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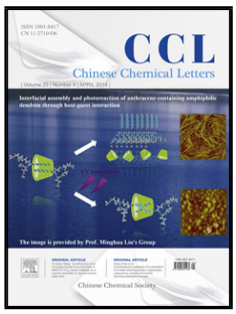

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Graphical Abstract

Microwave irradiation: Novel and facile methods for the synthesis of new pyrimidinones

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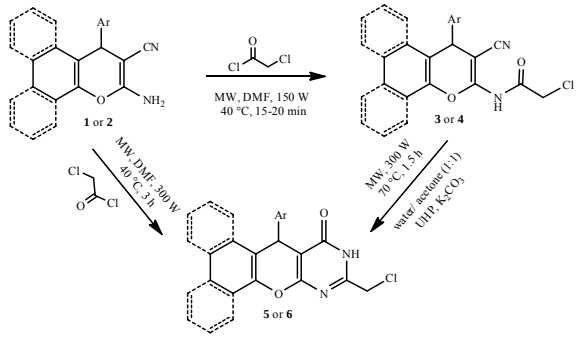

A synthesis of new pyrimidinones by two different methods utilizing microwave (MW) irradiation is described.

Original article

Microwave irradiation: Novel and facile methods for the synthesis of new pyrimidinones

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ABSTRACT

We describe here a rapid process for the preparation of new 9-chloromethyl-12-aryl-10,12-dihydrobenzo[5,6]chromeno[2,3-*d*]pyrimidin-11-ones **5a-d** and 10-chloromethyl-7-aryl-7,9-dihydrobenzo[7,8]chromeno[2,3-*d*]pyrimidin-8-ones **6a-d** by two different methods utilizing microwave irradiation. This methodology provides better yields (72%-80%) and high purity of the title compounds.

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1. Introduction

Heterocycles are a very important class of compounds and an interesting field for research with great opportunities for the synthesis of novel drugs. Pyrimidinone derivatives are widely distributed in nature and exhibit various biological activities such as antimalarials [1-3], antibacterial [4], antifungal [5], anti-HIV [6], antiviral [7], anticancer [8], and anti-inflammatory agents [9, 10]. In previous reports we demonstrated that aminonitrile naphtopyranique derivatives **1** or **2** are basic substrates for the synthesis of a new series of pyrimidinones [11-12], and new molecules with a broad range of biological activities, such as triazolopyrimidins [13] and quinoline derivatives [14-16]. We used microwave assisted synthesis to control pollution, convert hours into minutes in chemical preparation, enhance yields and stop excessive use of solvents [17].

The present work describes the synthesis of a new series of chloromethylnaphtopyranopyrimidinones **5a-d** and **6a-d** under mild conditions using microwave irradiation.

2. Experimental

Commercially available, reagent grade chemicals were used as received without additional purification. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with detection by UV light at 254 nm. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (4000-400 cm^{-1}) using KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were recorded on an AC Bruker spectrometer at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0 ppm) as internal reference and the following multiplicity abbreviations used: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) were recorded on a spectrometer (Finnigan LCQ Deca XP Max). The ionization method used is electrospray (ESI). All solvents were dried by standard methods. The microwave assisted reactions were carried out in a synthetic microwave apparatus: Monowave 300 with a maximum power of 300 W.

General procedure of method 1: To a solution of 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles **1a-d** or 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles **2a-d** (0.5g, 1.6 mmol) in DMF (4 mL), chloroacetylchloride (0.36 g, 3.2 mmol) was added dropwise at 0 °C. The reaction mixture was irradiated in a microwave at 40 °C, for 15-20 min at a power of 150 W. After cooling, 100 mL of water were added. A precipitate formed and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet) to give **3a-d** or **4a-d**. To a mixture of **3a-d** or **4a-d** (0.1 g, 0.26 mmol) and acetone/H_2O (1:1, v/v, 4 mL) was added K_2CO_3 (0.053 mmol) and urea hydrogen peroxide (UHP) (0.53 mmol). The reaction mixture was irradiated in a microwave at 70 °C, for 1.5-2 h at a power of 300 W. After cooling, 100 mL of water were added. A precipitate formed and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet) to give compounds **5a-d** and **6a-d**.

