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Aminolysis of 6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-one

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Abstract—The aminolysis of 6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-one with various amines in butan-1-ol and under solvent-free conditions is successful when the amino group in the reagent is sterically unshielded and the reaction medium is characterized by a high dielectric permittivity. Reactions of the title compound with sterically shielded amines are accompanied by alcoholysis where the amine acts as a base catalyst.

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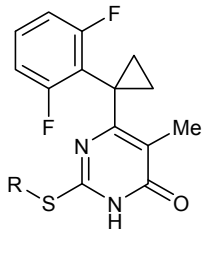
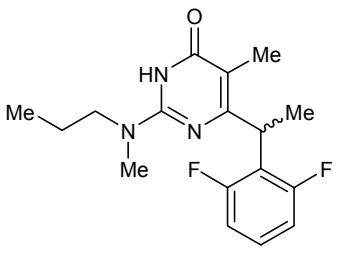
In continuation of our studies on the synthesis of functional non-nucleoside pyrimidine derivatives and their antiviral activity [1], we have found that 2-(alkylsulfanyl)-6-[1-(2,6-difluorophenyl)cyclopropyl]-pyrimidin-4(3*H*)-ones **A** at a nanomolar concentration exhibit a pronounced inhibitory effect on the replication of wild-type HIV-1 [2]. In this respect, 6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methyl-2-(nitroamino)pyrimidin-4-(3*H*)-one (**1**) turned out to be less active than the experimental drug MC1501 which is an isocytosine derivative [3, 4].

Attempted syntheses of direct analogs of MC1501 containing a 1-(2,6-difluorophenyl)cyclopropyl substituent in the 6-position of the pyrimidine ring have led to ambiguous results [5] due to considerable sensitivity of compound **1** to steric factor related to the structure and orientation of the 6-substituent, which affected nucleophilic attack of C^2. We have studied the aminolysis of **1** with various amines such as piperidine, morpholine, 4-methoxybenzylamine, 3-phenylpropan-1-amine, adamantan-2-amine, and (adamantan-1-yl)-methanamine and obtained isocytosine derivatives **2a**–**2c**, **2e**, and **2f**.

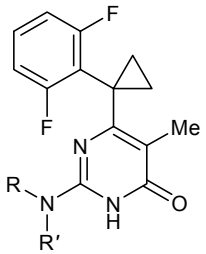
The choice of these amines was not accidental. As we showed previously, pyrimidine **1** reacted with cyclopentanamine in butan-1-ol to give the corresponding aminolysis products and that alcoholysis product was obtained in the reactions of **1** with



A



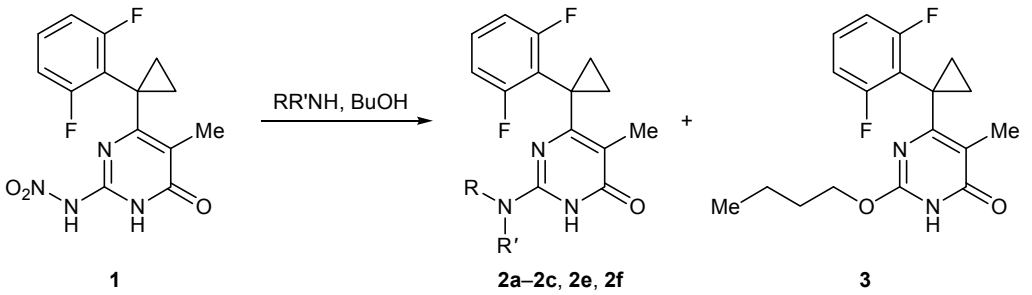
MC1501



2a–**2f**

A, R = $MeSCH_2CH_2$, *i*-Pr, Pr, EtCH(Me), *cyclo*-C_5H_9, Me_2CHCH_2, Bu; **2**, R = H, R′ = 4-$MeOC_6H_4CH_2$ (**a**), $Ph(CH_2)_3$ (**b**), 1-$AdCH_2$ (**c**), 2-Ad (**d**); RR′N = piperidin-1-yl (**e**), morpholin-4-yl (**f**).

