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Competing Processes in Condensation of 3,3-Bis(methylthio)-2-cyano-*N*-arylacrylamides with Cyanoacetanilides

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Abstract—Reaction of cyanoacetanilides with 3,3-bis(methylthio)-2-cyano-*N*-arylacrylamides proceeds to form isomeric *N*,1-diaryl-1,6-dihydropyridine-3-carboxamides. A single crystal consisting of 2-amino-4-methylthio-*N*-(2-methoxyphenyl)-6-oxo-1-phenyl-5-cyano-1,6-dihydropyridine-3-carboxamide and 2-amino-4-methylthio-1-(2-methoxyphenyl)-6-oxo-*N*-phenyl-5-cyano-1,6-dihydropyridine-3-carboxamide was studied by XRD.

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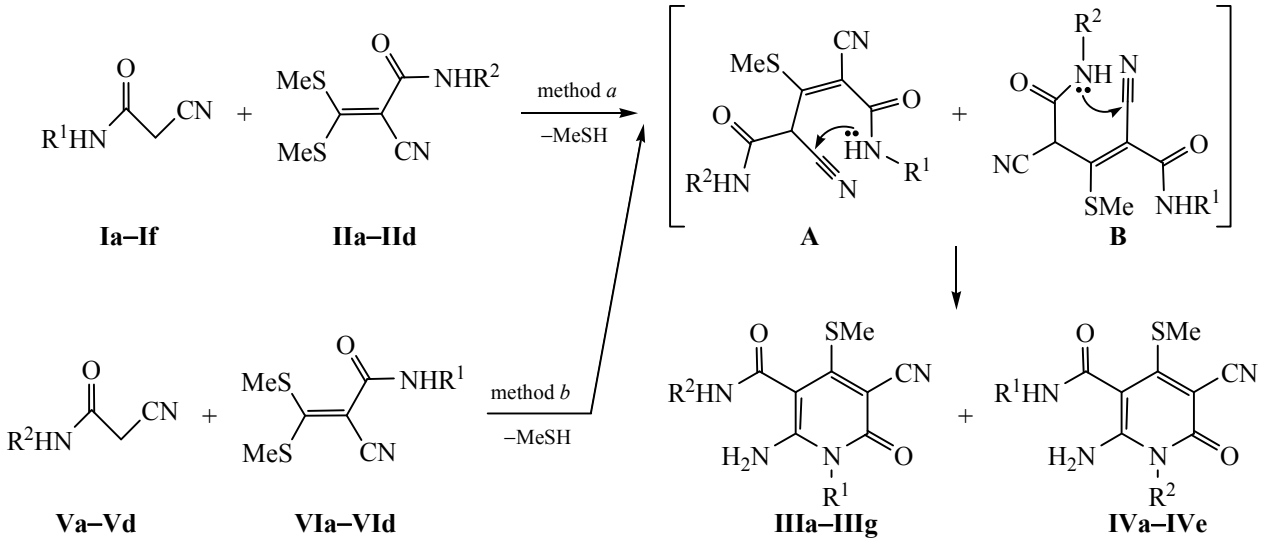
3,3-Bis(methylthio)acrylonitriles are the reagents widely used in organic synthesis. They easily enter the reactions of nucleophilic vinyl substitution (S_NVin) [1]. On their basis various heterocyclic compounds are prepared, among them the functionalized pyridines which exhibit a broad spectrum of biological activity [2]. Nicotine amide derivatives are the antagonists of 5-HT_3 serotonin and D_2 dopamine receptors [3], the growth inhibitors of different lines of cancer cells [4], and the antagonists of CB_2 receptors [5]. Hence, development of synthetic methods for preparing new pyridine-3-carboxamides as the potentially biologically active compounds is important.

We have found that the reaction of cyanoacetanilides **I** with 3,3-bis(methylthio)-2-cyano-*N*-arylacrylamides **II** under the conditions of S_NVin process goes along two competing pathways to form structural isomers, *N*,1-diaryl-1,6-dihydropyridine-3-carboxamides **III** and **IV**.



I–VI, R^1 = Ph, R^2 = *o*-$MeOC_6H_4$ (**a**), R^1 = Ph, R^2 = *m*-MeC_6H_4 (**b**), R^1 = *m*-MeC_6H_4, R^2 = *o*-MeC_6H_4 (**c**), R^1 = *o*-MeC_6H_4, R^2 = *p*-FC_6H_4 (**d**), R^1 = *o*-$MeOC_6H_4$, R^2 = *p*-FC_6H_4 (**e**), R^1 = R^2 = *o*-MeC_6H_4 (**f**), R^1 = R^2 = *m*-MeC_6H_4 (**g**).

