Monatsh Chem (2017) 148:1745–1752
DOI 10.1007/s00706-017-1979-8

ORIGINAL PAPER

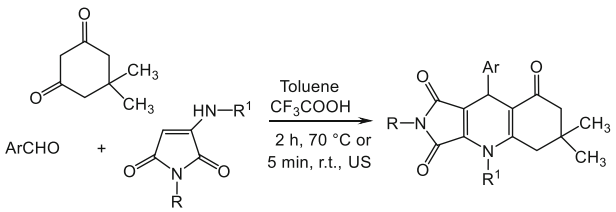
Catalyzed synthesis of functionalized pyrrolo[3,4-*b*]quinolines via one-pot three-component reactions under conventional and nonconventional conditions

Renata I. Eften'eva[1] · Oleg V. Kushnir[1] · Oleksandr S. Lyavinets[1] · Ionel I. Mangalagiu[2] · Myhailo V. Vovk[3]

Received: 5 February 2017 / Accepted: 3 April 2017 / Published online: 4 July 2017

Abstract A general, facile, and efficient method for the synthesis of pyrrolo[3,4-*b*]quinolines is presented. The reactions pathway involve one-pot three-component reactions of *β*-enamino imides, aromatic aldehydes, and dimedone catalyzed by trifluoroacetic acid, under conventional thermal heating or ultrasounds irradiation, as nonconventional method of synthesis. It is shown that under ultrasounds irradiation, the reaction time decreases significantly (from hours to minutes) and, in some cases, the yields are much better.

Graphical abstract



Keywords Pyrrolo[3,4-*b*]quinoline · Ultrasounds irradiation · *β*-Enamino imide · Multicomponent reactions · Cyclizations

Introduction

The synthesis of nitrogen-containing heterocycles is still the backbone of new pharmaceuticals. A famous representative is quinine. Its synthesis and derivatives thereof are still an inspiration for organic chemists [1–4]. The tricyclic system of pyrrolo[3,4-*b*]quinoline is a further interesting source object for construction of new bioactive structures. The nucleus of this system can be found in the natural alkaloids camptothecin [5] and luotonin A [6], while a wide spectrum of pharmaceutical activities (antitumor [7, 8], antibacterial [9], and interferon inducing [10]) is reported for its derivatives. Besides, acetylcholinesterase inhibitor [11] and K_{ATP} openers [12] have been found among these derivatives as well as some other compounds with the ability to bind benzodiazepine receptors [13, 14], inhibitors of PI3-kinase [15], phosphodiesterase inhibitor [16], PDE-V inhibitors active in the treatment of erectile disfunction [17], and modulators of γ-aminobutyric acid $(GABA)_a$ receptors [18].

β-Enamino imides are known as interesting two-center enamine-type reagents, being of highly interest for the three- and tetra-component reactions of cyclocondensation [19–22]. Also, there are many publications reporting the use of dimedone in the multicomponent reactions with various enamines [23–29].

During the last decades, using ultrasounds irradiation (sonochemistry), as a nonconventional method of work in chemistry, became a versatile tool in a large variety of syntheses, because of its numerous advantages resulting in

Electronic supplementary material The online version of this article (doi:10.1007/s00706-017-1979-8) contains supplementary material, which is available to authorized users.

✉ Oleg V. Kushnir
oleg_kushn@ukr.net

[1] Yu. Fedkovych Chernivtsi National University, 2 Kotsyubinsky St., Chernivtsi 58012, Ukraine

[2] "Al. I. Cuza" University of Iasi, Faculty of Chemistry, Bd. Carol 11, 700506 Iasi, Romania

[3] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska St., Kiev 02094, Ukraine

higher yields, shorter reaction times and milder reactions conditions [30–37]. Taking into consideration our experience in the field of multicomponent reactions [23] as well as that one in the area of sonochemistry [33–37], we decide to synthesize new pyrrolo[3,4-*b*]quinolines via catalyzed one-pot three-component reactions, both under conventional thermal heating and ultrasounds irradiation.

Results and discussion

In accordance with our goal, we have proposed a new effective approach for the synthesis of the polyfunctional pyrroloquinolines **4**, by the one-pot three-component cyclocondensation of aromatic aldehydes **1**, dimedone (**2**), and *β*-enamino imides **3**, catalyzed by trifluoroacetic acid. The reactions were carried out in toluene, both under conventional thermal heating (70 °C) or using ultrasounds irradiation (room temperature) (Scheme 1).

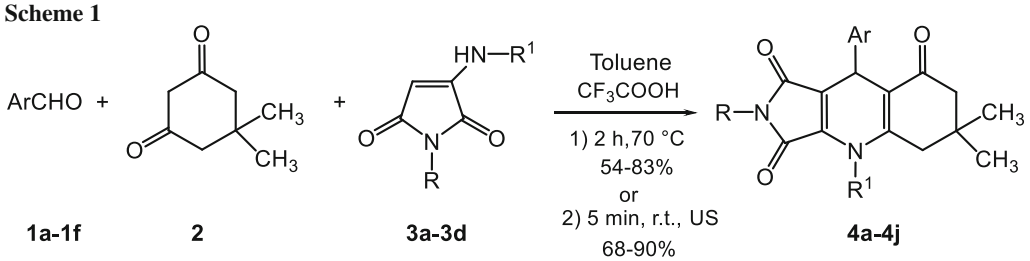
A model reaction between 4-fluorobenzaldehyde (**1a**) with dimedone (**2**) and 1-benzyl-3-(4-methylaniline)-1*H*-pyrrole-2,5-dione (**3a**) has been initially investigated to optimize the reaction conditions. It has been found that a complex mixture of the reaction products is formed in this reaction running in ethanol with L-proline [19] and DABCO. The product **4a** can be extracted from the mixture with a yield of 10% (L-proline) and a yield of 6% (DABCO). If a solution of trifluoroacetic acid in dichloromethane is used as a catalyst, the target product yield reaches 61% after 6 h of boiling. Then, other solvents such as acetonitrile, dichloroethane, acetic acid, and toluene were tested for their catalytic efficiency at heating to various temperatures with trifluoroacetic acid and the highest efficiency has been registered for the toluene mixture (see Table 1). Besides, the highest yield of the cyclocondensation product can be reached using the equimolar amount of trifluoroacetic acid after 2 h of heating to 70 °C.

