Supporting Information
for DOI: 10.1055/s-0028-1083631
© Georg Thieme Verlag KG Stuttgart · New York 2008
SUPPORTING INFORMATION

Rapid Pd-Catalyzed C3-Arylation of 2(1H)-Pyrazinones: Effect of simultaneous cooling on microwave-assisted reactions on solid support

Brajendra K. Singh, a,b Virinder S. Parmar, b and Erik Van der Eycken a*

aLaboratory for Organic & Microwave-Assisted Chemistry, Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Leuven
bBioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

* To whom correspondence should be addressed. E-mail: erik.vandereycken@chem.kuleuven.be

Table of Contents

General remarks – Page S2
Microwave Irradiation Experiments – Page S2
Representative experimental procedure for the cross-coupling reaction under conventional condition – Page S2
Representative experimental procedure for the cross-coupling reaction under Microwave Irradiation with Simultaneous Cooling at 35 °C – Page S3
Temperature-Power profile - Page S3
Spectral data of compounds 3{1-14}, 3{16-21}, 3{23} and 3{24,25,27,28,30} & 3{33-41} – Pages S4 to S9
Copy of the 1H- and 13C Spectra – Pages S10 to S43
General Remarks:

$^1$H NMR spectra were recorded on a Bruker Avance 300 MHz and 400 MHz instruments, using CDCl$_3$. The $^1$H and $^{13}$C chemical shifts are reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference. 

Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150-250 °C as required. High resolution EI-mass spectra were performed with a resolution of 10000. The low resolution spectra were obtained with a HP5989A MS instrument. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV$_{254}$ and 70-230 mesh silicagel (E.M.Merck)) were used. The Pd(PPh$_3$)$_4$, CuTC and boronic acids were purchased from Acros Organics (Janssen Pharmaceutical, Geel) and were used without further purification. All starting pyrazinones were prepared according to a known literature procedure.$^1$ All the compounds were fully characterised by comparison of their spectral data and melting points. Melting points of the compounds are uncorrected.

Microwave Irradiation Experiments:

All microwave irradiation experiments were carried out in a dedicated CEM-Discover-Coolmate™ monomode microwave apparatus (CEM Corporation P.O. Box 200 Matthews, NC 28106), operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. Reaction mixtures were efficiently stirred with a magnetic stirrer. The reactions were carried out in an open 10 mL double walled glass vial which was cooled to 0 °C - 35 °C using a microwave transparent cooling liquid.$^2$ The temperature of the cooling liquid was between 15 °C and 18 °C. Irradiation and cooling were started simultaneously, starting with the reaction mixture at rt. The temperature was measured with a fiber-optic probe device inserted into the reaction vessel (a schematic representation of the set-up can be found at http://cemsynthesis.com/).

General Procedure of Liebeskind Cross-Coupling of Pyrazinone 1{1} with Boronic Acids :

**Under conventional condition**: To a suspension of resin-bound pyrazinone, obtained from 0.176 mmol of trityl protected resin A1, in THF (5 mL) were added a boronic acid (0.53 mmol, 3 equiv), CuTC (0.35 mmol, 2 equiv) and Pd(PPh$_3$)$_4$ (0.0115 g, 0.01 mmol, 5 mol%). The reaction mixture was heated at different temperature for various time interval (Table 1). Reaction was monitored by GC-MS and TLC. After completion of the reaction, the solvent was filtered of with a polypropylene frit cartridge, and the resin was washed with THF-MeOH (1:1, v/v, 5 mL 3) and THF (5 mL x 3). The same procedure was repeated for the second time with completely washed and dried resin. The combined filtrate was absorbed on silica gel. The residue was loaded on a short silica gel plug and eluted with a mixture DCM-$n$-hexane (9:1). The solvent was concentrated in vacuum to provide 3-arylated pyrazinones 3{1}-3{5}.


$^2$ Cooling liquid used is Galden HT-110, purchased from Solvay Solexis, Thorofare, New Jersey.
**Under microwave irradiation condition:** To a suspension of resin-bound pyrazinone, obtained from 0.176 mmol of trityl protected resin A1, in THF (5 mL) were added a boronic acid (0.53 mmol, 3 equiv), CuTC (0.35 mmol, 2 equiv) and Pd(PPh$_3$)$_4$ (0.0115 g, 0.01 mmol, 5 mol%). The mixture was irradiated at different temperature at various power for different time interval (Table 3). After completion of the reaction, the solvent was filtered of with a polypropylene frit cartridge, and the resin was washed with THF-MeOH (1:1, v/v, 5 mL 3) and THF (5 mL x 3). The same procedure was repeated for the second time with completely washed and dried resin. The combined filtrate was absorbed on silica gel. The residue was loaded on a short silica gel plug and eluted with a mixture DCM-n-hexane (9:1). The solvent was concentrated in vacuum to provide 3-arylated pyrazinones 3{1}-3{32}.

