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Synthesis of 3-Oxoesters and Functional Derivatives of Pyrimidin-4(3*H*)-one Based on 1-(2,6-Dihalophenyl)cyclopropan-1-carboxylic Acids

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Abstract—Special features of the synthesis and chemical transformations of novel functional derivatives of 6-[1-(2,6-dihalophenyl)cyclopropyl]pyrimidin-4(3*H*)-one and ethyl esters of 3-[1-(2,6-dihalophenyl)cyclopropyl]-2-methyl-3-oxopropanoic acids prepared from 2-(2,6-dihalophenyl)acetonitriles have been revealed. Novel achiral structural analogs of experimental anti-HIV agent MC-1501 have been synthesized.

Keywords: 3-oxoester, pyrimidin-4(3*H*)-one derivative, 1-(2,6-dihalophenyl)-cyclopropane-1-carboxylic acid

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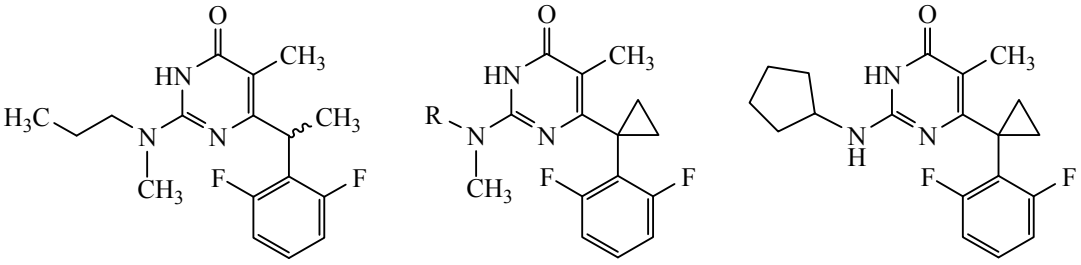
Extending the earlier reported studied on synthesis and comparative evaluation of biological activity of non-nucleotide derivatives of isocytosine exhibiting anti-HIV-1 activity [1–3], we obtained novel structural analogs of compound MC-1501 (Scheme 1).

The main difference of the prepared compounds **1** and **2** from the prototype is the presence of achiral 1,1-cyclopropylidene bridge between the benzene and pyrimidine rings. This avoids the stage of separation of optical isomers yet retaining the van der Waals repulsion between the 5-methyl group in the pyrimidine heterocycle and the dimethylene fragment of the cyclopropane cycle. This ensures the proper spatial orientation of the benzene and pyrimidine fragments demanded in view of high ant-HIV-1 activity. Moreover, to elucidate the effect of the aromatic ring substitution on the biological activity, we synthesized the corresponding 2-fluoro-6-chloro- and 2,6-dichlorophenyl structural analogs of the above-mentioned compounds. We have earlier demonstrated that such substitution can enhance the antiviral activity of the compounds [4].

We used 2-(2,6-dihalophenyl)acetonitriles **3a–3c** as the precursors of the target isocytosine derivatives. Their alkylation with 1,2-dibromoethane via the

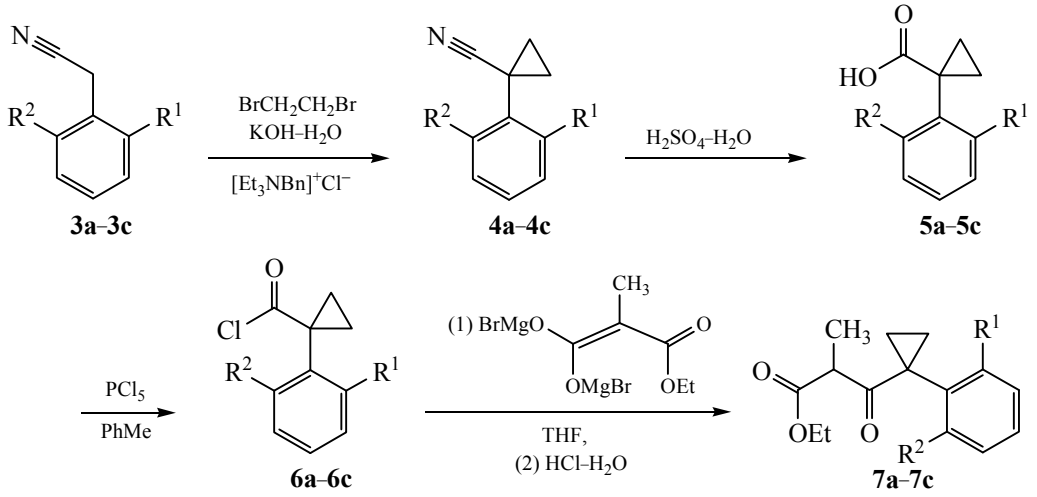
Scheme 1.



rats-MC-1501 **1a**, **1b** **2**

R = Pr (**a**), *i*-Pr (**b**).

