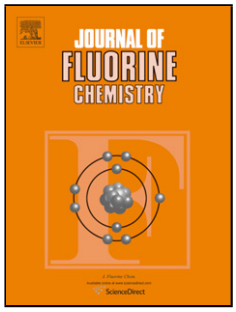

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Transformations of 3-acyl-4*H*-polyfluorochromen-4-ones under the action of amino acids and biogenic amines

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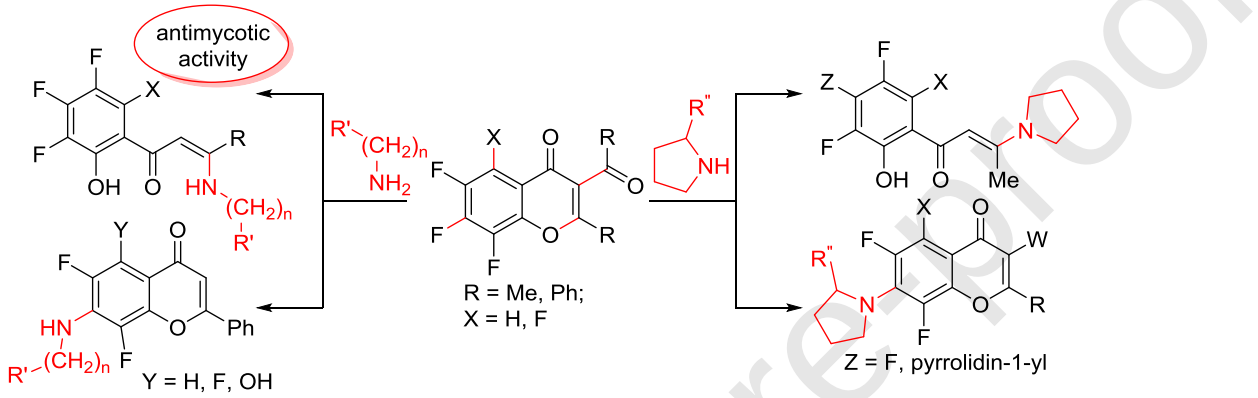
Graphical abstract



Highlights

- Synthesis of the new 3-benzoylpolyfluoroflavones
- The alternative routes for modification of 3-acylpolyfluorochromones with amino acids and biogenic amines
- New functionalized polyfluorinated chromones, flavones and aminoenketones
- *N*-substituted 3-amino-1-(2-hydroxypolyfluorophenyl)prop-2-en-1-ones as potential antimycotic agents

Abstract

For the first time 6,7,8-trifluoro- and 5,6,7,8-tetrafluorinated 3-benzoylflavones have been obtained. Their reactions with amino acids and biogenic amines were studied in comparison with polyfluorinated 3-acetyl-2-methylchromones. For chromones, reactions at the C-2 are preferred, which lead to the pyrone ring opening to form *N*-substituted aminoenketones. Whereas in the case of flavones the main route is the nucleophilic aromatic substitution of the fluorine atom at the C-7. Flavones and chromones react in the same way both with dopamine to give aminoenketones, and with proline to form 7-amino-substituted chromen-4-ones. All the reactions of chromen-4-ones are accompanied by deacylation, except ones of flavones with proline. Among the synthesized aminoenketones, compounds with high antimycotic and antibacterial action were found.

Keywords

3-acyl-4*H*-polyfluorochromen-4-ones; amines; nucleophilic aromatic substitution; pyrone ring opening; deacylation; antimycotic and antibacterial activity

1. Introduction

Chromen-4-ones (1,4-benzopyrones) are important scaffold in medicinal chemistry,[1] as there are numerous examples of natural and synthetic derivatives with diverse biological activities (antithrombotic,[2] antimicrobial[3] antitumor[4] vasodilating activity[5] *etc*.), some of which are successfully used as modern drugs (*flacoside*, *alvocidib*, *intal*, *quercetin*, *etc*.). In addition, because of their multifunctional nature chromen-4-ones are widely used in organic synthesis as block-synthons to form new open-chain and heterocyclic compounds.[6] Current studies show wide possibilities for the modification of chromone-based structures by amino acids that allow obtaining a new type of hybrid multifunctional compounds, which combine biological activity with high stability and bioavailability.[7]

Transformations of fluorine-containing compounds is of growing interest. It is well known that the presence of electron-withdrawing fluorine atoms in the organic molecules not only significantly changes their physical and chemical properties, offering new synthetic possibilities, but also leads to the spectrum variety of biological activity.[8] Polyfluorinated 3-acylchromen-4-ones are the promising multifunctional compounds, having several nonequivalent electrophilic centers, that make them convenient substrates for modification in reactions with nucleophilic reagents. Previously, we have found[9] that the main reaction route of 3-acetylpolyfluorochromones with highly basic aliphatic amines and esters of α-amino acids, similar to non-fluorinated substrates,[10] is pyrone ring opening, accompanied by deacylation, leading to formation of the corresponding substituted aminovinyl ketones. In contrast, 3-ethoxycarbonyl-substituted polyfluoroflavones are able not only to the pyrone ring opening, but also to formation of S_N^{Ar}-substitution products depending on the nature of the amine reagent.[11]

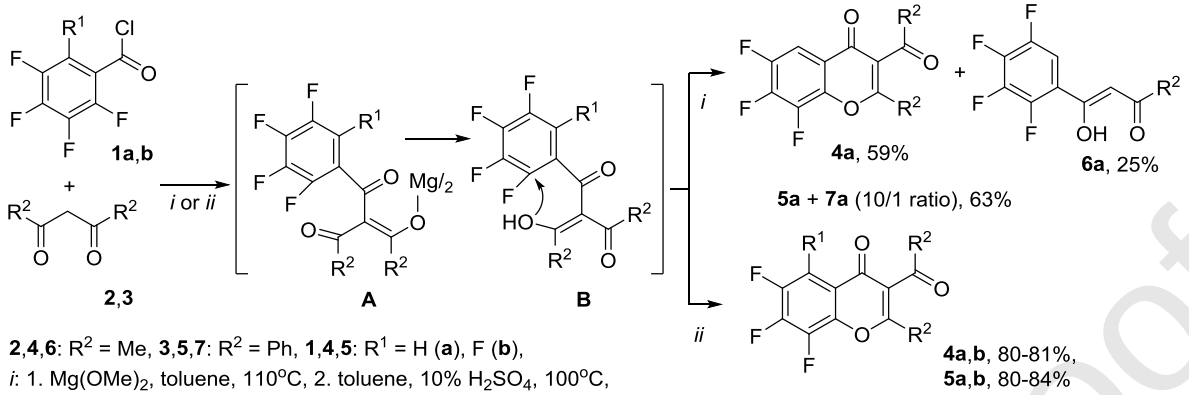
In this work, the interaction features of 3-acylpolyfluorochromen-4-ones with amino acids (β-alanine, γ-aminobutyric acid (GABA) and proline) and biogenic amines (dopamine and pyrrolidine) were studied. A wide range of their biological effect determined the aim of modifying of chromones and flavones with such amines. Based on amino acids the effective antihypertensive, hormonal drugs were designed. Dopamine is known to play an important role in the activity of the central and peripheral nervous system. The pyrrolidine fragment is a part of the natural alkaloids, for example, nicotine and hygrin, in drugs, such as *procyclidine* and *bepridil*.[12]

2. Results and discussion

Trifluoro- and tetrafluoro-substituted 3-acetylchromones **4a**,**b** and 3-benzoylflavones **5a**,**b** were selected as objects for the modification. For their synthesis the previously proposed method was used[13] based on acylation of 1,3-diketones **2**, **3**, activated with magnesium alkoxides, with polyfluorobenzoyl chlorides **1a**,**b**. It should be noted that 6,7,8-trifluoro- and 5,6,7,8-tetrafluoro-substituted 3-benzoyl-2-phenyl-4*H*-chromen-4-ones **5a**,**b** were synthesized for the first time using dibenzoylmethane **3** as a diketone component (Scheme 1). The formation of polyfluorinated chromones **4a**,**b** and flavones **5a**,**b** is caused by spontaneous cyclization of the intermediate triketones **B**, obtained by acid hydrolysis of their magnesium salts **A**. The cyclization proceeds through the intramolecular nucleophilic substitution of the *ortho*-fluorine atom of the polyfluorophenyl ring by hydroxyl group of the enolized diketone fragment.

However, to improve the yields of the compounds **4a**,**b** and **5a**,**b**, the previously used reaction conditions[13] were optimized. Necessity for the optimization was caused by the formation of asymmetric polyfluorinated 1,3-diketones **6a**, **7a** in reactions of acetylacetone **2** and dibenzoylmethane **3** with tetrafluorobenzoyl chloride **1a** as a result of deacylation of intermediates **B**, as by-products in addition to the target chromene-4-ones **4a**, **5a** (Scheme 1). Only 1,3-diketone **6a** was isolated, while its phenyl analogue **7a** was obtained only in a mixture with flavone **5a**. According to ^{1}H, ^{19}F NMR spectra, compound **6a** exists in $(CD_3)_2SO$ as a mixture of keto-enol tautomers in a ratio of 1÷3.

It was found that for more efficient synthesis of polyfluorinated chromen-4-ones **4a**,**b**, **5a**,**b**, it is necessary to remove excess of alcohol from the reaction mixture immediately after the activation of 1,3-diketones **2**, **3** with magnesium methoxide to prevent the esterification of polyfluorobenzoyl chlorides **1a**,**b**. Subsequent neutralization of magnesium salts **A** preferably should be proceeded by using of 0.5M HCl at room temperature, instead of 10% aqueous H_2SO_4 at heating, to prevent the deacylation of the intermediate triketones **B**. For the cyclization of triketones **B** to target chromen-4-ones **4a**,**b**, **5a**,**b** *N*,*N*-diisopropylethylamine (DIPEA) was used. As a result of the synthetic method optimization, the yields of products **4a**,**b**, **5a**,**b** were increased up to 80–84% (Scheme 1).

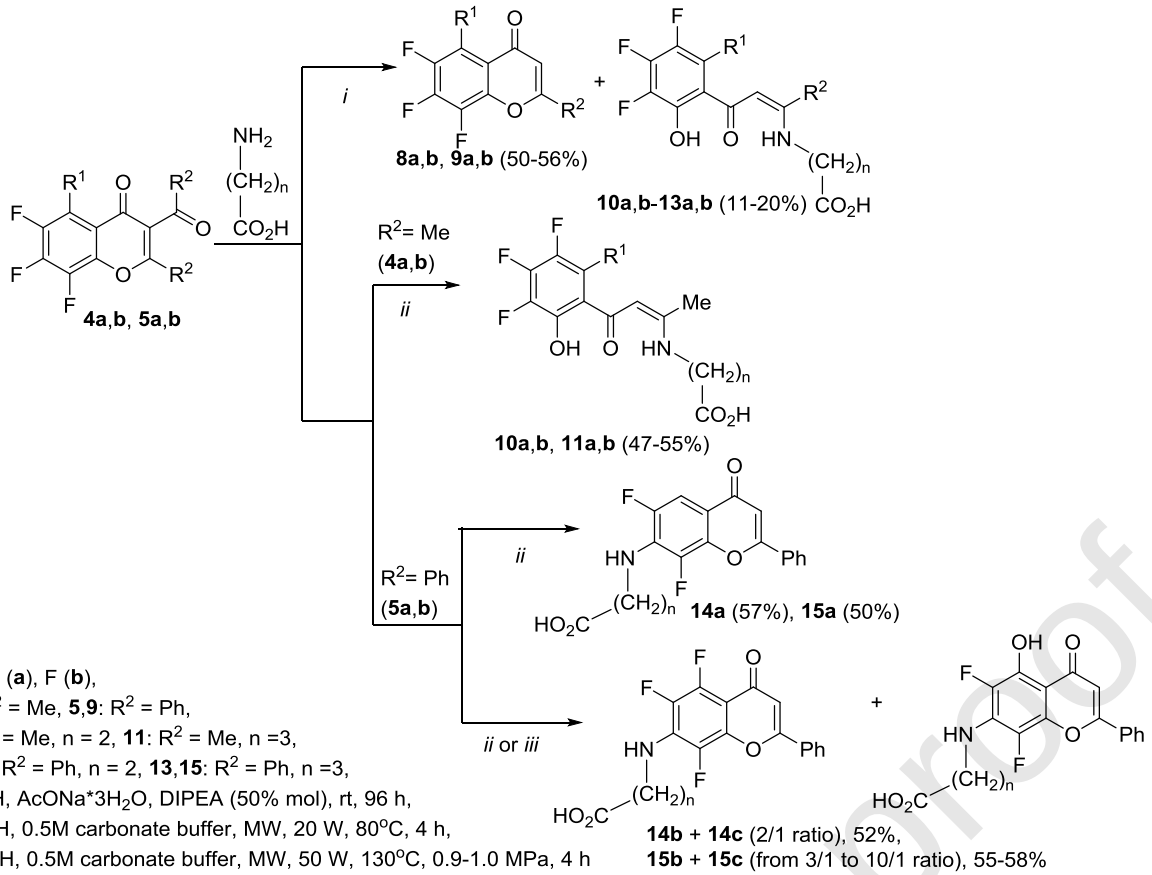


2,**4**,**6**: R^2 = Me, **3**,**5**,**7**: R^2 = Ph, **1**,**4**,**5**: R^1 = H (**a**), F (**b**),
i: 1. $Mg(OMe)_2$, toluene, 110°C, 2. toluene, 10% H_2SO_4, 100°C,
ii: 1. $Mg(OMe)_2$, toluene, 110°C, 2. toluene, 0.5M HCl, rt, 3. toluene, DIPEA, 110°C

