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REACTION OF METHYL 3-[(DIMETHYLAMINO)METHYLIDENE]-6-FLUORO-4-OXO -3,4-DIHYDROCHROMAN-2-CARBOXYLATE WITH PRIMARY AND SECONDARY AMINES*

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A method was developed for substitution of the dimethylamino group by bioisosteric fragments by the action of various primary and secondary amines on methyl 3-[(dimethylamino)methylidene]-6-fluoro-4-oxo-3,4-dihydrochroman-2-carboxylate.

Keywords: 3-aminomethylidenechroman-4-one, primary and secondary amines, chroman, bioisosteric displacements.

The chemical design of biologically active substances, including analogs of natural oxygen-containing heterocycles, is achieved by the combination of several pharmacophoric fragments in the molecule. This often leads to an increase in some therapeutic effect but sometimes also leads to the appearance of unexpected types of activity.

The interest in derivatives of chromans, very important oxygen-containing heterocycles, arises from a series of factors. Compounds of this class, which are present in the vegetable kingdom, have a broad spectrum of biological activity and are used in medical practice. The high reactivity of these compounds makes them attractive subjects for synthetic organic chemistry [1, 2].

The present work was devoted to the development of a method for the production of methyl 3-[(dimethylamino)methylidene]-6-fluoro-4-oxo-chroman-2-carboxylate **2** and study of its reaction with primary and secondary amines.

N,*N*-Disubstituted 3-aminomethylenechroman-4-ones were obtained earlier by the reaction of the corresponding 3-hydroxymethylenechroman-4-ones with dimethylamine [3, 4], diethylamine [5], pyrrolidine [6, 7], piperidine [3], *N*-methylaniline [3] and by the action of secondary amines on chroman-containing Morita–Baylis–Hillman adducts [8].

We first obtained methyl 3-[(dimethylamino)methylidene]-6-fluoro-4-oxochroman-2-carboxylate **2** by the reaction of methyl 6-fluoro-4-oxo-3,4-dihydro-2*H*-chroman-2-carboxylate (**1**) with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in DMF. It is known that the insertion of the residues of a secondary or tertiary amine into the structure of the molecule leads to promising compounds for medical use. Thus, in order to obtain potential biologically active substances we then used compound **2** in reactions with various primary and secondary amines.

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*Dedicated to the happy memory of M. O. Lozinskii.

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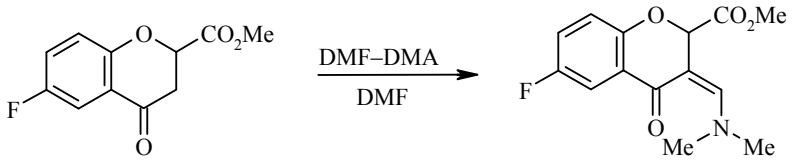
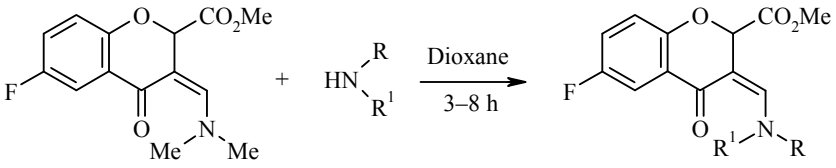
The high reactivity of the β-position of the enamino ketone fragment in compound **2** toward *N*-nucleophiles made it possible to obtain a wide range of 3-aminomethylidenechromanones **4**. For this purpose, we used the bioisosteric exchange method – the exchange of groups with similar physicochemical characteristics, like those with similar pharmacological effects [9].