General procedure of method 2: A mixture of **1a-d** or **2a-d** (1 g, 2.4 mmol) and chloroacetylchloride (6 equiv.) in DMF (4 mL), was irradiated in a microwave at 40 °C, for 2 h. at a power of 300 W. After cooling, the solid product that formed was filtered, washed with ether, and dried, to give compounds **5a-d** or **6a-d** in good yields.

Characterization data of the synthesized compounds are listed below.

2-Chloro-*N*-(2-cyano-1-phenyl-1*H*-benzo[*f*]chromen-3-yl)-acetamide (**3a**): Yellow solid, mp 236-238 °C; IR (KBr, cm^{-1}): 1670 (C=O), 2222(CN), 3340(NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.35 (s, 2H), 5.69 (s, 1H), 7.31–8.01 (m, 11H, arom.), 11.06 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.7, 43.0, 85.9, 114.8, 116.9, 117.3, 124.1, 125.9, 127.8, 127.8 (2C), 128.0 (2C), 129.4 (2C), 130.3, 130.5, 131.8, 143.7, 147.3, 150.5, 165.6; MS (ESI): *m/z* 373 (M^-).

2-Chloro-*N*-(2-cyano-1-*p*-methylphenyl-1*H*-benzo[*f*]chromen-3-yl)-acetamide (**3b**): Yellow solid, mp 228-230 °C; IR (KBr, cm^{-1}): 1723 (C=O), 2210 (CN), 3324 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.21 (s, 3H), 4.35 (s, 2H), 5.63 (s, 1H), 7.10–8.00 (m, 10H, arom.), 11.02 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0, 39.9, 43.0, 86.1, 114.9, 117.0, 117.2, 124.2, 125.8, 127.6, 127.9, 128.8 (2C), 129.7 (2C), 130.3, 130.4, 131.8, 137.1, 140.8, 147.2, 150.3, 165.6; MS (ESI): *m/z* 387 (M^-).

2-Chloro-*N*-(2-cyano-1-*p*-methoxyphenyl-1*H*-benzo[*f*]chromen-3-yl)-acetamide (**3c**): Yellow solid, mp 230-232 °C, IR (KBr, cm^{-1}): 1720 (C=O), 2210 (CN), 3216 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.66 (s, 3H), 4.45 (s, 2H), 5.68 (s, 1H), 7.01–8.01 (m, 10H, arom.), 11.08 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42,3, 43.1, 55.6, 85.7, 112.4, 114.6, 114.6, 116.9, 117.1, 120.2, 124.3, 125.8, 127.8, 129.1 (2C), 130.4, 130.5, 131.8, 145.2, 147.4, 150.88, 159.8, 165.7; MS (ESI): *m/z* 403 (M^-).

2-Chloro-*N*-(2-cyano-1-*m*-methoxyphenyl-1*H*-benzo[*f*]chromen-3-yl)-acetamide (**3d**): Yellow solid, mp 226-228 °C; IR (KBr, cm^{-1}): 1715 (C=O), 2220 (CN), 3214 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.70 (s, 3H), 4.35 (s, 2H), 5.66 (s, 1H), 6.79–8.01 (m, 10H, arom.), 11.04 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.9, 43.0, 55.4, 85.8, 112.5, 114.4, 114.7, 116.9, 117.2, 120.2, 124.2, 125.9, 127.8, 129.0 (2C), 130.4, 130.5, 131.7, 145.1, 147.3, 150.66, 159.9, 165.6; MS (ESI): *m/z* 403(M^-).

2-Chloro-*N*-(3-cyano-4-phenyl-4*H*-benzo[*h*]chromen-2-yl)-acetamide (**4a**): Yellow solid, mp 220-222 °C; IR (KBr, cm^{-1}): 1660 (C=O), 2200 (CN), 3300 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.45 (s, 2H), 5.25 (s, 1H), 7.18–8.16 (m, 11H, arom.), 11.19 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.4, 43.2, 83.7, 114.6, 117.0, 117.5, 121.0, 123.1, 125.6, 126.3, 127.6 (2C), 128.1, 128.2, 128.4 (2C), 129.4 (2C), 133.3, 143.2, 143.7, 151.5, 165.7; MS (ESI): *m/z* 373 (M^-).