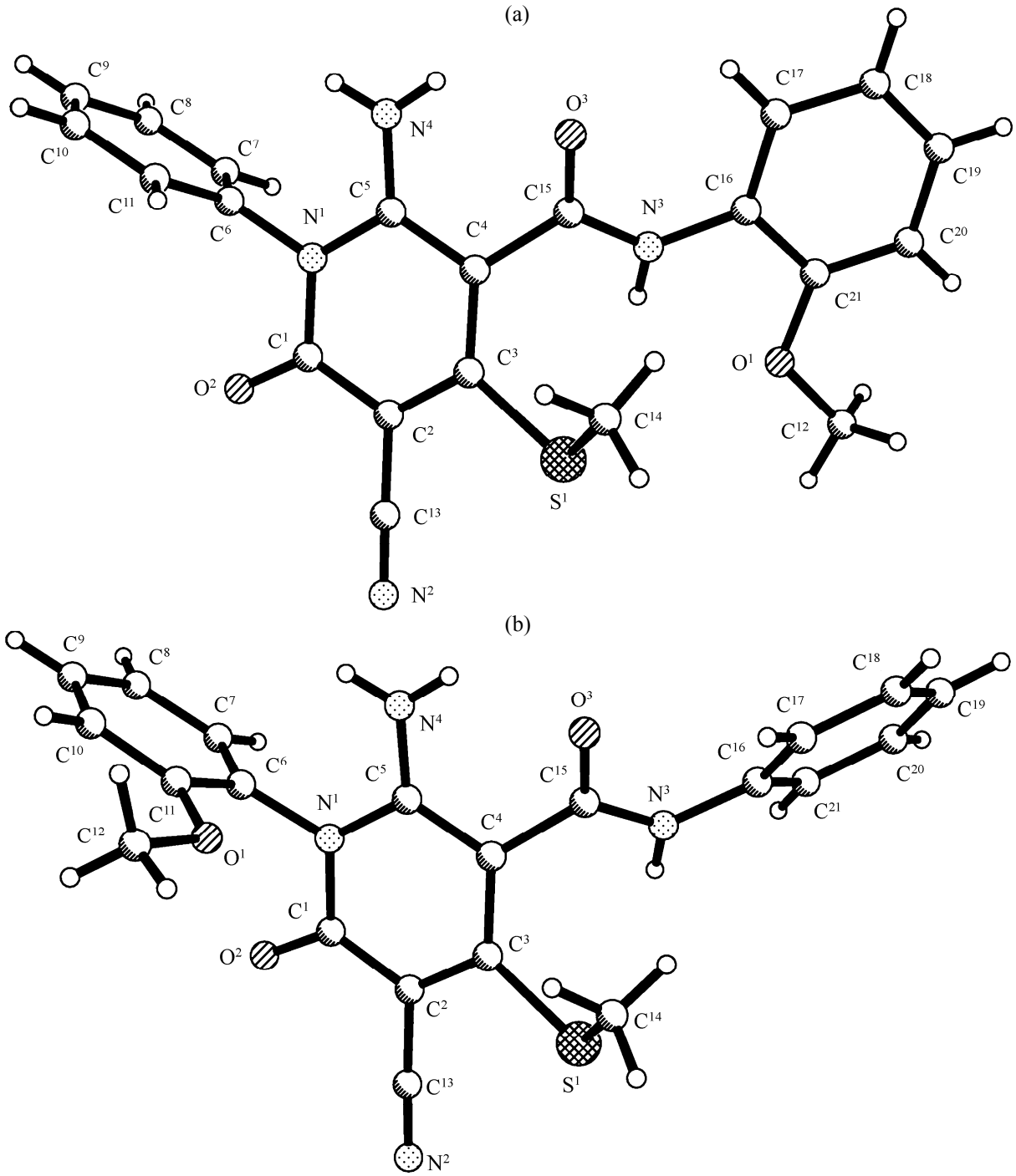


Fig. 1. Structure of 2-amino-4-methylthio-*N*-(2-methoxyphenyl)-6-oxo-1-phenyl-5-cyano-1,6-dihydropyrimidin-3-carboxamide **IIIa** (a) and 2-amino-1-(2-methoxyphenyl)-4-methylthio-6-oxo-*N*-phenyl-5-cyano-1,6-dihydropyridine-3-carboxamide **IVa** (b) according to the XRD study.

This reaction proceeds probably non-stereospecifically according to the addition-elimination mechanism [6] through the formation of two intermediates **A** and **B** which undergo intramolecular cyclization.

Direct (method *a*) and another (method *b*) syntheses of structural isomers **III** and **IV** from the compounds **I, II** and **V, VI** lead to the same products forming in the same ratio.

Table 1. Crystallographic data for the compounds **IIIa** and **IVa**

Parameter	**IIIa**	**IVa**
Crystal system	Rhombic	Monoclinic
a, Å	35.7534(17)	9.1885(14)
b, Å	5.4643(4)	16.664(3)
c, Å	9.9372(7)	13.221(3)
β, deg		98.783(17)
V, Å^3	1941.4(2)	2000.7(6)
Space group, Z	$Pca2_1$, 4	$P2_1/c$, 4
D_{calc}, g cm^{-3}	1.391	1.349
μ, mm^{-1}	0.198	0.192
F(000)	848	848
$2\Theta_{max}$	30.0	26.0
Number of reflections measured	26512	8459
Number of independent reflections [R_{int}]	5644 [0.042]	3921 [0.049]
Number of observed reflections with $F > 4\sigma(F)$	4201	2012
Number of refined parameters	265	264
wR_2, by all independent reflections	0.094	0.133
R_1, by all observed reflections	0.046	0.057
Refinement quality	0.99	0.96

Table 2. Interatomic distances (Å) in structures **IIIa** and **IVa**

Bond	**IIIa**	**IVa**	Bond	**IIIa**	**IVa**
S^1–C^3	1.7775(17)	1.774(3)	C^2–C^{13}	1.419(3)	1.436(4)
S^1–C^{14}	1.793(2)	1.799(4)	C^3–C^4	1.390(2)	1.409(4)
O^1–C^{11}		1.357(4)	C^4–C^5	1.420(2)	1.406(4)
O^1–C^{21}	1.365(2)		C^4–C^{15}	1.505(3)	1.513(4)
O^1–C^{12}	1.424(2)	1.424(4)	C^6–C^7	1.366(3)	1.365(4)
O^2–C^1	1.227(2)	1.238(4)	C^6–C^{11}	1.375(3)	1.407(4)
O^3–C^{15}	1.222(2)	1.229(3)	C^7–C^8	1.396(3)	1.383(5)
N^1–C^5	1.377(2)	1.368(4)	C^8–C^9	1.359(4)	1.377(5)
N^1–C^1	1.409(2)	1.421(3)	C^9–C^{10}	1.342(4)	1.376(5)
N^1–C^6	1.449(2)	1.444(4)	C^{10}–C^{11}	1.389(3)	1.379(4)
N^2–C^{13}	1.139(3)	1.143(3)	C^{16}–C^{17}	1.380(3)	1.376(4)
N^3–C^{15}	1.351(2)	1.348(4)	C^{16}–C^{21}	1.408(2)	1.384(4)
N^3–C^{16}	1.415(2)	1.414(4)	C^{17}–C^{18}	1.392(3)	1.385(5)
N^4–C^5	1.322(2)	1.321(3)	C^{18}–C^{19}	1.367(3)	1.364(5)
C^1–C^2	1.441(2)	1.415(4)	C^{19}–C^{20}	1.381(3)	1.381(6)
C^2–C^3	1.386(2)	1.391(4)	C^{20}–C^{21}	1.374(3)	1.370(5)