As we may notice from Table 1, under conventional thermal heating the reaction pathways had some major disadvantages, including low to moderate yields, long reaction time, high energy consumption, and considerable amounts of solvents. For these reasons, we decided to use ultrasounds irradiation, as nonconventional methods, for the synthesis (Scheme 1). It has been found that the reaction does not run in dichloromethane, dichloroethane, and toluene if no trifluoroacetic acid was added. However, introduction of the equimolar amount of the acid leads to shorter reaction time (less than 5 min) and higher yields (from 58 to 64% for dichloroethane; 61 to 69% for dichloromethane, and 83 to 90% for toluene; see Tables 1 and 2). Also, in the case of the reactions running up in toluene with trifluoroacetic acid as catalyst, the yields were rising with the time, reaching 78, 90, and 90% for the reaction times 3, 5, and 10 min, respectively. Therefore, 5 min is the most optimal reaction time (see Table 2, entries 6–8).

A possible mechanism of formation for the derivatives of pyrroloquinoline **4** is shown in Scheme 2. Activation of *β*-enamino imides **3** takes place in the presence of trifluoroacetic acid forming the Enol **A2**. In parallel, the aromatic aldehyde **1** and dimedone undergo a condensation reaction forming the Michael acceptor **B**. In the following condensation, **A2** and **B** form the Michael adduct **C**. Finally, in a third condensation, this Michael adduct undergoes intramolecular cyclocondensation forming the pyrroloquinoline nucleus **4**.

Table 3 lists a comparative study for the synthesis of pyrroloquinoline derivatives **4a**–**4j** via catalyzed one-pot three-component reactions, under thermal heating and ultrasounds irradiation. We may notice that under ultrasounds irradiation, the reaction time decreases significantly (from 2 h to 5 min) and, in some cases, the yields are much better (for instance, with 14% higher for the reaction product **4d**). It has been found that the reaction yield rises with increasing the aldehydes electrophilicity under conventional thermal heating conditions (**4d**: 54%, **4c**: 56%, **4e**: 69%), while under ultrasounds irradiation no significant differences were found.

Scheme 1



1a-1f **2** **3a-3d** **4a-4j**

1, Ar = 4-FC_6H_4 (**a**), 4-ClC_6H_4 (**b**), C_6H_5 (**c**), 4-MeC_6H_4 (**d**), 4-$NO_2C_6H_4$ (**e**), 3-$NO_2C_6H_4$ (**f**)

3, R = Bn, R^1 = 4-MeC_6H_4 (**a**), R^1 = 4-BrC_6H_4 (**b**); R = Me, R^1 = 4-MeC_6H_4 (**c**), R^1 = 4-BrC_6H_4 (**d**)

Table 1 Optimization of reaction conditions **4a**

No	Solvent	Catalyst (equiv.)	Temp/°C	Time/h	Yield/%
1	EtOH	–	Reflux	8	–
3	CH_3CN	–	Reflux	8	–
4	CH_2Cl_2	–	Reflux	8	–
5	$C_2H_4Cl_2$	–	Reflux	8	–
6	Toluene	–	80	8	–
7	EtOH	L-Proline (1.0)	Reflux	7	10
8	EtOH	DABCO (1.0)	Reflux	7	6
9	CH_3CN	CF_3COOH (1.0)	Reflux	7	12
10	CH_3COOH	CF_3COOH (1.0)	80	7	47
11	CH_2Cl_2	CF_3COOH (1.0)	Reflux	6	61
12	$C_2H_4Cl_2$	CF_3COOH (1.0)	Reflux	5	58
13	Toluene	CF_3COOH (1.0)	70	2	83
14	Toluene	CF_3COOH (0.5)	70	2	75
15	Toluene	CF_3COOH (1.5)	70	2	78

Reactions were performed with 4-fluorobenzaldehyde (0.4 mmol), dimedone (0.4 mmol), and 1-benzyl-3-(4-methylphenylamino)-1*H*-pyrrole-2,5-dione (0.4 mmol) in 5 cm^3 of solvent

Table 2 Optimization of reaction conditions **4a** under ultrasounds irradiation

No	Solvent	Catalyst (equiv.)	Time/min	Yield/%
1	CH_2Cl_2	–	20	Trace
2	$C_2H_4Cl_2$	–	20	–
3	Toluene	–	20	Trace
4	CH_2Cl_2	CF_3COOH (1.0)	5	69
5	$C_2H_4Cl_2$	CF_3COOH (1.0)	5	64
6	Toluene	CF_3COOH (1.0)	5	90
7	Toluene	CF_3COOH (1.0)	3	78
8	Toluene	CF_3COOH (1.0)	10	90

