

New multicomponent method for the synthesis of polyhydrogenated pyrazino[1,2-*a*]quinolines

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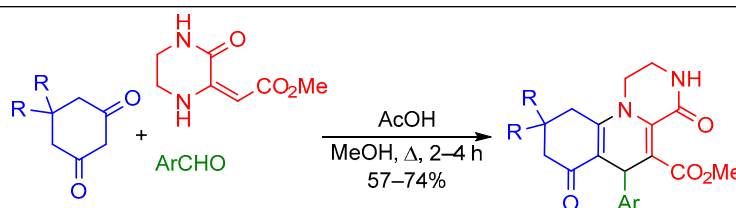
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A new one-pot method for the synthesis of 2,3,4,6,7,8,9,10-octahydro-1*H*-pyrazino[1,2-*a*]quinolines was developed based on a three-component reaction between methyl (3-oxopiperazin-2-ylidene)acetate, aromatic aldehydes, and cyclohexane-1,3-diones. It was shown by HPLC-MS analysis that this cascade reaction involved a sequence of steps including condensation between 1,3-diketone and aldehyde, addition of heterocyclic enaminone as a C-nucleophile, and intramolecular heterocyclization.

Keywords: methyl (3-oxopiperazin-2-ylidene)acetate, 2-oxopiperazine, pyrazino[1,2-*a*]quinoline, multicomponent reactions.

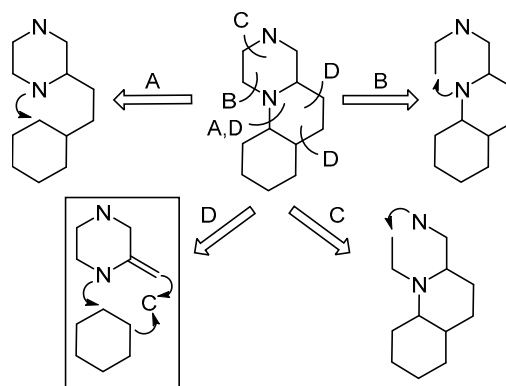
The structural motif of 2-oxopiperazine is found in many natural compounds with various degrees of structural complexity and biological activity,^{1–8} and in several alkaloids (for example, agelastatin A^{2,4} and marcfortine B,⁵ belonging to the phakellin family^{6–8}), where this fragment is fused with other rings. Many methods for the synthesis of polysubstituted 2-oxopiperazines, including chiral examples, are currently known,^{9–16} but only several of those result in the formation of 2-oxopiperazines fused at the C(3)–N(4) bond with other heterocycles.^{12–17} For example, reactions leading to pyrido[1,2-*a*]pyrazines¹² and pyrazino[1,2-*c*]pyrimidines have been described.^{13–14} Recently we developed an efficient method for the synthesis of a new polyazaheterocyclic system, decahydro-3*bH*-pyrrolo[3',4':3,4]pyrrolo[1,2-*a*]pyrazine, by 1,3-dipolar cycloaddition of maleimides to azomethine ylides based on alkyl (3-oxopiperazin-2-yl)acetates.¹⁵

The methods for synthesis of hydrogenated pyrazino[1,2-*a*]quinoline derivatives usually include annulation of hydroquinoline ring to piperazine moiety, featuring a key step of intramolecular aromatic nucleophilic substitution of the labile fluorine atom at *ortho* position relative to the carbonyl substituents (route A, Scheme 1).^{16,17} The alternative methods for obtaining pyrazino[1,2-*a*]quinolines are based on heterocyclization of 2-substituted

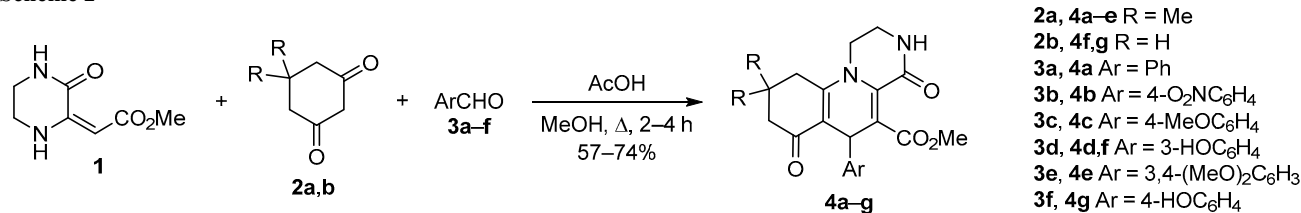
di- and tetrahydroquinolines, leading to the formation of piperazine ring by intramolecular nucleophilic substitution (for example, routes B and C).^{18–22} Multicomponent variations of the synthesis of polyhydropyrazino[1,2-*a*]quinolines (route D) have not yet been described in the literature.

