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Reactions of β-carbonyl-substituted 4*H*-chromenes and 1*H*-benzo[*f*]chromenes with 5-aminopyrazoles

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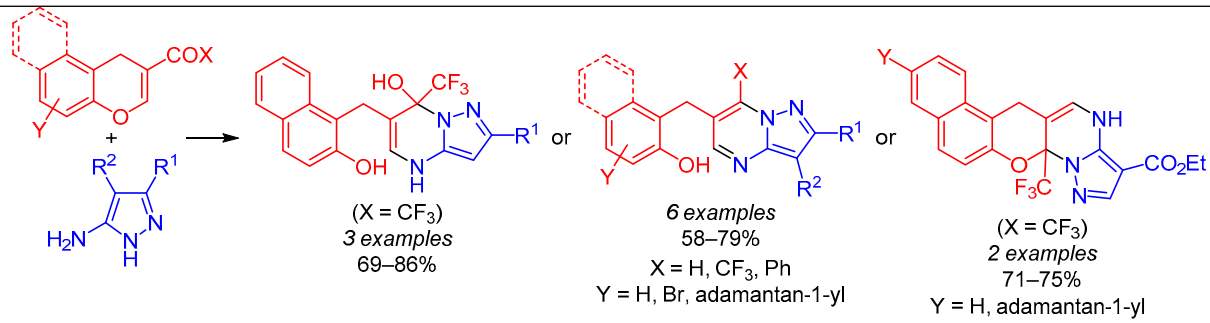


A method for the preparation of pyrazolo[1,5-*a*]pyrimidines containing a 2-hydroxybenzyl or (2-hydroxynaphthalen-1-yl)methyl group in position 6 based on the reaction of β-carbonyl-substituted 4*H*-chromenes and their benzo analogs with 5-aminopyrazoles is proposed. A new type of ring-chain tautomerism with the participation of 7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidines was discovered.

Keywords: 5-amino-1*H*-pyrazoles, 1*H*-benzo[*f*]chromene, β-carbonyl-substituted chromene, 4*H*-chromene, pyrazolo[1,5-*a*]pyrimidines, aza-Michael reaction, (3+3) cyclocondensation, tautomerism.

Pyrazolo[1,5-*a*]pyrimidines are traditionally regarded as privileged structures in medicinal chemistry,[1] and therefore the development of new approaches to their preparation attracts considerable interest.[2] Examples of pharmacologically active pyrazolo[1,5-*a*]pyrimidines include the Z-drugs zaleplon, indiplon, and ocinaplon, which are non-benzodiazepine sedatives,[3] and the dipeptidyl peptidase 4 inhibitor anagliptin[4] used in the treatment of type 2 diabetes (Fig. 1).

Azolopyrimidines are commonly synthesized by the action of 1,3-dicarbonyl compounds or their synthetic equivalents on aminoazoles.[2,5] One of the drawbacks of a number of existing methods is the formation of a mixture of regioisomers in the case of asymmetric 1,3-bielectrophiles.[6] 1-Unsubstituted 5-aminopyrazoles and acyclic 1,3-CCC-bielectrophiles are usually employed for the preparation of pyrazolo[1,5-*a*]pyrimidines.[7] At the same time, the use of heterocyclic compounds, for example, 3-carbonyl-substituted chromones, as three-carbon synthons in the construction of this heterocyclic system is much less common.[8]

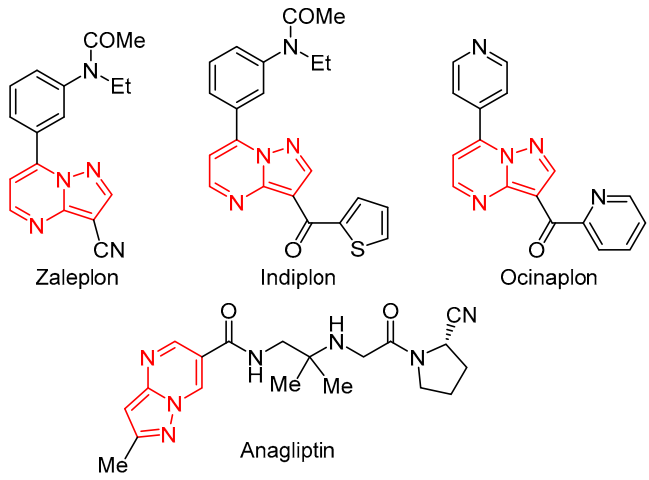


Figure 1. Drugs based on pyrazolo[1,5-*a*]pyrimidines.

In this work, we have shown that the less electrophilic, in comparison with 3-formylchromones, β-carbonyl-substituted 4*H*-chromenes and 1*H*-benzo[*f*]chromenes can

be used to prepare pyrazolo[1,5-*a*]pyrimidine derivatives containing the 2-hydroxybenzyl group at position 6. Such an indirect method of C-hydroxybenzylation of heterocyclic compounds is of interest because it is usually impossible to directly introduce this group into π-electron-deficient heterocycles.[9]

The presence of two nonequivalent electrophilic centers in acylchromenes **1** and four nonequivalent nucleophilic centers in 5-aminopyrazoles **2** gives rise to a wide range of products in the reaction of reagents **1** and **2** (Fig. 2). It is believed that, in comparison with the nitrogen atom of the amino group, the endocyclic nitrogen atom in 5-aminopyrazoles **2** is more basic and more sterically hindered as a result of which it attacks the less hindered and more electrophilic carbonyl carbon atom in conjugated systems.[10]

First, we investigated the reaction of 2-trifluoroacetyl-1*H*-benzo[*f*]chromene (**1a**) with 5-amino-1*H*-pyrazoles **2a–c** containing the adamantane pharmacophore fragment as well as a *tert*-butyl group. It turned out that when the reaction was carried out in the absence of acidic catalysts in CH_2Cl_2 at room temperature (method I), 7-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-ols **3a–c** (tautomeric forms **B**) formed which are stable in the solid state. Carrying out the reaction in boiling MeCN (method II) significantly reduces the duration of the process, but the yield of product **3a** is somewhat lower. Deprotonation of aminopyrazole **2a** by the action of NaH in DMF (method III) does not change the regioorientation of the reaction with chromene **1a**. In solution, the cyclic hemiaminal forms of compounds **3a–c** are in equilibrium with the corresponding enamino ketones (tautomeric forms **A**) (Scheme 1).

In DMSO-d_6 solution, form **B** of compounds **3a–c** predominates; however, in the first moment after dissolution, according to ^{1}H NMR spectroscopy data, the **B** to **A** ratio is slightly higher than after 1–2 h. Therefore, it can be assumed that in the solid state the compound exist in the form of cyclic 4,7-dihydropyrazolo[1,5-*a*]pyrimidines **3a–c** (tautomers **B**).[11] The ratio of tautomeric forms of products **3a–c** can be calculated from the integral intensities of singlet signals of fluorine atoms in the ^{19}F NMR spectra or the signals of the methylene protons in the ^{1}H NMR spectra and is approximately **B**:**A** = 6:4. The possibility of the existence of ring-chain tautomerism is largely due to the presence of an electron-withdrawing CF_3 group, which prevents easy elimination of H_2O and the formation of thermodynamically more stable pyrazolo[1,5-*a*]pyrimidines.

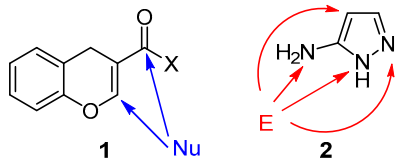


Figure 2. Ambident reactivity of β-carbonyl-substituted 4*H*-chromenes **1** and 5-aminopyrazoles **2**.

The most characteristic signals in the ^{1}H, ^{13}C, and ^{19}F NMR spectra for tautomers **A** or **B** of compounds **3a–c** are shown in Figure 3.

