DOI 10.1007/s10593-021-02945-z
Chemistry of Heterocyclic Compounds **2021**, *57*(5), 574–580

Synthesis of 2*H*-pyrano[3,2-*g*]quinolin-2-ones containing a pyrimidinone moiety and characterization of their anticoagulant activity *via* inhibition of blood coagulation factors Xa and XIa

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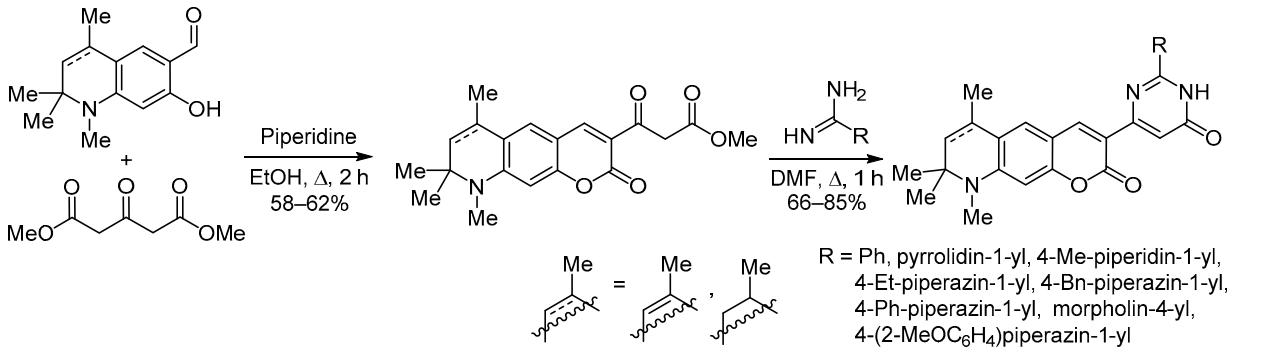
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2021, *57*(5), 574–580

Submitted December 12, 2020
Accepted January 18, 2021



The reactions of 7-hydroxy-1,2,2,4-tetramethylhydroquinoline-6-carbaldehydes with methyl 3-oxopentanedioate were used to synthesize 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-2*H*-pyrano[3,2-*g*]quinolin-3-yl)propanoates with various degrees of hydrogenation in the pyridine ring, the condensation of which with carboximidamides provided a series of new 6,8,8,9-tetramethyl-3-(6-oxo-1,6-dihydropyrimidin-4-yl)-2*H*-pyrano[3,2-*g*]quinolin-2-ones. It was found that some compounds of this class exhibited relatively high inhibitory activity against the blood coagulation factors Xa and XIa.

Keywords: carboximidamide, methyl 2-oxo-(2*H*-pyrano[3,2-*g*]quinolin-3-yl)propanoate, 3-(6-oxo-1,6-dihydro-4-pyrimidinyl)-2*H*-pyrano-[3,2-*g*]quinolin-2-one, 3-oxopentanedioate, pyrano[3,2-*g*]quinoline, pyrimidine, factor Xa, factor XIa, molecular hybridization.

One of the strategies in the modern rational efforts aimed at the discovery of new biologically active compounds is molecular hybridization, which relies on the combination of several pharmacophoric moieties into new molecular structures.[1–8] The pharmacophoric moieties are typically selected from privileged substructures that are part of already known active pharmaceutical preparations, providing a reliable avenue to the development and synthesis of new physiologically active compounds.[9,10] It is known that pyrimidine ring, which is the key structural feature of pyrimidine bases, thiamine, and orotic acid, plays an important role in medicinal chemistry. Certain pyrimidine derivatives show antiviral,[11] antitumor,[12–14] cardioprotective,[15] antihypertensive,[16] and antithrombotic[17,18] activity.

The main direction in the creation of effective oral anticoagulants is the search for inhibitors of factor Xa (the serine protease factor), linking the external and internal blood clotting pathways.[19–24] Some of these drugs have been already approved for clinical use.[25–27] In turn, the developed inhibitors for blood coagulation factor XIa are currently only in preclinical and clinical trials.[28–34] The range of compounds showing strong inhibitory activity against the blood coagulation factors Xa and XIa includes

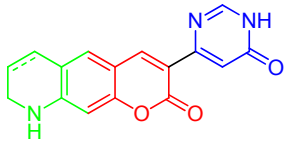


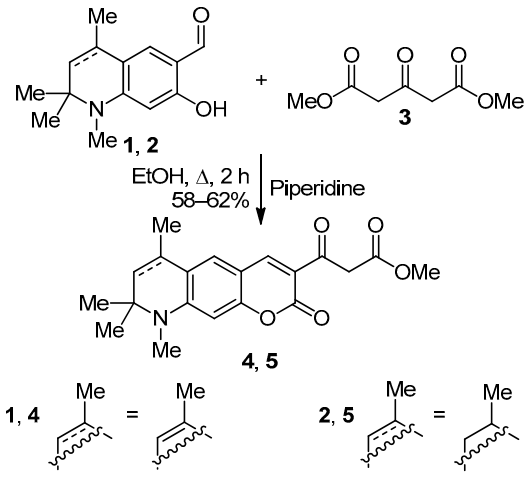
Figure 1. The hybrid structure of 2*H*-pyrano[3,2-*g*]quinolinone.

derivatives of dihydroquinolones[27,35] and tetrahydroquinolines.[29,30,36–38] Besides that, some coumarin derivatives have been also identified among the inhibitors of this type.[34,36,39] However, due to their drawbacks associated with the risk of uncontrollable hemorrhage, as well as the similar binding sites of serine protease factor and thrombin,[40,41] the search for new selective inhibitors of factors Xa and XIa still remains an important task.