Derivatives of the heterocyclic polyhydropyrazino[1,2-*a*]quinoline system are characterized by a wide range of biological activity, for example, direct agonist effect on serotonin receptors,¹⁹ as well as anti-shistosomiasis²⁰ and

Scheme 1



Scheme 2



hypotensive²¹ activity. The hydrogenated heterocyclic system of 2,3,4,6,7,8,9,10-octahydro-1*H*-pyrazino[1,2-*a*]quinoline contains a fused 5,6,7,8-tetrahydroquinoline ring, which, similarly to the 2-oxopiperazine ring, is known as key structural feature of many compounds that show diverse biological activity, such as antimicrobial,²³ anticancer,²⁴ antitrypanosomal,²⁵ antifungal,²⁶ antioxidative effects,²⁷ or act as calcium channel modulators,²⁸ C5a receptor antagonists (relevant to the treatment of autoimmune conditions),²⁹ are effective against human immunodeficiency virus (HIV-1),³⁰ etc. Thus, there is a significant interest in developing new synthetic approaches to hydrogenated pyrazino[1,2-*a*]quinolines containing 2-oxopiperazine and 5,6,7,8-tetrahydroquinoline rings annulated at the C(3)–N(4) and N(1)–C(2) bonds, respectively.

The aim of this work was to obtain polyhydrogenated pyrazino[1,2-*a*]quinolines by a multicomponent reaction of methyl (3-oxopiperazin-2-ylidene)acetate with aromatic aldehydes and cyclohexane-1,3-diones, and monitor the process by mass spectrometry in combination with liquid chromatography. Multicomponent variants of Hantzsch reaction are some of the most effective tools among various procedures that have been used for creating chemical libraries of polyfunctional structurally diversified biologically active compounds containing pyridine or quinoline rings.³¹ The synthesis of substituted 5,6,7,8-tetrahydroquinolines according to this method includes a three-component reaction of acyclic enamincarbonyl reagents with carbonyl-containing and cyclic 1,3-dicarbonyl components.^{32–34} This reaction gave the best results in alcohol medium in the presence of acidic catalysts.³⁵ Cyclic 1,3-C,N-dinucleophiles were used in order to obtain tetrahydroquinolines annulated with carbo- or heterocycles.^{36,37}

In a continuation of our work towards the synthesis of heterocyclic compounds based on substituted 2-oxopiperazines,^{14,15,38,39} we studied the reaction of methyl (3-oxopiperazin-2-ylidene)acetate (**1**) with cyclohexane-1,3-diones **2a,b** and aromatic aldehydes **3a–f**. The presence of enamincarbonyl moiety in piperazinone **1** enabled its use in the role of heterocyclic enamine component when performing a multicomponent Hantzsch reaction for the synthesis of hydrogenated pyrazino[1,2-*a*]quinolines according to route D (Scheme 1). Synthesis of methyl 6-aryl-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1*H*-pyrazino[1,2-*a*]quinoline-5-carboxylates **4a–g** was achieved by refluxing equimolar amounts of reagents **1–3** in ethanol in the presence of acetic acid as catalyst (Scheme 2).

The main challenge during the investigation of multicomponent processes is to establish the sequence of

mechanistic steps leading to the target products. Therefore, it is important to establish the structure of reaction intermediates, even though they are very rarely isolated from the reaction mixture. Mass spectral monitoring has been used for this purpose in recent years, including LC-MS techniques that allow to perform analysis of intermediates and products formed in liquid phase reactions.⁴⁰

HPLC-MS analysis with electrospray ionization in combination with UV detection was applied to studying the composition of the reaction mixture obtained from piperazinone **1**, 1,3-diketones **2**, and aldehydes **3** by using the example of piperazinone **1** with 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2a**) and benzaldehyde (**3a**) and performing the analysis 15 min, 1 h, and 3 h after starting the reaction.