Scheme 1. Synthesis of polyfluorinated 3-acyl-4*H*-chromen-4-ones

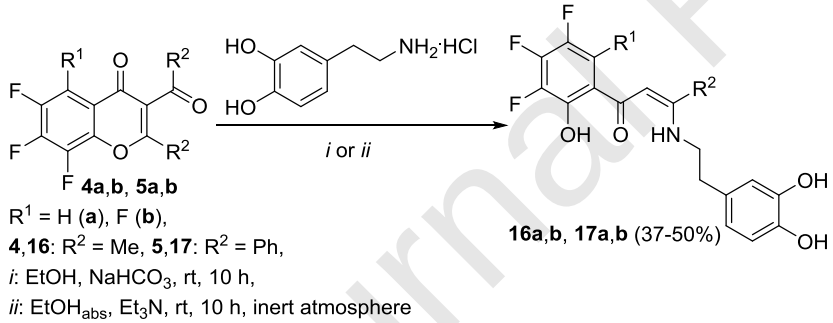
Further, it was found that the result of the interaction of polyfluorinated chromones **4a**,**b** and flavones **5a**,**b** with aliphatic amino acids depends on the reaction conditions. Amino acids are well known to exist predominantly in a zwitter-ionic form in an acidic or neutral media in low polar solvents.[14] In this regard, at first the reactions of compounds **4a**,**b**, **5a**,**b** with *β*-alanine and GABA were carried out in ethanol in the presence of AcONa and DIPEA at room temperature. However, under these conditions deacylated chromones **8a**,**b**, **9a**,**b** were obtained as the main products (50–56%) while *N*-substituted aminoenketones **10a**,**b**–**13a**,**b** were formed as minor products (11–20%), resulted from the subsequent pyrone ring opening of compounds **8a**,**b**, **9a**,**b** under the action of amino acids (Scheme 2). To increase the yields of open-chain products **10a**,**b**–**13a**,**b**, reactions of chromen-4-ones **4a**,**b**, **5a**,**b** with *β*-alanine and GABA were performed in a mixture of ethanol and 0.5M carbonate buffer (Na_2CO_3/$NaHCO_3$, pH 9.4) at 80˚C in a microwave reaction module at discrete power, limited up to 20 W. As a result, the yield of the target aminoenketones **10a**,**b**, **11a**,**b** was significantly increased up to 55% (Scheme 2).

In contrast to chromones **4a**,**b**, reactions of polyfluoroflavones **5a**,**b** with *β*-alanine and GABA proceeded an alternative pathway under these conditions. Trifluoroflavone **5a** reacted with *β*-alanine and GABA to give flavones **14a**, **15a**, having the amino acid fragment, as a result of the S_N^{Ar} mono-substitution of the fluorine atom at the C-7. Under similar conditions, tetrafluoroflavone **5b** formed a mixture of *N*-substituted 7-amino-5,6,8-trifluoroflavones **14b**, **15b** and 7-amino-6,8-difluoro-5-hydroxyflavones **14c**, **15c** (Scheme 2) in a ratio of 2÷1 (for **14b**, **14c**) and 3÷1 (for **15b**, **15c**). In the case of GABA, by ramping the reaction temperature and pressure (130°C, 0.9–1.0 MPa) it was succeeded to synthesize the mono-substituted flavone **15b** almost selectively, since its content in a mixture increased up to 10÷1, according to ^{19}F NMR spectroscopy data. However, we did not manage to find conditions for the selective synthesis of flavones **14b**, **14c**, and **15b**, **15c**, as well as to isolate them individually because of their joint crystallization and elution. The structure of compounds **14b**,**c**, **15b**,**c** was confirmed by ^1H, ^{19}F NMR and HRMS data of their mixtures.



Scheme 2. Reactions of 3-acyl-4*H*-cromen-4-ones with amino acids

Polyfluorochromen-4-ones **4a**,**b**, **5a**,**b** reacted with dopamine in ethanol at room temperature forming *N*-substituted aminoenketones **16a**,**b**, **17a**,**b** as a result of the pyrone ring opening and deacylation (Scheme 3). The transformations of flavones **5a**,**b** with dopamine were accompanied by a significant resinification of the reaction mass; therefore these reactions were carried out in absolute ethanol under argon atmosphere.



Scheme 3. Reactions of 3-acyl-4*H*-cromen-4-ones with dopamine hydrochloride

According to ^{1}H, ^{19}F NMR spectra, aminobutenones **10a**,**b**, **11a**,**b**, **16a**,**b** exist as mixtures of (*E*,*Z*)-isomers in $(CD_3)_2SO$ with a predominance of (*Z*)-form. While ^{1}H, ^{19}F NMR spectra of phenyl analogues **12a**,**b**, **13a**,**b**, **17a**,**b** contain the only one set of signals of the (*Z*)-isomer. (*Z*)-Aminobutenones **10a**,**b**, **11a**,**b**, **16a**,**b** are characterized by the low-field shift of a proton signal of the amino group (δ 10.83–11.08 ppm) that determined by intramolecular *H*-bonding with the carbonyl group, in contrast to the analogous signal of (*E*)-isomer (δ 7.68–8.48 ppm). Moreover, methylene proton of the (*Z*)-isomer, existing in pseudo-aromatic enol form, was registered in the low-field region, compared to the CH-signal of the (*E*)-isomer (see Supplementary material for full NMR data).

Structure of aminoenketones **10b** and **17a** in the solid state was confirmed by XRD. It was turned out that crystals of aminobutenone **10b**, having an acidic fragment, were isolated as the sodium salt **10b**·**Na**. According to XRD data (Fig. 1, 2), compounds **10b**·**Na**, **17a** exist in (*Z*)-aminoenketone form, stabilized by the two pairs of intramolecular hydrogen bonds O2–H2···O1 and N1–H1···O1 (**17a**, Fig. 1), and O4–H4···O1

and N1–H1···O1 (**10b·Na**, Fig. 2) (see Supplementary material for parameters of the hydrogen bond of compounds **10b·Na** and **17a**). Due to the stabilization, atoms of the aminoenketone fragment of the compounds **17a** ({N1,C15,C16,C17,O1}, Fig. 1) and **10b·Na** ({N1,C5,C6,C7,O1}, Fig. 2) are located in the plane of the fluoroaromatic ring. The molecules of compound **17a** are bound into dimers by intermolecular contacts between the amino and carbonyl groups of the aminoenketone fragment of one molecule and the hydroxyl group of the dopamine moiety of another one (Fig. 3). Zig zag layers with an interplanar distance of 3.333 Å are formed in the molecular packing of compound **17a** due to the π–π interaction of the fluoroaromatic fragment and the σ–π interaction of the dopamine moiety of the molecules (Fig. 3). The crystals of **10b·Na** are polymer structures, in which sodium ions are linked with each another through the two molecules of water; at the same time, each sodium ion binds another water molecule. Water molecules link dimers into polymer chains in direction to the *b*-axis due to the formation of intermolecular contacts, in which oxygen atoms of the carboxylate fragment are involved (Fig. 4).

Figure 1. Molecular structure of compound **17a** with atoms represented as thermal ellipsoids of thermal vibrations with a 50% probability

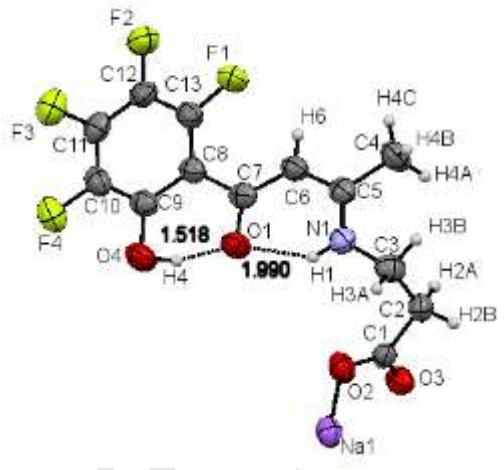


Figure 2. Molecular structure of compound **10b·Na** with atoms represented as thermal ellipsoids of thermal vibrations with a 50% probability

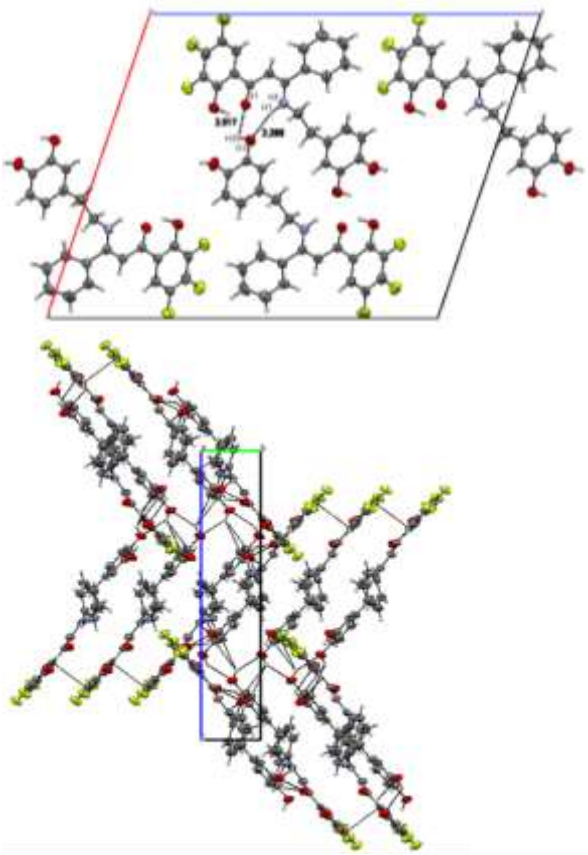


Figure 3. Molecular packaging of compound **17a**

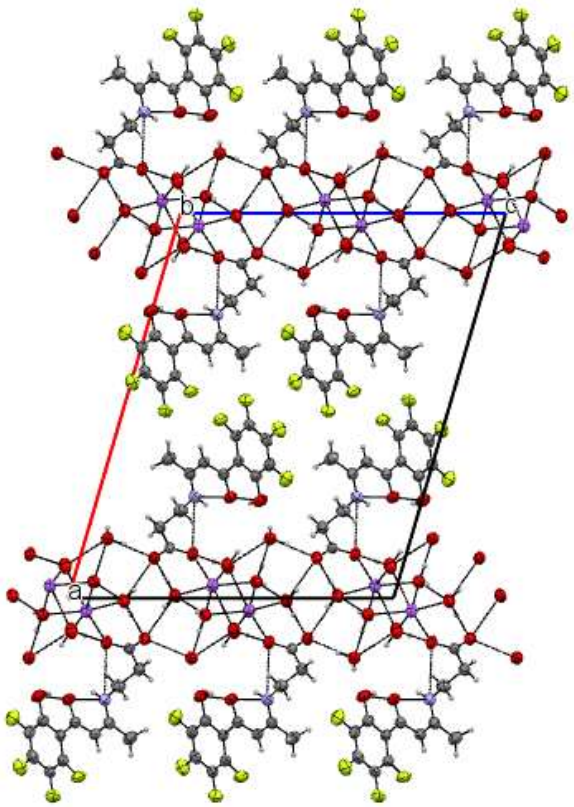
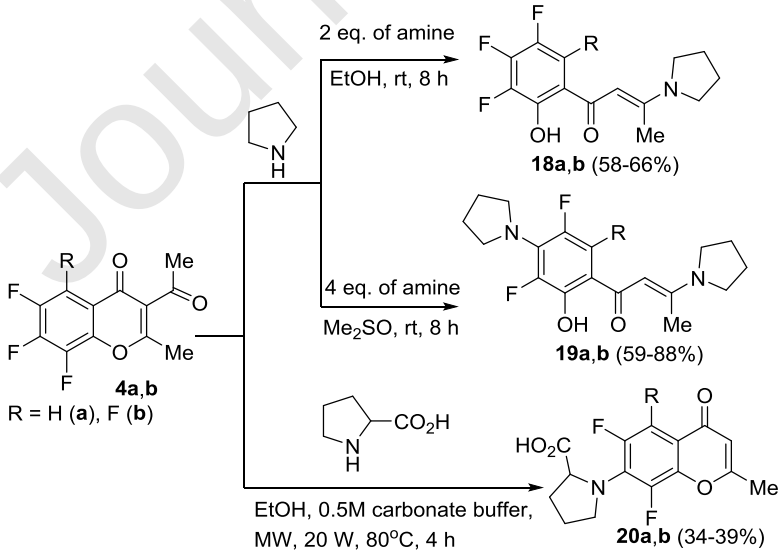