2-Chloro-*N*-(3-cyano-4-*p*-methylphenyl-4*H*-benzo[*h*]chromen-2-yl)-acetamide (**4b**): Yellow solid, mp 214-216 °C; IR (KBr, cm^{-1}): 1668 (C=O), 2210 (CN), 3350 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H) 4.44 (s, 2H), 5.19 (s, 1H), 7.15–8.15 (m, 10H, arom.), 11.17 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0, 42.0, 43.2, 117.0, 117.6, 121.0, 123.1, 125.5, 126.3, 127.5, 128.2, 128.3 (2C), 129.9 (2C), 133.2, 137.3, 140.9, 143.1, 151.3, 165.7; MS (ESI): *m/z* 387(M^-).

2-Chloro-*N*-(3-cyano-4-*p*-methoxyphenyl-4*H*-benzo[*h*]chromen-2-yl)-acetamide (**4c**): Yellow solid, mp 210-212 °C; IR (KBr, cm^{-1}): 1664 (C=O), 2213 (CN), 3250 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.73 (s, 3H), 4.60 (s, 2H), 5.69 (s, 1H), 7.03–8.03 (m, 10H,

arom.), 11.10 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.1, 43.4, 55.6, 86.7, 112.8, 114.5, 114.7, 116.8, 117.3, 120.2, 124.2, 125.9, 127.8, 129.0 (2C), 130.4, 130.5, 131.8, 145.2, 147.3, 150.6, 159.9, 165.7; MS (ESI): *m/z* 403 (M^-).

2-Chloro-*N*-(3-cyano-4-*m*-methoxyphenyl-4*H*-benzo[*h*]chromen-2-yl)-acetamide (**4d**): Yellow solid, mp 212-214 °C; IR (KBr, cm^{-1}): 1670 (C=O), 2200 (CN), 3320 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 3H) 4.45 (s, 2H), 5.22 (s, 1H), 6.85–8.15 (m, 10H, arom.), 11.17 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.3, 43.2, 55.5, 83.7, 113.1, 114.3, 114.5, 117.0, 117.4, 120.5, 121.0, 123.1, 125.6, 127.6, 128.0, 129.2 (2C), 130.6, 133.3, 145.2, 151.6, 160.0, 165.8; MS (ESI): *m/z* 403 (M^-).

9-Chloromethyl-12-phenyl-10,12-dihydrobenzo[5,6]chromeno[2,3-*d*]pyrimidin-11-ones (**5a**): White solid, mp 266-268 °C; IR (KBr, cm^{-1}): 1663 (C=O), 3396 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.46 (s, 2H), 5.21(s, 1H), 7.05–8.11 (m, 11H, arom.), 12.97 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.3, 42.2, 101.5, 112.5, 119.5, 121.5, 122.8, 124.5, 127.4, 128.0 (2C), 128.4 (2C),129.0 (2C), 129.7, 133.9, 137.8, 143.5, 158.6, 161.2, 166.1; MS (ESI): *m/z* 373 (M^-).

9-Chloromethyl-12-*p*-methylphenyl-10,12-dihydrobenzo[5,6]chromeno[2,3-*d*]pyrimidin-11-ones (**5b**): White solid, mp 268-270 °C; IR (KBr, cm^{-1}): 1683 (C=O), 3440 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.41 (s, 3H) 4.38 (s, 2H), 5.18 (s, 1H), 7.26–8.28 (m, 10H, arom.), 12.78 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3, 41.1, 43.2, 85.2, 105.1, 114.5, 120.2, 121.2, 123.6, 124.9, 127.1, 128.3 (2C), 128.9 (2C), 129.5 (2C), 133.2, 137.8, 143.8, 158.3, 161.7, 165.8; MS (ESI): *m/z* 387 (M^-).

9-Chloromethyl-12-*p*-methoxyphenyl-10,12-dihydrobenzo[5,6]chromeno[2,3-*d*]pyrimidin-11-ones (**5c**): White solid, mp 266-268 °C; IR (KBr, cm^{-1}): 1655 (C=O), 3390 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.65 (s, 3H) 4.49 (s, 2H), 5.28 (s, 1H), 7.19–8.19 (m, 10H, arom.), 12.92 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.3, 42.6, 55.5, 85.4, 102.8, 114.3, 119.6, 121.1, 123.5, 124.9, 127.1, 127.8 (2C), 128.2 (2C), 129.4 (2C), 133.2, 137.7, 143.9, 158.4, 161.4, 166.4; MS (ESI): *m/z* 403 (M^-).