Reactions were performed with 4-fluorobenzaldehyde (0.4 mmol), dimedone (0.4 mmol), and 1-benzyl-3-(4-methylphenylamino)-1*H*-pyrrole-2,5-dione (0.4 mmol) in 15 cm^3 of solvent

In continuing of our studies, we found that some other 1,3-dicarbonyl products, such as 1,3-cyclohexanedione and barbituric acid, can be used in analogous one-pot three-component reactions. Thus, 1,3-cyclohexanedione reacts like dimedone under optimized conditions forming pyrroloquinoline **5** (in moderate yields, 67% for thermal heating and 64% for ultrasounds irradiation). Also, the less CH-acid barbituric acid could be used instead of dimedone. Under the same conditions, a prolonging of the reaction times is observed (either 6 h of thermal heating either 20 min of ultrasounds irradiation). The yields of the desired pyrrolo[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine **6** are still high (74% for thermal heating and 72% for ultrasounds irradiation, see Scheme 3).

In conclusion, we present herein a general, straight, and efficient method for the synthesis of pyrrolo[3,4-*b*]quinolines under conventional thermal heating and ultrasounds irradiation. The reactions pathway involve a one-pot three-component reactions of β-enamino imides, aromatic aldehydes, and 1,3-diketone catalyzed by trifluoroacetic acid. It is shown that under ultrasounds irradiation, the reaction time decreases significantly (from hours to minutes) and, in some cases, the yields are much better.

Experimental

All melting points were determined on an MEL-TEMP II apparatus in open capillary tubes. IR data were recorded as films on KBr pellets on a FT-IR Shimadzu Prestige 8400 s spectrophotometer. The NMR measurements were carried out on a Bruker Avance III 500 MHz spectrometer with ^1H and ^{13}C frequencies of 500 and 125 MHz, respectively. HPLC/MS was carried out on a system consisting of an

Scheme 2

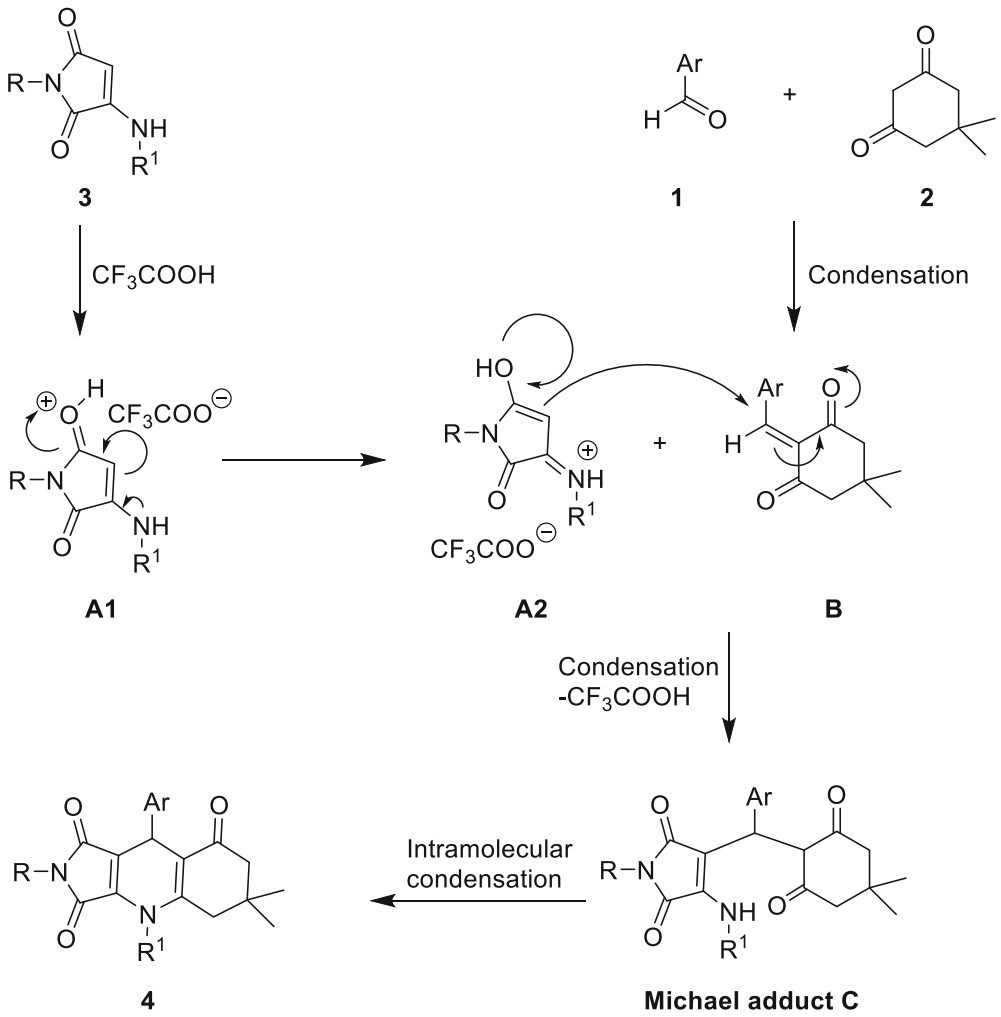
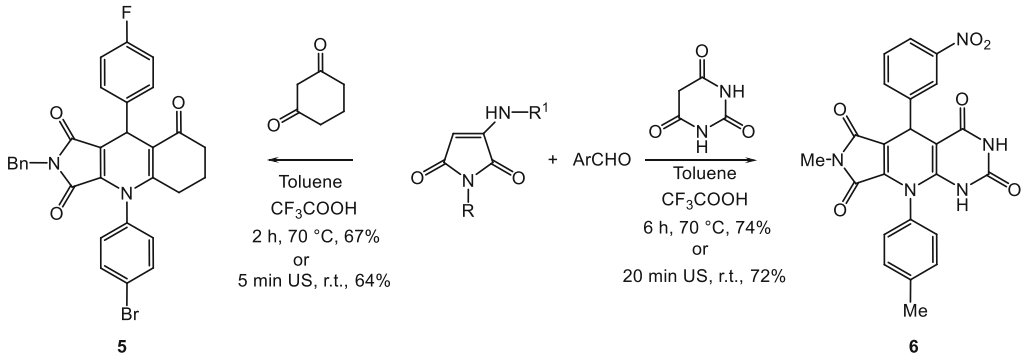