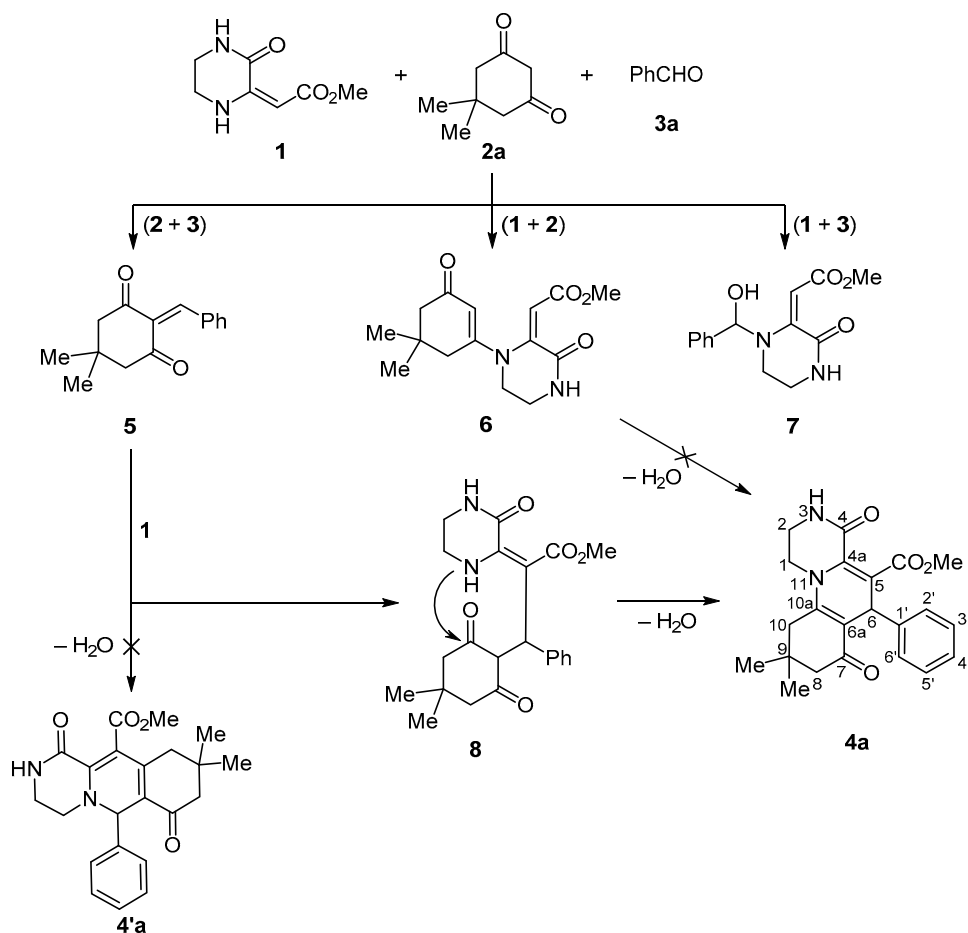
The possible interactions between starting materials in the multicomponent process are shown in Scheme 3. The initial reaction between dimedone (**2a**) and benzaldehyde (**3a**) (route **2 + 3**) can lead to the 2-benzylidene derivative **5**, which undergoes heterocyclization with piperazinone **1**, producing octahydropyrazino[1,2-*a*]quinoline **4a**. The route **1 + 2** can result in the formation of piperazine enamionone **6**, which can react with aldehyde, leading to the closure of hydropyridine ring, giving compound **4a**. The latter product can be formed *via* an intermediate step when piperazinone **1** adds as a nucleophile to the aldehyde **3a** (route **1 + 3**), followed by cyclization with cyclohexane-1,3-dione **2a**, although this direction is not very likely, and there are no literature precedents for similar heterocyclization.

According to high-resolution HPLC-MS data, the reaction mixture after 15 min contained only insignificant amounts of the starting materials, dimedone (**2a**) and piperazinone **1** and compounds showing protonated molecular ion signals with *m/z* values corresponding to structures **4a**, **5**, and **8** (Table 1). The intermediates **6** and **7** were not detected. Compounds **5** and **8** disappeared from the reaction mixture after prolonged heating (analyses performed after 1 h and 3 h).

This provides a reason to expect that the mechanism of multicomponent process (Scheme 3) includes the following sequence of steps: 1) condensation of cyclohexane-1,3-dione **2a** with aldehyde **3a**, leading to 2-arylidene derivative **5**; 2) nucleophilic addition (Michael reaction) of methoxycarbonylmethylenepiperazinone **1** at the activated C=C bond of compound **5**, forming the intermediate **8**; 3) intramolecular heterocyclization of the latter with elimination of water and formation of octahydropyrazino[1,2-*a*]quinoline **4a**.

The structures of the obtained compounds **4a–g** were established based on ¹H and ¹³C NMR spectroscopy

Scheme 3



(including the two-dimensional NOESY and ^1H - ^{13}C HMBC techniques), IR spectroscopy, and mass spectrometry. The majority of ^1H NMR signals in molecules of pyrazinoquinolines **4a–g** were assigned without difficulty, except for those corresponding to methylene protons in piperazinone and cyclohexenone rings (taking into account their different spatial orientation). Unambiguous identification was achieved by examining the NOESY cross peaks (in the example of compound **4a**, Fig. 1) between the following protons: NH (~ 8.53 ppm) and 2- CH_2 protons (~ 3.37 ppm); 1-CH (~ 3.91 ppm) and the second 1-CH proton (~ 3.55 ppm), 2- CH_2 (see above) of

piperazine, and 10-CH (doublet, 2.69 ppm, $J = 17.4$ Hz) of cyclohexene. The doublet at 2.46 ppm ($J = 17.4$ Hz) accordingly belongs to the other 10-CH proton, while the two doublets at 2.03 and 2.18 ppm ($J = 15.7$ Hz) can be assigned to the non-equivalent 8- CH_2 methylene protons of cyclohexene fragment. Cross peaks were observed in ^1H - ^{13}C HMBC spectrum of compound **4a** between the doublets of 8- CH_2 protons and the C-7 atom signal of carbonyl group (194.1 ppm, Table 2), also confirming the proposed assignment.

The presence of NOESY cross peak between proton signals of the 9- CH_3 methyl group (0.89 ppm) and the benzene ring pointed to formal *cis* configuration of these substituents. Besides that, this observation indicated an axial orientation of this methyl group and the corresponding orientation of geminal 8,10-CH protons, that was also confirmed by NOESY correlations. On the other hand, the identified 1- CH_2 -10- CH_2 correlations clearly excluded the possibility that the regioisomeric pyrazino[1,2-*b*]isoquinoline **4'a** could be formed (Scheme 3). The assignment of signals in ^{13}C NMR spectrum of octahydropyrazinoquinoline **4a** was based on correlations in ^1H - ^{13}C HMBC spectrum (Table 2). Correlations were absent between the C-4 atoms of lactam ring (159.7 ppm) and the CH_3O group of ester substituent (51.8 ppm). The signals of C-2',6' had equal chemical shifts, similarly to the signals of C-3',5' (127.2, 128.3 ppm, respectively).