Scheme 2.



$R^1 = R^2 = F$ (**a**), $R^1 = Cl$, $R^2 = F$ (**b**), $R^1 = R^2 = Cl$ (**c**).

procedure described elsewhere [5] afforded 1-(2,6-dihalophenyl)cyclopropane-1-carbonitriles **4a–4c** in practically quantitative yield (Scheme 2). Acid hydrolysis of those compounds via the procedure adopted from [6] gave the corresponding acids **5a–5c**. It should be noted that the prepared nitriles exhibited different stability under conditions of acid hydrolysis. For instance, nitrile **4a** was completely hydrolyzed into the acid **5a** via 4 h refluxing in 50% H_2SO_4. At the same time, complete hydrolysis of nitriles **4b** and **4c** under the same conditions required 8 and 18 h, respectively. Alkaline hydrolysis of the nitriles was not considered a possible route, since the major product of nitrile **4a** treatment with KOH in boiling glycol was a spirocyclic derivative of 4-fluoroindolin-2-one, whereas the acid **5a** was formed in low yield [5]. The substitution of the aromatic nucleus in acids **5a–5c** affected their solubility in toluene as well: it was the highest for compound **5a** and the lowest for acid **5c**.

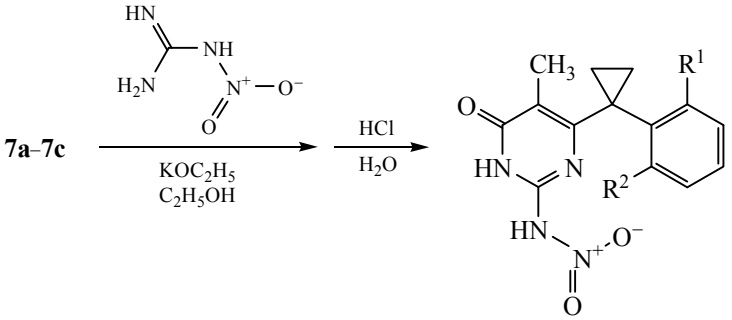
The procedure of 3-oxoesters synthesis has been earlier described by us for the preparation of ethyl 4-(2,6-difluorophenyl)-2-methyl-3-oxopentanoate [7]. However, in this work we used THF as solvent instead of diisopropyl ether, owing to the better solvation of intermediate reactive complexes by THF. When the reaction was performed in diisopropyl ether, those complexes precipitated. Furthermore, acyl chlorides **6a–6c** (prepared via the reaction of acids **5a–5c** with PCl_5 in anhydrous toluene) were used as the acylating agents instead of 2-(2,6-difluorophenyl)propanoyl chloride. The duration of the reaction was increased in comparison with the same reaction of the prototype [7] to 18 h, in view of spatial effects reducing the reactivity of acyl chlorides **6a–6c** (Scheme 2).

We investigated the possibility of cyclocondensation of the prepared 3-oxoesters with $H_2NC(NH)NHNO_2$ (picrite) in a KOEt solution in EtOH (Scheme 3). The reaction was performed via the adopted method earlier described for ethyl 4-(2,6-dihalophenyl)-2-methyl-4-methoxy-3-oxobutanoates [8]. It should be noted that we could only isolate N^2-nitroisocytosine **8a** in pure form with satisfactory yield.

In the case of the condensation of 3-oxoesters **7b** and **7c**, the target N^2-nitroisocytosines were formed in trace amount (HPLC/MS analysis of the crude reaction product), the reaction mixtures containing the starting 3-oxoesters and numerous products of their side reactions. Notably, the attempt of compounds **7b** and **7c** cyclocondensation with $(H_2N)_2CS$ under the earlier elaborated conditions [4] did not result in the formation of target 2-thiothymine derivatives as well. Similarly, HPLC/MS analysis of the reaction products revealed the presence of the unreacted 3-oxoesters **7b** and **7c** along with their decomposition products.