Figure 4. Molecular packaging of compound **10b**·**Na** along the *b*-axis

It was found that transformations of polyfluorinated chromen-4-ones **4a**,**b**, **5a**,**b** with the secondary heterocyclic amines (such as pyrrolidine and its 2-carboxylated analogue proline) under similar reaction conditions depend on the nature of fluorinated substrates and nucleophiles used (Schemes 4, 5). In ethanol (ε 24.3)[15] under the action of pyrrolidine, chromones **4a**,**b** undergo pyrone ring opening and deacylation, forming 3-(pyrrolidin-1-yl)-1-(polyfluorophenyl)but-2-en-1-ones **18a**,**b**. In more polar dimethylsulfoxide (ε 49)[15] these transformations are accompanied by substitution of a fluorine atom to form compounds **19a**,**b**, having two pyrrolidine fragments (Scheme 4). However, interaction of chromones **4a**,**b** with proline in the same reaction conditions had no significant conversion, therefore a mixture of EtOH and 0.5M carbonate buffer was used. Only 7-[2-(carboxy)pyrrolidin-1-yl]-substituted 4*H*-chromen-4-ones **20a**,**b** as products of S_N^{Ar} substitution of fluorine atoms were isolated in an individual form (Scheme 4).



Scheme 4. Reactions of 3-acetyl-4*H*-chromen-4-ones with pyrrolidine and proline

According to XRD data, 3-(pyrrolidinyl)buthenone **18b** is in (*E*)-aminoenketone form in the solid state, in contrast to aminoenketones **10a**,**b**–**13a**,**b**, **16a**,**b**, **17a**,**b** having an NH-group, which stabilizes the (*Z*)-isomer (Fig. 5). The molecules of **18b** are characterized by one intramolecular hydrogen bond O5–H5A···O1. Besides, the only one set of signals was registered in the ^{1}H, ^{19}F NMR spectra of compounds **18a**,**b**, **19a**,**b** in $(CD_3)_2SO$, corresponding to the (*E*)-form, obviously.

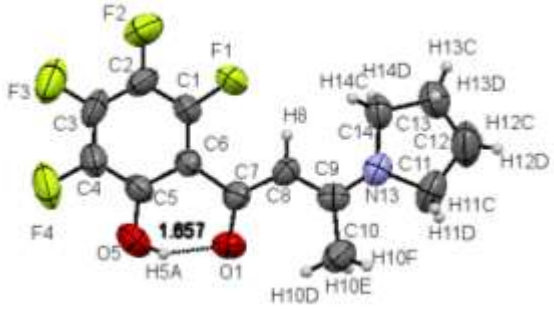
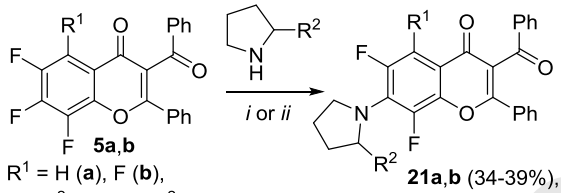


Figure 5. Molecular structure of compound **18b** with atoms represented as thermal ellipsoids of thermal vibrations with a 50% probability

Only 7-substituted 3-benzoylflavones **21a**,**b**, **22a**,**b** were isolated from the reaction of polyfluoroflavones **5a**,**b** with pyrrolidine and proline as products of nucleophilic aromatic substitution of fluorine atoms (Scheme 5). It should be noted that the isolated products **21a**,**b**, **22a**,**b** have retained benzoyl function in contrast to chromones **4a**,**b**.



R^1 = H (**a**), F (**b**),
21: R^2 = H, **22**: R^2 = CO_2H,
i: (R^2 = H) EtOH, rt, 10 h,
ii: (R^2 = CO_2H) EtOH, DIPEA (50% mol), 80°C, 8 h

Scheme 5. Reactions of 3-benzoyl-4*H*-chromen-4-ones with pyrrolidine and proline

We have studied antimycotic and antibacterial activities of some synthesized compounds. Antimycotic evaluations were carried out against eight fungal strains (Table 1). *Terbinafine* was used as a positive control. *N*-Substituted aminoenketones showed an antimycotic effect from moderate (compounds **10b**, **11b**, **12a**, **16a**,**b**) to high values (compounds **13b**, **17b**).

Tetrafluorinated 3-phenylpropenones **13b**, **17b** revealed the highest activity of the tested compounds. 3-Phenylpropenone **17b** having dopamine moiety showed the elevated antimycotic activity against *T. rubrum* and *M. canis* (MIC 1.56 μg/mL), *T. tonsurans* and *T. violaceum* (MIC 3.12 μg/mL) along with the moderate activity against *E. floccosum* and *C. albicans* (MIC 12.5 μg/mL). 3-Phenylpropenone **13b**, involving 4-aminobutanoic acid fragment, had the same activity against *T. rubrum* and *M. canis* (MIC 1.56 μg/mL). In contrast to tetrafluorinated compounds **13b**, **17b**, their trifluorinated analogues **13a**, **17a** exhibited the low antimycotic action. Change of phenyl substituent in the aminoenketones **13b**, **17b** to methyl group decreased the antimycotic avtivity of compounds **11a**,**b**, **16a**,**b**. We did not observe the clear correlation between fungicidal action and the number of the fluorine atoms in the case of compounds **11a**,**b**, **16a**,**b** In this series trifluorinated butenone **16a** containing dopamine moiety was more effective, suppressing *T. violaceum* strains at MIC of 12.5 μg/mL. In contrast to *N*-substituted aminoenketones, chromone derivatives **14a**, **15a**, **20a**, **21b**, **22a**, as well as diaminosubstituted aminoenketone **19b**, did not show antimycotic activity. Most antimicrobial drugs act by a non-enzymatic mechanism, accompanied by a destruction of the microbial cell membrane.[16] It is possible that chromones

14a, **15a**, **20a**, **21b**, **22a** possess the less adsorption on the surface of microbial cells, unlike open-chain products **13b**, **16a**, **17b**, having aminoenediketone fragment.

Table 1. Antimycotic activity of synthesized compounds.

Entry	Compound	Minimum inhibitory concentration (MIC), μg/mL							
		T. rubrum	*T. gypseum*	*T. tonsurans*	*T. violaceum*	*T. interdigitale*	*E. floccosum*	*M. canis*	*C. albicans*
1	**10a**	50	100	50	50	100	100	50	100
2	**10b**	25	50	50	50	50	50	25	100
3	**11a**	50	100	100	100	100	100	50	100
4	**11b**	>200	>200	>200	>200	50	25	25	>200
5	**12a**	25	200	200	>200	>200	>200	25	>200
6	**12b**	12.5	200	200	>200	200	200	200	>200
7	**13a**	25	50	50	>200	200	200	200	>200
8	**13b**	1.56	25	50	200	200	50	1.56	>200
9	**14a**	>200	>200	>200	>200	>200	>200	>200	>200
10	**15a**	>200	>200	>200	>200	>200	>200	>200	>200
11	**16a**	25	100	50	12.5	100	50	50	100
12	**16b**	25	25	25	25	100	100	100	>200
13	**17a**	50	100	100	>200	>200	>200	100	>200
14	**17b**	1.56	25	3.12	3.12	200	12.5	1.56	12.5
15	**19b**	>200	>200	>200	>200	>200	>200	>200	>200
16	**20a**	>200	>200	>200	200	>200	>200	>200	>200
17	**21b**	>200	>200	>200	>200	>200	>200	>200	>200
18	**22a**	200	>200	>200	100	>200	>200	200	>200
Terbinafine		0.002	0.001	–	0.01	0.01	0.01	0.02	6.25

Testing of synthesized compounds against eight strains of conditionally pathogenic microorganisms and *N. gonorrhoeae* revealed a higher activity of *N*-substituted aminoenketones **12a**, **16b** against *St. aureus* and *St. aureus MRSA* (MIC 15.6 mg/mL), compared to *Spectinomycin*.

Table 2. Antibacterial activity of synthesized compounds.

Entry	Compound	Minimum inhibitory concentration, MIC, μg/mL								
		N. gonorrhoeae	*E. coli*	*K. pneumoniae*	*C. braakii*	*S. marcescens*	*S. flexneri*	*P. auruginosa*	*St. aureus*	*St. aureus MRSA*
1	**10a**	125	125	250	125	250	250	>250	250	250
2	**10b**	62.5	125	>250	125	250	250	>250	62.5	62.5
3	**11a**	125	250	250	250	250	250	250	250	250
4	**11b**	n.d.	125	250	250	250	125	>250	62.5	62.5

5	**12a**	62.5	>250	>250	>250	>250	>250	>250	15.6	15.6
6	**12b**	62.5	>250	>250	>250	>250	>250	>250	>250	>250
7	**13a**	62.5	>250	>250	>250	>250	>250	>250	>250	>250
8	**13b**	62.5	>250	>250	>250	>250	>250	>250	>250	31.2
9	**14a**	31.2	>250	>250	>250	>250	>250	>250	>250	>250
10	**15a**	250	>250	>250	>250	>250	>250	>250	>250	>250
11	**16a**	125	>250	250	>250	>250	>250	>250	62.5	>250
12	**16b**	n.d.	>250	250	>250	>250	250	>250	15.6	15.6
13	**17a**	62.5	>250	>250	>250	>250	>250	>250	>250	>250
14	**17b**	250	>250	>250	>250	>250	>250	>250	>250	>250
15	**19b**	>250	>250	>250	>250	>250	>250	>250	>250	>250
16	**20a**	62.5	>250	>250	>250	>250	>250	>250	>250	>250
17	**21b**	31.2	>250	>250	>250	>250	>250	>250	>250	>250
18	**22a**	250	>250	>250	>250	>250	>250	>250	>250	125
Spectinomycin		15.6	15.6	15.6	31.25	15.6	7.8	250	31.25	n.a.

n.d. – not determined, n.a. – data not available

3. Conclusion

The present study has demonstrated that multifunctional character of polyfluorinated 3-acylchromen-4-ones **4a**,**b**, **5a**,**b** determines the different routes for their interaction with biogenic amines and amino acids, depending on the structure of the fluorine-containing substrate and nucleophilic reagent as well as reaction conditions. Chromones **4a**,**b** react with the primary amines (amino acids and dopamine) to give *N*-substituted aminoenketones as a result of nucleophilic attack at the C-2 with the subsequent pyron ring opening. In addition, flavones **5a**,**b** can react with amino acids with retention of the pyrone ring, forming products of the fluorine atom substitution. The S_N^{Ar} process becomes the main route for the reactions of flavones **5a**,**b** with secondary amines and an alternative for the similar transformations of chromones **4a**,**b**. At the same time, all these transformations are accompanied by deacylation, even under mild conditions, except for the interaction of flavones **5a**,**b** with secondary amines. Deacylation of acyl-functionalized derivatives is known to easily carry out under the basic conditions.[10,17] Differences in the reactivity of chromones **4a**,**b** and flavones **5a**,**b** when interacting with primary and secondary amines can be explained by the steric factors of an amine attack on the C-2 of the chromenone cycle. In the case of a difficult attack on C-2, an alternative path of transformations along the activated C-7 position of the aromatic cycle is realized. The presence of fluorine atoms in the aromatic part of the studied chromenones **4a**,**b**, **5a**,**b** provides the additional opportunities for their transformations. The case of simultaneous S_N^{Ar} substitution, pyrone ring opening and deacylation in the reaction of chromone **4a**,**b** with pyrrolidine was found. Among the synthesized aminoenketones, compounds with high antimycotic and antibacterial action were found. Moreover, 7-substituted flavones may reveal angioprotective activity, as well as GABA-modified aminoenketones may be of interest as neurotransmitters. Chromenes and aminoenketones, having dopamine fragment, can be the promising effectors of the corresponding dopamine receptors.