9-Chloromethyl-12-*m*-methoxyphenyl-10,12-dihydrobenzo[5,6]chromeno[2,3-*d*]pyrimidin-11-ones (**5d**): White solid, mp 270-272 °C; IR (KBr, cm^{-1}): 1656 (C=O), 3374 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.66 (s, 3H) 4.45 (s, 2H), 5.24 (s, 1H), 7.15–8.15 (m, 10H, arom.), 12.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.8, 44.0, 55.3, 95.7, 111.5, 114.7, 117.3, 118.0, 120.2, 123.8, 125.5, 127.5, 129.0, 129.6, 130.1, 130.7, 131.5, 146.6, 147.2, 148.9, 159.5, 165.0, 169.2; MS (ESI): *m/z* 403 (M^-).

10-Chloromethyl-7-phenyl-7,9-dihydrobenzo[7,8]chromeno[2,3-*d*]pyrimidin-8-ones (**6a**): White solid, mp 256-258 °C; IR (KBr, cm^{-1}): 1665 (C=O), 3401 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.45 (s, 2H), 5.20 (s, 1H), 6.91–8.20 (m, 11H, arom.), 13.01 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.7, 43.4, 99.5, 113.4, 118.3, 119.5, 123.4, 123.9, 127.3, 127.8 (2C), 128.1(2C), 129.5 (2C), 134.4, 137.7, 143.8, 147.3, 158.4, 163.1, 168.1; MS (ESI): *m/z* 373 (M^-).

10-Chloromethyl-7-*p*-methylphenyl-7,9-dihydrobenzo[7,8]chromeno[2,3-*d*]pyrimidin-8-ones (**6b**): White solid, mp 252-254 °C; IR (KBr, cm^{-1}): 1685 (C=O), 3442 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.45 (s, 3H) 4.35 (s, 2H), 5.15 (s, 1H), 7.25–8.29 (m, 10H, arom.), 12.91 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.4, 40.3, 42.8, 102.1, 113.9, 119.8, 121.3, 123.4, 124.7, 127.2, 127.8 (2C), 128.4 (2C), 129.5 (2C), 133.5, 137.9, 143.8, 147.3, 158.5, 165.1, 167.4; MS (ESI): *m/z* 387 (M^-).

10-Chloromethyl-7-*p*-methoxyphenyl-7,9-dihydrobenzo[7,8]chromeno[2,3-*d*]pyrimidin-8-ones (**6c)**: White solid, mp 250-252 °C; IR (KBr, cm^{-1}): 1682 (C=O), 3387 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.66 (s, 3H) 4.45 (s, 2H), 5.24 (s, 1H), 7.15–8.15 (m, 10H, arom.), 12.96 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.2, 42.6, 55.4, 102.8, 114.2, 119.6, 121.1, 123.5, 124.9, 127.1, 128.1 (2C), 128.9 (2C), 129.4 (2C), 133.1, 137.7, 143.9, 147.6, 158.4, 161.4, 167.2; MS (ESI): *m/z* 403 (M^-).

10-Chloromethyl-7-*m*-methoxyphenyl-7,9-dihydrobenzo[7,8]chromeno[2,3-*d*]pyrimidin-8-ones (**6d**): White solid, mp 250-252 °C; IR (KBr, cm^{-1}): 1683 (C=O), 3350 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.62 (s, 3H) 4.44 (s, 2H), 5.27 (s, 1H), 7.11–8.11 (m, 10H, arom.), 12.80 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.5, 42.7, 55.5, 101.9, 113.3, 119.6, 121.3, 123.6, 124.8, 127.1, 128.1 (2C), 128.8 (2C), 129.5 (2C), 133.2, 137.6, 143.8, 147.6, 158.4, 161.5, 167.6; MS (ESI): *m/z* 403 (M^-).

3. Results and discussion

The compounds, 9-chloromethyl-12-aryl-10,12-dihydrobenzo[5,6]chromeno[2,3-*d*]pyrimidin-11-ones **5a-d** and 10-chloromethyl-7-aryl-7,9-dihydrobenzo[7,8]chromeno[2,3-*d*]pyrimidin-8-ones **6a-d**, were synthesized by two different methods.

