DOI 10.1007/s10593-021-02980-w
Chemistry of Heterocyclic Compounds **2021**, *57*(7/8), 764–771

Novel approach to the synthesis of 3-amino-4-arylpyridin-2(1*H*)-one derivatives

Vladislav Yu. Shuvalov[1], Sergei A. Chernenko[1], Anton L. Shatsauskas[1], Anna L. Samsonenko[2], Maksim V. Dmitriev[3], Alexander S. Fisyuk[1,2]*

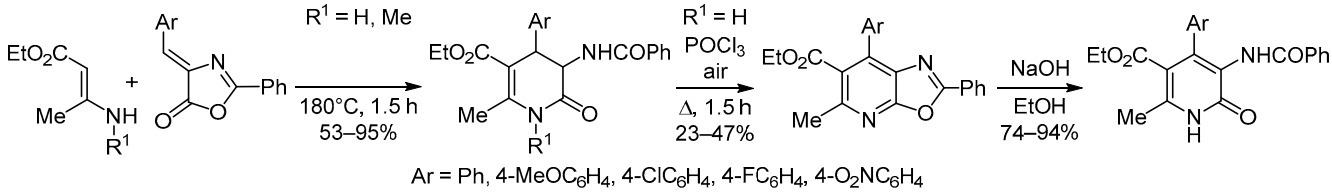
[1] *Omsk State Technical University, 11 Mira Ave., Omsk 644050, Russia*

[2] *Dostoevsky Omsk State University, 55a Mira Ave., Omsk 644077, Russia; e-mail: fisyuk@chemomsu.ru*

[3] *Perm State University, 15 Bukireva St., Perm 614990, Russia*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2021, *57*(7/8), 764–771

Submitted July 15, 2021
Accepted August 5, 2021



The reaction of 4-arylidene-2-phenyloxazol-5(4*H*)-ones with enamines of ethyl acetoacetate gave 4-aryl-2-methyl-6-oxo-5-[(phenylcarbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylic acid esters, which, when heated with phosphorus oxychloride, were converted into esters of 7-aryl-5-methyl-2-phenyloxazolo[5,4-*b*]pyridine-6-carboxylic acids. Alkaline hydrolysis of these compounds gave 4-aryl-2-methyl-6-oxo-5-[(phenylcarbonyl)amino]-1,6-dihydropyridine-3-carboxylic acid esters.

Keywords: 3-amino-4-arylpyridin-2(1*H*)-ones, azlactones, oxazolo[5,4-*b*]pyridines, alkaline hydrolysis, oxidation.

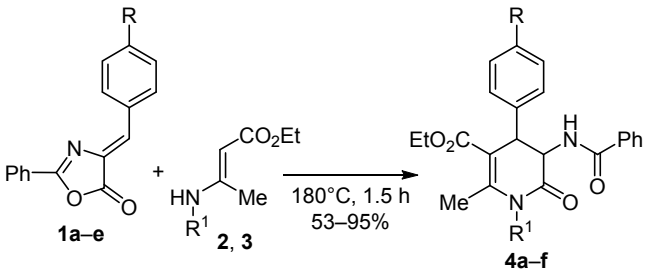
Pyridin-2(1*H*)-ones are privileged structures that are part of many biologically active compounds of natural and synthetic origin.[1] 3-Aminopyridin-2(1*H*)-ones are of particular interest since they contain an amino acid amide fragment in their structure and can be used for the synthesis of peptidomimetics. Among these compounds, enzyme inhibitors[2–6] such as M^{pro} protease which prevents the replication of the coronavirus SARS-CoV-2,[7,8] agonists and modulators of cannabinoid receptors CB2,[9,10] antagonists of prostaglandin receptor EP3,[11] and an inhibitor of jasmonate signaling[12] have been found. 5-Amino-3,4'-bipyridin-(1*H*)-one, known as the cardiotonic drug amrinone,[13] is widely used in clinical practice. 3-Aminopyridin-2(1*H*)-ones are used in the synthesis of more complex compounds.[14–16] Recently, it was shown that 3-amino-4-arylpyridin-2(1*H*)-ones are good antioxidants,[17,18] possess luminescent properties,[19] and can be used as luminescent dyes for enzyme-linked immunosorbent assay.[20] Despite the wide range of biological activity, the methods for the preparation of 3-amino-4-arylpyridin-2(1*H*)-ones are few and, as a rule, involve multistep synthesis.[19–22]

It was previously reported that azlactones are capable of reacting with enamines of 1,3-diketones and 1,3-keto esters to form the corresponding amides of 3-amino-4-aryl-3,4-dihydropyridin-2(1*H*)-ones,[23–25] which, in principle, can be oxidized to the corresponding amides of 3-aminopyridin-2(1*H*)-ones.[26–28] Therefore, it seemed necessary to study the possibility of such an approach to the synthesis of 3-amino-4-arylpyridin-2(1*H*)-one derivatives.

For this purpose, azlactones **1a**–**e** were synthesized by the known method[29] by condensation of hippuric acid with aromatic aldehydes in the presence of polyphosphoric acid. Compounds **1a**–**e** obtained in this way were subjected to a reaction with enamines **2**, **3** by heating at 180°C for 1.5 h without a solvent. As a result, ethyl 4-aryl-2-methyl-6-oxo-5-[(phenylcarbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylates **4a**–**f** were obtained. Compounds **4a**–**c** were isolated as *cis*-isomers, while compounds **4d**–**f** represented mixtures of *cis*-/*trans*-isomers with yields of 64/22% (compound **4d**), 79/16% (compound **4e**), 47/18% (compound **4f**); the mixtures were then resolved by silica gel column chromatography. It should be noted that the yields of dihydropyridones **4c**–**e** containing acceptor

substituents in the aryl fragment were higher than those of unsubstituted and methoxy-substituted products **4a**,**b** (Scheme 1, Table 1).

Scheme 1



1 a R = H, **b** R = OMe, **c** R = Cl, **d** R = F, **e** R = NO_2
2 R^1 = H; **3** R^1 = Me
4 a R = H, R^1 = H; **b** R = OMe, R^1 = H; **c** R = Cl, R^1 = H
d R = F, R^1 = H; **e** R = NO_2; R^1 = H; **f** R = H, R^1 = Me

Table 1. Yields of isomers of compounds **4a**–**f**

Compound	Yield, %	
	cis-Isomer	*trans*-Isomer
4a	58	–
4b	53	–
4c	74	–
4d	64	22
4e	79	16
4f	47	18

The structure and composition of the obtained compounds were confirmed by the data of IR, ^{1}H and ^{13}C NMR spectroscopy, X-ray structural analysis, and elemental analysis. In the ^{1}H NMR spectra of *cis*-isomers **4a**–**e**, the protons at position C-4 of the pyridone ring are present in the form of doublets, whereas at position C-5 – as doublets of doublets with $^3J_{5\text{-CH,NH}}$ = 5.3–6.7 Hz and total coupling constant $^3J_{4\text{-CH,5-CH}}$ = 7.4–8.0 Hz. Due to the low solubility of *trans*-isomers **4d**,**e** in $CDCl_3$, their ^{1}H NMR spectra were recorded in DMSO-d_6.