Acknowledgements

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synthesized compounds was performed at the Ural Research Institute of Dermatovenereology and Immunopathology.

4. Experimental section

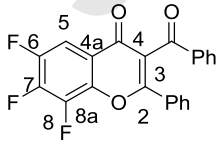
4.1. General information

All the reagents except fluorine-containing benzoyl chlorides, chromones and flavones are commercially available and used without further purification. Solvents were prepared according to standard methods of purification. Synthesis under microwave irradiation was carried out in a CEM Discover SP Explorer Hybrid microwave reaction module in closed reaction vessels. The Nuclear magnetic resonance spectra (NMR) of the synthesized compounds were recorded on a Bruker DRX-400 and Bruker AVANCE III 500 spectrometers (^{1}H, 400 (DRX400) and 500 (AV500) MHz, ^{13}C, 100.6 MHz, $SiMe_4$ as an internal standart, ^{19}F, 376 (DRX400) and 470 (AV500) MHz, C_6F_6 as internal standart (chemical shifts were converted to CCl_3F)). IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer using a diffuse reflectance attachment (DRA) in the range of 4000–400 cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a Bruker MaXis Impact HD mass spectrometer (ESI). Elemental (C, H, N) analysis was performed on a Perkin Elmer PE 2400 Series II CHNS-O EA 1108 elemental analyzer. Melting points were measured on a Stuart SMP3 in open capillaries and are uncorrected. The reaction progress was monitored by TLC on ALUGRAM SIL G/ UV_{254} plates. Column chromatography was performed on Alfa Aesar silica gel 60 (0.063–0.2 mm).

4.2. General procedure of synthesis of 3-acyl-4H-polyfluorochromen-4-ones 4a,b, 5a,b.

In a three-necked flask, equipped with a reflux condenser and a drop funnel, several iodine crystals and 1.2 g (50 mmol) of magnesium turnings were added, heated with stirring until the vigorous sublimation of iodine, then 10 mL (250 mmol) of MeOH and a few drops of CCl_4 were added. While vigorous hydrogen evoluation, 25 mL of absolute toluene was added to the mixture. Then 50 mmol of corresponding diketone **2**, **3** was added in portions while stirring. The mixture was refluxed until the magnesium turnings were completely dissolved, and then cooled to room temperature. The solvent was removed *in vacuo* till the mass thickening, then 25 mL of absolute toluene was added. Polyfluorobenzoyl chloride **1a**,**b** (50 mmol) in 20 mL of absolute toluene was added to the mixture dropwise with stirring at the room temperature. The mixture was stirred for 6 h at room temperature, then poured into 150 mL 0.5M HCl. An organic layer was separated and dried over anhydrous Mg_2SO_4. To the mixture, separated from Mg_2SO_4, 0.6 g (5 mmol) of DIPEA was added, and then refluxed for 2 h. The solvent was removed *in vacuo*, and the residue was crystallized fractionally from toluene.

*4.2.1. 3-Benzoyl-6,7,8-trifluoro-2-phenyl-4H-chromen-4-one (**5a**)* was synthesized from 11.2 g (50 mmol) of dibenzoylmethane **3** and 10.6 g (50 mmol) of tetrafluorobenzoyl chloride **1a**. Yield 15.2 g (80%), white powder, mp 181–182˚C. IR (DRA): ν 1676 (Bz), 1632 (C=O), 1523, 1496, 1447 (C=C, C–H), 1006, 927 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$+CCl_4): δ 7.39–7.91 (10H, m, 2 Ph), 7.79 (1H, m, H, C-5). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$+CCl_4): δ -152.11 (1F, d, *J* = 18.8 Hz), -150.48, -136.65 (2F, both m). Anal. calcd. for $C_{22}H_{11}F_3O_3$: C, 69.48; H, 2.92; found: C, 69.57; H, 3.18.



*4.2.2. 3-Benzoyl-5,6,7,8-tetrafluoro-2-phenyl-4H-chromen-4-one (**5b**)* was synthesized from 11.2 g (50 mmol) of dibenzoylmethane **3** and 11.5 g (50 mmol) of pentafluorobenzoyl chloride **1b**. Yield 16.7 g (84%), white powder, mp 178–180˚C. IR (DRA): ν 1674 (Bz), 1645 (C=O), 1522, 1502, 1448 (C=C, C–H), 994 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz,

$(CD_3)_2SO+CCl_4$): δ 7.39–7.95 (10H, m, 2 Ph). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO+CCl_4$): δ -162.17, -159.21, -148.87, -144.13 (4F, all m). Anal. calcd. for $C_{22}H_{10}F_4O_3$: C, 66.34; H, 2.53; found: C, 66.00; H, 2.66.

*4.2.3. 1-(2,3,4,5-Tetrafluorophenyl)butane-1,3-dione (**6a**)* was synthesized from 1.0 g (10 mmol) of acetylacetone **2** and 2.1 g (10 mmol) of tetrafluorobenzoyl chloride **1a** under reaction conditions.[13] Yield 585 mg (25%), orange powder, mp 82–85˚C ($CHCl_3/C_6H_{14}$). ^1H NMR (500.13 MHz, $(CD_3)_2SO$) spectrum of keto-enol mixture, 3÷1, enol form: δ 2.23 (3H, s, CH_3), 6.34 (1H, s, CH), 7.79–7.84 (1H, m, H, C_6HF_4), 15.82 (1H, br.s, OH); keto form: δ 2.23 (3H, s, CH_3), 4.25 (2H, d, J = 3.1 Hz, CH_2), 7.78–7.84 (1H, H, C_6HF_4). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$) spectrum of keto-enol mixture, enol form: δ -154.96, -150.28, -138.71, -137.57 (4F, all m), keto form: δ -155.02, -148.42, -138.60, -137.70 (4F, all m). Anal. calcd. for $C_{10}H_6F_4O_2$: C, 51.30; H, 2.58; found: C, 51.19; H, 2.65.

*4.2.4. 1-Phenyl-3-(2,3,4,5-tetrafluorophenyl)propane-1,3-dione (**7a**)* in a mixture with **5a** was synthesized from 11.2 g (50 mmol) of dibenzoylmethane **3** and 10.6 g (50 mmol) of tetrafluorobenzoyl chloride **1a** under reaction conditions. [13] ^1H NMR (500.13 MHz, $(CD_3)_2SO$): δ 7.08, (1H, s, CH), 7.57–8.18 (5H, m, Ph), 7.67 (1H, m, H, C-5). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -154.99, -149.97, -138.85, -137.54 (4F, all m).

4.3. General procedures for the synthesis of compounds 8–22.

Method A. 3-Acyl-4*H*-polyfluorochromen-4-one **4a**,**b**, **5a**,**b** (1 mmol), amino acid (2 mmol) and sodium acetate trihydrate (2 mmol) were suspended in 10 mL of EtOH, then 65 mg (0.5 mmol) of DIPEA were added to a mixture. Reaction mixture was stirred at room temperature for 96 hrs. At the end of the reaction, the mixture was poured onto 50 mL of 0.5M HCl, extracted with AcOEt, 3×10 mL. Organic layer was dried with Mg_2SO_4. Then mixture was separated from Mg_2SO_4, the solvent was removed in vacuo. The residue was purified by crystallization from a suitable solvent or by column chromatography on silica gel, using suitable eluent.

Method B. 3-Acyl-4*H*-polyfluorochromen-4-one **4a**,**b**, **5a**,**b** (1 mmol), nucleophile reagent (2 mmol) were suspended in a mixture of 5 mL of EtOH and 5 mL of 0.5M carbonate buffer. The mixture was placed in a reaction vessel and irradiated in a microwave reactor at a discrete power (10–20 W) and a constant temperature (80 °C) for 4 hrs while stirring. At the end of the reaction, the mixture was poured onto 50 mL of 0.5M HCl, extracted with AcOEt, 3×10 mL. Organic layer was dried with Mg_2SO_4. Then the mixture was separated from Mg_2SO_4, the solvent was removed *in vacuo*. The residue was purified by crystallization from a suitable solvent or by column chromatography on silica gel, using suitable eluent.

Method C. 3-Acyl-4*H*-polyfluorochromen-4-one **4a**,**b**, **5a**,**b** (1 mmol) was suspended in 10 mL of solvent, an excess of amine (2 or 4 mmol) was added to the mixture. The mixture was stirred at room temperature for 8 hrs. At the end of the reaction, the mixture was poured onto 50 mL of 0.5M HCl, the precipitate was filtered off, washed with water, and crystallized from a suitable solvent.

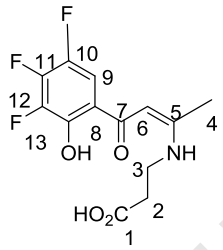
*4.3.1. 6,7,8-Trifluoro-2-methyl-4H-chromen-4-one (**8a**)* was synthesized according to the *method A* from 256 mg (1 mmol) of chromone **4a** and 2 mmol of the corresponding amino acid (*β*-alanine, GABA). White powder, mp 107–109˚C (EtOH). ^1H NMR (400.13 MHz, $(CD_3)_2SO$): δ 2.44 (3H, s, CH_3), 6.37 (1H, s, H, C-3), 7.80 (1H, d.d.d, J_{HF} = 10.2, 8.0, 2.3 Hz, H, C-5). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -152.14, -151.70, -137.74 (3F, all m). Anal. calcd. for $C_{10}H_5F_3O_2$: C, 56.09; H, 2.35; found: C, 56.44; H, 2.40.

*4.3.2. 5,6,7,8-Tetrafluoro-2-methyl-4H-chromen-4-one (**8b**)* was synthesized according to *method A* from 274 mg (1 mmol) of chromone **4b** and 2 mmol of the corresponding amino acid (*β*-alanine, GABA). White powder, mp 102–104°C (EtOH), (lit.[13a] 102–104°C). ^1H NMR (500.13 MHz, $(CD_3)_2SO$): δ 2.41 (3H, s, CH_3), 6.30 (1H, s, H, C-3). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -172.90, -164.97, -154.99, -139.67 (4F, all m).

*4.3.3. 6,7,8-Trifluoro-2-phenyl-4H-chromen-4-one (**9a**)* was synthesized according to *method A* from 380 mg (1 mmol) of flavone **5a** and 2 mmol of the corresponding amino acid (*β*-alanine, GABA). White powder, mp 203–206°C (EtOH). ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$): δ 7.18 (1H, s, H, C-3), 7.61–8.09 (5H, m, Ph), 7.87 (1H, d.d.d, J_{HF} = 10.0, 8.0, 2.3 Hz, H, C-5). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -152.02, -151.31, -137.38 (3F, all m). Anal. calcd. for $C_{15}H_7F_3O_2$: C, 65.23; H, 2.55; found: C, 65.28; H, 2.57.

*4.3.4. 5,6,7,8-Tetrafluoro-2-phenyl-4H-chromen-4-one (**9b**)* was synthesized according to *method A* from 398 mg (1 mmol) of flavone **5b** and 2 mmol of the corresponding amino acid (*β*-alanine, GABA). White powder, mp 224-226°C (EtOH). ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 7.13 (1H, s, H, C-3), 7.59–8.07 (5H, m, Ph). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -162.64, -159.10, -149.72, -145.42 (4F, all m). Anal. calcd. for $C_{15}H_6F_4O_2$: C, 61.24; H, 2.06; found: C, 61.72; H, 2.43.