Table 1. The composition of reaction mixture 15 min after starting the synthesis of compound **4a**, according to HPLC-MS data

Compound	Empirical formula	Calculated, m/z $[\text{M}+\text{H}]^+$	Found, m/z $[\text{M}+\text{H}]^+$
1	$\text{C}_7\text{H}_{10}\text{N}_2\text{O}_3$	171.0765	171.0762
2	$\text{C}_8\text{H}_{12}\text{O}_2$	141.0911	141.0905
4a	$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$	381.1810	381.1805
5	$\text{C}_{15}\text{H}_{16}\text{O}_2$	229.1224	229.1219
6	$\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4$	293.1497	–
7	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$	277.1184	–
8	$\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5$	399.1916	399.1914

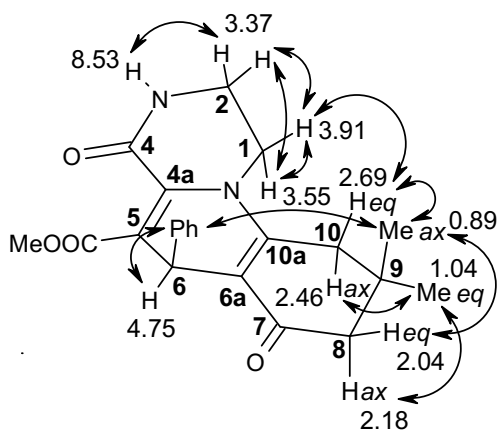


Figure 1. Correlations in NOESY spectrum of compound **4a** (the correlations between methyl group protons and geminal 8-CH₂, 10-CH₂ groups are omitted).

Downfield signals of phenolic OH groups (~9.20 ppm), as well as two multiplets of non-equivalent 9-CH₂ protons (~1.77 and 1.96 ppm) appeared in ¹H NMR spectra of compounds **4f,g**, which were obtained as products of multicomponent reactions between methyl (3-oxopiperazin-2-ylidene)acetate **1**, cyclohexane-1,3-dione **2b**, and hydroxybenzaldehydes **3d,f**, respectively. At the time, signals of geminal 9-C(CH₃)₂ groups were absent. The position and appearance of proton signals due to piperazinone methylene groups, methine 6-CH, lactam NH, and ester OCH₃ groups practically did not change. The multiplicity of 8(10)-CH₂ methylene group signals in cyclohexenone fragment increased in complexity, while the multiplet of the equatorial 8-CH_{eq} proton gave a signal shifted to lower field, overlapping with the signal of the axial 8-CH_{ax} proton.

Table 2. The correlations and chemical shifts of cross peaks in the ¹H–¹³C HMBC spectrum of pyrazinoquinoline **4a**

Protons (δ, ppm)	Atoms ¹³ C (δ, ppm)
CH _{3ax} (0.89)	CH _{3eq} (29.2), C-9 (31.7), C-10 (38.3), C-8 (49.4)
CH _{3eq} (1.04)	CH _{3ax} (26.9), C-9 (31.7), C-10 (38.3), C-8 (49.4)
8-CH _{eq} (2.04)	CH _{3ax} (26.9), CH _{3eq} (29.2), C-9 (31.7), C-10 (38.3), C-7 (194.1)
8-CH _{ax} (2.18)	CH _{3ax} (26.9), CH _{3eq} (29.2), C-9 (31.7), C-10 (38.3), C-7 (194.1)
10-CH _{ax} (2.46)	CH _{3ax} (26.9), CH _{3eq} (29.2), C-9 (31.7), C-8 (49.4), C-6a (108.2), C-10a (152.0)
10-CH _{eq} (2.69)	CH _{3ax} (26.9), C-9 (31.7), C-8 (49.4), C-6a (108.2), C-10a (152.0)
2-CH ₂ (3.35–3.40)	C-1 (43.3)
CH ₃ O (3.49)	COOCH ₃ (169.4)
1-CH (3.52–3.58)	C-2 (37.9)
1-CH (3.89–3.93)	C-2 (37.9), C-4a (131.1)
6-CH (4.75)	C-6a (108.2), C-5 (117.5), C-2',3',5',6' (127.2), C-4a (131.1), C-1' (144.0), C-10a (152.0), COOCH ₃ (169.4), C-7 (194.1)
H Ph (3H, 7.11–7.16)	C-6 (38.2), C-4' (126.5), C-2',3',5',6' (127.2, 128.3)

IR spectra of octahydropyrazinoquinolines **4a–g** contained a strong, broadened absorption band in the region of 3394–3178 cm⁻¹, caused by stretching vibrations of the NH bond in lactam (piperazinone) ring, as well as the phenol OH group (in spectra of compounds **4d,f,g**). The characteristic carbonyl absorption region contained a set of bands corresponding to the vibrations of conjugated ester (1724–1716 cm⁻¹), ketone carbonyl (1694–1681 cm⁻¹), and lactam groups ("amide I" band, 1650–1633 cm⁻¹). The "amide II" absorption band was also observed for the latter compound (1574–1550 cm⁻¹). The spectra of some compounds lacked the absorption band at ~1620 cm⁻¹, corresponding to conjugated C=C bond. Two or three bands were present in the region of 1257–1178 cm⁻¹, due to vibrations of the ester group C–(C=O)–O–Me. One of the nitro group absorption bands in spectrum of compound **4b** overlapped with the "amide I" band (1568 cm⁻¹), while the other was observed at 1356 cm⁻¹.