Table 3 Comparative data concerning synthesis of pyrrolo[3,4-*b*]quinolines **4a**–**4j** under conventional thermal heating and ultrasounds irradiation

Product	R	R^1	Ar	Conventional thermal heating		Ultrasounds irradiation	
				Time/min	Yield/%	Time/min	Yield/%
4a	Bn	4-MeC_6H_4	4-FC_6H_4	120	83	5	90
4b	Bn	4-MeC_6H_4	4-ClC_6H_4	120	77	5	80
4c	Bn	4-BrC_6H_4	Ph	120	56	5	69
4d	Bn	4-BrC_6H_4	4-MeC_6H_4	120	54	5	68
4e	Bn	4-BrC_6H_4	4-$NO_2C_6H_4$	120	69	5	72
4f	Me	4-MeC_6H_4	4-ClC_6H_4	120	65	5	71
4g	Me	4-MeC_6H_4	3-$NO_2C_6H_4$	120	77	5	83
4h	Me	4-BrC_6H_4	4-ClC_6H_4	120	72	5	73
4i	Me	4-BrC_6H_4	3-$NO_2C_6H_4$	120	80	5	85
4j	Me	4-BrC_6H_4	4-$NO_2C_6H_4$	120	79	5	79

Scheme 3



Agilent 1100 Series high-pressure liquid chromatography equipped with a diode matrix and Agilent LC/MSD SL mass-selective detector. HPLC/MS parameters: column: Zorbax SB-C18, 1.8 μ, 4.6 × 30 mm; ionization method: chemical ionization under atmospheric pressure; ionization mode: simultaneous scanning of positive and negative ions in *m/z* range 100–650. Microanalyses were performed with Euro EA 3000 Elemental Analyzer. Ultrasound-assisted reactions were carried out using reactor: Sonics (Sonics VCX-130, USA), with a nominal power of 130 W, frequency 20 kHz, the titanium standard probe tip (diameter 6 mm; length 116 mm), was fixed tightly to the ultrasounds converter and was immersed in the used solvent. Analytical thin-layer chromatography was performed with commercial silica gel plates 60 F_{254} (Merck) and visualized with UV light.

β-Enamino imides (**3**) were synthesized by the method [38]. All chemicals used in this study were commercially available and used without further purification.

General procedure

A solution of *β*-enamino imide (0.4 mmol), aromatic aldehyde (0.4 mmol), dimedone (0.4 mmol), and trifluoroacetic acid (0.4 mmol) in 5 cm^3 toluene was stirred at 70 °C for 2 h while checking the reaction progress by TLC. After completion, the reaction mass was concentrated under vacuum and the crude product was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to provide the analytically pure product.

Ultrasound-assisted reaction A solution of *β*-enamino imide (0.4 mmol), aromatic aldehyde (0.4 mmol), dimedone (0.4 mmol), and trifluoroacetic acid (0.4 mmol) in 15 cm^3 toluene was exposed to US irradiation for 5 min (best results were obtained applying a pulse irradiation—5 s pulse/5 s pause, 100% from the full power of the generator). After completion, the reaction mass was concentrated under vacuum and the crude product was purified by column chromatography (CH_2Cl_2/MeOH, 99:1) to provide the analytically pure product.

2-Benzyl-9-(4-fluorophenyl)-6,6-dimethyl-4-(4-methylphenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4a**, $C_{33}H_{29}FN_2O_3$)
Yellow solid; yield: 83% using CH (conventional heating), 90% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.48$; m.p.: 196–198 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.05 (d, 1H, $J = 17.5$ Hz, CH_2), 2.11 (d, 1H, $J = 17.5$ Hz, CH_2), 2.18 (d, 1H, $J = 16.0$ Hz, CH_2), 2.20 (d, 1H, $J = 16.0$ Hz, CH_2), 2.47 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 5.13 (s, 1H, CH^9), 6.98–7.02 (m, 2H, Ar), 7.14 (d, 2H, $J = 8.0$ Hz, Ar), 7.23–7.37 (m, 9H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$, 27.1, 29.4, 32.4, 33.4, 40.6, 41.3, 50.3, 113.8, 114.8, 115.4, 115.6, 119.9, 127.8, 128.6, 128.7, 129.5, 129.6, 129.9, 130.5, 134.6, 136.5, 137.5, 139.9, 140.4, 151.6, 160.9, 162.8, 163.8, 168.6, 195.9 ppm; IR (KBr): $\bar{\nu} = 3444$, 2960, 2872, 1766, 1714, 1664, 1643, 1572, 1508, 1429, 1361, 1257, 1219, 1155, 1097, 1018, 927, 837, 744, 698 cm^{-1}; HPLC/MS: $m/z = 520$ (M^+).