Carrying out the reaction of trifluoroacetylchromenes **1a–c** and pyrazoles **2a**,**b** in the presence of an acid catalyst allows one to directly obtain 7-(trifluoromethyl)pyrazolo-[1,5-*a*]pyrimidines **4a–c**. *i*-PrOH in the presence of $BF_3 \cdot OEt_2$ under reflux (method IV) or AcOH under reflux (method V) can be used. In addition, pyrazolo[1,5-*a*]-pyrimidine **4a** was obtained by dehydration of hemiaminal **3a** in *i*-PrOH in the presence of $BF_3 \cdot OEt_2$ (method VI), or in MeOH in the presence of catalytic amounts of *p*-TsOH under reflux (method VII) (Scheme 2).

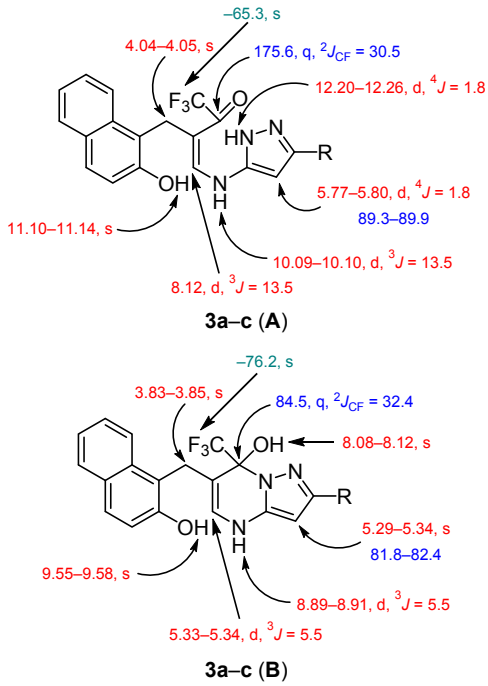
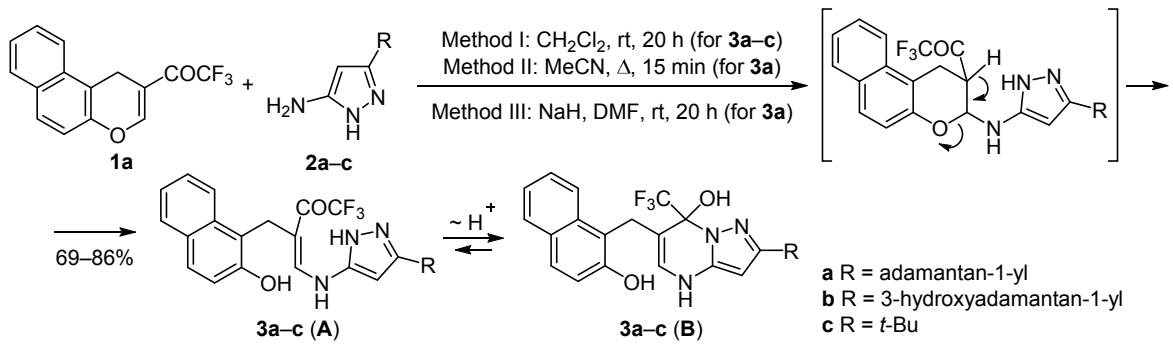
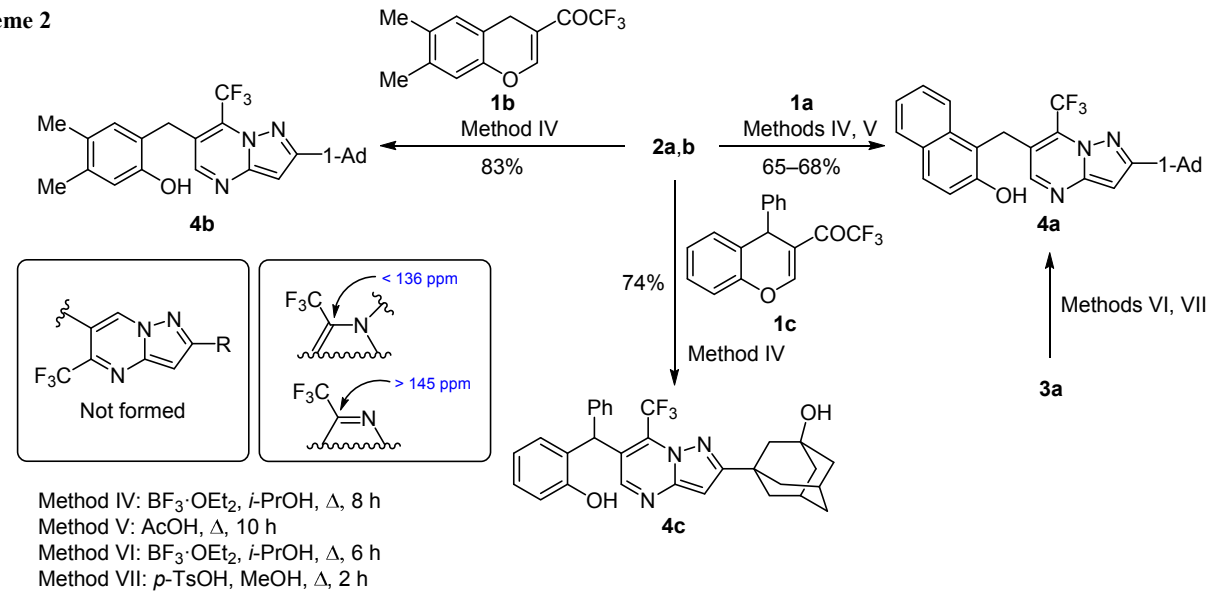


Figure 3. Identification of tautomers **A** and **B** of products **3a–c** by characteristic signals in ^{1}H (red), ^{13}C (blue), and ^{19}F (green) NMR spectra (δ in ppm, *J* in Hz).

Scheme 1



Scheme 2



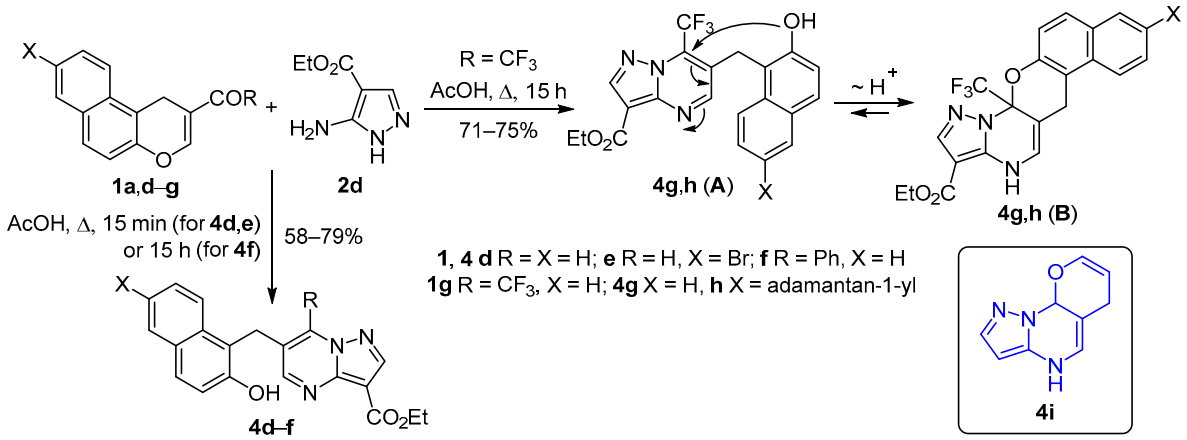
The assignment of the obtained products to 5- or 7-trifluoromethyl-substituted isomers is based on the fact that the enamine carbon atom bonded to the trifluoromethyl group and to the nitrogen atom with a single bond usually appears at 136 ppm, while the signal of the azomethine carbon atom bonded to the trifluoromethyl group resonates further downfield (at 145 ppm) in the spectrum of compounds with a fixed position of double bonds[5a,10,12] (Scheme 2). In the ^{13}C NMR spectra of compounds **4a–c**, the C-5 carbon atom of the pyrazolo[1,5-*a*]pyrimidine ring appears at 151.2–153.6 ppm. The strong deshielding is due to the acceptor effect of the neighboring pyridine-type nitrogen atom. The trifluoromethyl carbon atom and carbon atom C-7 are found as quartets at 121.2–121.7 ppm ($^1J_{CF}$ = 275.6 Hz) and 129.7–130.3 ppm ($^2J_{CF}$ = 34.3 Hz), respectively. These facts confirm the formation of regioisomers with a trifluoromethyl group at position 7. The carbon atom C-3 appears at 93.5–93.9 ppm.