Scheme 1.



1 **2a–2c**, **2e**, **2f** **3**

N-methylpropan-1-amine and *N*-methylpropan-2-amine [5]. In order to elucidate the predominant reaction pathway (alcoholysis or aminolysis), we used both primary but sterically hindered amines of the adamantane series and secondary cyclic amines (piperidine and morpholine) characterized by lower conformational flexibility of hydrocarbon fragments on the nitrogen atom than in *N*-methylpropan-1-amine. Taking into account fairly high dielectric permittivity of morpholine (ε = 7.3), the reaction of **1** with that amine was carried out without a solvent. The reactions of **1** with 4-methoxybenzylamine and 3-phenylpropan-1-amine could give compounds exhibiting a high antiviral activity, as might be expected on the basis of our previous results [6].

In all cases (except for the reaction with adamantan-2-amine), the reaction mixtures were kept for 60 days at room temperature and analyzed by HPLC using initial compound **1** and 2-butoxy derivative **3** (prepared as described in [5]) as external standards (retention times t_R = 4.79 and 19.36 min for compounds **1** and **3**, respectively; Scheme 1). The results are collected in the table.

Compound **1** reacted with piperidine in butan-1-ol at room temperature to give exclusively the alcoholysis product which is likely to be kinetically controlled. The reactions with other amines, including morpholine, followed the aminolysis pathway.

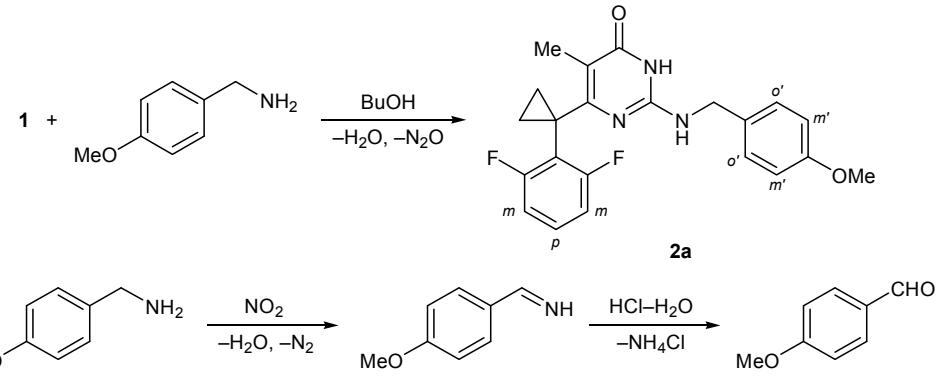
The subsequent heating of the reaction mixtures obtained with morpholine, 3-phenylpropan-1-amine, and (adamantan-1-yl)methanamine resulted in the formation of only aminolysis products. The reactions with 4-methoxybenzylamine and piperidine were not selective. In the reaction with 4-methoxybenzylamine, the mixture contained the corresponding aminolysis product and a by-product (t_R = 3.65 min) which was isolated with a purity of 84.9% by column chromatography and additionally purified by preparative TLC. It was identified as 4-methoxybenzaldehyde; obviously, it was formed by hydrolysis of the corresponding aldimine during the isolation procedure or during HPLC analysis of a sample of the reaction mixture (Scheme 2).

The reaction of **1** with piperidine in butan-1-ol under reflux involved concurrent aminolysis and alcoholysis of the initial compound. After a time, the concentration ratio of compounds **1** and **3** indicated that both of them underwent aminolysis (see table; Scheme 3). The reaction mixture was heated until initial compound was no longer detected by HPLC and only traces of butoxy derivative **3** were detected (the concentration of **3** no longer decreased). These findings were somewhat surprising. As shown in [7], 2-ethoxypirimidin-4(3*H*)-one can be converted to isocytosine by the action of alcoholic ammonia under pressure at elevated temperature. Analogous trans-