Table 3. Bond angles (deg) in structures **IIIa** and **IVa**

Angle	**IIIa**	**IVa**	Angle	**IIIa**	**IVa**
$C^3S^1C^{14}$	103.33(9)	102.81(15)	$C^7C^6N^1$	119.54(18)	122.4(3)
$C^{11}O^1C^{12}$		117.1(3)	$C^{11}C^6N^1$	118.55(17)	117.2(3)
$C^{21}O^1C^{12}$	117.76(16)		$C^6C^7C^8$	118.1(2)	120.7(3)
$C^5N^1C^1$	124.30(13)	122.9(2)	$C^9C^8C^7$	120.3(2)	119.2(3)
$C^5N^1C^6$	119.57(15)	118.7(2)	$C^{10}C^9C^8$	120.75(19)	120.7(3)
$C^1N^1C^6$	116.13(14)	118.2(2)	$C^9C^{10}C^{11}$	120.9(2)	120.7(3)
$C^{15}N^3C^{16}$	128.26(16)	126.4(3)	$O^1C^{11}C^{10}$		126.9(3)
$O^2C^1C^2$	125.26(17)	125.8(3)	$O^1C^{11}C^6$		114.8(3)
$O^2C^1N^1$	120.07(15)	118.4(3)	$O^1C^{21}C^{20}$	125.04(16)	
$C^2C^1N^1$	114.59(15)	115.7(3)	$O^1C^{21}C^{16}$	114.94(16)	
$C^3C^2C^1$	121.57(17)	121.9(2)	$C^{10}C^{11}C^6$	118.0(2)	118.4(3)
$C^3C^2C^{13}$	121.60(16)	120.9(3)	$N^2C^{13}C^2$	178.6(3)	177.7(4)
$C^1C^2C^{13}$	116.83(17)	117.1(3)	$O^3C^{15}N^3$	123.48(18)	123.2(3)
$C^2C^3C^4$	121.47(15)	119.7(3)	$O^3C^{15}C^4$	122.17(17)	121.0(3)
$C^2C^3S^1$	114.78(13)	116.8(2)	$N^3C^{15}C^4$	114.26(16)	115.5(2)
$C^4C^3S^1$	123.75(12)	123.4(2)	$C^{17}C^{16}C^{21}$	119.28(16)	119.7(3)
$C^5C^4C^3$	118.34(16)	118.9(3)	$C^{17}C^{16}N^3$	125.02(15)	123.4(3)
$C^5C^4C^{15}$	116.06(16)	116.5(2)	$C^{21}C^{16}N^3$	115.64(16)	116.9(3)
$C^3C^4C^{15}$	125.24(14)	124.4(3)	$C^{16}C^{17}C^{18}$	119.90(17)	119.5(4)
$N^4C^5N^1$	117.62(14)	117.5(3)	$C^{19}C^{18}C^{17}$	120.3(2)	120.5(4)
$N^4C^5C^4$	123.12(17)	122.8(3)	$C^{18}C^{19}C^{20}$	120.56(19)	120.1(4)
$N^1C^5C^4$	119.26(16)	119.8(2)	$C^{21}C^{20}C^{19}$	119.95(17)	119.7(4)
$C^7C^6C^{11}$	121.91(16)	120.4(3)	$C^{20}C^{21}C^{16}$	120.02(17)	120.4(4)

X-ray studies showed that the pyridin-2-ones obtained **IIIa** and **IVa** crystallize in one crystal. The crystal under investigation contained a mixture of isomers of *N*-(2-methoxyphenyl)-1-phenyl-1,6-dihydropyridine-3-carboxamide **IIIa** and 1-(2-methoxyphenyl)-*N*-phenyl-1,6-dihydropyridine-3-carboxamide **IVa** in 2.7:1 ratio (Fig. 1, Tables 1–3).

The molecules **IIIa** and **IVa** have similar spatial arrangement. In both structures the pyridine heteroring has significantly non-planar conformation with the largest endocyclic torsion angles C^5–N^1–C^1–C^2 –5.7(3)° for the structure **IIIa** and –9.1(4)° for the structure **IVa**, and C^2–C^3–C^4–C^5 –6.9(3)° (**IIIa)** and –10.8(4) for **IVa**. This arises obviously from the sterical repulsion between the phenylamide and thiomethyl substituents as indicated by the shortened intramolecular contacts $C^{14}\cdots C^{15}$ 3.14 Å (sum of van-der-Waals radii 3.42 Å [7]) and $S^1\cdots N^3$ 3.22 Å (**IVa**), 3.14 Å (**IIIa**). Due to that these substituents are turned with respect to the pyridine heteroring [C^5–C^4–C^{15}–O^3 torsion angle –44.0(3)° (**IIIa**), 41.6(4)° (**IVa**); and C^{14}–S^1–C^3–C^4 torsion angle –42.8(2)° (**IIIa**) and 40.4(3)° (**IVa**)].

On the other hand, on the basis of geometric parameters the existence of intramolecular attraction N^3-H$\cdots S^1$(H$\cdots$S 2.69Å (**IIIa**), 2.80 Å (**IVa**); N–H$\cdots$S 114° (**IIIa**), 112° (**IVa**) can be suggested. But the analysis of topology of the electronic density distribution calculated by M06-2X/6-311G** method for the experimentally obtained geometry of the molecules **IIIa** and **IVa** does not confirm thissuggestion. Between the phenylamide and thiomethyl substituents two critical bonding points (3, –1) were found (Table 4). The pathway of bond passing through one of these

Table 4. Values of electronic density (au) in critical points of (3, –1) bonds corresponding to the nonvalent interactions in molecules **IIIa** and **IVa** calculated by M06-2X/6-311G** method for the experimentally established molecular geometry

Critical points of bonds	**IIIa**	**IVa**
N^4–H···O^3	0.0233	0.0264
C^{17}–H···O^3	0.0160	0.0152
S^1–H···N^3	0.0146	0.0122
C^{14}–H···C^{15}		0.0126
C^{14}–H···N^3	0.0130	

points connects S^1 atom with N^3, but not with the amide hydrogen atom indicating the absence of hydrogen bond. Second critical point (3, –1) corresponds to the C^{14}–H···N^3 interaction in the structure **IIIa** and C^{14}–H···C^{15} in the structure **IVa.** These interactions may be both sterically repulsive and attractive, and they may have the electrostatic nature as well as arise from the C–H···π effect.

In the structures **IIIa** and **IVa** the phenyl substituent at N^3 is to some extent turned with respect to the amide fragment [C^{15}–N^3–C^{16}–C^{17} torsion angles are 18.9(3)° for **IIIa** and 27.2(5)° for **IVa**] despite the formation of intramolecular hydrogen bond C^{17}–H···O^3 [H···O 2.36 Å (**IIIa**), 2.40 Å (**IVa**); C–H···O 118° (**IIIa**), 112° (**IVa**)]. The presence of these interactions is confirmed also by the presence of critical point (3, –1) between these atoms in the calculated distribution of the electronic density. Note that the critical point corresponding to the possible intramolecular N^3–H···O^2 (2.22 Å) interaction in the structure **IIIa** is absent (Table 4). It arises probably from the too small value of N^3–H···O^1 angle 106° preventing the formation of a hydrogen bond.