Therefore, on the basis of molecular hybridization principles, it was considered worthwhile to search for new inhibitors of factors Xa and XIa by assembling a pyrimidine-substituted 2*H*-pyrano[3,2-*g*]quinolinone system that combines coumarin and hydroquinoline rings (Fig. 1).

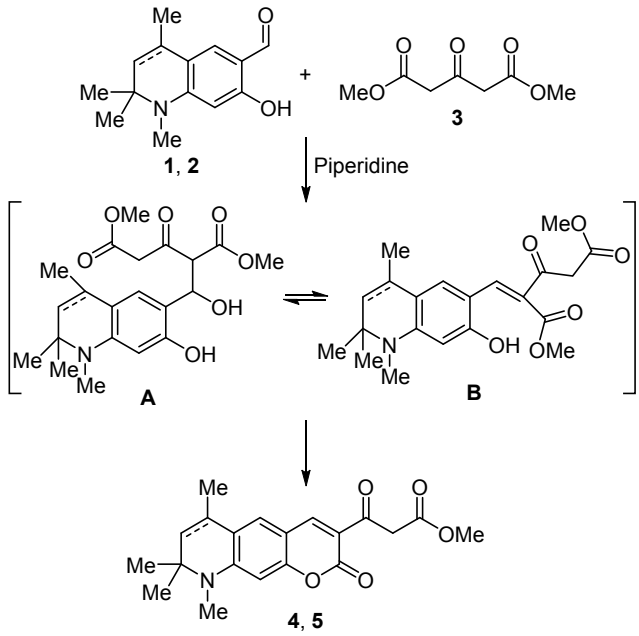
It has been demonstrated[42] that during the condensation of a salicylic aldehyde derivative with dimethyl 3-oxopentanedioate (dimethyl 1,3-acetonedicarboxylate), the reaction of two ester and methylene groups led to the formation of dicoumarinyl ketone. Subsequent studies[43–50] have shown that this reaction is applicable to the preparation of 3-oxo-3-(2-oxo-2*H*-chromen-3-yl)propanoates. By studying the condensation of 7-hydroxy-1,2,2,4-tetramethylhydroquinoline-6-carbaldehydes **1**, **2** with dimethyl 3-oxopentanedioate (**3**), we found that the use of compound **3** in a threefold excess provided relatively good yields of synthetically promising products: methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinolin-3-yl)propanoate (**4**) and methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]-quinolin-3-yl)propanoate (**5**) (58 and 62%, respectively) (Scheme 1).

Scheme 1



The proposed route for the reaction described above (Scheme 2) includes the formation of Knoevenagel adduct **A**, which undergoes dehydratation to arylidene derivative **B** that is susceptible to intramolecular cyclization leading to the final products **4**, **5** (Scheme 2).

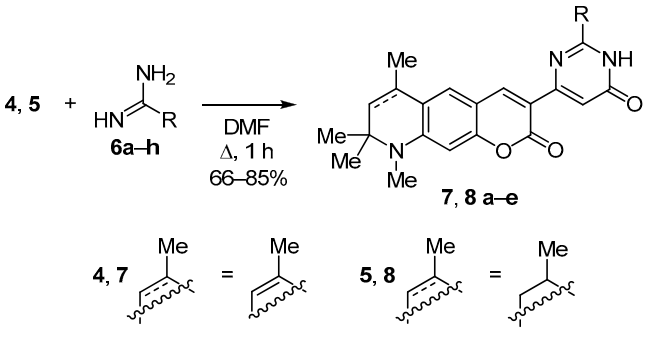
Scheme 2



It is known that compounds containing β-keto ester group have been employed as important building blocks for the synthesis of pyrimidines.[51–56] Besides that, a series of 3-oxo-3-(2-oxo-2*H*-chromen-3-yl)propanoates have been studied in three-component reactions with aldehydes and urea, providing a route for the assembly of tetrahydropyrimidine ring at position 3 of the 2-oxo-2*H*-chromene system.[50] As a confirmation of this, we established that the interaction of (2*H*-pyrano[3,2-*g*]quinolin-3-yl)propanoates **4**, **5** with various carboximidamides **6a–h** in refluxing DMF provided access to a series of new, potentially biologically active 6,8,8,9-tetramethyl-3-(6-oxo-1,6-dihydropyrimidin-4-yl)-2*H*-pyrano[3,2-*g*]quinolin-2-ones **7** and **8 a–e** (Scheme 3). 2*H*-Pyrano[3,2-*g*]quinolin-2-ones **7** and **8 a–e** were obtained in 66–85% yields.

All of the synthesized compounds were isolated as yellow crystals, the structure of which was determined by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.

