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Efficient Synthesis of 4-Phenyl-4*H*-pyran Derivatives *via* a DIPEA-catalyzed One-Pot Three-Component Reaction

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Abstract—A novel one-pot approach has been developed for a high-yield synthesis of 4-phenyl-4*H*-pyran derivatives by the three-component condensation of dimethyl 3-oxopentanedioate or 3-oxo-3-arylpropanoic acid esters, aldehydes, with malononitrile in the presence of a DIPEA catalyst in ethanol at room temperature. The significant features of the present strategy include efficiency, high yield, inexpensive catalyst, mild reaction conditions, and simple purification procedure.

Keywords: 4*H*-pyran, multicomponent reactions, synthetic methods

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Multicomponent reactions (MCRs) have been widely used in organic synthesis for the generation of complex products. They provide an efficient and a powerful tool for the production of a great diversity of molecules without isolation of intermediates, which features high atom-economy and excellent yields [1, 2]. A lot of heterocycles have been prepared by one-pot MCRs as the most efficient route to achieving structural diversity [3, 4].

Derivatives of 4*H*-pyran were found to possess anticancer, antiinflammatory, antimicrobial [5], anticoagulant, and antianaphylactic activity [6–8]. On the other hand, a fused pyran ring is a well-known heterocycle and an important structural unit both in natural compounds and synthetic heterocyclic molecules. Many types of bioactive molecules with broad medical and agrochemical applications contain a fused pyran ring, 4-phenylpyran among them [9]. In recent years, fused 4*H*-pyran and its derivatives have attracted high interest of researchers focusing on the development of efficient synthetic approaches and identification of novel biologically active compounds [10]. A lot of methods including various catalysts, such as Triton B [11], Mg/La mixed oxide [12], L-proline [13], Ni–Al_2O_3 [14], decaniobate ions [15], potassium phthalimide–*N*-oxyl [16], $SnCl_2$/nano SiO_2 [17], silica nanoparticles [18], and silica-bonded *N*-propyl-piperazine sodium *n*-propionate [19], have been developed. However, some of the mentioned methods suffer from at least one of the following drawbacks: low yields, expensive catalysts, and long reactions times. To the best of our knowledge, some basic catalysts, too, have been involved in MCRs [20–23], but the use of a DIPEA catalyst has never been reported.

In view of the aforesaid and preliminary results of our research on 4*H*-pyran derivatives, we designed a series of novel 4-phenyl-4*H*-pyran derivatives and set ourselves the goal was to develop a new methodology for their synthesis via one-pot condensation of 3-oxo-pentanedioates, malononitrile, and various aldehydes [24, 25], using DIPEA as a catalyst. We started with the condensation of 4-methoxybenzaldehyde (**1a**), malononitrile (**2**), and dimethyl 3-oxopentanedioate (**3**) at a molar ratio of 1 : 1 : 1 in ethanol as a solvent. To evaluate the catalytic performance of the catalyst, several basic catalysts were tested. As shown in Table 1, DIPEA proved to be an optimal catalyst (yield 71%). Further on the reaction conditions were optimized using DIPEA. Varying the solvents (ethanol, methanol, ethyl acetate, acetonitrile, DMF, and THF) showed that no other tested solvent could provide product **4a** in a yield higher than ethanol (71%; Table 2, entry 1).

The effect of the catalyst concentration was then investigated. Catalyst loadings from 0.5–3 equiv were tested (Table 3, entries 1–6). The reaction was carried out with 0.5 equiv of DIPEA in EtOH at room temperature (Table 3, entry 1), and the desired product was obtained in 66% yield. Similar reactions were per-

Table 1. Effect of the catalyst on the synthesis of 4*H*-pyran **4a** in ethanol[a]

Entry	Catalyst	Yield, %
1	Et_3N	61
2	Pyridine	55
3	Piperidine	63
4	DIPEA	71
5	CH_3COONH_4	58
6	CH_3COONa	67
7	DMAP	54
8	NaOH	21
9	*N*-Methylmorpholine	67

[a] Catalyst 1 equiv, ethanol 20 mL, reaction time 4 h.

formed using 1 and 1.5 equivs of DIPEA (Table 3, entries 2 and 3). The desired product was obtained in 71% and 73% yields, respectively. When the catalyst concentration was increased further to 2, 2.5, and 3 equivs, the yields gradually decreased (Table 3, entries 4, 5 and 6).

After the optimal solvent and catalyst had been determined, the temperature effect on the reaction was examined (Table 3, entries 3, 7, and 8). The product was obtained in a yield of 73% at room temperature, while the yields at 40 and under reflux were lower.

The obtained evidence allowed us to conclude that the reaction was the most efficient when conducted with 1.5 equiv of DIPEA in EtOH at room temperature.

With the optimal reaction conditions, we investigated the scope and limitations of the methodology with different aldehydes. Table 4 indicates that all the reactions proceeded smoothly, and the desired products were obtained in yields of 73–95%. In order to further explore the versatility of the developed protocol, a wide variety of reactions were investigated with aromatic aldehydes **5** and 3-oxo-3-arylpropanoic acid esters **6** containing electron-acceptor and electron-donor substituents, as well as halogens in different positions of the aromatic rings to obtain 4-aryl-4*H*-pyran derivatives **7** in high yields (Table 5). The resulting data suggested that the reactions can tolerate a wide variety of differently substituted aldehydes and 3-oxo-3-arylpropanoic acid esters.

All the synthesized compounds were previously unknown. and were characterized by the CHN analyses and ^1H and ^{13}C NMR and ESI–MS spectra.

