrum, δ, ppm: 378. Found, %: C 69.41; H 5.40; N 5.35. $C_{15}H_{14}FNO_2$. Calculated, %: C 69.49; H 5.44; N 5.40.

3-(2-Fluorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4d). Yield 0.15 g (66%), mp 82–84°C. IR spectrum, ν, cm^{-1}: 1700, 1620, 1600, 1580, 1510, 1470. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (2H, quin, *J* = 6.5, CH_2); 2.54 (2H, t, *J* = 6.5, CH_2); 3.06 (2H, t, *J* = 6.4, CH_2); 7.16–7.26 (2H, m, H Ar); 7.44–7.49 (1H, m, H Ar); 7.56–7.60 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 22.2; 23.3; 38.3; 115.1; 116.1 (d, J_{CF} = 21); 121.4 (d, J_{CF} = 5); 124.1 (d, J_{CF} = 3); 131.2; 132.2 (d, J_{CF} = 8); 155.4 (C-3); 160.5 (d, J_{CF} = 253, C-2'); 181.4 (C-7a); 191.6 (C-4). ^{19}F NMR spectrum, δ, ppm: –106.70 (m, F). Found, %: C 67.60; H 4.42; N 6.14. $C_{13}H_{10}FNO_2$. Calculated, %: C 67.53; H 4.36; N 6.06.

3-(3-Fluorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4e). Yield 0.17 g (75%), mp 48–50°C. IR spectrum, ν, cm^{-1}: 1685, 1640, 1615, 1590, 1575, 1470. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (2H, quin, *J* = 6.5, CH_2); 2.61 (2H, t, *J* = 6.5, CH_2); 3.07 (2H, t, *J* = 6.4, CH_2); 7.15–7.19 (1H, m, H Ar); 7.41–7.45 (1H, m, H Ar); 7.83–7.86 (1H, m, H Ar); 7.87–7.89 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 22.1; 23.6; 38.8; 114.2; 116.4 (d, J_{CF} = 24); 117.6 (d, J_{CF} = 24); 125.1 (d, J_{CF} = 3); 129.5 (d, J_{CF} = 8); 130.1 (d, J_{CF} = 8); 159.1 (C-3); 162.7 (d, J_{CF} = 246, C-3'); 182.5 (C-7a); 192.1 (C-4). ^{19}F NMR spectrum, δ, ppm: –112.50 (m, F). Found, %: C 67.59; H 4.40; N 6.11. $C_{13}H_{10}FNO_2$. Calculated, %: C 67.53; H 4.36; N 6.06.

3-(4-Fluorophenyl)-6,7-dihydro-1,2-benzisoxazol-4(5*H*)-one (4f). Yield 0.18 g (79%), mp 59–61°C. IR spectrum, ν, cm^{-1}: 1680, 1640, 1610, 1580, 1520, 1465. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (2H, quin, *J* = 6.4, CH_2); 2.60 (2H, t, *J* = 6.5, CH_2); 3.06 (2H, t, *J* = 6.3, CH_2); 7.12–7.16 (2H, m, H Ar); 8.08–8.10 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 22.1; 23.6; 38.9; 114.1; 115.6 (d, J_{CF} = 22); 123.6 (d, J_{CF} = 2); 131.5 (d, J_{CF} = 8); 159.2

(C-3); 164.3 (d, J_{CF} = 251, C-4'); 182.4 (C-7a); 192.3 (C-4). ^{19}F NMR spectrum, δ, ppm: –109.70 (m, F). Found, %: C 67.48; H 4.31; N 6.05. $C_{13}H_{10}FNO_2$. Calculated, %: C 67.53; H 4.36; N 6.06.

3-(2-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (5a). Yield 0.23 g (88%, from compound **3a**), mp 66–69°C. IR spectrum, ν, cm^{-1}: 1690, 1625, 1600, 1570, 1510, 1490, 1475, 1465. ^{1}H NMR spectrum, δ, ppm: 1.15 (6H, s, 2CH$_3$); 2.47 (2H, s, CH$_2$); 2.85 (2H, s, CH$_2$); 7.20–7.24 (1H, m, H Ar); 7.27–7.31 (1H, m, H Ar); 7.52–7.56 (1H, m, H Ar); 7.97–8.00 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.1; 34.6; 35.0; 53.6; 113.1; 115.0 (d, J_{CF} = 12); 116.5 (d, J_{CF} = 21); 124.1 (d, J_{CF} = 3); 131.1; 133.7 (d, J_{CF} = 9); 160.0 (d, J_{CF} = 258, C-2'); 163.8 (C-7a); 166.2 (C-3); 191.6 (C-4). ^{19}F NMR spectrum, δ, ppm: –112.18 (m, F). Found, %: C 69.42; H 5.38; N 5.34. $C_{15}H_{14}FNO_2$. Calculated, %: C 69.49; H 5.44; N 5.40.

3-(3-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (5b). Yield 0.22 g (86%, from compound **3b**), mp 77–80°C. IR spectrum, ν, cm^{-1}: 1690, 1610, 1590, 1570, 1475, 1450. ^{1}H NMR spectrum, δ, ppm: 1.15 (6H, s, 2CH$_3$); 2.51 (2H, s, CH$_2$); 2.84 (2H, s, CH$_2$); 7.23–7.27 (1H, m, H Ar); 7.48–7.52 (1H, m, H Ar); 8.26–8.29 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.1; 34.2; 35.1; 53.9; 111.9; 115.6 (d, J_{CF} = 25); 119.3 (d, J_{CF} = 21); 124.3 (d, J_{CF} = 2); 128.1 (d, J_{CF} = 9); 130.4 (d, J_{CF} = 8); 162.6 (d, J_{CF} = 247, C-3'); 164.5 (C-7a); 169.0 (C-3); 192.1 (C-4). ^{19}F NMR spectrum, δ, ppm: –112.28 (m, F). Found, %: C 69.42; H 5.40; N 5.35. $C_{15}H_{14}FNO_2$. Calculated, %: C 69.49; H 5.44; N 5.40.