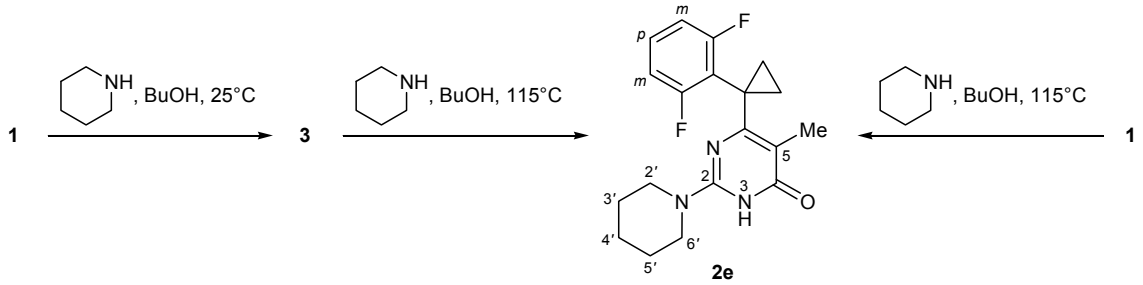
Fractions (%) of compounds **1**–**3** in the aminolysis of 6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methyl-2-(nitroamino)pyrimidin-4-(3*H*)-one (**1**) under different conditions

Comp. no.	t_R, min	48 h, ~115°C			60 h, ~115°C			72 h, ~115°C			90 h, ~115°C			1440 h, 25–30°C		
		1	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
2a	3.08	28.5	42.9	0	–	–	–	0.7	65.5	0	–	–	–	28.7	42.3	0
2b	3.41	–	–	–	–	–	–	–	–	–	0.7	98.4	0.7	61.9	3.63	0
2c	6.54	8.1	91.9	0	0.5	98.2	0	–	–	–	–	–	–	51	49	0
2e	3.92	13.1	72.0	14.2	0.3	44.3	53.3	0.3	84.7	12.1	0.5	85.1	10.0	44.9	0	49.2
2f	3.22	1.9	98.1	0	–	–	–	–	–	–	1.2	98.3	0.5	48.1	51.9	0

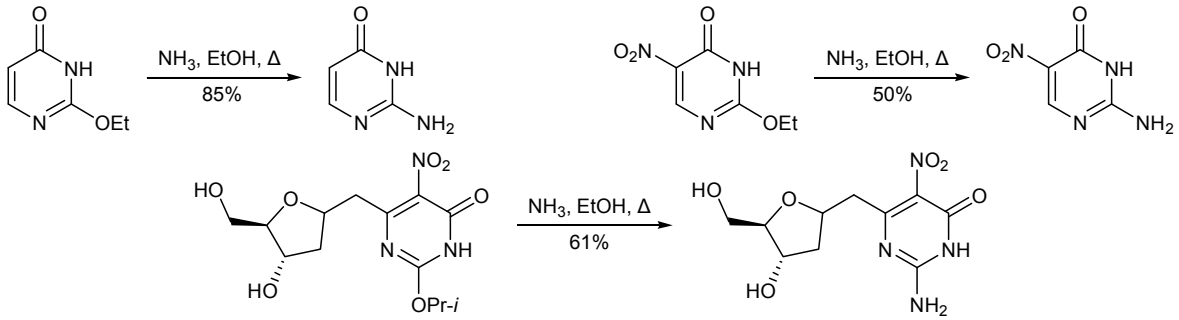
Scheme 2.



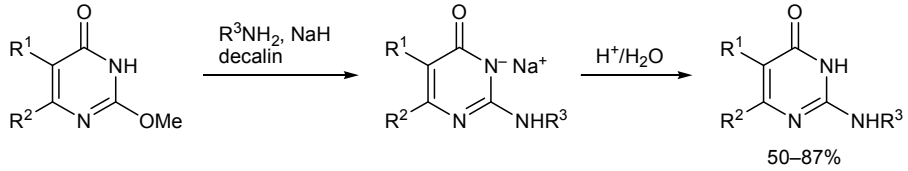
Scheme 3.



Scheme 4.



Scheme 5.