Isolation of intermediate products confirms the reaction mechanism which encompasses the conjugated addition of the exocyclic amino group of pyrazole **2** to the α-carbon atom of the pyran ring of chromene **1**, the opening of the dihydropyran fragment, and then the nucleophilic addition of the endocyclic nitrogen atom of the pyrazole ring to the carbonyl carbon atom, followed by dehydration in an acidic medium.

The reaction of 1*H*-benzo[*f*]chromene-2-carbaldehydes **1d**,**e** with 5-aminopyrazole **2d** in AcOH under reflux is complete in less than 15 min and leads to the formation of pyrazolo[1,5-*a*]pyrimidines **4d**,**e** in 73–79% yields. The reaction with such a sluggish Michael acceptor as 2-benzoyl-1*H*-benzo[*f*]chromene (**1f**) proceeds much more slowly and leads to product **4f** in 58% yield (Scheme 3). The formation of 7-phenyl-substituted derivative **4f** is confirmed by the presence in its ^{13}C NMR spectrum of a signal of the C-5 carbon atom at 155.4 ppm.[13]

The presence of an ester group in the structure of pyrazole **2d**, which is in direct conjugation with the amino group, leads to a decrease in the nucleophilicity of the latter, as a result of which the reaction rate of trifluoroacetylbenzochromenes **1a**,**g** with compound **2d** is lower than that with 5-aminopyrazoles **2a–c**. Moreover, in contrast to pyrazolo[1,5-*a*]pyrimidines **4a–f**, products **4g**,**h** exist in the solid state in the form of cyclic N,O-acetals (tautomeric form **B**) (Scheme 3), which for compound **4g** was confirmed by X-ray structural analysis (Fig. 4). It

Scheme 3



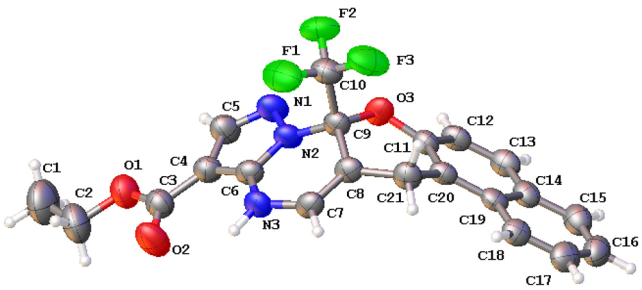


Figure 4. Molecular structure of compound **4g** with atoms represented as thermal vibration ellipsoids with 50% probability.

should also be noted that 4,9a-dihydro-6*H*-pyrano[3,2-*e*]-pyrazolo[1,5-*a*]pyrimidine **4i** (Scheme 3) and its various arene-condensed variants were not previously described.

In the DMSO-d_6 solution of compounds **4g**,**h**, tautomer **B** predominates, as well. The content of the minor isomers **4g**,**h** (**A**) is about 20%, which can be easily determined from the integrated intensities of signals of fluorine atoms in the ^{19}F NMR spectra which are detected at –60.0 (form **A**) and –75.5 ppm (form **B**). Nevertheless, upon dissolution of the colorless products **4g**,**h** in DMSO-d_6, the solution acquires a yellow color characteristic of pyrazolo[1,5-*a*]-pyrimidines. The ease of heterocyclization, in comparison with compounds **4a**–**c**, can be explained by the higher electrophilicity of the C-7 carbon atom of the pyrazolo[1,5-*a*]-pyrimidine ring due to the presence of an acceptor ester group and the contribution of the corresponding resonance structure to the distribution of electron density (Scheme 3).

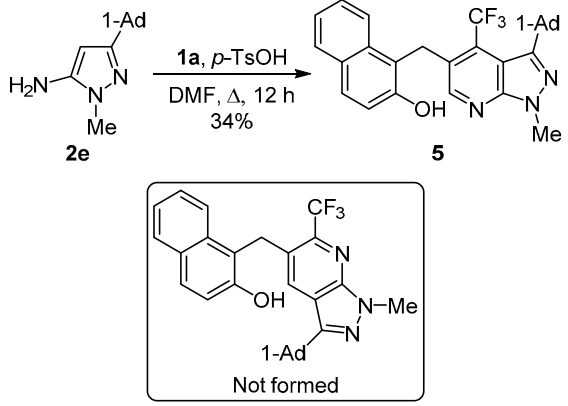
1-Unsubstituted aminopyrazoles **2a**–**d** act as 1,3-NCN-binucleophiles in all the reactions presented above. At the same time, 5-aminopyrazole **2e** substituted at position 1 reacts with 2-trifluoroacetyl-1*H*-benzo[f]chromene (**1a**) already as 1,3-NCC-binucleophile. This transformation was carried out in DMF under reflux in the presence of catalytic amounts of *p*-TsOH (Scheme 4). In the ^{13}C NMR spectrum of product **5**, the presence of the quartet signal of the carbon atom C-4 at 129.6 ppm ($^2J_{CF}$ = 29.6 Hz) and the strongly deshielded signal of the C-6 atom at 149.8 ppm indicates the formation of 4-(trifluoromethyl)-1*H*-pyrazolo-[3,4-*b*]pyridine **5** rather than its isomeric 6-trifluoromethyl derivative.[5a,14] Apparently, in this case, too, the initial step of the reaction is the aza-Michael reaction with the participation of an exocyclic amino group.

To conclude, we have demonstrated that β-carbonyl-substituted chromenes act as masked 1,3-dicarbonyl compounds in reactions with 5-aminopyrazoles and can be effective precursors for the preparation of 6-(2-hydroxybenzyl)pyrazolo[1,5-*a*]pyrimidines.

Experimental

IR spectra were registered on a Shimadzu IRAffinity-1 Fourier transform spectrometer equipped with a Specac Diamond ATR GS10800-B accessory. ^{1}H, ^{13}C, and ^{19}F NMR spectra (400, 100, and 376 MHz, respectively), as well as DEPT-135 spectra were registered on a JEOL JNM-ECX400 spectrometer in DMSO-d_6 (compounds **2b**, **3a**,**b**,**c**, **4a**–**e**,**g**,**h**, **5**) or $CDCl_3$ (compounds **2a**,**e**, **4f**) using the

Scheme 4



residual solvent signals (DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei; $CDCl_3$: 7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei) or $CFCl_3$ (0.0 ppm for ^{19}F nuclei) as internal standards. Elemental analysis was performed on a Euro Vector EA-3000 CHNS-analyzer. Melting points were determined by the capillary method on an SRS OptiMelt MPA100 apparatus. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Merck M60 F_{254} plates, eluent CH_2Cl_2, visualization with UV light at 254 nm or by iodine stain.

The starting chromenes **1a**–**g**,[15] as well as pyrazoles **2c**[16] and **2d**[17] were obtained by known methods.

3-(Adamantan-1-yl)-1*H*-pyrazol-5-amine monohydrate (2a). $N_2H_4 \cdot H_2O$ (100%, 10 ml) was added to a solution of 3-(adamantan-1-yl)-3-oxopropanenitrile (3.00 g, 15 mmol) in EtOH (50 ml), and the resulting mixture was heated under reflux for 5 h. The volatile components were evaporated under reduced pressure. The residue was coevaporated with PhMe (2×20 ml) and dissolved in cyclohexane (10 ml) by heating, then H_2O (0.3 ml, 17 mmol) was added. The formed precipitate was filtered off, washed with cyclohexane (2 ml), and dried in air at room temperature. Yield 1.66 g (47%), colorless crystals, mp 139–140°C. IR spectrum, ν, cm^{-1}: 3400–3050 (NH, NH_2, H_2O), 2904, 2846 (CH Ad), 1689, 1612, 1573, 1502, 1485, 1450, 1319, 1253, 1103, 991, 775, 713. ^{1}H NMR spectrum, δ, ppm: 1.69–1.77 (6H, m, $3CH_2$ Ad); 1.84–1.86 (6H, m, $3CH_2$ Ad); 2.03 (3H, br. s, 3CH Ad); 4.61 (5H, br. s, NH, NH_2, H_2O); 5.41 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 28.4 (3CH Ad); 33.1 (C Ad); 36.6 ($3CH_2$ Ad); 42.2 ($3CH_2$ Ad); 88.9 (C-4); 154.1; 155.6. Found, %: C 66.25; H 8.92; N 17.75. $C_{13}H_{19}N_3 \cdot H_2O$. Calculated, %: C 66.35; H 8.99; N 17.86.