Table 2. Effect of the solvent on the synthesis of 4*H*-pyran **4a** in the presence DIPEA[a]

Entry	Solvent	Yield, %
1	EtOH	71
2	MeOH	64
3	Ethyl acetate	53
4	Acetonitrile	59
5	DMF	54
6	THF	39

[a] DIPEA 1 equiv, solvent 20 mL, reaction time 4 h (2h in THF).

Table 3. Effect of the DIPEA concentration and temperature on the synthesis of 4*H*-pyran **4a** in ethanol[a]

Entry	DIPEA concentration, equiv	*T*, °C	Yield, %
1	0.5	rt	66
2	1	rt	71
3	1.5	rt	73
4	2	rt	71
5	2.5	rt	68
6	3	rt	65
7	1.5	40	63
8	1.5	Reflux	28

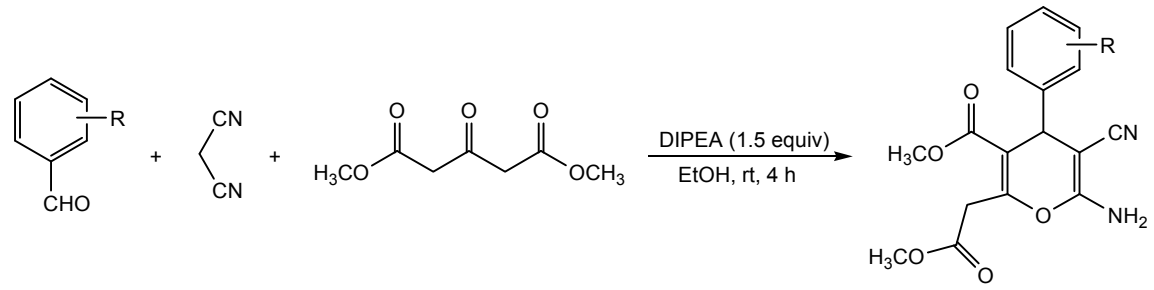
[a] Ethanol, 20 mL.

In conclusion, we have developed a simple, fast, and high-yield synthesis of 4-phenyl-4*H*-pyran derivatives **4a–4i** and **7a–7k** *via* a DIPEA-catalyzed one-pot three-component reaction of aryl aldehydes, malononitrile, and 3-oxopropanoic acid esters. The use of inexpensive starting materials, mild reaction conditions, and high yields are some notable characteristics of the developed strategy. The reaction products are easily separated by filtration and purified by recrystallization, rather than column chromatography, which facilitates the work-up procedure. The mentioned advantages make the described protocol an attraction option for the synthesis of 4-phenyl-4*H*-pyran derivatives.

EXPERIMENTAL

All reagents were obtained commercially and used without further purification unless otherwise specified.

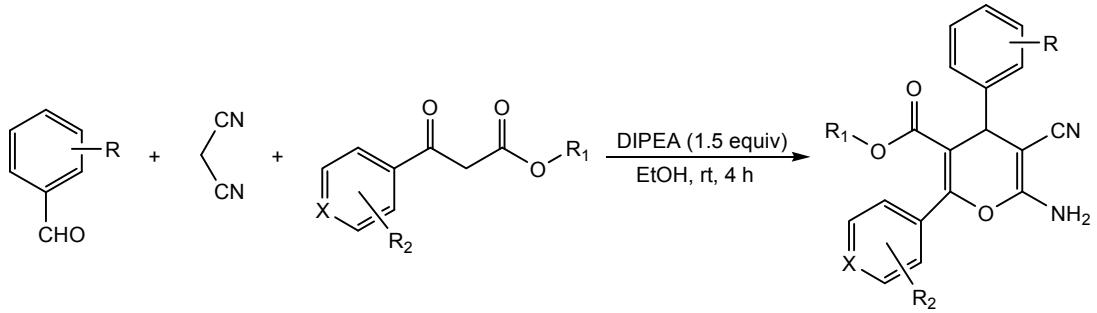
Table 4. Synthesis of 4-aryl-4*H*-pyran derivatives **4a–4i**



1a–1i **2** **3** **4a–4i**

Product no.	R	Yield, %
4a	4-OCH_3	73
4b	2,3,4-$(OCH_3)_3$	76
4c	4-CF_3	80
4d	4-Ph	84
4e	3-NO_2	95
4f	2,4-Cl_2	79
4g	2-Cl	76
4h	4-F	78
4i	4-Cl	78

Table 5. Synthesis of 4-aryl-4*H*-pyran derivatives **7a–7k**



5a–5k **2** **6a–6k** **7a–7k**

Product no.	X	R_1	R_2	R	Yield, %
7a	C	Et	4-COOEt	2-Cl	91
7b	N	CH_3	H	2,3,4-$(OCH_3)_3$	91
7c	C	Et	4-COOEt	2,4-Cl_2	85
7d	C	Et	4-COOEt	4-OCH_3	82
7e	C	CH_3	2,4-Cl_2	4-F	89
7f	C	Et	4-OCH_3	2,3,4-$(OCH_3)_3$	79
7g	C	Et	4-F	4-OCH_3	80
7h	N	CH_3	4-OCH_3	3-Br-4,5-$(OCH_3)_2$	87
7i	N	CH_3	H	3-NO_2	89
7j	N	CH_3	H	4-OCH_3	78
7k	C	Et	4-F	3-Br-4,5-$(OCH_3)_2$	81

The melting points were taken on a Beijing Taike X-4 microscopy melting point apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Biospin 600 MHz instrument in $CDCl_3$ with TMS as internal standard. All chemical shifts are reported in ppm. The IR spectra were recorded on a PerkinElmer Spectrum One FTIR spectrometer in KBr pellets. The mass spectra were measured on an Agilent 6460 QQQ LC/MS system (ESI, direct injection). The elemental analyses were obtained on a Carlo Erba 1108 analyzer.