R^3 = Bu: R^1 = H, R^2 = Me (77%); R^1 = R^2 = Me (52%); R^1R^2 = $(CH_2)_4$ (66%); R^3 = *cyclo*-C_6H_{11}: R^1 = H, R^2 = Me (65%); R^1 = R^2 = Me (50%); R^1R^2 = $(CH_2)_4$ (87%); R^3 = Ph: R^1 = H, R^2 = Me (70%); R^1 = R^2 = Me (65%); R^1R^2 = $(CH_2)_4$ (50%).

formation, but under milder conditions, was reported for 5-nitropyrimidin-4(3*H*)-one derivatives [8, 9] in which the nitro group favors the reaction due to its electron-withdrawing effect in combination with the hyperconjugation effect (Scheme 4).

Unlike ethoxy derivatives, the aminolysis of 2-methoxypirimidin-4(3*H*)-one required heating with sodium alkyl- or arylamide generated *in situ* in tetralin or decalin [10] (Scheme 5).

Our results indicated that not only the conditions given in [10] are unreasonably harsh but they also do not favor formation of the aminolysis products. First, both tetralin (ε = 2.773) and decalin (ε = 2.20) are less polar than butanol (ε = 17.8), which negatively affects

ionic reactions. Second, the reactions in tetralin or decalin are heterogeneous, and the solvent, unlike butan-1-ol, is hardly capable of effectively solvating transition state of the reaction because of its chemical nature.

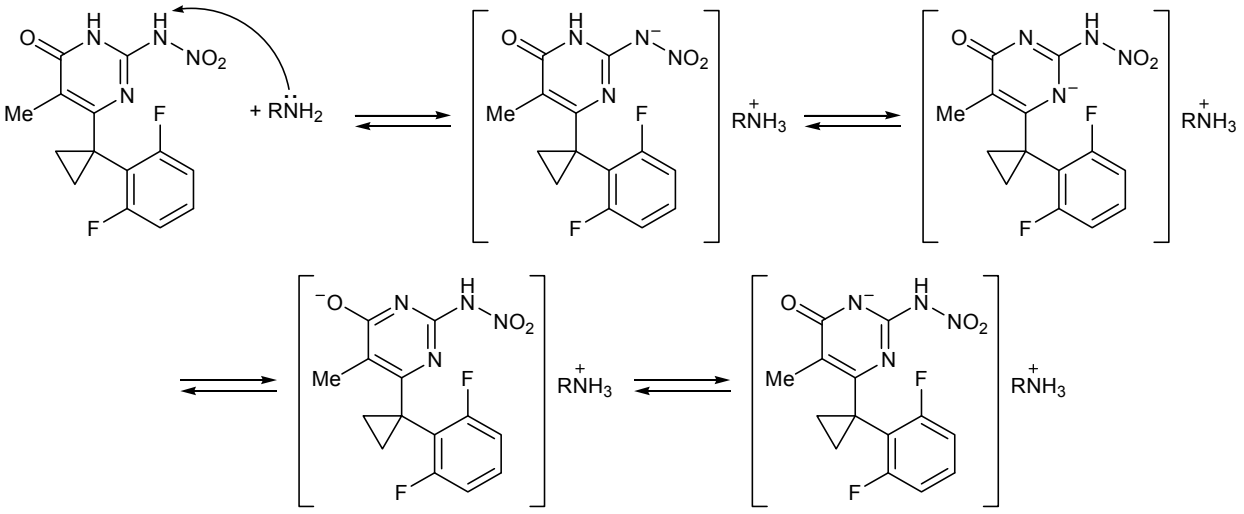
Finally, the crucial factors are acid–base equilibrium and concentration of the molecular form of initial compound **1** in the system. Due to relatively high NH acidity (pK_a 7.72) [11], compound **1** can be completely or partially deprotonated with the amine to give a salt-like coordination complex (Scheme 6). The presence of a negative charge on the pyrimidine fragment of this complex makes it resistant to attack of amine as neutral nucleophile.

If neutral molecules of amine and compound **1** form a contact pair surrounded by a solvate shell, nucleophilic attack of amine on the electron-deficient C^2 atom of the pyrimidine ring is possible. The direction of nucleophilic attack conforms well to the hard and soft acids and bases principle, according to which just the C^2 atom rather than nitrogen atom of the nitro group or C^4 becomes the reaction center (Scheme 7).