In the first method, the synthesis of compounds **5** and **6** involves two steps. Starting materials 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles **1a-d** or 2-amino-4-aryl-4*H*-benzo[*h*]chromene-3-carbonitriles **2a-d** reacted with excess of chloroacetylchloride (2 equiv.) to afford 2-chloro-*N*-(2-cyano-1-aryl-1*H*-benzo[*f*]chromen-3-yl)-acetamide **3a-d** or 2-chloro-*N*-(3-cyano-4-aryl-4*H*-benzo[*h*]chromen-2-yl)-acetamide **4a-d**, followed by Radziszewski's reaction using urea hydrogen peroxide (UHP) as a mild, safe and non-hazardous oxidizing agent, leading to compounds **5** and **6**. We proceeded initially by conducting the first step in both classical and microwave-assisted conditions, to compare these two methods (Scheme 1). Under classical conditions, compounds **3** and **4** are obtained in 39%-51% yields after 48 h reaction time, while with microwave irradiation the same products are isolated in 87%-98% yields after only 15-20 min reaction time (Table1). We then compared classical conditions *versus* microwave-assisted procedures for the second step of the first method. In classical conditions (72 h at 84 °C), the derivatives **5a-d** and **6a-d** are obtained in 39%-50% yields, and under microwave irradiation (2 h, reaction time at 70 °C), the same products are prepared in 69%-80% yields (Table 2). The mechanism of transformation of substrates **3** and **4** to products **5** and **6** proceed *via* oxidation of the nitrile function to amide followed by cyclization (Scheme 2).

In the second method, a one step reaction allows the synthesis of pyrimidinones derivatives **5a-d** and **6a-d** (Scheme 3).

Condensation of compounds **1a-d** or **2a-d** with a large excess (6 equiv.) of chloroacetylchloride provides the final product **5** or **6**. In this study, we investigate the reaction under classical conditions by varying the temperature and reaction time. After several assays, the optimum result is obtained when the reaction is carried out in DMF for seven days, at room temperature, but unfortunately, the yields (32%-35%) obtained were much lower than those previously observed. Under microwave irradiation, the best results are obtained in

DMF at 40 °C during 120 min of reaction (44%-56%) (Table 3). However, it was very difficult to determine conditions providing **5** or **6** without traces of intermediates **3** and **4**, even by increasing reaction time and temperature.

4. Conclusion

In the present study, we have investigated the preparation of new naphtopyranopyrimidinones **5a-d** and **6a-d** using microwave irradiation. This method is easily and rapidly performed and affords these compounds in very good yield. A second method allows us to readily synthesize, in one step, the same compounds from aminonitrile naphtopyranque and chloroacetylchloride. In conclusion, the microwave assisted methods offer significant advantages for the rapid synthesis in high yield and purity of all compounds presented in this study. The required reaction times and volumes of solvents are much lower.

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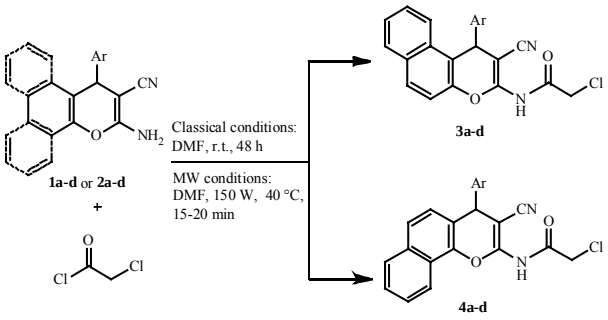
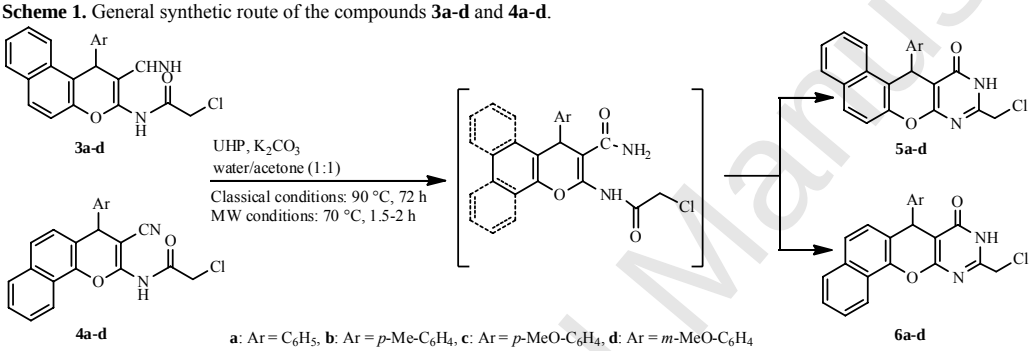