Scheme 3



6a, **8a** R = Ph; **6b**, **7a** R = pyrrolidin-1-yl
6c, **7b** R = 4-Me-piperidin-1-yl; **6d**, **7c** R = 4-Et-piperazin-1-yl
6e, **7d**, **8b** R = 4-Bn-piperazin-1-yl; **6f**, **7e**, **8c** R = 4-Ph-piperazin-1-yl
6g, **8d** R = 4-(2-MeOC$_6$H$_4$)piperazin-1-yl; **6h**, **8e** R = morpholin-4-yl

^{1}H NMR spectra of compounds **4** and **7a**–**e**, acquired in DMSO-d_6, featured singlets with integrated intensity equal to 6 protons, which were assigned to the protons of two equivalent methyl groups at position 8 of dihydropyridine ring in the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]-quinolin-2-one system, with the chemical shifts of 1.36 ppm (for compound **4**) and 1.34–1.35 ppm (for compounds **7a**–**e**). The three methyl group protons at position 6 of the dihydropyridine ring in the tricyclic system gave a signal at 1.92 ppm (for compound **4**) and in the range of 1.94–1.98 ppm (for compounds **7a**–**e**). The singlet signal arising from the three protons of NCH_3 group at position 9 of dihydropyridine ring of the tricyclic system was observed with a chemical shift of 2.92 ppm (for compound **4**) and in the range of 2.87–2.89 ppm (for compounds **7a**–**e**). The singlet from one proton at position 7 was observed at 5.50 ppm (for compound **4**) and over the range of 5.45–5.48 ppm (for compounds **7a**–**e**). The singlet due to one proton at position 10 of the tricyclic system appeared over the range of 6.37–6.40 ppm (for compounds **4** and **7a**–**e**). Thus, the electronic character of pyrimidine substituent at position 3 of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano-[3,2-*g*]quinolin-2-one system had little effect on the chemical shift values of all aforementioned protons. Analogous situation was observed for the signal assigned to the proton located at position 5 of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one system. Thus, its singlet had a chemical shift of 7.42 ppm in the spectrum of compound **4**, while the spectra of compounds **7a**–**e** contained this signal in the region of 7.38–7.42 ppm.

^{1}H NMR spectrum of compound **4** also contained two singlets with chemical shifts of 3.60 and 3.94 ppm. The integrals of these signals were equal to 3 and 2 protons, respectively. These singlet signals were assigned to the protons of carboxymethyl and methylene groups in the β-keto ester moiety at position 3 of 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one **4**.

Common features in ^{1}H NMR spectra of compounds **7a**–**e** were the proton signals arising from the pyrimidin-6-one rings – two singlets with integrated intensity of one proton each, observed in the regions of 6.70–6.86 and 10.85–11.24 ppm. The former of these were assigned to the CH group proton, while the latter – to the NH proton in the pyrimidin-6-one rings of compounds **7a**–**e**.

^{1}H NMR spectra of compounds **7a**–**e** also contained proton signals due to substituents at position 2 of the pyrimidin-6-one ring of these molecules. These signals were assigned to the cyclic aliphatic secondary amines present in the structure of the aforementioned substituents. For compounds **7d**,**e**, additional characteristic signals were those of the aromatic protons in the phenyl and benzyl moieties, respectively.

^{13}C NMR spectra of compounds **4** and **7a**–**e**, acquired for samples in DMSO-d_6 solutions, contained the signals of sp^3-hybridized carbon atoms of the tricyclic 6,8,8,9-tetramethyl-8,9-dihydro-2*H*-pyrano[3,2-*g*]quinolin-2-one system in the range of 12.4–66.4 ppm. The signals of sp^3-hybridized carbon atoms of substituents at position 2 of pyrimidin-6-one ring in the molecules of compounds **7a**–**e** and the sp^3-hybridized carbon atoms of β-keto ester group at position 3 of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano-[3,2-*g*]quinolin-2-one system in compound **4** also appeared in this region of spectrum. The signals of sp^2-hybridized carbon atoms in the tricyclic 6,8,8,9-tetramethyl-8,9-dihydro-2*H*-pyrano[3,2-*g*]quinolin-2-one system, the pyrimidin-6-one ring in the molecules of compounds **7a**–**e**, as well as the phenyl and benzyl groups in compounds **7d**,**e** appeared in the range of 95.6–189.8 ppm. The signals of the sp^2-hybridized carbon atoms in C=O groups of the pyranone part in the tricyclic system of compounds **4** and **7a**–**e** and the pyrimidinone ring in the case of compounds **7a**–**e** appeared in the region characteristic for carbonyl derivatives of coumarins and pyrimidinones. The signals of sp^2-hybridized carbon atoms of ester and ketone carbonyl groups of the β-keto ester moiety at position 3 of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one system in the spectrum of compound **4** showed chemical shifts of 168.6 and 189.5 ppm, respectively.