2-Benzyl-9-(4-chlorophenyl)-6,6-dimethyl-4-(4-methylphenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4b**, $C_{33}H_{29}ClN_2O_3$)
Yellow solid; yield: 77% using CH (conventional heating), 80% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.46$; m.p.: 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.89$ (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.04 (d, 1H, $J = 17.0$ Hz, CH_2), 2.11 (d, 1H, $J = 17.0$ Hz, CH_2), 2.18 (d, 1H, $J = 16.5$ Hz, CH_2), 2.20 (d, 1H, $J = 16.5$ Hz, CH_2), 2.47 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 5.12 (s, 1H, CH^9), 7.13 (d, 2H, $J = 8.0$ Hz, Ar), 7.18 (d, 2H, $J = 8.0$ Hz, Ar), 7.23–7.34 (m, 9H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$, 27.2, 29.4, 32.4, 33.7, 40.6, 41.4, 50.3, 113.6, 114.5, 125.4, 127.8, 128.3, 128.7, 128.7, 128.9, 129.1, 129.4, 130.5, 132.8, 134.6, 136.5, 137.6, 139.9, 143.1, 151.7, 163.8, 168.5, 195.8 ppm; IR (KBr): $\bar{\nu} = 3464$, 2956,

2872, 1768, 1712, 1668, 1641, 1572, 1512,1429, 1365, 1295, 1220, 1153, 1064, 1014, 835, 744 cm^{-1}; HPLC/MS: *m/z* = 537 (M^+).

2-Benzyl-4-(4-bromophenyl)-6,6-dimethyl-9-phenyl-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4c**, $C_{32}H_{27}BrN_2O_3$)
Yellow solid; yield: 56% using CH (conventional heating), 69% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.50$; m.p.: 213–215 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.91$ (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.02 (d, 1H, $J = 17.0$ Hz, CH_2), 2.09 (d, 1H, $J = 17.0$ Hz, CH_2), 2.19 (d, 1H, $J = 16.5$ Hz, CH_2), 2.20 (d, 1H, $J = 16.5$ Hz, CH_2), 4.44 (m, 2H, CH_2), 5.14 (s, 1H, CH^9), 7.17 (d, 2H, $J = 8.5$ Hz, Ar), 7.23–7.30 (m, 6H, Ar), 7.33 (d, 2H, $J = 7.5$ Hz, Ar), 7.37 (d, 2H, $J = 7.5$ Hz, Ar), 7.64 (d, 2H, $J = 8.5$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 27.2$, 29.4, 32.5, 34.0, 40.7, 41.4, 50.3, 114.2, 115.5, 123.9, 127.2, 127.8, 128.0, 128.7, 128.7, 128.8, 130.7, 133.1, 136.4, 136.4, 137.0, 144.2, 150.7, 163.9, 168.4, 195.7 ppm; IR (KBr): $\bar{\nu} = 3445$, 2958, 2872, 1766, 1710, 1668, 1575, 1491, 1429, 1361, 1261, 1147, 1072, 1012, 945, 842, 734, 696 cm^{-1}; HPLC/MS: *m/z* = 566 (M^+).

2-Benzyl-4-(4-bromophenyl)-6,6-dimethyl-9-(4-methylphenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4d**, $C_{32}H_{29}BrN_2O_3$)
Yellow solid; yield: 54% using CH (conventional heating), 68% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.39$; m.p.: 105–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.92$ (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.03 (d, 1H, $J = 17.5$ Hz, CH_2), 2.09 (d, 1H, $J = 17.5$ Hz, CH_2), 2.19 (d, 1H, $J = 16.5$ Hz, CH_2), 2.20 (d, 1H, $J = 16.5$ Hz, CH_2), 2.30 (s, 3H, CH_3), 4.43 (m, 2H, CH_2), 5.10 (s, 1H, CH^9), 7.12–7.17 (m, 4H, Ar), 7.24-7.34 (m, 7H, Ar), 7.65 (d, 2H, $J = 8.5$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.2$, 27.2, 29.4, 32.4, 33.6, 40.7, 41.3, 50.2, 114.2, 115.7, 123.8, 127.8, 127.8, 128.6, 128.6, 128.7, 129.5, 130.7, 133.1, 136.4, 136.4, 136.8, 136.8, 141.3, 150.6, 163.9, 168.4, 195.8 ppm; IR (KBr): $\bar{\nu} = 3445$, 2956, 2870, 1766, 1712, 1670, 1573, 1489, 1363, 1259, 1145, 1066, 1012, 943, 842, 744, 700 cm^{-1}; HPLC/MS: *m/z* = 580 (M^+).