Also the intramolecular N^4–H···O^3 hydrogen bond [H···O 2.11 Å (**IIIa**), 2.05 Å (**IVa**); N–H···O 130° (**IIIa**), 131° (**IVa**)] exists In the molecules **IIIa** and **IVa.** In this case no resonance reinforcement of hydrogen bond is observed demonstrating the absence of strong conjugation in the N^4–C^5–C^4–C^{15}–O^3 fragment. Values of bond lengths C^5–N^4 1.322(2) Å (**IIIa**), 1.321(3) Å (**IVa**) and C^{15}–O^3 1.222(2) Å (**IIIa**), 1.229(3) Å (**IVa**) are close to the average values of the ordinary C_{sp^2}–NH_2 bond 1.34 Å and the C=O double bond 1.21 Å respectively [8]. One of the reasons of this effect is the some degree of twisting of the C^4–C^{15} bond leading to a decrease in conjugation as seen in elongation of this bond to 1.505(3) Å (**IIIa**), 1.513(4) Å (**IVa**) compared to the average value of ordinary C_{sp^2}–C_{sp^2} bonds 1.46 Å [8].

For the analysis of intermolecular interactions in crystals of compounds **IIIa** and **IVa** all the molecules included in the first coordination sphere of the basic molecule were evaluated by means of the Voronoi-Dirichlet polyhedron method [9]. The molecules were considered to be located quite close if they possessed common facets of the Voronoi–Dirichlet polyhedrons. For all the adjacent molecules the energy of interaction with the basic molecule was calculated by quantum-chemical method. Analysis of topology of the electronic density distribution in the dimers formed permitted to obtain detailed information on the existing intermolecular interactions.

For the structure **IVa** the coordination number of molecule in crystal is 14. Starting from the calculated interaction energies in dimers (Table 5) it may be concluded that the strongest interactions take place only with 8 molecules (Fig. 2). The largest interaction energy was obtained for the central symmetric dimer 2–1 in which the molecules are bound by N^3–H···O^2 hydrogen bonds, by stacking interactions between the pyridine rings and cyano groups, and also by the attractive C^{21}–H···O^2 and C^7–H···S^1 contacts. Strong specific intermolecular interactions (N–H···N hydrogen bond) are also present in the dimer 2–3. With the rest five molecules the basic molecule is bound by the relatively weak interactions like C–H···π, C–H···O, and C–H···S hydrogen bonds (attractive contacts). Despite this fact the dimers formed by these interactions bring about 35% into the total energy of interaction of the basic molecule with its surrounding.

In Table 5 the electronic density values in the critical points of bonds corresponding to the intermolecular contacts are presented. These values usually well correlate with the energies of interaction, in particular, of hydrogen bonds [10, 11] and stacking interactions [12]. Results of calculations show that the strongest interactions taking place in the crystal **IVa** are N–H···O and N–H···N hydrogen bonds (electronic density values are 0.017–0.018 au) Relatively high values of electronic density were also calculated in critical points corresponding to the C–H···π bonds (up to 0.01 au) may be indicatind their sufficiently high energy. Electronic density in critical points of bonds corresponding to the stacking interactions (0.005–0.007 au) is comparable with the density in critical

Table 5. Energies of interaction of basic molecules with the adjacent ones in structure **IVa** (M06-2X/6-311G**), values of electronic density in critical points (3, –1) corresponding to intermolecular contacts, and geometrical characteristics of contacts

Dimer	Symmetry	E_{int}, cal mol^{-1}	Contact	ρ(RCP), au	Distance, Å	Angle, deg	Classification
IV-1	(1 – *x*, 1 – *y*, –*z*)	–29.0	N^3–H···O^2	0.0172	2.09	152	HB
			C^2···C^2	0.0073	3.39	0	stacking
			C^{21}–H···O^2	0.0062	2.64	137	AC
			C^7–H···S^1	0.0061	2.93	150	AC
			C^5···N^2	0.0049	3.41	0	stacking
IV-2	(1 – *x*, –0.5 + *y*, 0.5 – *z*)	–9.6	C^{14}–H···C^{11}	0.0102	2.57	139	CH···π
	(1 – *x*, 0.5 + *y*, 0.5 – *z*)		C^{18}–H···N^2	0.0074	2.76	136	CH... π
			S^1···H–C^{12}	0.0061	3.05	152	AC
			C^{21}···H–C^{12}	0.0041	3.10	119	CH···π
			C^{14}–H···O^2	0.0039	3.05	105	AC
			C^{19}–H···H–C^{14}	0.0016	3.05		
IV-3	(–1 + *x*, *y*, *z*)	–7.4	N^4–H···N^2	0.0179	2.12	143	HB
	(1 + *x*, *y*, *z*)						
IV-4	(–*x*, 1 – *y*, –*z*)	–6.1	C^8–H···C^{16}	0.0073	2.73	134	CH···π
			C^9–H···C^{21}	0.0070	2.79	128	CH···π
			C^8–H···O^3	0.0043	2.93	131	AC
			C^7–H···N^4	0.0024	3.36		
			N^4···N^4	0.0007	4.41		
IV-5	(–*x*, –0.5 + *y*, 0.5 – *z*)	–3.6	C^9–H···O^3	0.0076	2.54	128	AC
	(–x, 0.5 + *y*, 0.5 – *z*)		C^{10}–H···O^3	0.0043	2.89	114	AC
			C^{10}···H–C^{17}	0.0030	3.28	99	
			C^{12}–H···C^{18}	0.0016	3.52	103	
			N^4–H···H–C^{18}	0.0004	3.93		
IV-6	(2 – *z*, 1 – *y*, 1 – *z*)	–0.7					
IV-7	(–*x*, 0.5 – *y*, 0.5 + *z*)	–0.5	C^{12}–H···C^8	0.0040	3.12	119	CH···π
	(–*x*, 0.5 – *y*, 1.5 + *z*)		C^{10}–H···H–C^8	0.0029	2.62		
			C^{12}–H···O^2	0.0011	3.43	140	AC
IV-8	(–1 + *x*, 0.5 – *y*, –0.5 + *z*)	0.2					
	(1 + *x*, 0.5 – *y*, 0.5 + *z*)						
IV-9	(1 – *x*, 1 – *y*, 1– *z*)	0.3	C^{12}–H···H–C^{14}	0.0047	2.38		

points corresponding to the C–H···O and C–H···S attractive contacts (up to 0.0076 au and 0.0061 au respectively). From the data presented in the Table 4 it may be concluded that the contacts corresponding to the critical points with the electronic density below 0.004 au mostly do not correspond to any attractive interactions.