The general appearance of ^{1}H NMR spectra acquired for samples of compounds **5** and **8a**–**e** in DMSO-d_6 solutions was largely similar to the respective spectra of compounds **4** and **7a**–**e** that were described above. However, the replacement of dihydropyridine ring in the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one system with a tetrahydropyridine ring somewhat complicated the aliphatic region in ^{1}H NMR spectra of compounds **5** and **8a**–**e**. For example, the protons of methyl groups at position 8 of the tetrahydropyridine ring in the tricyclic system lost their equivalence and gave two singlet signals with integrated intensity of three protons each, with chemical shifts of 1.24–1.25 and 1.30 ppm, respectively. The proton signals of methyl groups at position 6 of the tricyclic system in spectra of compounds **8a**–**e** split due to the interaction with protons bonded to the carbon atom at position 6, and appeared as doublets in the region of 1.32–1.35 ppm, with integrated intensity equal to three protons and the spin-spin coupling constant of 6.4–6.5 Hz. In the spectrum of compound **5**, these signals were shifted upfield and overlapped with the proton signal of one of the methyl groups at position 8 of the tricyclic system. Two protons at position 7 formed a three-spin AMX system with the proton at position 6, where the proton X was additionally coupled to the protons of methyl group at position 6 of the tricyclic system. This system was manifested as a triplet having an integrated intensity of one proton with a spin-spin coupling constant of 12.7–13.2 Hz and a chemical shift of 1.41 ppm (1.40 ppm in the case of compound **4**) for proton A and a double doublet having integrated intensity of one proton with a spin-spin coupling constant of 12.7–13.2 Hz and chemical shift of 1.86–1.87 ppm for the proton M. The signal of proton X (the proton at position 6 of the tricyclic system) appeared as a weakly split septet having an integrated intensity of one proton, with unresolved spin-spin coupling constant and chemical shift of 2.78–2.79 ppm for compounds **8a**–**e** (2.76 ppm for compound **4**).

The signals assigned to protons at positions 4, 5, and 10 of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]-quinolin-2-one system in spectra of compounds **5** and **8a**–**e** matched the analogous signals in the spectra of compounds **4** and **7a**–**e**. The difference between the chemical shifts of these signals in the spectra of compounds containing the same substituents did not exceed 0.1 ppm. The same

situation was also observed for the proton signals of pyrimidin-6-one rings and the proton signals of substituents at position 2 of the pyrimidin-6-one ring in the spectra of molecules **7** and **8**. The proton signals of carboxymethyl and methylene groups in the β-keto ester substituent at position 3 of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano-[3,2-*g*]quinolin-2-one system were identical in the case of compounds **4** and **5**.

In ^{13}C NMR spectra of compounds **5** and **8a**–**e** that were acquired in DMSO-d_6, three new signals appeared in the region typical for sp^3-hybridized carbon atoms. The appearance of two of them could be explained by the replacement of dihydropyridine ring of the tricyclic 6,8,8,9-tetramethyl-2*H*-pyrano[3,2-*g*]quinolin-2-one system with a tetrahydropyridine ring. These signals could be assigned to the carbon atoms at positions 6 and 7 of the tetrahydropyridine ring in the tricyclic system. The third signal (26.6–26.8 ppm) belonged to the carbon atom of one of the methyl groups at position 8 of the tricyclic system. The same ring replacement also resulted in the loss of two sp^2-hybridized carbon signals at 120 and 130 ppm, which were assigned to the carbon atoms at positions 6 and 7 of the tetrahydropyridine ring of the tricyclic system in the spectra of compounds **4** and **7a**–**e**. Otherwise, ^{13}C NMR spectra of compounds **5** and **8a**–**f** were similar to the respective spectra of compounds **4** and **7a**–**e**.

The synthesized compounds **7b** and **8a**–**e** were submitted for primary *in vitro* screening at the laboratory of the Center for Theoretical Problems of Physico-Chemical Pharmacology, Russian Academy of Sciences, in order to identify potential lead compounds and to determine their inhibitory activity against the factors Xa and XIa. The reference compound used in these studies was rivaroxaban, a drug approved for clinical use that selectively inhibits the factor Xa and practically does not affect the factor XIa. The highest inhibitory activity against factor XIa was observed in the case of compound **8c**, which also exhibited moderate inhibitory activity against the factor Xa. In addition, 8,9-dihydro-2*H*-pyrano[3,2-*g*]quinolin-2-one (**7b**) had equal inhibitory effect on factors Xa and XIa (Table 1).

On the basis of the obtained data, further studies can be proposed for exploring the applicability of molecular hybridization methodology in the search for highly effective and selective inhibitors of blood coagulation factors among hydroquinoline derivatives.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on an Agilent MR 400+ instrument (400 and 100 MHz, respectively) for samples in DMSO-d_6 solutions, using the residual solvent signals as internal standards (2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei). HPLC-HRMS analysis was performed on an Agilent Technologies 1260 Infinity chromatograph equipped with an Agilent 6230 TOF LC/MS detector (high resolution time-of-flight detector), using double electrospray ionization. The signals were detected and recorded in positive ion mode; the nebulizer gas (N_2) pressure was 20 psi, the drying gas (N_2) flow was 6 ml/min, temperature 325°C; the mass detection range was 50–2000 Da. The capillary voltage was 4.0 kV, fragmenter +191 V, skimmer +66 V, OctRF 750 V. The following chromatographic conditions were used: Poroshell 120 EC-C_{18} column (4.6 × 50 mm, 2.7 μm). Gradient elution: MeCN/H_2O (0.1 % HCOOH), flow rate 0.4 ml/min. The results were processed using the MassHunter Workstation / Data Acquisition V.06.00 software. Melting points were determined on a Stuart SMP30 apparatus. The reaction progress was controlled and identification of the reactants and the obtained products were performed with TLC using Merck TLC Silica gel 60 F_{254} plates, eluents: $CHCl_3$, MeOH, and their mixtures in various ratios, with visualization under UV light and with iodine vapor.