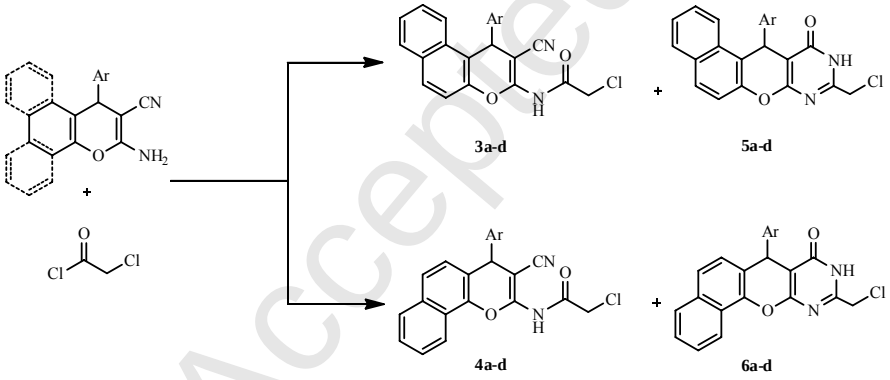
a: Ar = C_6H_5, **b**: Ar = *p*-Me-C_6H_4, **c**: Ar = *p*-MeO-C_6H_4, **d**: Ar = *m*-MeO-C_6H_4

Scheme 1. General synthetic route of the compounds **3a-d** and **4a-d**.



a: Ar = C_6H_5, **b**: Ar = *p*-Me-C_6H_4, **c**: Ar = *p*-MeO-C_6H_4, **d**: Ar = *m*-MeO-C_6H_4

Scheme 2. General synthetic route of the target compounds **5a-d** and **6a-d**.



a: Ar = C_6H_5, **b**: Ar = *p*-Me-C_6H_4, **c**: Ar = *p*-MeO-C_6H_4, **d**: Ar = *m*-MeO-C_6H_4

Scheme 3. General synthetic route of the target compounds **5a-d** and **6a-d** in one step.

Table 1
Microwave-assisted synthesis of compounds **3a-d** and **4a-d**.

Products	Ar	CC[a]		MW[b]	
		Yield (%)	Time (h)	Yield[c] (%)	Time (min)
3a	C_6H_5	51	48	98	15
3b	*p*-MeC_6H_4	44	48	89	16
3c	*p*-MeOC_6H_4	50	48	90	17
3d	*m*-MeOC_6H_4	42	48	87	17
4a	C_6H_5	45	48	96	15
4b	*p*-MeC_6H_4	45	48	90	20
4c	*p*-MeOC_6H_4	39	48	93	20
4d	*m*-MeOC_6H_4	40	48	88	20

[a] CC: classical conditions.
[b] MW: microwave conditions.
[c] Isolated yield.

Table 2
Microwave-assisted synthesis of compounds **5a-d** and **6a-d** with method **1**.

Products	CC[a]		MW[b]	
	Yield (%)	Time (h)	Yield[c] (%)	Time (h)
5a	48	72	78	1.5
5b	39	72	69	2
5c	42	72	72	1.5
5d	42	72	75	1.5
6a	50	72	80	2
6b	44	72	74	2
6c	45	72	78	1.5
6d	42	72	69	1.5

[a] CC: classical conditions.
[b] MW: microwave conditions.
[c] Isolated yield.

Table3
Microwave-assisted synthesis of compounds **5a-d** and **6a-d** with method **2**.

Products	CC[a]		MW[b]	
	Yield (%)	Time (days)	Yield[c] (%)	Time (h)
5a	35	6	50	2
5b	35	7	55	2.5
5c	32	6	56	2
5d	32	7	53	3
6a	35	7	48	2
6b	33	7	44	3
6c	35	6	52	2.5
6d	32	7	49	3

[a] CC: classical conditions.
[b] MW: microwave conditions.
[c] Isolated yield.