Synthesis and cytotoxic activity of heterocyclization products of 1,1-dicyano-2-hetaryl-2-trifluoromethylethylenes

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Methods for the synthesis of novel fluorinated compounds by reaction of 1,1-dicyano-2-hetaryl-2-trifluoromethylethylenes with a variety of nitrogen heterocycles have been developed. Cyctotoxicity of the obtained organofluorine heterocycles were studied *in vitro* at the U.S. National Cancer Institute (NCI) in the framework of the International Program for Development of Effective Antitumor Drugs. Cytotoxic activity in the series of fluorinated pyrazolo[1,5-*a*]pyrimidines has been observed for the first time, this strongly depending on the nature and position of the substituents.

Key words: cyano(hetaryl)ethylenes, heterocyclizarion, *in vitro* cytotoxicity.

Fluorinated cyanoethylenes are convenient precursors for heterocyclic compounds such as 3-trifluoromethylpyrazoles, 4-trifluoromethylpyrimidines, and others.[1] Heterocyclization of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene has previously been studied in our laboratory.[2] Further, these conversions were extended to 1,1-dicyanoethylenes with other fluorinated substituents and functional groups.[3,4] Several 1,4-dihydropyridine derivates, which were synthesized from the corresponding dicyanoehtylenes according to the method developed by us, have been patented as biologically active agents.[5] An essential part of the modern antitumor agents represent fluorinated pharmaceuticals.[6] Currently, a search for the antitumor agents in this direction is regarded as a very topical task. Thus about 100 structural types of fluorinated anticancer agents is given in a review,[7] most of which being heterocycles.

In continuation of this research, it was of interest to develop synthetic pathways towards 1,1-dicyano-2-hetaryl-2-trifluoromethylethylenes where one of the CF_3 groups is replaced by a heteroaromatic core and to study the cyclization of these novel compounds. This direction of the research can increase significantly the chemical diversity of the heterocyclic structures, which could be derived on the base of fluorinated 1,1-dicyanoethylenes, which is essential for the search for novel practically useful compounds. Pyrazole and thiophene derivatives were selected for functionalization of cyanoethylenes.

Results and Discussion

2-Chloro-1,1-dicyano-2-trifluoromethylethylene (**1**) was used as a starting compound for the synthesis of the target cyanoethylenes. Compound **1** was synthesized by condensation of ethyl trifluoroacetate with malononitrile in the presence of sodium ethoxide followed by treatment of the resulted alkoxide with phosphorus oxycloride.[8] It is known that alkene **1** readily reacts with nucleophiles to give cyanovinylation products, the chloride anion acting as a leaving group.[8,9] The mobility of the chlorine atom in alkene **1**, which is abnormal for vinyl chlorides, was discussed.[10] The initial step of the reaction of alkene **1** with RH-nucleophiles involved presumably the addition to the double bond of the alkene followed by elimination of HCl.[10] Similarly, tetracyanoethylene reacts with nucleophiles with elimination of hydrogen cyanide. In the present work, we extended this reaction to heteroaromatic compounds of π-donating nature. *N*-Methylpyrrole underwent noncatalyzed 2-cyanovinylation with alkene **1** at room temperature (Scheme 1). The target dicyanoethylene **2** was isolated in 77% yield by vacuum distillation. Indole, as well as its 2-methyl and 2-phenyl derivatives, underwent 3-substitution upon refluxing with alkene **1** in benzene to give cyanoethylenes **3—5**. The most stable 2-phenylindole gave the highest yield (95%) of the reaction product, derivative **5**. It was also found that anilines readily react with alkene **1** to give the corresponding 4-C-vinyl-

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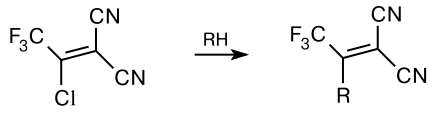
Scheme 1



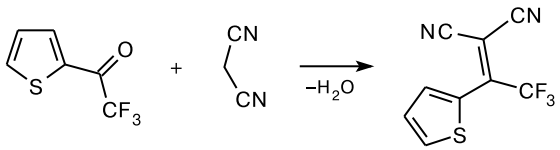
1 **2—8**

Compound	R
2	*N*-methylpyrrol-2-yl
3	Indol-3-yl
4	2-Methylindol-3-yl
5	2-Phenylindol-3-yl
6	*p*-Diethylaminophenyl
7	*p*-Morpholinophenyl
8	4-Amino-3,5-diisopropylphenyl

ation products **6—8**. It is of note that in the case of 2,6-diisopropylaniline this reaction, and not N-vinylation, proceeded in high yield (75%), which can probably be attributed to steric hindrance at the amino group due to the isopropyl groups.

An attempt of cyanovinylation of thiophene with alkene **1** was unsuccessful. No reaction was observed even at elevated temperature. The use of the Lewis acids ($AlCl_3$, $SnCl_4$, $ZnCl_2$) as the catalysts led to the resinification of the reaction mixture. An alternative pathway for the synthesis of alkenylthiophenes was developed, which involved condensation of 2-trifluoroacetylthiophene with malononitrile in benzene in the presence of piperidine and acetic acid (Scheme 2). The target compound **9** was isolated by vacuum distillation in 68% yield. The obtained conjugated systems **2—9** are bright-colored compounds. Their color allowed visual monitoring of their transformations, which involved addition at the double bond.

Scheme 2

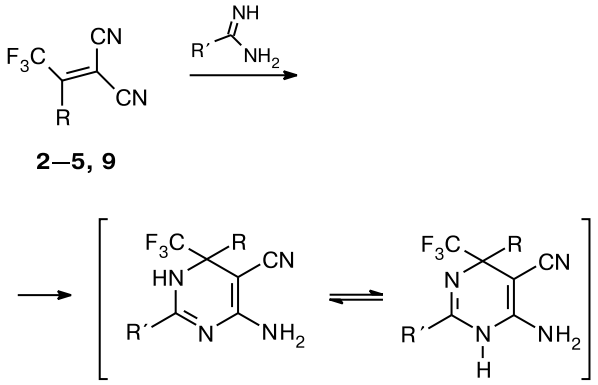


9

We have previously shown that 1,1-dicyano-2,2-bis-(trifluoromethyl)ethylene and 1,1-dicyanoethylenes bearing other fluoromethyl-substituents or an ester function instead of the CF_3 group react with amidines to give 1,4-dihydropyrimidines.[4,5] The reaction of synthesized alkenes **2—5** and **9** with *N*-unsubstituted carboxamidines (acetamidine and benzamidine) led to the corresponding 1,4-dihydropyrimidines (Scheme 3, Table 1).

The ^1H and ^{19}F NMR spectra of synthesized 1,4-dihydropyrimidines bearing the phenyl groups as the R´-substituents (compounds **11**, **13**, and **15**) or in the position 2 of the indole moiety (compound **16**) exhibited two sets of

Scheme 3



2—5, 9 **A** **B**

10—17 (10´—17´)

Compound	R	R´
10	*N*-Methylpyrrol-2-yl	Me
11	*N*-Methylpyrrol-2-yl	Ph
12	Indol-3-yl	Me
13	Indol-3-yl	Ph
14	2-Methylindol-3-yl	Me
15	2-Methylindol-3-yl	Ph
16	2-Phenylindol-3-yl	Me
17	2-Thienyl	Ph

signals for each of the characteristic nuclei (Table 2). Thus compound **11** showed two signals for the $N—CH_3$ group (δ_H 3.53 and 3.46), two signals for the NH_2 group (δ_H 6.69 and 6.87), two signals for each of three pyrrole CH groups, and two signals for the CF_3 group at δ_F 3.19 and 5.92. The intensity ratio of the signals in each pair is the same, 2 : 1. The signal intensity ratio for compounds **13**, **15**, and **16** is 3 : 1, 4 : 1, and 1 : 1, respectively.

In the case of substituted 1,4-dihydropyrimidines (R´ = methyl, compounds **10**, **12** and/or R = methyl in the position 2 of the indole moiety, compound **14**), the ^1H NMR spectra exhibited single set of signals for the methyl groups and broadened single signals for the NH-protons of the NH_2 groups and the heterocyclic core (Table 2). The ^{19}F NMR spectra of these compounds also contained markedly broadened single signal of the CF_3 group.

This spectral pattern, apparently, could be explained by the fact that compounds **10—17** can exist in solution in two tautomeric forms (see Scheme 3).

For compounds **11**, **13**, **15**, and **16**, tautomerization occurred slowly on the NMR time scale. The tautomeric equilibrium constant K_T could be determined from the intensity ratio of the characteristic signals. It could be expected, that in the ^{19}F NMR spectra the signals for the CF_3 group of tautomer **A** will appear at the lower fields than that of tautomer **B** due to stronger electron-withdrawing effect of the C=N fragment as compared with the MeC—NH fragment. On the base of this assumption, K_T values was calculated approximately 4, 9, 16, and 1 for