Table 1. The activity of factors Xa and XIa in the presence of the obtained compounds **7b**, **8a**–**e**, compared to the activity in their absence, %

Compound	Factor Xa	Factor XIa
7b	0.08	0.07
8a	0.58	0.15
8b	0.69	0.15
8c	0.38	0.04
8d	0.87	0.86
8e	0.76	0.99
Rivaroxaban	0.06	0.92

7-Hydroxy-1,2,2,4-tetramethylhydroquinoline-6-carbaldehydes **1**, **2** were obtained according to published procedures,[57,58] the starting carboximidamides **6a**–**h** were supplied by Alinda Chemical Ltd., while dimethyl 3-oxopentadioate was purchased from Acros Organics.

Synthesis of (2*H*-pyrano[3,2-*g*]quinolin-3-yl)propanoates 4, **5** (General method). A mixture of the appropriate 7-hydroxy-1,2,2,4-tetramethylquinoline-6-carbaldehyde **1** or **2** (0.05 mol), dimethyl 3-oxopentanedioate (**3**) (21.1 g, 0.15 mol), piperidine (1 ml), and EtOH (40 ml) was refluxed for 2 h. The precipitate that formed upon cooling of the reaction mixture was filtered off and recrystallized from *i*-PrOH.

Methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-8,9-dihydro-2*H*-pyrano[3,2-*g*]quinolin-3-yl)propanoate (4). Yield 10.31 g (58%), yellow crystals, mp 130–132°C. ^{1}H NMR spectrum, δ, ppm: 1.36 (6H, s, 8-CH_3); 1.92 (3H, s, 6-CH_3); 2.92 (3H, s, NCH_3); 3.60 (3H, s, $COOCH_3$); 3.94 (2H, s, CH_2); 5.50 (1H, s, 7-CH); 6.39 (1H, s, H-10); 7.42 (1H, s, H-5); 8.50 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 18.6; 29.2; 32.5; 48.5; 52.1; 58.8; 95.6; 108.2; 113.8; 120.4; 125.2; 125.5; 130.7; 148.6; 151.8; 159.2; 160.4; 168.6; 189.5. Found, *m*/*z*: 356.1490 $[M+H]^+$. $C_{20}H_{22}NO_5$. Calculated, *m*/*z*: 356.1494.

Methyl 3-oxo-3-(6,8,8,9-tetramethyl-2-oxo-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinolin-3-yl)propanoate (5). Yield 11.08 g (62%), yellow crystals, mp 123–125°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, 8-CH_3); 1.30 (6H, d, 6,8-CH_3); 1.40 (1H, t, *J* = 13.2, 7-CH_2); 1.87 (1H, dd, *J* = 13.2, *J* = 2.9, 7-CH_2); 2.71–2.79 (1H, m, 6-CH); 2.93 (3H, s, NCH_3); 3.60 (3H, s, $COOCH_3$); 3.94 (2H, s, CH_2); 6.43 (1H, s, H-10); 7.53 (1H, s, H-5); 8.53 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 19.3; 25.5; 26.6; 28.9; 32.9; 45.1; 48.5; 52.1; 56.6; 96.2; 108.0; 113.7; 127.3; 127.4; 148.7; 153.0; 157.8; 160.7; 169.9; 189.6. Found, *m*/*z*: 358.1651 $[M+H]^+$. $C_{20}H_{24}NO_5$. Calculated, *m*/*z*: 356.1650.

Synthesis of 6,8,8,9-tetramethyl-3-(6-oxo-1,6-dihydropyrimidin-4-yl)-2*H*-pyrano[3,2-g]quinolin-2-ones 7, 8a–e

(General method). A mixture of (2*H*-pyrano[3,2-*g*]-quinolin-3-yl)propanoate **4** or **5** (2 mmol) with the appropriate carboximidamide **6a–h** (2 mmol) in DMF (5 ml) was refluxed for 1 h. The precipitate that formed from the cooled reaction mixture was filtered off and recrystallized from *i*-PrOH.