Synthesis of 4-phenyl-4*H*-pyran derivatives 4a–4i and 7a–7k (*general procedure*). A mixture of aldehyde **1a–1i** or **5a–5k** (4 mmol), malononitrile (4 mmol), dimethyl 3-oxo-1,5-pentanedioate or methyl/ethyl 3-oxo-3-arylpropanoate (4 mmol), respectively, and DIPEA (6 mmol) in EtOH (20 mL) was stirred at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, the solid material that formed was collected by filtration and recrystallized from EtOH to obtain the desired product.

Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethyl)-4-(4-methoxyphenyl)-4*H*-pyran-3-carboxylate (4a). Yield 73%, mp 154–156°C (157–159°C [26]). IR spectrum, ν, cm^{-1}: 3415 (NH_2), 3326 (NH_2), 2187 (CN), 1757 (C=O), 1699 (C=O), 1676 (C=C_{arom}), 1641, 1603, 1439, 1415, 1362, 1329, 1275, 1167, 1120, 1068, 861 (δC–H_{arom}), 773. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.20 d (2H_{arom}, *J* 8.4 Hz), 6.87 d (2H_{arom}, *J* 8.4 Hz), 4.52 s (2H, NH_2), 4.45 s (1H, CH), 3.94 d (1H, CH_2, *J* 16.8 Hz), 3.80 s (3H, CH_3), 3.77 br.s (4H, CH_3, CH_2), 3.61 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.87 (CO), 165.83 ($CH_2\underline{C}O$), 158.82, 157.15, 152.74, 135.60, 128.54, 118.64, 114.13, 110.55, 63.02, 55.25 (OCH_3), 52.50 ($COO\underline{C}H_3$), 52.00 ($CH_2COO\underline{C}H_3$), 37.84 (CH), 37.82 (CH_2). Mass spectrum: *m*/*z* 381.2 [*M* + Na]$^+$. Found, %: C 60.38; H 5.02; N 7.85. $C_{18}H_{18}N_2O_6$. Calculated, %: C 60.33; H 5.06; N 7.82.

Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethyl)-4-(2,3,4-trimethoxyphenyl)-4*H*-pyran-3-carboxylate (4b). Yield 76%, mp 158–160°C. IR spectrum, ν, cm^{-1}: 3476 (NH_2), 3340 (NH_2), 3000, 2952, 2835, 2188(CN), 1747 (C=O), 1703 (C=O), 1682 (C=C_{arom}), 1640, 1598, 1493, 1465, 1399, 1354, 1280, 1174, 1094, 1070, 1039, 811 (δC–H_{arom}). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.90 d (2H_{arom}, *J* 8.4 Hz), 6.65 d (2H_{arom}, *J* 8.4 Hz), 4.84 s (1H, CH), 4.50 s (2H, NH_2), 3.97 s (3H, CH_3), 3.92 d (1H, CH_2, *J* 16.8 Hz), 3.88 s (3H, CH_3), 3.85 s (3H, CH_3), 3.79 br.s (4H, CH_2, CH_3), 3.59 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.94 (CO), 165.93 ($CH_2\underline{C}O$), 157.46, 153.18, 152.92, 151.41, 141.89, 129.17, 123.28, 118.87, 110.13, 107.45, 62.61 (3-OCH_3), 61.27 (2-OCH_3), 60.66, 55.91 (4-OCH_3), 52.45 ($COO\underline{C}H_3$), 51.88 ($CH_2COO\underline{C}H_3$), 37.83 (CH), 32.24 (CH_2). Mass spectrum: *m*/*z* 441.5 $[M + Na]^+$. Found, %: C 57.35; H 5.31; N 6.73. $C_{20}H_{22}N_2O_8$. Calculated, %: C 57.41; H 5.30; N 6.70.

Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethyl)-4-[4-(trifluoromethyl)phenyl]-4*H*-pyran-3-carboxylate (4c). Yield 80%, mp 156–158°C. IR spectrum, ν, cm^{-1}: 3415 (NH_2), 3326 (NH_2), 3005, 2956, 2187 (CN), 1757 (C=O), 1699 (C=O), 1676 (C=C_{arom}), 1642, 1603, 1439, 1415, 1362, 1329, 1275, 1167, 1120, 1068, 861 (δC–H_{arom}), 773 (CF_3). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.61 d (2H_{arom}, *J* 8.4 Hz), 7.42 d (2H_{arom}, *J* 8.4 Hz), 4.62 s (2H, NH_2), 4.56 s (1H, CH), 4.04 d (1H, CH_2, *J* 16.8 Hz), 3.79 s (3H, CH_3), 3.74 d (1H, CH_2, *J* 16.8 Hz), 3.61 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.69 (CO), 165.34 ($CH_2\underline{C}O$), 157.44, 153.89, 147.22, 129.60, 129.51, 127.77, 125.85, 125.00, 123.20, 118.19, 109.62, 61.91, 52.57 ($COO\underline{C}H_3$), 52.14 ($CH_2COO\underline{C}H_3$), 38.53 (CH), 37.90 (CH_2). Mass spectrum: *m*/*z* 419.7 $[M + Na]^+$. Found, %: C 54.51; H 3.84; N 7.10. $C_{18}H_{15}F_3N_2O_5$. Calculated, %: C 54.55; H 3.82; N7.07.

