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Synthesis fluorocontaining derivatives of pyrazolo[3,4-d]pyrimidines. Message 2. Synthesis of fluorocontaining substituted amides of 5-(fluorobenzoylamino)-1-phenyl-1H-pyrazol-4-carboxylic acid and substituted 5-aryl-6-aryl-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidine-4-ones.

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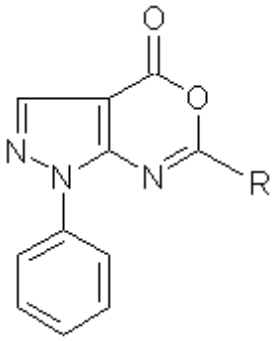
Abstract: *Synthesized according to the method developed by us earlier pyrazolo[3,4-d] [1,3]oxazine involved in the reaction with various primary and secondary amines to form amides of 5-(fluorobenzoylamino)-1-phenyl-1H-pyrazole-4-carboxylic acid. Synthesized previously benzamides of pyrazole-4-carboxylic acid was subjected to high temperature cyclization with the formation of substituted 5-aryl-6-aryl-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidine-4-ones.*

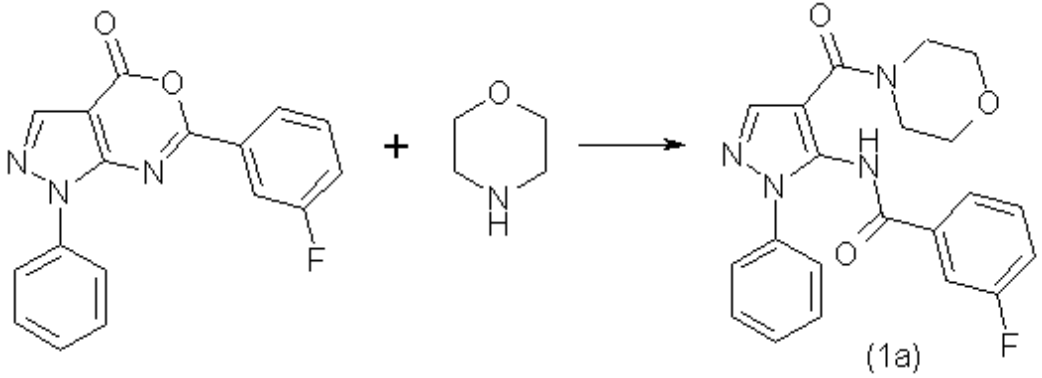
Keywords: *pyrazolo[3,4-d][1,3]oxazine, dihydropyrazolo-[3,4-d]pyrimidine-4-one, benzamide, thin layer chromatography, ^{1}H NMR spectra.*

As was shown in our previous article [1] derivatives of pyrazolo[3,4-d]pyrimidines currently presents a fairly extensive number of examples of biologically active substances with antimicrobial [2,3], antiviral [4,5], antiallergic [6], antihypotensives [7-9], antitumor [10], anti-inflammatory [11] and analgesic properties [12].

Synthesized by us earlier [1] according to the developed method derivatives of pyrazolo[3,4-d] [1,3]oxazin-4-one with general formula:

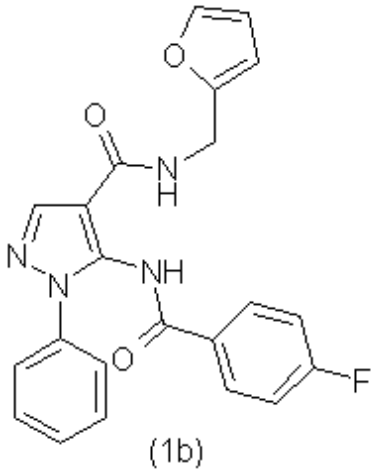


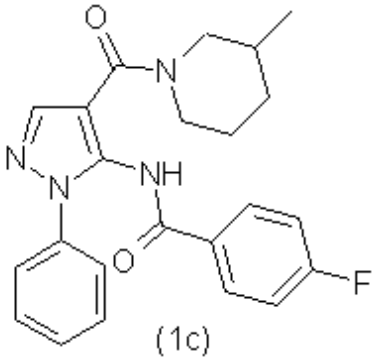
where R represents a 2,3 and 4 - fluorosubstituted phenyl fragment are highly reactive compounds. In addition to the previously discussed interaction with various substituted anilines we have implemented the interaction of substituted pyrazolo[3,4-d] [1,3]oxazin-4-ones with various primary and secondary amines that can be illustrated by the reaction of obtaining 5-(3-perbenzoate)-1-phenyl-1H-pyrazole-4-carboxylic acid morpholide(1a):