2-Benzyl-4-(4-bromophenyl)-6,6-dimethyl-9-(4-nitrophenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4e**, $C_{32}H_{26}BrN_3O_5$)
Yellow solid; yield: 69% using CH (conventional heating), 72% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.48$; m.p.: 136–138 °C;^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.92$ (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.05 (d, 1H, $J = 17.5$ Hz, CH_2), 2.11 (d, 1H, $J = 17.5$ Hz, CH_2), 2.19 (d, 1H, $J = 16.5$ Hz, CH_2), 2.22 (d, 1H, $J = 16.5$ Hz, CH_2), 4.45 (s, 2H, CH_2), 5.24 (s, 1H, CH^9), 7.16 (d, 2H, $J = 8.0$ Hz, Ar), 7.24 (m, 5H, Ar), 7.56 (d, 2H, $J = 8.5$ Hz, Ar), 7.67 (d, 2H, $J = 8.0$ Hz, Ar), 8.20 (d, 2H, $J = 8.5$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 27.2$, 29.8, 32.5, 33.6, 40.7, 41.5, 50.1, 113.3, 113.9, 124.1, 124.2, 128.0, 128.8, 128.8, 129.0, 130.6, 133.3, 135.9, 136.1, 136.6, 147.0, 151.0, 151.6, 163.4, 168.1, 195.6 ppm; IR (KBr): $\bar{\nu} = 3445$, 2960, 2872, 1766, 1714, 1668, 1643, 1575, 1508, 1429, 1361, 1257, 1155, 1097, 1018, 927, 837, 744, 696 cm^{-1}; HPLC/MS: *m/z* = 611 (M^+).

9-(4-Chlorophenyl)-2,6,6-trimethyl-4-(4-methylphenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4f**, $C_{27}H_{25}ClN_2O_3$)
Yellow solid; yield: 65% using CH (conventional heating), 71% using US (ultrasounds irradiation); TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.45$; m.p.: 193–195 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.91$ (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 2.07 (d, 1H, $J = 17.5$ Hz, CH_2), 2.13 (d, 1H, $J = 17.5$ Hz, CH_2), 2.18 (d, 1H, $J = 16.5$ Hz, CH_2), 2.21 (d, 1H, $J = 16.5$ Hz, CH_2), 2.47 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 5.12 (s, 1H, CH^9), 7.14 (d, 2H, $J = 8.0$ Hz, Ar), 7.28 (m, 2H, Ar), 7.34 (m, 4H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$, 23.4, 27.1, 29.4, 32.4, 33.6, 40.6, 50.3, 113.5, 114.5, 128.6, 128.8, 129.4, 130.5, 132.8, 134.6, 137.6, 140.0, 143.1, 151.7, 164.3, 168.8, 195.8 ppm; IR (KBr): $\bar{\nu} = 3435$, 2955, 2891, 1765, 1714, 1670, 1641, 1573, 1512, 1438, 1363, 1244, 1149, 1089, 972, 835, 748 cm^{-1}; HPLC/MS: *m/z* = 460 (M^+).

2,6,6-Trimethyl-4-(4-methylphenyl)-9-(3-nitrophenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4g**, $C_{27}H_{25}N_3O_5$)
Yellow solid; yield: 77% using CH (conventional heating), 83% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.41$; m.p.: 208–209 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.92$ (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.13 (d, 1H, $J = 17.5$ Hz, CH_2), 2.17 (d, 1H, $J = 17.5$ Hz, CH_2), 2.20 (d, 1H, $J = 16.5$ Hz, CH_2), 2.24 (d, 1H, $J = 16.5$ Hz, CH_2), 2.48 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 5.27 (s, 1H, CH^9), 7.18 (d, 2H, $J = 7.5$ Hz, Ar), 7.35 (d, 2H, $J = 8.0$ Hz, Ar), 7.50 (d, 1H, $J = 8.0$ Hz, Ar), 7.88 (d, 1H, $J = 7.7$ Hz, Ar), 8.07 (d, 1H, $J = 8.2$ Hz, Ar), 8.18 (s, 1H, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$, 23.5, 27.1, 29.4, 32.5, 34.1, 40.6, 50.2, 113.1, 113.8, 122.2, 122.6, 129.4, 130.7, 134.4, 134.7, 138.1, 140.2, 146.6, 148.8, 152.6, 164.0, 168.7, 195.8 ppm; IR (KBr): $\bar{\nu} = 3444$, 2956, 2868, 1768, 1710, 1670, 1645, 1577, 1529, 1438, 1365, 1344, 1246, 1151, 1103, 1035, 981, 827, 732, 688 cm^{-1}; HPLC/MS: *m/z* = 471 (M^+).

4-(4-Bromophenyl)-9-(4-chlorophenyl)-2,6,6-trimethyl-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4 h**, $C_{26}H_{22}BrClN_2O_3$)
Yellow solid; yield: 72% using CH (conventional heating), 73% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.48$; m.p.: 216–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.07 (d, 1H, $J = 17.5$ Hz, CH_2), 2.14 (d, 1H, $J = 17.5$ Hz, CH_2), 2.22 (d, 1H, $J = 16.5$ Hz, CH_2), 2.25 (d, 1H, $J = 16.5$ Hz, CH_2), 2.84 (s, 3H, CH_3), 5.14 (s, 1H, CH^9), 7.19 (d, 2H, $J = 8.5$ Hz, Ar), 7.29-7.35 (m, 4H, Ar), 7.70 (d, 2H, $J = 8.5$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.5$, 27.4, 29.4, 32.5, 33.7, 40.7, 50.2, 113.9, 115.1, 124.0, 128.9, 129.4, 130.6, 133.0, 133.2, 136.3, 137.2, 142.8, 150.9, 164.2, 168.6, 195.7 ppm; IR (KBr): $\bar{\nu} = 3462$, 2959, 2874, 1770, 1710, 1672, 1643, 1575, 1489, 1438, 1363, 1246, 1151, 1091, 1031, 981, 835, 748 cm^{-1}; HPLC/MS: *m/z* = 524 (M^+).