Methyl 4-([1,1'-biphenyl]-4-yl)-6-amino-5-cyano-2-(2-methoxy-2-oxoethyl)-4*H*-pyran-3-carboxylate (4d). Yield 84%, mp 180–186°C. IR spectrum, ν, cm^{-1}: 3412 (NH_2), 3324 (NH_2), 3027 (C–H_{arom}), 2950, 2183 (CN), 1738 (C=O), 1707 (C=O), 1669 (C=C_{arom}), 1637 (C=C_{arom}), 1438, 1384, 1157, 1068, 747 (δC–H_{arom}), 697. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.58 m (4H_{arom}), 7.45 m (2H_{arom}), 7.35 m (3H_{arom}), 4.57 s (2H, NH_2), 4.55 s (1H, CH), 3.99 d (1H, CH_2, *J* 16.8 Hz), 3.80 t (4H, CH_3, CH_2), 3.63 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.85 (CO), 165.76 ($CH_2\underline{C}O$), 157.39, 153.25, 142.35, 140.78, 140.24, 128.75, 127.83, 127.56, 127.26, 127.08, 118.62, 110.27, 62.62, 52.54 ($COO\underline{C}H_3$), 52.09 ($CH_2CO\cdot O\underline{C}H_3$), 38.28 (CH), 37.89 ($CH_2$). Mass spectrum: *m*/*z* 427.7 $[M + Na]^+$. Found, %: C 68.33; H 4.94; N 6.96. $C_{23}H_{20}N_2O_5$. Calculated, %: C 68.31; H 4.98; N 6.93.

Methyl 6-amino-5-cyano-2-(2-methoxy-2-oxoethyl)-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate (4e). Yield 95%, mp 155–156°C (135–136°C [26]). IR spectrum, ν, cm^{-1}: 3390 (NH_2), 3197 (NH_2), 2950, 2923, 2197(CN), 1754 (C=O), 1680 (C=O), 1637 (C=C_{arom}), 1535 (NO_2), 1384, 1354, 1273, 1070. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 8.12 br.s (2H_{arom}), 7.65 d (1H_{arom}, *J* 7.8 Hz), 7.52 t (1H_{arom}, *J* 7.8 Hz), 4.77 s (2H, NH_2), 4.61 s (1H, CH), 4.07 d (1H, CH_2, *J* 16.8 Hz), 3.79 s (3H, CH_3), 3.71 d (1H, CH_2, *J* 16.8 Hz), 3.60 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.53 (CO), 165.16 ($CH_2\underline{C}O$), 157.66, 154.37, 148.70, 145.71, 133.83, 129.79, 122.60, 122.35, 118.10, 109.14, 61.17, 52.75 ($COO\underline{C}H_3$), 52.24 ($CH_2COO\underline{C}H_3$), 38.57 (CH), 38.10 (CH_2). Mass spectrum: *m*/*z* 395.9 $[M + Na]^+$. Found, %: C 54.65; H 4.03; N 11.29. $C_{17}H_{15}N_3O_7$. Calculated, %: C 54.69; H 4.05; N 11.26.

Methyl 6-amino-5-cyano-4-(2,4-dichlorophenyl)-2-(2-methoxy-2-oxoethyl)-4*H*-pyran-3-carboxylate (4f). Yield 79%, mp 152–155°C (142–143°C [26]). IR spectrum, ν, cm^{-1}: 3468 (NH_2), 3344 (NH_2), 2955, 2196 (CN), 1737 (C=O), 1695 (C=O), 1678 (C=C_{arom}), 1637, 1384, 1363, 1277, 1188, 1168, 1124, 1069, 842 (δC–H_{arom}). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.37 d (1H_{arom}, *J* 1.8 Hz), 7.23 m (2H_{arom}), 5.08 s (1H, CH), 4.63 s (2H, NH_2), 4.04 d (1H_{arom}, CH_2, *J* 16.8 Hz), 3.76 s (3H, CH_3), 3.69 d (1H_{arom}, CH_2, *J* 16.8 Hz), 3.57 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.72 (CO), 165.30 ($CH_2\underline{C}O$), 157.61, 154.20, 139.57, 133.56, 130.81, 129.49, 127.99, 118.00, 109.13, 60.94, 52.57 ($COO\underline{C}H_3$), 52.13 ($CH_2COO\underline{C}H_3$), 37.80 (CH), 34.73 (CH_2). Mass spectrum: *m*/*z* 419.6 $[M + Na]^+$. Found, %: C 51.45; H 3.53; N 7.08. $C_{17}H_{14}Cl_2N_2O_5$. Calculated, %: C 51.41; H 3.55; N 7.05.

Methyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-(2-methoxy-2-oxoethyl)-4*H*-pyran-3-carboxylate (4g). Yield 76%, mp 161–164°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.34 m (1H_{arom}), 7.29 m (1H_{arom}), 7.24 m (1H_{arom}), 7.15 m (1H_{arom}), 5.12 s (1H, CH), 4.66 s (2H, NH_2), 3.99 d (1H, CH_2, *J* 16.8 Hz), 3.75 m (4H, CH_3, CH_2), 3.56 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.81 (CO), 165.55 ($CH_2\underline{C}O$), 157.67, 153.92, 140.84, 132.89, 129.87, 129.77,

128.52, 127.57, 118.29, 109.48, 61.16, 52.54 (CO·O<u>C</u>H$_3$), 52.03 (CH$_2$COO<u>C</u>H$_3$), 37.79 (CH), 35.04 (CH$_2$). Mass spectrum: *m*/*z* 385.7 [*M* + Na]$^+$. Found, %: C 56.24; H 4.15; N 7.76. $C_{17}H_{15}ClN_2O_5$. Calculated, %: C 56.29; H 4.17; N 7.72.

Methyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-(2-methoxy-2-oxoethyl)-4*H*-pyran-3-carboxylate (4h). Yield 78%, mp 154–155°C. IR spectrum, ν, cm^{-1}: 3418 (NH$_2$), 3835 (NH$_2$), 2956, 2912, 2192 (CN), 1740 (C=O), 1683 (C=O), 1645 (C=C$_{arom}$), 1609, 1510, 1439, 1407, 1347, 1269, 1228, 1144, 1067, 851 (δC–H$_{arom}$), 764. ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 7.24 m (2H$_{arom}$), 7.00 m (2H$_{arom}$), 4.61 s (2H, NH$_2$), 4.46 s (1H, CH), 3.96 d (1H, CH$_2$, *J* 16.8 Hz), 3.76 s (3H, CH$_3$), 3.72 d (1H, CH$_2$, *J* 16.8 Hz), 3.58 s (3H, CH$_3$). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 168.81 (CO), 165.62 (CH$_2$<u>C</u>O), 162.84, 161.22, 157.32, 153.20, 139.23, 129.05, 118.49, 115.70, 115.56, 110.18, 62.34, 52.54 (COO<u>C</u>H$_3$), 52.05 (CH$_2$COO<u>C</u>H$_3$), 37.98 (CH), 37.87 (CH$_2$). Mass spectrum: *m*/*z* 369.8 [*M* + Na]$^+$. Found, %: C 58.98; H 4.33; N 8.12. $C_{17}H_{15}FN_2O_5$. Calculated, %: C 58.96; H 4.37; N 8.09.

Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-(2-methoxy-2-oxoethyl)-4*H*-pyran-3-carboxylate (4i). Yield 78%, mp 148–152°C (142–143°C [26]). IR spectrum, ν, cm^{-1}: 3410 (NH$_2$), 3329 (NH$_2$), 2956, 2923, 2196 (CN), 1739 (C=O), 1682 (C=O), 1640 (C=C$_{arom}$), 1610, 1438, 1384, 1349, 1269, 1149, 1065, 840 (δC–H$_{arom}$). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 7.32 d (2H$_{arom}$, *J* 8.4 Hz), 7.24 d (2H$_{arom}$, *J* 8.4 Hz), 4.67 s (2H, NH$_2$), 4.49 s (1H, CH), 4.00 d (1H, CH$_2$, *J* 16.8 Hz), 3.79 s (3H, CH$_3$), 3.75 d (2H, CH$_2$, *J* 16.8 Hz), 3.61 s (3H, CH$_3$). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 168.77 (CO), 165.52 (CH$_2$<u>C</u>O), 157.38, 153.44, 141.95, 133.17, 128.96, 128.82, 118.41, 109.90, 62.05, 52.56 (COO<u>C</u>H$_3$), 52.09 (CH$_2$COO<u>C</u>H$_3$), 38.13 (CH), 37.89 (CH$_2$). Mass spectrum: *m*/*z* 384.6 [*M* + Na]$^+$. Found, %: C 56.26; H 4.13; N 7.75. $C_{17}H_{15}ClN_2O_5$. Calculated, %: C 56.29; H 4.17; N 7.73.

Ehyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-(4-(ethoxycarbonyl)phenyl)-4*H*-pyran-3-carboxylate (7a). Yield 91%, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3416 (NH$_2$), 3335 (NH$_2$), 3030, 3005, 2951, 2202 (CN), 1742 (C=O), 1685 (C=O), 1647 (C=C$_{arom}$), 1609, 1438, 1403, 1355, 1336, 1271, 1239, 1155, 1063, 830 (δC–H$_{arom}$), 755. ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 8.08 d (2H$_{arom}$, *J* 7.8 Hz), 7.50 d (2H$_{arom}$, *J* 7.8 Hz), 7.37 d (1H$_{arom}$, *J* 8.4 Hz), 7.33 d (1H$_{arom}$, *J* 7.8 Hz), 7.27 m (1H$_{arom}$), 7.20 m (1H$_{arom}$), 5.18 s (1H, CH), 4.67 br.s (2H, NH$_2$), 4.40 q (2H, OCH$_2$, *J* 7.2 Hz), 3.84 q (2H, OCH$_2$, *J* 7.2 Hz), 1.40 t (3H, CH$_3$, *J* 7.2 Hz), 0.84 t (3H, CH$_3$, *J* 7.2 Hz). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 165.88 (Ph<u>C</u>O), 165.04 (CO), 158.17, 154.54, 139.82, 137.21, 133.43, 131.83, 130.33, 130.21, 129.33, 128.84, 128.57, 127.44, 118.33, 109.22, 61.34 (COO<u>C</u>H$_2$CH$_3$), 61.04 (PhCOO<u>C</u>H$_2$CH$_3$), 60.58, 36.96 (CH), 14.32 (COOCH$_2$<u>C</u>H$_3$), 13.43 (PhCOOCH$_2$<u>C</u>H$_3$). Mass spectrum: *m*/*z* 453.4 [*M* + H]$^+$. Found, %: C 63.62; H 4.63; N 6.15. $C_{24}H_{21}ClN_2O_5$. Calculated, %: C 63.65; H 4.67; N 6.19.