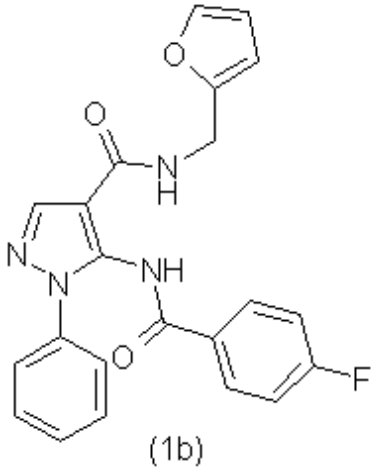


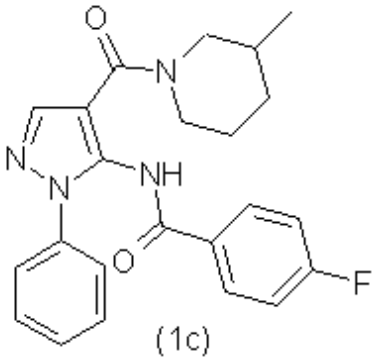
The reaction was carried out by mixing equimolar amounts of 6-(3-fluorophenyl)-1-phenyl-1H-pyrazolo-[3,4-d][1,3]oxazin-4-one and morpholine and in contrast to the reaction with aniline was accompanied by a strong exothermic effect.

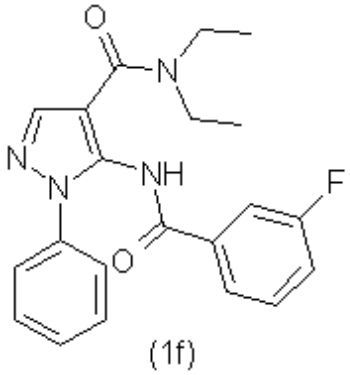
By the similar method using different amines, we have obtained the following compounds: using 2-furfurylamine was obtained compound (1b), using 3-methylpiperidine was obtained compound (1c), using 3-pyridylmethylamine was obtained compound (1d), using N-ethylpiperazine was obtained compound (1e), using N,N-diethylamine was obtained the compound (1f), using 4-methylpiperidine was obtained the compound(1g). The synthesized compounds have the following formulas:

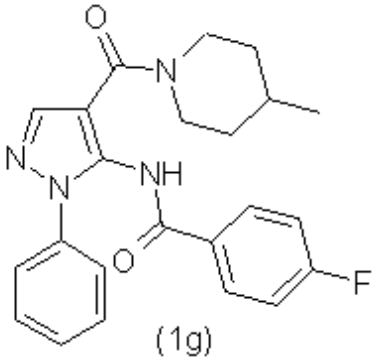






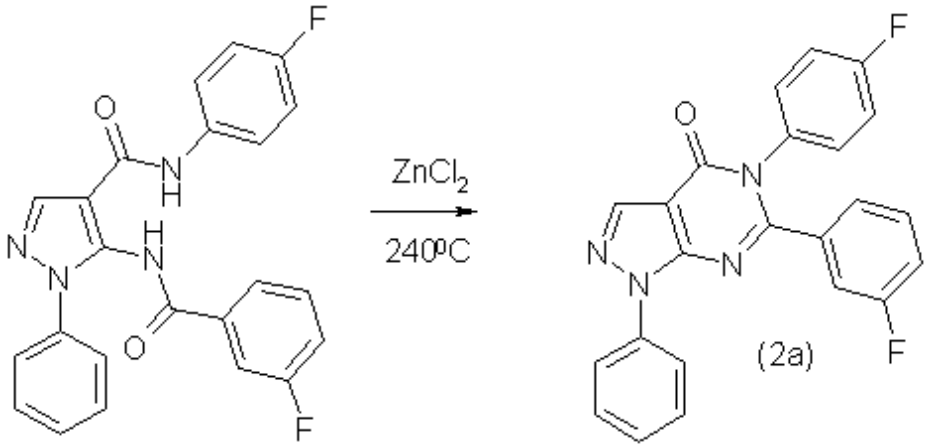




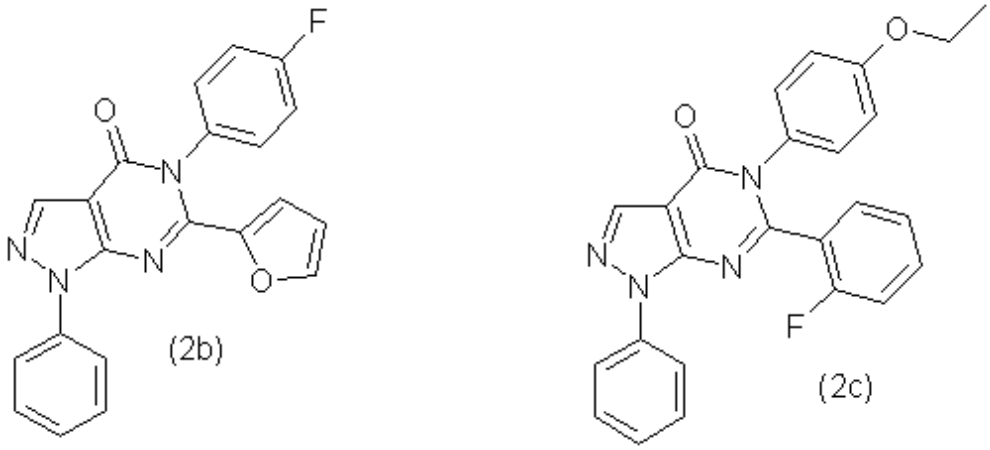


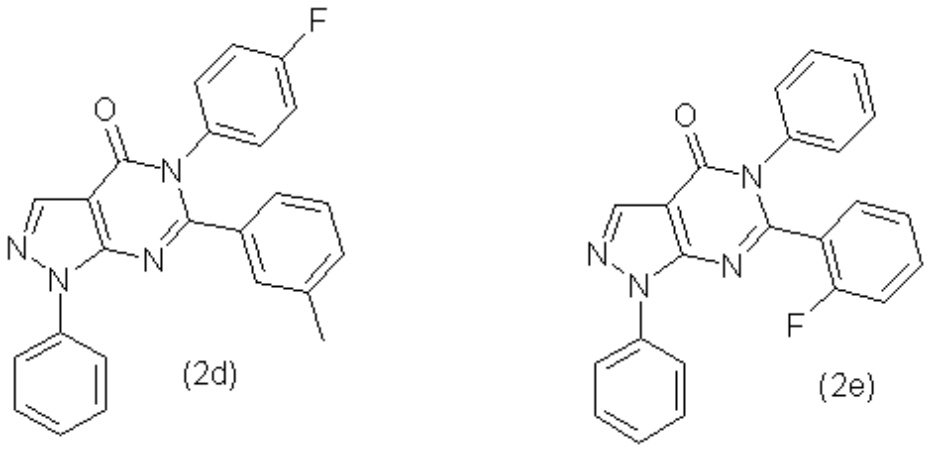
Synthesized according to the proposed method [1] substituted 5-(fluorobenzoylamino) arylamides of 1-phenyl-1H-pyrazole-4-carboxylic acid were subjected to thermal cyclization by using as a catalyst

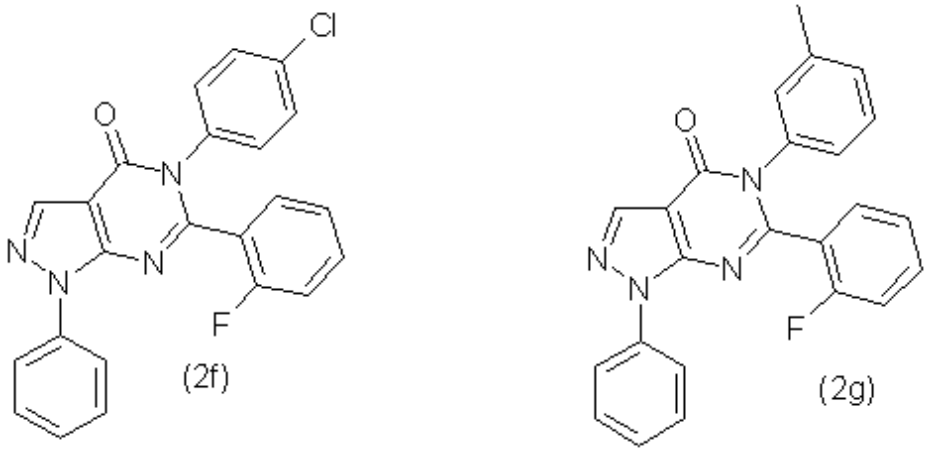
anhydrous zinc chloride. This process can be illustrated at the example of a 5-(4'-fluorophenyl)-6-(3''-fluorophenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one (2a):