**Figure 1:** Comparison of the Temperature-Power profiles

---

T = temperature (°C) and P = power (W)
All reactions were run for 1 h with a maximum power of 300W
T1 and P1: reaction at 35 °C and simultaneous liquid cooling
T2 and P2: reaction at 65 °C with simultaneous air cooling
T3 and P3: reaction at 65 °C without cooling
5-chloro-3-phenyl-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(1)). It was obtained as a yellow oil in 58 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 8.36-8.33\) (m, 2H), 7.44-7.42 (m, 3H), 7.31-7.28 (d, 2H, \(J = 8.2\) Hz), 7.16 (s, 1H), 6.91-6.88 (d, 2H, \(J = 9.12\) Hz), 5.04 (s, 2H), 3.79 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 160.10, 154.50, 152.24, 134.94, 130.74, 130.46, 129.37, 128.21, 126.56, 126.35, 125.22, 114.68, 55.41, 52.48. HRMS (EI): calcd for C\(_{19}\)H\(_{15}\)O\(_2\)Cl: 326.0822, found: 326.0817

5-chloro-3-(3-fluoromethylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(2)). It was obtained as a yellow solid m.p. 107-108 °C in 53 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 8.72\) (s, 1H), 8.63-8.60 (m, 1H), 7.71-7.68 (m, 1H), 7.58-7.53 (m, 1H)), 7.32-7.30 (d, 2H, \(J = 8.2\) Hz), 7.23 (s, 1H), 6.93-6.90 (d, 2H, \(J = 9.1\) Hz), 5.08 (s, 2H), 3.8 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 160.18, 154.25, 150.18, 135.50, 132.40, 121.97, 130.35, 129.03, 128.55, 126.98, 126.46, 126.08, 114.72, 114.23, 55.31, 52.49. HRMS (EI): calcd for C\(_{19}\)H\(_{15}\)O\(_2\)F\(_2\)Cl: 394.0696, found: 394.0684.

5-chloro-3-(3-ethoxyphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(3)). It was obtained as a yellow oil in 60 % yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.99-7.95\) (m, 2H), 7.34-7.25 (m, 3H), 7.14 (s, 1H), 7.00-6.98 (m, 1H), 6.89-6.87 (d, 2H, \(J = 8.36\) Hz), 5.03 (s, 2H), 4.11-4.06 (q, 2H, \(J = 6.9\) Hz), 3.76 (s, 3H), 1.42-1.39 (t, 3H, \(J = 6.9\) Hz). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 160.13, 158.78, 154.50, 151.9, 136.19, 130.46, 129.18, 126.41, 125.32, 121.93, 117.70, 114.81, 114.72, 63.66, 55.44, 52.45, 14.92. HRMS (EI): calcd for C\(_{20}\)H\(_{19}\)O\(_2\)Cl: 370.1084, found: 370.1071.

5-chloro-3-(4-methoxyphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(4)). It was obtained as a yellow solid m.p. 96-97 °C in 63 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 8.44-8.41\) (d, 2H, \(J = 9.1\) Hz), 7.30-7.27 (d, 2H, \(J = 8.2\) Hz), 7.1 (s, 1H), 6.95-6.88 (m, 4H), 5.03 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 161.78, 160.01, 154.53, 151.60, 131.26, 130.37, 127.75, 126.53, 124.07, 114.62, 113.56, 55.41, 52.36. HRMS (EI): calcd for C\(_{19}\)H\(_{15}\)O\(_2\)Cl: 356.0928, found: 356.0938.

5-chloro-3-(4-tert.butylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(5)). It was obtained as a yellow solid m.p. 98-99 °C in 54 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 8.31-8.28\) (d, 2H, \(J = 8.22\) Hz), 7.46-7.43 (d, 2H, \(J = 9.13\) Hz), 7.30-7.20 (d, 2H, \(J = 8.22\) Hz), 7.13 (s, 1H), 6.90-6.87 (d, 2H, \(J = 9.15\) Hz), 5.04 (s, 2H), 3.79 (s, 3H), 1.33 (s, 9H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 160.10, 154.56, 154.16, 152.40, 132.26, 130.43, 129.18, 126.56, 125.22, 124.74, 114.68, 55.44, 52.39, 34.97, 31.25. HRMS (EI): calcd for C\(_{22}\)H\(_{23}\)O\(_2\)Cl: 382.1448, found: 382.1447.