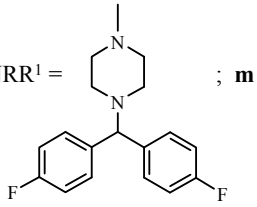
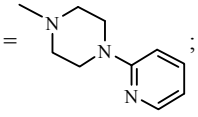
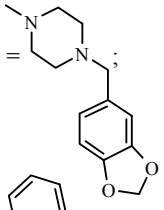
1 **2**

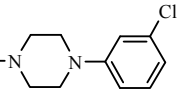
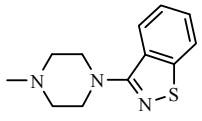
When heated with primary and secondary amines **3a-p** in dioxane, compound **2** gave compounds **4a-p**. For the isolation of compounds **4a-i** we used preparative column chromatography, and for the less soluble tertiary amines **4j-p** we used crystallization from acetonitrile.



2 **3a–p** **4a–p**

3, 4 a–i R^1 = H; **a** R = *n*-Pr, **b** R = *i*-Pr, **c** R = BocNH$(CH_2)_2$, **d** R = morpholin-4-yl$(CH_2)_2$,
e R = morpholin-4-yl$(CH_2)_3$, **f** R = Ph$(CH_2)_2$, **g** R = 1-benzylpiperidin-4-yl,
h R = *cyclo*-C_5H_9, **i** R = pyridin-3-yl(CH_2); **j** NRR^1 = piperidin-1-yl,
k NRR^1 = morpholin-4-yl;

l NRR^1 =  ; **m** NRR^1 =  ; **n** NRR^1 =  ;

o NRR^1 =  ; **p** NRR^1 = 

The reaction of the 3-dimethylaminomethylidenechromanone **2** with the primary amines **3a-i** proceeds more quickly than the reaction with the secondary amines **3j-p**, and the formation of the desired products is complete after 3-4 and 4-8 h respectively (Table 1). The rate of substitution of the dimethylamino group by the respective amine residue also depends on the size of the substituent. For example, the reaction with *tert*-butyl-(2-aminoethyl)carbamate (**3c**) takes 8 h, while the reaction with the less bulky pyridin-3-ylmethylamine (**3i**) takes 6 h.

Compounds **4a-p** can exist in the form of two geometric (*Z*,*E*)-isomers. According to the ^{1}H NMR spectra of the obtained compounds, with the exception of compound **4i,** one isomer is formed preferentially. In the ^{1}H NMR spectrum of compound **4i,** the signals of protons close to the exocyclic double bond are doubled, indicating the formation of a mixture of the isomers.