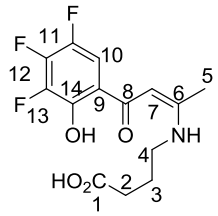
*4.3.5. N-[1-Methyl-3-oxo-3-(3,4,5-trifluoro-2-hydroxyphenyl)prop-1-enyl]-3-aminopropanoic acid, hydrate (**10a**)* was synthesized from 256 mg (1 mmol) of chromone **4a** and 179 mg (2 mmol) of *β*-alanine. Yield 45 mg (14% *method A*), 179 mg (55% *method B*), yellow powder, mp 135–140˚C ($CHCl_3$). IR (DRA): ν 3545, 3466 (N–H), 2970, 2924 (O–H), 1713 (CO_2H), 1596, 1566 (C=O), 1509, 1437, 1364, 1258 (C–N, C=C, C–H), 1032, 1010 (C–F) cm^{-1}. ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$) spectrum of (*E*,*Z*)-isomer mixture, 10÷1, (*Z*)-isomer: δ 2.18 (3H, s, CH_3), 2.59 (2H, t, $^{3}J_{HH}$ = 6.4 Hz, CH_2, C-2), 3.58 (2H, q, $^{3}J_{HH}$ = 6.4 Hz, CH_2, C-3), 5.88 (1H, s, H, C-6), 7.79 (1H, d.d.d, J_{HF} = 11.6, 9.0, 2.0 Hz, H, C-9), 10.87 (1H, t, $^{3}J_{HH}$ = 6.1 Hz, NH), 14.50 (1H, br.s, OH); (*E*)-isomer: δ 2.40 (3H, s, CH_3), 2.88 (2H, t, $^{3}J_{HH}$ = 6.3 Hz, CH_2, C-2), 3.49 (2H, m, CH_2, C-3), 5.74 (1H, s, H, C-6), 7.98 (1H, d.d.d, J_{HF} = 11.5, 8.9, 2.1 Hz, H, C-9), 8.34 (1H, br.s, NH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$) spectrum of (*Z*)-isomer: δ 19.21 (s, C-4), 34.26 (s, C-2), 39.40 (m, C-3+$(CD_3)_2SO$), 90.80 (s, C-6); 109.33 (br.s, C-9), 115.97 (br.s, C-8), 139.84 (m, C-12), 141.52 (m, C-10), 141.96 (m, C-11), 148.30 (m, C-13), 168.40 (m, C-5), 172.64 (s, C-1), 184.84 (br.s, C-7). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$) spectrum of (*E*,*Z*)-isomer mixture, 10÷1, (*Z*)-isomer: δ -159.33, -154.81, -149.45 (3F, all m); (*E*)-isomer: δ -160.01, -154.91, -150.22 (3F, all m). Anal. calcd. for $C_{13}H_{12}F_3NO_4 \cdot H_2O$: C, 48.60; H, 4.39; N, 4.36; found: C, 48.60; H, 4.15; N, 3.73.



*4.3.6. N-[1-Methyl-3-oxo-3-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)prop-1-enyl]-3-aminopropanoic acid, hemihydrate (**10b**)* was synthesized from 274 mg (1 mmol) chromone **4b** and 178 mg (2 mmol) *β*-alanine. Yield 66 mg (20% *method A*), 185 mg (54% *method B*), yellow powder, mp 239–240°C ($CHCl_3$). IR (DRA): ν 3117, 3007 (N–H), 2959 (O–H), 1719 (CO_2H), 1595, 1578 (C=O), 1513, 1433, 1363, 1285 (C–N, C=C, C–H), 1005, 981 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$) spectrum of (*E*,*Z*)-isomer mixture, 12÷1, (*Z*)-isomer: δ 2.12 (3H, s, CH_3), 2.46 (2H, t, $^{3}J_{HH}$ = 6.4 Hz, CH_2, C-2); 3.53 (2H, q, $^{3}J_{HH}$ = 6.4 Hz, CH_2, C-3), 5.49 (1H, s, H, C-6), 11.06 (1H, br.s, NH); (*E*)-isomer: δ 2.09 (3H, s, CH_3), 2.53 3.26 (4H, both m, 2 CH_2, C-2,3), 5.55 (1H, s, H, C-6), 8.52 (1H, br.s, NH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$) spectrum (*E*,*Z*)-isomer mixture, 12÷1, (*Z*)-isomer: δ -179.94, -166.62, -159.05, -143.09 (4F, all m); (*E*)-isomer: δ -177.10, -166.12, -157.65, -141.55 (4F, all m). Anal. calcd. for $C_{13}H_{11}F_4NO_4 \cdot ½H_2O$: C, 47.28; H, 3.66; N, 4.24; found: C, 47.35; H, 3.51; N, 4.12.

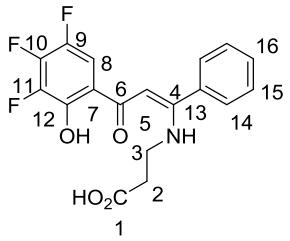
*4.3.7. N-[1-Methyl-3-oxo-3-(3,4,5-trifluoro-2-hydroxyphenyl)prop-1-enyl]-4-aminobutanoic acid (**11a**)* was synthesized from 256 mg (1 mmol) of chromone **4a** and 206

mg (2 mmol) of GABA. Yield 35 mg (11% *method A*), 171 mg (54% *method B*), yellow powder, mp 160–161˚C ($CHCl_3$, $EtOH_{aq}$). IR (DRA): ν 3066, 3011 (N–H), 2945 (O–H), 1704 (CO_2H), 1590, 1563 (C=O), 1506, 1445, 1349, 1247 (C–N, C=C, C–H), 1003 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO$) spectrum of (E,Z)-isomer mixture, 5÷1, (*Z*)-isomer: δ 1.81 (2H, qnt, $^3J_{HH}$ = 7.2 Hz, CH_2, C-3), 2.16 (3H, s, CH_3), 2.32 (2H, m, CH_2, C-2), 3.42 (2H, m, CH_2, C-4), 5.90 (1H, s, H, C-7), 7.79 (1H, d.d.d, J_{HF} = 11.6, 9.0, 2.0 Hz, H, C-10), 10.83 (1H, t, $^3J_{HH}$ = 6.1 Hz, NH), 12.24, 14.69 (2H, both br.s, 2 OH); (*E*)-isomer: δ 1.81 (2H, m, CH_2, C-3), 2.42 (3H, s, CH_3), 2.37, 3.29 (4H, both m, CH_2, C-2, C-4), 5.76 (1H, s, H, C-7), 7.94 (1H, m, H, C-10), 8.32 (1H, m, NH), 12.24 (1H, br.s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$) spectrum of (*Z*)-isomer: δ 19.13 (s, C-5), 24.74 (s, C-3), 30.69 (s, C-2), 42.59 (s, C-4), 90.79 (s, C-7), 109.37 (m, C-10), 115.96 (m, C-9), 139.66 (m, C-13), 141.72 (m, C-11), 141.99 (m, C-12), 148.19 (m, C-14), 168.73 (s, C-6), 173.74 (s, C-1), 184.85 (br.s, C-8). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$) spectrum of (*E,Z*)-isomer mixture, 5÷1, (*Z*)-isomer: δ -159.30, -154.80, -149.38 (3F, all m); (*E*)-isomer: δ -159.97, -154.93, -150.10 (3F, all m). Anal. calcd. for $C_{14}H_{14}F_3NO_4$: C, 53.00; H, 4.45; N, 4.41; found: C, 53.05; H, 4.38; N, 4.58.



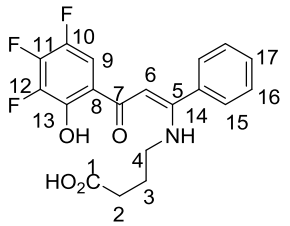
*4.3.8. N-[1-Methyl-3-oxo-3-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)prop-1-enyl]-4-aminobutanoic acid (**11b**)* was synthesized from 274 mg (1 mmol) chromone **4b** and 206 mg (2 mmol) of GABA. Yield 60 mg (18% *method A*), 157 mg (47% *method B*), yellow powder, mp 161–163˚C ($CHCl_3$). IR (DRA): ν 3012 (N–H), 2944 (O–H), 1712 (CO_2H), 1602, 1567 (C=O), 1509, 1450, 1340, 1245 (C–N, C=C, C–H), 998, 969 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO$) spectrum of (*E,Z*)-isomer mixture, 5÷1, (*Z*)-isomer: δ 1.82 (2H, qnt, $^3J_{HH}$ = 7.3 Hz, CH_2, C-3), 2.16 (3H, s, CH_3), 2.32 (2H, t, $^3J_{HH}$ = 7.3 Hz, CH_2, C-2), 3.45 (2H, m, CH_2, C-4), 5.59 (1H, s, H, C-7), 11.05 (1H, br.s, NH), 12.44, 14.07 (2H, both br.s, 2 OH); (*E*)-isomer: δ 1.83, 2.33 (4H, both m, CH_2, C-3, C-2), 2.43 (3H, s, CH_3), 3.18 (2H, m, CH_2, C-4), 5.61 (1H, s, H, C-7), 8.48 (1H, m, NH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$) spectrum of (*E,Z*)-isomer mixture, 5÷1, (*Z*)-isomer: δ -172.96, -165.00, -154.91, -139.61 (4F, all m); (*E*)-isomer: δ -173.53, -165.46, -155.20, -139.06 (4F, all m). Anal. calcd. for $C_{14}H_{13}F_4NO_4$: C, 50.16; H, 3.91; N, 4.18; found: C, 50.18; H, 4.09; N, 4.03.

*4.3.9. N-[3-Oxo-1-phenyl-3-(3,4,5-trifluoro-2-hydroxyphenyl)prop-1-enyl]-3-aminopropanoic acid, hydrochloride hydrate (**12a**)* was synthesized from 380 mg (1 mmol) flavone **5a** and 178 mg (2 mmol) *β*-alanine. Yield 59 mg (14% *method A*), yellow powder, mp 198–200˚C ($CHCl_3$). IR (DRA): ν 3002, 2928 (O–H), 1698 (CO_2H), 1565 (C=O), 1512, 1447, 1360, 1263 (C–N, C=C, C–H), 1005, 998 (C–F) cm^{-1}. ^1H NMR (500.13 MHz, $(CD_3)_2SO$): δ 2.57 (2H, t, $^3J_{HH}$ = 6.2 Hz, CH_2, C-2), 3.42 (2H, m, CH_2, C-3), 5.86 (1H, s, H, C-5), 7.54 (5H, m, Ph), 7.92 (1H, m, H C-8), 11.09 (1H, t, $^3J_{HH}$ = 5.2, NH), 14.18 (1H, br.s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 34.34 (s, C-2), 40.91 (s, C-3), 91.97 (s, C-5), 110.15 (m, C-7), 116.25 (m, C-8), 127.73 (s, C-14), 128.65 (s, C-15), 130.08 (s, C-16), 134.23 (s, C-13), 139.72 (m, C-11), 141.83 (m, C-9), 142.35 (m, C-10), 148.03 (m, C-12), 168.59 (s, C-4), 172.59 (s, C-1), 186.30 (m, C-6). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -159.06, -154.09, -149.07 (3F, all m). Anal. calcd. for $C_{18}H_{14}F_3NO_4 \cdot HCl \cdot H_2O$: C, 51.50; H, 4.08; N, 3.34; found: C, 51.27; H, 3.59; N, 3.61.



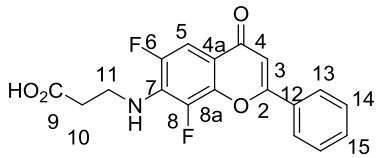
*4.3.10. N-[3-Oxo-1-phenyl-3-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)prop-1-enyl]-3-aminopropanoic acid (**12b**)* was synthesized from 398 mg (1 mmol) flavone **5b** and 178 mg (2 mmol) *β*-alanine. Yield 45 mg (11% *method A*), yellow powder, mp 210–211˚C ($CHCl_3$). IR (DRA): ν 3964 (N–H), 2927 (O–H), 1699 (CO_2H), 1603, 1582 (C=O), 1516, 1451, 1355 (C–N, C=C, C–H), 996 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, ($CDCl_3$): δ 2.59 (2H, t, $^3J_{HH}$ = 6.2 Hz, CH_2, C-2), 3.45 (2H, m, CH_2, C-3), 5.53 (1H, s, H C-5), 7.51–7.55 (5H, m, Ph), 11.17 (1H, br.s, NH), 12.51, 13.73 (2H, both br.s, 2 OH). ^{19}F NMR (376.44 MHz, ($CDCl_3$): δ -172.35, -164.31, -154.42, -140.09 (4F, all m). Anal. calcd. for $C_{18}H_{13}F_4NO_4$: C, 56.40; H, 3.42; N, 3.65; found: C, 56.35; H, 3.61; N, 3.36.

*4.3.11. N-[3-Oxo-1-phenyl-3-(3,4,5-trifluoro-2-hydroxyphenyl)prop-1-enyl]-4-aminobutanoic acid (**13a**)* was synthesized from 380 mg (1 mmol) flavone **5a** and 206 mg (2 mmol) of GABA. Yield 76 mg (20% *method A*), yellow powder, mp 175–178˚C ($CHCl_3$, $EtOH_{aq}$). IR (DRA): ν 2952 (O–H), 1704 (CO_2H), 1586, 1564 (C=O), 1511, 1448, 1368 (C–N, C=C, C–H), 1025, 1008 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.75 (2H, qnt, $^3J_{HH}$ = 7.1 Hz, CH_2, C-3), 2.21 (2H, t, $^3J_{HH}$ = 7.1 Hz, CH_2, C-2), 3.30 (2H, m, CH_2, C-4), 5.88 (1H, s, H, C-6), 7.51–7.55 (5H, m, Ph), 7.92 (1H, m, H, C-9), 11.00 (1H, t, $^3J_{HH}$ = 6.1 Hz, NH), 12.13, 14.27 (2H, both br.s, 2 OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -159.04, -154.13, -149.04 (3F, all m). Anal. calcd. for $C_{19}H_{16}F_3NO_4$: C, 60.16; H, 4.25; N, 3.69; found: C, 60.32; H, 4.57; N, 3.45.