4-(4-Bromophenyl)-2,6,6-trimethyl-9-(3-nitrophenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4i**, $C_{26}H_{22}BrN_3O_5$)
Yellow solid; yield: 80% using CH (conventional heating), 85% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.38$; m.p.: 221–223 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.10 (d, 1H, $J = 17.5$ Hz, CH_2), 2.15 (d, 1H, $J = 17.5$ Hz, CH_2), 2.20 (d, 1H, $J = 16.5$ Hz, CH_2), 2.24 (d, 1H, $J = 16.5$ Hz, CH_2), 2.82 (s, 3H, CH_3), 5.26 (s, 1H, CH^9), 7.20 (d, 2H, $J = 8.5$ Hz, Ar), 7.51 (t, 1H, $J = 8.0$ Hz, Ar), 7.69 (d, 2H, $J = 8.5$ Hz, Ar), 7.88 (d, 1H, $J = 7.7$ Hz, Ar), 8.07 (d, 1H, $J = 7.5$ Hz, Ar), 8.15 (t, 1H, $J = 2.0$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.6$, 27.1, 29.4, 32.6, 34.1, 40.7, 50.2, 113.4, 114.3, 122.3, 122.5, 124.2, 129.5, 130.6, 133.3, 134.7, 136.0, 137.6, 146.3, 148.8, 151.8, 163.9, 168.5, 195.7 ppm; IR (KBr): $\bar{\nu} = 3444$, 2960, 2870, 1768, 1707, 1674, 1645, 1577, 1533, 1491, 1442, 1363, 1246, 1147, 1066, 1031, 983, 846, 734, 694 cm^{-1}; HPLC/MS: *m/z* = 535 (M^+).

4-(4-Bromophenyl)-2,6,6-trimethyl-9-(4-nitrophenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**4j**, $C_{26}H_{22}BrN_3O_5$)
Yellow solid; yield: 79% using CH (conventional heating), 79% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.45$; m.p.: 204–205 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.08 (d, 1H, $J = 17.5$ Hz, CH_2), 2.14 (d, 1H, $J = 17.5$ Hz, CH_2), 2.20 (d, 1H, $J = 16.5$ Hz, CH_2), 2.24 (d, 1H, $J = 16.5$ Hz, CH_2), 2.82 (s, 3H, CH_3), 5.25 (s, 1H, CH^9), 7.18 (d, 2H, $J = 8.5$ Hz, Ar), 7.57 (d, 2H, $J = 8.5$ Hz, Ar), 7.68 (d, 2H, $J = 8.5$ Hz, Ar), 8.19 (d, 2H, $J = 8.5$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.6$, 27.2, 29.3, 32.5, 34.5, 40.7, 50.1, 113.3, 114.0, 124.1, 124.2, 129.0, 130.5, 133.3, 136.0, 137.6, 147.0, 151.1, 151.6, 163.93, 168.4, 195.6 ppm; IR (KBr): $\bar{\nu} = 3444$, 2958, 2874, 1770, 1710, 1672, 1643, 1575, 1519, 1489, 1363, 1244, 1145, 1066, 1031, 979, 827, 738, 698 cm^{-1}; HPLC/MS: *m/z* = 535 (M^+).

2-Benzyl-4-(4-bromophenyl)-9-(4-fluorophenyl)-5,6,7,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline-1,3,8(2H,4H)-trione (**5**, $C_{30}H_{22}BrFN_2O_3$)
Yellow solid; yield: 67% using CH (conventional heating), 64% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.49$; m.p.: 206–208 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.98$–2.07 (m, 2H, CH_2), 2.32–2.39 (m, 2H, CH_2), 2.57-2.67 (m, 2H, CH_2), 4.70 (s, 2H, CH_2), 5.49 (s, 1H, CH^9), 6.89 (t, 2H, $J = 8.5$ Hz, Ar), 7.01 (d, 2H, $J = 8.5$ Hz, Ar), 7.20 (m, 2H, Ar), 7.28-7.35 (m, 5H, Ar), 7.50 (d, 2H, $J = 8.5$ Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.4$, 27.2, 31.2, 37.0, 41.6, 114.9, 115.1, 116.9, 117.4, 120.4, 127.9, 128.4, 128.8, 129.9, 130.0, 132.9, 136.4, 137.5, 140.3, 142.2, 164.0, 167.8, 172.0, 196.6 ppm; IR (KBr): $\bar{\nu} = 3308$, 3119, 2951, 2872, 1761, 1691, 1635, 1541, 1492, 1440, 1357, 1215, 1176, 1134, 1076, 1016, 958, 837, 796, 709 cm^{-1}; HPLC/MS: *m/z* = 556 (M^+).

7-Methyl-9-(4-methylphenyl)-5-(3-nitrophenyl)-5,9-dihydro-1H-pyrrolo[3′,4′:5,6]pyrido[2,3-d]pyrimidine-2,4,6,8(3H,7H)-tetrone (**6**, $C_{23}H_{17}N_5O_6$)
Yellow solid; yield: 74% using CH (conventional heating), 72% using US; TLC (CH_2Cl_2/MeOH, 5:0.1): $R_f = 0.40$; m.p.: 205–206 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.16$ (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 4.36 (s, 1H, CH^5), 6.43 (d, 2H, $J = 8.0$ Hz, Ar), 6.85 (d, 2H, $J = 8.0$ Hz, Ar), 7.31 (m, 3H, Ar), 7.85 (m, 1H, Ar), 10.89 (s, 1H, NH), 11.14 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.2$, 23.5, 52.2, 120.7, 123.5, 123.6, 128.1, 128.3, 134.1, 134.7, 136.4, 136.5, 141.4, 141.5, 146.6, 146.7, 151.1, 166.7, 168.4, 168.8, 172.9 ppm; IR (KBr): $\bar{\nu} = 3358$, 3277, 3093, 2924, 2864, 1749, 1712, 1691, 1633, 1527, 1462, 1435, 1394, 1365, 1348, 1259, 1220, 1180, 1114, 1010, 881, 817, 756, 680 cm^{-1}; HPLC/MS: *m/z* = 459 (M^+).