5-chloro-3-(3-bromophenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(6)). It was obtained as a dark yellow solid m.p. 109-110 °C in 35 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 8.55\) (s, 1H), 8.37-8.34 (d, 1H, \(J = 8.22\) Hz), 7.57-7.55 (d, 1H, \(J = 6.39\) Hz), 7.32-7.25 (m, 3H), 7.20 (s, 1H), 6.92-6.89 (d, 2H, \(J = 8.22\) Hz), 5.05 (s, 2H), 3.80 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 160.19, 154.31, 150.32, 136.77, 133.60, 132.11, 130.49, 129.73, 127.97, 126.56, 126.11, 126.02, 122.39, 114.78, 55.47, 52.66. HRMS (EI): calcd for C\(_{19}\)H\(_{15}\)O\(_2\)ClBr: 403.9927, found: 403.9930.

5-chloro-3-(2-fluorophenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3(7)). It was obtained as a yellow solid m.p. 69-70 °C in 58 % yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.64-7.59\) (m, 1H), 7.46-7.39 (m, 1H), 7.33-7.31(d, 2H, \(J = 8.22\) Hz) 7.23-
7.21 (m, 2H) 7.18-7.11 (m, 1H) 6.92-6.90 (d, 2H, J = 8.22 Hz), 5.05 (s, 2H), 3.80 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 161.89, 160.17, 159.38, 153.91, 152.25, 131.83, 131.75, 131.25, 131.22, 130.64, 130.52, 126.24, 126.17, 126.11, 123.99, 123.96, 123.64, 123.55, 116.15, 115.93, 114.70, 55.33, 52.52. HRMS (EI): calcd for C\(_{18}\)H\(_{14}\)O\(_2\)N\(_2\)ClF: 344.0728, found: 344.0734.

5-chloro-3-(3-fluorophenyl)-1-(4-methoxybenzyl)-2(1\(\text{H}\))-pyrazinone (3\{8\}). It was obtained as a dark yellow solid m. p. 107-108 °C in 60 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.23-8.14 (m, 2H), 7.43-7.36 (m, 1H), 7.33-7.30 (d, 2H, J = 8.22 Hz) 7.20-7.14 (m, 2H) 6.92-6.90 (d, 2H, J = 8.22 Hz), 5.07 (s, 2H), 3.81 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 164.25, 161.02, 160.22, 154.38, 150.57, 130.55, 129.64, 126.53, 126.17, 125.89, 125.13, 117.82, 117.55, 116.45, 116.15, 114.81, 114.38, 55.50, 52.63. HRMS (EI): calcd for C\(_{18}\)H\(_{14}\)O\(_2\)N\(_2\)ClF: 344.0728, found: 344.0732.

5-chloro-3-(4-fluorophenyl)-1-(4-methoxybenzyl)-2(1\(\text{H}\))-pyrazinone (3\{9\}). It was obtained as a yellow solid m. p. 111-113 °C in 59 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.46-8.42 (m, 2H), 7.32-7.26 (m, 2H), 7.17-7.08 (m, 3H), 6.92-6.89 (m, 2H), 5.05 (s, 2H), 3.80 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 166.07, 162.72, 160.16, 154.44, 150.99, 131.77, 131.65, 131.16, 130.46, 115.38, 115.11, 55.44, 52.57. HRMS (EI): calcd for C\(_{18}\)H\(_{14}\)O\(_2\)N\(_2\)ClF: 344.0728, found: 344.0728.

5-chloro-3-(2,4-difluorophenyl)-1-(4-methoxybenzyl)-2(1\(\text{H}\))-pyrazinone (3\{10\}). It was obtained as a yellow solid m.p. 105-106 °C in 61 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.66-7.62 (m, 1H), 7.32-7.25 (m, 3H), 6.92-6.89 (m, 4H), 5.04 (s, 2H), 3.80 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 160.22, 154.28, 153.80, 153.61, 151.66, 151.51, 150.42, 150.23, 148.29, 148.22, 131.83, 130.49, 126.47, 126.05, 125.89, 118.80, 118.52, 114.78, 114.35, 55.44, 52.66. HRMS (EI): calcd for C\(_{18}\)H\(_{13}\)O\(_2\)N\(_2\)ClF\(_2\): 362.0634, found: 362.0630.