3-(5-Amino-1*H*-pyrazol-3-yl)adamantan-1-ol (2b). A mixture of 3-(3-hydroxyadamantan-1-yl)-3-oxopropanenitrile (0.90 g, 4.1 mmol), $N_2H_4 \cdot H_2O$ (100%, 3 ml), and EtOH (15 ml) was heated under reflux for 5 h. The solvent and excess $N_2H_4 \cdot H_2O$ were evaporated under reduced pressure, and the residue was recrystallized from $CHCl_3$–MeOH, 10:1 mixture. Yield 0.82 g (86%), colorless crystals, mp 143–145°C. IR spectrum, ν, cm^{-1}: 3450–3050 (OH, NH, NH_2), 2920, 2850 (CH Ad), 1612, 1566, 1492, 1454, 1338, 1315, 1257, 1118, 1080, 1033, 1002, 925, 798,

648. ^{1}H NMR spectrum, δ, ppm: 1.49 (2H, br. s, CH_2 Ad); 1.53–1.65 (10H, m, 5CH_2 Ad); 2.10 (2H, br. s, 2CH Ad); 4.37 (3H, br. s, NH_2, OH); 5.10 (1H, s, H-4); 9.98 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 30.6 (2CH Ad); 35.6 (CH_2 Ad); 36.3 (C Ad); 41.4 (2CH_2 Ad); 45.0 (2CH_2 Ad); 50.3 (CH_2 Ad); 67.0 (COH); 87.4 (C-4); 153.9 (2C). Found, %: C 67.02; H 8.16; N 17.90. $C_{13}H_{19}N_3O$. Calculated, %: C 66.92; H 8.21; N 18.01.

3-(Adamantan-1-yl)-1-methyl-1*H*-pyrazol-5-amine (2e). A mixture of 3-(adamantan-1-yl)-3-oxopropanenitrile (0.80 g, 3.9 mmol), $MeNHNH_2$ (2 ml), and EtOH (10 ml) was heated under reflux for 10 h. The solvent was evaporated under reduced pressure, and the residue was recrystallized from cyclohexane. Yield 0.51 g (56%), colorless crystals, mp 199–200°C. IR spectrum, ν, cm^{-1}: 3399, 3314, 3210 (NH_2), 2904, 2847 (CH Ad), 1632, 1562, 1523, 1450, 1419, 1385, 1361, 1315, 1265, 1250, 1172, 1103, 991, 748. ^{1}H NMR spectrum, δ, ppm: 1.71–1.75 (6H, m, 3CH_2 Ad); 1.86–1.89 (6H, m, 3CH_2 Ad); 2.00 (3H, br. s, 3CH Ad); 3.61 (3H, s, CH_3); 3.67 (2H, br. s, NH_2); 5.38 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 28.7 (3CH Ad); 34.0 (C Ad); 34.1 (CH_3); 36.9 (3CH_2 Ad); 42.6 (3CH_2 Ad); 87.5 (C-4); 144.9 (C-5); 161.0 (C-3). Found, %: C 72.76; H 9.11; N 18.08. $C_{14}H_{21}N_3$. Calculated, %: C 72.69; H 9.15; N 18.16.

2-(Adamantan-1-yl)-6-[(2-hydroxynaphthalen-1-yl)-methyl]-7-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-7-ol (3a). Method I. A solution of chromene **1a** (200 mg, 0.72 mmol) and pyrazole **2a** (156 mg, 0.72 mmol) in CH_2Cl_2 (5 ml) was kept without stirring at room temperature for 20 h. The formed precipitate was filtered off and recrystallized from EtOH.

Method II. A mixture of chromene **1a** (200 mg, 0.72 mmol), pyrazole **2a** (156 mg, 0.72 mmol), and MeCN (5 ml) was heated under reflux for 15 min. The mixture was cooled to 0°C, the formed precipitate was filtered off and recrystallized from EtOH.

Method III. NaH as 60% dispersion in mineral oil (40 mg, 1.0 mmol) was added to a solution of pyrazole **2a** (156 mg, 0.72 mmol) in DMF (4 ml). The mixture was stirred at room temperature for 10 min until the evolution of H_2 ceased, then chromene **1a** (200 mg, 0.72 mmol) was added, and the resulting mixture was kept without stirring at room temperature for 20 h. The mixture was poured into H_2O (10 ml), and AcOH was added to pH 6. The formed precipitate was filtered off, washed with H_2O (3 ml), and recrystallized from EtOH.

Yield 303 mg (85%, method I), 280 mg (78%, method II), 307 mg (86%, method III), colorless crystals, mp 209–210°C. IR spectrum, ν, cm^{-1}: 3233, 3144, 3117, 3047, 2985 (OH, NH), 2904, 2850 (CH Ad), 1659, 1618, 1597, 1566, 1489, 1462, 1415, 1333, 1315, 1230, 1196, 1138, 1026, 995, 964, 814, 787, 748. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): tautomer **A**: 1.68 (6H, br. s, 3CH_2 Ad); 1.81–1.83 (6H, m, 3CH_2 Ad); 1.97 (3H, br. s, 3CH Ad); 4.04 (2H, s, CH_2); 5.77 (1H, d, *J* = 1.8, H-4); 7.17–7.27 (2H, m, H Ar); 7.38 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.1, H Ar); 7.68 (1H, d, *J* = 9.0, H Ar); 7.74 (1H, d, *J* = 7.8, H Ar); 7.97 (1H, d, *J* = 8.5, H Ar); 8.12 (1H, d, *J* = 13.5, =C<u>H</u>NH); 10.09 (1H, d, *J* = 13.5, =CHN<u>H</u>); 11.10 (1H, br. s, OH); 12.20 (1H, d, *J* = 1.8, NH); tautomer **B**: 1.68 (6H, br. s, 3CH_2 Ad); 1.81–1.83 (6H, m, 3CH_2 Ad); 1.97 (3H, br. s, 3CH Ad); 3.83 (2H, s, CH_2); 5.29 (1H, s, H-3); 5.33 (1H, d, *J* = 5.5, H-5); 7.17–7.27 (2H, m, H Ar); 7.35 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.1, H Ar); 7.68 (1H, d, *J* = 9.0, H Ar); 7.74 (1H, d, *J* = 7.8, H Ar); 7.83 (1H, d, *J* = 8.5, H Ar); 8.08 (1H, s, C(CF_3)OH); 8.89 (1H, d, *J* = 5.5, NH); 9.55 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz) (mixture of tautomers **A** and **B**): 19.1 (CH_2); 23.0 (CH_2); 28.1 (3CH Ad, **A**); 28.6 (3CH Ad, **B**); 33.1 (C Ad, **A**); 34.4 (C Ad, **B**); 36.5 (3CH_2 Ad, **A**); 37.0 (3CH_2 Ad, **B**); 42.0 (3CH_2 Ad, **A**); 42.6 (3CH_2 Ad, **B**); 81.8 (C-3, **B**); 84.5 (q, $^2J_{CF}$ = 32.4, C-7, **B**); 89.3 (C-4, **A**); 101.5; 107.6; 116.2; 117.1; 118.0 (CH); 118.6 (CH); 118.7 (q, $^1J_{CF}$ = 291.8, CF_3); 122.9 (CH); 123.5 (CH); 123.9 (CH); 124.0 (CH); 125.0 (q, $^1J_{CF}$ = 292.7, CF_3); 125.0 (CH); 126.8 (CH); 127.0 (CH); 128.5 (CH); 128.7 (2C); 128.9 (2CH); 129.3; 133.9; 134.0; 140.5; 147.3 (q, $^4J_{CF}$ = 4.8, CH); 148.3; 151.3; 153.6; 155.4; 162.1; 175.7 (q, $^2J_{CF}$ = 30.5, C=O, **A**). ^{19}F NMR spectrum, δ, ppm: tautomer **A** (41%): –65.3 (s, CF_3); tautomer **B** (59%): –76.2 (s, CF_3). Found, %: C 67.92; H 5.65; N 8.36. $C_{28}H_{28}F_3N_3O_2$. Calculated, %: C 67.87; H 5.70; N 8.48.