TABLE 1. Physicochemical Properties of Compounds **4a-p**

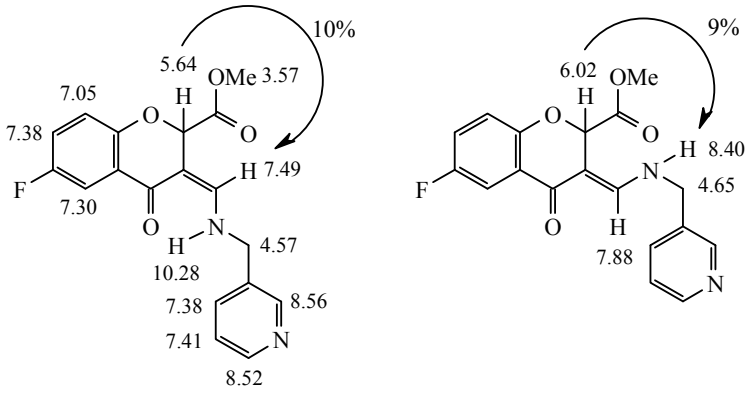
Compound	Empirical formula	Found, % / Calculated, %			mp., °C	*m/z* (I_{rel}, %), $[M+H]^+$	Reaction time, h	Yield, %
		C	H	N				
4a	$C_{15}H_{16}FNO_4$	61.43 / 61.36	5.50 / 5.43	4.78 / 4.61	96–97	294 (100)	3	89
4b	$C_{15}H_{16}FNO_4$	61.43 / 61.35	5.50 / 5.44	4.78 / 4.63	157–158	292* (100)	4	82
4c	$C_{19}H_{23}FN_2O_6$	57.86 / 57.71	5.88 / 5.73	7.10 / 7.02	126–128	395 (100)	8	73
4d	$C_{18}H_{21}FN_2O_5$	59.33 / 59.21	5.81 / 5.73	7.69 / 7.62	144–145	365 (100)	3.5	80
4e	$C_{19}H_{23}FN_2O_5$	60.31 / 60.24	6.13 / 6.06	7.40 / 7.33	107–108	379 (100)	3.5	80
4f	$C_{20}H_{18}FNO_4$	67.60 / 67.53	5.11 / 5.04	3.94 / 3.86	117–118	356 (100)	4	94
4g	$C_{24}H_{25}FN_2O_4$	67.91 / 67.86	5.94 / 5.87	6.60 / 6.53	132–133	425 (100)	4	73
4h	$C_{17}H_{18}FNO_4$	63.94 / 63.85	5.68 / 5.61	4.39 / 4.34	86–87	320 (100)	3.5	93
4i	$C_{18}H_{15}FN_2O_4$	63.15 / 63.08	4.42 / 4.36	8.18 / 8.12	151–152	343 (100)	4.5	84*[2]
4j	$C_{17}H_{18}FNO_4$	63.94 / 63.87	5.68 / 5.61	4.39 / 4.33	134–135	320 (99)	3–3.5	90
4k	$C_{16}H_{16}FNO_5$	59.81 / 59.75	5.02 / 4.93	4.36 / 4.29	141–142	320* (100)	3.5–4	93
4l	$C_{29}H_{25}F_3N_2O_4$	66.66 / 66.54	4.82 / 4.76	5.36 / 5.28	210–212	523 (100)	8	92
4m	$C_{21}H_{20}FN_3O_4$	63.47 / 63.39	5.07 / 5.01	10.57 / 10.02	185–187	398 (100)	7	94
4n	$C_{23}H_{21}FN_2O_6$	62.87 / 62.82	4.59 / 4.54	6.38 / 6.33	104–105	440 (100)	6	85
4o	$C_{22}H_{20}ClFN_2O_4$	61.47 / 61.39	4.46 / 4.37	6.52 / 6.46	145–147	430 (100)	6.5–7	92
4p	$C_{23}H_{20}FN_3O_4S$	60.92 / 60.86	4.45 / 4.39	9.27 / 9.21	156–158	452* (100)	8	81

*$[M-H]^+$

*[2]Ratio of isomers *Z*:*E* = 7:3.

Since the assignment of the series of signals in the ^1H NMR spectrum of compound **4i** constitutes a difficulty, we measured its correlation spectrum (COSY), which made it possible to assign the signals of both isomers (Fig. 1). For the minor component, the chemical shifts are only given for the signals of the protons whose chemical shifts differ from the chemical shifts of the main component.

It was possible to determine the geometric structure of the isomers by experiments employing the homonuclear Overhauser effect (NOE). The additional irradiation of the singlet corresponding to the H-2 proton of the chroman ring leads to a significant increase in the intensity of the doublet of the olefinic proton, absorbing at 7.49 ppm. This shows that the indicated protons are sterically close, i.e., that the double bond in the main isomer has the (*Z*)-configuration. This is also confirmed by the fact that the multiplet of the NH signal of this isomer is in the downfield region at 10.28 ppm on account of the formation of a strong intramolecular hydrogen bond with the carbonyl group of the chroman ring. In the minor isomer in the NOE experiment with additional irradiation of the signal of the H-2 proton, which absorbs at 6.02 ppm, a significant NOE is observed for the NH group located at 8.40 ppm. From this it follows that the exocyclic double bond in the given isomer has the (*E*)-configuration.