*4.3.12. N-[3-Oxo-1-phenyl-3-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)prop-1-enyl]-4-aminobutanoic acid, hydrate (**13b**)* was synthesized from 398 mg (1 mmol) of flavone **5b** and 206 mg (2 mmol) of GABA. Yield 67 mg (17% *method A*), yellow powder, mp 159–161˚C ($CHCl_3$). IR (DRA): ν 3172 (N–H), 2955 (O–H), 1737, 1715 (CO_2H), 1652, 1583 (C=O), 1515, 1452, 1349, 1288 (C–N, C=C, C–H), 997 (C–F) cm^{-1}. ^1H NMR (500.13 MHz, $(CD_3)_2SO$): δ 1.76 (2H, qnt, $^3J_{HH}$ = 7.2 Hz, CH_2, C-3), 2.22 (2H, t, $^3J_{HH}$ = 7.2 Hz, CH_2, C-2), 3.32 (2H, m, CH_2, C-4), 5.54 (1H, s, H, C-6), 7.48–7.55 (5H, m, Ph), 11.08 (1H, t, $^3J_{HH}$ = 5.4 Hz, NH), 12.14, 13.65 (2H, both br.s, 2 OH). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -172.36, -164.30, -154.54, -140.16 (4F, all m). Anal. calcd. for $C_{19}H_{15}F_4NO_4 \cdot H_2O$: C, 54.94; H, 4.13; N, 3.37; found: C, 55.59; H, 3.95; N, 3.56.

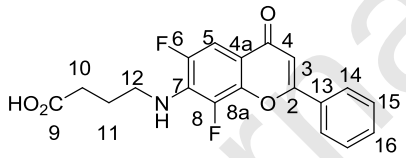
*4.3.13. N-(6,8-Difluoro-4-oxo-2-phenyl-4H-chromen-7-yl)-3-aminopropanoic acid (**14a**)* was synthesized according to *method B* from 380 mg (1 mmol) flavone **5a** and 178 mg (2 mmol) *β*-alanine. Yield 197 mg (57%), yellow powder, mp 235–238˚C ($CHCl_3$, $EtOH_{aq}$). IR (DRA): ν 3292 (N–H), 2965, 2921 (O–H), 1712 (CO_2H), 1641, 1632 (C=O), 1547, 1471, 1409, 1370 (C–N, C=C, C–H), 1017 (C–F) cm^{-1}. ^1H NMR (500.13 MHz, $(CD_3)_2SO$): δ 2.59 (2H, t, $^3J_{HH}$ = 7.1 Hz, CH_2, C-10), 3.67 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_2, C-11), 6.43 (1H, br.s, NH), 6.95 (1H, s, H, C-3), 7.44 (1H, d.d, J_{HF} = 12.0, 1.5 Hz, H, C-5), 7.58–8.04 (5H, m, Ph), 12.31 (1H, br.s, OH). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -154.65, -130.48 (2F, both m). Anal. calcd. for $C_{18}H_{13}F_2NO_4$: C, 62.61; H, 3.79; N, 4.06; found: C, 62.83; H, 3.59; N, 4.00.



*4.3.14. N-(5,6,8-Trifluoro-4-oxo-2-phenyl-4H-chromen-7-yl)-3-aminopropanoic acid (**14b**)* in a mixture with **14c** was synthesized according to *method B* from 398 mg (1 mmol) of flavone **5b** and 356 mg (4 mmol) *β*-alanine. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 2.58, 3.67 (4H, both m, 2 CH_2, C-10, C-11), 6.77 (1H, br.s, NH), 6.86 (1H, s, H, C-3), 7.56–8.03 (5H, m, Ph), 12.32 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -160.00, -159.68, -148.52 (3F, all m). HRMS (ESI), *m/z*: calcd. for $[C_{18}H_{11}F_3NO_4]^-$ 362.0646; found 362.0639.

*4.3.15. N-(6,8-Difluoro-5-hydroxy-4-oxo-2-phenyl-4H-chromen-7-yl)-3-aminopropanoic acid (**14c**)* in a mixture with **14b** was synthesized according to *method B* from 398 mg (1 mmol) of flavone **5b** and 356 mg (4 mmol) *β*-alanine. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 2.66, 3.68 (4H, both m, 2 CH_2, C-10, C-11), 6.62 (1H, br.s, NH), 6.99 (1H, s, H, C-3), 7.56–8.03 (5H, m, Ph), 12.41 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -167.35, -161.84 (2F, both m). HRMS (ESI), *m/z*: calcd. for $[C_{18}H_{12}F_2NO_5]^-$: 360.0689; found 360.0684.

*4.3.16. N-(6,8-Difluoro-4-oxo-2-phenyl-4H-chromen-7-yl)-4-aminobutanoic acid, hemihydrate (**15a**)* was synthesized according to *method B* from 380 mg (1 mmol) flavone **5a** and 206 mg (2 mmol) GABA. Yield 182 mg (50%), yellow powder, mp 204–207˚C ($CHCl_3$, $EtOH_{aq}$). IR (DRA): ν 3296 (N–H), 2977, 2941 (O–H), 1721 (CO_2H), 1641, 1622 (C=O), 1545, 1480, 1370 (C–N, C=C, C–H), 1022 (C–F) cm^{-1}. ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$): δ 1.83 (2H, qnt, $^{3}J_{HH}$ = 7.1 Hz, CH_2, C-11), 2.32 (2H, t, $^{3}J_{HH}$ = 7.1 Hz, CH_2, C-10), 3.45 (2H, q, $^{3}J_{HH}$ = 6.1 Hz, CH_2, C-12), 6.54 (1H, br.s, NH), 6.93 (1H, s, H, C-3), 7.40 (1H, d.d, J_{HF} = 11.9, 1.6 Hz, H, C-5), 7.58–8.02 (5H, m, Ph), 12.11 (1H, s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 25.65 (s, C-11), 30.87 (s, C-10), 43.60 (m, C-12), 104.18 (m, C-5), 106.33 (s, C-3), 111.34 (m, C-4a), 125.99 (s, C-14), 129.12 (s, C-15), 131.00 (s, C-13), 131.41 (m, C-7), 131.63 (s, C-16), 137.86 (m, C-8a), 143.06 (m, C-8), 149.02 (m, C-6), 161.31 (s, C-2), 174.22 (s, C-9), 174.93 (m, C-4). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -154.96, -130.44 (2F, both m). Anal. calcd. for $C_{19}H_{15}F_2NO_4 \cdot ½H_2O$: C, 61.96; H, 4.38; N, 3.80; found: C, 62.41; H, 4.27; N, 3.95.

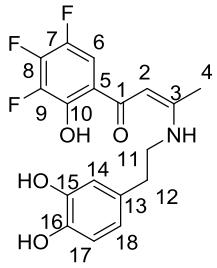


*4.3.17. N-(5,6,8-Trifluoro-4-oxo-2-phenyl-4H-chromen-7-yl)-4-aminobutanoic acid (**15b**)* in a mixture with **15c** was synthesized according to *method B* from 398 mg (1 mmol) of flavone **5b** and 412 mg (4 mmol) of GABA. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.83, 2.31, 3.45 (6H, all m, 3 CH_2, C-10, C-11, C-12), 6.85 (1H, s, H, C-3), 6.92 (1H, br.s, NH), 7.55–8.04 (5H, m, Ph), 12.32 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -160.25, -159.81, -148.58 (3F, all m). HRMS (ESI), *m/z*: calcd. for $[C_{19}H_{13}F_3NO_4]^-$: 376.0802; found 376.0798.

*4.3.18. N-(6,8-Difluoro-5-hydroxy-4-oxo-2-phenyl-4H-chromen-7-yl)-4-aminobutanoic acid (**15c**)* in a mixture with **15b** was synthesized according to *method B* from 398 mg (1 mmol) of flavone **5b** and 412 mg (4 mmol) of GABA. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.83, 2.28, 3.42 (2H, m, CH_2, C-10, C-11, C-12), 6.78 (1H, br.s, NH), 6.98 (1H, s, H, C-3), 7.55–8.04 (5H, m, Ph). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -167.46, -161.85 (2F, both m). HRMS (ESI), *m/z*: calcd. for $[C_{19}H_{14}F_2NO_5]^-$: 374.0846; found 374.0840.

*4.3.19. 3-{[2-(3,4-Dihydroxyphenyl)ethyl]amino}-1-(3,4,5-trifluoro-2-hydroxyphenyl)but-2-en-1-one (**16a**)* was synthesized according to *method A* from 256 mg

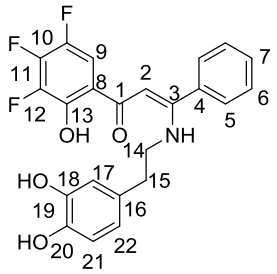
(1 mmol) of chromone **4a**, 379 mg (2 mmol) of dopamine hydrochloride and 168 mg (2 mmol) $NaHCO_3$. Yield 180 mg (49%), yellow powder, mp 154–156˚C ($CHCl_3/C_6H_{14}$). IR (DRA): ν 3458 (N–H), 2930, 2870 (O–H), 1595 (C=O), 1509, 1437, 1370 (C–N, C=C, C–H), 1001 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO+CCl_4$) spectrum of (*E*,*Z*)-isomer mixture, 17÷1, (*Z*)-isomer: δ 2.04 (3H, s, CH_3), 2.74 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2, C-12), 3.56 (2H, q, $^3J_{HH}$ = 6.9 Hz, CH_2, C-11), 5.72 (1H, s, H, C-2), 6.47–6.64 (3H, m, C_6H_3), 7.59 (1H, m, H, C-6), 8.51, 8.55 (2H, both s, 2 OH), 10.85 (1H, t, $^3J_{HH}$ = 5.1 Hz, NH), 14.45 (1H, s, OH); (*E*)-isomer: δ 2.66, 3.42 (4H, m, 2 CH_2, C-11, C-12), 5.60 (1H, s, H, C-2), 6.47–6.64 (3H, m, C_6H_3), 7.73 (1H, m, H, C-6), 8.07 (1H, m, NH), 8.46, 8.52 (2H, both s, 2 OH), 15.49 (1H, s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO+CCl_4$) spectrum of (*Z*)-isomer: δ 19.16 (s, C-4), 34.65 (s, C-12), 45.11 (s, C-11), 90.61 (s, C-2), 109.32 (m, C-6), 115.51 (s, C-14), 115.93 (m, C-5), 116.18 (s, C-17), 119.44 (s, C-18), 128.98 (s, C-13), 139.70 (m, C-9), 141.63 (m, C-7), 141.95 (m, C-8), 143.79 (s, C-16), 145.16 (s, C-15), 148.27 (m, C-10), 168.55 (s, C-3), 184.71 (s, C-1). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO+CCl_4$) spectrum of (*E*,*Z*)-isomer mixture, 17÷1, (*Z*)-isomer: δ -159.54 (1F, d, *J* = 19.5 Hz), -155.34, -149.96 (2F, both m); (*E*)-isomer: δ -160.19, -155.52, -150.75 (3F, all m). Anal. calcd. for $C_{18}H_{16}F_3NO_4$: C, 58.86; H, 4.39; N, 3.81; found: C, 58.24; H, 4.59; N, 3.91.