Table 1. Yields, physicochemical parameters, and elemental analysis data of compounds **10**—**61**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula
10	48	225—226	50.86 50.88	4.29 4.27	24.71 24.72	$C_{12}H_{12}F_3N_5$
11	67	249—250	56.45 56.43	3.76 3.79	21.95 21.93	$C_{15}H_{12}F_3N_5$
12	65	>240 decomp.	57.63 57.66	4.21 4.23	21.03 21.01	$C_{16}H_{14}F_3N_5$
13	59	>240 разл.	59.10 59.13	4.08 4.09	20.24 20.28	$C_{17}H_{14}F_3N_5$
14	58	>240 decomp.	62.97 62.99	3.71 3.70	18.39 18.36	$C_{20}H_{14}F_3N_5$
15	52	221—222	63.76 63.79	4.07 4.08	17.74 17.71	$C_{21}H_{16}F_3N_5$
16	68	190—191	63.73 63.79	4.09 4.08	17.75 17.71	$C_{21}H_{16}F_3N_5$
17	38	110—111	55.19 55.17	3.16 3.18	16.07 16.08	$C_{16}H_{11}F_3N_4S$
18	59	*	57.63 57.66	4.22 4.23	21.03 21.01	$C_{16}H_{14}F_3N_5$
19	53	*	57.64 57.66	4.21 4.23	21.02 21.01	$C_{16}H_{14}F_3N_5$
20	48	100—105	59.85 59.76	4.52 4.54	17.45 17.43	$C_{20}H_{18}F_3N_5O$
21	57	*	62.01 62.00	5.20 5.23	18.08 18.12	$C_{20}H_{20}F_3N_5$
22	61	*	60.88 60.85	3.42 3.40	19.73 19.71	$C_{18}H_{12}F_3N_5$
23	75	*	61.81 61.79	3.81 3.82	18.95 18.96	$C_{19}H_{14}F_3N_5$
24	63	*	61.77 61.79	3.83 3.82	18.98 18.96	$C_{19}H_{14}F_3N_5$
25	54	*	61.80 61.79	3.80 3.82	18.94 18.96	$C_{19}H_{14}F_3N_5$
26	49	*	53.56 53.57	3.31 3.30	16.64 16.66	$C_{15}H_{11}F_3N_4S$
27	47	*	53.58 53.57	3.32 3.30	16.68 16.66	$C_{15}H_{11}F_3N_4S$
28	61	*	50.63 50.65	3.61 3.60	27.25 27.26	$C_{13}H_{11}F_3N_6$
29	54	*	52.16 52.17	4.10 4.07	26.06 26.08	$C_{14}H_{13}F_3N_6$
30	47	*	55.38 55.32	4.39 4.47	21.53 21.48	$C_{18}H_{17}F_3N_6O$
31	65	*	60.48 60.56	4.67 4.67	16.93 16.86	$C_{25}H_{23}F_3N_6O_2$
32	58	*	57.55 57.49	4.02 4.06	16.78 16.84	$C_{24}H_{20}ClF_3N_6O$
33	45	*	57.44 57.32	5.09 5.03	22.33 22.22	$C_{18}H_{19}F_3N_6$
34	67	204—205	62.23 62.17	5.22 5.17	17.42 17.35	$C_{25}H_{25}F_3N_6O$
35	56	*	59.20 59.21	4.55 4.59	17.26 17.29	$C_{24}H_{22}ClF_3N_6$
36	49	222—224	59.40 59.39	5.73 5.75	20.78 20.77	$C_{20}H_{23}F_3N_6$
37	66	110—115	63.52 63.50	5.73 5.78	16.46 16.46	$C_{27}H_{29}F_3N_6O$
38	60	255—257	60.64 60.69	5.09 5.07	16.32 16.32	$C_{26}H_{26}ClF_3N_6$
39	56	*	55.83 55.82	3.21 3.22	24.45 24.47	$C_{16}H_{11}F_3N_6$
40	46	*	56.90 56.98	3.68 3.66	23.44 23.45	$C_{17}H_{13}F_3N_6$
41	53	*	58.13 58.10	3.16 3.10	18.49 18.48	$C_{22}H_{14}ClF_3N_6$
42	61	*	61.30 61.33	3.77 3.80	18.13 18.16	$C_{23}H_{17}F_3N_6O$
43	58	*	56.93 56.98	3.64 3.66	23.47 23.45	$C_{17}H_{13}F_3N_6$
44	56	*	58.03 58.06	4.02 4.06	22.55 22.57	$C_{18}H_{15}F_3N_6$
45	59	*	62.69 62.86	3.63 3.60	19.95 19.99	$C_{22}H_{15}F_3N_6$
46	42	*	51.23 51.25	2.61 2.63	16.58 16.60	$C_{18}H_{11}ClF_3N_5S$
47	44	*	54.65 54.67	3.40 3.38	16.76 16.78	$C_{19}H_{14}F_3N_5OS$
48	67	*	51.18 51.16	2.79 2.81	14.92 14.85	$C_{20}H_{13}F_6N_5S$
49	83	*	53.40 53.41	4.30 4.18	20.74 30.76	$C_{15}H_{14}F_3N_5O$
50	86	*	57.58 57.56	3.65 3.62	16.80 16.78	$C_{20}H_{15}F_3N_5O$
51	52	*	55.35 55.37	3.47 3.49	16.16 16.14	$C_{20}H_{15}ClF_3N_5O$
52	44	*	58.82 58.80	3.24 3.22	14.89 14.91	$C_{23}H_{15}ClF_3N_5O$
53	41	*	58.82 58.80	3.24 3.22	14.89 14.91	$C_{23}H_{15}ClF_3N_5O$
54	45	*	52.20 52.24	2.75 2.77	12.85 12.83	$C_{19}H_{13}ClF_3N_4OS$
55	40	*	58.08 58.10	4.12 4.11	14.28 14.26	$C_{19}H_{16}ClF_3N_4$
56	50	*	58.09 58.10	4.09 4.11	14.25 14.26	$C_{19}H_{16}ClF_3N_4$
57	53	*	66.69 66.66	4.72 4.70	12.43 12.44	$C_{25}H_{21}F_3N_4O$
58	51	*	68.22 68.24	5.03 5.01	13.25 13.26	$C_{24}H_{21}F_3N_4$
59	52	*	61.63 61.62	3.74 3.76	13.07 13.06	$C_{22}H_{16}ClF_3N_4$
60	55	*	65.10 65.09	4.49 4.51	13.23 13.20	$C_{23}H_{19}F_3N_4O$
61	43	*	6166 61.68	4.67 4.66	10.78 10.79	$C_{20}H_{18}F_3N_3S$

* Viscous glassy substance.

Table 2. ^{1}H and ^{19}F NMR spectral data (DMSO-d_6, δ, (*J*/Hz)) of compounds **1—47**

Compound	^{1}H NMR	^{19}F NMR (s, 3 F, CF_3)
10	8.86 (br.s, 1 H, NH); 6.84 (1 H, s, NH); 6.47 (br.s, 2 H, NH_2); 6.06 (s, 1 H, CH); 5.96 (m, 1 H, CH); 3.50 (s, 3 H, CH_3); 1.99 (s, 3 H, CH_3)	3.6
11	9.62 (s, 1 H, NH); 7.92 (d, 2 H, CH, *J* = 8); 7.58—7.46 (m, 3 H, CH); 6.69 (br.s, 2 H, NH_2); 6.50 (s, 1 H, CH); 6.15 (s, 1 H, CH); 5.99 (s, 1 H, CH); 3.53 (s, 3 H, CH_3)	3.19
11´	10.17 (s, 1 H, NH); 7.85 (m, 2 H, CH); 7.58—7.46 (m, 3 H); 6.87 (br.s, 2 H, NH_2); 6.71 (s, 1 H, CH); 6.08 (s, 1 H, CH); 5.93 (s, 1 H, CH); 3.46 (s, 3 H, CH_3)	5.92
12	9.87 (br.s, 1 H, NH); 7.44 (d, 1 H, CH, *J* = 8); 7.39 (d, 1 H, CH, *J* = 8); 7.29 (s, 1 H, CH); 7.14 (t, 1 H, CH, *J* = 8); 7.03 (t, 1 H, CH, *J* = 8); 6.33 (br.s, 2 H, NH_2); 1.99 (s, 3 H, CH_3)	3.37
13	11.31 (s, 1 H, NH); 9.44 (s, 1 H, NH); 7.91 (d, 2 H, CH, *J* = 8); 7.66—7.31 (m, 5 H, CH); 7.12 (d, 1 H, CH, *J* = 8); 6.99 (t, 1 H, CH, *J* = 8); 6.52 (br.s, 2 H, NH_2)	3.06
13´	11.16 (s, 1 H, NH); 10.07 (s, 1 H, NH); 7.85 (d, 2 H, CH, *J* = 8); 7.66—7.31 (m, 5 H, CH); 7.07 (t, 1 H, CH, *J* = 8); 6.94 (t, 1 H, CH, *J* = 8); 6.41 (br.s, 2 H, NH_2)	6.62
14	9.61 (br.s, 1 H, NH); 7.45—7.41 (m, 1 H, CH); 7.29 (d, 1 H, CH, *J* = 8); 7.03 (d, 1 H, CH, *J* = 8); 6.95 (t, 1 H, CH, *J* = 8); 6.92 (br.s, 2 H, NH_2); 2.34 (s, 3 H, CH_3); 1.98 (s, 3 H, CH_3)	5.10 (br.s)
15	11.61 (s, 1 H, NH); 9.07 (s, 1 H, NH); 7.50 (d, 1 H, CH, *J* = 8); 7.40—7.36 (m, 6 H, CH); 7.17—7.07 (m, 2 H, CH); 6.11 (br.s, 2 H, NH_2); 1.71 (s, 3 H, CH_3)	5.24
15´	11.23 (s, 1 H, NH); 9.30 (s, 1 H, NH); 7.92 (d, 2 H, CH, *J* = 8); 7.70—7.36 (m, 5 H, CH); 7.17—7.07 (m, 2 H, CH); 5.82 (br.s, 2 H, NH_2); 1.43 (s, 3 H, CH_3)	8.83
16	9.09 (s, 1 H, NH); 7.53—7.07 (m, 9 H, CH); 11.64 (br.s, 1 H, NH); 6.13 (br.s, 2 H, NH_2); 1.71 (s, 3 H, CH_3)	1.03
16´	11.25 (br.s, 1 H, NH); 9.34 (s, 1 H, NH); 7.53—7.07 (m, 9 H, CH); 5.87 (br.s, 2 H, NH_2); 1.41 (s, 3 H, CH_3)	2.63
17	10.16 (s, 1 H, NH); 7.88—7.87 (m, 2 H); 7.62—7.53 (m, 4 H, CH); 7.26 (d, 1 H, CH, *J* = 4); 7.09—7.07 (m, 1 H, CH); 6.53 (br.s, 2 H, NH_2)	0.57
18	7.48 (d, 1 H, CH, *J* = 8); 7.13 (br.s, 2 H, NH_2); 6.70 (s, 1 H, CH); 6.00 (br.s, 2 H, CH); 5.90 (t, 1 H, CH, *J* = 4); 3.52 (s, 3 H, N—CH_3); 2.04 (s, 3 H, CH_3)	8.79
19	7.35 (s, 1 H, CH); 7.11 (br.s, 2 H, NH_2); 6.91 (d, 1 H, CH, *J* = 8); 6.69 (br.s, 1 H, CH); 6.51 (d, 1 H, CH, *J* = 8); 6.00 (br.s, H, CH); 5.90—5.89 (t, 1 H, CH, *J* = 4); 3.51 (s, 3 H, N—CH_3); 1.95 (s, 3 H, CH_3)	8.82
20	7.36 (m, 3 H, CH); 7.07 (br.s, 2 H, NH_2); 6.95 (m, 3 H, CH); 6.65 (br.s, 1 H, CH); 6.05 (m, 1 H, CH); 3.71 (br.s, 4 H, 2 CH_2); 3.10 (br.s, 4 H, 2 CH_2)	3.57
21	7.39 (s, 1 H, CH); 7.25 (m, 2 H, CH) 7.03 (br.s, 2 H, NH_2); 6.98 (m, 1 H, CH); 6.60 (m, 3 H, CH); 6.06 (m, 1 H, CH); 3.29 (m, 4 H, 2 CH_2); 1.06 (m, 6 H, 2 CH_3)	3.68
22	11.13 (s, 1 H, NH); 7.66 (d, 1 H, CH, *J* = 8); 7.43 (d, 1 H, CH, *J* = 8); 7.36 (d, 1 H, CH, *J* = 8); 7.20 (s, 1 H, CH); 7.08—6.94 (m, 3 H, CH); 7.06 7.11 (br.s, 2 H, NH_2); 5.57 (d, 1 H, CH, *J* = 8); 6.06 (br.s, 1 H, CH);	2.25
23	11.11 (s, 1 H, NH); 7.67 (d, 1 H, CH, *J* = 8); 7.35 (d, 1 H, CH, *J* = 8); 7.25 (s, 1 H, CH); 7.18 (s, 1 H, CH); 7.06 (t, 1 H, CH, *J* = 8); 6.98 (br.s, 2 H, NH_2); 6.95 (m, 1 H, CH); 6.83 (d, 1 H, CH, *J* = 8); 6.55 (d, 1 H, CH, *J* = 8); 1.91 (s, 3 H, CH_3)	2.35
24	11.10 (s, 1 H, NH); 7.65 (d, 1 H, CH, *J* = 8); 7.40—7.35 (m, 2 H, CH); 7.07 (t, 1 H, CH, *J* = 8); 6.97 (br.s, 2 H, NH_2); 7.19 (s, 1 H, CH); 6.96—6.94 (m, 1 H, CH); 6.37 (s, 1 H, CH); 5.94 (d, 1 H, CH, *J* = 8);	1.98