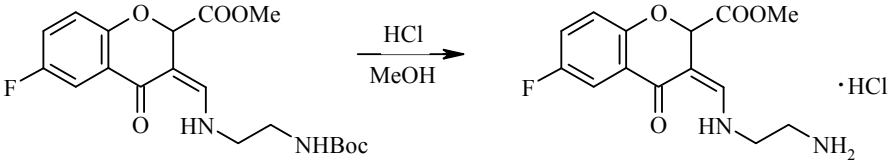


Main isomer Minor isomer

Data from experiments on the homonuclear Overhauser effect for the isomers of compound **4i.**

In the ^{1}H NMR spectra of 3-aminomethylidenechromans **4a-h,** the signal for the proton of the amino group appears in the form of a multiplet in the region of 10.01-10.26 ppm; the signal for the proton of the methylene group is characterized by a doublet in the region of 7.17-7.42 ppm (^3J = 14.0 Hz, Table 2). In compounds **4j-p,** this signal is observed in the form of a singlet in the region of 7.56-7.70 ppm (Table 2). On the basis of the obtained data, the products **4a-h**,**j-p** were assigned the (*Z*)-configuration.

Heating of compound **4c** in methanol with the addition of hydrochloric acid leads to removal of the protecting group and the release of methyl 3-{[(2-aminoethyl)amino]methylidene}-6-fluoro-4-oxo-3,4-dihydro-2*H*-chroman-2-carboxylate (**5**) with a high yield.



4c **5**

In the course of the present work, a simple and effective method was developed for the production of various 3-aminomethylidene-6-fluoro-4-oxo-3,4-dihydro-2*H*-chroman-2-carboxylates. The interest in these compounds arises from their potential biological activity and the possibility of using them as accessible highly reactive starting materials in the synthesis of more complex molecules.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in DMSO-d_6 solutions on a Mercury-400 spectrometer (400 MHz) with TMS as internal standard. The COSY spectra were measured by the standard procedure with gradient isolation of the signal. For the 1D gradient NOESY spectra. a mixing period of 200 ms was used. The measurement temperature was 20°C. The mass spectra were recorded with an Agilent 1100 LC/MSD chromatographic system (CI, 200 eV). Column chromatography was performed on silica gel (63-200 mesh, Merck) with a 7:3 mixture of CH_2Cl_2 and methanol as eluent. The melting points were determined with a Leica Galen III high-temperature microscope. The reactions and the individuality of the products were monitored by TLC on Merck 60 F_{254} plates with the 7:3 CH_2Cl_2–MeOH solvent system as eluent. Elemental analysis was performed on a Perkin-Elmer CHN analyzer. The solvents were purified and dried by the normal procedures.

Compound **1** was obtained by analogy with the method described in [10].