2-(3-Hydroxyadamantan-1-yl)-6-[(2-hydroxynaphthalen-1-yl)methyl]-7-(trifluoromethyl)-4,7-dihydropyrazolo-[1,5-*a*]pyrimidin-7-ol (3b) was obtained by method I of the synthesis of compound **3a** from chromene **1a** (200 mg, 0.72 mmol) and pyrazole **2b** (168 mg, 0.72 mmol). Yield 255 mg (69%, method I), colorless crystals, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3300–3050 (OH, NH), 2924, 2850 (CH Ad), 1659, 1597, 1566, 1489, 1462, 1415, 1333, 1311, 1230, 1196, 1138, 1087, 1026, 995, 960, 925, 903, 864, 814, 783, 744. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): tautomer **A**: 1.50–1.70 (12H, m, 5CH_2 Ad, 2CH Ad); 2.13 (2H, br. s, CH_2 Ad); 4.04 (2H, s, CH_2); 4.54 (1H, s, AdO<u>H</u>); 5.78 (1H, d, *J* = 1.8, H-4); 7.17–7.27 (2H, m, H Ar); 7.38 (1H, ddd, *J* = 8.2, *J* = 6.9, *J* = 1.1, H Ar); 7.68 (1H, d, *J* = 8.9, H Ar); 7.74 (1H, d, *J* = 7.8, H Ar); 7.97 (1H, d, *J* = 8.5, H Ar); 8.12 (1H, d, *J* = 13.5, =C<u>H</u>NH); 10.09 (1H, d, *J* = 13.5, =CHN<u>H</u>); 11.12 (1H, br. s, OH); 12.22 (1H, d, *J* = 1.8, NH); tautomer **B**: 1.50–1.70 (12H, m, 5CH_2 Ad, 2CH Ad); 2.13 (2H, br. s, CH_2 Ad); 3.84 (2H, s, CH_2); 4.40 (1H, s, Ad–O<u>H</u>); 5.29 (1H, s, H-3); 5.33 (1H, d, *J* = 5.5, H-5); 7.18–7.28 (2H, m, H Ar); 7.36 (1H, ddd, *J* = 8.2, *J* = 6.9, *J* = 1.1, H Ar); 7.68 (1H, d, *J* = 8.9, H Ar); 7.74 (1H, d, *J* = 7.8, H Ar); 7.83 (1H, d, *J* = 8.5, H Ar); 8.10 (1H, s, C(CF_3)OH); 8.91 (1H, d, *J* = 5.5, NH); 9.56 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz) (mixture of tautomers **A** and **B**): 19.1 (CH_2); 23.0 (CH_2); 30.4 (2CH Ad); 30.7 (2CH Ad); 35.3 (CH_2 Ad); 35.8 (CH_2 Ad); 36.3 (C Ad); 37.7 (C Ad); 41.1 (2CH_2 Ad); 41.7 (2CH_2 Ad); 44.8 (2CH_2 Ad); 45.1 (2CH_2 Ad); 49.9 (CH_2 Ad); 50.5 (CH_2 Ad); 66.9 (C–OH); 67.3 (C–OH); 81.9 (C-3, **B**); 84.5 (q, $^2J_{CF}$ = 32.4, C-7, **B**); 89.4 (C-4, **A**); 101.5; 107.6; 116.2; 117.1; 117.9 (CH); 118.6 (CH); 118.7 (q, $^1J_{CF}$ = 291.8, CF_3); 122.9 (CH); 123.5 (CH); 123.9 (CH); 124.0 (CH); 124.6 (q, $^1J_{CF}$ = 292.7, CF_3); 125.0 (CH); 126.8 (CH); 127.0 (CH); 128.5 (CH); 128.7 (2C); 128.9 (2CH); 129.3; 133.9; 134.0; 140.5; 147.2 (q, $^4J_{CF}$ = 4.8,

CH); 148.2; 151.3; 153.6; 154.5; 161.2; 175.7 (q, $^2J_{CF}$ = 30.5, C=O, **A**). ^{19}F NMR spectrum, δ, ppm: tautomer **A** (38%): –65.3 (s, CF_3); tautomer **B** (62%): –76.2 (s, CF_3). Found, %: C 65.71; H 5.45; N 8.16. $C_{28}H_{28}F_3N_3O_3$. Calculated, %: C 65.74; H 5.52; N 8.21.

2-(*tert*-Butyl)-6-[(2-hydroxynaphthalen-1-yl)methyl]-7-(trifluoromethyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-ol (3c) was obtained by method I of the synthesis of compound **3a** from chromene **1a** (200 mg, 0.72 mmol) and pyrazole **2c** (100 mg, 0.72 mmol). Yield 240 mg (80%, method I), colorless crystals, mp 216–218°C. IR spectrum, ν, cm^{-1}: 3219, 3148, 3119 (OH, NH), 2965, 2870, 1657, 1611, 1597, 1566, 1495, 1462, 1416, 1327, 1283, 1231, 1192, 1136, 1024, 995, 816, 789, 756, 745. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): tautomer **A**: 1.21 (9H, s, (CH_3) C); 4.05 (2H, s, CH_2); 5.80 (1H, d, *J* = 1.8, H-4); 7.18–7.27 (2H, m, H Ar); 7.38 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.1, H Ar); 7.68 (1H, d, *J* = 8.7, H Ar); 7.75 (1H, d, *J* = 8.0, H Ar); 7.98 (1H, d, *J* = 8.5, H Ar); 8.13 (1H, d, *J* = 13.5, =CHNH); 10.10 (1H, d, *J* = 13.5, =CHNH); 11.14 (1H, br. s, OH); 12.26 (1H, d, *J* = 1.8, NH); tautomer **B**: 1.20 (9H, s, (CH_3)C); 3.85 (2H, s, CH_2); 5.34–5.36 (2H, m, H-3,5); 7.18–7.27 (2H, m, H Ar); 7.36 (1H, ddd, *J* = 8.2, *J* = 7.1, *J* = 1.1, H Ar); 7.68 (1H, d, *J* = 8.7, H Ar); 7.75 (1H, d, *J* = 8.0, H Ar); 7.83 (1H, d, *J* = 8.5, H Ar); 8.12 (1H, s, C(CF_3)OH); 8.91 (1H, d, *J* = 5.3, NH); 9.58 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz) (mixture of tautomers **A** and **B**): 19.0 (CH_2); 23.0 (CH_2); 30.2 ($3CH_3$, **A**); 30.8 ($3CH_3$, **B**); 82.4 (C-3, **B**); 84.5 (q, $^2J_{CF}$ = 32.4, C-7, **B**); 89.9 (C-4, **A**); 101.5; 107.6; 116.2; 117.1; 117.9 (CH); 118.6 (CH); 118.7 (q, $^1J_{CF}$ = 291.8, CF_3); 122.8 (CH); 123.5 (CH); 123.9 (CH); 124.0 (CH); 124.6 (q, $^1J_{CF}$ = 292.7, CF_3); 125.0 (CH); 126.7 (CH); 126.9 (CH); 128.5 (CH); 128.6 (CH); 128.7; 128.9 (2CH); 129.3; 133.9; 134.0; 140.6; 147.3 (q, $^4J_{CF}$ = 4.8, CH); 148.2; 151.2; 153.5; 155.1; 161.8; 175.6 (q, $^2J_{CF}$ = 30.5, C=O, **A**). ^{19}F NMR spectrum, δ, ppm: tautomer **A** (36%): –65.3 (s, CF_3); tautomer (**B**) (64%): –76.2 (s, CF_3). Found, %: C 63.41; H 5.27; N 9.93. $C_{22}H_{22}F_3N_3O_2$. Calculated, %: C 63.30; H 5.31; N 10.07.