(*to be continued*)

Table 2 (*continued*)

Compound	^{1}H NMR	^{19}F NMR (s, 3 F, CF_3)
25	11.11 (s, 1 H, NH); 7.73 (d, 1 H, CH, J = 8); 7.37—7.33 (m, 2 H, CH); 7.21 (s, 1 H, CH); 2.03 (s, 3 H, CH_3) 7.06 (t, 1 H, CH, J = 8); 6.97 (br.s, 2 H, NH_2); 6.96—6.94 (m, 1 H, CH); 6.85 (br.s, 1 H, CH); 5.99 (br.s, 1 H, CH); 2.03 (s, 3 H, CH_3)	2.51
26	7.52 (d, 1 H, CH, J = 5); 7.35 (br.s, 1 H, CH); 7.15—7.13 (m, 1 H, CH); 7.13 (br.s, 2 H, NH_2); 7.04 (t, 1 H, CH, J = 5); 6.94 (d, 1 H, CH, J = 8); 6.59 (d, 1 H, CH, J = 8); 1.96 (s, 3 H, CH_3)	0.24
27	7.61—7.53 (m, 2 H, CH); 7.22 (br.s, 2 H, NH_2); 7.09 (m, 2 H); 6.54 (br.s, 1 H, CH); 6.15 (br.s, 1 H, CH); 2.15 (s, 3 H, CH_3)	0.26
28	8.38 (s, 1 H, NH); 7.51 (br.s, 2 H, NH_2); 7.50 (s, 1 H, CH); 6.89 (s, 1 H, CH); 6.13 (s, 1 H, CH); 5.98 (t, 1 H, CH, J = 4); 5.35 (s, 1 H, CH); 3.60 (s, 3 H, CH_3)	−0.41
29	8.26 (s, 1 H, NH); 7.34 (br.s, 2 H, NH_2); 6.88 (br.s, 1 H, CH); 6.11 (bt.s, 1 H, CH); 5.97 (t, 1 H, CH, J = 4); 5.21 (s, 1 H, CH); 2.11 (s, 3 H, CH_3)	−0.37
30	8.33 (s, 1 H, NH); 7.45 (m, 5 H, CH + NH_2); 7.00 (d, 2 H, CH); 5.39 (s, 1 H, CH); 3.74 (br.s, 4 H, 2 CH_2); 3.15 (br.s, 4 H, 2 CH_2)	2.72
31	8.42 (s, 1 H, NH); 7.79 (d, 2 H, CH); 7.47 (d, 2 H, CH); 7.38 (br.s, 2 H, NH_2); 7.00 (m, 4 H, CH); 5.79 (s, 1 H, CH); 3.77 (m, 7 H, 2 CH_2 + OCH_3); 3.15 (br.s, 4 H, 2 CH_2)	2.69
32	8.51 (s, 1 H, NH); 7.89 (d, 2 H, CH); 7.51 (m, 6 H, CH + NH_2); 7.01 (d, 2 H, CH); 5.89 (s, 1 H, CH); 3.74 (br.s, 4 H, 2 CH_2); 3.15 (br.s, 4 H, 2 CH_2)	2.59
33	8.23 (s, 1 H, NH); 7.49 (s, 1 H, CH); 7.36 (m, 4 H, CH + NH_2); 6.69 (d, 2 H, CH); 5.37 (s, 1 H, CH); 3.35 (m, 4 H, 2 CH_2); 1.08 (m, 6 H, 2 CH_3)	2.69
34	8.37 (s, 1 H, NH); 7.83 (d, 2 H, CH); 7.39 (m, 4 H, CH + NH_2); 7.03 (d, 2 H, CH); 6.74 (d, 2 H, CH); 5.81 (s, 1 H, CH); 3.84 (s, 3 H, OCH_3); 3.39 (m, 4 H, 2 CH_2); 1.13 (m, 6 H, 2 CH_3)	2.65
35	8.41 (s, 1 H, NH); 7.89 (d, 2 H, CH); 7.49 (d, 2 H, CH); 7.38 (m, 4 H, CH + NH_2); 6.69 (d, 2 H, CH); 5.86 (s, 1 H, CH); 3.36 (m, 4 H, 2 CH_2); 1.08 (m, 6 H, 2 CH_3)	2.58
36	8.22 (s, 1 H, NH); 7.48 (s, H, CH); 7.26 (br.s, 2 H, NH_2); 7.14 (s, 2 H, CH); 5.39 (s, 1 H, CH); 4.84 (br.s, 2 H, NH_2); 3.04 (m, 2 H, CH); 1.14 (m, 12 H, 4 CH_3)	2.79
37	8.32 (s, 1 H, NH); 7.78 (d, 2 H, CH); 7.26 (br.s, 2 H, NH_2); 7.16 (s, 2 H, CH); 6.97 (d, 2 H, CH); 5.77 (s, 1 H, CH); 4.85 (br.s, 2 H, NH_2); 3.79 (s, 3 H, OCH_3); 3.04 (m, 2 H, CH); 1.14 (m, 12 H, 4 CH_3)	2.87
38	8.40 (s, 1 H, NH); 7.87 (d, 2 H, CH); 7.47 (d, 2 H, CH); 7.35 (br.s, 2 H, NH_2); 7.15 (s, 2 H, CH); 5.86 (s, 1 H, CH); 4.85 (br.s, 2 H, NH_2); 3.04 (m, 2 H, CH); 1.14 (m, 12 H, 4 CH_3)	2.84
39	11.30 (s, 1 H, NH); 8.22 (br.s, 1 H, NH); 7.51 (s, 1 H, CH); 7.49 (d, 1 H, CH, J = 8); 7.45 (d, 1 H, CH, J = 8); 7.34 (s, 1 H, CH); 7.33 (br.s, 2 H, NH_2); 7.14 (t, 1 H, CH, J = 8); 7.01 (t, 1 H, CH, J = 8); 5.34 (s, 1 H, CH)	−0.70
40	11.30 (s, 1 H, NH); 8.15 (br.s, 1 H, NH); 7.49 (d, 1 H, CH, J = 8); 7.45 (d, 1 H, CH, J = 8); 7.33 (br.s, 1 H, CH); 7.22 (br.s, 2 H, NH_2); 7.14 (t, 1 H, CH, J = 8); 7.01 (t, 1 H, CH, J = 8); 5.20 (s, 1 H, CH);2.13 (s, 3 H, CH_3)	−0.69
41	11.33 (s, 1 H, NH); 8.44 (br.s, 1 H, NH); 7.92 (d, 2 H, CH, J = 8); 7.74—47 (m, 6 H); 7.45 (br.s, 2 H, NH_2); 7.37 (br.s, 1 H, CH); 7.15 (t, 1 H, CH, J = 8); 7.01 (t, 1 H, CH, J = 8); 5.82 (s, 1 H, CH)	−0.62
42	11.31 (s, 1 H, NH); 8.33 (br.s, 1 H, NH); 7.82 (d, 1 H, CH, J = 8); 7.54 (d, 1H, CH, J = 8); 7.46 (d, 1 H, CH, J = 8); 7.36 (br.s, 1 H, CH); 7.34 (br.s, 2 H, NH_2); 7.15 (t, 1 H, CH, J = 8); 7.01 (t, 1 H, CH, J = 8); 7.00 (d, 2 H, CH, J = 8); 5.75 (s, 1 H, CH); 3.80 (s, 3 H, OCH_3)	−0.59

(*to be continued*)

Table 2 (*continued*)