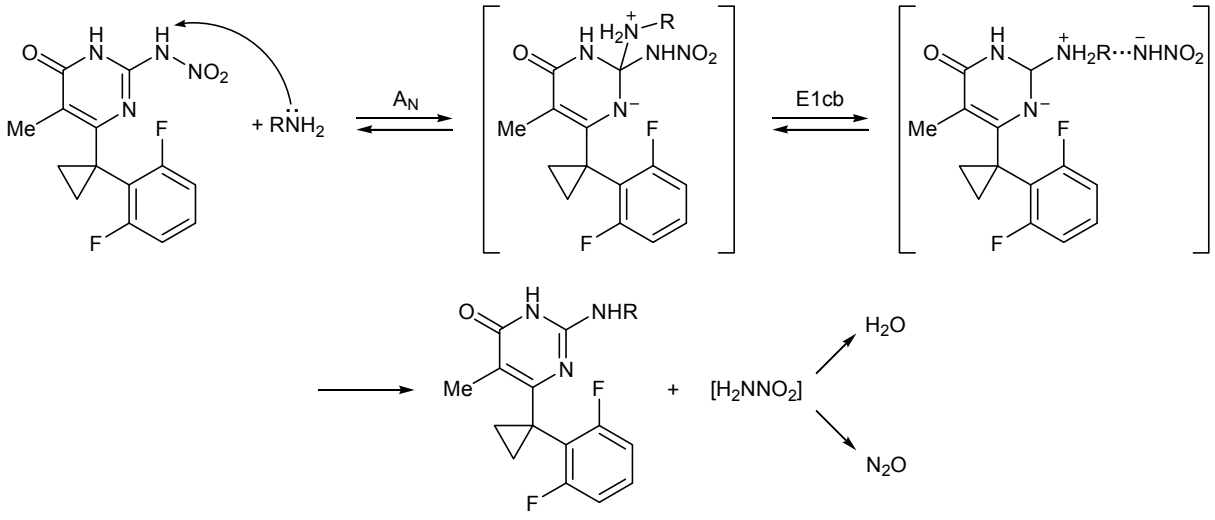
Deprotonation of NH-acidic pyrimidin-4(3*H*)-one derivative with sodium alkyl- or arylamide is almost irreversible, and the initial 2-alkoxypyrimidin-4(3*H*)-one is completely converted to the anion which is inert toward nucleophiles. Moderate yield of the aminolysis products is determined by extremely harsh reaction conditions which make the process thermodynamically controlled.

That is why the alcoholysis of 2-methoxypyrimidin-4(3*H*)-ones was successful only under very severe

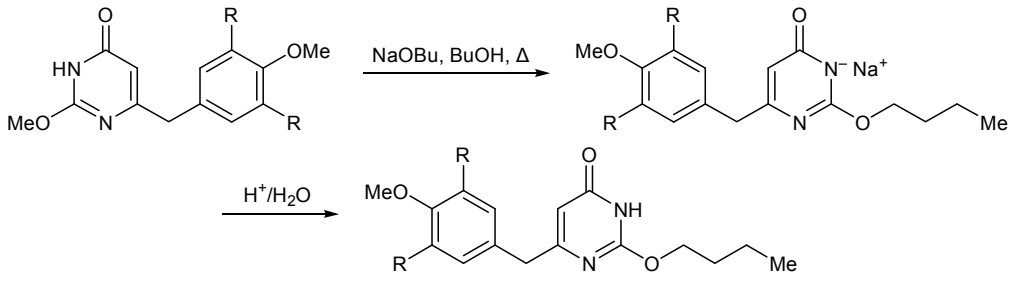
Scheme 6.



Scheme 7.



Scheme 8.



conditions, on treatment with 10 equiv of the corresponding potassium or sodium alkoxide [1, 12] (Scheme 8); i.e., the situation is almost the same as in the aminolysis of 2-methoxypyrimidin-4(3*H*)-ones with sodium amides.