4.3.20. 3-{[2-(3,4-Dihydroxyphenyl)ethyl]amino}-1-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)but-2-en-1-one ***(16b)*** was synthesized according to *method A* from 274 mg (1 mmol) of chromone **4b**, 379 mg (2 mmol) of dopamine hydrochloride and 168 mg (2 mmol) $NaHCO_3$. Yield 193 mg (50%), yellow powder, mp 177–179˚C ($CHCl_3/C_6H_{14}$). IR (DRA): ν 3405 (N–H), 2954, 2925 (O–H), 1656, 1595 (C=O), 1511, 1446, 1340 (C–N, C=C, C–H), 1004 (C–F) cm^{-1}. ^1H NMR (500.13 MHz, $(CD_3)_2SO+CCl_4$) spectrum of (*E*,*Z*)-isomer mixture, 14÷1, (*Z*)-isomer: δ 2.07 (3H, s, CH_3), 2.75 (2H, t, $^3J_{HH}$ = 7.2 Hz, CH_2, C-12), 3.59 (2H, q, $^3J_{HH}$ = 7.0 Hz, CH_2, C-11), 5.58 (1H, s, H, C-2), 6.47–6.64 (3H, m, C_6H_3), 8.54, 8.57 (2H, both s, 2 OH), 11.08 (1H, t, $^3J_{HH}$ = 5.5 Hz, NH), 14.60 (1H, s, OH); (*E*)-isomer: δ 2.44 (3H, s, CH_3), 2.72, 3.30 (4H, m, 2 CH_2, C-11, C-12), 5.69 (1H, s, H, C-2), 6.45–6.59 (3H, m, C_6H_3), 7.68 (1H, m, NH), 8.47 (2H, br.s, 2 OH), 15.50 (1H, s, OH). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO+CCl_4$) spectrum of (*E*,*Z*)-isomer mixture, 14÷1, (*Z*)-isomer: δ -173.91, -165.71, -155.01, -139.27 (4F, all m); (*E*)-isomer: δ -174.50, -166.12, -155.41, -138.94 (4F, all m). Anal. calcd. for $C_{18}H_{15}F_4NO_4$: C, 56.11; H, 3.92; N, 3.64; found: C, 56.04; H, 4.05; N, 3.80.

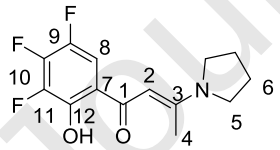
4.3.21. 3-{[2-(3,4-Dihydroxyphenyl)ethyl]amino}-3-phenyl-1-(3,4,5-trifluoro-2-hydroxyphenyl)prop-2-en-1-one ***(17a)*** was synthesized according to *method B* in inert atmosphere of argon, using EtOH as solvent from 380 mg (1 mmol) of flavone **5a** 379 mg (2 mmol) of dopamine hydrochloride and 202 mg (2 mmol) of Et_3N. The reaction vessel was filled with argon, dopamine hydrochloride 379 mg (2 mmol) was added to a mixture. Yield 159 mg (37%), yellow powder, mp 159–161˚C (column chromatography on silica gel, using $CHCl_3$). IR (DRA): ν 3535, 3223 (N–H), 2949, 2935 (O–H), 1590 (C=O), 1511, 1441, 1269 (C–N, C=C, C–H), 1021, 1003 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO$): δ 2.64 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2, C-15), 3.39 (2H, q, $^3J_{HH}$ = 6.7 Hz, CH_2, C-14), 5.83 (1H, s, H, C-2), 6.35–6.62 (3H, m, C_6H_3), 7.40–7.54 (5H, m, Ph), 7.89 (1H, m, H, C-9), 8.72, 8.75 (2H, both s, 2 OH), 10.99 (1H, t, $^3J_{HH}$ = 6.0 Hz, NH), 14.35 (1H, s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 35.31 (s, C-15), 46.75 (s, C-14), 91.68 (s, C-2), 110.02 (m, C-8), 115.47 (s, C-17), 116.05 (s, C-21), 116.21 (m, C-9), 119.32 (s, C-22), 127.53 (s, C-5), 128.49 (s, C-6), 128.71 (s, C-7), 129.94 (s, C-16), 134.25 (s, C-4),

139.37 (m, C-12), 141.74 (m, C-10), 142.42 (m, C-11), 143.80 (s, C-20), 145.13 (s, C-19), 148.02 (m, C-13), 168.56 (s, C-3), 186.09 (m, C-1). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -159.17, -154.22, -149.12 (3F, all m). Anal. calcd. for $C_{23}H_{18}F_3NO_4$: C, 64.34; H, 4.23; N, 3.26; found: C, 64.52; H, 4.57; N, 3.44.



4.3.22. 3-{[2-(3,4-Dihydroxyphenyl)ethyl]amino}-3-phenyl-1-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)prop-2-en-1-one ***(17b)*** was synthesized according to *method B* in inert atmosphere of argon, using EtOH as solvent from 398 mg (1 mmol) of flavone **5b** 379 mg (2 mmol) of dopamine hydrochloride and 202 mg (2 mmol) of Et_3N. The reaction vessel was filled with argon, dopamine hydrochloride 379 mg (2 mmol) was added to a mixture. Yield 170 mg (38%), yellow powder, mp 163–166˚C (column chromatography on silica gel, using $CHCl_3$). IR (DRA): ν 3443, 3378 (N–H), 2966, 2922 (O–H), 1653 (C=O), 1515, 1463, 1347 (C-N, C=C, C–H), 1002 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 2.66 (2H, t, $^3J_{HH}$ = 7.0 Hz, CH_2, C-15), 3.41 (2H, q, $^3J_{HH}$ = 6.8 Hz, CH_2, C-14), 5.51 (1H, s, H, C-2), 6.35–6.63 (3H, m, C_6H_3), 7.40–7.55 (5H, m, Ph), 8.73, 8.76 (2H, both s, 2 OH), 11.07 (1H, t, $^3J_{HH}$ = 5.8 Hz, NH), 13.88 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -172.46, -164.49, -154.45, -139.97 (4F, all m). Anal. calcd. for $C_{23}H_{17}F_4NO_4$: C, 61.75; H, 3.83; N, 3.13; found: C, 61.75; H, 3.75; N, 3.03.

4.3.23. 3-(Pyrrolidin-1-yl)-1-(3,4,5-trifluoro-2-hydroxyphenyl)but-2-en-1-one ***(18a)*** was synthesized according to *method C* from 256 mg (1 mmol) of chromone **4a** and 142 mg (2 mmol) of pyrrolidine, using EtOH as solvent. Yield 165 mg (58%), yellow powder, mp 174–177˚C (EtOH). IR (DRA): ν 2984, 2878 (O–H), 1641, 1539 (C=O), 1445, 1341, 1227 (C–N, C=C, C–H), 1022, 983 (C–F) cm^{-1}. ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$+CCl_4): δ 2.00 (4H, m, $(CH_2)_2$, C-6), 2.59 (3H, s, CH_3), 3.56 (4H, m, $(CH_2)_2$, C-5), 5.51 (1H, s, H, C-2), 7.67 (1H, d.d.d, J_{HF} = 11.6, 9.0, 2.2 Hz, H, C-8), 15.47 (1H, s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 18.54 (s, C-4), 24.25, 24.49 (both s, C-6), 48.90, 49.45 (both s, C-5), 89.66 (s, C-2), 109.69 (m, C-8), 117.08 (m, C-7), 139.90 (m, C-11), 141.44 (m, C-9), 142.40 (m, C-10), 149.42 (m, C-12), 165.21 (s, C-3), 185.30 (s, C-1). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$+CCl_4): δ -160.10, -155.65, -150.81 (3F, all m). Anal. calcd. for $C_{14}H_{14}F_3NO_2$: C, 58.95; H, 4.95; N, 4.91; found: C, 58.83; H, 5.12; N, 4.90.

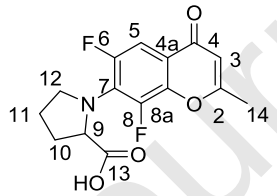


4.3.24. 3-(Pyrrolidin-1-yl)-1-(2,3,4,5-tetrafluoro-6-hydroxyphenyl)but-2-en-1-one ***(18b)*** was synthesized according to *method C* from 274 mg (1 mmol) chromone **4b** and 142 mg (2 mmol) of pyrrolidine, using EtOH as solvent. Yield 200 mg (66%), yellow powder, mp 144–145˚C (EtOH). IR (DRA): ν 2984, 2881 (O–H), 1650 (C=O), 1449, 1342, 1267 (C–N, C=C, C–H), 1000, 981 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.94 (4H, m, $(CH_2)_2$, C-6), 2.61 (3H, s, CH_3), 3.50 (4H, m, $(CH_2)_2$, C-5), 5.52 (1H, s H, C-2), 15.31 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -173.84, -165.61, -155.58, -139.22 (4F, all m). Anal. calcd. for $C_{14}H_{13}F_4NO_2$: C, 55.45; H, 4.32; N, 4.62; found: C, 55.67; H, 4.56; N, 4.52.

*4.3.25. 1-[3,5-Difluoro-2-hydroxy-4-(pyrrolidin-1-yl)phenyl]-3-(pyrrolidin-1-yl)but-2-en-1-one (**19a**)* was synthesized according to *method C* from 256 mg (1 mmol) of chromone **4a** and 284 mg (4 mmol) of pyrrolidine, using Me_2SO as solvent. Yield 296 mg (88%), yellow powder, mp 196–198˚C (EtOH). IR (DRA): ν 2972, 2890 (O–H), 1628 (C=O), 1442, 1355, 1216 (C–N, C=C, C–H), 1030, 1010 (C–F) cm^{-1}. ^1H NMR (500.13 MHz, $(CD_3)_2SO+CCl_4$): δ 1.94 (8H, m, $(CH_2)_4$, C-6), 2.56 (3H, s, CH_3), 3.53 (8H, m, $(CH_2)_4$, C-5), 5.40 (1H, s, H, C-2), 7.17 (1H, d.d, J_{HF} = 15.5, 1.5 Hz, H, C-8), 14.86 (1H, br.s, OH). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO+CCl_4$): δ -152.61, -136.65 (2F, both m). Anal. calcd. for $C_{18}H_{22}F_2N_2O_2$: C, 64.27; H, 6.59; N, 8.33; found: C, 64.53; H, 6.60; N, 8.22.

*4.3.26. 3-(Pyrrolidin-1-yl)-1-[2,3,5-trifluoro-6-hydroxy-4-(pyrrolidin-1-yl)phenyl]but-2-en-1-one (**19b**)* was synthesized according to *method C* from 274 mg (1 mmol) of chromone **4b** and 284 mg (4 mmol) of pyrrolidine, using Me_2SO as solvent. Yield 209 mg (59%), yellow powder, mp 178–180˚C (EtOH). IR (DRA): ν 2979, 2885 (O–H), 1641, 1618 (C=O), 1441, 1334, 1248 (C–N, C=C, C–H), 1027, 990 (C–F) cm^{-1}. ^1H NMR (500.13 MHz, $(CD_3)_2SO+CCl_4$): δ 1.95 (8H, m, $(CH_2)_4$, C-6), 2.59 (3H, s, CH_3), 3.52 (8H, m, $(CH_2)_4$, C-5), 5.57 (1H, s H, C-2), 15.25 (1H, s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 18.87 (s, C-4), 24.32, 24.52 (both s, C-6), 25.14 (s, C-6'), 48.62, 48.97 (both s, C-5), 50.99 (t, *J* = 6.3 Hz, C-5'), 94.62 (d, *J* = 18.5 Hz, C-2), 100.76 (d, *J* = 11.8 Hz, C-7), 130.13 (m, C-11), 133.73 (m, C-9), 136.64 (m, C-8), 146.51 (m, C-10), 148.61 (d.d, *J* = 12.6, 7.6 Hz, C-12), 164.25 (s, C-3), 183.22 (m, C-1). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO+CCl_4$): δ -165.80, -159.33, -140.89 (3F, all m). Anal. calcd. for $C_{18}H_{21}F_3N_2O_2$: C, 61.01; H, 5.97; N, 7.91; found: C, 61.11; H, 6.04; N, 7.87.

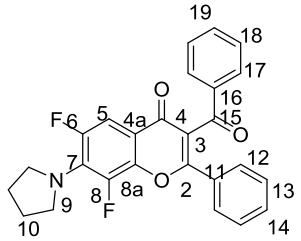
*4.3.27. 1-(6,8-Difluoro-2-methyl-4-oxo-4H-chromen-7-yl)proline (**20a**)* was synthesized according to *method B* from 256 mg (1 mmol) of chromone **4a** and 230 mg (2 mmol) of proline. Yield 105 mg (34%), white powder, mp 221–223˚C ($CHCl_3$, $EtOH_{aq}$). IR (DRA): ν 2964, 2892 (O–H), 1742 (CO_2H), 1639, 1616 (C=O), 1524, 1471, 1354, 1314 (C–N, C=C, C–H), 1035 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.92 (4H, m, $(CH_2)_2$, C-10, C-11), 2.37 (3H, s, CH_3), 3.75 (2H, m, CH_2, C-12), 4.70 (1H, m, H, C-9), 6.16 (1H, s, H, C-3); 7.36 (1H, d.d, J_{HF} = 13.9, 2.0 Hz, H, C-5), 12.70 (1H, br.s, OH). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 19.80 (s, C-14), 24.10 (s, C-11), 30.41(s, C-10), 52.20 (t, *J* = 6.4 Hz, C-12), 62.45 (t, *J* = 5.6 Hz, C-9), 104.94 (m, C-5), 109.30 (s, C-3), 112.93 (d, *J* = 8.1 Hz, C-4a), 130.31 (d.d, *J* = 14.6, 8.1 Hz, C-7), 139.92 (m, C-8), 112.93 (d, *J* = 11.2 Hz, C-8a), 150.13 (m, C-6), 165.87 (s, C-2), 173.61 (s, C-4), 174.55 (br.s, C-13). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -147.05, -124.19 (2F, both m). Anal. calcd. for $C_{15}H_{13}F_2NO_4$: C, 58.26; H, 4.24; N, 4.53; found: C, 58.10; H, 4.25; N, 4.50.