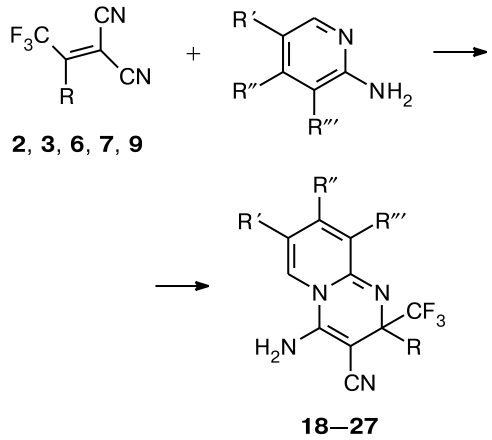
Compound	^{1}H NMR	^{19}F NMR (s, 3 F, CF_3)
43	11.27 (s, 1 H, NH); 8.17 (br.s, 1 H, NH); 7.51 (d, 1 H, CH, J = 1); 7.41 (d, 1 H, CH, J = 8); 7.32 (d, 1 H, CH, J = 8); 7.27 (br.s, 2 H, NH_2); 7.05 (t, 1 H, CH, J = 8); 6.95 (t, 1 H, CH, J = 8); 5.33 (d, 1 H, CH, J = 1); 2.38 (s, 3 H, CH_3)	0.44
44	11.28 (s, 1 H, NH); 8.10 (br.s, 1 H, NH); 7.39 (d, 1 H, CH, J = 8); 7.31 (d, 1 H, CH, J = 8); 7.17 (br.s, 2 H, NH_2); 7.04 (t, 1 H, CH, J = 8); 6.94 (t, 1 H, CH, J = 8); 5.18 (s, 1 H, CH); 2.37 (s, 3 H, CH_3); 2.11 (s, 3 H, CH_3)	0.74
45	10.44 (s, 1 H, NH); 7.98 (s, 1 H, CH); 7.58 (s, 1 H, CH); 7.37 (d, 1 H, CH, J = 8); 7.24—7.70 (m, 4 H); 7.22 (br.s, 2 H, NH_2); 7.11—7.07 (m, 1 H, CH); 6.93 (t, 1 H, CH, J = 8); 6.84 (t, 1 H, CH, J = 8); 6.59 (d, 1H, CH, J = 8); 6.54 (d, 1 H, CH, J = 2)	0.25
46	8.88 (s, 1 H, NH); 7.90 (d, 2 H, CH, J = 8.7); 7.71—7.70 (m, 1 H, CH); 7.55 (br.s, 2 H, NH_2); 7.50 (d, 2 H, CH, J = 8.7); 7.25 (br.s, 1 H, CH); 7.11—7.09 (m, 1 H, CH); 5.93 (s, 1 H, CH)	0.16
47	8.79 (s, 1 H, NH); 7.80 (d, 2 H, CH, J = 8.7); 7.70 (d, 1 H, CH, J = 5); 7.64 (br.s, 2 H, NH_2); 7.25 (br.s, 1 H, CH);7.10—7.08 (m, 1 H, CH); 6.99 (d, 2 H, CH, J = 8.7); 3.80 (s, 3 H, OCH_3)	0.19

compounds **11**, **13**, **15**, and **16**, respectively. The comparison of K_T values of compounds **13** and **15** indicated that the increase in the steric hindrance near the nitrogen atom in the position 6 of 1,4-dihydropyrimidines resulted in a decrease in the concentration of the tautomer **A**.

For compounds **10**, **12**, and **14**, the tautomerization is a considerably fast process on the NMR time scale, which results in averaging of the shielding of the characteristic groups. In this work, no detailed study of tautomerization was carried out. However, preliminary kinetic study by the dynamic NMR spectroscopy showed that in the ^{19}F NMR spectra the signal width at half height depends on the concentration. For example, the decrease in the concentration of compound **12** in DMSO from 0.02 to 0.005 mol L^{-1} broadened the signal of the fluorine atom from 100 to 295 Hz, which reflected the non-first-order kinetics of the tautomerization with respect to dihydropyrimidine derivatives. Since the change in the concentration led to the change in the width of NH-proton signals as well as in the width of the proton signals for water presented in DMSO, it could be assumed that all mobile protons of the system participated in the process, and the mechanism involved the formation of cyclic and acyclic associates as it has been shown for the known system of galvinoxyl (Coppinger's radical) with a spatially remote cation-acceptor centers.

It have been found that alkenes **2**, **3**, **6**, **7**, and **9** readily react with 2-aminopyridines to give pyrido[1,2-*a*]pyrimidine derivatives **18—27** (Scheme 4, Tables 1 and 2). The highest yields were observed in the heterocyclization reaction of alkene **3** with the corresponding aminopyridines.

Scheme 4

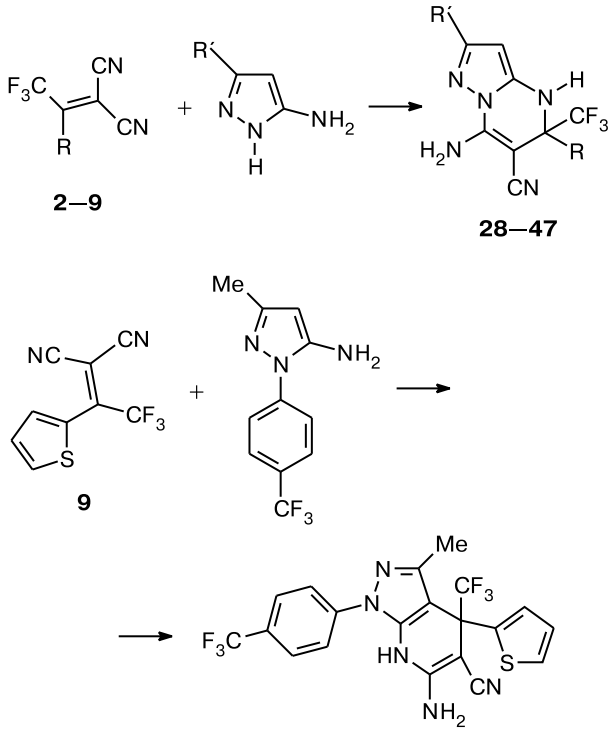


Compound	R	R′	R″	R‴
18	*N*-Methylpyrrol-2-yl	Me	H	H
19	*N*-Methylpyrrol-2-yl	H	Me	H
20	*p*-Morpholinophenyl	H	H	H
21	*p*-Diethylaminophenyl	H	H	H
22	Indol-3-yl	H	H	H
23	Indol-3-yl	Me	H	H
24	Indol-3-yl	H	Me	H
25	Indol-3-yl	H	H	Me
26	2-Thienyl	Me	H	H
27	2-Thienyl	H	Me	H

The reaction of 3-aminopyrazoles with dicyanotrifluoromethylethylenes has earlier been studied in our laboratory.[2—4] It was found that the reaction of alkenes **2—9** with 3-aminopyrazoles proceeded as cycloaddition to give pyrazolo[1,5-*a*]pyrimidines **28—47** (Scheme 5, Tables 1, 2).

The reaction of 3-amino-2-aryl-5-methylpyrazole with alkene **9** resulted in substituted dihydro-1*H*-pyrazolo-[3,4-*b*]pyridine **48** (Scheme 5, Table 1, 3).

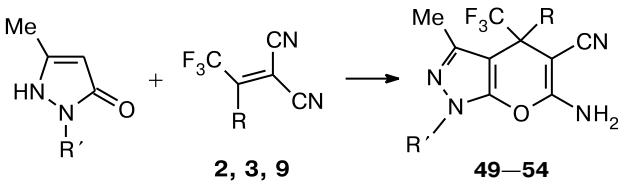
Scheme 5



Com-pound	R	R′
28	*N*-Methylpyrrol-2-yl	H
29	*N*-Methylpyrrol-2-yl	Me
30	*p*-Morpholinophenyl	H
31	*p*-Morpholinophenyl	*p*-$MeOC_6H_4$
32	*p*-Morpholinophenyl	*p*-ClC_6H_4
33	*p*-Diethylaminophenyl	H
34	*p*-Diethylaminophenyl	*p*-$MeOC_6H_4$
35	*p*-Diethylaminophenyl	*p*-ClC_6H_4
36	4-Amino-3,5-diisopropylphenyl	H
37	4-Amino-3,5-diisopropylphenyl	*p*-$MeOC_6H_4$
38	4-Amino-3,5-diisopropylphenyl	*p*-ClC_6H_4
39	Indol-3-yl	H
40	Indol-3-yl	Me
41	Indol-3-yl	*p*-ClC_6H_4
42	Indol-3-yl	*p*-$MeOC_6H_4$
43	2-Methylindol-3-yl	H
44	2-Methylindol-3-yl	Me
45	2-Methylindol-3-yl	H
46	2-Thienyll	*p*-ClC_6H_4
47	2-Thienyl	*p*-$MeOC_6H_4$

The reactions of the ethylenes **2**, **3**, and **9** with a variety of 2-aryl-5-methylpyrazol-3-one derivates were systematically studied. All reactions yielded the corresponding 1,4-dihydropyrano[2,3-*c*]pyrazoles **49—54** (Scheme 6, Tables 1, 3).

Scheme 6

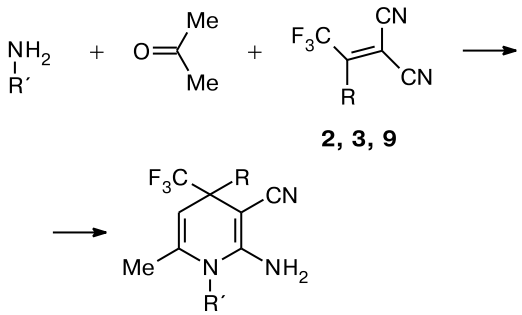


Compound	R	R′
49	*N*-Methylpyrrol-2-yl	Me
50	*N*-Methylpyrrol-2-yl	*p*-FC_6H_4
51	*N*-Methylpyrrol-2-yl	*m*-ClC_6H_4
52	Indol-3-yl	*o*-ClC_6H_4
53	Indol-3-yl	*p*-ClC_6H_4
54	2-Thienyl	*m*-ClC_6H_4

The reaction of 1,1-dicyano-2,2-bis(trifluoromethyl)-ethylene with anilines in the presence of an enolizable ketone, which furnished 1-aryl-1,4-dihydropyridines, has been studied earlier.[11]

It has been found that the three-component condensation of ethylenes **2** and **3** with diverse anilines and acetone at room temperature led to 1,4-dihydropyridine derivatives **55—60** (Scheme 7, Table 1, 4).