We succeeded in developing a milder and more efficient procedure for the synthesis of compounds of this series from 2-(nitroamino)pyrimidin-4(3*H*)-ones and alcohols in the presence of an aliphatic amine as base catalyst.

The reaction of **1** with adamantan-2-amine in butan-1-ol at room temperature was very slow, and it followed exclusively the alcoholysis pathway (according to the HPLC data). The alcoholysis remained the predominant reaction pathway under reflux conditions; however, as the ratio **3**:**1** reached 34.7:55.1, the alcoholysis almost stopped, and another product began to appear; the fraction of the latter gradually attained 10.2%. Judging by the HPLC data (t_R = 3.4 min), this compound may be the product of elimination of the nitro group from **1** by the action of adamantan-2-amine. In this case, the direction of nucleophilic attack is determined by spatial accessibility of the nitro group and considerable shielding of the amino group in adamantan-2-amine (Scheme 9).

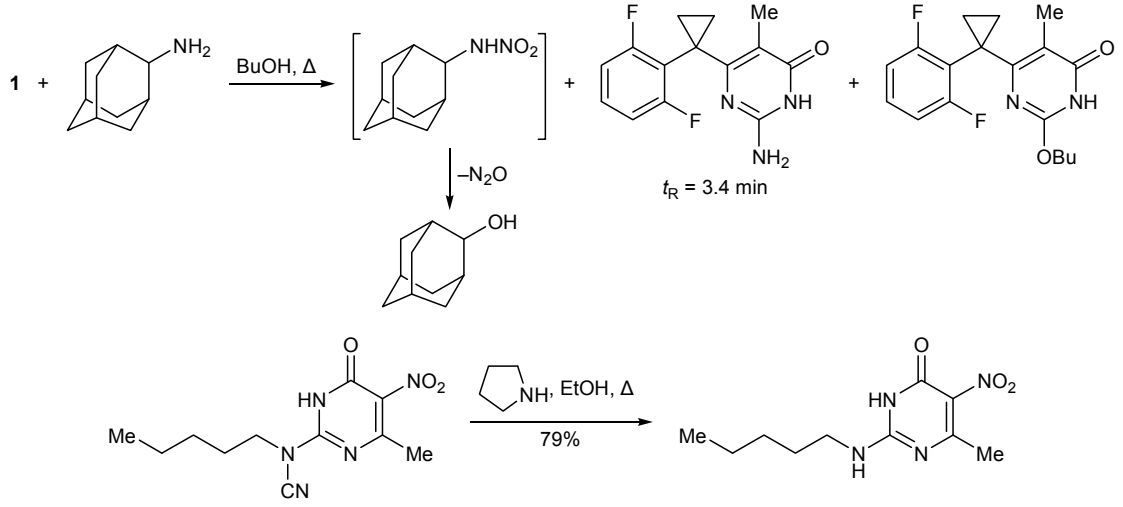
Analogous pattern was observed in the aminolysis of (4-methyl-5-nitro-6-oxo-1,6-dihydropyrimidin-2-yl)pentylcyanamide with pyrrolidine [13]. Nucleophilic attack of pyrrolidine is directed at the electron-deficient carbon atom of the cyano group, and the latter is removed.

Thus, we have developed efficient procedures for the synthesis of isocytosine derivatives by aminolysis of 6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methyl-2-(nitroamino)pyrimidin-4-(3*H*)-one (**1**) with primary amines in butan-1-ol and alcoholysis of the same substrate in the presence of secondary and tertiary amines as catalysts.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury 300 BB spectrometer at 300 MHz using hexamethyldisiloxane as internal standard. The ^{1}H NMR

Scheme 9.



spectrum of **2a** was measured on a Bruker 360 instrument at 360 MHz.

HPLC analysis was performed with a chromatographic system consisting of a Jasco PU-980 pump, Jasco UV-975 UV/Vis detector, and Rheodyne injector (Reprosil C18 AQ column, 150×4.6 mm, grain size 3 μm; eluent H_2O–MeCN–85% H_3PO_4, 200:200:1 by volume, flow rate 0.8 mL/min; λ 220 nm, 25°C). The elemental analyses were obtained on a Vario EL Cube analyzer. Polygram Sil G UV_{254} plates were used for TLC; spots were visualized under UV light, λ 254 nm. The products were isolated by column chromatography on silica gel L14002 (Alfa Aesar, 0.06–0.20 mm or 70–230 mesh). The reaction mixtures and extracts were concentrated using a Heidolph Hei-VAP Precision rotary evaporator.