Compound **8a** was introduced in the aminolysis reaction using cyclopentylamine, methylisopropyl-amine, and methylpropylamine in butanol (Scheme 4). The choice of the amines was based on the earlier discovered regularities of the anti-HIV activity for the related compounds as function of their structure [8]. It should be noted that the amine nature significantly affected the reaction course and its products composition. The use of more nucleophilic primary

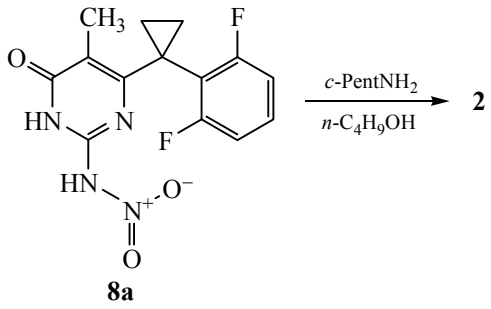
Scheme 3.



$R^1 = R^2 = F$ (**a**), $R^1 = Cl$, $R^2 = F$ (**b**), $R^1 = R^2 = Cl$ (**c**).

cyclopentylamine resulted in the full conversion of the starting pyrimidine derivative in the target aminolysis product 12 times faster than in the case of methylisopropylamine. Moreover, the target derivative of 2-(cyclopentylamino)pyrimidine **2** was practically completely crystallized from the reaction mixture.

Scheme 4.



The following features were marked for the reactions involving methylisopropylamine and methylpropylamine. First, the complete conversion of the starting derivative **8a** was attained faster with the use of methylisopropylamine. Second, the products of the reactions (after isolation, chromatographic purification, and recrystallization) revealed the identical melting point (127–128°C) and the R_f value (see the table); that was unlikely for the target isomers **1a** and **1b**.

The comprehensive study of the product by means of elemental analysis, HPLC/MS analysis, and correlation heteronuclear NMR spectroscopy revealed that in both cases the isolated compound was the product of alcoholysis of the starting compound **8a**: 2-butoxy-6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methylpyrimidin-4(3*H*)-one **9** (Scheme 5). That explained faster conversion of compound **8a** when using more sterically hindered, less nucleophilic yet more basic methylisopropylamine: the amine acted as base catalyst rather than nucleophilic agent.

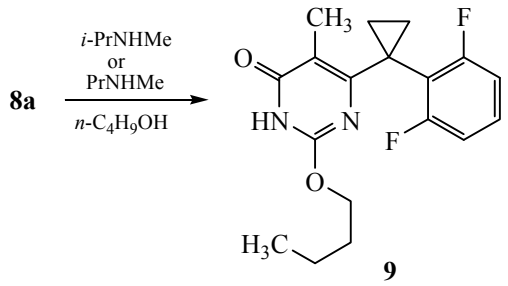
The revealed reaction pathway was not trivial and was likely explained by strong sensitivity of the starting substrate **8a** to spatial effects. That was in turn due to the orientation of the 1-(2,6-difluorophenyl)cyclopropyl substituent with respect to the pyrimidine ring.

Comparative analysis of correlation NMR spectra of compounds **8a**, **9**, and **2** revealed an important

R_f values for compound **8a** and products of its reaction with cyclopentylamine, methylpropylamine, and methylisopropylamine

Compound	Polygram SIL UV_{254}		Alugram Nano-SIL UV_{254}	
	C_6H_{14}–EtOAc–MeOH (12 : 3 : 1)	$CHCl_3$–MeOH (19 : 1)	C_6H_{14}–EtOAc–MeOH (12 : 3 : 1)	$CHCl_3$–MeOH (19 : 1)
8a	0.16	0.57	0.7	0.49
2	0.19	0.28	0.31	0.34
Product of reaction with PrNHMe	0.37	0.62	0.33	0.68
Product of reaction with *i*-PrNHMe	0.36	0.63	0.35	0.71

Scheme 5.



feature: in the case of derivatives **8a** and **9**, through-space spin-spin interaction of fluorine nucleus and carbon atom of the methyl group at the C^5 position of the pyrimidine cycle was observed. Such interaction has been scarcely observed in organic compounds [9], even though similar cases of fluorine-containing modified pyrimidine nucleosides have been described [10, 11]. The observation is extremely important, since the interaction of fluorine atom in the ligand molecule with the complementary part of the biological target can play a decisive role in the action of the pharmaceutically active compounds [12].