Methyl 6-amino-5-cyano-2-(pyridin-4-yl)-4-(2,3,4-trimethoxyphenyl)-4*H*-pyran-3-carboxylate (7b). Yield 91%, mp 178–181°C. IR spectrum, ν, cm^{-1}: 3461 (NH$_2$), 3415 (NH$_2$), 3005, 2950, 2191 (CN), 1706 (C=O), 1675, 1617 (C=C$_{arom}$), 1596, 1495, 1406, 1344, 1294, 1254, 1156, 1102. ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 8.72 br.s (2H$_{arom}$), 7.39 br.s (2H$_{arom}$), 6.90 d (1H$_{arom}$, *J* 8.4 Hz), 6.66 d (1H$_{arom}$, *J* 8.4 Hz), 4.84 s (1H, CH), 4.62 br.s (2H, NH$_2$), 3.98 s (3H, OCH$_3$), 3.89 s (3H, OCH$_3$), 3.87 s (3H, OCH$_3$), 3.45 s (3H, OCH$_3$). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 165.69 (CO), 157.86, 153.54, 152.12, 151.33, 148.98, 142.21, 141.87, 127.45, 123.73, 123.01, 118.63, 111.27, 107.24, 61.77 (3-OCH$_3$), 61.24 (2-OCH$_3$), 60.70, 55.94 (4-OCH$_3$), 51.98 (COO<u>C</u>H$_3$), 34.86 (CH). Mass spectrum: *m*/*z* 423.8 [*M* + H]$^+$. Found, %: C 62.46; H 5.04; N 9.90. $C_{22}H_{21}N_3O_6$. Calculated, %: C 62.41; H 5.00; N 9.92.

Ethyl 6-amino-5-cyano-4-(2,4-dichlorophenyl)-2-[4-(ethoxycarbonyl)phenyl]-4*H*-pyran-3-carboxylate (7c). Yield 85%, mp 170–172°C. IR spectrum, ν, cm^{-1}: 3430 (NH$_2$), 3308 (NH$_2$), 2988, 2923, 2188 (CN), 1714 (C=O), 1699 (C=O), 1601 (C=C$_{arom}$), 1514, 1468, 1384, 1329, 1290, 1253, 1154, 1091, 1021, 858 (δC–H$_{arom}$). ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 8.08 d (2H$_{arom}$, *J* 8.4 Hz), 7.49 d (2H$_{arom}$, *J* 8.4 Hz), 7.40 d (1H$_{arom}$, *J* 1.2 Hz), 7.26 br.s (2H$_{arom}$), 5.13 s (1H, CH), 4.69 s (2H, NH$_2$), 3.99 s (3H, Ar-OCH$_3$), 4.40 q (2H, COCH$_2$, *J* 7.2 Hz), 3.85 q (2H, COCH$_2$, *J* 7.2 Hz), 1.40 t (3H, CH$_3$, *J* 7.2 Hz), 0.86 t (3H, CH$_3$, *J* 7.2 Hz). ^{13}C NMR spectrum (CDCl$_3$), δ, ppm: 165.82 (Ph<u>C</u>O), 164.89 (CO), 158.20, 154.86, 138.54, 137.03, 134.12, 133.94, 131.96, 131.22, 129.97, 129.35, 128.55, 127.81, 118.10, 108.77, 61.37 (COO<u>C</u>H$_2$CH$_3$), 61.16 (PhCOO<u>C</u>H$_2$CH$_3$), 60.17, 36.70 (CH), 14.32 (COOCH$_2$<u>C</u>H$_3$), 13.47 (PhCOOCH$_2$<u>C</u>H$_3$). Mass spectrum: *m*/*z* 487.5 [*M* + H]$^+$. Found, %: C 59.13; H 4.11; N 5.78. $C_{24}H_{20}Cl_2N_2O_5$. Calculated, %: C 59.15; H 4.14; N 5.75.

Ethyl 6-amino-5-cyano-2-(4-(ethoxycarbonyl)-phenyl)-4-(4-methoxyphenyl)-4*H*-pyran-3-carboxylate (7d). Yield 82%, mp 181–184°C. IR spectrum, ν, cm^{-1}: 3416 (NH_2), 3316 (NH_2), 3195, 2979, 2938, 2189 (CN), 1715 (C=O), 1674 (C=O), 1605 (C=C_{arom}), 1510, 1464, 1406, 1367, 1328, 1314, 1291, 1174, 1154, 1127, 1093, 1032, 1021, 859 (δC–H_{arom}), 778. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.09 d (2H_{arom}, *J* 8.4 Hz), 7.51 d (2H_{arom}, *J* 8.4 Hz), 7.26 d (2H_{arom}, *J* 8.4 Hz), 6.90 d (2H_{arom}, *J* 8.4 Hz), 4.60 br.s (2H, NH_2), 4.56 s (1H, CH), 4.42 q (2H, $COCH_2$, *J* 7.2 Hz), 3.87 q (2H, $COCH_2$, *J* 7.2 Hz), 3.82 s (3H, Ar-OCH_3), 1.43 t (3H, CH_3, *J* 7.2 Hz), 0.86 t (3H, CH_3, *J* 7.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.88 (Ph<u>C</u>O), 165.57 (CO), 159.01, 157.75, 152.91, 137.31, 134.84, 131.75, 129.28, 128.86, 128.58, 118.67, 114.20, 110.92, 62.39 (COO<u>C</u>H_2CH_3), 61.33 (PhCOO<u>C</u>H_2·CH_3), 60.98, 55.28 (OCH_3), 39.04 (CH), 14.31 (CO·OCH_2<u>C</u>H_3), 13.50 (PhCOOCH_2<u>C</u>H_3). Mass spectrum: *m*/*z* 449.1 [*M* + H]$^+$. Found, %: C 66.92; H 5.35; N 6.29. $C_{25}H_{24}N_2O_6$. Calculated, %: C 66.95; H 5.39; N 6.25.