Scheme 7



Com-pound	R	R′
55	*N*-Methylpyrrol-2-yl	*m*-ClC_6H_4
56	*N*-Methylpyrrol-2-yl	*p*-ClC_6H_4
57	*N*-Methylpyrrol-2-yl	*p*-$OPhC_6H_4$
58	Indol-3-yl	2,6-$Me_2C_6H_3$
59	Indol-3-yl	*p*-ClC_6H_4
60	Indol-3-yl	*p*-$OMeC_6H_4$
61	2-Thienyl	3,4-$Me_2C_6H_3$

It should be noted that the one-step three-component condensation of alkene **9** under conditions described above failed. The target 1,4-dihydropyridine **61** was synthesized by the reaction of ethylene **9** with the Schiff base derived from 3,4-dimethylaniline and acetone.[12]

The study of the cytotoxic activity of the synthesized trifluoromethyl-containing heterocycles was carried out *in vitro* against a standard panel consisting of 60 human tumor cell lines at the U.S. National Cancer Institute

Table 3. ^{1}H and ^{19}F NMR spectral data ($CDCl_3$, δ, (*J*/Hz)) of compounds **48**—**54**

Compound	^{1}H NMR	^{19}F NMR
48	7.85—7.80 (m, 4 H); 7.69 (d, 1 H, CH, *J* = 5); 7.23 (s, 1 H, CH); 7.07—7.05 (m, 1 H, CH); 5.50 (br.s, 2 H, NH_2); 1.52 (s, 3 H, CH_3)	17.58 (s, 3 F, CF_3); 2.07 (s, 3 F, CF_3)
49	6.58 (t, 1 H, CH, *J* = 2); 6.43 (t, 1 H, CH, *J* = 2); 6.11—6.09 (m, 1 H, CH); 5.08 (br.s, 2 H, NH_2); 3.74 (s, 3 H, NCH_3); 3.19 (s, 3 H, NCH_3); 1.59 (s, 3 H, CH_3)	4.30 (s, 3 F, CF_3)
50	7.65—7.61 (m, 2 H, CH); 7.21—7.17 (m, 2 H, CH); 6.62 (s, 1 H, CH); 6.65 (br.s, 1 H , CH); 6.14—6.12 (m, 1 H, 2 H, CH); 5.08 (br.s, 2 H, NH_2); 3.29 (s, 3 H, NCH_3); 1.77 (s, 3 H, CH_3)	4.40 (s, 3 F, CF_3); −35.0 (1 F, CF)
51	7.72 (t, 1 H, CH, *J* = 2); 7.61—7.59 (m, 1 H, CH); 7.42 (t, 1 H, CH, *J* = 8); 7.33 (d, 1 H, CH, *J* = 8); 6.62 (br.s, 1 H, CH); 6.46 (m, 1 H, CH); 6.13 (m, 1 H, CH); 5.14 (br.s, 2 H, NH_2); 3.23 (s, 3 H, NCH_3); 1.78 (s, 3 H, CH_3)	4.38 (s, 3 F, CF_3)
52	9.91 (s, 1 H, NH); 7.49—7.46 (m, 2 H, CH); 7.36—7.33 (m, 2 H, CH); 7.30 (d, 1 H, CH, *J* = 8); 7.01 (t, 1 H, CH, *J* = 8); 6.91 (d, 1 H, CH, *J* = 8); 6.79 (t, 1 H, CH, *J* = 8); 5.86 (br.s, 2 H, NH_2); 1.53 (s, 3 H, CH_3)	4.35 (s, 3 F, CF_3)
53	8.48 (s, 1 H, NH); 7.66 (m, 2 H); 7.46—7.44 (m, 2 H, CH); 7.36 (d, 1 H, CH, *J* = 8); 7.16—7.13 (m, 1 H, CH); 6.93 (s, 2 H, CH); 5.13 (br.s, 2 H, NH_2); 1.65 (s, 3 H, CH_3)	4.35 (s, 3 F, CF_3)
54	7.72 (br.s, 1 H, CH); 7.57 (d, 1 H, CH, *J* = 8); 7.42 (s, 1 H, CH); 7.40—7.37 (m, 1 H, CH); 7.34—7.30 (m, 2 H, CH); 7.04—7.02 (m, 1 H, CH); 5.17 (br.s, 2 H, NH_2); 1.94 (s, 3 H, CH_3)	5.62 (s, 3 F, CF_3)

Table 4. ^{1}H and ^{19}F NMR spectral data (DMSO-d_6, δ, (*J*/Hz)) of compounds **55**—**61**

Com-pound	H NMR	^{19}F NMR (s, 3 F, CF_3)
55	7.60 (m, 2 H, CH); 7.43 (br.s, 1 H, CH); 7.23 (d, 1 H, CH, *J* = 8); 5.95—5.91 (m, 2 H, CH); 5.72 (br.s, 2 H, NH_2); 4.67 (s, 1 H, CH); 3.65 (s, 3 H, N—CH_3); 1.54 (s, 3 H, CH_3)	3.58
56	7.57 (d, 2 H, CH, *J* = 8); 7.30 (d, 2 H, CH, *J* = 8); 6.76 13 (m, 1 H, CH); 5.94 (m, 2 H); 5.67 (br.s, 2 H, NH_2); 4.66 (d, 1 H, CH, *J* = 1); 3.64 (s, 3 H, N—CH_3); 1.52 (s, 3 H, CH_3)	3.58
57	7.46—7.42 (m, 2 H, CH); 7.28—7.19 (m, 3 H, CH); 7.15—7.08 (m, 4 H, CH); 6.75 (s, 1 H, CH); 5.94—5.91 (m, 2 H); 5.63 (br.s, 2 H, NH_2); 4.65 (s, 1 H, CH); 3.65 (s, 3 H, N—CH_3); 1.54 (s, 3 H, CH_3)	3.37
58	11.11 (s, 1 H, NH); 7.23 (d, 1 H, CH, *J* = 8); 7.42 (d, 1 H, CH, *J* = 8); 7.34—7.26 (m, 3 H); 7.12 (br.s, 1 H, CH); 7.11 (t, 1 H, CH, *J* = 8); 7.70 (t, 1 H, CH, *J* = 8); 5.28 (br.s, 2 H, NH_2); 4.75 (s, 1 H, CH); 2.35 (s, 3 H, CH_3); 2.17 (s, 3 H, CH_3); 1.41 (s, 3 H, CH_3)	3.32
59	11.12 (s, 1 H, NH); 7.66 (d, 1 H, CH, *J* = 8); 7.62 (s, 1 H, CH); 7.59 (s, 1 H, CH); 7.42—7.37 (m, 3 H); 7.20 (br.s, 1 H, CH); 7.13 (t, 1 H, CH, *J* = 8); 7.04 (t, 1 H, CH, *J* = 8); 5.55 (br.s, 2 H, NH_2); 4.48 (s, 1 H, CH); 1.54 (s, 3 H, CH_3)	3.48
60	11.12 (s, 1 H, NH);); 7.67 (d, 1 H, CH, *J* = 8); 7.42 (d, 1 H, CH, *J* = 8); 7.34 (s, 1 H, CH); 7.20 (s, 1 H, CH); 7.15—7.02 (m, 5 H, CH); 5.36 (br.s, 2 H, NH_2); 4.63 (s, 1 H, CH); 3.81 (br.s, 3 H, OCH_3)	3.47
61	7.32 (d, 1 H, CH, *J* = 5); 7.25—7.23 (m, 2 H, CH); 7.07—6.97 (m, 3 H, CH); 4.50 (s, 1 H, CH); 4.34 (br.s, 2 H, NH_2); 2.33 (s, 3 H, CH_3); 2.31 (s, 3 H, CH_3); 1.69 (s, 3 H, CH_3)	−1.71

(NCI) in the framework of the International Program for Screening and Development of Effective Antitumor Drugs in accordance with the known procedure.[13] This set of the cell lines have previously been used for the study of the cytotoxicity of heterocyclization products of cyano(trifluoromethyl)vinylphosphonates.[14]

The protocol used for the study of the mentioned group of the compounds has been slightly modified. The study was carried out in two steps. Initially, all compounds were studied against the full panel of the human tumor cells with incubation period of 24 h and with the use of the single concentration for all compounds (10^{-5} mol L^{-1}). The compounds that exhibited cytotoxic activity were subjected to further *in vitro* investigation against the same panel of cells with the use of five logarithmic concentrations 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} mol L^{-1}.

The results of the study of the cytotoxic activity are given in Tables 5—7.

The presented data should be considered as the results of the first step of the investigation in the group of compounds, which allowed identification of promising clusters or individual compounds for subsequent research. The residual growth values of the cell cultures after incubation with the assayed compounds at the concentration of 10^{-5} mol L^{-1} in percent to the control are presented in Tables 5 and 6. The values above 100% indicated the growth stimulation of the cell cultures. The negative values indicated the cell death in percent to the control. This test revealed six compounds of the pyrazolo[1,5-*a*]pyrimidine series that were subjected to further research (Table 7).

The cytotoxic activity of fourteen compounds including four pyrido[1,2-*a*]pyrimidines and ten pyrazolo[1,5-*a*]-pyrimidines were studied. In general, compounds of the pyrazolo[1,5-*a*]pyrimidine series turned to be more active as compared with substituted pyrido[1,2-*a*]pyrimidines. None of CF_3-substituted pyrido[1,2-*a*]pyrimidines (compounds **19**, **20**, **21**, and **24**) possessed cytotoxic activity sufficient for further study in five concentrations. No influence of the nature of the substituent at the position 2 on the cytotoxicity was found. On the contrary, for several cell lines the growth stimulation was observed.