The EI ionization mass spectra obtained for octahydropyrazino[1,2-*a*]quinolines **4a–g** featured molecular ion peaks of low intensity (5–15%), which underwent further fragmentation by two routes. According to the first route, elimination of benzene ring gave strong signals of fragment ions (for compounds **4a,b,d–f** the maximum intensity was 100%). A parallel process occurred with elimination of CH₃OH followed by elimination of HCN (this process gave a fragment ion of maximum intensity (100%) for compound **4c**). The elimination of HCN molecule indicated a higher stability of tetrahydroquinoline system in compounds **4a–g**, compared to the piperazine ring.

Thus, derivatives of the polyhydrogenated heterocyclic 2,3,4,6,7,8,9,10-octahydropyrazino[1,2-*a*]quinoline system were obtained by a new three-component reaction between methyl (3-oxopiperazin-2-ylidene)acetate, aromatic aldehydes, and cyclohexane-1,3-diones. The sequence of steps in this cascade of multicomponent reactions (condensation of 1,3-diketones with aldehydes → addition of heterocyclic enamionone as a C-nucleophile → intramolecular heterocyclization), was confirmed by HPLC-MS. Such approach also can be used in the synthesis of other condensed heterocyclic compounds containing piperazine moiety.

Experimental

IR spectra were recorded on a Bruker Vertex 70 spectrometer with a Platinum ATR accessory. ¹H and ¹³C NMR spectra were acquired on a Bruker DRX-500 instrument (500 and 125 MHz, respectively) in DMSO-*d*₆. The residual solvent proton signal was used as standard for ¹H NMR spectra (δ_H 2.50 ppm), and DMSO-*d*₆ signal was used as standard for ¹³C NMR spectra (δ_C 39.5 ppm). Mass spectra with electron impact ionization were recorded on a Finnigan MAT Incos 50 instrument with direct introduction of sample at 100–150°C and acceleration voltage of 70 V. The LC-MS monitoring of the multicomponent reaction was performed by HPLC on an Agilent 1260 Infinity liquid chromatograph with Agilent 6230 TOF LC/MS interface. Electrospray ionization was used, positive mode scanning, capillary voltage 4 kV, fragmentor voltage 191 V, skimmer voltage 65 V. The scanned *m/z* range was 50–2000.

Gradient elution with acetonitrile–water (containing 0.1% of formic acid); flow rate 0.3 ml/min; column thermostat set at 23°C. Poroshell 120 EC-C18 column (4.6 × 50 mm, 2.7 μm). Software: MassHunter Qualitative Analysis, B.06.00 (Agilent Tech). The mixture prior to HPLC-MS analysis was dissolved in acetonitrile (approximately 1 mg/ml concentration) and centrifuged on an IKA mini G laboratory minicentrifuge for 10–15 min. Elemental analysis was performed with a Perkin Elmer 2400 instrument. Melting points were determined on a PTP-M apparatus. The reaction progress and purity of the obtained compounds were controlled by TLC on Merck TLC Silica gel 60 F₂₅₄ plates in 10:1 EtOAc–MeOH system (visualization under UV light). The commercially available reagents were purchased from Lancaster.

The starting compound **1** was synthesized according to a published procedure.⁴¹

Preparation of methyl 6-aryl-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-*a*]quinoline-5-carboxylates 4a–g (General method). A mixture of methyl (3-oxopiperazin-2-ylidene)acetate (**1**) (0.85 g, 5 mmol) with the respective cyclohexane-1,3-dione **2a,b** (5 mmol) in MeOH (15–20 ml) was treated with acetic acid (2–3 drops) and the respective aromatic aldehyde **3** (5 mmol), and refluxed for 2–4 h (control by TLC). The powdery precipitate obtained after cooling was filtered off and recrystallized from DMF.

Methyl 9,9-dimethyl-4,7-dioxo-6-phenyl-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-*a*]quinoline-5-carboxylate (4a). Yield 1.37 g (72%), light-yellow powder, mp 250–251°C (DMF). IR spectrum, ν , cm⁻¹: 3228 (br, NH), 1718 ((MeO)C=O), 1690 (C=O, ketone), 1633 (C=O, amide I, lactam), 1574 (C=O, amide II, lactam), 1251, 1214 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 0.89 (3H, s, 9-CH₃ax); 1.04 (3H, s, 9-CH₃eq); 2.04 (1H, d, *J* = 15.7, 8-CHeq); 2.18 (1H, d, *J* = 15.7, 8-CHax); 2.46 (1H, d, *J* = 17.4, 10-CHax); 2.69 (1H, d, *J* = 17.4, 10-CHeq); 3.35–3.40 (2H, m, 2-CH₂); 3.49 (3H, s, CO₂CH₃); 3.52–3.58 (1H, m) and 3.91 (1H, dt, *J* = 12.1, *J* = 3.3, 1-CH₂); 4.75 (1H, s, 6-CH); 7.11–7.16 (3H, m, H Ph); 7.21–7.25 (2H, m, H Ph); 8.52–8.54 (1H, m, NH). ¹³C NMR spectrum, δ , ppm: 26.9 (9-CH₃ax); 29.2 (9-CH₃eq); 31.7 (C-9); 37.9 (C-2); 38.2 (C-6); 38.3 (C-10); 43.3 (C-1); 49.4 (C-8); 51.8 (CO₂CH₃); 108.2 (C-6a); 117.5 (C-5); 126.5 (C-4'); 127.2 (C-2',6'(3',5')); 128.3 (C-3',5'(2',6')); 131.1 (C-4a); 144.0 (C-1'); 152.0 (C-10a); 159.7 (C-4); 169.4 (CO₂CH₃); 194.1 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 380 [M]⁺ (15), 348 [M–CH₃OH]⁺ (10), 321 [M–CH₃OH–HCN]⁺ (25), 303 [M–Ph]⁺ (100). Found, %: C 69.34; H 6.51; N 7.48. C₂₂H₂₄N₂O₄. Calculated, %: C 69.46; H 6.36; N 7.36.