5-chloro-3-(3,4-difluorophenyl)-1-(4-methoxybenzyl)-2(1\(\text{H}\))-pyrazinone (3\{11\}). It was obtained as a yellow solid m.p. 80-81 °C in 54 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.40-8.33 (m, 1H), 8.26 (bs, 1H), 7.31-7.28 d, 2H, J = 8.22 Hz), 7.21-7.17 (m, 2H) 6.92-6.89 (d, 2H, J = 8.22 Hz), 5.06 (s, 2H), 3.80 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 160.22, 154.28, 153.80, 153.61, 151.66, 151.51, 150.42, 150.23, 148.29, 148.22, 131.83, 130.49, 126.47, 126.05, 125.89, 118.80, 118.52, 114.78, 114.35, 55.44, 52.66. HRMS (EI): calcd for C\(_{18}\)H\(_{13}\)O\(_2\)N\(_2\)ClF\(_2\): 362.0634, found: 362.0629.

5-chloro-3-(2-chlorophenyl)-1-(4-methoxybenzyl)-2(1\(\text{H}\))-pyrazinone (3\{12\}). It was obtained as a yellow solid m.p. 98-99 °C in 33 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.46-7.33 (m, 3H), 7.30-7.27 (m, 4H), 6.91-6.89 (m, 2H), 5.06 (s, 2H), 3.80 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): 160.13, 154.74, 134.54, 133.69, 133.30, 130.95, 130.83, 130.58, 129.85, 126.81, 126.14, 114.71, 55.41, 52.57. HRMS (EI): calcd for C\(_{18}\)H\(_{14}\)O\(_2\)N\(_2\)Cl\(_2\): 360.0432, found: 360.0429.

5-chloro-3-(3-chlorophenyl)-1-(4-methoxybenzyl)-2(1\(\text{H}\))-pyrazinone (3\{13\}). It was obtained as a yellow solid m.p. 124-125 °C in 56 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.39-8.36 (d, 2H, J = 8.22 Hz), 7.40-7.37 (d, 2H, J = 8.22 Hz), 7.30-7.27 (d, 2H, J = 8.22 Hz), 7.17 (s, 1H), 6.91-6.88 (d, 2H, J = 8.22 Hz), 5.04 (s, 2H), 3.79 (s, 3H) \(^{13}\)C NMR (75 MHz,
5-chloro-3-(4-chlorophenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{14}). It was obtained as a yellow solid m.p. 128-129 °C in 51 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.41 (s, 1H), 8.32-8.29 (d, 1H, \(J = 8.22\) Hz), 7.39-7.35 (m, 2H), 7.31-7.28 (d, 2H, \(J = 8.22\) Hz), 7.20 (s, 1H), 6.91-6.88 (d, 2H, \(J = 8.22\) Hz), 5.05 (s, 2H), 3.79 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): 160.16, 154.28, 150.35, 136.52, 134.24, 130.65, 130.46, 129.43, 129.21, 127.48, 126.47, 126.11, 125.99, 114.74, 55.44, 52.60. HRMS (EI): calcd for C\(_{18}\)H\(_{14}\)O\(_2\)N\(_2\)Cl\(_2\): 360.0432, found: 360.0431.

5-chloro-3-(3,4-dichlorophenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{16}). It was obtained as a yellow solid m.p. 114-115 °C in 54 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.62-8.61 (m, 1H), 8.35-8.32 (m, 1H), 7.51-7.48 (d, 1H, \(J = 8.22\) Hz), 7.32-7.29 (d, 2H, \(J = 8.22\) Hz), 7.22 (s, 1H), 6.93-6.91 (d, 2H, \(J = 8.22\) Hz), 5.07 (s, 2H), 3.81 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): 160.16, 154.28, 150.35, 136.52, 134.24, 130.65, 130.46, 129.43, 129.21, 127.48, 126.47, 126.11, 125.99, 114.74, 55.44, 52.60. HRMS (EI): calcd for C\(_{19}\)H\(_{15}\)ON\(_2\)Cl\(_3\): 394.0043, found: 394.0028.

5-chloro-3-(2-methylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{17}). It was obtained as a yellow solid m.p. 115-116 °C in 21 % yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.46-7.44 (d, 1H, \(J = 7.4\) Hz), 7.31-7.29 (m, 3H), 7.25-7.23 (m, 3H), 6.91-6.89 (d, 2H, \(J = 8.7\) Hz), 5.03 (s, 2H), 3.80 (s, 3H), 2.31 (s, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): 161.27, 157.08, 155.46, 137.20, 134.95, 130.74, 130.55, 129.70, 126.50, 126.17, 125.61, 114.80, 55.46, 52.57, 20.11. HRMS (EI): calcd for C\(_{19}\)H\(_{17}\)O\(_2\)N\(_2\)Cl: 340.0978, found: 340.0979.