Commercial reagents from Alfa Aesar and solvents from *Komponent-Reaktiv* were used. Acetonitrile (Panreac 221074, HPLC-gradient grade) and phosphoric acid (*Komponent-Reaktiv*, ultrapure grade 17-4) were used for HPLC. The solvents were dried and purified by standard procedures [14]. The study was performed using the equipment of the "Physicochemical Methods of Study" Joint Center and "Polymeric Composite Materials and Technologies" Engineering Center of the Volgograd State Technical University.

6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-(piperidin-1-yl)pyrimidin-4(3*H*)-one (2e). A mixture of 0.5 g (1.55 mmol) of compound **1**, 10 mL of butan-1-ol, and 2 mL (1.7 g, 20 mmol) of piperidine was shaken until a transparent solution was obtained. The solution was refluxed with stirring until compound **1** disappeared (HPLC), and only traces of 2-butoxypirimidin-4(3*H*)-one **3** were detected. The solvent was distilled off under reduced pressure, the residue was treated with toluene, and the solvent was distilled off. This operation was repeated three times. The residue was dissolved in a minimum amount of 2-methyltetrahydrofuran, the solution was applied onto silica gel, and the product was isolated by column chromatography using ethyl acetate–cyclohexane (3:1 by volume) as eluent. Fractions containing the aminolysis product were evaporated to dryness, and the residue was recrystallized from hexane until constant melting point. Yield 300 mg (56%), purity 98.7% (HPLC), colorless needles, mp 164.5–165.5°C (from hexane), R_f 0.48 (EtOAc–C_6H_{14}, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.05–1.16 m (2H, H_{ax}, cyclopropyl), 1.43–1.51 m (8H, CH_2, 3′-H, 4′-H, 5′-H, H_{eq}, cyclopropyl), 1.53–1.65 m (3H, CH_3), 3.41–3.53 m (4H, 2′-H, 6′-H), 6.94–6.99 m (2H, *m*-H), 7.26–7.31 m (1H, *p*-H), 11.00 s (1H, N^3H). Found, %: C 65.81; H 5.89; N 11.94. $C_{19}H_{21}F_2N_3O$. Calculated, %: C 66.07; H 6.13; N 12.17.

Compounds **2a**–**2c** were synthesized in a similar way.

6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-[(4-methoxybenzyl)amino]pyrimidin-4(3*H*)-one (2a) was obtained in the reaction of **1** with 2 mL (2.1 g, 15.3 mmol) of 4-methoxybenzylamine. The major and minor products were isolated by column chromatography. The major product was additionally purified by preparative HPLC. Yield 160 mg (26%), purity 98.2%, R_f 0.35 (EtOAc–C_6H_{14}, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13–1.16 m (2H, H_{ax}, cyclopropyl), 1.55–1.58 m (2H, H_{eq}, cyclopropyl), 3.73 s (3H, CH_3O), 4.37 d (2H, CH_2, J = 5.8 Hz), 6.49 t (1H, 2-NH, J = 5.8 Hz), 6.87 d (2H, *o*′-H, J = 8.6 Hz), 7.01 t (2H, *m*′-H, J = 8.6 Hz), 7.27 d (2H, *m*-H, J = 8.6 Hz), 7.28–7.36 m (1H, *p*-H), 10.64 s (1H, N^3H). Found, %: C 66.21; H 4.98; N 10.94. $C_{22}H_{21}F_2N_3O_2$. Calculated, %: C 66.49; H 5.33; N 10.57.

The minor product contained 84.9% of the main substance (HPLC, t_R = 3.65 min).