In the structure **IIIa** the coordination number of molecule is 10. In this case similarly to the structure **IVa** the interactions stronger than 4 kcal mol^{-1} take place only with 8 molecules (Table 6, Fig. 3). The strongest interactions are again observed between the molecules bound with the intermolecular N–H···O hydrogen bond and stacking interaction. The last ones

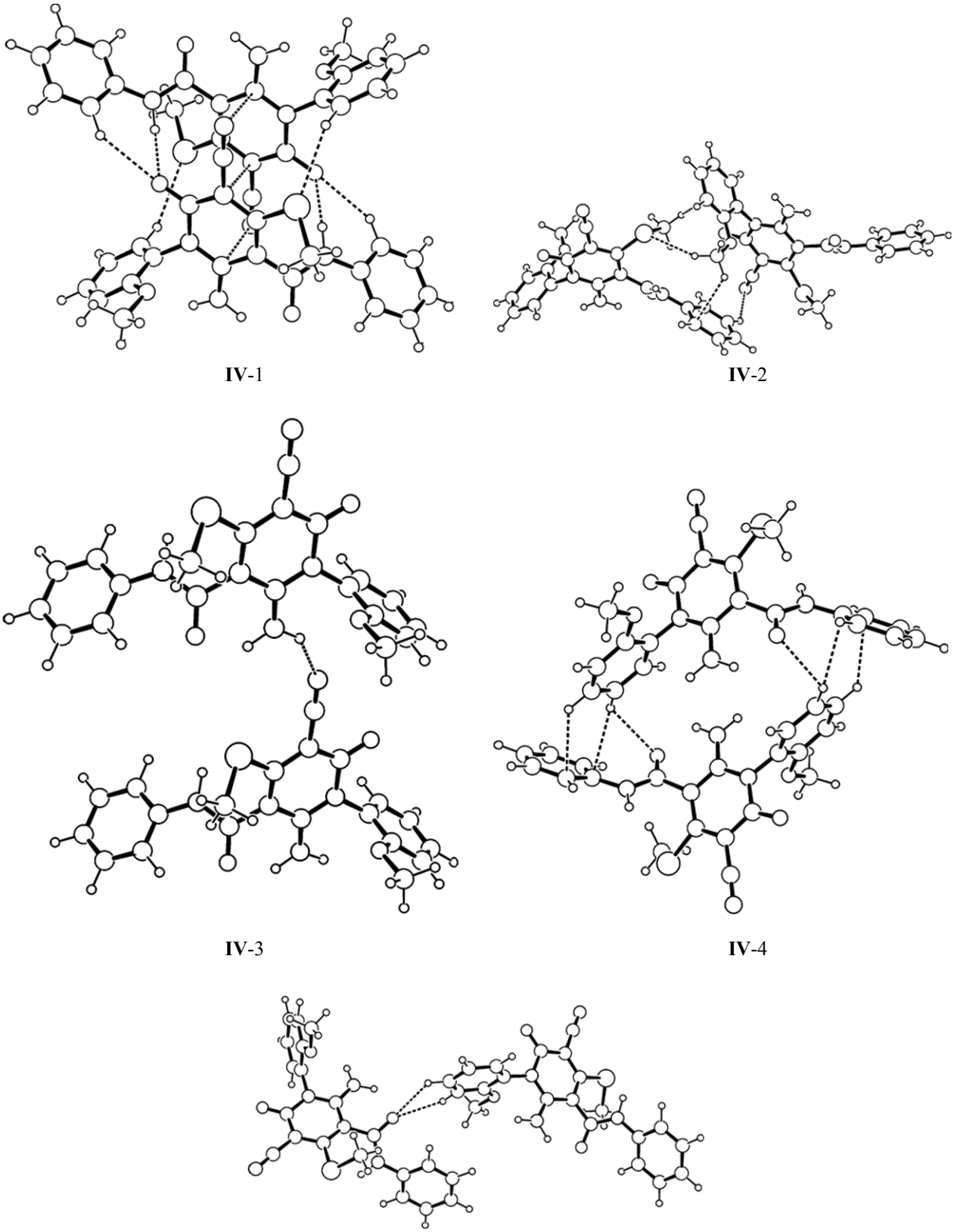


Fig. 2. Structures of the strongest interacting dimers of the adjacent molecules **IVa** in crystal.

Table 6. Energies of interaction of basic molecules with the adjacent ones in structure **IIIa** (M06-2X/6-311G**), values of electronic density in critical points (3, –1) corresponding to intermolecular contacts and geometrical characteristics of contacts

Dimer	Symmetry	E_{int}, cal mol^{-1}	Contact	ρ(RCP), au	Distance, Å	Angle, deg	Classification
III-1	$(1-x, 1-y, -0.5+z)$	–14.0	$O^2\cdots H-N^4$	0.0135	2.19	139	HB
	$(1-x, 1-y, 0.5+z)$		$C^9-H\cdots C^{17}$	0.0074	2.74	135	CH···π
			$N^2\cdots C^9$	0.0061	3.35		stacking
			$N^4\cdots C^{11}$	0.0044	3.61	19	stacking
			$O^2\cdots C^7$	0.0039	3.58	18	stacking
			$C^{11}-H\cdots H-C^7$	0.0031	2.69		
III-2	$(x, -1+y, z)$	–9.4	$O^2\cdots H-C^{11}$	0.0085	2.45	164	AC
	$(x, 1+y, z)$		$N^2\cdots H-C^{14}$	0.0070	2.65	167	AC
			$C^{12}-H\cdots C^{18}$	0.0067	2.83	153	CH···π
			$S^1\cdots H-C^{14}$	0.0044	3.17	119	AC
			$C^7-H\cdots C^{11}$	0.0038	3.19	109	CH···π
			$C^{12}-H\cdots H-C^{14}$	0.0038	2.62		
			$C^8\cdots H-C^{10}$	0.0036	3.39	99	CH···π
			$C^7-H\cdots N^4$	0.0033	3.09	162	
			$N^3-H\cdots O^3$	0.0025	3.01	132	AC
			$C^2\cdots C^4$	0.0012	4.46		
			$C^1\cdots N^4$	0.0009	4.37		
III-3	$(0.5+x, -y, -1+z)$	–4.4	$C^{14}-H\cdots C^{20}$	0.0056	2.92	136	CH···π
	$(0.5+x, -y, z)$		$C^{12}-H\cdots H-C^{19}$	0.0046	2.58		
			$O^1\cdots H-C^{19}$	0.0041	2.91	131	AC
			$S^1\cdots H-C^{20}$	0.0040	3.18	127	AC
			$C^{12}-H\cdots H-C^{20}$	0.0036	2.89		
			$S^1\cdots H-C^{12}$	0.0024	3.43	152	AC
III-4	$(1-x, 2-y, -0.5+z)$	–4.0	$N^2\cdots H-C^8$	0.0116	2.33	171	AC
	$(1-x, 2-y, 0.5+z)$		$O^2\cdots H-C^7$	0.0023	3.06	137	AC
III-5	$(x, y, -1+z)$	–0.4	$C^{14}-H\cdots H-C^{18}$	0.0033	2.62		
	$(x, y, 1+z)$		$S^1\cdots C^{18}$	0.0020	4.26		

found for the dimer 3–1 can be considered non-classic because they are realized not between two aromatic rings, but between the aromatic ring and the cyano, the amino, or the carbonyl group. In the rest dimers calculated for the structure **IIIa** relatively weak C–H···O, C–H···N, C–H···σ, and C–H···π attractive interactions take place.