5-chloro-3-(3-methylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{18}). It was obtained as a yellow solid m.p. 151-152 °C in 59 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.17-8.15 (bs, 2H), 7.34-7.24 (m, 4H), 7.14 (s, 1H), 6.90-6.87 (m, 2H), 5.02 (s, 2H), 3.78 (s, 3H), 2.39 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): 160.04, 154.47, 152.46, 137.20, 134.95, 130.74, 130.55, 129.70, 126.50, 126.17, 125.61, 114.80, 55.46, 52.57, 20.11. HRMS (EI): calcd for C\(_{19}\)H\(_{17}\)O\(_2\)N\(_2\)Cl: 340.0978, found: 340.0980.

5-chloro-3-(4-methylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{19}). It was obtained as a yellow solid m.p. 108-109 °C in 62 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.31-8.28 (d, 2H, \(J = 8.22\) Hz), 7.31-7.28 (d, 2H, \(J = 9.12\) Hz), 7.22-7.12 (d, 2H, \(J = 8.22\) Hz), 7.13 (s, 1H), 6.91-6.88 (d, 2H, \(J = 9.15\) Hz), 5.04 (s, 2H), 3.80 (s, 3H), 2.39 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): 160.13, 154.59, 152.30, 141.22, 132.32, 130.46, 129.40, 129.0, 126.56, 124.71, 114.71, 55.47, 52.45, 21.65. HRMS (EI): calcd for C\(_{19}\)H\(_{17}\)O\(_2\)N\(_2\)Cl: 340.0978, found: 340.0979.

5-chloro-3-(3,4-dimethylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{20}). It was obtained as a yellow solid m.p. 179-180 °C in 57 % yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.96 (s, 2H), 7.32-7.29 (d, 2H, \(J = 9.15\) Hz), 7.14 (s, 1H), 7.09 (s, 1H), 6.91-6.88 (d, 2H, \(J = 9.12\) Hz), 5.05 (s, 2H), 3.80 (s, 3H), 2.36 (s, 6H). \(^13\)C NMR (75 MHz, CDCl\(_3\)): 160.10, 154.56,
152.82, 137.68, 134.88, 132.60, 130.43, 127.11, 126.50, 124.89, 114.71, 55.44, 52.42, 21.50. HRMS (EI): calcd for C$_{20}$H$_{19}$O$_2$N$_2$Cl: 354.1135, found: 354.1133.

5-chloro-3-(3,5-dimethylphenyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{21}). It was obtained as a yellow solid m.p. 190-193 °C in 59 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.96 (s, 2H), 7.31-7.29 (d, 2H, $J = 8.22$ Hz), 7.14 (s, 1H), 7.09 (s, 1H), 6.91-6.88 (d, 2H, $J = 9.15$ Hz), 5.04 (s, 2H), 3.79 (s, 3H), 2.36 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): 160.10, 154.56, 152.79, 137.718, 134.88, 132.63, 130.43, 127.11, 126.50, 124.95, 114.68, 55.44, 52.42, 21.50. HRMS (EI): calcd for C$_{20}$H$_{19}$O$_2$N$_2$Cl: 354.1135, found: 354.1133.

5-chloro-3-(2-ethoxycarbonyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{24}). It was obtained as a yellow oil in 26 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.97-7.95 (d, 1H, $J = 8.22$ Hz), 7.61-7.52 (m, 3H), 7.32-7.29 (d, 2H, $J = 9.15$ Hz), 7.19 (s, 1H), 6.90-6.88 (d, 2H, $J = 9.12$ Hz), 4.98 (s, 2H), 4.23-4.16 (q, 2H, $J = 6.8$ Hz), 3.79 (s, 3H), 1.43-1.38 (t, 3H, $J = 7.29$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): 166.32, 160.13, 154.38, 150.72, 138.84, 131.86, 130.46, 129.24, 126.56, 126.29, 126.11, 114.71, 61.22, 55.41, 52.60, 14.40. HRMS (EI): calcd for C$_{21}$H$_{19}$O$_4$N$_2$Cl: 398.1033, found: 398.1028.