*4.3.28. 1-(5,6,8-Trifluoro-2-methyl-4-oxo-4H-chromen-7-yl)proline (**20b**)* was synthesized according to *method C* from 274 mg (1 mmol) of chromone **4b** and 230 mg (2 mmol) of proline. Yield 128 mg (39%), yellow powder, mp 230–232˚C ($CHCl_3$, $EtOH_{aq}$). IR (DRA): ν 3061 (O–H), 1693 (CO_2H), 1625 (C=O), 1521, 1480, 1353 (C-N, C=C, C–H), 1036, 1024 (C–F) cm^{-1}. ^1H NMR (400.13 MHz, $(CD_3)_2SO$): δ 1.93 (4H, m, $(CH_2)_2$, C-10, C-11), 2.33 (3H, s, CH_3), 3.78 (2H, m, CH_2, C-12), 4.71 (1H, m, H, C-9), 6.07 (1H, s, H, C-3), 12.80 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -154.91, -153.41, -148.08 (3F, all m). Anal. calcd. for $C_{15}H_{12}F_3NO_4$: C, 55.05; H, 3.70; N, 4.28; found: C, 55.54; H, 4.05; N, 4.01.

*4.3.29. 3-Benzoyl-6,8-difluoro-2-phenyl-7-(pyrrolidin-1-yl)-4H-chromen-4-one (**21a**)* was synthesized according to *method C* from 380 mg (1 mmol) of flavone **5a** and 142 mg (2 mmol) of pyrrolidine, using EtOH as solvent. Yield 169 mg (39%), yellow powder, mp 210–

214˚C (EtOH). IR (DRA): ν 2978, 2883 (O–H), 1668, 1615 (C=O), 1479, 1447, 1349 (C–N, C=C, C–H), 1036, 1025 (C–F) cm^{-1}. ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$): δ 1.92 (4H, m, $(CH_2)_2$, C-10), 3.72 (4H, m, $(CH_2)_2$, C-9), 7.62 (1H, m, H, C-5), 7.42–7.92 (10H, m, 2 Ph). ^{13}C NMR (125.76 MHz, $(CD_3)_2SO$): δ 25.32 (s, C-10), 51.34 (s, C-9), 105.35 (m, C-5), 111.39 (m, C-4a), 121.35 (s, C-3), 128.17 (s, C-12), 128.85 (s, C-17), 128.94 (s, C-13), 129.13 (s, C-14), 131.30 (s, C-11), 131.48 (s, C-14), 134.08 (s, C-19), 136.46 (s, C-16), 138.34–154.40 (all m, C-6, C-7, C-8, C-8a), 160.56 (br.s, C-2), 173.39 (br.s, C-4), 192.97 (s, C-15). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -149.19, -123.75 (2F, both m). Anal. calcd. for $C_{26}H_{19}F_2NO_3$: C, 72.38; H, 4.44; N, 3.25; found: C, 72.96; H, 4.45; N, 3.35.



*4.3.30. 3-Benzoyl-5,6,8-trifluoro-2-phenyl-7-pyrrolidin-1-yl-4H-chromen-4-one (**21b**)* was synthesized according to *method C* from 398 mg (1 mmol) of flavone **5b** and 142 mg (2 mmol) of pyrrolidine, using EtOH as solvent. Yield 153 mg (34%), yellow powder, mp 224–227˚C (EtOH). IR (DRA): ν 2980, 2886 (O–H), 1669, 1648 (C=O), 1494, 1448, 1352 (C–N, C=C, C–H), 1003 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO+CCl_4$): δ 1.98 (4H, m, $(CH_2)_2$, C-10), 3.77 (4H, m, $(CH_2)_2$, C-9), 7.37–7.89 (10H, m, 2 Ph). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO+CCl_4$): δ -155.68, -155.06 (2F, all m), -146.99 (1F, d.d, J = 17.7, 9.2 Hz). Anal. calcd. for $C_{26}H_{18}F_3NO_3$: C, 69.49; H, 4.04; N, 3.12; found: C, 69.71; H, 4.25; N, 3.02.

*4.3.31. 1-(3-Benzoyl-6,8-difluoro-4-oxo-2-phenyl-4H-chromen-7-yl)proline (**22a**)* was synthesized according to *method B* from 380 mg (1 mmol) of flavone **5a** and 230 mg (2 mmol) of proline. Yield 171 mg (35%), yellow powder, mp 230–232˚C ($CHCl_3$). IR (DRA): ν 2979 (O–H), 1736 (CO_2H), 1674 (C=O), 1522, 1471, 1394 (C–N, C=C, C–H), 1038, 1019 (C–F) cm^{-1}. ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$): δ 2.08 (4H, m, $(CH_2)_2$, C-10, C-11), 3.82 (2H, m, CH_2, C-12), 4.78 (1H, m, H, C-9), 7.42–7.94 (10H, m, 2 Ph), 7.62 (1H, m, H, C-5), 12.79 (1H, br.s, OH). ^{19}F NMR (470.52 MHz, $(CD_3)_2SO$): δ -147.65 (1F, d, J = 11.9 Hz), -123.14 (1F, m). Anal. calcd. for $C_{27}H_{19}F_2NO_5$: C, 68.21; H, 4.03; N, 2.95; found: C, 68.30; H, 4.28; N, 2.98.

*4.3.32. 1-(3-Benzoyl-5,6,8-trifluoro-4-oxo-2-phenyl-4H-chromen-7-yl)proline (**22b**)* was synthesized according to *method B* from 398 mg (1 mmol) of flavone **5b** and 230 mg (2 mmol) of proline. Yield 199 mg (40%), yellow powder, mp 265–268˚C ($CHCl_3$). IR (DRA): ν 2983, 2884 (O–H), 1748 (CO_2H), 1674 (C=O), 1523, 1479, 1368 (C–N, C=C, C–H), 1003 (C–F) cm^{-1}. ^{1}H NMR (400.13 MHz, $(CD_3)_2SO$): δ 2.14 (4H, m, $(CH_2)_2$, C-10, C-11), 3.85 (2H, m, CH_2, C-12), 4.80 (1H, m, H, C-9), 7.43–7.98 (10H, m, 2 Ph), 12.90 (1H, br.s, OH). ^{19}F NMR (376.44 MHz, $(CD_3)_2SO$): δ -154.11, -153.97 (2F, both m), -147.71 (1F, d.d, J = 18.3, 9.1 Hz). Anal. calcd. for $C_{27}H_{18}F_3NO_5$: C, 65.72; H, 3.68; N, 2.84; found: C, 65.91; H, 3.90; N, 3.24.

4.4. The X-ray structural analysis of compounds **10b·Na**, **17a**, **18b** was performed on an Xcalibur 3 automatic diffractometer (Oxford Diffraction, UK) with a CCD detector (graphite monochromator, λ (MoKα) 0.71073 Å, ω-scan). Absorption was corrected analytically using a multi-facet crystal model as implemented in the program CrysAlis RED v.1.171.39.38a. The structures were solved with the direct method from differential Fourier syntheses and refined by full-matrix least-squares F2 using the software package SHELXTL.[18] Refinement for non-hydrogen atoms was performed in the anisotropic approximation. Hydrogen atoms were placed in geometrically calculated positions and were included in the refinement according to the "rider" model in an isotropic approximation with thermal parameters dependent on the "parent" atoms.

4.4.1. Crystals of compound ***10b·Na*** ($C_{13}H_{18}F_4NNaO_8$, *M* 415.27) are monoclinic; spatial symmetry group *P2(1)/ c*; *a* 21.106(2), *b* 5.1186(4), *c* 17.0736(19) Å; α 90.00, β 106.223(12), γ 90.00°; *V* 1771.1(3) Å^3; *Z* 4; d_{calc} 1.557 g/cm^3; μ 0.172 mm^{-1}. 4763 total reflections, 2109 independent reflections, *R*-factor 0.0555, 289 refinable parameters (measured at 295(2) K).

4.4.2. Crystals of compound ***17a*** ($C_{23}H_{18}F_3NO_4$, *M* 429.38) are monoclinic; spatial symmetry group *P2(1)/ c*; *a* 19.237(4), *b* 4.5309(8), *c* 23.426(5) Å; α 90.00, β 108.76(3), γ 90.00°; *V* 1933.4(7) Å^3; *Z* 4; d_{calc} 1.475 g/cm^3; μ 0.120 мм$^{-1}$. 4735 total reflections, 1736 independent reflections, *R*- factor 0.0716, 296 refinable parameters (measured at 295(2) K).

4.4.3. Crystals of compound ***18b*** ($C_{14}H_{13}F_4NO_2$, *M* 303.25) are triclinic; spatial symmetry group $P1^{-}$; *a* 7.6785(16), *b* 13.215(2), *c* 13.531(3) Å; α 80.743(16), β 80.049(18), γ 75.127(17)°; *V* 1297.2(4) Å^3; *Z* 2; d_{calc} 1.553 g/cm^3; μ 0.142 мм$^{-1}$. 4394 total reflections, 1417 independent reflections, *R*- factor 0.0401, 382 refinable parameters (measured at 295(2) K).

The full set of X-ray structural data for compounds **10b·Na**, **17a**, **18b** were deposited at Cambridge Crystallographic Data Center (deposits CCDC 1901179, CCDC 1901173, CCDC 1901184).

4.5. Microbiological activity assay. Evaluation of antimicrobial properties (fungistatic and bactericidal) was performed by the serial dilution method recommended by the Institute of Clinical and Laboratory Standards (CLSI). Test strains of fungi: *Trichophyton rubrum* (RCPF F-1408), *Trichophyton mentagrophytes var. gypseum* (RCPF F-1425), *Trichophyton tonsurans* (RCPF F-1458), *Trichophiton violaceum* (RCPF F-1393/658), *Trichophyton mentagrophytes var. interdigitale* (RCPF F-1229), *Epidermophyton floccosum* (RCPF F-1174), *Microsporum canis* (RCPF F-1403), *Candida albicans* (RCPF Y-401 / NCTC 885-653) (Table 1), and test strains of clinically significant obligate and conditionally pathogenic bacteria: *Escherichia coli* (ATCC 8739), *Klebsiella pneumoniae* (ATCC 13883 / NCTC9633), *Citrobacter braakii* (ATCC 101/57), *Serratia marcescens* (ATCC 13880 / NCTC 10211), *Shigella flexneri* (1a8516), *Pseudomonas aeruginosa* (ATCC 9027 / NCTC 12924), *Staphylococcus aureus* (ATCC 25923 / NCTC 12981 (F-49)), *Staphylococcus aureus MRSA* (NCTC12493) (Table 2).

Fungi were cultivated at 27˚C on Sabouraud Dextrose Agar (SDA) and MIC was determined by using Sabouraud Dextrose Broth (SDB). The tested compounds and standard were dissolved in DMSO, 1÷10 and applied in different concentrations (from 1000 till 0.19 μg/mL). DMSO was used as a negative control and antifungal (Terbinafine) as positive control. The broth dilution test was performed in test tubes. The inoculum suspension, which gave the final concentration of $1^{x}10^8$ CFU/mL, was prepared. A growth control tube and sterility control tube were used in each test. After 14 days incubation at 27˚C, the MIC was determined visually as the lowest concentration that inhibits growth, evidenced by the absence of turbidity.

The Muller-Hinton medium was used for testing antibacterial activity. Adjust the density of the suspension to contain $1.5^{x}10^8$ CFU/mL by comparison with a 0.5 McFarland turbidity standard. For suspension, using colonies from an overnight (20 to 24-hour) agar plate incubated in 5% CO_2 36±1°C. Dilute this suspension 1÷100 in Muller-Hinton to give 10^6 CFU/mL. The test compounds concentrations: 1000, 500, 250, 125, 62.5, 31.25, 15.6, 7.8, 3.9, 1.9, 0.97 μg/mL (solvent – DMSO, diluent – H_2O and GC agar base).

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