Hence, in the structure **IIIa** the energy of interaction in the most strongly bound dimer is almost two times less than in the structure **IVa**. In the structure **IIIa** only one relatively strong intermolecular N–H···O hydrogen bond is formed. Due to that the summary energy of interaction of the basic molecule with its surrounding in the structure **IIIa** is –64.6 kcal mol^{-1} which is significantly less as compared to the calculated overall energy for the structure **IVa**, –77.1 kcal mol^{-1}.

All the pyridine-2-ones **III, IV** synthesized fluoresce under the UV irradiation.

EXPERIMENTAL

Melting points were measured on a Köffler block. IR spectra were recorded on a Perkin-Elmer FIR "Spectrum One" device in KBr. ^{1}H NMR spectra were

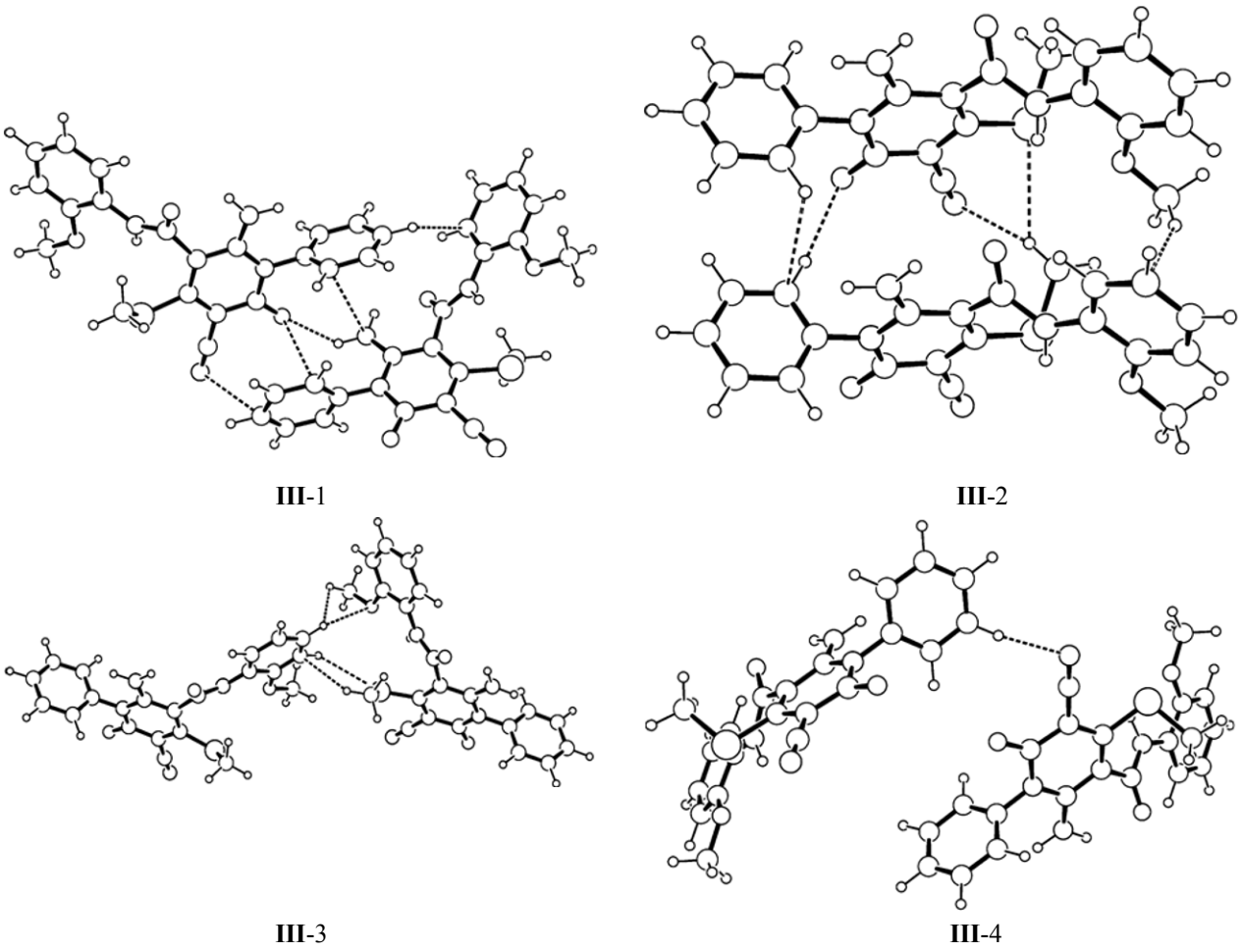


Fig. 3. Structures of the strongest interacting dimers of the adjacent molecules **IIIa** in crystal.

taken on a Bruker Avance II 400 (399.9601 MHz) spectrometer in DMSO-d_6 against internal TMS. Mass spectra were obtained on a MX-1321 apparatus (70 eV) with the direct injection of substance in the ion source and a Crommas GC/MS-Hewlett-Packard 5890/5972 instrument equipped with a HP-5MS column (70 eV) (compounds **IIIc.IVc**). Reaction progress and individuality of the compounds obtained were controlled by TLC on Silufol UV-254 plates, elution with 3:5 acetone-hexane, development with iodine vapor and UV radiation.

XRD studies of compounds **IIIa IVa** were carried out at 298 K on a four-circle Xcalibur 3 diffractometer (MoK_α, graphite monochromator, CCD detector, ω-scanning). Structures were solved by the direct method and refined in the anisotropic approximation for the nonhydrogen atoms by the SHELX-97 complex of programs [13]. Location of hydrogen atoms was calculated geometrically and refined in the *rider* model with $U_{iso} = nU_{eq}$ of the carrying atom (n = 1.5 for methyl groups and 1.2 for the rest hydrogen atoms). Crystal of compounds **IIIa** and **IVa** was a racemic twin with the component increments 0.73(7): 0.27(7). Crystallographic data are listed in Table 1, bond lengths and bond angles, in Tables 2 and 3 respectively. They were deposited in the Cambridge Crystallographic Data Center, deposit numbers CCDC 764323, 784324.