Six compounds from ten of the pyrazolo[1,5-*a*]pyrimidine series were selected and studied in a complete *in vitro* screening program, namely, at five different concentrations. It should be noted, that all active compounds have 4-chlorophenyl of 4-methoxyphenyl group in the position 2 of the pyrazole moiety. In terms of cytotoxicity, the presence of this type of substituent could be regarded as more important than the variation of the substituents in

Table 5. The *in vitro* cytotoxicity of CF_3-substituted pyrido[1.2-*a*]pyrimidines **19—21**, **24** and pyrazolo[1.5-*a*]pyrimidines **29—31** at concentration of 10^{-5} mol L^{-1}

Cell culture	Residual growth of the cell culture (% to control)						
	19	**20**	**21**	**24**	**29**	**30**	**31**
				Non-small cell lung cancer			
A549/ATCC	113.91	107.33	80.39	82.08	92.28	104.06	46.75
EKVX	105.83	105.61	112.13	108.42	108.78	108.06	72.78
HOP-62	111.87	98.29	95.41	92.91	94.55	102.48	90.58
HOP-92	99.44	90.93	90.35	77.52	103.59	98.03	75.64
NCI-H226	107.98	95.48	94.17	93.60	106.15	98.19	60.01
NCI-H23	101.60	99.58	93.50	90.42	98.58	98.98	71.76
NCI-H322M	97.99	99.91	107.67	97.53	88.76	100.73	90.48
NCI-H460	114.64	113.16	116.81	108.46	109.83	117.23	83.47
NCI-H522	93.95	91.31	79.27	76.34	67.65	89.86	58.78
				Colon cancer			
COLO 205	123.22	119.84	129.45	111.99	106.22	112.98	95.88
HCC-2998	113.87	77.94	88.59	87.22	88.05	88.55	87.58
HCT-116	108.21	105.14	93.47	95.57	101.79	104.97	57.58
HCT-15	109.19	94.28	99.66	59.64	114.30	104.14	61.01
HT 29	115.58	118.96	119.45	104.77	101.19	110.85	54.64
KM 12	109.42	109.03	110.65	106.25	106.59	108.77	93.09
SW-620	115.88	106.26	116.09	111.44	108.98	112.98	99.37
				Breast cancer			
BT-549	120.27	97.13	99.73	101.91	125.12	106.73	90.15
HS578T	127.48	113.02	122.35	113.22	139.21	121.20	127.38

(*to be continued*)

Table 5 (*continued*)

Cell culture	Residual growth of the cell culture (% to control)						
	19	**20**	**21**	**24**	**29**	**30**	**31**
				Breast cancer			
MCF7	106.81	92.87	112.26	88.86	104.57	98.95	76.07
MDA-MB-231/ ATCC	127.87	90.36	99.47	97.66	101.72	90.71	83.64
MDA-MB-435	103.14	104.28	103.46	98.11	99.58	101.45	77.42
NCI/ADR-RES	102.68	90.74	94.27	91.27	98.43	93.76	80.09
T-47D	110.27	108.37	82.68	91.73	98.20	108.29	32.61
				Ovarian cancer			
IGROV1	75.88	66.31	59.11	60.37	−57.34	103.81	54.53
OVCAR-3	121.81	114.39	110.72	100.21	110.01	127.45	97.54
OVCAR-4	111.57	104.43	106.43	95.58	98.79	103.40	75.30
OVCAR-5	105.86	87.97	105.91	95.79	93.02	78.99	97.97
OVCAR-8	94.87	99.95	80.42	93.26	92.91	102.59	73.68
SK-OV-3	112.27	99.37	105.13	86.34	99.16	99.20	99.06
				Leukemia			
CCRF- CEM	81.22	187.72	93.42	79.25	123.73	191.35	67.71
HL-60(TB)	91.85	84.70	86.98	108.41	121.47	89.50	28.18
K-562	85.14	97.43	82.25	91.60	—	90.90	42.04
MOLT-4	57.71	83.57	58.44	96.14	149.13	97.31	35.44
RPMI-8226	111.61	112.50	101.76	85.60	120.31	113.13	4.59
SR	88.96	105.48	93.44	89.05	185.74	115.02	52.41
				Renal cancer			
768-0	100.81	100.99	102.95	96.16	102.36	101.47	74.13
A 498	118.47	94.03	115.61	89.40	136.85	96.56	70.66
ACHN	113.87	108.10	112.88	79.03	115.57	116.79	100.97
CAKI-1	99.93	101.45	99.13	91.62	99.74	99.79	73.98
RXF-393	−22.09	−3.01	−20.55	2.08	7.37	−0.78	−15.50
SN12C	113.24	103.60	106.45	110.12	80.72	90.40	71.43
TK-10	112.76	125.56	123.56	92.74	103.83	129.13	87.33
UO-31	47.41	71.76	69.01	35.57	75.02	84.45	57.99
				Melanoma			
LOX IMVI	104.25	101.39	96.42	76.96	97.39	105.43	90.23
M14	107.49	106.16	105.43	108.09	102.40	109.74	88.66
MALME-3M	114.61	121.22	120.77	106.27	107.98	117.29	98.08
SK-MEL-2	88.04	62.10	52.63	55.13	55.27	96.84	48.93
SK-MEL-28	128.32	118.11	121.86	113.45	112.80	130.11	106.01
SK-MEL-5	100.54	87.40	98.87	93.21	114.09	104.32	49.70
UACC-257	117.24	115.64	98.66	112.01	97.35	105.21	54.68
UACC-62	105.07	86.93	86.92	93.67	93.57	89.89	64.15
				Prostate cancer			
DU-145	121.63	120.86	116.91	110.45	137.60	126.71	98.92
PC-3	98.41	98.74	103.88	99.57	107.54	107.23	75.50
				CNS cancer			
SF-268	110.41	98.57	108.80	101.15	109.99	104.50	79.20
SF-295	105.32	102.16	99.81	99.01	107.47	94.02	75.73
SF-539	107.35	105.12	109.16	108.75	110.12	108.13	97.09
SNB-19	106.47	96.02	104.43	101.56	96.31	106.98	80.00
SNB-75	98.32	90.50	92.75	84.36	60.54	102.87	109.08
U251	114.46	103.48	102.00	55.48	106.58	108.39	80.22

Table 6. The *in vitro* cytotoxicity of CF_3-substituted pyrido[1.2-*a*]pyrimidines **32—38** at concentration of 10^{-5} mol L^{-1}

Cell culture	Residual growth of the cell culture (% to control)						
	32	**33**	**34**	**35**	**36**	**37**	**38**
				Non-small cell lung cancer			
A549/ATCC	46.72	1.57	79.7	37.45	98.16	10.72	41.11
EKVX	57.8	26.01	93.41	47.74	109.72	26.65	38.89
HOP-62	82.98	47.7	94.89	80.61	100.16	47.54	55.25
HOP-92	50.4	6.23	77.7	43.08	95.73	–33.49	20.62
NCI-H226	72.12	32.76	79.08	52.34	93.91	40.71	56.18
NCI-H23	71.01	24.65	104.2	47.39	99.51	35.6	44.9
NCI-H322M	72.21	40.85	95.31	68.58	86.5	57.88	33.55
NCI-H460	57.85	11.66	103.91	52.2	107.32	30.39	10.88
NCI-H522	66.54	–7.04	88.72	27.34	85.91	25.45	41.91
				Colon cancer			
COLO 205	56.59	–33.84	98.06	55.07	108.58	0.58	29.71
HCC-2998	81.56	32.91	74.49	72.98	84.21	5.85	41.01
HCT-116	48.54	17.17	81.36	42.86	95.37	32.83	30.06
HCT-15	52.13	19.24	50.13	92.47	95.75	24.37	31.15
HT 29	20.96	–9.04	88.37	43.3	106.07	40.09	40.78
KM 12	74.54	21.92	120.86	51.0	99.08	28.33	5.78
SW-620	74.3	19.87	107.85	70.82	114.14	44.37	56.56
				Breast cancer			
BT-549	91.18	42.26	109.75	73.1	115.38	44.61	61.03
HS578T	98.69	69.68	119.53	100	128.64	37.69	56.51
MCF7	37.64	1.86	84.65	21.62	100.93	24.55	26.14
MDA-MB-231/ ATCC	82.1	5.69	77.64	69.45	100.97	25.43	20.2
MDA-MB-435	65.13	27.69	77.63	44.39	107.08	24.84	33.0
NCI/ADR-RES	78.82	27.73	78.47	49.27	96.02	30.85	35.48
T-47D	38.24	-8.45	74.64	37.55	82.19	–15.19	22.52
				Ovarian cancer			
IGROV1	8.2	—	49.17	–0.47	21.62	30.87	26.07
OVCAR-3	81.24	30.88	111.17	65.29	116.03	24.55	46.01
OVCAR-4	54.08	17.1	79.27	45.23	91.51	22.77	48.02
OVCAR-5	90.21	46.04	100.34	93.51	95.29	55.03	71.78
OVCAR-8	70.61	11.62	92.22	48.23	95.97	31.06	30.62
SK-OV-3	88.25	49.25	98.08	79.53	94.14	62.27	75.07
				Leukemia			
CCRF- CEM	32.31	19.59	69.78	38.71	93.77	—	32.43
HL-60(TB)	–17.5	–35.41	65.69	–6.4	88.81	–9.4	–4.58
K-562	28.38	7.24	83.54	26.19	83.37	19.67	23.77
MOLT-4	11.56	–21.45	42.81	13.38	75.26	9.45	19.24
RPMI-8226	33.41	–23.49	63.79	17.65	92.1	–40.88	14.03
SR	35.35	8.67	78.36	43.81	89.92	10.53	9.31
				Renal cancer			
768-0	85.86	38.89	101.41	69.01	103.22	43.46	41.83
A 498	71.92	–4.87	60.98	40.51	109.11	27.36	42.98
ACHN	82.29	22.14	62.81	99.73	109.08	21.49	33.67
CAKI-1	69.45	35.29	98.92	61.44	108.57	39.13	43.16
RXF-393	–31.85	–47.29	–18.7	–1.37	19.87	1.58	–16.3
SN12C	78.8	28.05	94.14	63.15	87.09	40.72	41.67
TK-10	92.83	44.43	93.55	62.72	119.6	40.84	28.95
UO-31	32.09	1.51	35.24	11.9	73.3	13.36	20.47

(*to be continued*)

Table 6 (*continued*)

Cell culture	Residual growth of the cell culture (% to control)						
	32	**33**	**34**	**35**	**36**	**37**	**38**
				Melanoma			
LOX IMVI	78.5	26.36	58.62	87.59	89.03	28.91	37.58
M14	66.68	33.23	104.51	72.43	118.99	55.16	49.06
MALME-3M	76.29	29.19	111	63.53	99.36	61.12	12.92
SK-MEL-2	36.91	−9.31	49.22	21.08	71.49	−11.23	6.82
SK-MEL-28	103.32	57.16	121.1	97.87	128.69	61.87	76.93
SK-MEL-5	31.32	−30.57	80.23	21.86	106.32	38.72	49.45
UACC-257	29	−21.66	92.53	45.1	99.19	46.26	74.3
UACC-62	75.21	45.12	79.63	60.11	77.84	45.18	59.03
				Prostate cancer			
DU-145	85.21	62.99	101.93	88.83	124.13	72.92	80.55
PC-3	55.46	23.17	83.85	50.07	106.03	-2.49	34.34
				CNS cancer			
SF-268	73.69	31.88	74.16	59.35	102.77	37.26	37.17
SF-295	50.92	−18.29	75.99	21.21	91.47	−18.09	3.12
SF-539	86.92	60.41	108.41	84.21	106.51	43.62	51.17
SNB-19	84.41	27.01	91.09	68.22	88.01	29.47	40.55
SNB-75	77.03	33.71	89.42	77.79	55.51	8.48	49.81
U251	74.37	28.21	48.56	88.63	100.43	15.63	42.76

the position 5. Thus compound **30** with unsubstituted pyrazole ring and bearing a 4-morpholinophenyl group in the position 5 as in compounds **31** and **32** exhibited no cytotoxic activity. At the same time, compounds **31** and **32** with 4-methoxyphenyl and 4-chlorophenyl groups in the position 2 exhibited significant cytotoxicity of the same level against the majority of the cell lines. The similar conclusions can be drawn from the consideration of compounds **36** and **37** bearing the same 4-amino-3,5-diisopropylphenyl group in the position 5. Compound **36** unsubstituted in the position 2 exhibited no cytotoxic activity. Compounds **37** and especially **38** with 4-methoxyphenyl and 4-chlorophenyl groups in the position 2, respectively, exhibited the strongest nonselective cytotoxic activity against the majority of the cell cultures of all subpanels.