Methyl 9,9-dimethyl-6-(4-nitrophenyl)-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-*a*]quinoline-5-carboxylate (4b). Yield 1.57 g (74%), yellow powder, mp 221–222°C (DMF). IR spectrum, ν , cm⁻¹: 3394 (br, NH), 1719 ((MeO)C=O), 1694 (C=O, ketone), 1650 (C=O, amide I, lactam), 1627 (C=C), 1569 (C=O, amide II, lactam, NO₂), 1356 (NO₂), 1254, 1217, 1178 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 0.89 (3H, s, 9-CH₃ax); 1.04 (3H, s, 9-CH₃eq); 2.05 (1H, d, *J* = 15.8, 8-CHeq); 2.20 (1H, d, *J* = 15.8, 8-CHax); 2.48 (1H, d, *J* = 17.6, 10-CHax); 2.69 (1H, d, *J* = 17.6, 10-CHeq); 3.35–3.40

(1H, m) and 3.42–3.48 (1H, m, 2-CH₂); 3.50 (3H, s, CO₂CH₃); 3.57–3.63 (1H, m) and 3.90 (1H, dt, *J* = 12.2, *J* = 3.5, 1-CH₂); 4.90 (1H, s, 6-CH); 7.42 (2H, d, *J* = 8.8, H-2',6' Ar); 8.12 (2H, d, *J* = 8.8, H-3',5' Ar); 8.59–8.62 (1H, m, NH). ¹³C NMR spectrum, δ , ppm: 27.0 (9-CH₃ax); 29.1 (9-CH₃eq); 31.8 (C-9); 37.8 (C-2); 38.2 (C-6); 38.5 (C-10); 43.3 (C-1); 49.2 (C-8); 51.9 (CO₂CH₃); 107.2 (C-6a); 116.0 (C-5); 123.7 (C-2',6'); 128.5 (C-3',5'); 131.8 (C-4a); 146.3 (C-1'); 151.2 (C-10a); 152.6 (C-4'); 159.4 (C-4); 169.0 (CO₂CH₃); 194.1 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 425 [M]⁺ (8), 393 [M–CH₃OH]⁺ (8), 366 [M–CH₃OH–HCN]⁺ (14), 303 [M–Ar]⁺ (100). Found, %: C 62.23; H 5.32; N 9.77. C₂₂H₂₃N₃O₆. Calculated, %: C 62.11; H 5.45; N 9.88.

Methyl 6-[4-(methoxy)phenyl]-9,9-dimethyl-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-*a*]quinoline-5-carboxylate (4c). Yield 1.31 g (64%), yellow powder, mp 180–181°C (DMF). IR spectrum, ν , cm⁻¹: 3393, 3198 (br, NH), 1723 ((MeO)C=O), 1681 (C=O, ketone), 1635 (C=O, amide I, lactam), 1611 (C=C), 1562 (C=O, amide II, lactam), 1243, 1218, 1180 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 0.89 (3H, s, 9-CH₃ax); 1.04 (3H, s, 9-CH₃eq); 2.02 (1H, d, *J* = 15.7, 8-CHeq); 2.17 (1H, d, *J* = 15.7, 8-CHax); 2.45 (1H, d, *J* = 17.3, 10-CHax); 2.67 (1H, d, *J* = 17.3, 10-CHeq); 3.33–3.40 (2H, m, 2-CH₂); 3.49 (3H, s, CO₂CH₃); 3.51–3.57 (1H, m) and 3.89 (1H, dt, *J* = 12.2, *J* = 3.2, 1-CH₂); 3.69 (3H, s, OCH₃); 4.68 (1H, s, 6-CH); 6.78 (2H, d, *J* = 8.7, H-3',5' Ar); 7.03 (2H, d, *J* = 8.7, H-2',6' Ar); 8.51–8.53 (1H, m, NH). ¹³C NMR spectrum, δ , ppm: 26.9 (9-CH₃ax); 29.2 (9-CH₃eq); 31.7 (C-9); 37.4 (C-2); 37.9 (C-6); 38.1 (C-10); 43.3 (C-1); 49.4 (C-8); 51.8 (CO₂CH₃); 55.0 (OCH₃); 108.5 (C-6a); 113.7 (C-3',5'); 117.8 (C-5); 128.2 (C-2',6'); 130.9 (C-4a); 136.3 (C-1'); 151.7 (C-10a); 157.9 (C-4'); 159.8 (C-4); 169.5 (CO₂CH₃); 194.1 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 410 [M]⁺ (11), 378 [M–CH₃OH]⁺ (12), 351 [M–CH₃OH–HCN]⁺ (100), 303 [M–Ar]⁺ (87). Found, %: C 67.50; H 6.27; N 6.91. C₂₃H₂₆N₂O₅. Calculated, %: C 67.30; H 6.38; N 6.82.