Quantum chemistry calculations of molecules of compounds **IIIa** and **IVa** were carried out by the density functional method M06-2X/6-311G** according to the Gaussian 09 program [14]. The interaction energies in dimers were calculated with the consideration of correction of the superposition error of the basis set. Experimentally established molecular geometry was used for the calculations. Element−hydrogen bond lengths were accepted to be 1.09 Å for CH_3 groups, 1.08 Å for C_{ar}–H, and 1.01 Å

Table 7. Yields, melting points, and elemental analysis data of the compounds obtained

Comp. no.	Yield, %, method *a*/*b*	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa and **IVa**	80/78	185–190 (EtOH)	62.14	4.26	13.65	$C_{21}H_{18}N_4O_3S$	62.05	4.46	13.78
IIIb and **IVb**	80/81	245–247 (BuOH)	64.52	4.33	14.28	$C_{21}H_{18}N_4O_2S$	64.60	4.65	14.35
IIIc and **IVc**	74/82	233–235 (BuOH)	65.25	4.86	13.72	$C_{22}H_{20}N_4O_2S$	65.33	4.98	13.85
IIId and **IVd**	40/54	245–250 (BuOH)	61.64	4.10	13.64	$C_{21}H_{17}FN_4O_2S$	61.75	4.19	13.72
IIIe and **IVe**	62/71	250–253 (BuOH)	59.35	3.95	13.11	$C_{21}H_{17}FN_4O_3S$	59.42	4.04	13.20
IIIf	82	223–225 (EtOH)	65.28	4.84	13.77	$C_{22}H_{20}N_4O_2S$	65.33	4.90	13.85
IIIg	85	253–255 (EtOH)	65.21	4.85	13.70	$C_{22}H_{20}N_4O_2S$	65.33	4.98	13.85

for N–H ones. Topology of the electronic density distribution was analyzed with the help of AIM2000 program [15]. Analysis of the crystal packing and plotting of the Voronoi–Dirichlet polyhedrons was carried out by the Topos 4.0 program [16].

Synthesis of compounds III–IV. Methods *a* and *b*. To the suspension of 10 mmol of KOH in 10 ml of DMSO 10 mmol of cyanoacetanilide **I** (method *a*) or **V** (method *b*) was added and the mixture obtained was stirred for 15 min. After that 10 mmol of corresponding 3,3-bis(methylthio)-2-cyano-*N*-arylacrylamide **II** (method *a*) or **V** (method *b*) was added, the reaction mixture was stirred for 1 h and heated for 15 min at 80°C. The resulting mixture was left for 2 h, poured in cold water, and acidified with equimolar amount of aqueous 30% HCl. The precipitate formed was filtered off, washed with water, and then crystallized from the suitable solvent. Structural isomers **III** and **IV** have very close R_f values complicating their separation (Table 7). Ratio of isomers for compounds **IIIa** and **IVa** is known from the XRD data. For the rest compounds **IIIb–IIIe** and **IVb–IVe** it was impossible to make a conclusion about the ratio of signals in the NMR spectra.

2-Amino-4-methylthio-*N*-(2-methoxyphenyl)-6-oxo-1-phenyl-5-cyano-1,6-dihydropyridine-5-carboxamide IIIa and 2-amino-4-methylthio-1-(2-methoxyphenyl)-6-oxo-*N*-phenyl-5-cyano-1,6-dihydropyridine-3-carboxamide (IVa). IR spectrum, ν, cm^{-1}: 3368, 3287 (N–H); 2219 (C≡N); 1660 (NC=O); 1641 [δ(NH_2)]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.53 s and 2.57 major s (2H, SCH_3), 3.77 s and 3.81 major s (2H, OCH_3), 6.95 major t (1H, H_{arom}, *J* 7.6 Hz), 7.0 major br.s (2H, NH_2), 7.06–7.11 m (2H, H_{arom}), 7.13 d and 7.28 d (1H, H_{arom}, *J* 8.4 Hz), 7.18 major t and 7.33 t (1H, H_{arom}, *J* 8.0 Hz), 7.31 d (1H, H_{arom}, *J* 7.6 Hz), 7.51–7.63 m (2H, H_{arom}), 7.69 major d and 7.99 major d (1H, H_{arom}, *J* 8.0 Hz), 9.71 major br.s and 10.51 br.s (1H, NH). Mass spectrum (electron impact, 70 eV), *m/z* (I_{rel}, %): 406 (8.8) $[M]^+$, 314 (8.4), 284 (12.3), 123 (100), 119 (18.4), 108 (20.9), 93 (11.5), 77 (44.8). Ratio of compounds **IIIa** and **IVa** according to NMR data is 3:1, according to XRD data onpacking in crystal takes place in 2.7:1 ratio.

2-Amino-4-methylthio-6-oxo-*N*-*m*-tolyl-1-phenyl-5-cyano-1,6-dihydropyridine3-carboxmide IIIb and 2-amino-4-methylthio-6-oxo-1-*m*-tolyl-*N*-phenyl-5-cyano-1.6-dihydropyridine-3-carboxamide (IVb). IR spectrum, ν, cm^{-1}: 3437, 3321 (N–H); 2209 (C≡N); 1644 (NC=O); 1635 [δ(NH_2)]. ^{1}H NMR spectrum, δ, ppm (J,Hz): 2.29 major s and 2.38 s (3H, CH_3), 2.54 s (3H, SCH_3), 6.91 major d (1H, H_{arom}, *J* 7.6 Hz), 7.02 br.s (2H, NH_2), 7.05–7.11 m (2H, H_{arom}), 7.21 major t and 7.48 t (1H, H_{arom}, *J* 7.8 Hz), 7.27–7.38 m (2H, H_{arom}), 7.42 major d and 7.67 d (1H, H_{arom}, *J* 8.0 Hz), 7.55–7.62 m (2H, H_{arom}), 10.40 major br.s and 10.47 br.s (1H, NH). Mass spectrum (electron impact, 70 eV), *m/z* (I_{rel}, %): 390 (17.8) $[M]^+$, 298 (36.9), 284 (22.2), 257 (13.0), 241 (3.0), 181 (2.96), 133 (12.2), 107 (100), 65 (38). Ratio of compounds **IIIb** and **IVb** according to NMR data is 3:2.