Similarly, in accordance with this method were synthesized compounds 2b, 2c, 2d, 2e, 2f and 2g, which has the following formula:







Experimental

^{1}H NMR spectra (external reference TMS) were obtained in DMSO-d6 on the device Bruker AM-400 (400 MHz), melting temperatures of the substances were defined on the device Mettler FP5. Monitoring the progress of the reaction and individuality of the obtained compounds was carried out by TLC on plates Silufol UV-254 in the system of toluene-acetone 4:1.

5-(3-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid morpholide (1a).

In a three-neck flask on 25 ml, equipped with condenser were placed 1 g (0,003 mol) 6-(3-fluorophenyl)-1-phenyl-1H-pyrazolo-[3,4-d][1,3]oxazin-4-one and 2 ml of freshly distilled morpholine. The reaction takes place with a significant thermal effect and ends within 15 minutes. Then, to the reaction mixture was added 10 ml of ethyl alcohol. While cooling in an ice bath falls white precipitate, which is filtered off, washed with ethyl alcohol and dried first on the filter and then in vacuum. Thus was prepared 0,98 g (76,18%) 5-(3-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid morpholide as a white crystals with mp. 170 – 173 °C. R_f 0,35 (toluene-acetone 4:1). NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **3,55** (8H, s, morph), **7,40** (1H, m, C_6H_5), **7,50** (3H, m, C_6H_5), **7,58** (3H, m, C_6H_5), **7,65** (1H, m, C_6H_5), **7,73** (1H, m, C_6H_5), **7,94** (1H, s, -CH=), **10,40** (1H, s, NH). Found, %: C 63,81; H 4,88; N 14,55; F 4,73. **$C_{21}H_{19}FN_4O_3$** Calculated, %: C 63,95; H 4,86; N 14,21; F 4,82.

According to the similar method were synthesized the following compounds:

-5-(4-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid (2-furfuryl)amide (1b) with output 89,0% as the white powder with mp.180-183 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **4,41** (2H, d, CH_2), **6,25**(1H, d, C_6H_5), **6,38** (1H, m, C_6H_5), **7,38** (3H, m, C_6H_5), **7,45** (2H, t, C_6H_5), **7,95** (2H, m, C_6H_5), **8,26** (1H, s, -CH=), **8,61** (1H, t, NH), **10,42** (1H, s, NH). Found, %: C 65,57; H 4,19; N 13,59; F 4,83. **$C_{22}H_{17}FN_4O_3$** Calculated, %: C 65,34; H 4,24; N 13,85; F 4,70.

-5-(4-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid (3-piperidyl)amide (1c) with output 81,3% as the white powder with mp.192-195 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **0,80** (2H, d, CH_3), **1,10** (1H, m, CH), **1,50** (3H, m, CH), **1,70** (1H, d, CH_2), **2,60** (1H, m, CH), **3,00** (1H, m, CH), **3,80** (1H, m, CH), **4,30** (1H, m, CH), **7,35** (3H, m, C_6H_5), **7,45** (2H, t, C_6H_5), **7,55** (2H, d, C_6H_5), **7,85** (1H, s, -CH=), **7,90** (2H, m, C_6H_5), **10,50** (1H, s, NH). Found, %: C 68,02; H 5,59; N 13,83; F 4,51. **$C_{23}H_{13}FN_4O_2$** Calculated, %: C 67,97; H 5,70; N 13,78; F 4,67.