In the considered case, the marked spin-spin interaction could be likely related to a set of simultaneously acting factors. First, the van der Waals repulsion of the methyl group and the cyclopropyl moiety favored the conformation presuming close approach of the CH_3 group and the fluorine atom. On the other hand, hyperconjugation of electron-accepting nitroamino group and electron-donating methyl group via the system of conjugated multiple $C^2{=}N^1$ and $C^6{=}C^5$ bonds of the pyrimidine cycle enhanced the positive charge at the corresponding carbon atom. Hence, certain electrostatic attraction appeared between the methyl group and the fluorine atom. The origin of the effect could be better understood using quantum-chemical simulation results (cf. the similar case of 2-substituted derivatives of 6-(2,6-dihalobenzyl)-5-methylpyrimidin-4(3*H*)-one in [13]). Evidently, butoxy group, being a stronger electron acceptor as compared to cyclopentylamino one, also favored the electrostatic attraction of the methyl group in thymine fragment and fluorine atom in the aromatic nucleus.

In summary, we prepared novel derivatives of pyrimidin-4(3*H*)-one based on 1-(2,6-difluorophenyl)cyclopropane-1-carboxylic acid. Significant difference in the course and the products composition of solvolysis of compound **8a** depending on the reactant nature (primary or secondary amine) was demonstrated. Two of the synthesized derivatives of 6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methylpyrimidin-4(3*H*)-one are promising structural analogs of compound MC-1501, whereas the earlier unknown derivative of N^2-nitroisocytosine is a prospective building block for preparation of antiviral derivatives of pyrimidine.

EXPERIMENTAL

^1H, ^{13}C, and ^{19}F NMR spectra were recorded using Varian Mercury 300 BB (HDMS as internal reference) and Bruker Avance III 400 (TMS as internal reference) instruments in DMSO-d_6 at 30°C. HPLC analysis was performed using a chromatographic system consisting of a Jasco PU-980 pumping block, a Jasco UV-975 UV/Vis detector, and a Rheodyne injection system (column Reprosil C18 AQ 150×4.6 mm, 3 μm, 0.75 mL/min, λ 220 nm, 30°C, mobile phase H_2O–MeCN–85% H_3PO_4, 200 : 200 : 1 v/v/v). HPLC/MS analysis was performed using an Agilent 1200 instrument under the following conditions: column Reprosil-Pur Basic C18, 250×4.6 mm, 5 μm (Dr. Maisch GmbH); eluents 0.01% CF_3COOH–H_2O (A) or 0.01% CF_3COOH–MeCN (B); flow rate 1 mL/min; detection with a VWD single-wave UV/Vis detector, ELSD detector, and an Agilent 6310 Ion Trap LCMS ion trap (in the positive ions mode). Mass spectra were recorded under conditions of electrospray ionization. GLC/MS analysis of compounds **7a–7c** was performed using a Varian Saturn 2100 instrument under conditions of electron impact ionization (70 eV). Elemental analysis was performed using a Vario EL Cube instrument. Melting points were determined via the capillary method using a Buchi M-565 instrument at heating rate of 1 deg/min (the corrected values are reported). TLC analysis was performed using Polygram Sil G, UV_{254}, and Alugram Nano-SIL UV_{254} (Machery Nagel) plates developing with UV irradiation, λ 254 nm. L14002 silica gel (Alfa Aesar), 0.06–0.20 mm (70–230 mesh) was used for column chromatography.

Chemicals were purchased from Alfa Aesar and Acros Organics; the solvents were purchased from Komponent-Reaktiv and dried via conventional procedures [14].

6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-(cyclopentylamino)pyrimidin-4(3*H*)-one (2). A mixture of 1 g (3.1 mmol) of compound **8a**, 10 mL of *n*-butanol, and 4 mL (3.452 g, 40.5 mmol) of cyclo-