TABLE 2. ^{1}H NMR Spectra of 3-Aminomethylidenechroman-2-carboxilates **4a–p**

Compound	Chemical shifts, δ, ppm (*J*, Hz)					
	NH (1H, m)	=CH* (1H)	C_6H_3F	H-2 (1H, s)	CO_2CH_3 (3H, s)	R, R[1]
1	2	3	4	5	6	7
4a	10.07	7.23 (d)	7.33 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.12 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.93 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.45	3.60	3.29 (2H, m, C<u>H</u>$_2$CH$_2$CH$_3$); 1.61 (2H, m, CH$_2$C<u>H</u>$_2$CH$_3$); 0.95 (3H, t, *J* = 8.0, CH$_2$CH$_2$C<u>H</u>$_3$)
4b	10.06	7.32 (d)	7.34 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.14 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.92 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.47	3.53	3.66 (1H, m, C<u>H</u>(CH$_3$)$_2$); 1.30 (6H, d, *J* = 8.0, CH(C<u>H</u>$_3$)$_2$)
4c	10.01	7.42 (d)	7.73 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.49 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.98 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.45	3.72	6.62 (1H, m, NHBoc); 3.75 (2H, m, C<u>H</u>$_2$CH$_2$NHBoc); 3.26 (2H, m, CH$_2$C<u>H</u>$_2$NHBoc); 1.37 (9H, s, C(CH$_3$)$_3$)
4d	10.04	7.24 (d)	7.35 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.14 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.92 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.45	3.60	3.57 (4H, m, 2C<u>H</u>$_2$N morpholine); 3.56 (2H, m, NHC<u>H</u>$_2$CH$_2$N); 3.42 (2H, m, NHCH$_2$C<u>H</u>$_2$N); 2.48 (4H, m, 2CH$_2$O morpholine)
4e	10.09	7.22 (d)	7.36 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.14 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.94 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.45	3.60	3.54–3.62 (4H, m, 2CH$_2$N morpholine); 3.54 (2H, m, NHC<u>H</u>$_2$CH$_2$CH$_2$N); 3.40 (2H, m, NHCH$_2$CH$_2$C<u>H</u>$_2$N); 2.36 (4H, m, 2CH$_2$O morpholine); 1.73 (2H, m, NHCH$_2$C<u>H</u>$_2$CH$_2$N)
4f	10.08	7.24 (d)	7.39 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.20 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.97 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.44	3.62	7.24–7.29 (5H, m, H Ph); 3.58 (2H, m, NC<u>H</u>$_2$CH$_2$Ph); 2.94 (2H, t, *J* = 8.0, NCH$_2$C<u>H</u>$_2$Ph)
4g	10.16	7.17 (d)	7.37 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.14 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.92 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.47	3.59	7.23–7.29 (5H, m, H Ph); 3.47 (2H, s, NCH$_2$Ph); 3.34 (1H, t, NCH); 2.78 (2H, m, CH$_2$N piperidinyl); 2.13 (2H, m, C<u>H</u>$_2$N piperidinyl); 2.09 (2H, m, C<u>H</u>$_2$CH$_2$N piperidinyl); 1.93 (2H, m, C<u>H</u>$_2$CH$_2$N piperidinyl)
4h	10.11	7.34 (d)	7.37 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.17 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.95 (1H, dd, $^4J_{H–F}$ = 4.0, ^3J = 8.0, H-8)	5.51	3.63	3.89 (1H, m, NHCH); 2.06–2.02 (8H, m, (CH2)4)

TABLE 2 (continued)

1	2	3	4	5	6	7
4i	10.28	7.49 (d)	7.38 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.30 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 7.05 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	5.64	3.57	8.56 (1H, s, H-2 Py); 8.52 (1H, d, J = 4.4, H Py); 7.41 (1H, d, J = 7.2, H Py); 7.38 (1H, d, J = 13.2, H-5 Py); 4.57 (2H, m, NHC$\underline{H}_2$Py)
4j	—	7.56 (s)	7.36 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.16 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.94 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.16	3.61	3.57–3.61 (4H, m, 2NC$\underline{H}_2$CH$_2$CH$_2$); 1.61 (6H, m, NCH$_2$(C$\underline{H}_2$)$_3$)
4k	—	7.59 (s)	7.38 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.17 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.95 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.22	3.71	3.65 (4H, m, 2CH$_2$N); 2.56 (4H, m, 2CH$_2$O)
4l	—	7.56 (s)	7.43 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.16 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.94 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.15	3.57	7.43–7.04 (8H, m, H Ar); 4.41 (1H, s, NC$\underline{H}$(C$_6$H$_4$F)$_2$); 3.69–2.44 (8H, m, (CH$_2$)$_4$ piperazine)
4m	—	7.69 (s)	7.36 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.18 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.97 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.27	3.63	8.09 (1H, d, J = 4.0, H-6 Py); 7.52 (1H, m, H-4 Py); 6.78 (1H, d, J = 8.0, H-3 Py); 6.63 (1H, dd, J = 13.2, H-5 Py); 3.72–3.79 (8H, m, (CH$_2$)$_4$ piperazine)
4n	—	7.58 (s)	7.35 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.18 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.96 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.19	3.63	6.87 (1H, s, H Ar); 6.75 (2H, s, H Ar); 5.96 (2H, s, OCH$_2$O); 3.70–3.58 (8H, m, (CH$_2$)$_4$ piperazine)
4o	—	7.67 (s)	7.38 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.18 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.97 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.28	3.63	7.20 (1H, t, J = 7.2, H Ar); 6.92 (1H, s, H Ar); 6.87 (1H, d, J = 8.4, H Ar); 6.77 (1H, d, J = 8.2, H Ar); 3.85–3.33 (8H, m, (CH$_2$)$_4$ piperazine)
4p	—	7.70 (s)	7.37 (1H, dd, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, H-5); 7.19 (1H, td, $^3J_{H\text{-}F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.97 (1H, dd, $^4J_{H\text{-}F}$ = 4.0, ^3J = 8.0, H-8)	6.30	3.58	8.06 (1H, d, J = 7.6, H Ar); 7.95 (1H, d, J = 8.0, H Ar); 7.54 (1H, t, J = 6.8, H Ar); 7.42 (1H, t, J = 6.8, H Ar); 3.96–33.62 (8H, m, (CH$_2$)$_4$ piperazine)