The above described pattern was also fully confirmed for compounds **33**, **34**, and **35** bearing the same 4-diethylaminophenyl-substituent in the position 5. Compound **33** without substituent in the position 2 showed no cytotoxicity. At the same time, compounds **34** and **35** with 4-methoxyphenyl and 4-chlorophenyl groups in the position 2, respectively, exhibited significant nonselective cytotoxic activity. The importance of the substituent in the position 2 followed from the lack of cytotoxic activity of compound **29** with the methyl substituent in the position 2.

In summary, for the first time data on the *in vitro* cytotoxic activity of fourteen novel CF_3-substituted pyrazolo[1,5-*a*]pyrimidines and pyrido[1,2-*a*]pyrimidines against broad range of human cancer cells of diverse origin have been obtained. It has been shown that pyrido[1,2-*a*]-pyrimidines exhibited no cytotoxic activity. In the series of pyrazolo[1,5-*a*]pyrimidines, several highly active cytotoxic agents were found. The strong dependence of cytotoxicity on the nature of the substituent in the position 2 has been found. The 4-methoxyphenyl or 4-chlorophenyl groups favor significant increase in the nonselective cytotoxicity against the majority of the cell lines. Hence, variation of the substituents in the position 2 could lead to discovery of new and more effective cytotoxic agents. For the identification of compounds with the highest cytotoxic activity in the series under study, the state-of-the-art *in silico* screening should be applied. Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives with 4-aminophenyl, 4-hydrohyphenyl, 4-alkylaminophenyl, and hetaryl groups as well as their possible combinations is also the point of interest.

Experimental

The ^1H and ^{19}F NMR spectra were recorded on a Bruker AMX-400 instrument at 400.13 MHz and 376.50 MHz, respectively. Chemical shifts were determined relative to the residual signal of the deuterated solvent and refined relative to Me_4Si. The ^{19}F NMR spectra were referenced to CF_3COOH as the external standard. Mass spectra were obtained on a Cratos MS-890 mass spectrometer (EI, 70 eV). The starting compounds 5-methyl-2,3-dihydropyrazol-3-ones and 3-aminopyrazoles were synthesized by the known procedures.[15,16]

Table 7. Cytotoxicity of compounds **31**, **32**, **34**, **35**, **37**, **38**

Cell culture	GI_{50}/μmol L^{-1}					
	31	**32**	**34**	**35**	**37**	**38**
			Leukemia			
CCRF- CEM	3.33	2.2	2.41	2.96	1.98	1.7
HL-60(TB)	1.65	1.02	0.596	—	1.47	1.26
K-562	4.24	1.32	2.28	—	1.58	1.49
MOLT-4	2.09	1.29	1.78	—	1.69	1.52
RPMI-8226	2.28	2.15	0.101	2.72	0.801	0.36
SR	1.17	1.7	1.22	—	1.38	0.236
			Non-small cell lung cancer			
A549/ATCC	7.36	8.52	5.18	3.57	3.5	3.03
EKVX	3.35	2.77	2.11	3.5	3.93	2.19
HOP-62	>100	28.2	7.67	5.4	2.15	1.29
HOP-92	7.35	3.67	2.94	1.29	0.261	2.53
NCI-H226	>100	24.6	8.64	5.93	4.38	2.4
NCI-H23	>100	11.7	5.11	3.84	2.57	1.81
NCI-H322M	1.75	11.2	8.03	15	4.74	4.42
NCI-H460	8.28	3.94	4.88	2.01	2.11	1.66
NCI-H522	>100	5.59	4.27	3.15	2.48	1.82
			Colon cancer			
COLO 205	4.57	5.15	4.03	3.16	1.98	1.68
HCC-2998	56.2	3.51	1.51	4.74	3.21	1.7
HCT-116	53.1	2.98	4.07	2.52	5.7	1.44
HCT-15	4.13	3.13	3.9	2.91	2.43	1.58
HT 29	4.6	2.93	4.99	2.88	4.58	3.11
KM 12	39.8	3.52	10.1	3.49	3	1.6
SW-620	>100	4.06	—	3.67	2.55	2.15
			CNS cancer			
SF-268	>100	7.24	8.24	4.02	2.79	2.08
SF-295	2.88	1.6	2.09	3.85	3.01	1.55
SF-539	>100	40.5	11.9	4.11	2.34	1.7
SNB-19	>100	19.8	8.4	7.81	2.25	1.8
SNB-75	>100	12.4	11.8	11.6	2.17	1.81
U251	>100	22.1	7.92	4.65	2.9	1.75
			Melanoma			
LOX IMVI	>100	10.9	6.62	3.5	3.51	1.62
MALME-3M	3.16	4.53	5.49	5.11	2.56	2.53
M14	>100	6.8	6.93	3.65	2.23	2.09
SK-MEL-2	5.06	4.62	2.97	4.03	1.01	1.38
SK-MEL-28	>100	5.27	8.05	4.67	2.96	1.88
SK-MEL-5	6.05	3.49	2.9	0.869	1.42	1.48
UACC-257	15	3.42	5.8	3.05	3.44	2.14
UACC-62	>100	36.8	7.64	2.84	3.19	2.21
			Ovarian cancer			
IGROV1	>100	6.98	7.4	2.56	2.13	1.86
OVCAR-3	63.9	4.11	5.52	3.48	1.97	1.63
			Ovarian cancer			
OVCAR-4	7.09	3.88	3.96	7.87	4.1	4.28
OVCAR-5	>100	34.6	65.1	20.7	6.58	2.99
OVCAR-8	>100	5.87	8.1	3.66	3.23	3.13
SK-OV-3	>100	18.7	30.5	24.1	3.86	2.55
			Renal cancer			
768-0	10.2	29.9	0.567	3.4	2.49	1.07
A 498	41.1	17.3	13.1	2.69	1.38	1.6
ACHN	>100	15.2	5.98	4.37	3.01	2.62
CAKI-1	>100	6.59	8.29	3.14	2.01	1.35
RXF-393	10.1	12.7	8.19	3.52	2.03	1.27
SN12C	>100	18.7	28.4	3.93	2.6	3.05
TK-10	1.65	15	9.13	12.2	4.15	2.98
UO-31	5.48	3.51	2.8	1.77	1.5	1.56
			Prostate cancer			
PC-3	3.09	3.38	0.528	3.81	4.43	1.58
DU-145	>100	6.35	70.8	6.28	3.82	2.31
			Breast cancer			
MCF7	6.2	1.08	2.63	2.11	2.28	1.69
NCI/ADR-RES	>100	9.34	4.75	3.51	2.75	2.36
MDA-MB-231/A	>100	11.8	34.4	2.49	1.93	1.44
HS 578T	>100	3.78	25.7	2.73	2.3	1.61
MDA-MB-435	8.06	4.71	4.15	3.22	3	2.07
MDA-N	4.26	2.89	2.54	—	0.467	—
BT-549	1.42	3.08	3.65	6.39	1.73	2.27
T-47D	3.66	2.35	5.41	4.27	2.72	1.6

Note. GI_{50} (growth inhibition) is the concentration of compound causing 50% retardation of the cell growth rates.

1,1-Dicyano-2-(*N*-methylpyrrol-2-yl)-2-trifluoromethylethylene (2). To a solution of *N*-methylpyrrole (1 g) in diethyl ether (10 mL), a solution of compound **1** (1.11 g) in diethyl ether (5 mL) was added with stirring at room temperature. After 1 h of stirring, the precipitate that formed was filtered off, the solvent was evaporated *in vacuo* and the residue was redistilled to give compound **2** in a yield of 1.06 g (77%), b.p. 92—93 °C (1 Torr). ^{1}H NMR (acetone-d_6), δ: 7.46 (m, 1 H, CH); 6.97 (m, 1 H, CH); 6.44 (m, 1 H, CH); 3.85 (s, 3 H, CH_3). ^{19}F NMR (acetone-d_6), δ: −17.2 (s, CF_3). Found (%): C, 53.39; H, 2.70; F, 25.32. $C_{10}H_6F_3N_3$. Calculated (%): C, 53.34; H, 2.69; F, 25.31.

1,1-Dicyano-2-(indol-3-yl)-2-trifluoromethylethylene (3). To a solution of indole (1.6 g) in benzene (20 mL), a solution of compound **1** (2.5 g) in benzene (10 mL) was added dropwise with stirring. The mixture was refluxed until evolution of HCl ceased (5 h), then the solvent was removed *in vacuo* and the residue was recrystallized from hexane—benzene mixture (5 : 1) to give brown-colored compound **3** (2.7 g, 75%), m.p. 127—128 °C. ^{1}H NMR (CD_3CN), δ: 10.70 (br.s, 1 H, NH); 8.08 (s, 1 H, CH); 7.71 (m, 2 H, CH); 7.42 (m, 2 H, CH). ^{19}F NMR (CD_3CN), δ: −16.7 (s, CF_3). Found (%): C, 59.55; H, 2.31; F, 21.57. $C_{13}H_6F_3N_3$. Calculated (%): C, 59.32; H, 2.28; F, 21.67.

1,1-Dicyano-2-(2-methylindol-3-yl)-2-trifluoromethylethylene (4) was synthesized as described above for compound **3** in a yield of 47%, m.p. 168—170 °C. ^{1}H NMR (acetone-d_6), δ: 11.50 (br.s, 1 H, NH); 7.50 (m, 2 H, CH); 7.24 (m, 2 H, CH); 2.65 (s, 3 H, CH_3). ^{19}F NMR (acetone-d_6), δ: −17.7 (s, CF_3). Found (%): C, 61.05; H, 2.91; F, 20.77. $C_{14}H_8F_3N_3$. Calculated (%): C, 61.09; H, 2.91; F, 20.73.