pentylamine was isolated from moisture and carbon dioxide and refluxed until complete conversion of the starting pyrimidine derivative (TLC). After cooling the reaction mixture to ambient, the precipitate was filtered off, washed with 5 mL of *n*-BuOH, dried, and recrystallized from MeCN. Yield 487 mg (60%), mp 202–204°C (CH_3CN). ^{1}H NMR spectrum (400.16 MHz, DMSO-d_6), δ, ppm: 1.16 m (2H, CH), 1.39 m (2H, $C^{2,5}H_2^{eq}$, *c*-Pent), 1.54 m (2H, $C^{3,4}H_2^{eq}$, *c*-Pent), 1.6 m (2H, CH), 1.61 s (3H, 5-CH_3), 1.63 m (2H, $C^{3,4}H_2^{ax}$, *c*-Pent), 1.91 m (2H, $C^{2,5}H_2^{ax}$, *c*-Pent), 4.06 m (1H, CH, *c*-Pent), 6.08 br.d (1H, NH, $^3J_{HH}$ = 7.9 Hz), 7.01 d.d (2H, $C^{3,5}H$, $^3J_{HH}$ = 7.9, $^3J_{HF}$ = 8.0 Hz), 7.33 m (1H, C^4H), 10.32 br.s (1H, NH). ^{13}C NMR spectrum (100.62 MHz, DMSO-d_6), δ_C, ppm: 9.14 (5-CH_3), 15.28 (CH_2, *c*-Pr), 20.59 (C, *c*-Pr), 23.17 ($C^{3,4}$, *c*-Pent), 32.27 ($C^{2,5}$, *c*-Pent), 51.88 (C^1, *c*-Pent), 107.38 (C^5, pyrimidine), 111.55 d.d ($C^{3,5}_{arom}$, $^2J_{CF}$ = 19.2, $^4J_{CF}$ = 5.5 Hz), 119.39 t (C^1_{arom}, $^2J_{CF}$ = 16.5 Hz), 150.63 (C^2, pyrimidine), 162.04 d.d ($C^{2,6}_{arom}$, $^1J_{CF}$ = 251.3, $^3J_{CF}$ = 8.7 Hz), 162.12 (C^6, pyrimidine), 163.48 (C^4, pyrimidine). Found, %: C 65.81; H 5.98; N 11.94. $C_{19}H_{21}F_2N_3O$. Calculated, %: C 66.07; H 6.13; N 12.17.

2-Butoxy-6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methylpyrimidin-4(3*H*)-one (9). A mixture of 1 g (3.1 mmol) of compound **8a**, 10 mL of *n*-BuOH, and 4 mL (2.8 g, 38.4 mmol) of methylisopropylamine was isolated from moisture and carbon dioxide and refluxed until complete conversion of the starting pyrimidine derivative (TLC). After the reaction was complete, the solvent was distilled off under reduced pressure. The residue was dissolved in THF, mixed with silica gel, and evaporated to dryness. The adsorbed product was transferred to a column and eluted with a EtOAc–*c*-C_6H_{14} mixture (5→50% EtOAc by volume). The fractions containing the target product were combined, evaporated under reduced pressure, and recrystallized from hexane. Yield 652 mg (63%), mp 127–128°C (CH_3CN). ^{1}H NMR spectrum (400.16 MHz, DMSO-d_6), δ, ppm: 0.90 t (3H, $C\underline{H}_3CH_2CH_2CH_2$, J = 7.5 Hz), 1.22 m (2H, CH_2^{ax}, *c*-Pr), 1.36 sextet (2H, $CH_3C\underline{H}_2CH_2CH_2$, J = 7.2 Hz), 1.59 m (2H, CH_2^{eq}, *c*-Pr), 1.65 quintet (2H, $CH_3CH_2C\underline{H}_2CH_2$, J_1 6.8, J_2 7.2 Hz), 1.71 s (3H, 5-CH_3), 4.28 t (3H, $CH_3CH_2CH_2C\underline{H}_2$, J = 6.8 Hz), 7.03 m (2H, $C^{3,5}H$), 7.35 m (1H, C^4H), 12.14 br.s (1H, NH). ^{13}C NMR spectrum (100.62 MHz, DMSO-d_6), δ_C, ppm: 9.58 t (5-CH_3, $^6J_{CF}$ = 2.4 Hz), 13.55 ($\underline{C}H_3CH_2CH_2CH_2$), 15.29 ($CH_2$, *c*-Pr), 18.42 ($CH_3\underline{C}H_2CH_2CH_2$), 20.39 (C, *c*-Pr), 30.09 ($CH_3CH_2\underline{C}H_2CH_2$), 66.42 ($CH_3CH_2CH_2\underline{C}H_2$), 111.75 d.d ($C^{3,5}_{arom}$, $^1J_{CF}$ = 19.4, $^2J_{CF}$ = 6.1 Hz), 113.29 (C^5, pyrimidine), 118.80 (C^1_{arom}, J_{CF} = 17.1 Hz), 129.48 t (C^4_{arom}, J_{CF} = 10.5 Hz), 153.84 ($C^{2,6}$, pyrimidine), 160.33 (C^4, pyrimidine), 162.05 d ($C^{2,6}_{arom}$, $^1J_{CF}$ = 248.5, $^2J_{CF}$ = 7.8 Hz). Found, %: C 65.00; H 5.89; N 8.38. $C_{18}H_{20}F_2N_2O_2$. Calculated, %: C 64.66; H 6.03; N 8.38.