According to X-ray diffraction data, the crystal of compound **4a** consists of molecules of only one pair of enantiomers with the *cis* arrangement of substituents and the 3*R**,4*R** configuration of the atoms of the methine groups (the numbering of atoms is shown in Figure 1). The conformation of the pyridone ring can be described as a highly distorted boat. Atoms N(1), C(1), C(2), and C(3) lie in the same plane, atoms C(5) and C(4) deviate from this plane to one side by 0.15 and 0.67 Å, respectively. In the solid state, molecules are linked into infinite chains *via* N(1)–H(1)···O(2) hydrogen bonds.

To oxidate obtained 3,4-dihydropyridin-2(1*H*)-ones, MnO_2,[27,28] $FeCl_3$,[30] and DDQ[31,32] were employed. However, in our case, oxidation with these reagents, chloranil, $NaNO_2$ in AcOH, $K_2S_2O_8$ in MeCN, by heating compounds **4a**,**f** with $KMnO_4$ in Me_2CO or heating with 10% Pd/C in xylene did not lead to the formation of pyridones **5a**,**f** (Scheme 2).

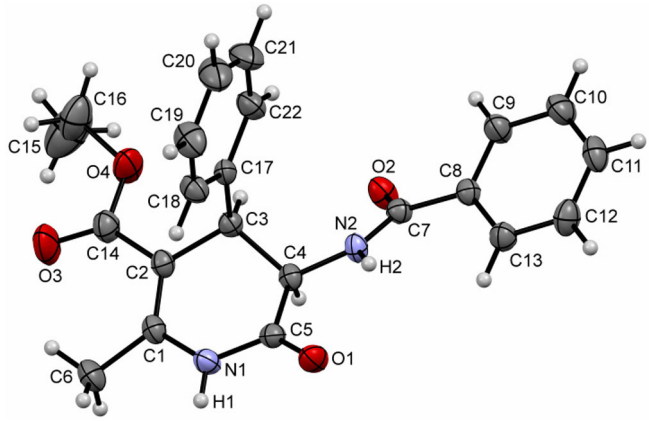
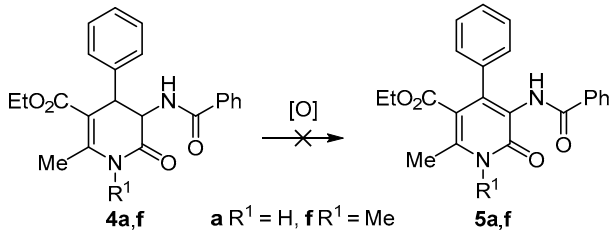


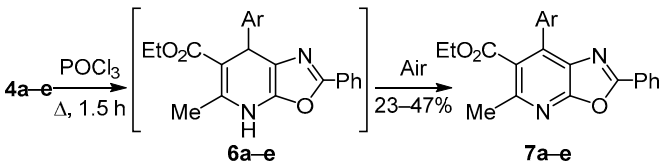
Figure 1. The molecular structure of compound **4a** with atoms represented as thermal vibration ellipsoids with 30% probability.

Scheme 2



It is known that 1,4-dihydropyridines can be easily oxidized to pyridines. In some cases, oxidation with atmospheric oxygen occurs already upon the preparation of 1,4-dihydropyridines (Scheme 3).[33] We studied the possibility of obtaining 4,7-dihydrooxazolo[5,4-*b*]pyridine **6a** by the action of the following dehydrating reagents on compound **4a** (Scheme 3, Table 2): $POCl_3$, $SOCl_2$, polyphosphoric acid (PPA), Ac_2O in the presence of H_2SO_4. Heating compound **4a** with $POCl_3$, $SOCl_2$, or Ac_2O

Scheme 3

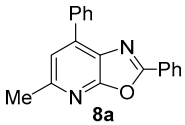


a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-ClC_6H_4,
d Ar = 4-FC_6H_4, **e** Ar = 4-$O_2NC_6H_4$

Table 2. Yields of oxazolo[5,4-*b*]pyridine **7a** by the action of dehydrating reagents on compound **4a**

Reagent	Temperature, °C	Time, h	Yield, %
$POCl_3$	25	24	0
$POCl_3$	110	1.5	40
$SOCl_2$	25	24	0
$SOCl_2$	75	3	34
Ac_2O, H_2SO_4	140	17	10
PPA	150	10	0

Table 3. The data of absorption and fluorescence spectra of compounds **7a–e** and **8a**

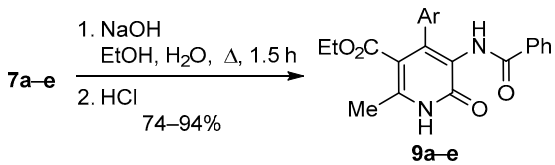
Compound	UV spectrum		Photoluminescence			
	$^{max}\lambda_{abs}$, nm	ε, 10^3 $M^{-1}\cdot cm^{-1}$	λ_{ex}, nm	$^{max}\lambda_{em}$, nm	Stokes shift, eV; nm	Quantum yield, Φ_f
7a	256, 313	31.0 ± 0.5 (λ 313 nm)	290, 310	366	0.57; 53	0.16 ± 0.00
7b	266, 314	31.9 ± 0.6 (λ 314 nm)	310, 315	412	0.94; 98	0.19 ± 0.01
7c	258, 315	31.0 ± 0.8 (λ 315 nm)	310, 315	371	0.59; 56	0.19 ± 0.01
7d	258, 314	30.5 ± 0.9 (λ 314 nm)	310, 315	366	0.56; 52	0.14 ± 0.01
7e	279, 323	25.7 ± 0.3 (λ 323 nm)	315	–	–	0.00 ± 0.00
 **8a**	259, 319	27.5 ± 0.7 (λ 319 nm)	310; 320	364	0.48; 45	0.82 ± 0.03

in H_2SO_4 as a result of oxidation of intermediate **6a** with atmospheric oxygen gave oxazolo[5,4-*b*]pyridine **7a**, isolated in 40, 34, and 10% yields (Scheme 3, Table 2). The yields of oxazolo[5,4-*b*]pyridines **7a–e** obtained by heating compounds **4a–e** with $POCl_3$ were 23–47%.

Comparison of the electronic spectrum of compound **7a** with the previously reported[34] spectrum of oxazolo[5,4-*b*]-pyridine **8a**, which does not contain an ethoxycarbonyl group at the C-5 position of the heterocycle, showed that they differ little from each other (Table 3, Fig. 2). The introduction of an acceptor substituent into the pyridine ring results in a hypsochromic shift of both absorption and luminescence bands by 15–35 nm and a decrease in the luminescence quantum yield from 0.82 to 0.16. The absorption spectra of oxazolo[5,4-*b*]pyridines **7a–e** have two maxima centered at 256–279 and 313–323 nm. Compound **7e**, containing a nitro group, does not luminesce, whereas compounds **7a**,**c**,**d** contain an intense band at 366–371 nm in the luminescence spectrum. The introduction of electron-donating methoxy group into the aryl substituent (compound **7b**) results in a significant bathochromic shift. The center of the emission band in the spectrum of compound **7b** is shifted by 46 nm compared with the spectrum of 5-methyl-2,7-diphenyloxazolo[5,4-*b*]-pyridine-6-carboxylic acid ethyl ester (**7a**), while the Stokes shift increases from 0.57 (compound **7a**) to 0.94 eV (compound **7b**). The luminescence quantum yields of compounds **7a–d** are 0.14–0.19.