1,1-Dicyano-2-(2-phenylindol-3-yl)-2-trifluoromethylethylene (5) was synthesized as described above for compound **3** in a yield of 93%, m.p. 211—213 °C. ^{1}H NMR (CD_3CN), δ: 10.80 (br.s, 1 H, NH); 7.68 (m, 1 H, CH); 7.64 (s, 5 H, CH); 7.39 (m, 3 H, CH). ^{19}F NMR (CD_3CN), δ: −17.6 (s, CF_3). Found (%): C, 67.60; H, 2.98; F, 16.94. $C_{19}H_{10}F_3N_3$. Calculated (%): C, 67.66; H, 2.97; F, 16.91.

1,1-Dicyano-2-(*p*-diethylaminophenyl)-2-trifluoromethylethylene (6). To a solution of *N,N*-diethylaniline (3.1 g) in diethyl ether (25 mL), a solution of compound **1** (1.9 g) in diethyl ether (5 mL) was added dropwise with stirring at room temperature. After 1 h of stirring, the precipitate that formed was filtered off, the mother liquor was concentrated *in vacuo* and the residue was recrystallized from hexane—benzene mixture (3 : 1) to give crimson-colored compound **6** (2.4 g, 78%), m.p. 45—46 °C. ^{1}H NMR (acetone-d_6), δ: 7.72 (d, 2 H, CH, J = 9 Hz); 7.21 (d, 2 H, CH, J = 9 Hz); 4.02 (q, 4 H, CH_2, J = 7 Hz); 1.28 (t, 6 H, CH_3, J = 7 Hz). ^{19}F NMR (acetone-d_6), δ: 17.5 (s, CF_3). Found (%): C, 61.25; H, 4.73; F, 19.43. $C_{15}H_{14}F_3N_3$. Calculated (%): C, 61.43; H, 4.81; F, 19.43

1,1-Dicyano-2-(*p*-morpholinophenyl)-2-trifluoromethylethylene (7) was synthesized in accordance with the procedure described for **6** to give compound **7** (85%), crimson crystals, m.p. 143—144 °C. ^{1}H NMR (acetone-d_6) δ: 7.68 (d, 2 H, CH, J = 9 Hz); 7.14 (d, 2 H, CH, J = 9 Hz); 3.82 (t, 4 H, CH_2, J = 5 Hz); 3.47 (t, 4 H, CH_2, J = 5 Hz). ^{19}F NMR (acetone-d_6), δ: 17.8 (s, CF_3). Found (%): C, 58.61; H, 4.00; F, 18.51. $C_{15}H_{12}F_3N_3O$. Calculated (%): C, 58.63; H, 3.94; F, 18.55.

2-(4-Amino-3,5-diisopropylphenyl)-1,1-dicyano-2-trifluoromethylethylene (8) was synthesized as described above for compound **6** in a yield of 75% as a red amorphous substance. ^{1}H NMR ($CDCl_3$) δ: 7.34 (s, 2 H, CH); 4.57 (br.s, 2 H, NH_2); 2.88 (m, 2 H, CH); 1.31 (d, 12 H, CH_3, J = 6.5 Hz). ^{19}F NMR ($CDCl_3$), δ: 16.2 (s, CF_3). Found (%): C, 63.41; H, 5.65; F, 17.69. $C_{17}H_{18}F_3N_3$. Calculated (%): C, 63.54; H, 5.65; F, 17.74.

1,1-Dicyano-2-(2-thienyl)-2-trifluoromethylethylene (9). To a solution of 2-trifluoroacetylthiophene (1.27 g) in benzene (1 mL), a solution of malononitrile (0.47 g) in benzene (10 mL), glacial acetic acid and piperidine (3 drops of each) were added with stirring. The reaction mixture was refluxed for 5 h, the solvent was removed *in vacuo* and the residue was distilled to give compound **9** in a yield of 1.1 g (68%) as yellow oil, b.p. 64—65 °C (2.5 Torr). ^{1}H NMR ($CDCl_3$) δ: 7.95 (br.s, 1 H, CH); 7.94 (br.s, 1 H, CH); 7.31 (t, 1 H, CH, J = 5 Hz). ^{19}F NMR ($CDCl_3$), δ: 17.98 (s, CF_3). Found (%): C, 47.35, H, 1.35, N, 12.27. $C_9H_3F_3N_2S$. Calculated (%): C, 47.37, H, 1.33, N, 12.28.

6-Amino-5-cyano-2-methyl-4-(*N*-methylpyrrol-2-yl)-4-trifluoromethyl-1,4-dihydropyrimidine (10). To a solution of acetamide (0.06 g, 1 mmol) in MeCN (7 mL), a solution of compound **2** (0.23 g, 1 mmol) in MeCN (5 mL) was added at ~20 °C. The reaction mixture was stirred for 8 h, the precipitate that formed was filtered off and recrystallized from diethyl ether to give compound **10** in a yield of 0.12 g (48%).

Compounds **11**—**17** were synthesized analogously from alkenes **2**—**5**, **9** and the corresponding amidines. Physicochemical data, the ^{1}H and ^{19}F NMR spectral data, and elemental analysis data of compounds **10**—**17** are given in Tables 1 and 2.

4-Amino-3-cyano-7-methyl-2-(*N*-methylpyrrol-2-yl)-2-trifluoromethyl-2*H*-pyrido[1,2-*a*]pyrimidine (18). To a solution of 2-amino-5-methylpyridine (0.11 g, 1 mmol), a solution of compound **2** (0.23 g, 1 mmol) in MeCN (5 mL) was added dropwise at room temperature. After 8 h of stirring, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica gel, carbon tetrachloride : acetone, 4 : 1) yielded compound **18** (0.20 g, 59%).

Compounds **19**—**27** were synthesized as described above for **18** from alkenes **2**, **3**, **6**, **7**, and **9** and the corresponding aminopyridines. Physicochemical data, the ^{1}H and ^{19}F NMR spectral data, and elemental analysis data of compounds **18**—**27** are given in Tables 1 and 2.

7-Amino-6-cyano-5-(*N*-methylpyrrol-2-yl)-5-trifluoromethyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine (28). To a solution of 3-aminopyrazole (0.08 g, 1 mmol) in diethyl ether (20 mL), a solution of compound **2** (0.23 g, 1 mmol) in diethyl ether (10 mL) was added dropwise at ~20 °C. The reaction mixture was stirred for 12 h and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chloroform : acetone, 3 : 1) yielded compound **28** (0.19 g, 61%).

Compounds **29**—**47** were synthesized as described above for **28** from alkenes **2**—**9** and the corresponding aminopyrazoles. Physicochemical data, the ^{1}H and ^{19}F NMR spectral data, and elemental analysis data of compounds **28**—**47** are given in Tables 1 and 2.

6-Amino-5-cyano-3-methyl-4-(2-thienyl)-4-trifluoromethyl-1-(4-trifluoromethylphenyl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine (48). To a solution of 5-amino-3-methyl-1-(4-trifluoromethylphenyl)pyrazole (0.24 g, 1 mmol) in MeCN (15 mL), a solution of alkene **9** (0.23 g, 1 mmol) in MeCN (5 mL) was added dropwise. The reaction mixture was refluxed for 20 h and then the solvent was removed *in vacuo*. Purification by column chromatography (silica gel, carbon tetrachloride : acetone, 3 : 1) afforded compound **48** in a yield of 0.32 g (67%). Physicochemical data, the ^{1}H and ^{19}F NMR spectral data, and elemental analysis data of compound **48** are given in Tables 1 and 3.

6-Amino-1-(3-chlorophenyl)-5-cyano-3-methyl-4-(*N*-methylpyrrol-2-yl)-4-trifluoromethyl-1,4-dihydropyrano[2,3-*c*]pyrozole (49). To a solution of 5-methyl-2,3-dihydropyrazolone (0.12 g, 1 mmol), a solution of alkene **2** (0.23 g, 1 mmol) in anhydrous MeCN (10 ml) was added dropwise. The reaction mixture was refluxed for 36 h, solvent was removed *in vacuo*. Purification of the residue by column chromatography (silica gel, ethyl acetate : hexanes, 3 : 1) afforded compound **49** in a yield of 0.29 g (83%).

Compounds **50**—**54** were synthesized as described above for **49** from alkenes **2**, **3**, **9** and the corresponding 5-methyl-2,3-dihydropyrazolones. Physicochemical data, the ^{1}H and ^{19}F NMR spectral data, and elemental analysis data of compounds **49**—**54** are given in Tables 1 and 3.

2-Amino-1-(3-chlorophenyl)-3-cyano-6-methyl-4-(*N*-methylpyrrol-2-yl)-4-trifluoromethyl-1,4-dihydropyridine (55). A solution of compound **2** (0.23 g, 1 mmol) and 3-chloroaniline (0.13 g, 1 mmol) in acetone (4 mL) was stirred for 10 h. The solvent was removed *in vacuo*. Purification of the residue by

column chromatography (silica gel, carbon tetrachloride : acetone, 5 : 1) yielded compound **55** (0.25 g, 40%).

Compounds **56**—**60** were synthesized as described above for **55** from alkenes **2**, **3** and the corresponding anilines. Physicochemical data, the ^{1}H and ^{19}F NMR spectral data and elemental analysis data of compounds **55**—**60** are given in Tables 1 and 4.

2-Amino-1-(3-chlorophenyl)-3-cyano-6-methyl-4-(2-thienyl)-4-trifluoromethyl-1,4-dihydropyridine (61). A solution of 3,4-dimethylaniline (0.05 g) and *p*-toluenesulfonic acid (0.01 g) in a mixture of benzene (20 mL) and acetone (2 mL) was refluxed with azeotropic distillation for 1 h, then alkene **9** (0.09 g, 0.4 mmol) was added. After stirring for 8 h, the solvent was removed *in vacuo*. Purification of the residue by column chromatography (silica gel, carbon tetrachloride : acetone, 6 : 1) afforded compound **61** in a yield of 0.06 g (43%). Physicochemical data, the ^{1}H and ^{19}F NMR spectral data, and elemental analysis data of compound **61** are given in Tables 1 and 4.

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