6,8,8,9-Tetramethyl-3-[6-oxo-2-(pyrrolidin-1-yl)-1,6-dihydropyrimidin-4-yl]-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinolin-2-one (7a). Yield 0.60 g (72%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm: 1.34 (6H, s, 8-CH_3); 1.91 (4H, br. s, CH_2 pyrrolidine); 1.96 (3H, s, 6-CH_3); 2.88 (3H, s, NCH_3); 3.52 (4H, br. s, CH_2 pyrrolidine); 5.46 (1H, s, 7-CH); 6.38 (1H, s, H-10); 6.70 (1H, s, CH pyrimidine); 7.38 (1H, s, H-5); 8.81 (1H, s, H-4); 10.85 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 18.8; 25.2; 29.0; 32.0; 47.0; 54.0; 58.1; 95.6; 108.5; 112.2; 114.8; 120.0; 121.3; 121.9; 123.3; 123.9; 126.0; 130.5; 136.0; 139.1; 144.7; 150.0; 157.3. Found, *m*/*z*: 419.2079 $[M+H]^+$. $C_{24}H_{27}N_4O_3$. Calculated, *m*/*z*: 419.2079.

6,8,8,9-Tetramethyl-3-[2-(4-methylpiperidin-1-yl)-6-oxo-1,6-dihydropyrimidin-4-yl]-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinolin-2-one (7b). Yield 0.69 g (77%), yellow crystals, mp 289–291°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, d, *J* = 6.2, CH_3 piperidine); 1.05–1.13 (2H, m, CH_2 piperidine); 1.35 (6H, s, 8-CH_3); 1.58–1.69 (3H, m, CH_2 piperidine); 1.97 (3H, s, 6-CH_3); 2.84–2.91 (5H, m, CH_2 piperidine, NCH_3); 4.49 (2H, br. s, CH_2 piperidine); 5.46 (1H, s, 7-CH); 6.39 (1H, s, H-10); 6.75 (1H, s, CH pyrimidine); 7.42 (1H, s, H-5); 8.77 (1H, s, H-4); 11.00 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 19.4; 24.1; 25.5; 26.7; 29.0; 32.7; 44.2; 45.3; 56.2; 66.4; 96.5; 107.5; 117.3; 121.4; 126.5; 126.9; 148.7; 149.1; 152.2; 155.9; 157.2; 159.2; 159.8; 167.9; 189.8. Found, *m*/*z*: 447.2390 $[M+H]^+$. $C_{26}H_{31}N_4O_3$. Calculated, *m*/*z*: 447.2392.

3-[2-(4-Ethylpiperazin-1-yl)-6-oxo-1,6-dihydropyrimidin-4-yl]-6,8,8,9-tetramethyl-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinolin-2-one (7c). Yield 0.62 g (67%), yellow crystals, mp 285–287°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 1.35 (6H, s, 8-CH_3); 1.97 (3H, s, 6-CH_3); 2.58 (2H, q, *J* = 7.1, CH_3C<u>H</u>$_2$); 2.42 (4H, br. s, CH_2 piperazine); 2.88 (3H, s, NCH_3); 3.69 (4H, br. s, CH_2 piperazine); 5.46 (1H, s, 7-CH); 6.38 (1H, s, H-10); 6.81 (1H, s, CH pyrimidine); 7.41 (1H, s, H-5); 8.79 (1H, s, H-4); 11.10 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 12.4; 18.6; 29.0; 32.1; 44.5; 52.0; 52.5; 58.1; 95.6; 108.5; 110.5; 114.5; 120.0; 124.1; 125.9; 130.5; 144.6; 149.1; 150.1; 155.8; 157.1; 160.0; 161.3. Found, *m*/*z*: 462.2501 $[M+H]^+$. $C_{26}H_{32}N_5O_3$. Calculated, *m*/*z*: 462.2501.

3-[2-(4-Benzylpiperazin-1-yl)-6-oxo-1,6-dihydropyrimidin-4-yl]-6,8,8,9-tetramethyl-8,9-dihydro-2*H*-pyrano-[3,2-*g*]quinolin-2-one (7d). Yield 0.69 g (66%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm: 1.34 (6H, s, 8-CH_3); 1.94 (3H, s, 6-CH_3); 2.43 (4H, br. s, CH_2 piperazine); 2.87 (3H, s, NCH_3); 3.51 (2H, s, CH_2 benzyl); 3.70 (4H, br. s, CH_2 piperazine); 5.45 (1H, s, 7-CH); 6.37 (1H, s, H-10); 6.82 (1H, s, CH pyrimidine); 7.26–7.35 (5H, m, H Ph); 7.39 (1H, s, H-5); 8.79 (1H, s, H-4); 11.12 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 18.8; 29.0; 32.0; 44.6; 52.7; 58.1; 62.3; 95.6; 108.5; 114.5; 117.0; 120.0; 122.5; 124.0; 125.9; 127.5; 128.7; 129.4; 130.4; 138.3; 143.6; 144.7; 150.1; 157.1; 155.9; 156.0; 156.1; 159.2; 160.0. Found, *m*/*z*: 524.2655 $[M+H]^+$. $C_{31}H_{34}N_5O_3$. Calculated, *m*/*z*: 524.2658.