Methyl 6-amino-5-cyano-2-(2,4-dichlorophenyl)-4-(4-fluorophenyl)-4*H*-pyran-3-carboxylate (7e). Yield 89%, mp 149–152°C. IR spectrum, ν, cm^{-1}: 3412 (NH_2), 2950, 2923, 2198 (CN), 1680 (C=O), 1637 (C=C_{arom}), 1583, 1507, 1384, 1350, 1263, 1155, 1091, 847 (δC–H_{arom}). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.51 s (1H_{arom}), 7.33 m (4H_{arom}), 7.06 t (2H_{arom}, *J* 8.4 Hz), 4.64 s (1H, CH), 4.59 s (2H, NH_2), 3.44 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 164.73 (CO), 162.99, 161.36, 157.81, 152.38, 138.70, 136.59, 131.18, 129.62, 129.34, 129.29, 127.19, 118.33, 115.83, 115.69, 111.82, 62.28, 52.02 (COO<u>C</u>H_3), 38.61 (CH). Mass spectrum: *m*/*z* 419.2 [*M* + H]$^+$. Found, %: C 57.32; H 3.16; N 6.64. $C_{20}H_{13}Cl_2FN_2O_3$. Calculated, %: C 57.30; H 3.13; N 6.68.

Ethyl 6-amino-5-cyano-2-(4-methoxyphenyl)-4-(2,3,4-trimethoxyphenyl)-4*H*-pyran-3-carboxylate (7f). Yield 79%, mp 142–145°C. IR spectrum, ν, cm^{-1}: 3459 (NH_2), 3326 (NH_2), 2938, 2837, 2193 (CN), 1697 (C=O), 1677 (C=O), 1603 (C=C_{arom}), 1514, 1491, 1465, 1418, 1340, 1277, 1253, 1176, 1095, 1042, 838 (δC–H_{arom}),791. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.39 d (2H_{arom}, *J* 8.4 Hz), 6.92 m (3H_{arom}), 6.65 d (1H_{arom}, *J* 8.4 Hz), 4.85 s (1H, CH), 4.51 s (2H, NH_2), 3.99 s (3H, Ar-OCH_3), 3.99 m (5H, Ar-OCH_3, $COCH_2$), 3.86 s (6H, Ar-OCH_3), 0.92 t (3H, CH_3, *J* 7.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 166.33 (CO), 160.92, 158.29, 154.31, 153.13, 152.02, 142.10, 130.05, 128.67, 125.52, 123.71, 119.29, 113.47, 108.58, 107.19, 61.82 (<u>C</u>H_2CH_3), 61.25 (3-OCH_3), 60.65 (2-OCH_3), 60.63, 55.94 (4-OCH_3), 55.38 (PhO<u>C</u>H_3), 34.56 (CH), 13.64 (CH_2<u>C</u>H_3). Mass spectrum: *m*/*z* 467.3 [*M* + H]$^+$. Found, %: C 64.32; H 5.60; N 6.03. $C_{25}H_{26}N_2O_7$. Calculated, %: C 64.37; H 5.62; N 6.01.

Ethyl 6-amino-5-cyano-2-(4-fluorophenyl)-4-(4-methoxyphenyl)-4*H*-pyran-3-carboxylate (7g). Yield 80%, mp 156–159°C. IR spectrum, ν, cm^{-1}: 3386 (NH_2), 3326 (NH_2), 3204, 2981, 2937, 2194 (CN), 1715 (C=O), 1681 (C=O), 1605 (C=C_{arom}), 1510, 1464, 1409, 1368, 1335, 1253, 1175, 1154, 1083, 1032, 838 (δC–H_{arom}), 817. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.43 m (2H_{arom}), 7.24 d (2H_{arom}, *J* 8.4 Hz), 7.11 t (2H_{arom}, *J* 8.4 Hz), 6.90 d (2H_{arom}, *J* 8.4 Hz), 4.60 br.s (3H, NH_2, CH), 4.42 q (2H, CH_2, *J* 7.2 Hz), 3.88 q (2H, CH_2, *J* 7.2 Hz), 3.81 s (3H, OCH_3), 0.89 t (3H, CH_3, *J* 7.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.79, 164.44, 162.78, 158.96, 157.82, 153.10, 135.09, 130.74, 130.69, 129.22, 129.20, 128.82, 118.79, 115.33, 115.19, 114.17, 110.19, 62.31 (<u>C</u>H_2CH_3), 60.88 (4-OCH_3), 55.28, 39.06 (CH), 13.55 (CH_2<u>C</u>H_3). Mass spectrum: *m*/*z* 395.4 [*M* + H]$^+$. Found, %: C 67.04; H 4.89; N 7.09. $C_{22}H_{19}FN_2O_4$. Calculated, %: C 67.00; H 4.86; N 7.10.