2-Amino-4-methylthio-6-oxo-1-*o*-tolyl-*N*-*m*-tolyl-5-cyano-1,6-dihydropyridine-3-carboxamide (IIIc) and 2-amino-4-methylthio-6-oxo-1-*m*-tolyl-*N*-*o*-tolyl-5-cyano-1.6-dihydropyridine-3-carboxamide (IVc). IR spectrum, ν, cm^{-1}: 3403, 3290 (N–H); 2209 (C≡N); 1661 (NC=O); 1644 [δ(NH_2)]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.05 s and 2.29 s (3H, CH_3), 2.30 s and

2.38 s (3H, CH_3), 2.55 s and 2.61 s (3H, SCH_3), 6.91 d (1H, H_{arom}, *J* 7.8 Hz), 7.0 br.s (2H, NH_2), 7.07–7.23 m (2H, H_{arom}), 7.36 d (1H, H_{arom}, *J* 8.0 Hz), 7.41–7.51 m (2H, H_{arom}), 7.57 s (1H, H_{arom}), 7.73 d (1H, H_{arom}, *J* 8.0 Hz), 9.86 br.s and 10.42 br.s (1H, NH). Mass spectrum (electron impact, 70 eV). *m/z* (I_{rel}, %): 405 $[M + 1]^+$ (100). Ratio of compounds **IIIc** and **IVc** according to NMR data is 1:1.

2-Amino-4-methylthio-6-oxo-1-*o*-tolyl-*N*-(*p*-fluorophenyl)-5-cyano-1,6-dihydropyridine-3-carboxamide IIId and 2-amino-4-methylthio-6-oxo-*N*-*o*-tolyl-1-(*p*-fluorophenyl)-5-cyano-1.6-dihydropyridine-3-carboxamide (IVd). IR spectrum, ν, cm^{-1}: 3343, 3284 (N–H); 2210 (C≡N), 1716 (NC=O), 1669 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.05 s and 2.29 s (3H, CH_3), 2.56 s and 2.62 s (3H, SCH_3), 7.06 br.s (2H, NH_2), 7.09 d (1H, H_{arom}, *J* 7.4 Hz), 7.17–7.22 m (2H, H_{arom}), 7.33–7.46 m (3H, H_{arom}), 7.69–7.71 m (1H, H_{arom}), 7.74 d (1H, H_{arom}, *J* 7.6 Hz), 9.84 br.s and 10.55 br.s (1H, NH). Mass spectrum (electron impact, 70 eV). *m/z* (I_{rel}, %): 408 (24.6) $[M]^+$, 298 (100) $[M - p\text{-}FC_6H_4NH]^+$**,** 252 (2.0), 133 (12.7). 111 (65.6), 75 (25.1) Ratio of compounds **IIId** and **IVd** according to NMR data is 1:1.

2-Amino-4-methylthio-6-oxo-1-(2-methoxyphenyl)-*N*-(*p*-fluorophenyl)-5-cyano-1,6-dihydropyridine-3-carboxamide IIIe and 2-amino-4-methylthio-6-oxo-*N*-(2-methoxyphenyl)-1-(*p*-fluorophenyl)-5-cyano-1.6-dihydropyridine-3-carboxamide (IVe). IR spectrum, ν, cm^{-1}: 3480, 3343 (N–H); 2211 (C≡N); 1673 (NC=O); 1633 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.53 s and 2.56 s (3H, SCH_3), 3.76 s and 3.81 s (3H, OCH_3), 6.95 t (1H, H_{arom}, *J* 7.4 Hz), 7.05 br.s (2H, NH_2), 7.12–7.24 m (2H H_{arom}), 7.26 d (1H, H_{arom}, *J* 8.4 Hz), 7.35–7.54 m (2H, H_{arom}), 7.69–7.72 m (2H, H_{arom}), 8.02 d (1H, H_{arom}, *J* 7.6 Hz), 9.66 br.s and 10.57 br.s (1H, NH). Mass spectrum (electron impact, 70 eV). *m/z* (I_{rel}, %): 424 (5.9) $[M]^+$, 314 (3.7), 302 (9.1), 256 (2.1), 184 (2.7), 137 (23.8), 123 (100), 75 (33.4). Ratio of compounds **IIIe** and **IVe** according to NMR data is 1:1.

2-Amino-4-methylthio-6-oxo-*N*,1-di(*o*-tolyl)-5-cyano-1,6-dihydropyridine-3-carboxamide (IIIf). IR spectrum, ν, cm^{-1}: 3425, 3312 (N–H); 2214 (C≡N); 1694 (NC=O), 1613 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.06 s (3H, CH_3), 2.31 s (3H, CH_3), 2.63 s (3H, SCH_3), 7.02 br.s (2H, NH_2), 7.10 t (1H, H_{arom}, *J* 7.6 Hz), 7.18–7.22 m (3H, H_{arom}), 7.39-7.47 m (3H, H_{arom}), 7.75 d (1H, H_{arom}, *J* 8.0 Hz), 9.89 br.s (1H, NH). Mass spectrum (electron impact, 70 eV), *m/z* (I_{rel}, %); 404 (10.4) $[M]^+$, 298 (28.1) $[M - o\text{-}MeC_6H_4NH]^+$, 133 (10.5), 107 (100) $[o\text{-}MeC_6H_4NH_2]^+$**.**

2-Amino-4-methylthio-6-oxo-*N*,1-di(*m*-tolyl)-5-cyano-1.6-dihydropyridine-3-carboxamide IIIg. IR spectrum, ν, cm^{-1}: 3407, 3311 (N–H); 2211 (C≡N), 1632 (NC–O), 1603 [δ(NH)]. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.29 s (3H, CH_3), 2.38 s (3H, CH_3), 2.54 s (3H, SCH_3), 6.91 d (1H, H_{arom}, *J* 7.6 Hz), 7.0 br.s (2H, NH_2), 7.07 d (1H, H_{arom}, *J* 8.0 Hz), 7.1 s (1H, H_{arom}), 7.21 t (1H, H_{arom}, *J* 7.6 Hz), 7.37 d (1H, H_{arom}, *J* 7.6 Hz), 7.43 d (1H, H_{arom}, *J* 7.4 Hz), 7.48 t (1H, H_{arom}, *J* 8.0 Hz), 7.57 s (1H, H_{arom}), 10.40 br.s (1H, NH). Mass spectrum (electron impact, 70 eV) *m*/z (I_{rel}, %): 404 (12.9) $[M]^{+\cdot}$, 298 (25.4) $[M - m\text{-}MeC_6H_4NH]^+$, 133 (14.3), 108 (100) $[m\text{-}MeC_6H_4NH]^+$, 77 (13.9), 65 (16.6), 39 (8.1).

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