5-chloro-3-(4-ethoxycarbonyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{25}). It was obtained as a yellow solid m.p. 117-118 °C in 61 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.48-8.45 (d, 2H, $J = 8.22$ Hz), 8.09-8.07 (d, 2H, $J = 8.22$ Hz), 7.32-7.28 (m, 3H, $J = 9.15$ Hz), 6.91-6.88 (d, 2H, $J = 9.15$ Hz), 5.06 (s, 2H), 4.42-4.35 (q, 2H, $J = 6.8$ Hz), 3.79 (s, 3H), 1.22-1.18 (t, 3H, $J = 7.29$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$): 167.05, 160.04, 157.60, 154.80, 135.98, 133.57, 131.47, 130.49, 130.31, 129.73, 129.52, 126.47, 125.47, 114.59, 61.25, 55.41, 52.30, 14.13. HRMS (EI): calcd for C$_{21}$H$_{19}$O$_4$N$_2$Cl: 398.1033, found: 398.1028.

5-chloro-3-(4-formyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{27}). It was obtained as a yellow solid m.p. 145-148 °C in 59 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 10.04 (s, 1H), 8.56-8.54 (d, 2H, $J = 8.22$ Hz), 7.93-7.90 (d, 2H, $J = 8.22$ Hz), 7.33-7.28 (m, 3H), 6.92-6.89 (d, 2H, $J = 9.15$ Hz), 5.08 (s, 2H), 3.79 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): 192.50, 167.22, 160.52, 154.73, 150.62, 140.63, 137.46, 135.20, 134.20, 133.41, 130.85, 130.18, 129.72, 128.44, 127.07, 126.25, 115.07, 55.73, 53.11. HRMS (EI): calcd for C$_{19}$H$_{15}$O$_3$N$_2$Cl: 354.0771, found: 354.0783.

5-chloro-3-(4-hydroxy)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{28}). It was obtained as a yellow solid m.p. 184-185 °C in 59 % yield. $^1$H NMR (300 MHz, CDCl$_3$ + DMSO): δ 9.53 (s, 1H), 8.31-8.28 (d, 2H, $J = 8.22$ Hz), 7.43 (s, 1H), 7.33-7.28 (m, 3H), 6.92-6.89 (d, 2H, $J = 9.15$ Hz), 5.08 (s, 2H), 3.79 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$ + DMSO): 159.19, 158.79, 155.44, 153.40, 130.28, 129.31, 126.44, 126.23, 125.50, 125.07, 114.90, 115.26, 113.47, 54.40, 51.23. HRMS (EI): calcd for C$_{18}$H$_{15}$O$_3$N$_2$Cl: 342.0771, found: 342.0783.

5-chloro-3-(4-acetyl)-1-(4-methoxybenzyl)-2(1H)-pyrazinone (3{30}). It was obtained as solid m.p. 174-175 °C in 56 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.51-8.48 (d, 2H, $J = 8.22$ Hz), 8.02-7.99 (d, 2H, $J = 8.22$ Hz), 7.34-7.31 (d, 2H, $J = 9.15$ Hz), 7.24 (s, 1H), 6.94-6.91 (m, 2H), 5.09 (s, 2H), 3.82 (s, 3H), 2.64 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): 197.97,
5-chloro-1-(cyclohexylmethyl)-3-(4-methoxyphenyl)-2(1H)-pyrazinone (3{33}). It was obtained as a yellow solid m.p. 207 °C in 52 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.45-8.42 (d, 2H, $J = 9.12$ Hz), 7.09 (s, 1H) 6.95-6.92 (d, 2H, $J = 9.12$ Hz), 3.86 (s, 3H), 3.78-3.75 (d, 2H, $J = 7.29$ Hz), 1.73-1.57 (m, 5H), 1.26-1.22 (m, 3H), 1.07-0.99 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): 161.78, 154.68, 151.57, 131.29, 127.84, 126.08, 125.47, 113.59, 56.90, 55.50, 36.82, 30.70, 26.25, 25.67. HRMS (EI): calcd for C$_{18}$H$_{21}$O$_2$N$_2$Cl: 332.1292, found: 332.1305.

5-chloro-3-(4-methoxyphenyl)-1-(3-phenylpropyl)-2(1H)-pyrazinone (3{34}). It was obtained as a yellow solid m.p. 96-97 °C in 59 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.44-8.41 (d, 2H, $J = 9.12$ Hz), 7.30-7.18 (m, 5H), 7.06 (s, 1H), 6.95 -6.93 (m, 2H), 3.98-3.93 (t, 2H, $J = 7.29$ Hz), 3.86 (s, 3H), 2.75-2.70 (t, 2H, $J = 7.32$ Hz), 2.21-2.10 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): 161.81, 154.53, 151.57, 140.27, 131.29, 128.76, 128.42, 127.75, 126.53, 126.41, 124.80, 113.62, 55.50, 50.32, 32.89, 29.85. HRMS (EI): calcd for C$_{20}$H$_{19}$O$_2$N$_2$Cl: 354.1135, found: 354.1135.