Upon heating with an aqueous ethanol solution of NaOH for 1.5 h, opening of the oxazole ring of oxazolo[5,4-*b*]-pyridines **7a–e** takes place leading to amides **9a–e** in 74–94% yields (Scheme 4).

Scheme 4



a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-FC_6H_4, **e** Ar = 4-$O_2NC_6H_4$

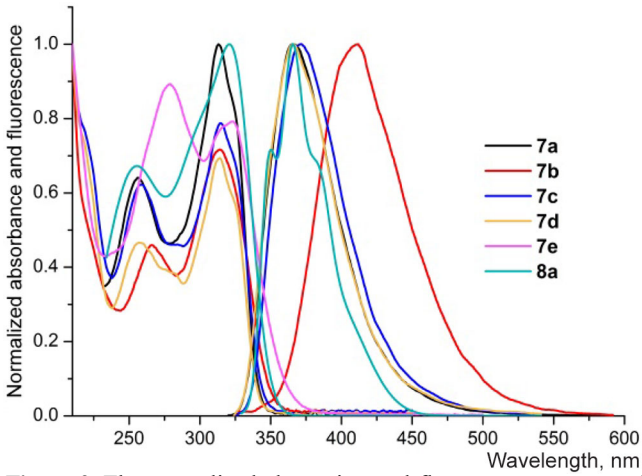


Figure 2. The normalized absorption and fluorescence spectra of compounds **7a–e** and **8a** in EtOH.

To conclude, we developed a simple method for the preparation of 7-aryloxazolo[5,4-*b*]pyridines based on the accessible azlactones and enamines of ethyl acetoacetate. The photophysical properties of these compounds were studied and it has been shown that their hydrolysis leads to 3-aminopyridin-2(1*H*)-one derivatives in good yields.

Experimental

IR spectra were registered on a Simex FT-801 Fourier transform spectrometer in KBr pellets. Absorption spectra were recorded on a PerkinElmer Lambda 750 diode array spectrophotometer, photoluminescence spectra were recorded on a Cary Eclipse fluorescence spectrophotometer. In both cases, the test compounds were dissolved in EtOH so that the concentration of the resulting solutions was lower than 10^{-5} mol/dm^3. The molar light absorption coefficient was determined according to the described method.[35] The quantum yield was determined relative to quinine sulfate in 0.5 M H_2SO_4 (Φ_f 0.546) using the comparison method.[36] ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6, with the residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H nuclei and 77.0 ppm for ^{13}C nuclei; DMSO-d_6: 2.50 ppm for ^{1}H

nuclei and 39.5 ppm for ^{13}C nuclei) serving as internal standards. Elemental analysis was performed on a Carlo Erba EA 1106 CHN-analyzer. Melting points were determined on a Reach Devices RD-MP apparatus and are uncorrected. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silufol UV-254 plates, eluents $CHCl_3$ and $CHCl_3$–EtOAc, 10:1. Visualization of plates was done under UV light. Silica gel 60 (0.063–0.200 mm, Macherey-Nagel) was used for column chromatography.

The starting azlactones **1a–e** were obtained according to a known procedure[29] by condensation of hippuric acid with aromatic aldehydes in the presence of polyphosphoric acid. The starting enamines of acetoacetic ester **2**, **3** were obtained by the previously described methods.[37]

Synthesis of 1,4,5,6-tetrahydropyridin-6-ones 4a–f (General method). A mixture of azlactone **1a–e** (10 mmol) and enamine **2** or **3** (10 mmol) was heated at 180°C for 1.5 h. The mixture was then cooled and purified by column chromatography on silica gel, eluent $CHCl_3$–EtOAc, 10:1.

Ethyl *cis*-2-methyl-6-oxo-4-phenyl-5-[(phenylcarbonyl)-amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*cis*-4a). Yield 2190 mg (58%), colorless crystals, mp 205–206°C (EtOH) (mp 200–201°C (PhH)[24]). IR spectrum, ν, cm^{-1}: 3397, 3337, 3165, 3031, 2992, 2979, 2953, 2904, 1701, 1645, 1634, 1602, 1580, 1528, 1490, 1454, 1401, 1295, 1255, 1226, 1193, 1171, 1082, 941, 734, 716, 697, 647. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.46 (3H, s, 2-CH_3); 3.99–4.12 (2H, m, $C\underline{H}_2CH_3$); 4.71 (1H, d, *J* = 7.8, 4-CH); 5.21 (1H, dd, *J* = 7.8, *J* = 6.7, 5-CH); 6.46 (1H, d, *J* = 6.7, 5-N<u>H</u>COPh); 7.08–7.11 (2H, m, H Ph); 7.23–7.25 (3H, m, H Ph); 7.36–7.40 (2H, m, H Ph); 7.46–7.50 (1H, m, H Ph); 7.62–7.64 (2H, m, H Ph); 7.99 (1H, s, 1-NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0; 18.8; 42.3; 53.4; 60.4; 108.9; 127.0; 127.7; 128.3; 128.6; 128.7; 131.8; 133.9; 136.8; 145.2; 166.2; 167.4; 169.2. Found, %: C 69.96; H 6.03; N 7.46. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.83; H 5.86; N 7.40.

Ethyl *cis*-4-(4-methoxyphenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*cis*-4b). Yield 2160 mg (53%), beige crystals, mp 161–162°C (*i*-PrOH) (mp 212–214°C (PhH)[24]). IR spectrum, ν, cm^{-1}: 3397, 3232, 3156, 3067, 2982, 2955, 2938, 2906, 2838, 1701, 1637, 1612, 1581, 1529, 1512, 1489, 1465, 1445, 1399, 1385, 1374, 1288, 1249, 1206, 1177, 1091, 1030, 831, 765, 712, 693, 647. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.14 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.45 (3H, s, 2-CH_3); 3.74 (3H, s, OCH_3); 3.99–4.13 (2H, m, $C\underline{H}_2CH_3$); 4.65 (1H, d, *J* = 7.8, 4-CH); 5.17 (1H, dd, *J* = 7.8, *J* = 6.7, 5-CH); 6.46 (1H, d, *J* = 6.7, 5-N<u>H</u>COPh); 6.75–6.79 (2H, m, H-3,5 Ar); 7.00–7.03 (2H, m, H-2,6 Ar); 7.37–7.41 (2H, m, H Ph); 7.46–7.50 (1H, m, H Ph); 7.64–7.67 (2H, m, H Ph); 7.98 (1H, br. s, 1-NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0; 18.8; 41.5; 53.6; 55.2; 60.3; 109.2; 114.0; 127.0; 128.6 (2C); 129.3; 131.8; 133.9; 144.9; 159.1; 166.3; 167.4; 169.3. Found, %: C 67.50; H 5.98; N 6.92. $C_{23}H_{24}N_2O_5$. Calculated, %: C 67.63; H 5.92; N 6.86.