-5-(4-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid (3-pyridyl)methylamide (1d) with output 78,1% as the white powder with mp.180-185 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **4,45** (2H, d, CH_2), **7,35** (4H, m, C_6H_5), **7,49** (2H, t, C_6H_5), **7,55** (2H, d, C_6H_5), **7,70** (1H, d, C_6H_5), **7,95** (2H, m, C_6H_5), **8,26** (1H, s, -CH=), **8,48** (1H, d, C_6H_5), **8,53** (1H, m, C_6H_5), **8,78** (1H, t, NH), **10,43** (1H, s, NH). Found, %: C 66,37; H 4,29; N 16,91; F 4,52. **$C_{23}H_{23}FN_4O_2$** Calculated, %: C 66,50; H 4,37; N 16,86; F 4,37.

-5-(4-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid (N-ethylpiperazine)amide (1e) with output 87,7% as the white powder with mp.152-155 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **0,95** (3H, t, CH_3), **2,28** (6H, m, CH_2), **3,50** (4H, s, CH_2), **7,36** (3H, q, C_6H_5), **7,46** (2H, t, C_6H_5), **7,57** (2H, d, C_6H_5), **7,90** (1H, s, -CH=), **7,94** (2H, m, C_6H_5), **10,56** (1H, s, NH). Found, %: C 65,81; H 5,59; N 16,71; F 4,47. **$C_{23}H_{24}FN_5O_2$** Calculated, %: C 65,54; H 5,74; N 16,62; F 4,51.

-5-(3-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid (N,N-diethylamide (1f) with output 81,2% as the white powder with mp.180-183 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **1,08** (6H, s, CH_3), **3,30** (4H, s, CH_2), **7,39** (1H, t, C_6H_5), **7,49** (3H, m, C_6H_5), **7,60** (4H, m, C_6H_5), **7,70** ((1H, m, C_6H_5), **7,92** (1H, s, -CH=), **10,40** (1H, s, NH). Found, %: C 66,17; H 5,49; N 14,81; F 4,77. **$C_{21}H_{21}FN_4O_2$** Calculated, %: C 66,30; H 5,56; N 14,73; F 4,99.

-5-(4-Fluorobenzoylamino)-1-phenyl-1H-pyrazolo-4-carboxylic acid (4-piperidyl)amide (1g) with output 90,1% as the white powder with mp.175-177 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **0,85** (3H, d, CH_3), **1,00** (2H, m, CH), **1,60** (3H, m, CH), **2,80** (2H, m, CH), **3,85** (1H, m, CH), **4,35** (1H, m, CH), **7,37** (3H, q, C_6H_5), **7,48** (2H, t, C_6H_5), **7,57** (2H, d, C_6H_5), **7,88** (1H, s, -CH=), **7,92** (2H, m, C_6H_5), **10,55** (1H, s, NH). Found, %: C 66,41; H 4,23; N 16,89; F 4,42. **$C_{23}H_{23}FN_4O_2$** Calculated, %: C 66,50; H 4,37; N 16,86; F 4,37.

5-(4'-Fluorophenyl)-6-(3''-fluorophenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one (2a)

In a three-neck flask on 10 ml, equipped with condenser, mechanical stirrer and thermometer were placed 1,15 g (0,0028 mol) 5-(3-fluorobenzoylamino)-1-phenyl-1H-pyrazol-4-carboxylic acid (4-fluorophenyl) amide and several crystals of anhydrous zinc chloride. The reaction mixture was heated to 220 – 240 °C and kept at this temperature until the termination of allocation of water (about 30 minutes). Then the reaction mass is then cooled to room temperature, add 5 ml of ethanol and heated to boiling for 5 minutes. The resulting dark colored solution is cooled in an ice bath, the precipitated precipitate is filtered on the filter, washed with ethyl alcohol and dried in the beginning on the filter and then in vacuum.

Thus was prepared 0,79 g (71,27%) 5-(4'-Fluorophenyl)-6-(3''-fluoro-phenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one as the white powder with mp. 210 – 213 °C. R_f 0,41 (toluene-acetone 4:1). NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **7,17** (1H,t, C_6H_5), **7,45** (3H, m, C_6H_5), **7,58** (3H, m, C_6H_5), **7,68** (3H, m, C_6H_5), **7,70** (1H, d, C_6H_5), **8,42** (1H, s, -CH=). Found, %: C 66,27; H 3,81; N 13,42; F 9,12. **$C_{23}H_{16}F_2N_4O_2$** Calculated, %: C 66,03; H 3,85; N 13,39; F 9,08.