1-{[2-(Adamantan-1-yl)-7-(trifluoromethyl)pyrazolo-[1,5-*a*]pyrimidin-6-yl]methyl}naphthalen-2-ol (4a). Method IV. $BF_3{\cdot}OEt_2$ (20 μl, 20 mol %) was added to a mixture of chromene **1a** (200 mg, 0.72 mmol), pyrazole **2a** (156 mg, 0.72 mmol), and *i*-PrOH (5 ml), and the mixture was heated under reflux for 8 h. The solvent was evaporated under reduced pressure, the residue was suspended at reflux in MeOH (2 ml), then kept at –30°C for 2 h. The product was filtered off, washed with chilled (–30°C) MeOH (2 ml), and recrystallized from EtOH.

Method V. A mixture of chromene **1a** (200 mg, 0.72 mmol), pyrazole **2a** (156 mg, 0.72 mmol), and AcOH (5 ml) was heated under reflux for 10 h. The formed precipitate was filtered off, washed with AcOH (2 ml), and recrystallized from EtOH.

Method VI. $BF_3{\cdot}OEt_2$ (20 μl, 80 mol %) was added to a solution of compound **3a** (99 mg, 0.20 mmol) in *i*-PrOH (3 ml), and the resulting mixture was heated under reflux for 6 h. The solvent was evaporated under reduced pressure, the residue was recrystallized from EtOH.

Method VII. A crystal of *p*-TsOH was added to a solution of compound **3a** (99 mg, 0.20 mmol) in MeOH (6 ml), and the resulting mixture was heated under reflux for 2 h. The solvent was evaporated under reduced pressure, and the residue was recrystallized from EtOH.

Yield 235 mg (68%, method IV), 225 mg (65%, method V), 75 mg (80%, method VI), 78 mg (82%, method VII), light-yellow crystals, mp 246–247°C. IR spectrum, ν, cm^{-1}: 3209, 3070 (OH), 2904, 2850 (CH Ad), 1631, 1604, 1546, 1516, 1440, 1400, 1357, 1296, 1271, 1249, 1192, 1157, 1072, 1022, 987, 813, 786, 740. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70 (6H, br. s, $3CH_2$ Ad); 1.93 (6H, br. s, $3CH_2$ Ad); 1.99 (3H, br. s, 3CH Ad); 4.57 (2H, s, CH_2); 6.66 (1H, s, H-3); 7.20 (1H, d, *J* = 8.9, H Ar); 7.28 (1H, t, *J* = 7.6, H Ar); 7.42 (1H, ddd, *J* = 8.2, *J* = 6.9, *J* = 1.1, H Ar); 7.76 (1H, d, *J* = 8.7, H Ar); 7.79–7.82 (2H, m, H-5, H Ar); 7.86 (1H, d, *J* = 8.5, H Ar); 10.00 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 23.8 (CH_2); 28.4 (3CH Ad); 34.8 (C Ad); 36.7 ($3CH_2$ Ad); 42.4 ($3CH_2$ Ad); 93.5 (C-3); 114.8; 118.6 (CH); 120.7; 121.7 (q, $^1J_{CF}$ = 275.6, CF_3); 122.7 (CH); 123.2 (CH); 127.5 (CH); 128.8; 129.2 (CH); 129.7 (q, $^2J_{CF}$ = 34.3, C-7); 129.7 (CH); 133.7; 148.2; 151.2 (C-5); 154.1; 167.4. ^{19}F NMR spectrum, δ, ppm: –60.4 (s, CF_3). Found, %: C 70.50; H 5.41; N 8.77. $C_{28}H_{26}F_3N_3O$. Calculated, %: C 70.43; H 5.49; N 8.80.

2-{[2-(Adamantan-1-yl)-7-(trifluoromethyl)pyrazolo-[1,5-*a*]pyrimidin-6-yl]methyl}-4,5-dimethylphenol (4b) was obtained by method IV of the synthesis of compound **4a** from chromene **1b** (184 mg, 0.72 mmol) and pyrazole **2a** (156 mg, 0.72 mmol). Yield 270 mg (83%, method IV), light-yellow crystals, mp 179–180°C (MeOH). IR spectrum, ν, cm^{-1}: 3206 (OH), 2908, 2850 (CH Ad), 1601, 1547, 1516, 1462, 1431, 1415, 1354, 1292, 1250, 1188, 1157, 1080, 945, 887, 783. ^{1}H NMR spectrum, δ, ppm: 1.71 (6H, br. s, $3CH_2$ Ad); 1.94–2.05 (15H, m, $3CH_2$ Ad, 3CH Ad, $2CH_3$); 4.04 (2H, s, CH_2); 6.56 (1H, s, H Ar); 6.64 (1H, s, H Ar); 6.72 (1H, s, H-3); 8.40 (1H, s, H-5); 9.23 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 18.9 (CH_3); 19.7 (CH_3); 28.4 (3CH Ad); 28.9 (CH_2); 34.8 (C Ad); 36.7 ($3CH_2$ Ad); 42.4 ($3CH_2$ Ad); 93.6 (C-3); 116.9 (CH); 120.6; 121.3 (q, $^1J_{CF}$ = 275.6, CF_3); 122.5; 126.8; 129.9 (q, $^2J_{CF}$ = 34.3, C-7); 130.8 (CH); 136.0; 148.6; 153.2; 153.6 (C-5); 167.3. ^{19}F NMR spectrum, δ, ppm: –61.5 (s, CF_3). Found, %: C 68.47; H 6.21; N 9.15. $C_{26}H_{28}F_3N_3O$. Calculated, %: C 68.56; H 6.20; N 9.22.

6-[(2-Hydroxyphenyl)(phenyl)methyl]-3-{7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-2-yl}adamantan-1-ol (4c) was obtained by method IV of the synthesis of compound **4a** from chromene **1c** (219 mg, 0.72 mmol) and pyrazole **2b** (168 mg, 0.72 mmol). Yield 275 mg (74%, method IV), light-yellow crystals, mp 229–231°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52–1.66 (6H, m, $3CH_2$ Ad); 1.77–1.84 (6H, m, $2CH_2$ Ad, 2CH Ad); 2.17 (2H, br. s, CH_2 Ad); 4.51 (1H, s, Ad–OH); 6.22 (1H, s, CHPh); 6.67 (1H, dd, *J* = 7.6, *J* = 1.4, H Ar); 6.71–6.75 (1H, m, H Ar); 6.76 (1H, s, H-3); 6.79 (1H, d, *J* = 8.0, H Ar); 7.07–7.12 (3H, m, H Ar); 7.25 (1H, t, *J* = 7.3, H Ar); 7.30–7.34 (2H, m, H Ar); 8.07 (1H, s, H-5); 9.67 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.6 (2CH Ad); 35.5 (CH_2 Ad);

38.2 (C Ad); 41.5 (2CH_2 Ad); 42.9 (q, $^4J_{CF}$ = 3.8, CHPh); 44.9 (2CH_2 Ad); 50.1 (CH_2 Ad); 67.1 (COH); 93.9 (C-3); 115.8 (CH); 119.6 (CH); 121.2 (q, $^1J_{CF}$ = 275.6, CF_3); 123.0; 127.4 (CH); 128.7; 129.0 (CH); 129.3 (2CH); 129.5 (2CH); 130.0 (CH); 130.3 (q, $^2J_{CF}$ = 34.3, C-7); 141.5; 148.5; 151.3 (C-5); 155.0; 167.0. ^{19}F NMR spectrum, δ, ppm: –60.8 (s, CF_3). Found, %: C 69.42; H 5.40; N 7.98. $C_{30}H_{28}F_3N_3O_2$. Calculated, %: C 69.35; H 5.43; N 8.09.