1-(2,6-Difluorophenyl)cyclopropane-1-carboxylic acid (5a). A mixture of 15.3 g (100 mmol) of 2-(2,6-difluorophenyl)acetonitrile, 152.5 g (70 mL, 812 mmol) of dibromoethane, and 32.7 g (144 mmol) of $Et_3BnN^+Cl^-$ was isolated from moisture and carbon dioxide and vigorously stirred at 60°C. A solution prepared from 95 g (1430 mmol, ≈84.5%) of KOH and 95 mL of water was then added dropwise; the mixture was stirred during 6 h at 60–65°C, and left overnight. On the next day, the reaction mixture was extracted with *t*-BuOMe (3×100 mL), the combined organic fractions were evaporated, and residual water was removed via azeotropic distillation with toluene. Then 60 mL of water and 40 mL of concentrated sulfuric acid were added to the obtained 1-(2,6-difluorophenyl)-cyclopropanecarbonitrile, and the mixture was refluxed during 4 h. The reaction mass was cooled to ambient; the precipitate was filtered off and dried. Yield 17.82 g (90%), mp 156–157°C (toluene). IR spectrum, ν, cm^{-1}: 412 s, 772 m, 946 m, 994 m, 1048 s, 1246 m, 1270 m, 1306 m, 1324 m, 1414 m, 1468 m, 1474 m, 1504 s, 1624 m, 1666 m, 1726 s. ^{1}H NMR spectrum (400.16 MHz, DMSO-d_6), δ, ppm: 1.18 m (2H, CH_2^{eq}, *c*-Pr), 1.58 m (2H, CH_2^{ax}, *c*-Pr), 7.03 m (2H, $C^{3,5}H$), 7.36 m (1H, C^4H), 12.54 br.s (1H, OH). Mass spectrum (EI), m/z (I_{rel}, %): 197.9 (100) $[M]^+$, 153.0 (37) $[M - COOH]^+$, 133.0 (35) $[M - COOH - HF]^+$, 127.2 (32) $[2,6\text{-}F_2C_6H_3CH_2]^+$. Found, %: C 60.50; H 4.08. $C_{10}H_8F_2O_2$. Calculated, %: C 60.61; H 4.07.

1-(2-Fluoro-6-chlorophenyl)cyclopropane-1-carboxylic acid (5b) was prepared similarly from 17 g (100 mmol) of 2-(2-fluoro-6-chlorophenyl)acetonitrile. Yield 19.9 g (93%), mp 165–166.5°C (toluene). ^{1}H NMR spectrum (400.16 MHz, DMSO-d_6), δ, ppm: 1.21 s (2H, CH_2^{eq}, *c*-Pr), 1.66 s (2H, CH_2^{ax}, *c*-Pr), 7.19 d.d (1H, C^4H, J_1 0.8, J_2 7.2 Hz), 7.29–7.37 m (2H, $C^{3,5}H$), 12.52 s (1H, COOH). ^{13}C NMR spectrum (100.62 MHz, DMSO-d_6), δ_C, ppm: 17.80 d (CH_2, *c*-Pr, J = 10.8 Hz), 21.51 d (C, *c*-Pr, J = 6.4 Hz), 114.46 d (C^4_{arom}), 125.56 q (C^3_{arom}, J = 16.1, J = 3.3 Hz), 129.79 d (C^5_{arom}, J = 39.2 Hz), 136.75 d (C^1, J = 19.6 Hz), 160.84 (C^2_{arom}), 163.31 (C^6_{arom}), 173.84 (COOH). Found, %: C 56.21; H 4.00. $C_{10}H_8ClFO_2$. Calculated, %: C 55.96; H 3.76.