Methyl 6-(3-hydroxyphenyl)-9,9-dimethyl-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-*a*]quinoline-5-carboxylate (4d). Yield 1.21 g (61%), yellow powder, mp 287–289°C (DMF). IR spectrum, ν , cm⁻¹: 3179 (br, NH, OH), 1716 ((MeO)C=O), 1687 (C=O, ketone), 1638 (C=O, amide I, lactam), 1565 (C=O, amide II, lactam), 1257, 1211 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 0.90 (3H, s, 9-CH₃ax); 1.04 (3H, s, 9-CH₃eq); 2.04 (1H, d, *J* = 15.8, 8-CHeq); 2.17 (1H, d, *J* = 15.8, 8-CHax); 2.45 (1H, d, *J* = 17.4, 10-CHax); 2.67 (1H, d, *J* = 17.4, 10-CHeq); 3.36–3.40 (2H, m, 2-CH₂); 3.50 (3H, s, CO₂CH₃); 3.52–3.58 (1H, m) and 3.89 (1H, dt, *J* = 12.2, *J* = 3.0, 1-CH₂); 4.67 (1H, s, 6-CH); 6.50–6.53 (1H, m, H-4'(6') Ar); 6.54–6.57 (2H, m, H-2',6'(4') Ar); 7.00 (1H, t, *J* = 8.0, H-5' Ar); 8.54 (1H, s, NH); 9.20 (1H, s, OH). ¹³C NMR spectrum, δ , ppm: 27.0 (9-CH₃ax); 29.2 (9-CH₃eq); 31.8 (C-9); 37.9 (C-2); 38.1 (C-6); 38.2 (C-10); 43.4 (C-1); 49.5 (C-8); 51.8 (CO₂CH₃); 108.3 (C-6a); 113.5; 114.1; 117.8 (C-2',4',6'), 117.5 (C-5); 129.2 (C-5'); 131.3 (C-4a); 145.3 (C-1'); 151.8 (C-10a); 157.3 (C-3'); 159.8 (C-4); 169.4 (CO₂CH₃); 194.1 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 396 [M]⁺ (11), 364 [M–CH₃OH]⁺ (9), 337 [M–CH₃OH–HCN]⁺ (21), 303 [M–Ar]⁺ (100). Found, %:

C 66.53; H 6.22; N 7.21. C₂₂H₂₄N₂O₅. Calculated, %: C 66.65; H 6.10; N 7.07.

Methyl 6-[3,4-bis(methoxy)phenyl]-9,9-dimethyl-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-a]quinoline-5-carboxylate (4e). Yield 1.52 g (69%), light-yellow powder, mp 236–237°C (DMF). IR spectrum, ν , cm⁻¹: 3393, 3360 (br, NH), 1724 ((MeO)C=O), 1686 (C=O, ketone), 1641 (C=O, amide I, lactam), 1620 (C=C), 1573 (C=O, amide II, lactam), 1252, 1211, 1184 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 0.92 (3H, s, 9-CH₃ax); 1.05 (3H, s, 9-CH₃eq); 2.05 (1H, d, *J*=15.7, 8-CHeq); 2.20 (1H, d, *J*=15.7, 8-CHax); 2.46 (1H, d, *J*=17.4, 10-CHax); 2.70 (1H, d, *J*=17.4, 10-CHeq); 3.34–3.38 (2H, m, 2-CH₂); 3.51 (3H, s, CO₂CH₃); 3.53–3.58 (1H, m) and 3.91 (1H, dt, *J*=12.1, *J*=3.2, 1-CH₂); 3.66 (3H, s, OCH₃); 3.68 (3H, s, OCH₃); 4.69 (1H, s, 6-CH); 6.61 (1H, dd, *J*=8.3, *J*=2.0, H-6' Ar); 6.66 (1H, d, *J*=2.0, H-2' Ar); 6.79 (1H, d, *J*=8.3, H-5' Ar); 8.52 (1H, t, *J*=3.5, NH). ¹³C NMR spectrum, δ , ppm: 26.8 (9-CH₃ax); 29.3 (9-CH₃eq); 31.7 (C-9); 37.6 (C-2); 37.9 (C-6); 38.1 (C-10); 43.3 (C-1); 49.4 (C-8); 51.8 (CO₂CH₃); 55.3 (OCH₃); 55.5 (OCH₃); 108.3 (C-6a); 110.8; 111.7 (C-2',5'); 117.8 (C-5); 118.9 (C-6'); 131.0 (C-4a); 136.6 (C-1'); 147.5, 148.5 (C-3',4'); 151.9 (C-10a); 159.8 (C-4); 169.5 (CO₂CH₃); 194.2 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 440 [M]⁺ (6), 408 [M–CH₃OH]⁺ (8), 381 [M–CH₃OH–HCN]⁺ (65), 303 [M–Ar]⁺ (100). Found, %: C 65.58; H 6.53; N 6.50. C₂₄H₂₈N₂O₆. Calculated, %: C 65.44; H 6.41; N 6.36.