According to the similar method were synthesized the following compounds:

- *5-(4'-Fluorophenyl)-6-(2''-furoyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one (2b)* with output 76,7 % as the white powder with mp. 230-235 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **5,88** (1H, d, C_6H_5), **6,52** (1H, m, C_6H_5), **7,43** (3H, m, C_6H_5), **7,52** (2H, m, C_6H_5), **7,60** (2H, t, C_6H_5), **7,85** (1H, d, C_6H_5), **8,18** (2H, d, C_6H_5), **8,43** (1H, s, -CH=). Found, %: C 67,69; H 3,61; N 15,02; F 4,99. **$C_{21}H_{13}FN_4O_2$** Calculated, %: C 67,74; H 3,52; N 15,05; F 5,10.

- *5-(4'-Ethoxyphenyl)-6-(2''-fluorophenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one (2c)* with output 79,8 % as the white powder with mp. 240-245 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **1,28** (3H, t, CH_3), **3,94** (2H, q, CH_2), **6,83** (2H, d, C_6H_5), **7,16** (4H, m, C_6H_5), **7,39** (2H, m, C_6H_5), **7,55** (3H, t, C_6H_5), **8,02** (2H, d, C_6H_5), **8,50** (1H, s, -CH=). Found, %: C 67,69; H 3,61; N 15,02; F 4,99. **$C_{25}H_{19}FN_4O_2$** Calculated, %: C 70,41; H 4,49; N 13,14; F 4,45.

- *5-(4'-Fluorophenyl)-6-(3''-methylphenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]pyrimidin-4-one (2d)* with output 82,9 % as the grey powder with mp. 165-170 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **2,20** (3H, s, CH_3), **7,16** (6H, m, C_6H_5), **7,38** (3H, m, C_6H_5), **7,56** (2H, t, C_6H_5), **8,08** (2H, d, C_6H_5), **8,48** (1H, c, -CH=). Found, %: C 72,59; H 4,34; N 14,28; F 4,71. **$C_{24}H_{17}FN_4O$** Calculated, %: C 72,72; H 4,32; N 14,13; F 4,79.

- *5-Phenyl-6-(2''-fluorophenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]-pyrimidin-4-one (2e)* with output 85,2 % as the grey powder with mp. 245-250 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **7,06** (1H, t, C_6H_5), **7,14** (1H, t, C_6H_5), **7,30** (5H, m, C_6H_5), **7,42** (1H, t, C_6H_5), **7,58** (4H, t, C_6H_5), **8,02** (2H, d, C_6H_5), **8,52** (1H, s, -CH=). Found, %: C 72,31; H 4,02; N 14,58; F 4,91. **$C_{23}H_{15}FN_4O$** Calculated, %: C 72,24; H 3,95; N 14,65; F 4,97.

- *5-(4'-Chlorophenyl) -6-(2''-fluorophenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]-pyrimidin-4-one (2f)* with output 91,2 % as the grey powder with mp. 233-235 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **7,12** (1H, m, C_6H_5), **7,20** (1H, t, C_6H_5), **7,40** (8H, м, C_6H_5), **7,60** (2H, m, C_6H_5), **8,00** (1H, m, C_6H_5), **8,55** (1H, s, -CH=). Found, %: C 66,19; H 3,42; N 13,52; F 4,52. **$C_{23}H_{14}ClFN_4O$** Calculated, %: C 66,27; H 3,39; N 13,44; Cl 8,51; F 4,56.

- *5-(3'-метилфенил) -6-(2''-fluorophenyl)-1-phenyl-1,5-dihydropyrazolo-[3,4-d]-pyrimidin-4-one (2g)* with output 83,2 % as the grey powder with mp. 241-243 °C. NMR spectrum ^{1}H (20% in $CDCl_3$), δ, m.d.: **2,20** (3H, s, CH_3), **7,15** (7H, m, C_6H_5), **7,35** (3H, m, C_6H_5), **7,55** (2H, m, C_6H_5), **8,00** (1H, d, C_6H_5), **8,45** (1H, c, -CH=). Found, %: C 72,59; H 4,41; N 14,22; F 4,83. **$C_{24}H_{17}FN_4O$** Calculated, %: 72,72; H 4,32; N 14,13; F 4,79.

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Recommended for publication by Prof. A. F. Eleev