Ethyl 6-[(2-hydroxynaphthalen-1-yl)methyl]pyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (4d). 1*H*-Benzo[*f*]chromene-2-carbaldehyde (**1d**) (210 mg, 1.0 mmol) was added to a solution of pyrazole **2d** (155 mg, 1.0 mmol) in AcOH (2 ml). The mixture was heated under reflux with vigorous stirring for 15 min and cooled to room temperature. The formed precipitate was filtered off and recrystallized from EtOH–DMF, 4:1 mixture. Yield 255 mg (73%), light-yellow crystals, mp 271–273°C. IR spectrum, ν, cm^{-1}: 3246, 3055 (OH), 1720 (C=O), 1627, 1516, 1056, 808. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.1, CH_3); 4.21 (2H, q, *J* = 7.1, CH_2O); 4.42 (2H, s, CH_2); 7.24–7.28 (2H, m, H Ar); 7.42 (1H, ddd, *J* = 8.5, *J* = 6.9, *J* = 1.4, H Ar); 7.73 (1H, d, *J* = 8.7, H Ar); 7.78 (1H, d, *J* = 7.6, H Ar); 8.04 (1H, d, *J* = 8.9, H Ar); 8.49 (1H, s, H-2); 8.77 (1H, d, *J* = 2.1) and 8.94 (1H, d, *J* = 2.1, H-5,7); 10.09 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 14.9 (CH_3); 24.6 (CH_2); 60.0 (CH_2O); 102.1; 116.4; 118.6 (CH); 123.0 (CH); 123.2 (CH); 124.8; 127.3 (CH); 128.8; 129.1 (CH); 129.3 (CH); 133.3; 134.8 (C-7); 146.1; 147.5 (C-2); 153.3; 155.3 (C-5); 162.1 (C=O). Found, %: C 69.22; H 4.88; N 12.01. $C_{20}H_{17}N_3O_3$. Calculated, %: C 69.15; H 4.93; N 12.10.

Ethyl 6-[(6-bromo-2-hydroxynaphthalen-1-yl)methyl]-pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4e) was obtained by the method of the synthesis of compound **4d** from pyrazole **2d** (155 mg, 1.0 mmol) and 8-bromo-1*H*-benzo[*f*]-chromene-2-carbaldehyde (**1e**) (289 mg, 1.0 mmol). Yield 335 mg (79%), light-yellow crystals, mp 300–302°C. IR spectrum, ν, cm^{-1}: 3240, 3051 (OH), 1708 (C=O), 1627, 1274, 1058. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, CH_3); 4.22 (2H, q, *J* = 7.1, CH_2O); 4.41 (2H, s, CH_2); 7.29 (1H, d, *J* = 8.9, H-3 naphthalene); 7.51 (1H, dd, *J* = 9.1, *J* = 2.3, H-7 naphthalene); 7.73 (1H, d, *J* = 8.9, H-4 naphthalene); 8.01 (1H, *J* = 9.1, H-8 naphthalene); 8.05 (1H, d, *J* = 2.3, H-5 naphthalene); 8.50 (1H, s, H-2); 8.74 (1H, d, *J* = 2.1) and 8.93 (1H, d, *J* = 2.1, H-5,7); 10.27 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 14.9 (CH_3); 24.6 (CH_2); 60.0 (CH_2O); 102.1; 116.1; 116.8; 119.9 (CH); 124.5; 125.6 (CH); 128.6 (CH); 130.0 (CH); 130.1; 130.8 (CH); 131.9; 134.8 (C-7); 146.2; 147.6 (C-2); 153.9; 155.2 (C-5); 162.1 (C=O). Found, %: C 56.30; H 3.83; N 9.75. $C_{20}H_{16}BrN_3O_3$. Calculated, %: C 56.35; H 3.78; N 9.86.

Ethyl 6-[(2-hydroxynaphthalen-1-yl)methyl]-7-phenyl-pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4f) was obtained by the method of the synthesis of compound **4d** from pyrazole **2d** (155 mg, 1.0 mmol) and (1*H*-benzo[*f*]-chromen-2-yl)(phenyl)methanone (**1f**) (286 mg, 1.0 mmol). Reaction time 15 h. Yield 245 mg (58%), colorless crystals, mp 270–272°C. IR spectrum, ν, cm^{-1}: 3182, 3057 (OH), 1699 (C=O), 1529, 1246, 1056, 810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.1, CH_3); 4.37 (2H, q, *J* = 7.1, CH_2O); 4.41 (2H, s, CH_2); 7.09–7.13 (2H, m, H Ar); 7.19–7.23 (2H, m, H Ar); 7.35 (1H, d, *J* = 8.7, H Ar); 7.62–7.66 (1H, m, H Ar); 7.70–7.82 (5H, m, H Ar); 8.55 (1H, s, H-2); 8.75 (1H, s, H-5); 9.63 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 14.6 (CH_3); 24.2 (CH_2); 60.6 (CH_2O); 102.8; 116.7; 118.2 (CH); 122.2 (CH); 122.4; 122.8 (CH); 126.5 (CH); 128.9 (2C); 129.1 (2C); 129.2 (2CH); 130.2 (2CH); 131.3 (CH); 132.9; 146.0; 146.4; 147.3 (C-2); 152.6; 155.4 (C-5); 162.9 (C=O). Found, %: C 73.79; H 4.95; N 9.83. $C_{26}H_{21}N_3O_3$. Calculated, %: C 73.74; H 5.00; N 9.92.

Ethyl 13a-(trifluoromethyl)-4,13a-dihydro-6*H*-benzo-[5,6]chromeno[3,2-*e*]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4g) was obtained by the method of the synthesis of compound **4d** from pyrazole **2d** (155 mg, 1.0 mmol) and chromene **1a** (278 mg, 1.0 mmol). Reaction time 15 h. Yield 295 mg (71%), light-yellow crystals, mp 249–250°C (EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): tautomer **A**: 1.21 (3H, t, *J* = 7.1, CH_3); 4.20 (2H, q, *J* = 7.1, CH_2O); 4.64 (2H, s, CH_2); 7.17 (1H, d, *J* = 8.9, H Ar); 7.27–7.31 (1H, m, H Ar); 7.42–7.46 (1H, m, H Ar); 7.78 (1H, d, *J* = 8.5, H Ar); 7.82 (1H, d, *J* = 8.7, H Ar); 7.89 (1H, d, *J* = 8.5, H Ar); 8.19 (1H, s, H Ar); 8.68 (1H, s, H Ar); 10.05 (1H, s, OH); tautomer **B**: 1.25 (3H, t, *J* = 7.1, CH_3); 3.76 (1H, d, *J* = 18.5, 6-CH_2); 4.21 (2H, q, *J* = 7.1, CH_2); 4.27 (1H, d, *J* = 18.5, 6-CH_2); 7.16 (1H, d, *J* = 8.9, H-12); 7.22 (1H, d, *J* = 5.0, H-5); 7.40–7.44 (1H, m) and 7.54–7.58 (1H, m, H-8,9); 7.77 (1H, d, *J* = 8.9, H Ar); 7.85 (1H, d, *J* = 8.2, H Ar); 7.89 (1H, d, *J* = 8.5, H Ar); 7.97 (1H, s, H-2); 10.19 (1H, d, *J* = 5.0, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): tautomer **A**: 14.8 (CH_3); 24.1 (CH_2); 60.4 (CH_2O); 103.4; 114.3; 118.6 (CH); 122.7 (CH); 123.3 (CH); 123.8; 127.6 (CH); 128.8; 129.2 (CH); 130.0 (CH); 131.0 (q, $^2J_{CF}$ = 34.5, $\underline{C}CF_3$); 133.7; 146.9; 147.4 (C-2); 154.2; 155.9 (C-5); 161.8 (C=O) (the quartet signal of the carbon atom of the CF_3 group could not be recorded due to its low intensity); tautomer **B**: 15.0 (CH_3); 24.0 (C-6); 60.2 (CH_2O); 84.6 (q, $^2J_{CF}$ = 34.3, C-13a); 94.2; 94.8; 114.2; 118.3 (CH); 122.9 (CH); 123.4 (q, $^1J_{CF}$ = 292.7, CF_3); 125.0 (CH); 127.2 (CH); 127.5 (CH); 129.0 (CH); 129.1 (CH); 129.7; 131.7; 142.0; 142.5 (C-2); 148.7; 162.6 (C=O). ^{19}F NMR spectrum, δ, ppm: tautomer **A** (22%): –60.0 (s, CF_3); tautomer **B** (78%): –75.5 (s, CF_3). Found, %: C 60.65; H 3.94; N 10.01. $C_{21}H_{16}F_3N_3O_3$. Calculated, %: C 60.72; H 3.88; N 10.12.