Ethyl *cis*-4-(4-chlorophenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*cis*-4c). Yield 3060 mg (74%), colorless crystals, mp 197–198°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3416, 3235, 3133, 2985, 2962, 2902, 1702, 1660, 1635, 1580, 1517, 1487, 1394, 1298, 1270, 1228, 1184, 1103, 1085, 1014, 832, 790, 717, 668. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.47 (3H, s, 2-CH_3); 4.01–4.12 (2H, m, $C\underline{H}_2CH_3$); 4.73 (1H, d, *J* = 7.8, 4-CH); 5.15 (1H, dd, *J* = 7.8, *J* = 6.0, 5-CH); 6.56 (1H, d, *J* = 6.0, 5-N<u>H</u>COPh); 7.00–7.03 (2H, m, H-2,6 Ar); 7.18–7.22 (2H, m, H-3,5 Ar); 7.38–7.43 (2H, m, H Ph); 7.48–7.52 (1H, m, H Ph); 7.64–7.67 (2H, m, H Ph); 8.04 (1H, br. s, 1-NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0; 18.8; 41.5; 53.4; 60.5; 108.6; 127.0; 128.7; 128.8; 129.6; 132.0; 133.5; 133.6; 135.3; 145.4; 166.0; 167.5; 169.0. Found, %: C 63.81; H 5.18; N 6.74. $C_{22}H_{21}ClN_2O_4$. Calculated, %: C 64.00; H 5.13; N 6.79.

Ethyl *cis*-4-(4-fluorophenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*cis*-4d). Yield 2530 mg (64%), colorless crystals, mp 180–181°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3408, 3246, 3135, 2979, 2874, 1707, 1634, 1604, 1581, 1510, 1486, 1387, 1299, 1230, 1160, 1097, 1083, 941, 837, 786, 718, 694. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.47 (3H, s, 2-CH_3); 4.02–4.10 (2H, m, $C\underline{H}_2CH_3$); 4.74 (1H, d, *J* = 7.8, 4-CH); 5.15 (1H, dd, *J* = 7.8, *J* = 6.0, 5-CH); 6.53 (1H, d, *J* = 6.0, 5-N<u>H</u>COPh); 6.89–6.95 (2H, m, H-3,5 Ar); 7.03–7.08 (2H, m, H-2,6 Ar); 7.38–7.42 (2H, m, H Ph); 7.48–7.52 (1H, m, H Ph); 7.63–7.66 (2H, m, H Ph); 8.16 (1H, br. s, 1-NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 14.0; 18.8; 41.4; 53.5; 60.4; 108.9; 115.5 (d, *J* = 21.7); 127.0; 128.6; 129.8 (d, *J* = 7.8); 131.9; 132.5 (d, *J* = 3.5); 133.7; 145.2; 162.3 (d, *J* = 246.2); 166.1; 167.5; 169.1. Found, %: C 66.86; H 5.47; N 7.15. $C_{22}H_{21}FN_2O_4$. Calculated, %: C 66.66; H 5.34; N 7.07.

Ethyl *trans*-4-(4-fluorophenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*trans*-4d). Yield 870 mg (22%), colorless crystals, mp 183–184°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3240, 3160, 3069, 2979, 2962, 2931, 1709, 1644, 1604, 1580, 1537, 1511, 1492, 1366, 1275, 1226, 1192, 1124, 1097, 1016, 833, 693. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.88 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.30 (3H, s, 2-CH_3); 3.80–3.91 (2H, m, $C\underline{H}_2CH_3$); 4.19 (1H, d, *J* = 6.7, 4-CH); 4.59 (1H, dd, *J* = 8.0, *J* = 6.7, 5-CH); 7.10–7.14 (2H, m, H-3,5 Ar); 7.21–7.25 (2H, m, H-2,6 Ar); 7.43–7.54 (3H, m, H Ph); 7.79 (2H, d, *J* = 7.4, H Ph); 8.91 (1H, d, *J* = 8.0, 5-N<u>H</u>COPh); 10.15 (1H, s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.7; 17.9; 44.8; 55.1; 59.3; 104.3; 115.2 (d, *J* = 21.7); 127.5; 128.2; 129.0 (d, *J* = 7.8); 131.4; 133.9; 137.1 (d, *J* = 2.6); 146.2; 161.0 (d, *J* = 242.7); 166.5 (2C); 167.1. Found, %: C 66.87; H 5.46; N 7.15. $C_{22}H_{21}FN_2O_4$. Calculated, %: C 66.66; H 5.34; N 7.07.

Ethyl *cis*-2-methyl-4-(4-nitrophenyl)-6-oxo-5-[(phenyl-carbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*cis*-4e). Yield 3340 mg (79%), light-yellow crystals, mp 201–202°C (*i*-PrOH) (mp 201–202°C (PhH)[24]). IR spectrum, ν, cm^{-1}: 3399, 3238, 3126, 2977, 2869, 1707, 1634, 1603, 1581, 1521, 1486, 1446, 1388, 1349, 1298,

1233, 1212, 1169, 1084, 939, 855, 789, 719, 694. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.12 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.51 (3H, s, 2-CH_3); 4.00–4.13 (2H, m, $C\underline{H}_2CH_3$); 4.95 (1H, d, *J* = 8.0, 4-CH); 5.16 (1H, dd, *J* = 8.0, *J* = 5.3, 5-CH); 6.64 (1H, d, *J* = 5.3, 5-N<u>H</u>COPh); 7.24–7.27 (2H, m, H-2,6 Ar); 7.39–7.42 (2H, m, H Ph); 7.49–7.53 (1H, m, H Ph); 7.63–7.65 (2H, m, H Ph); 8.02 (1H, s, 1-NH); 8.06–8.10 (2H, m, H-3,5 Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0; 18.9; 41.9; 53.4; 60.7; 108.0; 123.8; 127.0; 128.8; 129.2; 132.2; 133.2; 144.8; 145.8; 147.5; 165.8; 167.6; 168.4. Found, %: C 62.80; H 5.12; N 9.97. $C_{22}H_{21}N_3O_6$. Calculated, %: C 62.41; H 5.00; N 9.92.

Ethyl *trans*-2-methyl-4-(4-nitrophenyl)-6-oxo-5-[(phenylcarbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*trans*-4e). Yield 677 mg (16%), light-yellow crystals, mp 157–158°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3243, 3163, 3075, 2979, 1711, 1645, 1603, 1581, 1519, 1490, 1349, 1267, 1195, 1103, 1080, 1014, 841, 701. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.82 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.31 (3H, s, 2-CH_3); 3.79–3.85 (2H, m, $C\underline{H}_2CH_3$); 4.35 (1H, d, *J* = 6.7, 4-CH); 4.65 (1H, dd, *J* = 7.1, *J* = 6.7, 5-CH); 7.43–7.57 (5H, m, H Ph); 7.72–7.83 (2H, m, H-2,6 Ar); 8.11–8.22 (2H, m, H-3,5 Ar); 8.93 (1H, d, *J* = 7.1, 5-N<u>H</u>COPh); 10.24 (1H, s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.6; 17.9; 45.6; 54.6; 59.4; 103.5; 123.7; 127.4; 128.3; 128.6; 131.5; 133.7; 146.4; 146.9; 149.7; 166.2; 166.5; 166.8. Found, %: C 62.82; H 5.10; N 9.98. $C_{22}H_{21}N_3O_6$. Calculated, %: C 62.41; H 5.00; N 9.92.