6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-[(3-phenylpropan-1-yl)amino]pyrimidin-4(3*H*)-one (2b) was obtained in the reaction with 2 mL (1.9 g, 14.1 mmol) of 3-phenylpropan-1-amine. The residue was dissolved in ethyl acetate, the solution was washed with 1 M aqueous HCl and brine, dried over anhydrous Na_2SO_4, and filtered, and the solvent was distilled off. The residue was treated three times with toluene, followed by evaporation under reduced pressure, and purified by column chromatography. The product was recrystallized from C_6H_{14}–EtOAc until constant melting point. Yield 250 mg (41%), purity 99.2% (HPLC), off-white finely crystalline powder, mp 199.5–200.5°C (decomp.). R_f 0.38 (EtOAc–C_6H_{14}, 4:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29–1.41 m (2H, H_{ax}, cyclopropyl), 1.50–1.62 m (2H, H_{eq}, cyclopropyl), 1.80–1.90 m (5H, $PhCH_2C\mathbf{H}_2$, CH_3), 2.60–2.68 m (2H, CH_2), 3.23–3.35 m (2H, CH_2), 7.04–7.24 m (7H, Ph, *m*-H), 7.35–7.37 m (1H, *p*-H), 9.51 br.s (1H, 2-NH), 11.77 br.s (1H, N^3H). Found, %: C 70.10; H 6.00; N 11.02. $C_{23}H_{23}F_2N_3O$. Calculated, %: C 69.86; H 5.86; N 10.63.

2-{[(Adamantan-1-yl)methyl]amino}-6-[1-(2,6-difluorophenyl)cyclopropyl]-5-methylpyrimidin-

4(3*H*)-one (2c) was obtained in the reaction with 2 mL (2.2 g, 13.3 mmol) of (adamantan-1-yl)methanamine. The product crystallized from the reaction mixture. The mixture was cooled and filtered, and the precipitate was washed on a filter with butan-1-ol and recrystallized from ethanol until constant melting point. Yield 500 mg (76%), purity 99.5% (HPLC), colorless crystalline powder, decomposition point >282.5°C (from EtOH), R_f 0.41 (EtOAc–C_6H_{14}, 4:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03–1.15 m (2H, H_{ax}, cyclopropyl), 1.32–1.44 m (6H, 2-H, 8-H, 9-H, Ad), 1.50–1.55 m (9H, 4-H, 6-H, 10-H, Ad; CH_3), 1.81–1.93 m (3H, 3-H, 5-H, 7-H, Ad), 2.89–3.01 m (2H, C**H**$_2$NH), 6.04 br.s (1H, 2-NH), 6.90–7.00 m (2H, *m*-H), 7.21–7.33 m (1H, *p*-H), 10.36 br.s (1H, N^{3}H). Found, %: C 70.22; H 7.02; N 10.04. $C_{25}H_{29}F_2N_3O$. Calculated, %: C 70.57; H 6.87; N 9.88.

6-[1-(2,6-Difluorophenyl)cyclopropyl]-5-methyl-2-(morpholin-4-yl)pyrimidin-4(3*H*)-one (2f). A solution of compound **1** in 10 mL (10.1 g, 116 mmol) of anhydrous morpholine was refluxed with stirring until the reaction was complete (HPLC). The mixture was cooled, diluted with water, and neutralized with acetic acid. The precipitate was filtered off, washed with water, dried, and recrystallized from acetonitrile until constant melting point. Yield 320 mg (60%), purity 99.41% (HPLC), fine needles, mp 190–190.5°C (from MeCN), R_f 0.28 (EtOAc–C_6H_{14}, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.06–1.18 m (2H, H_{ax}, cyclopropyl), 1.46–1.58 m (2H, H_{eq}, cyclopropyl), 1.58–1.64 m (3H, CH_3), 3.40–3.52 m (4H, NCH_2), 3.52–3.60 m (2H, OCH_2), 6.68–6.72 m (2H, *m*-H), 7.20–7.36 m (1H, *p*-H), 11.15 br.s (1H, N^{3}H). Found, %: C 61.88; H 5.50; N 12.20. $C_{18}H_{19}F_2N_3O_2$. Calculated, %: C 62.24; H 5.51; N 12.10.

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