Ethyl 9-(adamantan-1-yl)-13a-(trifluoromethyl)-4,13a-dihydro-6*H*-benzo[5,6]chromeno[3,2-*e*]pyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (4h) was obtained by the method of the synthesis of compound **4d** from pyrazole **2d** (155 mg, 1.0 mmol) and 1-[8-(adamantan-1-yl)-1*H*-benzo-[*f*]chromen-2-yl]-2,2,2-trifluoroethan-1-one (**1g**) (412 mg, 1.0 mmol). Reaction time 15 h. Yield 410 mg (75%), colorless crystals, mp 289–291°C (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): tautomer **A**: 1.21 (3H, t, *J* = 7.1, CH_3); 1.71 (6H, br. s, 3CH_2 Ad); 1.89 (6H, br. s, 3CH_2 Ad); 2.03 (3H, br. s, 3CH Ad); 4.20 (2H, q, *J* = 7.1, CH_2O); 4.61 (2H, s, CH_2); 7.16 (1H, d, *J* = 8.9, H Ar); 7.51 (1H, d, *J* = 8.9, H Ar); 7.67 (1H, s, H Ar); 7.75 (1H, d, *J* = 8.7, H Ar); 7.80 (1H, d, *J* = 8.9, H Ar); 8.20 (1H, s,

H Ar); 8.68 (1H, s, H Ar); 9.92 (1H, s, OH); tautomer **B**: 1.25 (3H, t, J = 7.1, CH_3); 1.71 (6H, br. s, $3CH_2$ Ad); 1.89 (6H, br. s, $3CH_2$ Ad); 2.03 (3H, br. s, 3CH Ad); 3.73 (1H, d, J = 18.8, 6-CH_2); 4.20–4.25 (3H, m, CH_2O, 6-CH_2); 7.11 (1H, d, J = 8.9, H-12); 7.21 (1H, d, J = 4.8, H-5); 7.63 (1H, d, J = 8.9, H Ar); 7.70 (1H, s, H-10); 7.74 (1H, d, J = 8.7, H Ar); 7.82 (1H, d, J = 8.9, H Ar); 7.96 (1H, s, H-2); 10.17 (1H, d, J = 4.8, NH). ^{13}C NMR spectrum, δ, ppm (J, Hz): tautomer **A**: 14.8 (CH_3); 24.0 (CH_2); 28.8 (3CH Ad); 36.0 (C Ad); 36.7 ($3CH_2$ Ad); 43.0 ($3CH_2$ Ad); 60.4 (CH_2O); 103.4; 114.0; 118.4 (CH); 122.5 (CH); 123.9; 124.1 (CH); 128.8; 129.1 (CH); 130.0 (CH); 131.0 (q, $^2J_{CF}$ = 34.5, $\underline{C}CF_3$); 131.9; 145.6; 146.9; 147.4 (C-2); 153.6; 156.0 (C-5); 161.8 (C=O) (the quartet signal of the carbon atom of the CF_3 group could not be recorded due to its low intensity); tautomer **B**: 15.0 (CH_3); 24.0 (C-6); 28.8 (3CH Ad); 36.2 (C Ad); 36.7 ($3CH_2$ Ad); 43.0 ($3CH_2$ Ad); 60.1 (CH_2O); 84.6 (q, $^2J_{CF}$ = 34.3, C-13a); 94.4; 94.8; 113.9; 118.0 (CH); 122.7 (CH); 123.4 (q, $^1J_{CF}$ = 293.7, CF_3); 123.8 (CH); 125.5 (CH); 127.0 (CH); 129.1 (CH); 129.8; 129.9; 142.0; 142.4 (C-2); 147.4; 148.2; 162.6 (C=O). ^{19}F NMR spectrum, δ, ppm: tautomer **A** (19%): –60.0 (s, CF_3); tautomer **B** (81%): –75.5 (s, CF_3). Found, %: C 67.67; H 5.53; N 7.55. $C_{31}H_{30}F_3N_3O_3$. Calculated, %: C 67.75; H 5.50; N 7.65.

1-{[3-(Adamantan-1-yl)-1-methyl-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]methyl}naphthalen-2-ol (5). A crystal of *p*-TsOH was added to a solution of pyrazole **2e** (169 mg, 0.73 mmol) and chromene **1a** (200 mg, 0.72 mmol) in DMF (5 ml). The mixture was heated under reflux for 12 h, cooled, and poured into H_2O (10 ml) with stirring. The formed precipitate was filtered off and recrystallized from MeOH. Yield 120 mg (34%), light-yellow crystals, mp 117–118°C. IR spectrum, ν, cm^{-1}: 3500–3150 (OH), 2904, 2850 (CH Ad), 1628, 1566, 1512, 1442, 1404, 1361, 1327, 1215, 1179, 1126, 1087, 1011, 987, 904, 810, 744, 705. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.74 (6H, br. s, $3CH_2$ Ad); 2.06 (3H, br. s, 3CH Ad); 2.16 (6H, br. s, $3CH_2$ Ad); 3.88 (3H, s, CH_3); 4.59 (2H, s, CH_2); 7.21–7.27 (2H, m, H Ar); 7.33 (1H, ddd, J = 8.0, J = 6.9, J = 1.2, H Ar); 7.55 (1H, d, J = 8.5, H Ar); 7.76–7.83 (3H, m, H Ar); 10.01 (1H, s, OH). ^{13}C NMR spectrum (100°C), δ, ppm (J, Hz): 26.3 (CH_2); 29.0 (3CH Ad); 34.2 (CH_3); 37.0 ($3CH_2$ Ad); 38.5 (C Ad); 41.7 ($3CH_2$ Ad); 107.5; 116.2; 118.9 (CH); 122.4 (CH); 123.1 (CH); 124.3 (q, $^1J_{CF}$ = 274.6, CF_3); 127.3 (CH); 128.5; 129.1 (CH, C); 129.4 (CH); 129.6 (q, $^2J_{CF}$ = 29.6, C-4); 133.9; 149.8 (C-6); 150.0; 151.3; 154.0. ^{19}F NMR spectrum, δ, ppm: –52.4 (s, CF_3). Found, %: C 70.78; H 5.70; N 8.63. $C_{29}H_{28}F_3N_3O$. Calculated, %: C 70.86; H 5.74; N 8.55.

X-ray structural analysis of compound 4g was performed on an Agilent SuperNova diffractometer using a microfocus X-ray source (CuKα radiation, λ 1.54060 Å) and an Atlas S2 coordinate CCD detector. Crystals suitable for structural analysis were obtained by slow evaporation at room temperature of an EtOH solution of compound **4g**. The collection of reflections, solving and refinement of the unit cell parameters was carried out using the CrysAlisPro specialized software package.[18] The structure was solved using the SHELXT program[19] and solved employing the SHELXL program,[20] molecular graphics were rendered and preparation of the material for publication was performed using the OLEX2 software package.[21] The full set of X-ray structural data for compound **4g** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2038689).

Supplementary information file containing the synthetic procedures and spectral-analytical characteristics of the starting compounds for the preparation of adamantyl-substituted pyrazoles **2a**,**b**,**e** and the principal crystallographic data and parameters of the X-ray structural analysis of compound **4g** is available at the journal website at http://link.springer.com/journal/10593.

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