Ethyl *cis*-1,2-dimethyl-6-oxo-4-phenyl-5-[(phenylcarbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*cis*-4f). Yield 1840 mg (47%), beige crystals, mp 127–128°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3389, 3070, 3034, 2979, 2931, 2849, 1687, 1651, 1627, 1601, 1579, 1521, 1486, 1383, 1318, 1291, 1259, 1240, 1193, 1177, 1115, 1089, 1037, 919, 843, 803, 788, 765, 714, 589. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.13 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.62 (3H, s, 2-CH_3); 3.31 (3H, s, 1-NCH_3); 4.01–4.15 (2H, m, $C\underline{H}_2CH_3$); 4.73 (1H, d, *J* = 7.4, 4-CH); 5.07 (1H, dd, *J* = 7.4, *J* = 5.7, 5-CH); 6.67 (1H, d, *J* = 5.7, 5-N<u>H</u>COPh); 6.94–6.99 (2H, m, H Ph); 7.20–7.24 (3H, m, H Ph); 7.36–7.41 (2H, m, H Ph); 7.46–7.51 (1H, m, H Ph); 7.65–7.68 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0; 16.9; 30.0; 41.2; 53.6; 60.5; 112.2; 127.0; 127.6; 128.2; 128.5; 128.6; 131.7; 134.1; 136.0; 148.4; 166.5; 167.2; 168.4. Found, %: C 70.76; H 5.97; N 6.69. $C_{23}H_{24}N_2O_4$. Calculated, %: C 70.39; H 6.16; N 7.14.

Ethyl *trans*-1,2-dimethyl-6-oxo-4-phenyl-5-[(phenylcarbonyl)amino]-1,4,5,6-tetrahydropyridine-3-carboxylate (*trans*-4f). Yield 706 mg (18%), beige crystals, mp 187–188°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3311, 3061, 3035, 2962, 2920, 2850, 1695, 1637, 1602, 1578, 1547, 1491, 1455, 1365, 1332, 1288, 1273, 1203, 1177, 1123, 1105, 1093, 1075, 1053, 1006, 904, 860, 799, 754, 719, 701, 693, 692, 586. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.43 (3H, d, *J* = 1.6, 2-CH_3); 3.18 (3H, s, 1-NCH_3); 3.79–3.89 (2H, m, $C\underline{H}_2CH_3$); 4.19 (1H, dd, *J* = 7.6, *J* = 1.6, 4-CH); 4.96 (1H, dd, *J* = 8.4, *J* = 7.6, 5-CH); 6.38 (1H, d, *J* = 8.4, 5-N<u>H</u>COPh); 7.10–7.22 (5H, m, H Ph); 7.28–7.32 (2H, m, H Ph); 7.37–7.42 (1H, m, H Ph); 7.55–7.59 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.7; 16.7; 29.9; 45.6; 54.8; 60.5; 110.6; 127.1; 127.4; 127.5; 128.5; 128.7; 131.7; 134.0; 138.5; 145.9; 167.3 (3C). Found, %: C 70.75; H 5.99; N 6.73. $C_{23}H_{24}N_2O_4$. Calculated, %: C 70.39; H 6.16; N 7.14.

Synthesis of oxazolo[5,4-*b*]pyridines 7a–e (General method). A mixture of 1,4,5,6-tetrahydropyridin-6-one **4a–e** (1 mmol) and $POCl_3$ (3 ml) was heated under reflux for 1.5 h. The reaction mixture was evaporated to dryness, diluted with cold H_2O (10 ml) and triturated to a homogeneous powder, which was filtered and washed with H_2O (3×5 ml). The product was purified by column chromatography on silica gel (eluent $CHCl_3$) and recrystallized from *i*-PrOH.

Ethyl 5-methyl-2,7-diphenyloxazolo[5,4-*b*]pyridine-6-carboxylate (7a). Yield 143 mg (40%), colorless crystals, mp 145–146°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3062, 3056, 3034, 2980, 2941, 2929, 2904, 1720, 1623, 1602, 1595, 1573, 1549, 1495, 1480, 1451, 1419, 1380, 1371, 1361, 1352, 1316, 1270, 1253, 1199, 1184, 1176, 1158, 1079, 1048, 1021, 950, 911, 825, 787, 780, 763, 723, 708, 690, 669, 651. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.01 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.73 (3H, s, 5-CH_3); 4.14 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.45–7.55 (6H, m, H Ph); 7.62–7.65 (2H, m, H Ph); 8.23–8.26 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.6; 23.0; 61.6; 126.4 (2C); 127.9; 128.4; 128.9; 129.1; 129.3; 130.1; 132.1; 133.8; 140.6; 152.1; 159.4; 163.2; 168.5. Found, %: C 73.95; H 4.87; N 7.38. $C_{22}H_{18}N_2O_3$. Calculated, %: C 73.73; H 5.06; N 7.82.

Ethyl 5-methyl-7-(4-methoxyphenyl)-2-phenyloxazolo-[5,4-*b*]pyridine-6-carboxylate (7b). Yield 89 mg (23%), beige crystals, mp 155–156°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3068, 3050, 3013, 2985, 2956, 2933, 2903, 2837, 1720, 1622, 1612, 1603, 1546, 1518, 1484, 1464, 1451, 1443, 1381, 1371, 1362, 1353, 1320, 1294, 1274, 1260, 1252, 1203, 1184, 1161, 1082, 1051, 1031, 1021, 914, 835, 782, 714, 708, 692. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.10 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.71 (3H, s, 5-CH_3); 3.87 (3H, s, OCH_3); 4.20 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.01–7.05 (2H, m, H-3,5 Ar); 7.47–7.56 (3H, m, H Ph); 7.61–7.64 (2H, m, H-2,6 Ar); 8.23–8.26 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.8; 22.9; 55.3; 61.7; 114.0; 126.0; 126.2; 126.5; 127.9; 128.9; 130.0; 130.9; 132.1; 140.2; 152.0; 159.3; 160.5; 162.9; 168.8. Found, %: C 70.98; H 5.23; N 7.25. $C_{23}H_{20}N_2O_4$. Calculated, %: C 71.12; H 5.19; N 7.21.

Ethyl 7-(4-chlorophenyl)-5-methyl-2-phenyloxazolo-[5,4-*b*]pyridine-6-carboxylate (7c). Yield 185 mg (47%), light-beige crystals, mp 148–149°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3070, 3034, 2986, 2937, 2901, 2871, 1721, 1621, 1603, 1543, 1498, 1484, 1474, 1452, 1423, 1382, 1372, 1362, 1353, 1320, 1276, 1257, 1202, 1183, 1157, 1091, 1081, 1073, 1053, 1021, 1010, 956, 939, 328, 915, 872, 831, 783, 734, 712, 692. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.09 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.72 (3H, s, 5-CH_3); 4.18 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.47–7.60 (7H, m, H Ph, H Ar); 8.22–8.24 (2H, m, H Ph). ^{13}C NMR spectrum

($CDCl_3$), δ, ppm: 13.7; 23.0; 61.8; 126.2; 126.3; 127.9; 128.8; 129.0; 130.0; 130.7; 132.2; 132.3; 135.5; 139.1; 152.3; 159.4; 163.4; 168.3. Found, %: C 67.06; H 4.18; N 7.15. $C_{22}H_{17}ClN_2O_3$. Calculated, %: C 67.26; H 4.36; N 7.13.