*Compound **4a-i** ^3J = 14.0 Hz

Methyl (3*Z*)-3-[(Dimethylamino)methylidene]-6-fluoro-4-oxo-3,4-dihydro-2H-chroman-2-carboxylate (2). To a solution of methyl 6-fluoro-4-oxo-3,4-dihydro-2*H*-chroman-2-carboxylate (**1**) (4.48 g, 20 mmol) in DMF (10 ml), DMF–DMA (4.76 g, 40 mmol) was added. The reaction mixture was heated with stirring at 150°C for 6 h. At the end of the reaction, the solvent was evaporated, and the residue was crystallized from a methanol–acetone mixture, 1:1. Yield 4.6 g (77%); mp 156-157°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.61 (1H, s, =CHNMe$_2$); 7.38 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.16 (1H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.95 (1H, dd, $J_{H–F}$ = 4.0, ^3J = 8.0, H-8); 6.22 (1H, s, H-2); 3.61 (3H, s, $CO_2C\underline{H}_3$); 3.26 (6H, s, N(CH_3)$_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 280 $[M+H]^+$ (100). Found, %: C 60.11; H 4.92; N 4.96. $C_{14}H_{14}FNO_4$. Calculated, %: C 60.21; H 5.05; N 5.02.

Methyl 3-Aminomethylidene-6-fluoro-4-oxo-3,4-dihydro-2*H*-chroman-2-carboxylates (4a-p) (General Method). To a solution of compound **2** (0.27 g, 1 mmol) in dioxane (5 ml), corresponding amine **3a-p** (2.5 mmol) was added. The reaction mixture was boiled with stirring for 3-8 h, and the reaction was monitored by TLC. At the end of the reaction the reaction mixture was evaporated, and the residue was chromatographed (compounds **4a-i**) or crystallized from acetonitrile (compounds **4j-p**).

Methyl (3*Z*)-3-{[(2-Aminoethyl)amino]methylidene}-6-fluoro-4-oxo-3,4-dihydro-2*H*-chroman-2-carboxylate Hydrochloride (5). A solution of compound **4c** (0.39 g, 1 mmol) in methanol (10 ml) and conc HCl (1 ml) was boiled for 2 h. At the end of the reaction, the solvent was evaporated and the residue was crystallized from 2-propanol. Yield 0.31 g (93%); mp 115-116°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.81 (1H, m, NH); 8.61 (1H, s, =CHN); 8.41 (3H, m, NH_2·HC1); 7.34 (1H, dd, $^3J_{H–F}$ = 8.0, ^4J = 3.0, H-5); 7.12 (H, td, $^3J_{H–F}$ = 8.0, ^4J = 3.0, ^3J = 8.0, H-7); 6.91 (H, dd, $J_{H–F}$ = 4.0, ^3J = 8.0, H-8); 6.16 (1H, s, H-2); 3.62 (2H, m, $C\underline{H}_2CH_2NH_2$); 3.57 (3H, s, CO_2CH_3); 2.99 (2H, m, $CH_2C\underline{H}_2NH_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 331 $[M+H]^+$ 100. Found, %: C 50.71; H 4.73; N 8.41. $C_{14}H_{16}ClFN_20_4$. Calculated, %: C 50.84; H 4.88; N 8.47.

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