Acknowledgement This work was financially supported by the Ministry of Education and Science of Ukraine, Scientific Research Project (Project Number: 0116U006958).

References

1. Filimon SA, Hrib CG, Randoll LS, Neda I, Jones PG, Tamm M (2010) Z Anorg Allg Chem 636:691
2. Maftei E, Maftei CV, Franz MH, Kelter G, Fiebig HH, Tamm M, Neda I (2016) Rev Roum Chim 61:251
3. Neda I, Kaukorat T, Fischer AK (2003) Eur J Org Chem 19:3784

4. Neda I, Fodor E, Maftei CV, Mihorianu M, Ambrosi HD, Franz MH (2013) Eur J Org Chem 35:7876
5. Wall ME, Wani MC, Cook CE, Palmer KH, MacPhail AT, Sim GA (1966) J Am Chem Soc 88:3888
6. Ma ZZ, Hano Y, Nomura T, Chen YJ (1997) Heterocycles 46:541
7. Nagarapu L, Gaikwad HK, Bantu GR, Manikonda SR (2011) Eur J Med Chem 46:2152
8. Xiao XS, Antony S, Pommier Y, Cushman M (2006) J Med Chem 49:1408
9. Fujita M, Egawa H, Miyamoto T, Nakano J, Matsumoto J (1996) Eur J Med Chem 31:981
10. Crenshaw RR, Luke GM, Siminoff P (1976) J Med Chem 19:262
11. Isomae K, Morimoto S, Hasegawa H, Morita K, Kamei J (2003) Eur J Pharm 465:97
12. Carroll WA, Agrios KA, Altenbach RJ, Buckner SA, Chen Y, Coghlan MJ, Daza AV, Henry RF, Kort ME, Kym PR, Smith JC, Tang R, Turner SC, Whiteaker KL, Zhang H, Sullivan JP (2004) J Med Chem 47:3180
13. Anzini M, Cappelli A, Vomero S, Cagnotto A, Skorupska M (1992) Il Farmaco 47:191
14. Cappelli A, Giuliani G, Valenti S, Anzini M, Vomero S, Giorgi G, Sogliano C, Maciocco E, Biggio G, Concas A (2008) Bioorg Med Chem 16:3428
15. Peng H, Kim DI, Sarkaria JN, Cho YS, Abraham RT, Zalkow LH (2002) Bioorg Med Chem 10:167
16. Qiu Y, Bhattacharjee S, Kraft P, Jonh TM, Craig E, Haynes-Johnson D, Guan J, Jiang W, Macielag M, Sui Z, Clancy J, Lundeen S (2003) Eur J Pharmacol 472:73
17. Willemsens B, Vervest I, Ormerod D, Aelterman W, Fannes C, Mertens N, Marko IE, Lemaire S (2006) Org Process Res Dev 10:1275
18. Moran MD, Wilson AA, Elmore CS, Parkes J, Sadovski O, Graff A, Daskalakis ZJ, Houle S, Chapdelaine MJ, Vasdev N (2012) Bioorg Med Chem 20:4482
19. Chen ZP, Wang HB, Wang YQ, Zhu QH, Xie Y, Liu SW (2014) Tetrahedron 70:4379
20. Wang C, Jiang YH, Yan CG (2014) Mol Divers 18:809
21. Jiang YH, Xiao M, Yan CG (2016) RSC Adv 6:35609
22. Jiang YH, Yan CG (2016) Chin J Chem 34:1255
23. Eften'eva RI, Kushnir OV, Lyavinets OS, Mangalagiu II, Vovk MV (2016) Monatsh Chem 147:2127
24. Curran CW (1976) J Chem Soc Perkin Trans 1:975
25. Kantevari S, Chary MV, Vuppalatari VN (2007) Tetrahedron 63:13024
26. To QH, Lee YR, Kim SH (2012) Bull Kor Chem Soc 33:1170
27. Sun Y, Cai PJ, Wang XS (2015) Res Chem Intermed 41:7393
28. Alizadeh A, Rezvanian A (2014) C R Chim 17:103
29. Verma GK, Raghuvanshi K, Kumar R, Singh MS (2012) Tetrahedron Lett 53:399
30. Luche JL (1998) Synthetic Organic Sonochemistry. Plenum Press, New York
31. Cravotto G, Cintas P (2006) Chem Soc Rev 35:180
32. Belhani B, Bouzina A, Barredjem M, Aouf N (2015) Monatsh Chem 146:1871
33. Bejan V, Moldoveanu C, Mangalagiu II (2009) Ultrason Sonochem 16:312
34. Mantu D, Moldoveanu C, Nicolescu A, Deleanu C, Mangalagiu II (2009) Ultrason Sonochem 16:452
35. Bejan V, Mantu D, Mangalagiu II (2012) Ultrason Sonochem 19:999
36. Zbancioc G, Florea O, Jones P, Mangalagiu II (2012) Ultrason Sonochem 19:399
37. Zbancioc G, Mangalagiu II, Moldoveanu C (2015) Ultrason Sonochem 23:376
38. Yin G, Zhu Y, Wang N, Lu P, Wang Y (2013) Tetrahedron 69:8353