Ethyl 7-(4-fluorophenyl)-5-methyl-2-phenyloxazolo-[5,4-*b*]pyridine-6-carboxylate (7d). Yield 173 mg (46%), beige crystals, mp 143–144°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3074, 2984, 2939, 2903, 1720, 1620, 1608, 1544, 1517, 1483, 1452, 1361, 1317, 1273, 1256, 1239, 1198, 1179, 1163, 1079, 1069, 1053, 1023, 950, 916, 877, 836, 803, 781, 735, 709, 691, 574. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.72 (3H, s, 5-CH_3); 4.17 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.17–7.23 (2H, m, H-3,5 Ar); 7.47–7.56 (3H, m, H Ph); 7.62–7.65 (2H, m, H-2,6 Ar); 8.22–8.24 (2H, m, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 13.7; 23.0; 61.7; 115.6 (d, *J* = 22.5); 126.3 (2C); 127.9; 128.9; 129.8 (d, *J* = 8.7); 130.0; 131.4 (d, *J* = 8.7); 132.2; 139.3; 152.2; 159.4; 163.3 (d, *J* = 249.7); 163.3; 168.4. Found, %: C 70.56; H 4.39; N 7.38. $C_{22}H_{17}FN_2O_3$. Calculated, %: C 70.20; H 4.55; N 7.44.

Ethyl 5-methyl-7-(4-nitrophenyl)-2-phenyloxazolo-[5,4-*b*]pyridine-6-carboxylate (7e). Yield 161 mg (40%), colorless crystals, mp 192–193°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3110, 3074, 3035, 2988, 2969, 2944, 2904, 2856, 1721, 1622, 1595, 1581, 1543, 1516, 1483, 1452, 1351, 1320, 1275, 1256, 1205, 1182, 1157, 1108, 1081, 1053, 1021, 1009, 945, 928, 916, 865, 859, 844, 782, 753, 723, 711, 692. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.75 (3H, s, 5-CH_3); 4.18 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.49–7.53 (2H, m, H Ph); 7.55–7.59 (1H, m, H Ph); 7.79–7.82 (2H, m, H-2,6 Ar); 8.22–8.24 (2H, m, H Ph); 8.35–8.39 (2H, m, H-3,5 Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.8; 23.1; 62.0; 123.6; 125.9; 126.0; 128.0; 129.0; 130.0; 130.5; 132.6; 137.7; 140.4; 148.1; 152.7; 159.5; 164.0; 167.8. Found, %: C 65.30; H 4.16; N 10.53. $C_{22}H_{17}N_3O_5$. Calculated, %: C 65.50; H 4.25; N 10.42.

Synthesis of ethyl 4-aryl-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,6-dihydropyridine-3-carboxylates 9a–e (General method). A solution of NaOH (120 mg, 3 mmol) in H_2O (0.8 ml) was added to a suspension of oxazolo[5,4-*b*]-pyridine **7a–e** (1 mmol) in EtOH (7 ml). The mixture was heated under reflux for 1.5 h, then concentrated *in vacuo* to 1/3 of its original volume. The residue was poured into H_2O (15 ml) and acidified with 10% aqueous HCl to pH ~3. The precipitate that formed was filtered, washed with H_2O, and recrystallized.

Ethyl 2-methyl-6-oxo-4-phenyl-5-[(phenylcarbonyl)-amino]-1,6-dihydropyridine-3-carboxylate (9a). Yield 316 mg (84%), colorless crystals, mp >250°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3287, 3121, 3051, 2984, 1721, 1674, 1642, 1615, 1517, 1488, 1398, 1287, 1201, 1157, 1089, 1027, 913, 898, 766, 705, 633. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.76 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.33 (3H, s, 2-CH_3); 3.79 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.18–7.21 (2H, m, H Ph); 7.23–7.31 (3H, m, H Ph); 7.35–7.39 (2H, m, H Ph); 7.44–7.48 (1H, m, H Ph); 7.64–7.67 (2H, m, H Ph); 9.08 (1H, br. s, 5-N$\underline{H}$COPh); 11.95 (1H, br. s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 12.9; 16.9; 60.2; 111.4; 123.0; 127.1; 127.3 (2C); 127.4; 127.8; 130.9; 134.1; 136.2; 144.4; 148.7; 159.7; 165.9; 166.0. Found, %: C 70.60; H 5.34; N 7.26. $C_{22}H_{20}N_2O_4$. Calculated, %: C 70.20; H 5.36; N 7.44.

Ethyl 4-(4-methoxyphenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,6-dihydropyridine-3-carboxylate (9b). Yield 300 mg (74%), beige crystals, mp >250°C (PhMe). IR spectrum, ν, cm^{-1}: 3249, 3132, 3054, 2981, 2932, 2907, 2837, 2781, 1720, 1671, 1644, 1611, 1580, 1553, 1514, 1486, 1466, 1444, 1396, 1366, 1291, 1249, 1199, 1178, 1157, 1110, 1088, 1028, 906, 872, 834, 781, 711, 692, 661, 634, 583. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.77 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.30 (3H, s, 2-CH_3); 3.68 (3H, s, OCH_3); 3.82 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 6.87 (2H, d, *J* = 8.8, H-3,5 Ar); 7.12 (2H, d, *J* = 8.8, H-2,6 Ar); 7.38–7.44 (2H, m, H Ph); 7.46–7.52 (1H, m, H Ph); 7.73 (2H, d, *J* = 7.4, H Ph); 9.32 (1H, br. s, 5-N$\underline{H}$COPh); 12.21 (1H, br. s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.3; 17.2; 55.1; 60.5; 111.7; 113.2; 123.2; 127.4; 128.2; 128.5; 128.7; 131.3; 134.1; 144.4; 148.6; 158.9; 160.1; 166.1; 166.3. Found, %: C 67.78; H 5.33; N 6.72. $C_{23}H_{22}N_2O_5$. Calculated, %: C 67.97; H 5.46; N 6.89.

Ethyl 4-(4-chlorophenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,6-dihydropyridine-3-carboxylate (9c). Yield 366 mg (89%), light-beige crystals, mp >250°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3288, 3127, 3056, 2981, 2928, 2869, 2788, 1722, 1674, 1642, 1606, 1582, 1571, 1556, 1517, 1487, 1445, 1393, 1366, 1286, 1247, 1200, 1188, 1157, 1087, 1027, 1015, 904, 871, 832, 822, 787, 707, 691, 662, 632. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.75 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.34 (3H, s, 2-CH_3); 3.81 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.18 (2H, d, *J* = 8.4, H-2,6 Ar); 7.38–7.43 (4H, m, H Ph, H-3,5 Ar); 7.50 (1H, t, *J* = 7.3, H Ph); 7.70 (2H, d, *J* = 7.4, H Ph); 9.37 (1H, br. s, 5-N$\underline{H}$COPh); 12.34 (1H, br. s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.2; 17.4; 60.5; 110.7; 123.4; 127.4; 127.8; 128.2; 129.2; 131.4; 132.5; 133.9; 135.3; 145.5; 147.7; 159.9; 165.9; 166.0. Found, %: C 64.13; H 4.75; N 6.90. $C_{22}H_{19}ClN_2O_4$. Calculated, %: C 64.32; H 4.66; N 6.82.