1-(2,6-Dichlorophenyl)cyclopropane-1-carboxylic acid (5c) was prepared similarly from 18.6 g (100 mmol) of 2-(2,6-dichlorophenyl)acetonitrile. Yield 19.32 g (84%), mp 217.5–219°C (toluene). ^{1}H NMR spectrum (400.16 MHz, DMSO-d_6), δ, ppm: 1.25 q (2H, CH_2^{eq}, *c*-Pr, J = 3.7 Hz), 1.74 q (2H, CH_2^{ax}, *c*-Pr, J = 4.0 Hz), 7.30–7.35 m (1H, H^4), 7.44 d (1H, $H^{3,5}$, J = 8.0 Hz), 12.48 s (1H, COOH). ^{13}C NMR spectrum (100.62 MHz, DMSO-d_6), δ_C, ppm: 19.91 d (CH_2, *c*-Pr, J = 57.6 Hz), 25.91 (C, *c*-Pr), 128.71 d ($C^{3,5}_{arom}$, J = 42.6 Hz), 129.78 d (C^4_{arom}, J = 23.4 Hz), 135.50 (C^1_{arom}), 137.25 ($C^{2,6}_{arom}$), 173.46 (COOH). Found, %: C 52.10; H 3.38. $C_{10}H_8Cl_2O_2$. Calculated, %: C 51.98; H 3.49.

1-(2,6-Difluorophenyl)cyclopropane-1-carbonyl chloride (6a). 17.8 g (85.4 mmol) of PCl_5 was added to a solution of 15.8 g (79.8 mmol) of acid **5a** in 60 mL of anhydrous toluene. The reaction mixture was refluxed during 2 h preventing its contact with air moisture. On the next day, a mixture of toluene and $P(O)Cl_3$ was distilled off under reduced pressure, and the residue was distilled in vacuum. Yield 15.3 g (89%), bp 101°C (9 mmHg).

1-(2-Fluoro-6-chlorophenyl)cyclopropane-1-carbonyl chloride (6b) was prepared similarly from 10 g (46.7 mmol) of acid **5b**. Yield 10.3 g (95%), bp 102–105°C (3.7 mmHg).

1-(2,6-Dichlorophenyl)cyclopropane-1-carbonyl chloride (6c) was prepared similarly from 10 g (43.3 mmol) of acid **5c**. Yield 9.18 g (91%), bp 124–126°C (3.6 mmHg).

Ethyl 3-[1-(2,6-difluorophenyl)cyclopropyl]-2-methyl-3-oxopropanoate (7a). A solution of the Grignard reagent prepared from 9 g (≈370 mol) of Mg and 35 mL (45.9 g, 372 mmol) of *i*-PrBr in 400 mL of anhydrous THF was added dropwise to a solution of 27 g (184.8 mmol) of 2-(ethoxycarbonyl)propanoic acid in 200 mL of anhydrous THF at stirring and cooling, preventing the contact with air moisture and carbon dioxide. The resulting mixture was stirred during 15–20 min, cooled to –8°C with an ice/NaCl mixture, and treated with a solution of 13.5 g (58.2 mmol) of acyl chloride **6a** in 175 mL of anhydrous THF at stirring. Upon addition of the acyl chloride, the reaction mixture was stirred during 18 h on a cooling bath, then the temperature was raised to ambient, and stirring was continued during further 1 h at room temperature. The prepared solution was cooled with icy water and treated at stirring with 110 mL of 12% HCl. The reaction product was extracted with *t*-BuOMe (3×200 mL). The organic extracts were washed from acids with 10% aqueous solution of K_2CO_3 (during the phases separation, the mixture was filtered on a Buchner funnel to remove small amount of $MgCO_3$ precipitate), washed with water to neutral reaction, and dried with anhydrous $MgSO_4$. The filtrate was evaporated, and the residue was purified by fractional distillation under reduced pressure using a short Vigreaux column. Yield 15.3 g (93%), bp 127–128°C (2.5 mmHg). Major component content 95% (GLC/MS). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 1.05–1.42 m (7H, CH_3CH_2, CH_2, *c*-Pr), 1.72–1.83 m (3H, CH_3), 3.51–3.59 m (1H, CH), 3.85–4.01 m (2H, CH_2), 6.76–6.89 m (2H, $C^{3,5}H$), 7.18–7.29 m (1H, C^4H). The product was a mixture of the keto and the (*E,Z*)-enol form in dynamic equilibrium. The keto form: fraction 81.1%. Mass spectrum, *m*/*z* (I_{rel}, %): 284/ 283/282 (9/64/42) $[M]^+$, 254 (15), 209 (15), 188 (10), 181 (33), 153 (100), 133 (34), 127 (30); t_R 13.92 min. The enol form: fraction 18.9%. Mass spectrum (EI), *m*/*z* (I_{rel}, %): 283/282 (21/70) $[M]^+$, 237/236/235 (48/100/24), 207 (21), 153 (14), 127 (19), 83 (35); t_R 15.00 min. Found, %: C 64.20; H 6.00. $C_{15}H_{16}F_2O_3$. Calculated, %: C 63.82; H 5.71.