6,8,8,9-Tetramethyl-3-[6-oxo-2-(4-phenylpiperazin-1-yl)-1,6-dihydropyrimidin-4-yl]-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinolin-2-one (7e). Yield 0.85 g (83%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (6H, s, 8-CH_3); 1.98 (3H, s, 6-CH_3); 2.89 (3H, s, NCH_3); 3.22 (4H, br. s, CH_2 piperazine); 3.86 (4H, br. s, CH_2 piperazine); 5.48 (1H, s, 7-CH); 6.40 (1H, s, H-10); 6.78–6.86 (2H, m, CH pyrimidine, H-4 Ph); 6.98 (2H, d, *J* = 7.1, H-2,6 Ph); 7.23 (2H, t, *J* = 7.1, H-3,5 Ph); 7.39 (1H, s, H-5); 8.85 (1H, s, H-4); 11.24 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 18.9; 29.0; 32.1; 39.6; 44.5; 48.6; 58.2; 95.6; 108.5; 114.3; 116.3; 119.7; 120.0; 124.0. 125.9; 129.5; 130.5; 138.9; 142.1; 145.2; 150.1; 155.0; 156.9; 157.2; 157.3; 158.2; 160.0. Found, *m*/*z*: 510.2500 $[M+H]^+$. $C_{30}H_{32}N_5O_3$. Calculated, *m*/*z*: 510.2501.

6,8,8,9-Tetramethyl-3-(6-oxo-2-phenyl-1,6-dihydropyrimidin-4-yl)-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]-quinolin-2-one (8a). Yield 0.68 g (80%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, 8-CH_3); 1.30 (3H, s, 8-CH_3); 1.35 (3H, d, *J* = 6.4, 6-CH_3); 1.41 (1H, t, *J* = 13.2, 7-CH_2); 1.87 (1H, dd, *J* = 13.2, *J* = 2.6, 7-CH_2); 2.76–2.84 (1H, m, 6-CH); 2.90 (3H, s, NCH_3); 6.44 (1H, s, H-10); 7.37 (1H, s, H-5); 7.53–7.61 (4H, m, CH pyrimidine, H-3–5 Ph); 8.28 (2H, d, *J* = 6.8, H-2,6 Ph); 9.07 (1H, s, H-4); 12.61 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 19.5; 25.6; 26.8, 29.0; 32.6; 45.5; 56.0; 96.1; 108.3; 113.3; 126.2; 126.9; 128.4; 129.1; 129.2; 132.2; 145.5; 148.9; 151.5; 155.9; 159.3; 160.3; 166.8. Found, *m*/*z*: 428.1968 $[M+H]^+$. $C_{26}H_{26}N_3O_3$. Calculated, *m*/*z*: 428.1970.

3-[2-(4-Benzylpiperazin-1-yl)-6-oxo-1,6-dihydropyrimidin-4-yl]-6,8,8,9-tetramethyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinolin-2-one (8b). Yield 0.88 g (84%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, s, 8-CH_3); 1.30 (3H, s, 8-CH_3); 1.32 (3H, d, *J* = 6.5, 6-CH_3); 1.41 (1H, t, *J* = 13.0, 7-CH_2); 1.86 (1H, dd, *J* = 13.0, *J* = 2.6, 7-CH_2); 2.44 (4H, br. s, CH_2 piperazine); 2.73–2.79 (1H, m, 6-CH); 2,89 (3H, s, NCH_3); 3.52 (2H, s, CH_2 benzyl); 3.70 (4H, br. s, CH_2 piperazine); 6.42 (1H, s, H-10); 6.82 (1H, s, CH pyrimidine); 7.23–7.28 (1H, m, H-4 Ph); 7.31–7.34 (4H, m, H-2,3,5,6 Ph); 7.46 (1H, s, H-5); 8.81 (1H, s, H-4); 11.07 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 19.6; 25.5; 26.8; 29.0; 32.5; 44.6; 45.6; 52.7; 55.9; 62.4; 96.1; 108.2; 114.2; 125.9; 126.7; 127.5; 128.7; 129.4; 138.4; 144.8; 151.2; 155.8; 157.8; 158.3; 159.7; 160.2. Found, *m*/*z*: 526.2812 $[M+H]^+$. $C_{31}H_{36}N_5O_3$. Calculated, *m*/*z*: 526.2814.

6,8,8,9-Tetramethyl-3-[6-oxo-2-(4-phenylpiperazin-1-yl)-1,6-dihydropyrimidin-4-yl)]-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinolin-2-one (8c). Yield 0.87 g (85%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, s, 8-CH_3); 1.30 (3H, s, 8-CH_3); 1.35 (3H, d, *J* = 6.4, 6-CH_3); 1.41 (1H, t, *J* = 13.1, 7-CH_2); 1.87 (1H, dd, *J* = 13.1, *J* = 2.6, 7-CH_2); 2.74–2.81 (1H, m, 6-CH); 2,89 (3H, s, NCH_3); 3.22 (4H, br. s, CH_2 piperazine); 3.86 (4H, br. s, CH_2 piperazine); 6.43 (1H, s, H-10); 6.80 (1H, t, *J* = 7.1, H-4 Ph); 6.86 (1H, s, CH pyrimidine); 6.97 (2H, d, *J* = 8.0, H-2,6 Ph); 7.23 (2H, t, *J* = 8.0, H-3,5 Ph); 7.50 (1H, s, H-5); 8.86 (1H, s, H-4); 11.23 (1H, s, NH

pyrimidine). ^{13}C NMR spectrum, δ, ppm: 19.6; 25.6; 26.8; 29.0; 32.5; 45.6; 48.6; 55.7; 64.7; 96.2; 103.8; 108.1; 114.2; 116.3; 119.7; 125.9; 126.8; 129.4; 151.2; 151.3; 155.7; 158.1; 160.3; 166.4; 190.9. Found, *m*/*z*: 512.2654 $[M+H]^+$. $C_{30}H_{34}N_5O_3$. Calculated, *m*/*z*: 512.2658.