Ethyl 4-(4-fluorophenyl)-2-methyl-6-oxo-5-[(phenyl-carbonyl)amino]-1,6-dihydropyridine-3-carboxylate (9d). Yield 315 mg (80%), beige crystals, mp >250°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3280, 3127, 3057, 2982, 2932, 2870, 2789, 1721, 1674, 1643, 1611, 1595, 1582, 1556, 1512, 1486, 1446, 1410, 1396, 1367, 1288, 1229, 1200, 1155, 1115, 1088, 1027, 1015, 903, 837, 800, 787, 710, 663, 635. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.76 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 2.33 (3H, s, 2-CH_3); 3.81 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 7.14–7.22 (4H, m, H Ar); 7.35–7.45 (2H, m, H Ph); 7.46–7.54 (1H, m, H Ph); 7.69 (2H, d, *J* = 7.4, H Ph); 9.36 (1H, br. s, 5-N$\underline{H}$COPh); 12.31 (1H, br. s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 13.3; 17.3; 60.5; 111.1; 114.6 (d, *J* = 21.7); 123.4; 127.4; 128.2; 129.5 (d, *J* = 7.8); 131.4; 132.8 (d, *J* = 3.5); 134.0; 145.2; 148.0; 160.0; 161.7 (d, *J* = 244.5); 166.0 (2C). Found, %: C 67.10; H 4.76; N 7.04. $C_{22}H_{19}FN_2O_4$. Calculated, %: C 67.00; H 4.86; N 7.10.

Ethyl 2-methyl-4-(4-nitrophenyl)-6-oxo-5-[(phenylcarbonyl)amino]-1,6-dihydropyridine-3-carboxylate (9e). Yield 396 mg (94%), colorless crystals, mp 229–230°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3280, 3119, 2982, 2940, 2893, 2842, 2763, 2661, 1721, 1665, 1634, 1595, 1515, 1476, 1446, 1385, 1346, 1292, 1285, 1263, 1214, 1171, 1114, 1089, 1032, 965, 841, 782, 735, 689. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.68 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.27 (3H, s, 2-CH_3); 3.75 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.20–7.29 (4H, m, H Ph, H-2,6 Ar); 7.33 (2H, t, *J* = 7.4, H Ph); 7.38–7.45 (1H, m, H Ph); 8.20 (2H, d, *J* = 8.6, H-3,5 Ar); 9.44 (1H, br. s, 5-N<u>H</u>COPh); 12.00 (1H, br. s, 1-NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.2; 13.8; 60.3; 109.7; 122.9; 126.9; 128.2; 129.5; 130.4; 132.2; 133.5; 134.0; 141.1; 144.8; 146.4; 157.0; 160.2; 165.8. Found, %: C 62.51; H 4.58; N 10.05. $C_{22}H_{19}N_3O_6$. Calculated, %: C 62.70; H 4.54; N 9.97.

X-ray structural analysis of compound 4a. Crystals suitable for X-ray structural analysis were obtained by slow evaporation of a solution of compound **4a** in benzene at room temperature. The set of reflections was obtained on an Xcalibur Ruby (Agilent technologies, UK) diffractometer with a CCD detector according to the standard routine (MoKα radiation, 295(2)K, ω-scanning with a step of 1°). Absorption was corrected empirically using the SCALE3 ABSPACK algorithm.[38] The structure was solved using the SHELXS[39] program and refined using the SHELXL[40] program with the OLEX2 graphical interface.[41] The positions of the H atoms was refined using the rider model. The positions of the H atoms of the NH groups were refined independently in the isotropic approximation. The crystals of compound **4a** ($C_{22}H_{22}N_2O_4$, *M* 378.41) are monoclinic, spatial symmetry group $P2_1/c$; *a* 10.433(3), *b* 9.748(2), *c* 20.107(6) Å; β 99.60(3)°; *V* 2016.1(10) $Å^3$; *Z* 4; d_{calc} 1.247 g/cm^3; μ 0.086 mm^{-1}. The final refinement parameters: R_1 0.0660 (for 2716 reflections with $I > 2\sigma(I)$), wR_2 0.2089 (for all 4801 independent reflections, R_{int} 0.0417), *S* 1.021. The X-ray structural analysis data was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2096420).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all new compounds is available at the journal website at http://link.springer.com/journal/10593.

The study was carried out with the financial support of the Russian Foundation for Basic Research within the framework of scientific project No. 19-33-90229.