1-benzyl-5-chloro-3-(4-methoxyphenyl)-6-methyl-2(1H)-pyrazinone (3{35}). It was obtained as a yellow solid m.p. 164-166 °C in 61 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.45-8.42 (d, 2H, $J = 9.12$ Hz), 7.33-7.27 (m, 3H), 7.19-7.17 (d, 2H, $J = 6.39$ Hz), 6.95-6.92 (d, 2H, $J = 8.22$ Hz), 3.84 (s, 3H), 2.41 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): 161.44, 155.53, 148.25, 134.91, 133.63, 130.92, 129.15, 128.03, 127.97, 126.78, 113.59, 55.47, 48.98, 17.08. HRMS (EI): calcd for C$_{19}$H$_{17}$O$_2$N$_2$Cl: 340.0979, found: 340.0968.

5-chloro-3-(4-methoxyphenyl)-1,6-dimethyl-2(1H)-pyrazinone (3{36}). It was obtained as a yellow solid m.p. 156-159 °C in 60 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.39-8.36 (d, 2H, $J = 9.12$ Hz), 6.93-6.90 (d, 2H, $J = 9.12$ Hz), 3.83 (s, 3H), 3.54 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): 161.20, 147.19, 133.69, 130.68, 127.90, 126.08, 113.40, 55.34, 32.71, 17.24. HRMS (EI): calcd for C$_{13}$H$_{13}$O$_2$N$_2$Cl: 364.0666, found: 364.0653.

5-chloro-1-(cyclohexyl)-3-(3-ethoxyphenyl)-2(1H)-pyrazinone (3{37}). It was obtained as a yellow oil in 57 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.97 (s, 2H), 7.35-7.30 (t, 1H, $J = 8.22$ Hz), 7.27(s, 1H), 7.00-6.97 (m, 1H), 4.84-4.81 (m, 1H), 4.13-4.06 (q, 2H, $J = 6.42$ Hz), 3.78-3.76 (d, 2H, $J = 7.32$ Hz), 1.91-1.85 (m, 1H), 1.72-1.69 (m, 6H), 1.44-1.39 (t, 3H, $J = 7.29$ Hz), 1.25-1.21.(m, 2H), 1.06-0.99 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): 158.76, 154.04, 151.45, 136.43, 129.12, 126.75, 122.39, 121.93, 117.73, 114.78, 63.69, 55.38, 32.25, 25.74, 25.34, 14.95. HRMS (EI): calcd for C$_{19}$H$_{21}$O$_2$N$_2$Cl: 364.0666, found: 364.0653.

5-chloro-1-(cyclohexylmethyl)-3-(3-ethoxyphenyl)-2(1H)-pyrazinone (3{38}). It was obtained as a yellow solid m.p. 79-80 °C in 54 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.99-7.97 (m, 2H), 7.35-7.30 (t, 1H, $J = 8.22$ Hz), 7.27(s, 1H), 7.01-6.97 (m, 1H), 4.13-4.06 (q, 2H, $J = 6.42$ Hz), 3.78-3.76 (d, 2H, $J = 7.32$ Hz), 1.91-1.85 (m, 1H), 1.72-1.69 (m, 6H), 1.44-1.39 (t, 3H, $J = 7.29$ Hz), 1.25-1.21.(m, 2H), 1.06-0.99 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): 158.76, 154.56, 151.76, 136.22,
129.12, 126.62, 125.95, 121.90, 117.70, 114.81, 63.66, 56.93, 36.76, 30.64, 26.19, 25.61, 14.92. HRMS (EI): calcd for C₁₉H₂₃O₂N₂Cl: 346.1448, found: 346.1450.

5-chloro-3-(3-ethoxyphenyl)-1-(3-phenylpropyl)-2(1H)-pyrazinone (3{39}). It was obtained as a yellow oil in 60 % yield. ¹H NMR (300 MHz, CDCl₃): δ 7.98-7.95 (m, 1H), 7.36-7.18 (m, 7H), 7.12(s, 1H), 7.02-6.98 (m, 1H), 4.14-4.07 (q, 2H, J = 7.32 Hz), 3.99-3.94 (t, 2H, J = 7.29 Hz), 2.76-2.71 (t, 4H, J = 7.29 Hz), 2.21-2.11 (p, 2H, J = 7.29 Hz) 1.45-1.40 (t, 2H, J = 7.29 Hz). ¹³C NMR (75 MHz, CDCl₃): 158.76, 154.38, 151.69, 140.15, 136.13, 129.15, 128.73, 128.36, 126.50, 126.29, 126.05, 121.87, 117.73, 114.78, 63.66, 50.41, 32.88, 29.76, 14.92. HRMS (EI): calcd for C₂₁H₂₁O₂N₂Cl: 368.1291, found: 368.1288.