3-(4-Fluorophenyl)-6,6-dimethyl-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (5c). Yield 0.25 g (95%, from compound **3c**), mp 93–96°C. IR spectrum, ν, cm^{-1}: 1690, 1600, 1565, 1520, 1490, 1430. ^{1}H NMR spectrum, δ, ppm: 1.15 (6H, s, 2CH$_3$); 2.50 (2H, s, 5-CH$_2$); 2.83 (2H, s, 7-CH$_2$); 7.18–7.32 (2H, m, H-3',5'); 8.50–8.55 (2H, m, H-2',6'). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.2 (2CH$_3$); 34.3 (C-6); 35.3 (C-7); 54.0 (C-5); 111.3 (C-3a); 116.1 (d, J_{CF} = 22, C-3',5'); 122.8 (d, J_{CF} = 2, C-1'); 131.3 (d, J_{CF} = 9, C-2',6'); 164.6 (C-7a); 165.2 (d, J_{CF} = 255, C-4'); 169.5 (C-3); 192.3 (C-4). ^{19}F NMR spectrum, δ, ppm: –105.50 (m, F). ^{15}N NMR spectrum, δ, ppm: 366. Found, %: C 69.58; H 5.47; N 5.45. $C_{15}H_{14}FNO_2$. Calculated, %: C 69.49; H 5.44; N 5.40.

3-(2-Fluorophenyl)-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (5d). Yield 0.21 g (91%, from compound **3d**), 0.05 g (22%, from compound **1d**), mp 53–54°C (yellow oil[28]). IR spectrum, ν, cm^{-1}: 1690, 1620, 1590, 1580, 1570, 1475, 1455. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.18 (2H, quin, *J* = 6.5, CH$_2$); 2.59 (2H, t, *J* = 6.4, CH$_2$); 3.00 (2H, t, *J* = 6.5, CH$_2$); 7.20–7.30 (2H, m, H Ar); 7.51–7.56 (1H, m, H Ar); 7.91–7.95 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.8; 22.5; 39.8; 115.1; 115.7 (d, J_{CF} = 13); 116.6 (d, J_{CF} = 21); 124.2 (d, J_{CF} = 3); 131.3; 133.8 (d, J_{CF} = 9); 160.2 (d, J_{CF} = 258, C-2'); 164.4 (C-7a); 166.5 (C-3); 192.1 (C-4). ^{19}F NMR spectrum, δ, ppm: –109.40 (m, F). Found, %: C 67.46; H 4.29; N 6.00. $C_{13}H_{10}FNO_2$. Calculated, %: C 67.53; H 4.36; N 6.06.

3-(3-Fluorophenyl)-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (5e). Yield 0.22 g (95%, from compound **3e**), mp 88–90°C. IR spectrum, ν, cm^{-1}: 1680, 1615, 1590, 1570, 1485, 1470, 1450. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15–2.20 (2H, m, CH$_2$); 2.64 (2H, t, *J* = 6.4, CH$_2$); 2.98 (2H, t, *J* = 6.4, CH$_2$); 7.22–7.26 (1H, m, H Ar); 7.46–7.51 (1H, m, H Ar); 8.23–8.26 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.9; 22.3; 40.2; 112.9; 115.7 (d, J_{CF} = 25); 119.4 (d, J_{CF} = 21); 124.5 (d, J_{CF} = 2); 128.2 (d, J_{CF} = 9); 130.5 (d, J_{CF} = 8); 162.7 (d, J_{CF} = 246, C-3'); 165.1 (C-7a); 169.3 (C-3); 192.6 (C-4). ^{19}F NMR spectrum, δ, ppm: –111.30 (m, F). Found, %: C 67.48; H 4.30; N 6.01. $C_{13}H_{10}FNO_2$. Calculated, %: C 67.53; H 4.36; N 6.06.

3-(4-Fluorophenyl)-6,7-dihydro-2,1-benzisoxazol-4(5*H*)-one (5f). Yield 0.21 g (89%, from compound **3f**), mp 68–70°C. IR spectrum, ν, cm^{-1}: 1685, 1675, 1605, 1565, 1520, 1490, 1460. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.16 (2H, quin, CH$_2$); 2.62 (2H, t, *J* = 6.4, CH$_2$); 2.97 (2H, t, *J* = 6.4, CH$_2$); 7.17–7.21 (2H, m, H Ar); 8.48–8.52 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 21.9; 22.3; 40.1; 112.2; 116.1 (d, J_{CF} = 22); 122.8 (d, J_{CF} = 3); 131.4 (d, J_{CF} = 9); 165.1 (C-7a); 165.1 (d, J_{CF} = 255, C-4'); 169.8 (C-3); 192.7 (C-4). ^{19}F NMR spectrum, δ, ppm: –105.50 (m, F). Found, %: C 67.60; H 4.41; N 6.11. $C_{13}H_{10}FNO_2$. Calculated, %: C 67.53; H 4.36; N 6.06.

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