Methyl 6-(3-hydroxyphenyl)-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-a]quinoline-5-carboxylate (4f). Yield 1.16 g (63%), white powder, mp 310–312°C (DMF). IR spectrum, ν , cm⁻¹: 3252 (br, NH, OH), 1722 ((MeO)C=O), 1686 (C=O, ketone), 1644 (C=O, amide I, lactam), 1619 (C=C), 1562 (C=O, amide II, lactam), 1250, 1209, 1185 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.75–1.80 (1H, m) and 1.97 (1H, dt, *J*=13.2, *J*=5.1, 9-CH₂); 2.19–2.23 (2H, m, 8-CH₂); 2.51–2.56 (1H, m) and 2.82 (1H, dt, *J*=17.7, *J*=5.1, 10-CH₂); 3.36–3.40 (2H, m, 2-CH₂); 3.51 (3H, s, CO₂CH₃); 3.52–3.58 (1H, m) and 3.88 (1H, dt, *J*=12.1, *J*=3.1, 1-CH₂); 4.72 (1H, s, 6-CH); 6.50–6.57 (3H, m, H Ar); 6.98–7.02 (1H, m, H Ar); 8.54 (1H, t, *J*=3.5, NH); 9.20 (1H, s, OH). ¹³C NMR spectrum, δ , ppm: 20.5 (C-9); 24.9 (C-10); 35.9 (C-8); 37.8 (C-2); 37.9 (C-6); 43.4 (C-1); 51.8 (CO₂CH₃); 109.4 (C-6a); 113.5, 114.1, 117.9 (C-2',4',6'); 117.4 (C-5); 129.2 (C-5'); 131.3 (C-4a); 145.4 (C-1'); 153.7 (C-10a); 157.3 (C-3'); 159.9 (C-4); 169.5 (CO₂CH₃); 194.3 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 368 [M]⁺ (5), 336 [M–CH₃OH]⁺ (9), 309 [M–CH₃OH–HCN]⁺ (17), 275 [M–Ar]⁺ (100). Found, %: C 65.34; H 5.57; N 7.73. C₂₀H₂₀N₂O₅. Calculated, %: C 65.21; H 5.47; N 7.60.

Methyl 6-(4-hydroxyphenyl)-4,7-dioxo-2,3,4,6,7,8,9,10-octahydro-1H-pyrazino[1,2-a]quinoline-5-carboxylate (4g). Yield 1.05 g (57%), white powder, mp 290–292°C (DMF). IR spectrum, ν , cm⁻¹: 3179 (br, NH, OH), 1716 ((MeO)C=O), 1681 (C=O, ketone), 1639 (C=O, amide I, lactam), 1608 (C=C), 1550 (C=O, amide II, lactam), 1256, 1220, 1186 (C–(C=O)–O–Me). ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.75–1.77 (1H, m) and 1.93–1.98 (1H, m, 9-CH₂); 2.18–2.21 (2H, m, 8-CH₂); 2.51–2.55 (1H, m) and 2.82 (1H, dt, *J*=17.6, *J*=5.1, 10-CH₂); 3.35–3.38 (2H, m, 2-CH₂); 3.49 (3H, s,

CO₂CH₃); 3.51–3.57 (1H, m) and 3.88 (1H, dt, *J*=12.1, *J*=3.3, 1-CH₂); 4.66 (1H, s, 6-CH); 6.60 (2H, d, *J*=8.5, H-3',5' Ar); 6.90 (2H, d, *J*=8.5, H-2',6' Ar); 8.49 (1H, t, *J*=3.5, NH); 9.16 (1H, s, OH). ¹³C NMR spectrum, δ , ppm: 20.6 (C-9); 24.9 (C-10); 35.9 (C-8); 37.2 (C-2); 37.8 (C-6); 43.3 (C-1); 51.7 (CO₂CH₃); 109.8 (C-6a); 115.0 (C-3',5'); 118.1 (C-5); 128.2 (C-2',6'); 130.7 (C-4a); 134.8 (C-1'); 153.5 (C-10a); 156.0 (C-4'); 159.9 (C-4); 169.6 (CO₂CH₃); 194.3 (C-7). Mass spectrum, *m/z* (*I*_{rel}, %): 368 [M]⁺ (6), 336 [M–CH₃OH]⁺ (2), 309 [M–CH₃OH–HCN]⁺ (16), 275 [M–Ar]⁺ (12). Found, %: C 65.37; H 5.56; N 7.73. C₂₀H₂₀N₂O₅. Calculated, %: C 65.21; H 5.47; N 7.60.

Supplementary information file containing IR, ¹H and ¹³C NMR, and mass spectra of compounds 4a–g and the results from monitoring the synthesis of pyrazinoquinoline 4a by HPLC-MS is available online at <http://link.springer.com/journal/10593>.

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