References

1. (a) Sośnicki, J. G.; Idzik, T. J. *Synthesis* **2019**, 3369. (b) Przhevalskii, N. M.; Laypanov, R. K.; Tokmakov, G. P.; Lukina, I. V.; Vershinkin, D. A.; Tafeenko, V. A. *Russ. Chem. Bull., Int. Ed.* **2021**, *70*, 555. [*Izv. Akad. Nauk, Ser. Khim.* **2021**, 555.]
2. Fearon, D.; Westwood, I. M.; van Montfort, R. L. M.; Bayliss, R.; Jones, K.; Bavetsias, V. *Bioorg. Med. Chem.* **2018**, *26*, 3021.
3. Lim, N.-K.; Zhang, H.; Sowell, C. G.; Gosselin, F. *Tetrahedron Lett.* **2020**, *61*, 152447.
4. Crawford, J. J.; Lee, W.; Johnson, A. R.; Delatorre, K. J.; Chen, J.; Eigenbrot, C.; Heidmann, J.; Kakiuchi-Kiyota, S.; Katewa, A.; Kiefer, J. R.; Liu, L.; Lubach, J. W.; Misner, D.; Purkey, H.; Reif, K.; Vogt, J.; Wong, H.; Yu, C.; Young, W. B. *ACS Med. Chem. Lett.* **2020**, *11*, 1588.
5. Semple, G.; Ashworth, D. M.; Baker, G. R.; Batt, A. R.; Baxter, A. J.; Benzies, D. W.; Elliot, L. H.; Evans, D. M.; Franklin, R. J.; Hudson, P.; Jenkins, P. D.; Pitt, G. R.; Rooker, D. P.; Sheppard, A.; Szelke, M.; Yamamoto, S.; Isomura, Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1337.
6. Bernstein, P. R.; Andisik, D.; Bradley, P. K.; Bryant, C. B.; Ceccarelli, C.; Damewood, J. R., Jr.; Earley, R.; Edwards, P. D.; Feeney, S.; Gomes, B. C.; Kosmider, B. J.; Steelman, G. B.; Thomas, R. M.; Vacek, E. P.; Veale, C. A.; Williams, J. C.; Wolanin, D. J.; Woolson, S. A. *J. Med. Chem.* **1994**, *37*, 3313.
7. Zhang, L.; Lin, D.; Sun, X.; Curth, U.; Drosten, C.; Sauerhering, L.; Becker, S.; Rox, K.; Hilgenfeld, R. *Science* **2020**, *368*, 409.
8. Mengist, H. M.; Fan, X.; Jin, T. *Signal Transduction Targeted Ther.* **2020**, *5*, 67.
9. Kusakabe, K.-i.; Tada, Y.; Iso, Y.; Sakagami, M.; Morioka, Y.; Chomei, N.; Shinonome, S.; Kawamoto, K.; Takenaka, H.; Yasui, K.; Hamana, H.; Hanasaki, K. *Bioorg. Med. Chem.* **2013**, *21*, 2045.
10. Gado, F.; Mannelli, L. D. C.; Lucarini, E.; Bertini, S.; Cappelli, E.; Digiacomo, M.; Stevenson, L. A.; Macchia, M.; Tuccinardi, T.; Ghelardini, C.; Pertwee, R. G.; Manera C. *J. Med. Chem.* **2019**, *62*, 276.
11. Li, Y. H.; Tseng, P.-S.; Evans, K. A.; Jaworski, J.-P.; Morrow, D. M.; Fries, H. E.; Wu, C. W.; Edwards, R. M.; Jin, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6744.
12. Meesters, C.; Mönig, T.; Oeljeklaus, J.; Krahn, D.; Westfall, C. S.; Hause, B.; Jez, J. M.; Kaiser, M.; Kombrink, E. *Nat. Chem. Biol.* **2014**, *10*, 830.
13. Ward, A.; Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1983**, *26*, 468.
14. Kulakov, I. V.; Shatsauskas, A. L.; Matsukevich, M. V.; Palamarchuk, I. V.; Seilkhanov, T. M.; Gatilov, Yu. V.; Fisyuk, A. S. *Synthesis* **2017**, 3700.
15. Kulakov, I. V.; Matsukevich, M. V.; Levin, M. L.; Palamarchuk, I. V.; Seilkhanov, T. M.; Fisyuk, A. S. *Synlett* **2018**, 1741.
16. Palamarchuk, I. V.; Matsukevich, M. V.; Kulakov, I. V.; Seilkhanov, T. M.; Fisyuk, A. S. *Chem. Heterocycl. Compd.* **2019**, *55*, 788. [*Khim. Geterotsikl. Soedin.* **2019**, *55*, 788.]
17. Kulakov, I. V.; Matsukevich, M. V.; Shulgau, Z. T.; Sergazy, S.; Seilkhanov, T. M.; Puzari, A.; Fisyuk, A. S. *Chem. Heterocycl. Compd.* **2015**, *51*, 991. **[***Khim. Geterotsikl. Soedin.* **2015**, *51*, 991.]
18. Kulakov, I. V.; Palamarchuk, I. V.; Shulgau, Z. T.; Seilkhanov, T. M.; Gatilov, Yu. V.; Fisyuk, A. S. *J. Mol. Struct.* **2018**, *1166*, 262.
19. Shatsauskas, A. L.; Abramov, A. A.; Chernenko, S. A.; Kostyuchenko, A. S.; Fisyuk, A. S. *Synthesis* **2020**, 227.
20. Shatsauskas, A.; Shatalin, Yu.; Shubina, V.; Zablodtskii, Y.; Chernenko, S.; Samsonenko, A.; Kostyuchenko, A.; Fisyuk, A. *Dyes Pigm.* **2021**, *187*, 109072.
21. Fisyuk, A. S.; Kostyuchenko, A. S.; Goncharov, D. S. *Russ. J. Org. Chem.* **2020**, *56*, 1863. [*Zh. Org. Khim.* **2020**, *56*, 1649.]
22. Shatsauskas, A. L.; Abramov, A. A.; Saibulina, E. R.; Palamarchuk, I. V.; Kulakov, I. V.; Fisyuk, A. S. *Chem. Heterocycl. Compd.* **2017**, *53*, 186. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 186.]
23. Vanden Eynde, J. J.; Labuche, N.; Van Haverbeke, Y. *Synth. Commun.* **1997**, *27*, 3683.

24. Maquestiau, A.; Vanden Eynde, J.-J.; Papleux, P. *Bull. Soc. Chim. Belg.* **1985**, *94*, 849.
25. Cunha, S.; Filho, R. F. dos S.; Saraiva, K. H.; Azevedo-Santos, A. V.; Menezes, D. *Tetrahedron Lett.* **2013**, *54*, 3366.
26. Wang, S.; Sun, J.; Yu, G.; Hu, X.; Liu, J. O.; Hu, Y. *Org. Biomol. Chem.* **2004**, *2*, 1573.
27. Yonezawa, Y.; Konn, A.; Shin, C.-g. *Heterocycles* **2004**, *63*, 2735.
28. Hussenether, T.; Troschütz, R. *J. Heterocycl. Chem.* **2004**, *41*, 857.
29. Rao, Y. S. *J. Org. Chem.* **1976**, *41*, 722.
30. Wang, S.; Pan, J.; Hu, Y.; Hu, H. *Synthesis* **2005**, 753.
31. Worayuthakarn, R.; Nealmongkol, P.; Ruchirawat, S.; Thasana, N. *Tetrahedron* **2012**, *68*, 2864.
32. Liu, J.; Cremosnik, G. S.; Otte, F.; Pahl, A.; Sievers, S.; Strohmann, C.; Waldmann, H. *Angew. Chem.*, *Int. Ed.* **2021**, *60*, 4648.
33. Hamama, W. S.; Ibrahim, M. E.; Zoorob, H. H. *Arch. Pharm. Chem. Life Sci.* **2012**, *345*, 468.
34. Shatsauskas, A. L.; Mamonova, T. E.; Stasyuk, A. J.; Chernenko, S. A.; Slepukhin, P. A.; Kostyuchenko, A. S.; Fisyuk, A. S. *J. Org. Chem.* **2020**, *85*, 10072.
35. (a) Kumar, A.; Singh, S.; Mudahar, G. S.; Thind, K. S. *Radiat. Phys. Chem.* **2006**, *75*, 737. (b) Williams, A. T. R.; Winfield, S. A.; Miller, J. N. *Analyst* **1983**, *108*, 1067.
36. (a) Allen, M. W. *Measurement of Fluorescence Quantum Yields*; Thermo Fisher Scientific: Madison. Technical note: 52019. (b) Brouwer, A. M. *Pure Appl. Chem.* **2011**, *83*, 2213.
37. (a) R., C.; Pise, A.; Shah, S. K.; D., R.; V., S.; Tiwari, K. N. *Org. Lett.* **2020**, *22*, 6557. (b) Xia, B.; Chen, W.; Zhao, Q.; Yu, W.; Chang, J. *Org. Lett.* **2019**, *21*, 2583.
38. *CrysAlisPro, Version 1.171.37.33 (release 27-03-2014)*; Agilent Technologies.
39. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A*: *Found. Crystallogr.* **2008**, *A64*, 112.
40. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. C*: *Struct. Chem.* **2015**, *C71*, 3.
41. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.