Methyl 6-amino-4-(3-bromo-4,5-dimethoxyphenyl)-5-cyano-2-(6-methoxypyridin-3-yl)-4*H*-pyran-3-carboxylate (7h). Yield 87%, mp 178–181°C. IR spectrum, ν, cm^{-1}: 3414 (NH_2), 3323 (NH_2), 2954, 2193 (CN), 1700 (C=O), 1671 (C=O), 1601 (C=C_{arom}), 1567, 1493, 1377, 1356, 1287, 1248, 1154, 1131, 1089, 1044, 1016, 1004, 830 (δC–H_{arom}), 764. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.24 d (1H_{arom}, *J* 2.4 Hz), 7.63 d.d (1H_{arom}, *J* 2.4, 9.0 Hz), 7.01 d (1H_{arom}, *J* 1.8 Hz), 6.80 m (2H_{arom}), 4.67 br.s (2H, NH_2), 4.54 s (1H, CH), 3.98 s (3H, OCH_3), 3.87 s (3H, OCH_3), 3.84 s (3H, OCH_3), 3.49 s (3H, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.90 (CO), 165.11, 158.00, 153.74, 153.16, 147.40, 145.79, 40.03, 138.75, 123.36, 121.96, 118.45, 118.11, 111.38, 110.30, 109.12, 61.67 (4-OCH_3), 60.57, 56.16 (5-OCH_3), 53.88 (Ar-O<u>C</u>H_3), 52.04 (COO<u>C</u>H_3), 39.36 (CH). Mass spectrum: *m*/*z* 502.1 [*M* + H]$^+$. Found, %: C 52.64; H 4.03; N 8.337. $C_{22}H_{20}BrN_3O_6C$. Calculated, %: C 52.60; H 4.01; N 8.37.

Methyl 6-amino-5-cyano-4-(3-nitrophenyl)-2-(pyridin-4-yl)-4*H*-pyran-3-carboxylate (7i). Yield

89%, mp 177–180°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.73 d ($2H_{arom}$, *J* 6.0 Hz), 8.17 d ($2H_{arom}$, *J* 1.8 Hz), 7.68 d ($1H_{arom}$, *J* 7.7 Hz), 7.57 d ($1H_{arom}$, *J* 8.4 Hz), 7.34 q ($2H_{arom}$), 4.7 d (2H, NH_2, *J* 12.6 Hz), 3.41 s (3H, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.03 (CO), 158.01, 153.09, 150.02, 148.80, 144.56, 140.27, 134.08, 129.96, 123.02, 122.60, 117.74, 110.05, 110.00, 60.95, 62.17 ($COO\underline{C}H_3$), 39.55 (CH). Mass spectrum: *m*/*z* 379.6 $[M + H]^+$. Found, %: C 60.30; H 3.71; N 14.86. $C_{19}H_{14}N_4O_5$. Calculated, %: C 60.32; H 3.73; N 14.81.

Methyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2-(pyridin-4-yl)-4*H*-pyran-3-carboxylate (7j). Yield 78%, mp 178–180°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.72 d ($2H_{arom}$, *J* 6.0 Hz), 7.32 d ($2H_{arom}$, *J* 6.0 Hz), 7.24 d ($2H_{arom}$, *J* 8.4 Hz), 6.91 d ($2H_{arom}$, *J* 8.4 Hz), 4.60 d (2H, NH_2, *J* 4.8 Hz), 3.82 s (3H, OCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.69 (CO), 159.13, 157.56, 151.25, 149.90, 140.67, 134.35, 128.78, 122.62, 118.35, 114.32, 111.60, 62.48, 55.38 (4-OCH_3), 51.99 ($COO\underline{C}H_3$), 38.97 (CH). Mass spectrum: *m*/*z* 364.5 $[M + H]^+$. Found, %: C 66.15; H 4.74; N 11.52. $C_{20}H_{17}N_3O_4$. Calculated, %: C 66.11; H 4.72; N 11.56.

Ethyl 6-amino-4-(3-bromo-4,5-dimethoxyphenyl)-5-cyano-2-(4-fluorophenyl)-4*H*-pyran-3-carboxylate (7k). Yield 81%, mp 150–153°C. IR spectrum, ν, cm^{-1}: 3439 (NH_2), 3334 (NH_2), 3197, 2981, 2928, 2200 (CN), 1719 (C=O), 1681 (C=O), 1599 (C=C_{arom}), 1566, 1510, 1487, 1415, 1370, 1339, 1278, 1264, 1145, 1132, 1083, 1046, 1002, 843 (δC–H_{arom}). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.44 d.d ($2H_{arom}$, *J* 8.4, 5.4 Hz), 7.12 t ($2H_{arom}$, *J* 8.4 Hz), 7.05 d ($1H_{arom}$, *J* 1.8 Hz), 6.83 br.s ($1H_{arom}$), 4.65 s (2H, NH_2), 4.56 s (1H, CH), 3.91 m (5H, OCH_3, $COCH_2$), 3.86 s (3H, OCH_3), 0.92 t (3H, CH_3, *J* 7.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 165.52 (CO), 164.56, 162.90, 158.06, 153.86, 153.69, 145.79, 140.00, 130.75, 128.96, 123.56, 118.52, 118.03, 115.42, 115.27, 111.56, 109.37, 61.50 ($\underline{C}H_2CH_3$), 61.05 (4-OCH_3), 60.57, 56.16 (5-OCH_3), 39.44 (CH), 13.57 ($CH_2\underline{C}H_3$). Mass spectrum: *m*/*z* 503.5 $[M + H]^+$. Found, %: C 54.86; H 4.03; N 5.59. $C_{23}H_{20}BrFN_2O_5$. Calculated, %: C 54.89; H 4.01; N 5.57.

SUPPLEMENTARY MATERIALS

Supplementary materials are available for this article at https://doi.org/10.1134/S107042801911023X and are accessible for authorized users.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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