Ethyl 3-[1-(2-fluoro-6-chlorophenyl)cyclopropyl]-2-methyl-3-oxopropanoate (7b) was prepared similarly from 14.5 g (58.2 mmol) of compound **6b**. The product was additionally purified via adsorptive filtration [15]. Yield 14.42 g (83%). Major component content 95% (GLC/MS). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 298/299/300 (100/22/34) $[M]^+$, 225 (22), 189/190/191 (11/59/17), 161/162 (19/13); t_R 15.32 min. Found, %: C 59.97; H 5.78. $C_{15}H_{16}ClFO_3$. Calculated, %: C 60.31; H 5.40.

Ethyl 3-[1-(2,6-dichlorophenyl)cyclopropyl]-2-methyl-3-oxopropanoate (7c) was prepared similarly from 15.4 g (58.2 mmol) of compound **6c**. The product was additionally purified via adsorptive filtration [15]. Yield 15.78 g (86%). Major component content 95% (GLC/MS). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 314/315/316/317/318 (100/86/77/53/17) $[M]^+$, 206 (29); t_R 17.05 min. Found, %: C 56.78; H 4.95. $C_{15}H_{16}Cl_2O_3$. Calculated, %: C 57.16; H 5.12.

6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-(nitroamino)-pyrimidin-4(3*H*)-one (8a). 3.64 g (≈35 mmol) of nitroguanidine dried in dessicator over KOH to constant mass and 8.86 g (34.9 mmol) of 3-oxoester **7a** were added to a solution of KOEt prepared via dissolution of 2.8 g (71.8 mmol) of potassium in 100 mL of anhydrous EtOH. The

prepared mixture was refluxed at stirring during 24 h, preventing the contact with air moisture and carbon dioxide. The solvent was removed, and the residue was dissolved in 200 mL of water and filtered. The filtrate was extracted with *t*-BuOMe (3×75 mL), treated with activated carbon (about 1 g), and filtered; the product was precipitated from the aqueous solution by addition of 12% HCl to pH 2 at stirring. Yield 3.48 g (31%), mp 217°C (decomp., CH_3CN). ^{1}H NMR spectrum (400.16 MHz, DMSO-d_6), δ, ppm: 1.41 m (2H, CH), 1.57 m (2H, CH), 2.08 s (3H, 5-CH_3), 7.15 d.d (2H, $C^{3,5}H$, $^3J_{HH}$ = 7.9, $^3J_{HF}$ = 8.0 Hz), 7.44 m (1H, C^4H), 12.25 br.s (1H, NH, pyrimidine), 12.69 br.s (1H, NH). ^{13}C NMR spectrum (100.62 MHz, DMSO-d_6), δ_C, ppm: 10.16 t (5-$\underline{C}H_3$, J_{CF} = 16.5 Hz), 14.26 (CH_2), 16.89 ($CH_2\underline{C}$), 112.28 d.d ($C^{3,5}_{arom}$, $^2J_{CF}$ = 20.2, $^4J_{CF}$ = 6.3 Hz), 115.45 t (C^1_{arom}, $^2J_{CF}$ = 17.7 Hz), 116.71 (C^5, pyrimidine), 130.74 t (C^4_{arom}, $^3J_{CF}$ = 10.9 Hz), 145.76 (C^6, pyrimidine), 152.88 (C^2, pyrimidine), 161.69 d.d ($C^{2,6}_{arom}$, $^1J_{CF}$ = 251.3, $^3J_{CF}$ = 8.7 Hz), 161.82 (C^4, pyrimidine). Found, %: C 51.87; H 4.01; N 17.20. $C_{14}H_{12}F_2N_4O_3$. Calculated, %: C 52.18; H 3.75; N 17.39.

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