1-benzyl-5-chloro-3-(3-ethoxyphenyl)-6-methyl-2(1H)-pyrazinone (3{40}). It was obtained as a yellow solid m.p. 135-136 °C in 62 % yield. ¹H NMR (300 MHz, CDCl₃): δ 8.00-7.97 (m, 2H), 7.38-7.20 (m, 6H), 7.14 (s, 1H), 7.03-7.00 (m, 1H), 4.15-4.08 (q, 2H, J = 7.32 Hz), 4.01-3.96 (t, 2H, J = 7.26 Hz ), 2.78-2.72 (t, 2H, J = 7.29 Hz), 2.23-2.13 (m, 2H), 1.44-1.39 (t, 3H, J = 7.29 Hz). ¹³C NMR (75 MHz, CDCl₃): 158.82, 155.47, 148.34, 136.43, 135.09, 134.76, 129.18, 128.09, 126.81, 126.62, 121.66, 119.65, 117.24, 114.62, 113.47, 63.66, 49.10, 17.21, 14.95. HRMS (EI): calcd for C₂₀H₁₉O₂N₂Cl: 354.1135, found: 354.1132.

5-chloro-3-(3-ethoxyphenyl)-1,6-dimethyl-2(1H)-pyrazinone (3{41}). It was obtained as a yellow solid m.p. 155-156 °C in 63 % yield. ¹H NMR (300 MHz, CDCl₃): δ 7.94 (s, 1H), 7.35-7.30 (t, 1H, J = 8.22 Hz), 7.26 (s, 1H), 6.98-6.96 (d, 1H, J = 7.29 Hz), 4.14-4.07 (q, 2H, J = 7.32 Hz), 3.64 (s, 3H), 2.5 (s, 3H), 1.45-1.40 (t, 3H, J = 7.29 Hz). ¹³C NMR (75 MHz, CDCl₃): 158.73, 155.32, 147.28, 136.43, 135.15, 129.06, 126.11, 121.48, 117.03, 114.41, 63.57, 32.86, 17.39, 14.92. HRMS (EI): calcd for C₁₄H₁₅O₂N₂Cl: 278.0822, found: 278.0824.
$^1$H and $^{13}$C spectra of compound 3(1)
$^1$H and $^{13}$C spectra of compound 3[2]
$^{1}H$ and $^{13}C$ spectra of compound 3(3)
$^1$H and $^{13}$C spectra of compound 3(4)
$^1$H and $^{13}$C spectra of compound 3(5)
$^1$H and $^{13}$C spectra of compound 3[6]
$^{1}H$ and $^{13}C$ spectra for compound 3[7]
$^1$H and $^{13}$C spectra for compound 3(8)
$^1$H and $^{13}$C spectra of compound 3(9)
$^1$H and $^{13}$C spectra of compound 3[10]
$^1$H and $^{13}$C spectra of compound 3[11]
$^1$H and $^{13}$C spectra of compound 3(12)
$^1$H and $^{13}$C spectra of compound 3(13)
$^1$H and $^{13}$C spectra of compound 3[14]
$^1$H and $^{13}$C spectra of compound 3[16]
$^1$H and $^{13}$C spectra of compound 3[17]
$^1$H and $^{13}$C spectra of compound 3[18]
$^1$H and $^{13}$C spectra of compound 3[19]
$^1$H and $^{13}$C spectra of compound 3[20]
$^1$H and $^{13}$C spectra of compound 3[21]
$^1$H and $^{13}$C spectra of compound 3{24}
\(^1\)H and \(^{13}\)C spectra of compound 3[25]
$^1$H and $^{13}$C spectra of compound 3[27]
$^1$H and $^{13}$C spectra of compound 3[28]
\(^1\)H and \(^{13}\)C spectra of compound 3[30]
$^1$H and $^{13}$C spectra of compound 3[33]
$^1$H and $^{13}$C spectra of compound 3[34]
$^1$H and $^{13}$C spectra of compound 3[35]
$^1$H and $^{13}$C spectra of compound 3[36]
\[^1\text{H} \text{ and } ^{13}\text{C} \text{ spectra of compound } 3[37]\]
$^1$H and $^{13}$C spectra of compound 3[38]
$^1$H and $^{13}$C spectra of compound 3[39]
$^1$H and $^{13}$C spectra of compound 3[40]
$^1$H and $^{13}$C spectra of compound 3[41]