3-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]-6,8,8,9-tetramethyl-6-oxo-1,6-dihydropyrimidin-4-yl}-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinolin-2-one (8d). Yield 0.88 g (81%), yellow crystals, mp >300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, s, 8-CH_3); 1.30 (3H, s, 8-CH_3); 1.34 (3H, d, *J* = 6.4, 6-CH_3); 1.41 (1H, dd, *J* = 13.2, *J* = 2.6, 7-CH_2); 1.87 (1H, dd, *J* = 13.2, *J* = 2.6, 7-CH_2); 2.74–2.81 (1H, m, 6-CH); 2.89 (3H, s, NCH_3); 3.03 (4H, br. s, CH_2 piperazine); 3.80 (3H, s, OCH_3); 3.85 (4H, br. s, CH_2 piperazine); 6.42 (1H, s, H-10); 6.84–7.00 (5H, m, H Ar, CH pyrimidine); 7.52 (1H, s, H-5); 8.87 (1H, s, H-4); 11.17 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 19.5; 25.5; 26.8; 29.0; 32.5; 44.8; 45.6; 50.4; 55.8; 55.9; 96.1; 108.2; 112.3; 114.2; 118.6; 121.3; 123.6; 125.9; 126.7; 141.3; 114.8; 137.9; 144.9; 151.2; 152.4; 155.8; 156.0; 159.3; 160.3. Found, *m*/*z*: 542.2760 $[M+H]^+$. $C_{31}H_{36}N_5O_4$. Calculated, *m*/*z*: 542.2764.

6,8,8,9-Tetramethyl-3-[2-(morpholin-4-yl)-6-oxo-1,6-dihydropyrimidin-4-yl]-6,7,8,9-tetrahydro-2*H*-pyrano-[3,2-*g*]quinolin-2-one (8e). Yield 0.70 g (80%), yellow crystals, mp 292–294°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, s, 8-CH_3); 1.30 (3H, s, 8-CH_3); 1.34 (3H, d, *J* = 6.5, 6-CH_3); 1.41 (1H, t, *J* = 13.1, 7-CH_2); 1.87 (1H, dd, *J* = 13.1, *J* = 2.6, 7-CH_2); 2.73–2.81 (1H, m, 6-CH); 2.89 (3H, s, NCH_3); 3.67 (8H, br. s, CH_2 morpholine); 6.42 (1H, s, H-10); 6.85 (1H, s, CH pyrimidine); 7.49 (1H, s, H-5); 8.83 (1H, s, H-4); 11.13 (1H, s, NH pyrimidine). ^{13}C NMR spectrum, δ, ppm: 19.5; 25.5; 26.8; 29.0; 32.5; 45.0; 45.6; 55.9; 66.3; 96.1; 108.2; 110.0; 125.9; 126.8; 144.8; 150.1; 151.2; 156.0; 156.1; 158.8; 160.2. Found, *m*/*z*: 437.2185 $[M+H]^+$. $C_{24}H_{29}N_4O_4$. Calculated, *m*/*z*: 437.2185.

Testing of compounds 7b, 8a–e for inhibitory activity against the blood coagulation factors Xa and XIa. The inhibition of factors Xa and XIa by compounds **7b**, **8a–e** was determined by measuring the hydrolysis reaction kinetics of substrates specific to each of these enzymes in the presence of the test compounds. In the case of factor Xa, a specific low molecular mass chromogenic substrate S2765 was used (Z-D-Arg-Gly-Arg-pNA, 2HCl, a Chromogenix product by Instrumentation Laboratory), while substrate S2366 was used for factor XIa (pyroGlu-Pro-Arg-pNA·HCl, a Chromogenix product by Instrumentation Laboratory).

The wells of a 96-well plate were charged with a pH 8.0 buffer solution containing 140 mM NaCl, 20 mM HEPES, 0.1% PEG (6000), then the factor Xa was added to the final concentration of 2.5 nM or factor XIa – to the final concentration of 0.8 nM, followed by substrate S2765 (final concentration – 200 μM) or S2366 (final concentration – 200 μM), respectively, as well as the test compounds at the concentration of 30 μM and DMSO at an amount not exceeding 2%. The kinetics of *p*-nitroaniline (pNA) formation were measured with a THERMOmax Microplate Reader (Molecular Devices Corporation) by the absorbance of the obtained solution at 405 nm wavelength. The initial rate of the substrate cleavage reaction was determined by the starting slope of the graph showing the formation of pNA. The ratio of substrate cleavage rate by enzyme in the presence or absence of test compound was calculated. The results were processed with GraphPad Prism[59] (GraphPad) and OriginPro 8[60] (OriginLab Corporation) software.

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

This study was funded by a grant from the Russian Science Foundation (project No. 18-74-10097).

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